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Choice of Primary Anesthetic Regimen Can Influence Intensive Care Unit Length of Stay after Coronary Surgery with Cardiopulmonary Bypass

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Background: **Volatile anesthetics protect the myocardium during coronary surgery. This study hypothesized that the use of a volatile agent in the anesthetic regimen would be associated with a shorter intensive care unit (ICU) and hospital length of stay (LOS), compared with a total intravenous anesthetic regimen.**

Methods: **Elective coronary surgery patients were randomly assigned to receive propofol (n = 80), midazolam (n = 80), sevoflurane (n = 80), or desflurane (n = 80) as part of a remifentanil-based anesthetic regimen. Multiple logistic regression analysis was used to identify the independent variables associated with a prolonged ICU LOS.**

Results: **Patient characteristics were similar in all groups. ICU and hospital LOS were lower in the sevoflurane and desflurane groups ($P < 0.01$). The number of patients who needed a prolonged ICU stay (> 48 h) was also significantly lower (propofol: n = 31; midazolam: n = 34; sevoflurane: n = 10; desflurane: n = 15; $P < 0.01$). Occurrence of atrial fibrillation, a postoperative troponin I concentration greater than 4 ng/ml, and the need for prolonged inotropic support (> 12 h) were identified as the significant risk factors for prolonged ICU LOS. Postoperative troponin I concentrations and need for prolonged inotropic support were lower in the sevoflurane and desflurane group ($P < 0.01$). Postoperative cardiac function was also better preserved with the volatile anesthetics. The incidence of other postoperative complications was similar in all groups.**

Conclusions: **The use of sevoflurane and desflurane resulted in a shorter ICU and hospital LOS. This seemed to be related to a better preservation of early postoperative myocardial function.**

IN the 1980s, several studies indicated that, in patients undergoing elective coronary artery surgery, the choice of the primary anesthetic agents did not result in different outcome.[1,2] However, starting from the 1990s, it seems that the development of fast-track anesthetic techniques for cardiac surgery has helped to decrease intensive care unit (ICU) and hospital length of stay (LOS) with lower resource utilization and cost without adversely affecting mortality and morbidity.[3–5] Fast-track anesthetic protocols were mainly based on the use of short-acting intravenous drugs. Compared with the previously used large-dose opioid techniques, fast-track protocols had a shorter recovery time, which has led to a significant reduction in tracheal intubation time and hence a decrease in ICU LOS.[3–7] Although inhalation-based techniques could also be suitable for early extubation protocols,[8] it was suggested that especially patients with impaired left ventricular (LV) function may not tolerate inhaled anesthetic–induced reduction in myocardial function.[5]

Recently, experimental evidence has indicated that volatile anesthetics may have direct cardioprotective properties by a preconditioning effect,[9,10] a beneficial effect on myocardial reperfusion injury,[11,12] or both. In clinical practice, these cardioprotective effects were associated with improved cardiac function in the immediate postoperative period.[13–17] However, the impact of this phenomenon on postoperative morbidity and clinical recovery remains to be established. We hypothesized that, compared with a total intravenous anesthetic regimen, the use of a volatile anesthetic agent in the fast-track regimen may result in a better postoperative cardiac function and hence in a better early postoperative recovery, with consequently a shorter ICU and hospital LOS.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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. Three hundred twenty patients scheduled to undergo elective coronary surgery with cardiopulmonary bypass (CPB) were enrolled. Exclusion criteria were previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy, or LV aneurysm repair), unstable angina, valve insufficiency, documented myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynamic instability requiring medical or mechanical sup-

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port, 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 < 50% of predicted or < 2.0 l), or history of neurologic disturbances.

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

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 ICU and on 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. Premedication was standardized for all patients (2.5 mg sublingual lorazepam [Temesta Expidet®; AHP Pharma, Louvain-la-Neuve, Belgium] 90 min before surgery and 1 μg/kg fentanyl plus 50 μg/kg, given intramuscularly 60 min before surgery).

Patients were allocated to receive either a complete intravenous anesthetic regimen, based on propofol (Diprivan®; AstraZeneca, Brussels, Belgium) or midazolam (Dormicum®; Roche, Brussels, Belgium), or an inhalational anesthetic regimen, based on sevoflurane (Sevorane®; Abbott, Louvain-la-Neuve, Belgium) or desflurane (Suprane®; Baxter, Lessines, Belgium). In all groups, a continuous infusion of remifentanil (Ultiva®; GlaxoSmithKline, Genval, Belgium) between 0.2 and 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered throughout the operation. Muscle relaxation was obtained with 0.1 mg/kg pancuronium bromide (Pavulon®; Organon, Brussels, Belgium).

In the propofol group (n = 80), 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. Anesthesia was maintained with 0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and target-controlled infusion propofol set at a plasma target concentration of 2–4 μg/ml.

In the midazolam group (n = 80), anesthesia was induced with a continuous infusion of remifentanil at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.1 mg/kg midazolam. Anesthesia was maintained with 0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 0.5–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ midazolam.

In the sevoflurane group (n = 80), anesthesia was also induced with a continuous infusion of remifentanil at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.1 mg/kg midazolam. Anesthesia was maintained with 0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 0.5–2% sevoflurane.

In the desflurane group (n = 80), anesthesia was induced with a continuous infusion of remifentanil at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.1 mg/kg midazolam. Anesthesia was maintained with 0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 1–4% desflurane.

Perioperative Procedures

In the operating room, patients received routine monitoring, including five-lead electrocardiography, radial and pulmonary artery catheters with continuous cardiac output measurement (Swan Ganz CCO/VIP; Edwards Lifesciences 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. Concentration of anesthetic agents in all groups was titrated to maintain a Bispectral Index value of less than 50 throughout the procedure.

Patients included in the study were treated by two experienced cardiothoracic anesthesiologists according to the protocols described and operated on by three surgeons, all using the same surgical technique. Routine cardioprotective strategies were used in all patients. This included the intravenous administration of 2 g methylprednisolone after induction of anesthesia and a high-dose aprotinin (Trasylol®; Bayer, Leverkusen, Germany) regimen (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). 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 an activator) was kept above 450 s throughout the CPB period. Systemic temperature was allowed to drift during CPB to 32°C. Hematocrit concentrations were maintained between 20 and 25%, and on CPB, a nonpulsatile 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.

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 Car-

diovascular 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).

After the surgical procedure, reperfusion of the heart (reperfusion time was set at 50% of the aortic cross clamping 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. After removal of the aortic cannula, heparin activity was neutralized with protamine sulfate (Protamine®; Leo Pharma) at a ratio of 1 mg protamine for 100 U heparin. Protamine administration was further guided by activated clotting time measurements aiming at a value of 140 s. At the end of the surgical procedure, patients were transferred to the ICU.

Inotrope and Vasoactive Therapy

In this study, filling pressures were kept constant (central venous pressure $>$ 10 mmHg and pulmonary capillary wedge pressure $>$ 12 mmHg) throughout the entire observation period by the administration of intravenous fluids (crystalloids and gelatins). *Hypotension* was defined as a mean arterial blood pressure less than 60 mmHg. Administration of inotrope and vasoactive drugs was performed according to the following protocol:

1. If hypotension persisted despite adequate filling pressures and cardiac index greater than 2.4 $l \cdot min^{-1} \cdot m^{-2}$, intravenous phenylephrine was administered in boluses of 0.01 mg until pressure returned to a mean greater than 60 mmHg.
2. If perfusion pressure decreased below 45 mmHg during CPB, phenylephrine was administered in boluses of 0.1 mg until pressure recovered.
3. If perfusion pressure greater than 70 mmHg occurred during CPB, anesthesia was deepened, and if necessary, a continuous infusion of isosorbide dinitrate was administered starting at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increasing in 0.1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ steps until the perfusion pressure decreased to the fixed range.
4. If, after the end of CPB, the patient was normotensive but the cardiac index was less than 2.4 $l \cdot min^{-1} \cdot m^{-2}$, isosorbide dinitrate was administered starting at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increasing in 0.1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ steps until the hemodynamic goals were achieved.
5. If, despite this therapy, cardiac index remained less than 2.4 $l \cdot min^{-1} \cdot m^{-2}$, dobutamine was initiated as an intravenous infusion starting at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increasing in 1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ steps until the hemodynamic goals were achieved. If cardiac index remained less than 2.4 $l \cdot min^{-1} \cdot m^{-2}$ despite increasing doses dobutamine up to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, milrinone was started at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$.
6. If, after the end of CPB, the patient was hypotensive and cardiac index was less than 2.4 $l \cdot min^{-1} \cdot m^{-2}$ despite adequate filling pressures, dobutamine was initiated as an intravenous infusion starting at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increasing in 1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ steps until the hemodynamic goals were achieved. If cardiac index remained less than 2.4 $l \cdot min^{-1} \cdot m^{-2}$ despite increasing doses dobutamine up to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, milrinone was started at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If the patient remained hypotensive, norepinephrine was started at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increased in 0.1-$\mu g \cdot kg^{-1} \cdot min^{-1}$ steps until the hemodynamic goals were achieved.

Hemodynamic Data Analysis

Global hemodynamic data (mean arterial pressure, pulmonary capillary wedge pressure, central venous pressure, cardiac index, stroke volume index, and systemic vascular resistance index) were registered just before the start of surgery, before the start of CPB, 15 min after the end of CPB (post-CPB),[18] and at the end of the operation, 6 h after installation in the ICU, and 12 and 24 hours 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.

In each group, the 30 first patients were in addition instrumented with a sterilized, prezeroed electronic tipmanometer (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 settings of the tipmanometers were also checked against a high-fidelity pressure gauge (Druck Ltd., Leicester, United Kingdom) after removal. Heart rate was kept constant by atrioventricular sequential pacing at a rate of 90 beats/min. All measurements were obtained with the ventilation suspended at end expiration. The measurements consisted of recordings of consecutive electrocardiographic and LV pressure tracings during an increase of systolic and diastolic pressures obtained by raising the caudal part of the surgical table by 45° resulting in raising of the legs. Leg elevation resulted in a rapid beat-to-beat increase in LV pressures.

A first set of measurements was obtained before CPB. After this measurement, the catheters were removed, the venous canula 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 the electrocardiogram. 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} (maximal rate of LV pressure decline) (= end-systolic pressure), and dP/dt_{max} (maximal rate of LV pressure development). 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.[19] 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.[20–22] 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* greater than 0.92 in all patients.

Transfusion Protocols

Transfusion of packed erythrocytes was guided by clinical judgment taking into account not only the hemoglobin concentration, but also the physical status of the patient (age, estimated blood volume, cardiovascular and respiratory functions) and the extent of postoperative bleeding. As a rule, patients with a hemoglobin concentration above 10 g/dl never received transfusions, whereas patients with a hemoglobin concentration below 7 g/dl usually received transfusions.[23]

Platelets and fresh frozen plasma were transfused in the presence of abnormal clinical bleeding, using the algorithm developed by Despotis *et al.*,[24] based on the platelet count, and prothrombin and partial thromboplastin times.

Extubation and Discharge Protocols

In the ICU, patients were routinely kept sedated for 2 h according to the local protocol with a continuous infusion of 0.3–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol until hemodynamic variables and temperature were stable and no signs of excessive bleeding (> 150 ml/h) were present. A standardized method of weaning from ventilation and tracheal extubation was then started. The extubation regimen was started when the following criteria were met: temperature greater than 36°C, hemodynamically stable, chest tube drainage less than 100 ml/h, and urine output 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ or greater. At that moment (±45 min before anticipated extubation), all patients received 0.2 mg/kg morphine and 1 g paracetamol (Perfusalgan®; Bristol-Myers Squibb, Waterloo, Belgium), and propofol was turned off. After 15 min, remifentanil was titrated down at 10-min intervals. Patients were assessed for vital signs, pain, and sedation. If patients experienced pain, an additional bolus of 5 mg morphine was administered. Patients were extubated when the following criteria were achieved: adequate response to command, oxygen saturation measured by pulse oximetry (Spo_2) 95% or greater at a fraction of inspired oxygen (Fio_2) of 0.5 or less, pH 7.3 or greater, arterial carbon dioxide tension ($Paco_2$) 55 mmHg or less, and adequate respiratory effort. For patients who were unable to meet these criteria within 6 h after arrival in the ICU, the propofol and remifentanil infusions were titrated until the weaning procedure could be started.

Patients were eligible to transfer out of the ICU when the following criteria were met: Spo_2 90% or greater at an Fio_2 of 0.5 or less by facemask, adequate cardiac stability with no hemodynamically significant arrhythmia, chest tube drainage less than 50 ml/h, urine output greater than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$, no intravenous inotropic or vasopressor therapy, and no seizure activity.

The criteria for eligibility for hospital discharge were hemodynamic and cardiac rhythm stability, the presence of clean and dry incisions, afebrile condition, the ability to void and move bowels, and independent ambulating and feeding.

According to the routine strategies, patients routinely spend 24 h in the ICU and are discharged to a medium-care unit the day after, where they spend the second day postoperatively before they are discharged to the ward. Normal total LOS in the hospital for an uneventful procedure was at the time of the study between 8 and 10 days. For the current study, particular care was taken to ensure that all patients were also actually discharged from the moment that they met the criteria for discharge from the ICU and the hospital. In addition, the times of fitness for criteria discharge from the ICU and the hospital were noted and compared to the actual discharge times.

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 ICU and on the ward were performed by physicians who were blinded to the type of anesthesia used. Preoperative data collected included sex, age, weight, height, body mass index, degree and extent of coronary disease, medical history, and chronic treatment. Risk stratification was performed using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) risk stratification model.[25] Intraoperative data collected included number of bypasses, number of arterial grafts, aortic cross clamping time, and CPB du-

ration. In addition, hemodynamic variables and need for and duration of inotropic and vasoconstrictive support after CPB and in the ICU were carefully recorded. Additional postoperative data collected were number of deaths, number of acute myocardial infarctions, incidence of atrial fibrillation, duration of tracheal intubation, amount of postoperative bleeding and need for transfusion, any kind of adverse event, concentrations of troponin I and serum creatinine, LOS in the ICU, and total hospital stay together with the time needed to fit criteria for discharge.

Biochemical Analysis

In all patients, blood was sampled for determination of cardiac troponin I and serum creatinine. These samples were obtained before surgery at arrival in the ICU and after 6, 12, 24, and 48 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. In our institutional practice, troponin I values above 2 ng/ml are indicative of myocardial damage related to coronary surgery.[17,18] Serum creatinine was measured using the reflectometry method (Vitros 950®; Orthoclinical Diagnostics). The limit of quantification for creatinine is 0.1 mg/dl (normal values between 0.7 and 1.4 mg/dl).

Statistical Analysis

The primary outcome variables in the current study were ICU and hospital LOS and actual time to meet fit-for-discharge criteria. For the ICU LOS, a minimum detected difference of 24 h between the intravenous and the volatile anesthesia groups was considered clinically significant. For a power of 0.8 and an α value of 0.05, a sample size of 70 patients in each group was calculated to be appropriate. For the hospital LOS, a minimum detected difference of 2 days between the different treatment groups was considered clinically significant. For a power of 0.8 and an α value of 0.05, a sample size of 72 patients in each group was calculated to be appropriate. Secondary outcome variables used were cardiac troponin I concentration and the post-CPB hemodynamic variables stroke volume index and dP/dt_{max}. For the cardiac troponin I concentration, a minimum detected difference of 2 ng/ml between the different groups (propofol, midazolam, sevoflurane, and desflurane) was considered clinically significant. For a power of 0.8 and an α value of 0.05, a sample size of 64 patients in each group was calculated to be appropriate. For the post-CPB stroke volume index, a minimum detected difference of 5 ml between the different groups was considered clinically significant. For a power of 0.8 and an α value of 0.05, a sample size of 32 patients in each group was calculated to be appropriate. For the post-CPB dP/dt_{max}, a minimum detected difference of 100 mmHg/s between the different groups was considered clinically significant. For a power of 0.8 and an α value of 0.05, a sample size of 18 patients in each group was calculated to be appropriate.

Statistical analysis was performed using the SigmaStat 2.03 software package (SPSS, Leuven, Belgium). Patient characteristics and postoperative complications between groups were compared using one-way analysis of variance and chi-square analysis where appropriate. Serial troponin I concentrations within one group were compared with the Friedman repeated-measures analysis of variance on ranks followed by the Dunnett method for multiple comparisons *versus* control. Troponin I concentrations between groups were compared using the Kruskal-Wallis one-way analysis of variance test on ranks followed by the Dunn test for pairwise multiple comparison. 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.

Length of stay in the ICU may depend on factors other than strict medical indications. Therefore, the patients were classified as those who needed an ICU LOS longer than 48 h (complicated recovery) and those with an LOS of less than 48 h (uncomplicated recovery). For all patients, the presence of the following variables was noted: *preoperative*: female sex, age older than 70 yr, ejection fraction less than 50%, diabetes, EuroSCORE greater than 4, and daily intake of β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, nitrates, diuretics, oral antidiabetic agents, and antiplatelet drugs; *intraoperative*: CPB time greater than 100 min and inotropic support; *postoperative*: myocardial infarction; atrial fibrillation; troponin I greater than 4 ng/ml; inotropic support greater than 12 h, prolonged intubation (> 10 h), reintubation, bleeding greater than 750 ml/6 h, reexploration, and creatinine greater than 1.5 mg/dl. These variables were entered as independent variables into a multiple logistic regression model with complicated recovery (ICU LOS > 48 h) as the dependent variable (SigmaStat 2.03 software package; SPSS).

Results

Preoperative and intraoperative patient characteristics were similar in all groups (table 1). Time to meet fit-for-discharge criteria and actual ICU and hospital LOS were

Table 1. Patient Characteristics

	Propofol (n = 80)	Midazolam (n = 80)	Sevoflurane (n = 80)	Desflurane (n = 80)
Preoperative data				
Sex, M/F	65/15	64/16	66/14	65/15
Age, yr	67 ± 9	66 ± 9	65 ± 10	69 ± 8
Body mass index, kg/m^2	27.2 ± 4.1	27.6 ± 4.6	26.7 ± 3.0	26.1 ± 3.0
Ejection fraction, %	69 ± 12	68 ± 10	65 ± 12	68 ± 10
Diabetes	22	24	22	22
EuroSCORE, median (range)	4 (0–12)	4 (0–13)	4 (0–12)	3 (0–11)
Chronic preoperative medication, No. of patients				
β Blockers	69	68	67	68
Calcium channel blockers	25	24	22	22
ACE inhibitors	23	25	22	24
Nitrates	33	28	36	32
Diuretics	19	19	16	16
Oral antidiabetics	14	15	15	13
Insulin	11	10	11	10
Acetyl salicylic acid	46	49	44	45
Oral anticoagulants	4	4	4	4
Low-molecular-weight heparin	18	18	19	20
Thienopyridines	17	19	19	16
Dipyridamole	3	3	3	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	27 ± 15	32 ± 16	31 ± 14
CPB time, min	92 ± 31	100 ± 31	98 ± 27	96 ± 29

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; CPB = cardiopulmonary bypass; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

significantly lower in the sevoflurane and the desflurane groups (fig. 1). The number of patients who needed an ICU stay longer than 48 h was also significantly lower with the volatile anesthetics (propofol: n = 31; midazolam: n = 34; sevoflurane: n = 10; desflurane: n = 15; $P < 0.01$).

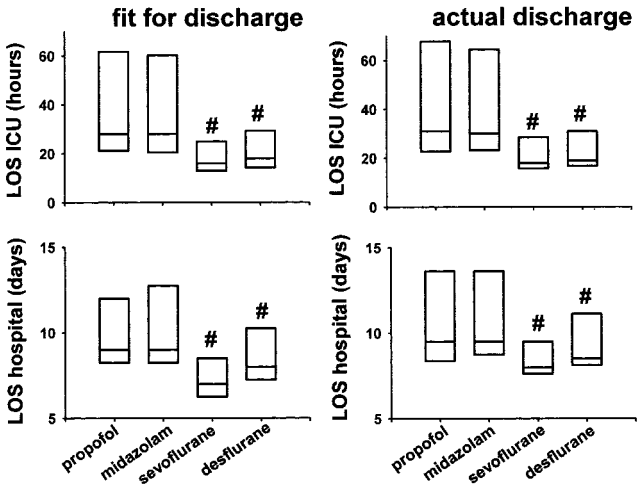

Fig. 1. Length of stay (LOS) in the intensive care unit (ICU) and in the hospital with the different anesthetic regimens used. Data are shown for the time to meet the "fit for discharge" criteria and the actual time of discharge. Data are expressed as median with 25% and 75% percentiles. LOS was significantly shorter with sevoflurane and desflurane anesthesia. # Statistically significant difference ($P < 0.05$) with the total intravenous anesthetic regimen.

To analyze the possible reasons for the shorter ICU stay in the groups with the volatile anesthetics, the duration of ventilation and the incidence of postoperative complications were compared between the groups. Duration of postoperative ventilation was similar in the four groups (propofol: 5.9 ± 1.8 h; midazolam: 6.1 ± 1.7 h; sevoflurane: 5.3 ± 2.0 h; desflurane: 5.8 ± 2.1 h). The number of patients requiring prolonged ventilation (defined *a priori* as postoperative intubation time > 10 h) or reintubation was also similar in the different groups (table 2). Prolonged ventilation was mainly observed in the patients with preexisting pulmonary disease and in the patients who underwent reexploration for bleeding. All patients who had to be reintubated were patients with known pulmonary disease who developed acute respiratory failure. Of the 320 patients, 2 (0.6%) died in the hospital because of myocardial failure. In 9 patients (2.8%), perioperative myocardial infarction developed. Troponin I increased transiently with all anesthetic regimens used, but this increase was significantly lower in the sevoflurane and desflurane groups (fig. 2). The incidence of important myocardial damage (defined as a postoperative troponin I > 4 ng/ml) was also significantly lower in the sevoflurane and desflurane groups. The need for inotropic support was significantly lower

Table 2. Postoperative Morbidity

Complications	Propofol (n = 80)	Midazolam (n = 80)	Sevoflurane (n = 80)	Desflurane (n = 80)	*P* Value
Death	1 (1.3%)	1 (1.3%)	0 (0%)	0 (0%)	0.569
Myocardial infarction	4 (5.0%)	3 (3.8%)	1 (1.3%)	1 (1.3%)	0.378
Increased postoperative troponin I (>4 ng/ml)	58 (72.5%)	52 (65.0%)	28 (35.0%)	32 (40.0%)	<0.001*
Prolonged inotropic support (>12 h)	16 (20.0%)	17 (21.3%)	3 (3.8%)	5 (6.3%)	<0.001*
Atrial arrhythmia	9 (11.3%)	7 (8.8%)	5 (6.3%)	11 (13.8%)	0.427
Pulmonary edema	3 (3.8%)	3 (3.8%)	1 (1.3%)	2 (2.5%)	0.739
Prolonged ventilation	9 (11.3%)	8 (10.0%)	6 (7.5%)	9 (11.3%)	0.946
Reintubation	2 (2.5%)	2 (2.5%)	1 (1.3%)	2 (2.5%)	0.932
Postoperative serum creatinine > 1.5 mg/dl	8 (8.8%)	9 (7.5%)	4 (6.3%)	5 (7.5%)	0.416
Reexploration for bleeding	2 (2.5%)	1 (1.3%)	1 (1.3%)	2 (2.5%)	0.878
Total blood loss, ml/kg	18 ± 12	19 ± 10	18 ± 14	17 ± 13	0.873
Transfusion of packed erythrocytes	25 (31%)	22 (28%)	26 (33%)	24 (30%)	0.915
Transfusion of fresh frozen plasma	4 (5%)	5 (6%)	4 (5%)	4 (5%)	0.980
Transfusion of platelets	2 (2.5%)	1 (1.3%)	1 (1.3%)	2 (2.5%)	0.878
Readmission to ICU	2 (2.5%)	2 (2.5%)	1 (1.3%)	1 (1.3%)	0.878

Data are presented as incidence of complications: No. (%). Total blood loss is expressed as mean ± SD.

* Statistically significant.

ICU = intensive care unit.

with the volatile anesthetic regimens (fig. 3). The number of patients who needed prolonged inotropic support (> 12 h) in the ICU was also significantly lower with the volatile anesthetics. The need for vasoconstrictive therapy did not differ between the primary anesthetics used in this study design. Incidence of atrial arrhythmia and pulmonary edema was similar in all groups. Total blood loss was similar in the different groups. Six patients had to undergo reexploration for bleeding. The number of patients who needed transfusion of packed erythrocytes, fresh frozen plasma, and platelets also did not differ between groups. A total of 26 patients (8.1%) had a transient increase in serum creatinine greater than 1.5 mg/dl. None of the patients had renal insufficiency necessitating specific treatment. Severe neurologic (seizure or stroke) or gastrointestinal symptoms did not develop in any of the patients included. Six patients (1.9%) had to be readmitted from the ward to the ICU because of respiratory failure.

Intensive care LOS may depend on factors other than strict medical indications. Accordingly, patients were classified as those who needed an ICU LOS longer than 48 h (complicated recovery) and those with an LOS less than 48 h (uncomplicated recovery). Multiple logistic regression analysis (table 3) identified the occurrence of atrial fibrillation, postoperative troponin I greater than 4 ng/ml, and the need for prolonged inotropic support (> 12 h) as the significant risk factors for prolonged (> 48 h) ICU LOS. Incidence of atrial fibrillation was similar in all groups, but the incidence of increased postoperative troponin I concentrations and need for prolonged inotropic support were significantly lower in

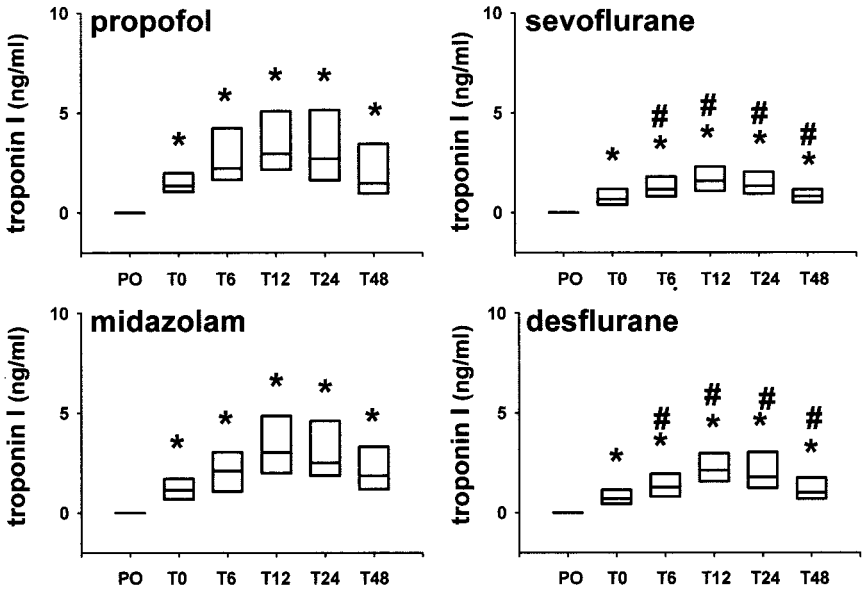

Fig. 2. Cardiac troponin I concentrations in the different study groups before surgery (PO), at arrival in the intensive care unit (T0), and after 6 (T6), 12 (T12), 24 (T24), and 48 (T48) hours. Data are expressed as median with 25% and 75% percentiles. In all groups, troponin I values increased. This increase in troponin I concentrations was significantly lower with sevoflurane and desflurane at T6, T12, T24, and T48. * Statistically significant ($P < 0.05$) difference with the baseline value (PO); # statistically significant difference ($P < 0.05$) with the total intravenous anesthetic regimen.

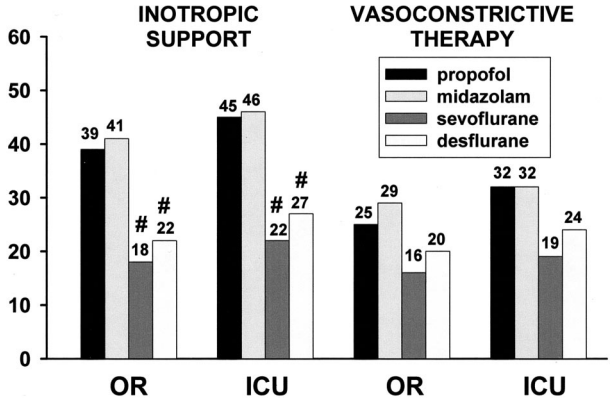

Fig. 3. Number of patients necessitating inotropic and vasoconstrictive support in the operating room (OR) and the intensive care unit (ICU) for the different anesthetic regimens used. # Statistically significant difference ($P < 0.05$) with the total intravenous anesthetic regimen.

the sevoflurane and desflurane groups. The better myocardial performance with the volatile anesthetic regimen was also apparent from the hemodynamic data. Stroke volume index transiently decreased in the propofol and the midazolam group, whereas it remained unchanged in the sevoflurane and desflurane groups (table 4). Similarly, LV performance remained preserved after CPB with sevoflurane and desflurane but was impaired with propofol and midazolam, as was evident from the changes in variables of myocardial contraction and relaxation (table 5) and the response to increased cardiac load (table 6 and fig. 4).

Discussion

The current data indicated that in patients undergoing coronary surgery with CPB, both ICU and hospital LOS were significantly lower with the volatile anesthetic agents sevoflurane and desflurane. Four fast-track anesthetic protocols were used, two based on a total intravenous regimen and two based on the use of a volatile anesthetic agent. The opioid used as part of the four anesthetic protocols was remifentanil given at similar dosage in the different groups. Patient characteristics, surgical and cardioprotective strategies, duration of CPB and aortic cross clamping, and postoperative sedation and analgesia were similar in all groups. This implies that the only difference between the groups was the choice of associated anesthetic drug: propofol, midazolam, sevoflurane, or desflurane.

This is the first larger-scale study that identifies the use of volatile agents in the anesthetic regimen as one of the factors that may affect ICU and hospital LOS. A first

Table 3. Multiple Logistic Regression Analysis of the Different Independent Variables Associated with Prolonged ICU Duration of Stay (> 48 h) in the Study Population

Variable	Prevalence	Odds Ratio	5% and 95% Confidence Limits	*P* Value
Preoperative				
Female sex	18%	1.14	0.67–1.93	0.621
Age > 70 yr	38%	1.16	0.45–2.94	0.760
Ejection fraction < 50%	9%	1.80	0.52–6.17	0.352
Diabetes	28%	0.84	0.29–2.48	0.247
EuroSCORE > 4	39%	1.87	0.74–4.69	0.184
Preoperative medication				
β Blockers	84%	0.89	0.33–2.35	0.806
Calcium channel blockers	29%	1.00	0.36–2.76	0.996
ACE inhibitors	29%	1.00	0.42–2.44	0.984
Nitrates	40%	1.15	0.44–2.99	0.777
Diuretics	22%	0.60	0.21–1.77	0.358
Oral antidiabetics	18%	0.70	0.21–2.35	0.564
Antiplatelet drugs	63%	0.81	0.36–2.17	0.258
Intraoperative				
CPB time > 100 min	38%	1.39	0.63–3.06	0.410
Inotropic support	38%	1.53	0.71–3.38	0.387
Postoperative				
Myocardial infarction	3%	136.00	0.00–∞	0.983
Atrial fibrillation	10%	5.60	1.77–17.70	0.003*
Troponin I > 4 ng/ml	54%	17.51	7.73–39.71	<0.001*
Inotropic support > 12 h	13%	22.87	5.83–53.28	<0.001*
Prolonged intubation	10%	1.34	0.35–5.15	0.673
Reintubation	2%	6.15	0.11–39.52	0.372
Bleeding > 750 ml/6 h	3%	0.64	0.29–4.20	0.477
Reexploration	2%	6.71	0.11–41.16	0.365
Creatinine > 1.5 mg/dl	8%	1.95	0.71–5.39	0.231

* Statistically significant.

ACE = angiotensin-converting enzyme; CPB = cardiopulmonary bypass; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICU = intensive care unit.

Table 4. Perioperative and Postoperative Hemodynamic Data

	Baseline	Before CPB	After CPB	End	ICU T6	ICU T12
MAP, mmHg						
Propofol	72 ± 11	72 ± 10	72 ± 11	73 ± 8	75 ± 10	72 ± 11
Midazolam	74 ± 15	73 ± 12	71 ± 10	75 ± 9	76 ± 10	74 ± 10
Sevoflurane	71 ± 10	71 ± 8	72 ± 10	73 ± 9	73 ± 8	73 ± 11
Desflurane	69 ± 11	70 ± 10	68 ± 8	71 ± 10	71 ± 9	72 ± 9
PCWP, mmHg						
Propofol	14 ± 3	13 ± 2	14 ± 3	14 ± 3	13 ± 3	14 ± 2
Midazolam	15 ± 3	14 ± 3	14 ± 2	14 ± 2	15 ± 2	14 ± 2
Sevoflurane	14 ± 3	14 ± 2	13 ± 3	13 ± 2	13 ± 2	14 ± 3
Desflurane	13 ± 4	14 ± 3	13 ± 3	14 ± 3	14 ± 3	13 ± 4
CVP, mmHg						
Propofol	11 ± 4	11 ± 4	11 ± 3	11 ± 3	12 ± 3	11 ± 3
Midazolam	12 ± 3	13 ± 4	13 ± 3	13 ± 3	13 ± 2	12 ± 2
Sevoflurane	11 ± 4	11 ± 3	11 ± 3	12 ± 3	12 ± 3	11 ± 3
Desflurane	12 ± 3	11 ± 3	12 ± 3	13 ± 3	13 ± 3	12 ± 3
HR, beats/min						
Propofol	70 ± 11	73 ± 15	0 ± 0*	0 ± 0*	0 ± 0*	0 ± 0*
Midazolam	69 ± 14	73 ± 13	0 ± 0*	0 ± 0*	0 ± 0*	0 ± 0*
Sevoflurane	72 ± 13	75 ± 10	0 ± 0*	0 ± 0*	0 ± 0*	0 ± 0*
Desflurane	71 ± 14	75 ± 13	0 ± 0*	0 ± 0*	0 ± 0*	0 ± 0*
CI, $l \cdot min^{-1} \cdot m^{-2}$						
Propofol	2.6 ± 0.5	2.5 ± 0.6	2.3 ± 0.5†	2.4 ± 0.4†	2.5 ± 0.5†	3.1 ± 0.7*
Midazolam	2.6 ± 0.5	2.6 ± 0.6	2.4 ± 0.5†	2.4 ± 0.5†	2.5 ± 0.5†	3.1 ± 0.6*
Sevoflurane	2.5 ± 0.6	2.5 ± 0.7	3.2 ± 0.4*	3.3 ± 0.5*	3.2 ± 0.4*	3.3 ± 0.6*
Desflurane	2.6 ± 0.6	2.5 ± 0.6	3.1 ± 0.5*	3.2 ± 0.5*	3.2 ± 0.5*	3.2 ± 0.7*
SVI, $ml \cdot beats^{-1} \cdot m^{-2}$						
Propofol	35 ± 6	34 ± 6	26 ± 5†	27 ± 4†	27 ± 5†	32 ± 5
Midazolam	35 ± 7	35 ± 6	27 ± 4*†	27 ± 5*†	27 ± 6*†	33 ± 5
Sevoflurane	34 ± 5	33 ± 5	35 ± 5	36 ± 6	36 ± 5	34 ± 5
Desflurane	35 ± 6	34 ± 6	33 ± 5	34 ± 6	35 ± 6	33 ± 5
SVRI, $dyn \cdot s \cdot cm^{-5} \cdot m^{-2}$						
Propofol	1,745 ± 325	1,714 ± 378	1,776 ± 339	1,831 ± 389	1,791 ± 441	1,849 ± 382
Midazolam	1,761 ± 462	1,784 ± 317	1,831 ± 407	1,787 ± 343	1,764 ± 356	1,795 ± 466
Sevoflurane	1,755 ± 422	1,799 ± 307	1,795 ± 288	1,831 ± 251	1,777 ± 348	1,789 ± 306
Desflurane	1,824 ± 285	1,757 ± 323	1,727 ± 314	1,750 ± 361	1,780 ± 339	1,812 ± 276
Temperature, °C						
Propofol	36.3 ± 0.4	36.2 ± 0.4	36.2 ± 0.4	36.2 ± 0.4	36.2 ± 0.3	36.3 ± 0.4
Midazolam	36.3 ± 0.4	36.1 ± 0.5	36.3 ± 0.6	36.4 ± 0.5	36.3 ± 0.5	36.4 ± 0.4
Sevoflurane	36.2 ± 0.4	36.2 ± 0.4	36.2 ± 0.4	36.2 ± 0.5	36.3 ± 0.5	36.2 ± 0.5
Desflurane	36.3 ± 0.4	36.2 ± 0.4	36.2 ± 0.4	36.2 ± 0.3	36.2 ± 0.4	36.3 ± 0.5

Data are presented as mean ± SD.

* Different compared with baseline ($P < 0.05$). † Different between intravenous and inhalational anesthetics ($P < 0.05$).

CPB = cardiopulmonary bypass; CI = cardiac index; CVP = central venous pressure; HR = heart rate; ICU = intensive care unit; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index.

explanation for this observation could be that a different level of anesthesia was present among the study groups, which may have resulted in prolonged postoperative ventilation times in certain groups. Intubation times were similar in the four groups, and comparable with what has been reported into literature with fast-track protocols[6,7] (taking into account the local routine of keeping the patients asleep in the ICU for 2 h before starting the weaning procedure). Also, the number of patients requiring prolonged ventilation (> 10 h) was similar in all groups. Therefore, the longer ICU LOS cannot be attributed to a difference in time to extubation or need for prolonged ventilation between groups.

Another possible explanation is that the incidence of postoperative complications might be different between groups. In the current study, multiple logistic regression analysis identified the occurrence of atrial fibrillation, postoperative troponin I greater than 4 ng/ml, and the need for prolonged inotropic support (> 12 h) as the independent risk factors for prolonged (> 48 h) ICU LOS. The incidence of atrial fibrillation did not differ between the groups, but the concentrations of troponin I and the need for prolonged inotropic support were significantly lower in the sevoflurane and desflurane groups. In addition, postoperative myocardial function was better preserved in these two groups.

It can therefore be hypothesized that the better preservation of early cardiac function with sevoflurane and desflurane (evident from data on hemodynamics and myocardial function, concentrations of postoperative troponin I, and need for inotropic support) may result in an improved global tissue perfusion with a better recov-

Table 5. Left Ventricular Pressure Data before and after Cardiopulmonary Bypass

	Before CPB	After CPB
EDP, mmHg		
Propofol	11 ± 5	15 ± 4*
Midazolam	12 ± 4	14 ± 3*
Sevoflurane	11 ± 3	14 ± 3*
Desflurane	12 ± 3	15 ± 4*
dP/dt_{max}, mmHg/s		
Propofol	945 ± 76	679 ± 88*†
Midazolam	923 ± 82	661 ± 73*†
Sevoflurane	924 ± 95	881 ± 83
Desflurane	913 ± 92	877 ± 97
Peak LVP, mmHg		
Propofol	92 ± 10	83 ± 8*†
Midazolam	94 ± 11	85 ± 7*†
Sevoflurane	93 ± 10	92 ± 7
Desflurane	95 ± 11	93 ± 8
dP/dt_{min}, mmHg/s		
Propofol	704 ± 73	617 ± 66*†
Midazolam	699 ± 82	609 ± 71*†
Sevoflurane	707 ± 94	698 ± 68
Desflurane	692 ± 78	687 ± 81
ESP, mmHg		
Propofol	61 ± 5	53 ± 4*†
Midazolam	59 ± 6	51 ± 4*†
Sevoflurane	60 ± 4	59 ± 3
Desflurane	61 ± 3	61 ± 4
τ, ms		
Propofol	59 ± 5	65 ± 3*†
Midazolam	60 ± 4	65 ± 4*†
Sevoflurane	59 ± 4	60 ± 3
Desflurane	58 ± 4	59 ± 4

Data are presented as mean ± SD. n = 30/group.

* Different between before and after CPB ($P < 0.05$). † Different between intravenous and inhalational anesthetics ($P < 0.05$).

CPB = cardiopulmonary bypass; dP/dt_{max} = maximal rate of left ventricular pressure development; dP/dt_{min} = maximal rate of left ventricular pressure decline; EDP = end-diastolic pressure; ESP = end-systolic pressure; LVP = left ventricular pressure; τ = time constant of isovolumic relaxation.

Table 6. Changes in Left Ventricular Pressure Data with Leg Elevation before and after Cardiopulmonary Bypass

	Before CPB	After CPB
Δ EDP, mmHg		
Propofol	4 ± 2	7 ± 2*†
Midazolam	3 ± 1	7 ± 3*†
Sevoflurane	3 ± 1	3 ± 1
Desflurane	4 ± 2	4 ± 2
Δ dP/dt_{max}, mmHg/s		
Propofol	38 ± 40	−48 ± 31*†
Midazolam	43 ± 37	−52 ± 39*†
Sevoflurane	36 ± 47	45 ± 27
Desflurane	42 ± 36	27 ± 33
Δ Peak LVP, mmHg		
Propofol	10 ± 3	5 ± 3*†
Midazolam	9 ± 3	4 ± 3*†
Sevoflurane	10 ± 3	9 ± 3
Desflurane	11 ± 3	9 ± 3
Δ dP/dt_{min}, mmHg/s		
Propofol	73 ± 37	49 ± 52
Midazolam	66 ± 29	51 ± 47
Sevoflurane	83 ± 43	63 ± 37
Desflurane	72 ± 35	59 ± 42
Δ ESP, mmHg		
Propofol	7 ± 4	5 ± 3
Midazolam	6 ± 3	5 ± 2
Sevoflurane	8 ± 3	7 ± 2
Desflurane	7 ± 3	6 ± 3
Δ τ, ms		
Propofol	0 ± 3	4 ± 2*†
Midazolam	1 ± 3	4 ± 2*†
Sevoflurane	0 ± 2	1 ± 2
Desflurane	1 ± 2	1 ± 2
R, ms/mmHg		
Propofol	0.38 ± 0.42	0.78 ± 0.53*†
Midazolam	0.43 ± 0.45	0.85 ± 0.36*†
Sevoflurane	0.33 ± 0.29	0.37 ± 0.34
Desflurane	0.39 ± 0.38	0.44 ± 0.43

Data are presented as mean ± SD. n = 30/group.

* Different between before and after cardiopulmonary bypass (CPB) ($P < 0.05$). † Different between intravenous and inhalational anesthetics ($P < 0.05$).

dP/dt_{max} = maximal rate of left ventricular pressure decline; dP/dt_{min} = maximal rate of left ventricular pressure decline; EDP = end-diastolic pressure; ESP = end-systolic pressure; LVP = left ventricular pressure; *R* = afterload dependency of left ventricular pressure decrease; τ = time constant of isovolumic relaxation.

ery from surgery. However, the current study only analyzed variables of myocardial function with only routine clinical assessment of the other organ systems. Therefore, further studies are necessary to elucidate how the preservation of early postoperative cardiac function may be responsible for an earlier recovery. Nevertheless, other clinical studies have offered some circumstantial evidence that may endorse the hypothesis. For example, perioperative optimization of stroke volume has been shown to significantly improve tissue perfusion in patients undergoing elective cardiac surgery.[26] This was also associated with a reduced cardiac morbidity and a shorter ICU LOS. In two other studies on coronary surgery patients, sevoflurane, compared with a total intravenous anesthetic regimen, was associated with a lower release in plasma cystatin C (a sensitive marker of changes in the renal glomerular filtration rate)[17] and a reduced production of tumor necrosis factor α.[27] However, it remains to be established whether these beneficial effects are secondary to better cardiac performance or whether they are indicative of a direct protective effect of sevoflurane on other systems.

Over the years, different risk profiles have been identified for patients scheduled to undergo coronary surgery. In a study on consecutive patients undergoing coronary artery surgery with a fast-track cardiac anesthetic protocol, Wong *et al.*[28] identified three preoperative variables (increased age, female sex, and myocardial infarction < 1 week) and five postoperative variables (usage of intraaortic balloon pump, inotropes, excessive bleeding, renal insufficiency, and atrial arrhythmia) that were associated with a prolonged (> 48 h) ICU LOS. These risk factors were somewhat different from those observed in the current study. This is most likely related to differences in patient selection criteria (exclusion of patients with recent myocardial infarction, preoperative

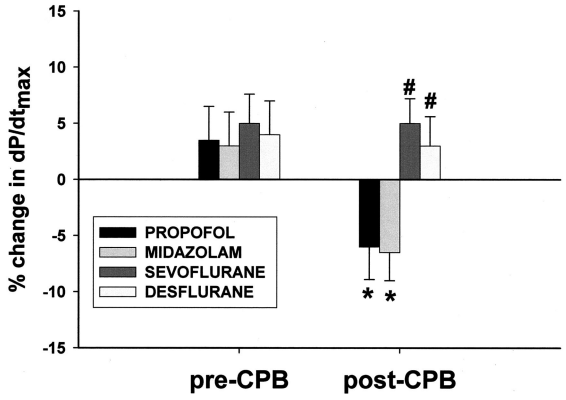

Fig. 4. Percentage change in maximal rate of pressure development (dP/dt_{max}) with leg elevation before and after cardiopulmonary bypass (CPB) with the different anesthetic regimens. With desflurane and sevoflurane, the response to leg elevation is similar before and after CPB. With propofol and midazolam, dP/dt_{max} decreased significantly after CPB. Data are presented as mean ± SD. * Statistically significant ($P < 0.05$) difference with pre-CPB; # statistically significant ($P < 0.05$) difference with the total intravenous anesthetic regimen.

inotropic support, preoperative renal or hepatic dysfunction, or severe chronic obstructive pulmonary disease). It has indeed been shown that the application of predictive models derived from elsewhere can only reliably be performed when the patient characteristics, surgical management, and anesthetic protocols are comparable.[29] Therefore, further studies should clarify whether the beneficial effects of the volatile anesthetic regimens on ICU LOS observed in the current study also apply for patients with a different risk profile.

A number of methodologic issues deserve attention. To date, the use of β-blocking agents is the only well-established prophylactic measure against perioperative myocardial ischemia resulting in a reduction in morbidity and mortality, also in the coronary surgery population.[30,31] In the current study, almost 85% of the patients in the four groups received β-blocking therapy. The observed cardioprotective effect in the sevoflurane and desflurane groups can therefore not be attributed to a better β-blocking effect. The current study mainly focused on LOS and postoperative cardiac function as outcome variables and did not aim to relate the choice of the anesthetic agent to mortality or postoperative myocardial infarction because it was not sufficiently powered to address this issue. To demonstrate a reduction in mortality rate from 1.2 to 0.6%, assuming a power of 0.8 and an α value of 0.05, an estimated sample size of 4,215 patients is needed. Similarly, to demonstrate a reduction in postoperative myocardial infarction from 4% to 2%, an estimated sample size of 1,239 patients would be needed. We did also not address the potential economic implications of the shorter ICU and hospital LOS. The introduction of fast-track anesthetic protocols in cardiac surgery has allowed a decrease in total costs per coronary artery bypass surgery of 25%, predominantly by a reduction in nursing and cardiovascular ICU costs.[3] It can be expected that any measure resulting in a decrease in ICU and hospital LOS may result in further cost savings.

The intubation times in the current study are largely comparable to what has been reported in other studies using fast-track anesthesia protocols, whereas LOS in the ICU and in the hospital were longer than those reported by some North American centers.[6,7] However, other studies reported LOS values that were more in accord with those that we observed.[32,33] These different reports clearly indicate that a great variability may exist between centers, which is probably in part related to institutional and federal (economically driven) decisions and guidelines. Nevertheless, within the limits of the protocols practiced in our hospital, the use of sevoflurane and desflurane significantly reduced LOS compared with the use of propofol and midazolam in the anesthetic protocol. Further studies must elucidate whether these observations are also valid when different ICU and hospital discharge protocols are used.

The four different anesthetic agents used were part of a multidrug anesthetic regimen including a continuous infusion of remifentanil at similar doses in each group. In addition, a number of other drugs with potential cardioprotective effects were used as part of the routine surgical and anesthetic protocol. All patients received a high-dose regimen of aprotinin and 2 g methylprednisolone. Treatment with aprotinin has been shown to decrease perioperative blood loss and has been associated with an almost twofold decrease in mortality after cardiac surgery.[34] In addition, it has been shown to produce a reduction in immunologic activation during cardiac surgery.[35] The administration of corticosteroids to minimize the inflammatory response to CPB remains controversial. Although some studies have reported a potential beneficial effect,[36] others observed no effect[37] or even a detrimental response.[38] Finally, all patients also routinely received lidoflazine, which is an adenosine transport inhibitor. It has been shown to preserve the myocardial stores of adenosine triphosphate during ischemia and to protect the myocardium against deterioration of function and structure after ischemia.[39] Because all these drugs were given in all patients of the four groups, their potential cardioprotective effects are probably not the reason for the observed differences between groups. However, it cannot be excluded that these drugs may have shown some complex interaction with the anesthetic techniques used, which could have influenced some of the results.

In conclusion, the data of the current study indicate that the use of sevoflurane and desflurane in a multidrug fast-track anesthetic regimen resulted in a shorter ICU and hospital LOS than a total intravenous regimen. The shorter ICU LOS seemed to be related to a better preservation of early postoperative myocardial function.

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