Coronary Heart Disease

Randomized Comparison of Sevoflurane Versus Propofol to Reduce Perioperative Myocardial Ischemia in Patients Undergoing Noncardiac Surgery

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Background—Volatile anesthetics provide myocardial preconditioning in coronary surgery patients. We hypothesized that sevoflurane compared with propofol reduces the incidence of myocardial ischemia in patients undergoing major noncardiac surgery.

Methods and Results—We enrolled 385 patients at cardiovascular risk in 3 centers. Patients were randomized to maintenance of anesthesia with sevoflurane or propofol. We recorded continuous ECG for 48 hours perioperatively, measured troponin T and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) on postoperative days 1 and 2, and evaluated postoperative delirium by the Confusion Assessment Method. At 6 and 12 months, we contacted patients by telephone to assess major adverse cardiac events. The primary end point was a composite of myocardial ischemia detected by continuous ECG and/or troponin elevation. Additional end points were postoperative NT-proBNP concentrations, major adverse cardiac events, and delirium. Patients and outcome assessors were blinded. We tested dichotomous end points by \( \chi^2 \) test and NT-proBNP by Mann–Whitney test on an intention-to-treat basis. Myocardial ischemia occurred in 75 patients (40.8%) in the sevoflurane and 81 (40.3%) in the propofol group (relative risk, 1.01; 95% confidence interval, 0.78–1.30). NT-proBNP release did not differ across allocation on postoperative day 1 or 2. Within 12 months, 14 patients (7.6%) suffered a major adverse cardiac event after sevoflurane and 17 (8.5%) after propofol (relative risk, 0.90; 95% confidence interval, 0.44–1.83). The incidence of delirium did not differ (11.4% versus 14.4%; \( P = 0.379 \)).

Conclusions—Compared with propofol, sevoflurane did not reduce the incidence of myocardial ischemia in high-risk patients undergoing major noncardiac surgery. The sevoflurane and propofol groups did not differ in postoperative NT-proBNP release, major adverse cardiac events at 1 year, or delirium.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00286585.

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Key Words: acute coronary syndrome ▪ cardiovascular events ▪ preconditioning ▪ volatile anesthetics

Cardiac complications after noncardiac surgery represent a major population health problem. In a large study in noncardiac surgical patients aged ≥45 years with atherosclerosis or at risk for it, myocardial infarction was found in 5% and troponin release in 8% of patients.1 In a noncardiac surgical population with documented coronary artery disease (CAD) or at high risk for it, we previously found troponin elevation in 16% and myocardial ischemia on continuous ECG (cECG) in 46% of patients.2 Multiple studies have reported an independent association between postoperative myocardial ischemia and major adverse cardiac events (MACE) and mortality, in both the short and long terms.1–3 The estimated global volume of surgical procedures is 200 million per year.4 As such, every year millions of patients may suffer perioperative myocardial ischemia after noncardiac surgery, and even more patients are at risk for future cardiac events.

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Extensive evidence from animal studies supports a protective preconditioning effect of volatile anesthetics on ischemic myocardial injury.5–7 In patients undergoing coronary artery bypass graft (CABG) surgery, some preliminary but incon

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sistent evidence suggests clinically relevant preconditioning by volatile anesthetics.8–10 Volatile anesthetics significantly reduced troponin release in a meta-analysis of 32 randomized, controlled trials (RCTs); however, the results showed relevant heterogeneity.10 Furthermore, the results were not conclusive in regard to mortality. A systematic review and meta-analysis that included studies comparing sevoflurane versus total intravenous anesthesia (TIVA) during CABG surgery found similar results for on-pump CABG but did not detect a preconditioning effect of sevoflurane in off-pump CABG patients.9 In contrast, Landoni and coworkers8 found a significant reduction of in-hospital mortality and in-hospital myocardial infarction without heterogeneity in their meta-analysis in studies addressing either sevoflurane or desflurane versus TIVA during cardiac surgery.

On the basis of this preliminary but promising evidence in patients undergoing on-pump CABG surgery, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines11 recommend the use of volatile anesthetics as beneficial in hemodynamically stable patients at cardiovascular risk undergoing noncardiac surgery (class IIa recommendation). However, data on myocardial preconditioning by volatile anesthetics during noncardiac surgery are scarce. A systematic review failed to retrieve studies with data on perioperative myocardial ischemia in patients undergoing noncardiac surgery,12 and a small RCT13 published in the meantime did not detect any protective effect of volatile anesthetics on cardiovascular end points in noncardiac surgical patients.

The objective of the Trial on the Effect of Anesthetics on Morbidity and Mortality (TEAM) (NCT00286585) was to evaluate the hypothesis that anesthesia maintenance with sevoflurane compared with propofol reduces the incidence of myocardial ischemia in patients at cardiovascular risk who undergo major noncardiac surgery.

Methods

Study Design

After approval from the local ethics committee (Ethikkommission beider Basel), we conducted a parallel RCT with fixed 1:1 allocation at a tertiary care center, the University Hospital Basel, Basel, Switzerland (February 2006 to October 2010), and at 2 secondary care centers, the Bürgerspital Solothurn, Solothurn, Switzerland (August 2006 to October 2010), and the Kantonsspital Liestal (May 2007 to November 2007), Liestal, Switzerland. We used a computer-generated random allocation sequence stratified by site and by number. Allocation concealment occurred with the use of stratification and by blinding of the research personnel. The patients, laboratory personnel, attending physicians, and data analysts were blinded to allocation.

Eligibility Criteria

Patients scheduled for surgery under general anesthesia were eligible if they either (1) had proven CAD and were scheduled for major surgery or (2) had ≥2 risk factors for CAD and were scheduled for major vascular surgery.

Proof of CAD was predefined as a history of myocardial infarction or coronary revascularization, or a >50% stenosis on coronary angiography, or myocardial ischemia induced by radionuclide or echocardiographic stress testing. Major surgery was defined as high or intermediate risk procedures according to the ACC/AHA guidelines.11,14 We considered head and neck surgery to result in intermediate risk11,14 in the presence of an expected duration of ≥120 minutes and potential blood loss of ≥1000 mL.15 Eligible procedures included thoracotomies; laparotomies; orthopedic surgeries of spine, hip, pelvis, or lower limb; open urological surgeries of prostate, kidney, or bladder; and extensive neck and throat surgery (eg, neck dissection).

The predefined risk factors for CAD were age >70 years, diabetes mellitus requiring treatment (oral antidiabetic medications or insulin), arterial hypertension, history of stroke, functional capacity <4 metabolic equivalent task, absence of sinus rhythm, and abnormal ECG (signs of left ventricular hypertrophy, left bundle branch block, or abnormalities of the ST-segment or T-wave). Major vascular surgery was defined as open surgery of the abdominal aorta or lower limb arteries.

We excluded patients in case of the following: (1) current medication with sulfonlurea derivatives16 or theophylline17 unless stopped ≥2 days before surgery because these drugs reportedly inhibit anesthetic preconditioning; (2) current congestive heart failure; (3) current unstable angina pectoris; (4) preoperative hemodynamic instability, defined as the use of vasopressors; (5) hepatic disease, defined as alanine aminotransferase and/or aspartate aminotransferase values >100 U/L; (6) renal insufficiency, defined as creatinine clearance <30 mL/min; (7) emergent surgery; (8) severe chronic obstructive pulmonary disease, defined as forced expiratory volume in the first second of expiration <1 L; (9) prior enrollment in the study; (10) concurrent enrollment in another RCT; (11) pregnancy; or (12) absence of written informed consent.

Intervention

The study protocol mandated anesthesia induction with etomidate in all patients and anesthesia maintenance with the allocated drug (sevoflurane or propofol). The agent was started immediately after anesthesia induction and confirmation of the correct tube position. In accordance with the pragmatic purpose of the study, the protocol did not regulate dosage for the induction or maintenance of anesthesia or any other aspects of intraoperative management. Thus, the anesthesiologist in charge was not limited in the decision of choice and dosage of opioids, muscle relaxants, fluids, or transfusion of blood products and choice of vasopressor, if any. In addition, extent of perioperative monitoring, type of postoperative analgesia, and specifics of postoperative care were at the discretion of the attending physicians.

Outcomes

The predefined primary end point was a composite of any ischemic episode, as detected by 3-lead ECG and/or by troponin T elevation on postoperative days 1 and 2. The definition of ischemia by ECG followed the guidelines for ECG interpretation and required an ST-segment deviation of ≥1 minute in duration.18 Secondary end points were the single components of the primary composite end points (myocardial ischemia detected by cECG or troponin elevation) and a composite of myocardial ischemia by the cECG, troponin elevation, and postoperative Q-wave development (Minnesota codes I.1-a-g, I.2-a-i, I.3-a-c). Minnesota codes I.2 and I.3 represent Q and QS patterns that are more sensitive but less specific than those applied in clinical routine to define Q-wave infarctions (Minnesota code I.1).19 Additional secondary end points were postoperative N-terminal prohormone of brain natriuretic peptide (NT-proBNP) release, MACE, and all-cause mortality after discharge up to 12 months. MACE was defined as a composite of cardiac death, acute coronary events, and congestive heart failure or arrhythmia requiring hospitalization. Acute coronary events included unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction.20 Congestive heart failure requiring hospitalization was defined as hospitalization as a
Monitoring and Methods of Follow-Up and Outcome Adjudication

Three-lead cECG monitoring (Schiller MT 100 or Schiller MT 101, Schiller Reomed AG, Baar, Switzerland) was applied shortly before anesthesia induction and recorded for 48 hours. The leads were an inferior lead, V5, and an inverse Nehb J lead.22 Troponin T and NT-proBNP were measured before induction of anesthesia and on postoperative days 1 and 2. A 12-lead ECG was recorded preoperatively and on postoperative day 7 or on the day of hospital discharge, whichever occurred first. Research personnel visited the patients shortly after surgery and on postoperative days 1, 2, and 7 to ensure compliance with the cECG and troponin monitoring and to assess Confusion Assessment Method, PONV, and overall patient satisfaction. Patient satisfaction was assessed with a numeric rating score with a range from 0 to 10, the latter indicating highest satisfaction. Blinded research personnel contacted the patients by telephone 6 and 12 months after randomization. If patients reported an event after discharge, the research personnel contacted their treating physicians to obtain appropriate documentation.

Two trained, blinded investigators independently analyzed the cECG and adjudicated on myocardial ischemia as defined by the ACC/AHA guidelines for interpretability of cECG18 from computer-aided analysis of processed cECG recordings (Schiller MT 200 Schiller Reomed AG). Inconsistencies were resolved by discussion. The ACC/AHA guidelines for the interpretability of cECG recommend that the cECG recordings fulfill a set of 12-lead ECG– and medication-based criteria and of cECG-based criteria to be considered suitable for ST monitoring.18 Because adherence to the cECG-based interpretability criteria has been shown to not improve the association between cECG-based ischemia and outcome at 12 months,23 we analyzed all cECG recordings for ST monitoring that fulfilled the 12-lead ECG– and medication-based criteria. Blinded research personnel entered all cECG data into the database in duplicate.

All blood samples were analyzed centrally at the laboratory of the University Hospital Basel. Laboratory personnel were blinded to allocation and were unaware of the study question. From February 2006 to January 2010, the central laboratory measured fourth-generation troponin T (Elecsys, Roche Diagnostics, Rotkreuz, Switzerland). The 99th percentile of fourth-generation generation troponin T is 0.03 μg/L.24 Thereafter, the hospital laboratory switched to the measurement of fifth-generation troponin T (Roche Diagnostics). Given that quality controls applied thereafter to the fifth-generation assay, we measured fifth-generation troponin T after January 2010. The upper limit of the norm for fifth-generation troponin T is <0.014 μg/L. Blinded research personnel entered all of the measured troponin concentrations into the database in duplicate. NT-proBNP was measured by Elecsys proBNP (Roche Diagnostics), which has an upper limit of the norm of 127 pg/mL.

Two trained, blinded investigators evaluated the 12-lead ECG for the development of Q waves (codes I.1.a-g, I.2.a-i, I.3.a-c) according to the Minnesota criteria.19 Inconsistencies were resolved by discussion. Blinded research personnel entered all of the 12-lead ECG data into the database in duplicate.

Two blinded investigators independently adjudicated all cardiac events during follow-up 12 months after surgery. Blinded research personnel entered all of the events into the database in duplicate.

Research staff previously trained by a neuropsychologist assessed the occurrence of delirium by the Confusion Assessment Method at baseline, on postoperative days 1, 2, and 7, or on the day of hospital discharge, whichever occurred first. Postoperative delirium on postoperative day 1, 2, or 7 was defined according to the Confusion Assessment Method as suggestive of delirium according to the interpretation algorithm published by Inouye and coworkers.21

Statistical Analysis

The sample size estimation (n = 187 per arm) was based on an event rate of 46% for myocardial ischemia on cECG2 in the control group, a relative risk reduction of 30%,10,25 a 2-sided α of 0.05, and power of 80% in the χ² test. The statistical analysis followed a prespecified analysis plan and was conducted blindly. We applied a 2-sided α=0.05 for statistical significance. All calculations were performed with the use of IBM SPSS Statistics 20 (IBM Corporation, Somers, NY). All analyses were based on the intention-to-treat principle.

Continuous data are reported as mean (SD) or as median (interquartile range [quartile 1 to quartile 3]), as appropriate. Agreement in the adjudication of myocardial ischemia on cECG was assessed by κ statistics.

As primary efficacy analysis, we conducted an intention-to-treat analysis of the incidence of the composite of myocardial ischemia as detected on cECG and/or troponin elevation in each group by χ² test. Supportive efficacy analyses included comparison of the secondary end points by χ² test, of time to MACE by log-rank test, and of differences in the distribution of postoperative NT-proBNP by Mann–Whitney U test.

Furthermore, we compared the incidence of delirium on days 1, 2, or 7 and of PONV on days 1 and 2 by χ² test (tertiary end point). We
tested for differences in the numeric rating score distribution by Mann–Whitney U test (tertiary end point).

Finally, post hoc, we assessed the impact of the troponin assay (fourth- and fifth-generation troponin) on the primary end point with the use of the \( \chi^2 \) test for heterogeneity. We did not model missing data but assumed that missing cECG, troponin T, and 12-lead ECG data did not demonstrate ischemia.

### Results

We enrolled 385 patients between February 2006 and October 2010 (Figure 1). Seventeen patients (4.4%) were randomized erroneously. In 2 patients (both in the sevoflurane group), sulfonyl urea intake was recognized after randomization, and 15 other patients (7 [3.9%] in the sevoflurane and 8 [4.0%] in the propofol group) were randomized despite a calculated creatinine clearance of <30 mL/min. Three patients (0.8%) underwent minor surgery instead of the planned major procedure. The data of all of these patients were included in the intention-to-treat analysis. One patient (0.5%) allocated to propofol received both propofol and sevoflurane. Crossover did not occur. The unequal number of patients allocated to sevoflurane and propofol was a consequence of the use of an allocation sequence without randomization blocks (see Strengths and Limitations).

Table 1 reports the baseline characteristics of the patients by allocation. All patients were white. Patients in the sevoflurane group were more frequently administered phenylephrine (71.6% versus 61%; \( P=0.029 \)). Continuous vasopressor requirements did not differ between groups.

cECG was missing in 10 patients (2.6%); 4 (2.2%) in the sevoflurane group and 6 (3%) in the propofol group. Agreement in the cECG adjudication was high (\( \kappa=0.85; \) observed agreement, 0.92; 95% confidence interval, 0.89–0.95). Troponin data on both postoperative days 1 and 2 were missing in 7 patients (1.8%): 3 (1.6%) in the sevoflurane and 4 (2%) in the propofol group. In none of the patients were both troponin values and the cECG recording missing. Twelve-month follow-up could be obtained for all patients.

### Cardiovascular End Points

The primary composite end point occurred in 75 patients (40.8%) after sevoflurane and 81 (40.3%) after propofol anesthesia (Table 2). There was no evidence of heterogeneity in the results of either the primary composite end point (test for heterogeneity, \( P=0.407 \)) or troponin T elevation (test for heterogeneity, \( P=0.291 \)) on the basis of the troponin T assay. There were no sex-based differences (test for heterogeneity, \( P=0.291 \)) on the basis of the troponin T assay.

Fourteen patients (7.6%) allocated to sevoflurane and 17 patients (8.5%) allocated to propofol suffered the composite end point of MACE at 12 months (log-rank test, \( P=0.772 \)) (Table 2 and Figure 2). All-cause mortality at 12 months was 8.5% in the sevoflurane and 8.1% in the propofol group. The primary composite end point occurred in 75 patients (40.8%) after sevoflurane and 81 (40.3%) after propofol. No differences were observed in the incidence of MACE at 12 months occurred in 6.3% (11/174) and 6.8% (13/191) of the patients in the sevoflurane and propofol groups, respectively (\( P=0.772 \)). In an analysis excluding the patients with preoperatively elevated troponin, the relative risk for the primary end point was 1.07 (95% confidence interval, 0.80–1.43).

### Other End Points

The incidence of delirium did not differ between groups (Table 3). PONV was more frequent after sevoflurane anesthesia on postoperative day 1. However, this difference in PONV did not persist on day 2 after surgery (Table 3).

Patient satisfaction was systematically assessed in 2 of the 3 study centers (n=284). The numeric rating score distribution did not differ across the 2 groups at any time point (Table 3).

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**Table 1. Baseline Characteristics by Treatment Group**

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=184)</th>
<th>Propofol (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>72 (8)</td>
<td>73 (8)</td>
</tr>
<tr>
<td>Men</td>
<td>138 (75.0)</td>
<td>156 (77.6)</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21 (11.4)</td>
<td>32 (15.9)</td>
</tr>
<tr>
<td>III</td>
<td>155 (84.2)</td>
<td>160 (79.6)</td>
</tr>
<tr>
<td>IV</td>
<td>8 (4.3)</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>128 (69.6)</td>
<td>156 (77.6)</td>
</tr>
<tr>
<td>History of TIA/stroke</td>
<td>21 (11.4)</td>
<td>24 (12.0)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>4 (2.2)</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>42 (22.8)</td>
<td>41 (20.4)</td>
</tr>
<tr>
<td>Creatinine &gt;170 mmol/L</td>
<td>5 (2.8)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>136 (73.9)</td>
<td>145 (72.1)</td>
</tr>
<tr>
<td>Aspirin discontinued ≥7 d before surgery*</td>
<td>33 (24.3)</td>
<td>32 (22.1)</td>
</tr>
<tr>
<td>Chronic β-blocker</td>
<td>130 (70.7)</td>
<td>139 (69.2)</td>
</tr>
<tr>
<td>New β-blocker</td>
<td>1 (0.6)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>ACE inhibitor/angiotensin II receptor blocker</td>
<td>122 (66.3)</td>
<td>119 (59.2)</td>
</tr>
<tr>
<td>Statins</td>
<td>121 (65.8)</td>
<td>131 (65.2)</td>
</tr>
<tr>
<td>Insulin (with or without oral antidiabetic drugs)</td>
<td>21 (11.4)</td>
<td>17 (8.4)</td>
</tr>
<tr>
<td>Oral antidiabetic drugs only</td>
<td>16 (8.7)</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major general</td>
<td>24 (13.0)</td>
<td>31 (15.4)</td>
</tr>
<tr>
<td>Major orthopedic</td>
<td>46 (25.0)</td>
<td>55 (27.4)</td>
</tr>
<tr>
<td>Major vascular</td>
<td>111 (60.3)</td>
<td>114 (56.7)</td>
</tr>
<tr>
<td>Surgery duration, min</td>
<td>187 (86)</td>
<td>193 (90)</td>
</tr>
<tr>
<td>Preoperative troponin elevation</td>
<td>13 (7.1)</td>
<td>15 (7.5)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or mean (SD), as appropriate. ASA indicates American Society of Anesthesiologists; CAD, coronary artery disease; TIA, transient ischemic attack; CHF, congestive heart failure; and ACE, angiotensin-converting enzyme.

*Percentage refers to patients with preoperative aspirin therapy.

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minor surgery instead of the planned major procedure. Seventy patients (40.2%) in the sevoflurane group and 76 patients (39.8%) in the propofol group suffered the primary end point (\( P=0.932 \)). In the per-protocol analysis, MACE at 12 months occurred in 6.3% (11/174) and 6.8% (13/191) of the patients in the sevoflurane and propofol groups, respectively (\( P=0.772 \)). In an analysis excluding the patients with preoperatively elevated troponin, the relative risk for the primary end point was 1.07 (95% confidence interval, 0.80–1.43).
Discussion

In the present trial, anesthesia maintenance with sevoflurane compared with propofol did not reduce the incidence of perioperative myocardial ischemia in high-risk patients undergoing major noncardiac surgery. In addition, our study did not suggest any effect of sevoflurane on postoperative NT-proBNP release or on MACE at 12 months.

Perioperative myocardial ischemia occurs frequently after noncardiac surgery.1–3 The present trial confirms these findings with the observation of a 40% incidence of perioperative ischemia, defined as ischemia detection by cECG or postoperative troponin elevation, in patients at cardiovascular risk undergoing major noncardiac surgery. The high incidence of myocardial ischemia occurred despite a perioperatively continued state-of-the-art medication with β-blockers, statins, and aspirin in a large proportion of patients. The definition of a perioperative ischemic event is not established; and researchers have applied various definitions.1,2,26–29 Perioperative troponin elevation is of prognostic importance because it is associated with postoperative morbidity and mortality.1–3 A meta-analysis of cohorts30 reported an odds ratio 6.7 (95% confidence interval, 5.1–10.9) for 12-month mortality and 1.8 (95% confidence interval, 1.4–2.3) for >12-month mortality. The independent association of postoperative troponin elevation with mortality is well documented in a number of patient populations.31–35 Furthermore, recent studies have suggested that noncardiac surgery is associated with increased mortality in the in-hospital period.36–38

Table 2. Study End Points and 12-Month Outcome by Treatment

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=184)</th>
<th>Propofol (n=201)</th>
<th>RR or HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia (cECG and troponin)</td>
<td>75 (40.8)</td>
<td>81 (40.3)</td>
<td>RR=1.01 (0.78–1.30)</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial ischemia on cECG*</td>
<td>41 (36.3)</td>
<td>36 (28.1)</td>
<td>RR=1.29 (0.87–1.91)</td>
</tr>
<tr>
<td>Troponin T elevation</td>
<td>46 (25.0)</td>
<td>57 (28.4)</td>
<td>RR=0.88 (0.62–1.25)</td>
</tr>
<tr>
<td>Myocardial ischemia or any Q-wave development</td>
<td>85 (46.2)</td>
<td>94 (46.8)</td>
<td>RR=0.99 (0.79–1.24)</td>
</tr>
<tr>
<td>Any Q-wave development (Minnesota codes I1–3)</td>
<td>17 (9.2)</td>
<td>18 (9.0)</td>
<td>RR=1.03 (0.52–2.0)</td>
</tr>
<tr>
<td>Q-wave infarction</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>RR=1.09 (0.03–39.8)</td>
</tr>
<tr>
<td>NT-proBNP, postoperative day 1, median (Q1–Q3), pg/mL</td>
<td>526 (257–1031.5)</td>
<td>559 (238–1234.5)</td>
<td>P=0.709</td>
</tr>
<tr>
<td>NT-proBNP, postoperative day 2, median (Q1–Q3), pg/mL</td>
<td>932.5 (450.5–1670.5)</td>
<td>928.5 (417.75–2068.5)</td>
<td>P=0.766</td>
</tr>
<tr>
<td>12-Month outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>14 (7.6)</td>
<td>17 (8.5)</td>
<td>HR=0.90 (0.44–1.83)</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>5 (2.7)</td>
<td>5 (2.5)</td>
<td>HR=1.09 (0.32–3.77)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>25 (13.6)</td>
<td>23 (11.4)</td>
<td>HR=1.19 (0.67–2.09)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median (quartiles 1–3 [Q1–Q3]), as appropriate. RR indicates relative risk; HR, hazard ratio; CI, confidence interval; cECG continuous ECG; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; and MACE, major adverse cardiac event, defined as a composite of cardiac death, acute coronary events, congestive heart failure, or arrhythmia requiring hospitalization.

*Percentage refers to number of patients with cECG suitable for ischemia analysis according to the American Heart Association/American College of Cardiology guidelines for cECG interpretability; any Q-wave development was defined as the development of Minnesota codes I.1.a-g, I.2.a-i, I.3.a-c; Q-wave infarction was defined as the development of Minnesota codes I.1.a-g.

Figure 2. Major adverse cardiac event (MACE)–free survival by treatment after discharge.

Table 3. Patient Satisfaction and Incidence of Delirium and PONV

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=184)</th>
<th>Propofol (n=201)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative delirium</td>
<td>21 (11.4)</td>
<td>29 (14.4)</td>
<td>0.379</td>
</tr>
<tr>
<td>PONV day 1</td>
<td>29 (15.8)</td>
<td>18 (8.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>PONV day 2</td>
<td>17 (9.2)</td>
<td>15 (7.5)</td>
<td>0.544</td>
</tr>
<tr>
<td>NRS, median (Q1–Q3), day 1</td>
<td>7 (5–8)</td>
<td>7 (5–8)</td>
<td>0.173</td>
</tr>
<tr>
<td>NRS, median (Q1–Q3), day 2</td>
<td>7 (5–8)</td>
<td>7 (5–8)</td>
<td>0.734</td>
</tr>
<tr>
<td>NRS, median (Q1–Q3), day 7</td>
<td>8 (6–9)</td>
<td>7 (5–9)</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median (quartiles 1–3 [Q1–Q3]), as appropriate. PONV indicates postoperative nausea and vomiting; NRS, numerical rating scale for satisfaction.
elevations independent of ischemic symptoms was reported for 30-day mortality, and the population-attributable risk of postoperative elevated troponin for 30-day mortality was quantified at 42% in >15,000 patients. Presence or absence of ischemic symptoms was not considered in this last analysis. In the present trial of patients at high cardiovascular risk, the incidence of troponin elevations within the first 2 days after noncardiac surgery was 26.7%. This estimate was consistent with reported incidences in patients at cardiovascular risk undergoing noncardiac surgery. Despite the incidence of perioperative myocardial ischemia, little progress has been made in its prevention over the last decade, and there is still no established efficacious and safe prophylaxis for perioperative myocardial ischemia. Animal models of myocardial ischemia suggest pharmacological preconditioning by volatile anesthetics as a potential approach for prevention of perioperative myocardial ischemia. Furthermore, the administration of volatile anesthetics resulted in a significant reduction of troponin release in patients undergoing CABG surgery. These promising results prompted the recommendation by the AHA/ACC guidelines in 2007 to use volatile anesthetics in patients at cardiovascular risk undergoing noncardiac surgery.

However, data on the effect of volatile anesthetics on perioperative risk in noncardiac surgical patients were not available at that time and still are scarce. A secondary, retrospective analysis of data obtained in a phase II study in 784 vascular surgical patients at cardiac risk failed to detect an effect of volatile anesthetics on troponin release and incidence of postoperative cardiac events compared with propofol. A recent small prospective and randomized study of sevoflurane versus propofol also did not detect any difference in the incidence of troponin elevation in 88 patients with CAD undergoing thoracic or vascular surgery. The results of our adequately sized RCT did not detect an effect of volatile anesthetics on perioperative ischemia in noncardiac surgical patients with CAD or at risk for it. It was therefore in agreement with the preliminary results of the 2 previous studies.

In patients undergoing valvular cardiac surgery, data are scarce and do not support a protective effect by sevoflurane. The results of studies investigating the effects of volatile anesthetics on perioperative ischemia and postoperative cardiac events in patients undergoing CABG surgery are inconsistent. The largest multicenter RCT in patients undergoing on-pump CABG surgery allocated a total of 414 patients to sevoflurane versus desflurane versus TIVA but did not detect any difference in postoperative troponin release between the groups. In contrast, a previous systematic review and meta-analysis that focused on studies comparing sevoflurane versus TIVA during CABG surgery suggested reduced troponin release and improved cardiac index in the sevoflurane group. These results, however, showed significant heterogeneity. Another meta-analysis including any volatile anesthetics during CABG surgery also found reduced troponin release after administration of a volatile anesthetic in the pooled results. However, significant heterogeneity affects the validity of these results as well. Data suggesting an effect of volatile preconditioning on the incidence of postoperative cardiac complications rely on a very limited number of events in CABG patients and are inconsistent. One meta-analysis assessing sevoflurane or desflurane versus TIVA during cardiac surgery of mostly CABG patients reported a reduced incidence of in-hospital fatalities and in-hospital myocardial infarction. In contrast, 2 other meta-analyses and a large multicenter RCT published more recently failed to reproduce these findings.

Overall, some data suggest a clinically relevant preconditioning effect of volatile anesthetics in patients undergoing on-pump CABG surgery, although these results are conflicting and open to diverging interpretations. In contrast, no data suggest a clinically relevant preconditioning effect of volatile anesthetics outside the CABG surgery setting. The present, adequately sized RCT as well as a previous small study failed to detect a clinically relevant effect of volatile anesthetics on the incidence of perioperative myocardial ischemia in noncardiac surgical patients at coronary risk. This growing evidence questions the recommendation to preferentially use volatile anesthetics in noncardiac surgical patients at cardiac risk because volatile anesthetics are also associated with specific adverse effects. Several potential explanations have been proposed for the divergence of animal and clinical data. Researchers hypothesized that the nontransferability of the promising animal results to the clinical setting may depend on comedication, age, and comorbidities that attenuate the preconditioning response. The inconsistent results during on-pump CABG surgery may arise from varying protocols, particularly in terms of continuous versus intermittent aortic cross-clamping, which in itself may induce preconditioning secondary to repeated ischemia and reperfusion stimuli (ischemic preconditioning).

Our finding of similar NT-proBNP release in both groups is consistent with the similar incidence of ischemia because ischemia and volume overload causing wall stress are triggers of natriuretic peptide release. Delirium is an unsolved problem after major surgery. The pathophysiological mechanisms of delirium have not been elucidated. Animal data have demonstrated neuroprotection to ischemia by exposure to volatile anesthetics. Preliminary human data suggest that inhalational anesthetics may be associated with better short-term cognitive performance after on-pump CABG surgery. In contrast, the incidence of delirium did not differ between the desflurane and propofol groups. In the present trial, we also did not detect an influence of the volatile anesthetic sevoflurane on the incidence of delirium.

Major cardiovascular complications and deaths did not differ in larger trials, which randomized patients to combined anesthesia techniques. The results of this trial may therefore be viewed in the broader evidence context, suggesting that the applied anesthetic technique may not play a major role in the occurrence of major cardiovascular complication and death after noncardiac surgery.

Strengths and Limitations
The validity of our results is supported by a randomized design and a blinded cECG analysis with high interreader agreement. We achieved complete follow-up at 12 months,
and all events were adjudicated independently by 2 blinded investigators. Furthermore, prognostic balance at the end of the trial was maintained by an intention-to-treat analysis. In addition, the statistical analysis followed a predefined analysis plan and was performed by a blinded data analyst. Extensive consistency checks and duplicate entry of all end point data supported high data quality.

We are aware of the following limitations. First, we renounced using a double-dummy approach because it was not clinically feasible to reliably blind the anesthesiologists. However, outcome assessment and adjudication (eEGC, troponin T, NT-proBNP measurement, 12-lead ECG analysis, and long-term follow-up) occurred blindly. A second limitation is the switch from fourth- to fifth-generation troponin T assays during the study period. However, we did not detect any interaction by troponin assay. A third limitation resulted from the erroneous enrollment of a small number of patients with a creatinine clearance level <30 mL/min. We included the data of these patients in the analysis per the intention-to-treat protocol. The number of patients with reduced creatinine clearance did not differ between groups. Therefore, we do not expect that the inclusion of these patients may have biased our findings. Furthermore, none of the end points differed in the per-protocol analysis excluding erroneously randomized patients. Fourth, the sample size of the study was powered to compare the incidence of perioperative ischemia (ie, the primary end point) and not to compare postoperative cardiac events. Therefore, the interpretation of MACE results warrants caution. If present findings are used as pilot data for calculating the sample size to compare the incidence of MACE, >14,000 patients are needed to achieve a power of 80%. Because our data do not suggest any relevant anesthetic preconditioning effect at the myocardial damage level (ie, at the level of the assumed pathophysiological link between preconditioning and outcome), we consider the realization of such a large trial as not justified. A final limitation is that we did not use randomization blocks, which resulted in a larger number of patients allocated to propofol than sevoflurane.

Conclusions
This RCT found that sevoflurane compared with propofol anesthesia does not reduce the incidence of myocardial ischemia in patients at high risk for cardiac complications undergoing major noncardiac surgery. Our study also did not detect an effect of sevoflurane on NT-proBNP release, MACE, or delirium.

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Disclosures
Roche Diagnostics Switzerland provided in-kind support (assay kits). Abbott AG Switzerland provided some financial support for the conduction of the study. No other potential conflicts of interest are to be disclosed for any of the authors.

References


**CLINICAL PERSPECTIVE**

On the basis of promising evidence in patients undergoing on-pump coronary artery bypass graft surgery, the American College of Cardiology/American Heart Association guidelines recommend the use of volatile anesthetics as beneficial in hemodynamically stable patients at cardiovascular risk undergoing noncardiac surgery (class IIa recommendation). In the present randomized, controlled trial, anesthesia maintenance with sevoflurane compared with propofol did not reduce the incidence of perioperative myocardial ischemia in patients with coronary artery disease or at risk for it undergoing major noncardiac surgery. In addition, the data did not suggest any effect of sevoflurane on postoperative N-terminal prohormone of brain natriuretic peptide release or on major adverse cardiac events at 12 months. These results are in agreement with observational data and data generated in a small randomized trial. This growing evidence questions the recommendation to preferentially use volatile anesthetics in noncardiac surgical patients at cardiac risk.
Randomized Comparison of Sevoflurane Versus Propofol to Reduce Perioperative Myocardial Ischemia in Patients Undergoing Noncardiac Surgery
Giovanna A.L. Lurati Buse, Philippe Schumacher, Esther Seeberger, Wolfgang Studer, Regina M. Schuman, Jens Fassl, Jorge Kasper, Miodrag Filipovic, Daniel Bolliger and Manfred D. Seeberger

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