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Sevoflurane Provides Greater Protection of the Myocardium than Propofol in Patients Undergoing Off-pump Coronary Artery Bypass Surgery

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Background: **Sevoflurane, like other halogenated anesthetics, has been shown to have a protective effect on the myocardium at risk after an ischemic injury. The current study tested the hypothesis that such beneficial effects, so far mainly seen in the laboratory, are reproducible in humans.**

Methods: **After institutional review board approval, 20 patients scheduled to undergo elective off-pump coronary artery bypass surgery were randomized to receive general anesthesia with either sevoflurane or propofol. Except for this, anesthetic and surgical management was the same in both groups. For assessing myocardial injury, troponin I and myocardial fraction of creatine kinase were determined during the first 24 postoperative hours. Systemic hemodynamic variables were measured before, during, and after completion of coronary artery bypass.**

Results: **Troponin I concentrations increased significantly more in propofol-anesthetized patients than in patients anesthetized with sevoflurane.**

Conclusion: **Patients receiving sevoflurane for off-pump coronary artery surgery had less myocardial injury during the first 24 postoperative hours than patients receiving propofol. The results further support cardioprotective effects of sevoflurane.**

A VARIETY of *in vitro* studies and *in vivo* animal experiments have shown that halogenated volatile anesthetics have a protective effect on the ischemic myocardium. Volatile anesthetics improve postischemic recovery[1] and decrease myocardial infarction size.[2] They thereby mimic ischemic preconditioning, which is a powerful mode of reducing myocardial infarction size after ischemia.[3,4] Intravenous anesthetics such as propofol do not seem to have comparable protective properties.[3] The underlying mechanisms are still under investigation, but it seems that protection of cardiomyocytes is mediated through an effect on mitochondrial adenosine triphosphate-regulated potassium (K_{ATP}) channels triggered by protein kinase C-coupled signaling pathways.[5] In addition, reduced polymorphonuclear neutrophil and platelet adhesion to the vascular endothelium may contribute to the protective effect.[6,7]

Cardioprotective effects of halogenated anesthetics have meanwhile been confirmed in patients after coronary revascularization with use of a cardiopulmonary bypass.[8–10] In a recently published study, anesthesia with sevoflurane was associated with preserved cardiac function after weaning from bypass, and postoperative concentrations of troponin I were lower than in patients who underwent propofol anesthesia for the same procedure.[11] Because surgery-related events such as the use of cardiopulmonary bypass are known to have a profound impact on preservation of all organs including the heart, we sought to investigate the cardioprotective potential of anesthetics during surgery without extracorporal circulation. Patients undergoing off-pump coronary bypass surgery do not require cardiopulmonary bypass and, in addition, have a predictable and predefined ischemic zone during bypass surgery.

In addition, inflammatory mediators released as a consequence of intraoperative events such as ischemic trauma and reperfusion or cardiopulmonary bypass may activate endothelial cells in remote organs that are not exposed to the initial ischemic injury.[12] This distant response to ischemia and reperfusion can result in leukocyte-dependent microvascular injury that is characteristic of the multiple organ dysfunction syndrome.[13] Cardiac surgery using cardiopulmonary bypass is associated with release of inflammatory mediators and often also severe systemic inflammatory reactions, which may lead to multiorgan failure and increased postoperative morbidity and mortality. Elevated systemic inflammatory markers have been reported also after off-pump coronary artery bypass graft procedures.[14] Sevoflurane is able to modulate the interaction of polymorphonuclear neutrophils with the microvascular endothelium, and this may play a crucial role in the initiation of reperfusion injury, even more when cardiopulmonary bypass is used.[15,16] Off-pump coronary surgery eliminates the profound cellular activation and enzyme release due to cardiopulmonary bypass and thereby an interference of these mediators with reperfusion injury.

Therefore, we evaluated the protective potential of sevoflurane *versus* propofol anesthesia in patients undergoing elective off-pump coronary revascularization procedures. Cardioprotection was assessed by postoperative troponin I, which was considered the primary outcome variable, as well as by the myocardial fraction

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of creatine kinase and postbypass hemodynamics. Markers of systemic inflammation were determined as well.

Materials and Methods

The study was performed prospectively in 20 patients scheduled for off-pump coronary artery bypass surgery. Institutional review board approval had been obtained (Ludwig-Maximilians-Universität, Munich, Germany). Criteria for enrolling a patient were written informed consent, age greater than 18 yr, elective surgery, body mass index below 150% of ideal, and American Society of Anesthesiologists (ASA) physical status of II–IV. Exclusion criteria were a previous unusual response to an anesthetic, an experimental drug within 28 days before surgery, severe accompanying disease (hepatic, renal), previous surgical coronary artery repair, severe cardiac dysrhythmias or an ejection fraction below 0.3 (preoperative cardiac catheterization), and combined surgery involving a second organ (*e.g.*, carotid endarterectomy). Patients taking oral glibenclamide or other sulfonylurea drugs were excluded, as well. Only patients with one-vessel or two-vessel coronary artery disease suitable for repair without cardiopulmonary bypass were included. Patients were randomized immediately before anesthesia in a 1:1 ratio to receive either sevoflurane or propofol as their primary anesthetic.

Anesthesia and Surgical Procedure

Anesthesia and surgery were conducted similarly in both groups. All preoperative cardiac medication was continued until the morning of surgery. Oral midazolam (7.5 mg) was given for premedication on the morning of surgery. In all patients, analgesia was achieved with sufentanil by a loading dose of 1.0 μg/kg followed by continuous infusion (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$) until the end of surgery. For induction of anesthesia, patients in the sevoflurane group received an intravenous bolus of etomidate (0.3 mg/kg); in the propofol group, a target-controlled infusion was started at 2 μg/ml. This was followed by pancuronium bromide (0.1 mg/kg) to facilitate tracheal intubation. After tracheal intubation and for the whole duration of the procedure, anesthesia was maintained with either 2 vol% end-tidal sevoflurane (approximately 1 minimum alveolar concentration [MAC]) or 2–3 μg/ml propofol *via* target-controlled infusion.

Patients received routine monitoring for off-pump coronary artery surgery. Besides standard measures for coronary revascularization procedures (five-lead electrocardiogram, arterial and central venous lines, pulse oximetry, capnography, temperature), monitoring included transesophageal echocardiography and a pulmonary artery catheter.

Surgical access to the heart depended on location and number of bypasses needed. A left lateral thoracotomy was performed for procedures in which the left internal mammary artery was used for revascularization of the left anterior descending artery. If the circumflex artery or the right coronary artery were the target for revascularization or when more that one vessel had to be bypassed, a median sternotomy was performed for gaining access to the heart. Five thousand units of heparin were given before surgical manipulation of the coronary arteries was started. When patients showed signs of severe systemic hypotension after occlusion of an artery (*i.e.*, when unusually high infusion rates of catecholamines were required), the procedure was interrupted and continued when cardiopulmonary bypass had been initiated. After the end of surgery, patients were transferred to the intensive care unit. As soon as normothermia was reached, patients were weaned from the respirator and extubated.

Biochemical Analyses

For quantification of tissue injury, troponin I (fluorescence-immunoassay), creatine kinase (optical standard technique at 25°C), and the myocardial fraction of creatine kinase were measured. Procalcitonin (luminescence-immunoassay), interleukin 6 (enzyme-linked immunosorbent assay), and C-reactive protein (CRP; immunoassay) were determined as indicators of systemic inflammatory reaction. All analyses were performed in the central hospital laboratory using routine laboratory procedures. Specimens were sampled before induction of anesthesia, after skin incision, after 15 min of reperfusion, at the time of arrival in the intensive care unit, and 3, 6, 12, 18, and 24 h after admission to the intensive care unit. Sensitivity of troponin I determination in the laboratory is 0.5 ng/ml.

Hemodynamic Data

Patients were carefully monitored throughout the perioperative period. Global hemodynamic variables for subsequent statistical analysis (*i.e.*, heart rate, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, wedge pressure, cardiac output) were recorded after skin incision, during preparation of the anastomosis (after approximately 50% of the ischemic period), 15 min after reperfusion, and at the end of the surgical procedure during skin closure. Cardiac output was measured by thermodilution technique and considered the mean of triplicate injections of ice-cold saline. Flow through vessel grafts was assessed by transit time flow technique (Cardio-Med®; Medi-Stim AS, Oslo, Norway).

Statistical Analysis

Troponin I served as the primary outcome variable. A sample size calculation performed with data from 10 preceding patients with comparable procedures anticipated a minimum of 17 evaluable patients to detect a

Table 1. Patient Characteristics

	Sevoflurane (n = 10)	Propofol (n = 10)
Patients		
Sex (M/F)	8/2	6/4
Age, yr	62 ± 9	65 ± 8
Height, cm	170 ± 12	172 ± 9
Weight, kg	77 ± 15	80 ± 11
NYHA class	2.5 (2.0–3.0)	3.0 (2.0–4.0)
ASA class	III (II–IV)	III (III–IV)
EF, %	63 ± 10	64 ± 15
Surgery		
No. of bypasses (1/2)	7/3	5/5
Duration of ischemia no. 1, min	20 ± 5	20 ± 5
Duration of ischemia no. 2, min	27 ± 5	28 ± 21
Flow vessel graft no. 1, ml/min	49 ± 27	37 ± 14
Flow vessel graft no. 2, ml/min	69 ± 56	28 ± 9
Duration		
Anesthesia, min	334 ± 93	351 ± 90
Surgery, min	227 ± 81	243 ± 69

Data are given as absolute number, median and range, or mean ± SD as appropriate. There were no statistically significant differences between the two groups.

ASA = American Society of Anesthesiologists (physical status); EF = ejection fraction; NYHA = New York Heart Association.

1-ng/ml difference in serum troponin I between anesthetics using an α level of 0.05 (two-sided) with a power of 0.80. Biochemical serum markers and hemodynamic data were compared using two-way analysis-of-variance techniques for repeated measurements. Patient characteristics were compared with an unpaired *t* test and Fisher exact test where appropriate. Data are expressed as mean ± SD unless otherwise indicated. A *P* value of 0.05 or less was considered statistically significant.

Results

Patients in the sevoflurane and propofol groups were not different in terms of sex, age, size, weight, New York Heart Association classification, ASA physical classification, preoperative ejection fraction, and number of coronary arteries grafted. Also, the operative conditions were comparable (durations of anesthesia, surgery, ischemic periods; table 1). Ten patients receiving sevoflurane and 10 patients receiving propofol were evaluated. Three additional patients met exclusion criteria after having been enrolled, *i.e.*, were not included into the data analysis: One patient of the sevoflurane group had excessive bleeding after revascularization and required a second surgery within 12 h; one patient of each group had severe hemodynamic instability during clamping of the coronary artery so that cardiopulmonary bypass was necessary. For replacement, the next enrolled patient received the same anesthetic again. In the evaluated patients, anesthesia, surgery, and postoperative course were uneventful.

There was no difference in preoperative cardiac medication, and concomitant morbidity was comparable among groups. Patients with sevoflurane had a slightly higher incidence of one vessel disease (7 *vs.* 5) but without statistical significance. Bypasses were placed on the following arteries (sevoflurane/propofol, n): left anterior descending (9/10), first diagonal branch (1/2), circumflex (0/2), right coronary (3/1). Durations of anesthesia and surgery were comparable (table 1). Until occlusion of the vessel to be bypassed, no patient exhibited myocardial ischemia intraoperatively, as judged by automated ST-segment analysis and wedge pressure tracing.

Heart rate, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, and pulmonary capillary wedge pressure were comparable between groups at the beginning of surgery and did not change during the observation period (table 2). Cardiac index during sevoflurane increased from the beginning to the end of surgery from 2.3 ± 0.4 to 3.1 ± 0.6 $l \cdot min^{-1} \cdot m^{-2}$ ($P = 0.006$), whereas cardiac index remained constant with propofol, 2.5 ± 0.7 *versus* 2.7 ± 0.6 $l \cdot min^{-1} \cdot m^{-2}$ ($P = 0.599$). The left ventricular systolic rate–pressure product as gross measure of oxygen demand at these measuring points increased slightly from 5,896 ± 722 to 6,996 ± 1,341 mmHg/min with sevoflurane and from 6,411 ± 1,549 to 7,534 ± 1,593 mmHg/min with propofol but was not statistically significant.

Troponin I concentrations were below the detection limit of 0.5 ng/ml before and during revascularization in both groups but started to increase after reperfusion. Troponin I increased significantly with both anesthetics, and peak values were reached approximately 6 h after the end of surgery (figs. 1 and 2 and table 3). However, troponin increased significantly more in patients anesthetized with propofol than with sevoflurane (two-way analysis of variance: $P = 0.009$).

Values of creatine kinase and myocardial fraction of creatine kinase were also comparable at the beginning of surgery in both groups (table 3). Both parameters started to increase toward the end of surgery. Early in the postoperative course, myocardial fraction of creatine kinase was lower after sevoflurane than after propofol at most measuring points, but this difference did not reach statistical significance ($P = 0.62$).

Serum markers of systemic inflammation (procalcitonin, interleukin 6, and CRP) increased postoperatively with both anesthetics from comparable baseline values. Concentrations of interleukin 6 started to decline after a peak had been reached approximately 3–6 h after surgery but were still elevated at the end of the observation period. Procalcitonin and CRP were still increasing at the end of the observation period 24 h after surgery (Table 4). CRP increased significantly more (two-way analysis of variance: $P = 0.002$) and interleukin 6 increased significantly less ($P = 0.027$) with propofol, whereas there was no difference in procalcitonin.

Table 2. Intraoperative Hemodynamic Data

	Start of Surgery	During Ischemia	15 min after Ischemia	End of Surgery
HR, beats/min				
Sevoflurane	55 ± 8	58 ± 7	60 ± 9	61 ± 11
Propofol	61 ± 8	62 ± 8	62 ± 11	67 ± 10
MAP, mmHg				
Sevoflurane	74 ± 11	78 ± 12	73 ± 10	79 ± 12
Propofol	71 ± 9	70 ± 13	72 ± 8	75 ± 10
MPAP, mmHg				
Sevoflurane	21 ± 4	23 ± 7	21 ± 4	21 ± 4
Propofol	23 ± 9	26 ± 10	23 ± 10	22 ± 6
CVP, mmHg				
Sevoflurane	10 ± 3	12 ± 4	9 ± 4	9 ± 3
Propofol	10 ± 4	13 ± 6	11 ± 6	9 ± 5
PCWP, mmHg				
Sevoflurane	13 ± 2	14 ± 5	10 ± 4	11 ± 4
Propofol	12 ± 4	15 ± 7	12 ± 6	9 ± 5
CO, l/min				
Sevoflurane	4.3 ± 1.1	4.4 ± 1.5	6.2 ± 1.8*	5.9 ± 1.6*
Propofol	4.8 ± 1.5	3.9 ± 1.0	5.3 ± 1.1	5.1 ± 1.0
SVR, dyn · s · cm^{-5}				
Sevoflurane	1,219 ± 291	1,278 ± 462	959 ± 336	953 ± 259
Propofol	1,250 ± 400	1,342 ± 352	1,026 ± 354	950 ± 228

Data are given as mean value ± SD.

* $P < 0.05$ *vs.* "start of surgery."

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

Almost all patients required inotropic support with 0.05–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ norepinephrine intraoperatively and especially during suturing of the anastomoses, *i.e.*, ischemia. This was mainly because of manipulation of the heart resulting in mechanical obstruction of venous return and reduced ventricular filling. However, there was no significant difference between the two groups.

Postoperatively, there were no deaths, and no patient had a transmural myocardial infarction. Hospital and intensive care unit stays were normal in all patients of both groups.

Discussion

The results from this investigation indicate that patients receiving sevoflurane for off-pump coronary vascular surgery had less myocardial injury than patients receiving propofol for the same intervention. This is

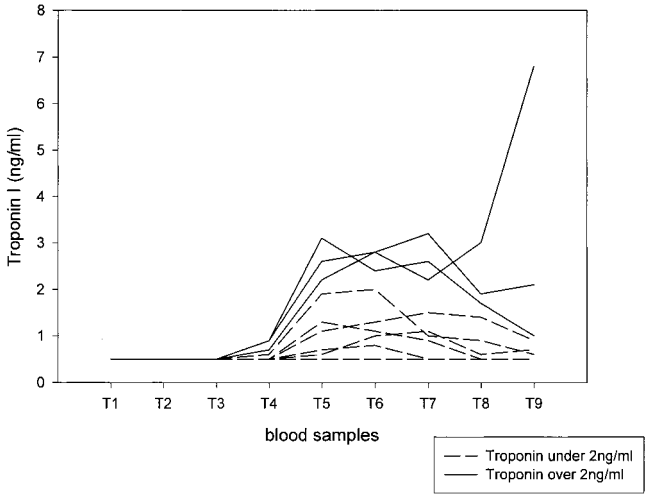

Fig. 1. Cardiac troponin I concentrations in sevoflurane-anesthetized patients during and after anesthesia. Samples were obtained before induction of anesthesia (*T1*), before ischemia (*T2*), 15 min after reperfusion (*T3*), at arrival in the postanesthetic care unit (*T4*), and 3 (*T5*), 6 (*T6*), 12 (*T7*), 18 (*T8*), and 24 h (*T9*) after arrival.

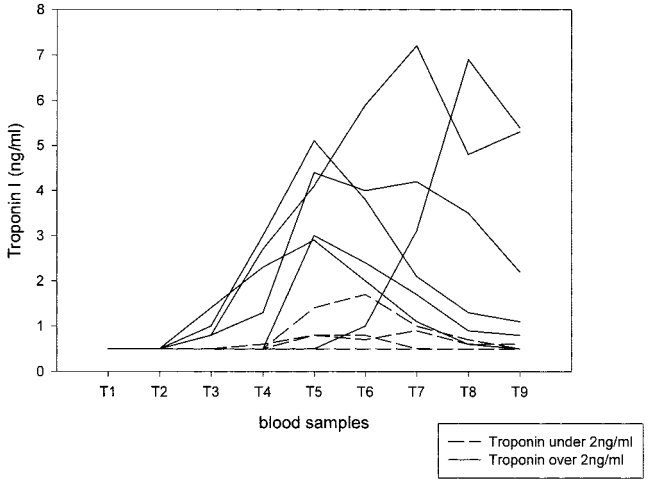

Fig. 2. Cardiac troponin I concentrations in propofol-anesthetized patients during and after anesthesia. Samples were obtained before induction of anesthesia (*T1*), before ischemia (*T2*), 15 min after reperfusion (*T3*), at arrival in the postanesthetic care unit (*T4*), and 3 (*T5*), 6 (*T6*), 12 (*T7*), 18 (*T8*), and 24 h (*T9*) after arrival.

Table 3. Perioperative Markers of Cellular Injury

	Start of Anesthesia	Start of Surgery	15 min after Reperfusion	End of Surgery	After Arrival in PACU				
					3 h	6 h	12 h	18 h	24 h
Troponin I, ng/ml									
Sevoflurane*	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.61 ± 0.17	1.45 ± 0.95	1.54 ± 0.92	1.40 ± 0.96	1.15 ± 0.84	1.41 ± 1.96
Propofol	0.5 ± 0.0	0.5 ± 0.0	0.70 ± 0.31	1.24 ± 1.03	2.35 ± 1.77	2.28 ± 1.77	2.23 ± 2.11	2.03 ± 2.26	1.74 ± 1.96
CK-MB, U/l									
Sevoflurane	1.34 ± 0.68	1.19 ± 0.51	1.65 ± 0.8	2.35 ± 1.15	3.56 ± 2.47	4.25 ± 3.67	5.96 ± 4.54	7.37 ± 4.48	7.83 ± 5.22
Propofol	1.46 ± 0.91	1.43 ± 0.71	2.16 ± 1.02	3.15 ± 1.54	5.19 ± 3.81	5.50 ± 5.20	6.34 ± 6.39	6.46 ± 5.26	5.88 ± 4.56
CK, U/l									
Sevoflurane	45.1 ± 62.5	36.2 ± 42.6	35.0 ± 24.1	50.5 ± 29.8	86.0 ± 67.0	127.7 ± 111.8	238.8 ± 240.2	294.6 ± 276.1	330.4 ± 248.6
Propofol	16.8 ± 8.4	20.2 ± 9.6	29.5 ± 15.4	45.5 ± 23.7	89.7 ± 95.5	116.9 ± 127.0	169.1 ± 204.4	174.6 ± 164.6	176.7 ± 149.0

Blood samples were obtained before induction of anesthesia, at the beginning of surgery, 15 min after reperfusion, at skin closure, and 3, 6, 12, 18, and 24 h after arrival in the postanesthesia care unit (PACU). Troponin I concentrations were similar for both groups at the beginning of anesthesia and during the first half of surgery. Values started to increase after completion of vessel anastomoses, significantly more in patients receiving propofol. Data are given as mean ± SD.

* $P < 0.05$, two-way analysis of variance, sevoflurane *vs.* propofol.

CK-MB = myocardial fraction of creatine kinase.

inferred from a significantly lower release of troponin I during the first 24 postoperative hours. Moreover, cardiac function apparently recovered better with sevoflurane, as cardiac output increased after revascularization with sevoflurane but not with propofol.

The data presented herein are in good agreement with recent studies also reporting cardioprotection by application of halogenated inhalational anesthetics in cardiac surgical patients. These studies noted a lower release of serum markers of cellular injury,[8] an improved recovery of ventricular function,[9,10] or both.[11] A cardiopulmonary bypass was necessary for surgery in all patients in these studies. Cardiac surgery involving cardiopulmonary bypass has been amply shown to be associated with liberation of a number of inflammatory mediators, intracellular enzymes, and cytokines. Such mediators might influence function of cardiac myocytes, especially in the presence of reperfusion injury; on the other hand, the choice of the anesthetic interferes with the degree by which those substances are released into the circulation.[17] Therefore, the applicability of these results to the general surgical patient population may be questioned. The protocol used in our current study deliberately excluded patients on cardiopulmonary bypass. Although off-pump surgery still involves manipulation of the heart and the coronaries, none of which are present in the noncardiac patient population, we assume that our data more closely reflect the situation of surgical patients experiencing a myocardial ischemic event during general anesthesia.

There is a growing body of literature to indicate that volatile anesthetics have protective properties at the cellular level. Cardioprotection by halogenated anesthetics against ischemia and reperfusion injury includes reduction of dysrhythmias,[1,18] energy preservation,[19] improvement of cardiac function,[15,20] and decreases in infarct size[2] compared to control groups. Several potential mechanisms for cardioprotection have been identified. For example, volatile anesthetics open intracellular K_{ATP} channels,[5,21] activate adenosine receptors,[22] and inhibit Na^+/K^+ pump.[23] Although the opening of K_{ATP} channels may play the pivotal role in acquisition of all

Table 4. Perioperative Biochemical Markers of Systemic Inflammation

	Start of Anesthesia	Start of Surgery	15 min after Reperfusion	End of Surgery	After Arrival in PACU				
					3 h	6 h	12 h	18 h	24 h
IL-6, pg/ml									
Sevoflurane*	4 ± 2	10 ± 7	92 ± 106	281 ± 269	979 ± 416	1,289 ± 664	849 ± 640	621 ± 378	437 ± 213
Propofol	6 ± 4	18 ± 22	137 ± 145	409 ± 290	1,105 ± 751	969 ± 627	492 ± 339	285 ± 116	191 ± 89
PCT, ng/ml									
Sevoflurane	0.10 ± 0.0	0.11 ± 0.03	0.11 ± 0.03	0.11 ± 0.03	0.11 ± 0.0	0.14 ± 0.07	0.46 ± 0.72	0.58 ± 1.14	0.84 ± 1.82
Propofol	0.10 ± 0.0	0.10 ± 0.0	0.10 ± 0.0	0.10 ± 0.0	0.14 ± 0.13	0.35 ± 0.19	0.75 ± 0.54	0.85 ± 0.58	0.95 ± 0.57
CRP, mg/dl									
Sevoflurane*	0.3 ± 0.3	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.3	0.4 ± 0.4	1.0 ± 0.6	5.1 ± 2.3	11.0 ± 2.8	17.0 ± 2.6
Propofol	0.6 ± 0.6	0.5 ± 0.5	0.5 ± 0.5	0.5 ± 0.4	0.7 ± 0.4	1.8 ± 0.6	6.9 ± 1.9	13.5 ± 3.3	18.6 ± 3.8

Data are given as mean ± SD. Blood samples were obtained before induction of anesthesia, before ischemia, 15 min after reperfusion, at arrival in the postanesthesia care unit, and 3, 6, 12, 18, and 24 h after arrival. Concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) were similar for both groups at begin of anesthesia. Values increased thereafter, IL-6 significantly less and CRP significantly more in patients receiving propofol.

* $P < 0.05$, two-way analysis of variance, sevoflurane *vs.* propofol.

PCT = procalcitonin.

types of pharmacologically induced preconditioned states in the heart, including those elicited by volatile anesthetics,[24] other mechanisms might contribute to myocardial protection, especially in the human perioperative setting.

Volatile anesthetics have been shown to reduce adhesion of polymorphonuclear neutrophils in the coronary system and thereby to preserve postischemic cardiac function.[6,15] Such beneficial effects have not been shown with propofol in the same isolated heart preparation,[25] on reduction of infarct size in isolated rat hearts,[26] or on K_{ATP} channel activity in isolated rat ventricular myocytes.[27] Certainly, the underlying mechanisms for the differential responses with sevoflurane and propofol observed in such laboratory experiments cannot be elucidated from the current study. However, together with other recently published data,[8–11] the results of this investigation strongly suggest that the choice of an anesthetic is also of importance in the clinical situation.

Cardioprotection is defined as the prevention or attenuation of myocardial dysfunction and necrosis that occurs on reperfusion. Myocardial stunning denotes a state of reversible dysfunction that may persist for hours or days after ischemia and reperfusion. Experimental findings also suggest a beneficial effect of sevoflurane against myocardial stunning,[28] whereas no protection has been reported with propofol.[29] There are no data in our study to directly substantiate the hypothesis that the increase in cardiac output in patients receiving sevoflurane was due to a reduction of stunning. Although all patients had a transesophageal echo probe in place, qualitatively acceptable views of the left ventricle could only be obtained at the beginning and the end of surgery. Manipulation of the heart precluded reproducible images, especially during the most crucial periods of the procedures.

Myocardial necrosis can be recognized by the appearance in the blood of different proteins released into the circulation due to damaged myocytes. The most recently described and preferred biomarker for myocardial damage is cardiac troponin I, which has a nearly absolute myocardial tissue specificity and a high sensitivity, thereby reflecting even very small zones of myocardial necrosis. There are currently no data available to demonstrate a threshold below which increases in troponin are harmless and without negative implications for prognosis. Even detection of a very small myocardial necrosis/infarction in this setting augurs a worse prognosis for the patient, rather than if biochemical markers had been normal.[30] Therefore, also, the absence of adverse cardiac outcomes in the patients studied in our investigation does not mean that the differences are without significance for the surgical patient population.

A common characteristic feature of various types of inflammatory processes is the interaction of circulating polymorphonuclear neutrophils with the postcapillary venular endothelium. This interaction in turn may result in activation of clotting and generation of numerous secondary inflammatory mediators including prostaglandins, leukotrienes, proteases, and cytokines, whereas antiinflammatory compounds such as interleukin 6 may serve as negative feedback.[31] As halogenated anesthetics have been reported to inhibit leukocyte–endothelium interaction after ischemia and reperfusion, we measured clinically used markers of systemic inflammation. Procalcitonin, the propeptide of calcitonin, has been found to be increased after conventional and minimally invasive coronary artery bypass grafting with considerably higher concentrations after procedures requiring cardiopulmonary bypass.[14] CRP is an acute-phase protein that is produced by hepatocytes and released during a variety of conditions such as trauma, surgery, or tissue infarction.[32] After propofol anesthesia, patients had higher postoperative plasma concentrations of CRP and procalcitonin, whereas interleukin 6 increased less when compared to sevoflurane. Although there may be no hard evidence in our data, this differential behavior is in accordance with the hypothesis of a reduced interaction of leukocytes with the vascular endothelium in sevoflurane-anesthetized patients.

Several potential limitations exist in this study. First, both sevoflurane and propofol were used as a part of a multidrug anesthetic regimen. All patients received oral midazolam before anesthesia and had a continuous infusion of sufentanil throughout the operation. At least the opioid fentanyl has been shown to afford protection of isolated cardiomyocytes due to activation of protein kinase C and increased activity of mitochondrial K_{ATP} channels, whereas midazolam had no effect.[27] Sufentanil apparently has not been tested in this regard. Even if there were a beneficial effect by sufentanil, this would not decrease the significance of the differences observed in this study because its dosage was comparable in both groups.

Second, patients in the propofol group received this anesthetic both for induction and for maintenance of anesthesia. Patients in the sevoflurane group received etomidate for induction, followed by sevoflurane after intubation. It is not clear whether the single dose of etomidate had an influence on the results. *In vitro* experiments showed no effects of etomidate on postischemic neutrophil adhesion in isolated hearts.[25] Also, etomidate did not activate mitochondrial K_{ATP} channels.[27] In combination with its short half-life, we do not assume an impact of etomidate on the results, suggesting that the observed differences were related indeed to the choice between sevoflurane and propofol.

Third, our sample size was insufficient to detect a

significant difference in adverse cardiac outcomes between groups. Two major considerations led us to limit the sample size and to select patients very carefully. (1) Patients with a higher degree of coronary artery disease requiring more than two vascular bypasses were not enrolled. This was done to keep the patient population as homogeneous as possible, excluding patients with very long procedures and/or a high number of ischemia–reperfusion situations. (2) We cannot exclude an influence on the measured parameters by the surgeon himself. Therefore, only patients operated on by one cardiac surgeon were enrolled. Both considerations in turn precluded us from studying a significantly higher number of patients in a reasonable period of time.

Fourth, the cardioprotective effects of sevoflurane may depend on the concentration used. Recent laboratory investigations reported beneficial effects with 1.0 MAC. Lower concentrations often showed no effect, whereas higher concentrations did not result in further protection.[7,33] With these results in mind, we used a relatively high end-tidal sevoflurane concentration throughout the procedures. A concentration of 1.0 MAC is not unusual in surgical patients, but we are well aware that adequate anesthesia may also be achieved with lower concentrations. Comparably beneficial effects have been reported recently when sevoflurane concentrations between 0.5 and 1.0 MAC were given to patients on cardiopulmonary bypass.[11] Further studies will need to evaluate the question of a dose dependency of cardioprotective effects and look for a potential threshold for protection.

Fifth, although troponin sensitively reflects myocardial injury, it does not indicate its mechanism. Tissue injury can be expected to result from arterial occlusion and subsequent reperfusion as well as from other sources such as trauma by sewing needles. Also, the study design does not allow us to state that sevoflurane is cardioprotective. An equally plausible interpretation of the results would be that propofol was deleterious.

In conclusion, patients receiving sevoflurane for off-pump coronary artery surgery had significantly lower postoperative release of troponin I than patients receiving propofol for the same procedure. Moreover, cardiac output improved with sevoflurane but not with propofol, suggesting better maintenance of myocardial function. This study supports cardioprotective effects of halogenated inhalational anesthetics so far only documented in patients after cardiopulmonary bypass and suggests that the choice of an anesthetic with respect to myocardial reperfusion injury might be of importance also in the general surgical patient population.

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