Cardioprotective effect of sevoflurane in patients with coronary artery disease undergoing vascular surgery

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ABSTRACT

Objectives: The present study was conducted to evaluate the cardioprotective effect of sevoflurane compared with propofol in patients with coronary artery disease (CAD) undergoing peripheral vascular surgery; and to address the question whether a volatile anesthetic might improve cardiac outcome in these patients.

Methods: One hundred twenty-six patients scheduled for elective peripheral vascular surgery were prospectively randomized to receive either sevoflurane inhalation anesthesia or total intravenous anesthesia. ST-segment monitoring was performed continuously during intra- and post-operative 48 h periods. The number of ischemic events and the cumulative duration of ischemia in each patient were recorded. Blood was sampled in all patients for the determination of cTnI. Samples were obtained before the induction of anesthesia, on admission to the ICU, and at 6, 12, 24, and 48 h after admission to the intensive care unit (ICU). Patients were followed-up during their hospital stay for any adverse cardiac events.

Results: The incidence of ischemia were comparable among the groups [16 (25%) patients in sevoflurane group vs 24 (39%) patients in propofol group; \[P = 0.126\]]. Duration, cumulative duration, and magnitude of ST-segment depression of ischemic events in each patient were significantly less in sevoflurane group \([P = 0.008, 0.048, 0.038, \text{respectively}].\) cTnI levels of the overall population were significantly less in sevoflurane group vs propofol group \((P \text{ values } <0.0001)\) from 6 h postoperative and onward. Meanwhile, cTnI levels at 6, 12, 24, and 48 h after admission to the ICU in patients who presented with ischemic electrocardiographic (ECG) changes were significantly lower in sevoflurane group than in the propofol group \((P <0.0001, <0.0001, <0.0001, 0.0003).\) None of the patients presented with unstable angina, myocardial infarction, congestive heart failure, or serious arrhythmia either during ICU or hospital stay. Conclusion: Patients with CAD receiving sevoflurane for peripheral vascular surgery had significantly lower release of cardiac troponin I at 6 h postoperatively and lasting for 48 h than patients receiving propofol for the same procedure with significant decrease in duration, cumulative duration of ischemic events, and degree of ST depression in each patient.

Key words: Coronary artery disease, cardioprotective, sevoflurane, vascular surgery

INTRODUCTION

Patients undergoing vascular surgery have a high prevalence (50%–60%) of coronary artery disease (CAD) and are at a significant risk for perioperative myocardial ischemia (PMI).\(^1\)\(^2\) A variety of studies have shown that volatile anesthetics have a cardioprotective effect on ischemic myocardium.\(^3\)\(^4\) The underlying mechanism of the cardioprotective effect seems to be mediated through an effect on mitochondrial and sarcolemmal adenosine triphosphate-regulated potassium (K\(_{\text{ATP}}\)) channels; in addition to reduction of polymorphonuclear neutrophils adhesion in the coronary system.\(^5\) Sevoflurane and desflurane appear to have the most prominent cardioprotective properties following cardiac surgery in terms of improved early postoperative recovery of myocardial function and reduced postoperative cardiac...
troponin I (cTnI) release, requirements for postoperative inotropic support, incidence of postoperative cardiac events and intensive care unit (ICU) length of stay.\[3\] Whereas no protection has been reported with propofol.\[3,4\]

Such beneficial effects have led the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery to suggest the use of volatile anesthetics during noncardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia (class IIa, level of evidence B).\[6\] Yet, there is no published data to support the cardioprotective effect of volatile anesthetics in the vascular surgery.

The present study was conducted to evaluate the cardioprotective effect of sevoflurane inhalation anesthesia compared with total intravenous anesthesia (TIVA) using propofol in patients with CAD undergoing peripheral vascular surgery; and to address the question whether a volatile anesthetic might improve cardiac outcome in these patients.

**METHODS**

After obtaining the institutional ethical committee approval, patients with CAD scheduled for elective vascular surgery using proximal lower extremity or infrainguinal vascular cross-clamping were included in the study. All patients were informed and had given written consents.

History taking, physical examination, and necessary investigations, including complete blood picture, blood sugar, serum electrolytes, renal function tests, liver function tests, coagulation profile, X-ray chest, ECG and echocardiography were performed for all patients before surgery. Inclusion criteria were as follows: patients having CAD, which was defined as documented history of myocardial infarction, more than 50% stenosis in a coronary angiogram, previous coronary revascularization or angioplasty, and positive stress echocardiography, or stress ECG, or dipyridamole thallium scintigraphy.\[7\]

Exclusion criteria included: (1) ejection fraction <40%; (2) CAD requiring immediate revascularization; (3) previous myocardial infarction within 30 days before surgery; (4) valvular heart disease; (5) patients have left bundle branch block, atrial fibrillation or flutter, which may preclude detection of ischemia; (6) patients taking antiarrhythmic or digoxin therapy; (7) history of stroke, severe obstructive or restrictive pulmonary disease, and severe renal or hepatic impairment; (8) body mass index > 35kg/m²; and (9) anticipated difficult intubation.

Preoperative cardiac medications except for calcium antagonists, angiotensin-converting enzyme inhibitors (ACEI), and the angiotensin II receptor antagonists were continued until the morning of surgery.

Patients were premedicated with diazepam (0.1 mg/kg) orally at night. On admission to the operating room, they were monitored using continuous 12-lead ECG with continuous ST-segment analysis (Datex-Ohmeda, GE Health Care, Helsinki, Finland), pulse oximetry, noninvasive arterial blood pressure, endtidal CO₂, end-tidal anesthetic gas concentration, arterial line, central venous line, and urinary catheter.

In the operating room, patients were managed by the same surgical and anesthesia teams. They were randomized using closed sealed envelopes to receive either inhalation anesthesia (sevoflurane group) or TIVA (propofol group). The anesthesia team and postoperative assessors were blinded regarding the study and worked according to the designed protocol of the investigators.

In sevoflurane group, anesthesia was induced by 8% sevoflurane (Sevorane®, Abbott Laboratories SA, USA) with high 100% oxygen; and maintained at 1–1.5 minimal alveolar concentration.

In propofol group, anesthesia was induced by 1–2 mg/kg; and maintained with continuous infusion of 2–3 mg/kg/h of propofol (Diprivan®, Fresenius Kabi, Austria). In both groups, fentanyl (1 µg/kg) was given at induction followed by continuous infusion (0.5 µg/kg/h) to provide adequate analgesia. Endotracheal intubation was facilitated with rocuronium (0.6mg/kg). Then, controlled ventilation was established with a tidal volume of 8–10 mL/kg, inspiratory/expiratory ratio of 1:2, and ventilatory frequency of 10–12/min aiming at normocapnia.

In both the groups, additional doses of fentanyl (0.5 µg/kg) was used in the presence of signs of awareness (e.g., increase arterial pressure greater than the targeted mean arterial pressure, tearing, or sweating) and rocuronium (0.2 µg/kg) were administered as required to maintain neuromuscular blockade, respectively.

Appropriate amounts of Ringer lactate solution for maintenance, replacement of deficit, and replacement of blood loss were calculated and administered. Hemoglobin was maintained at 10 g/dL or higher and hematocrit at 30% or higher. Anesthetic concentration was adjusted to maintain heart rate and blood pressure within 20% of
preoperative ward measurements. Hemodynamic variations were first treated by using anesthetic medications.

If hemodynamic variation did not begin to correct within 1 min, the following drugs were given: phenylephrine for hypotension, nitroglycerine for hypertension, atropine for bradycardia, and esmolol for tachycardia. Myocardial ischemia defined as a transient ST-segment elevation or depression in at least one lead, measuring ≥0.1 mV, and lasting ≥1 min in the absence of hemodynamic variations was managed with continuous nitroglycerine infusion.

Ischemic events were treated with adjustment of hemodynamics and intravenous nitroglycerine if persisted. Morphine (0.15 mg/kg) IM and paracetamol (1 g) IV were administered during closure of the surgical incision. Upon completion of surgery, the anesthetic agents were discontinued, muscle relaxant was reversed, and patients were extubated and transferred to the ICU. Management of analgesia and hemodynamics in the ICU was left to the judgment of the ICU physicians who were blinded to the study design.

ST-segment monitoring was performed continuously during intra- and postoperative 48 h periods. The ST-segment deviation was measured 60 milliseconds after the J point. Ischemic event was defined as a transient ST-segment elevation or depression in at least one lead, measuring ≥0.1 mV, and lasting ≥1 min. ST-segment changes were measured concomitantly in leads II, V₄, and V₅. ST-segment changes were confirmed by ECG printouts. After the elimination of artifacts, the trends of ST-segment monitoring, ECG printouts, and the preoperative 12-lead ECG of each patient were examined by a cardiologist blinded to the study design. For each ischemic event, the duration and magnitude of ST-segment deviation were measured. The number of ischemic events and the cumulative duration of ischemia in each patient were also recorded.

Blood was sampled in all patients for determination of cTnI. Samples were obtained before the induction of anesthesia, on admission to the ICU (T₀), and at 6 (T₆), 12 (T₁₂), 24 (T₂₄), and 48 (T₄₈) h after admission to the ICU. cTnI was measured using immunoassay method (Architect stat Troponin-I, Abbott Laboratories, North Chicago, Illinois, USA). Analytic sensitivity of cTnI was ≤0.01 ng/mL. Myocardial infarction was defined as a rise in cTnI level > 1.5 ng/mL accompanied by at least one of the following: typical ischemic symptoms, ECG changes indicative of ischemia (ST-segment depression or elevation) or new pathologic Q wave.[9]

After discharge from the ICU, all patients were followed up during their hospital stay. Any adverse cardiac events, such as unstable angina, myocardial infarction, arrhythmia, or congestive heart failure were recorded.

Statistical analysis
Results were analyzed using SPSS V.11.5. Data are expressed as mean±SD unless otherwise indicated. The data were compared using unpaired t test, Fisher exact test, Mann–Whitney U test, and Wilcoxon Signed Ranks test where appropriate. If a patient had multiple ischemic events, mean values of their duration and ST-segment deviation were used in the analysis. A P value of 0.05 or less was considered statistically significant.

RESULTS
One hundred twenty-six patients fulfilled the criteria for enrollment in the study. They were randomized into sevoflurane group (n=64 patients) and propofol group (n=62 patients). The groups were demographically similar with no differences in terms of age, sex, weight, ASA physical status, New York Heart Association (NYHA) grading, left ventricular ejection fraction (EF), associated medical illness, duration of anesthesia, and duration of surgery (P>0.05) [Table 1].

All patients were on beta-blockers, ACEI or angiotensin II receptor antagonists, nitrates, antiplatelets, and statins for control of myocardial ischemia and hypertension. Fourteen patients in the sevoflurane group and 10 patients in the propofol group were receiving calcium channel blockers. Insulin was used for control of blood sugar in diabetic patients. Preoperatively, the laboratory results (including complete blood picture, blood sugar, serum electrolytes, renal function tests, liver function tests, coagulation profile) were comparable in both the groups.

### Table 1: Demographic data

|                      | Sevoflurane n=64 | Propofol n=62 |
|----------------------|------------------|---------------|
| Age (years)          | 59.4±3.8         | 60.7±3.1      |
| Sex (male/female)    | 56 (87.5)/8 (12.5) | 50 (80.6)/12 (19.4) |
| Weight (kg)          | 78.1±18.6        | 79.2±10.1     |
| ASA II/III           | 30 (47)/34 (53)  | 32 (51.6)/30 (48.4) |
| NYHA I/II            | 38 (59.4)/26 (40.6) | 34 (55)/28 (45) |
| EF                   | (45±3.8)         | (45±3.9)      |
| Comorbidity [n]      |                  |               |
| Smokers              | 32 (50)          | 40 (65)       |
| Hypertension         | 30 (98)          | 42 (71)       |
| Diabetes             | 36 (56)          | 26 (42)       |
| Previous myocardial infarction | 32 (50) | 32 (52) |
| Duration of anesthesia (min) | 185±7.9 | 188±10.2 |
| Duration of surgery (min) | 172±7.7 | 176±9.7 |

ASA - American society of anesthesiologists; NYHA - New York heart association; EF - Ejection fraction; Figures in parenthesis are in percentage
During and after surgery, there was no difference in the amount of administered packed red blood cells (113±14 mL vs 116±9 mL in both groups, respectively, P=0.156), crystalloids (1915±245 mL vs 1985±203 mL in both groups, respectively, P=0.083) between groups. The postoperative analgesic medications did not differ between the studied groups and included, intramuscular morphine sulfate, intravenous paracetamol, and intravenous fentanyl as rescue analgesic. Induction of anesthesia was smooth and well tolerated by all patients.

No episodes of coughing, laryngospasm, or excitation was observed. Fentanyl administration did not differ between patients receiving sevoflurane or TIVA (225±23 vs 232±28, P=0.127). Intraoperatively, hemodynamic events did not differ between groups; the most frequent hemodynamic event was hypotension [38 (59%) vs 44 (71%) patients in sevoflurane and propofol groups, respectively, P=0.19].

Tachycardia occurred in 28 (43.7%) patients in the propofol group compared with 19 (30.6%) patients, in the sevoflurane group P=0.097. Hypertension occurred in 10 (16%) patients in sevoflurane group and 12 (19%) patients in the propofol group. Six patients in the sevoflurane group and 4 patients in the propofol group required atropine.

The incidence of ischemia was comparable among groups [16 (25%) patients in sevoflurane group vs 24 (39%) patients in the propofol group; P=0.126]. The highest frequency of ischemia was noted in the postoperative period 10 (16%) vs 16 (26%) patients in the sevoflurane and propofol group, respectively, P=0.189).

No patients presented myocardial ischemia during induction of anesthesia. The number of ischemic events in each patient (median: 3 and range: 2–5 vs median: 4 and range: 2–5 in the sevoflurane and propofol group, respectively) were similar between groups; P=0.8. All the ischemic events were silent and occurred in the form of ST-segment depression.

The mean duration of the ischemic events, cumulative duration of ischemia over the entire monitoring period, and mean ST-segment depression in each patient was significantly less in sevoflurane group (P=0.008, 0.041, 0.038, respectively) [Table 2].

Meanwhile, cTnI levels in patients who presented ECG ischemic changes were significantly lower in the sevoflurane group than in the propofol group 6, 12, 24, and 48 h after admission to the ICU; P<0.05; (P<0.0001, <0.0001, <0.0001, 0.0003) [Figure 1, Table 3]. Both groups showed a significant increase in the cTnI levels compared with the preoperative levels; P<0.0001. cTnI levels in patients who did not show ECG ischemic changes did not differ between groups; P=0.318, 0.08, 0.165, 0.085, 1, 0.25, respectively) [Figure 2].

Postoperatively, none of the patients presented unstable angina, myocardial infarction, congestive heart failure, or serious arrhythmia either during ICU or hospital stay. Only 4 patients in the propofol group presented episodes of premature ventricular contractions (>5/min) in the ICU and responded for medical treatment.

DISCUSSION

The most important result of this study is to document, for the first time, the cardioprotective properties of volatile agents in the field of noncardiac surgery.

The incidence of perioperative myocardial ischemia in vascular surgery patients ranges from 14% to 47% and that of perioperative myocardial infarction ranges from 1% to 26%.[9] Perioperative myocardial ischemia is often demand-mediated resulting from excessive myocardial oxygen requirements during a period of surgical stress, commonly presents as episodes of ST-segment depression indicating endocardial (nontransmural) ischemia rather than ST-segment elevation (expected with supply-related ischemia) and mostly silent in nature occurring within the first 2 days after surgery.[10,11]

| Table 2: Characteristics of ischemic events |
| Sevoflurane n=16 | Propofol n=24 | P |
| --- | --- | --- |
| Duration (min) | 8.5±2.2 | 10.8±2.8 | 0.008* |
| Cumulative duration (min) | 38.3±12.9 | 48.1±15.3 | 0.043* |
| ST-depression (mm) | 1.8±0.3 | 2.1±0.5 | 0.038* |

*Significant difference P<0.05. Data expressed as mean±SD

| Table 3: Cardiac troponin I (ng/mL) levels in patients who presented ischemia |
| Sevoflurane n=16 | Propofol n=24 | P |
| --- | --- | --- |
| Preop. | 0.21±0.02 | 0.21±0.04 | 1 |
| T1 | 0.66±0.3 | 0.48±0.3 | 0.078 |
| T3 | 0.81±0.3 | 1.18±0.37 | <0.0001* |
| T4 | 0.91±0.18 | 1.17±0.14 | <0.0001* |
| T7 | 0.93±0.07 | 1.33±0.15 | <0.0001* |
| T10 | 0.68±0.18 | 0.88±0.14 | 0.0003* |

*Significant difference P<0.05. Data expressed as mean±SD
the ST-segment is an effective method for the detection of silent myocardial ischemia in patients with known CAD or those undergoing vascular surgery.\cite{12}

The authors compared the effects of a total intravenous anesthesia to a sevoflurane-based anesthesia on the occurrence of perioperative myocardial ischemia and postoperative troponin release in vascular surgery patients. Postoperative troponin I release was lower in the sevoflurane-treated patients at 6 h postoperative and continued onward during the study period.

The effects of a volatile anesthetic to a nonvolatile anesthetic regimen were compared, retrospectively, on the incidence of postoperative cardiac events, including the postoperative elevation of troponin I values after vascular surgery in high-risk patients.\cite{13,14} In the setting of abdominal aortic surgery, the incidence of postoperative elevated troponin levels tended to be lower in the inhalation group; but not in the patients undergoing peripheral arterial surgery nor in the total population.\cite{13,14}

Recently, Zangrillo et al.\cite{13} reported no significant reduction of postoperative cTnl values in patients undergoing vascular or thoracic surgery who received sevoflurane inhalation anesthesia compared with those who received propofol for TIVA. Several limitations should be considered when interpreting the results of these studies, such as variability in the type of surgery, type of volatile and intravenous anesthetics used, anesthetic techniques, and volatile anesthetic dosages across the study population. The difference between the results of Zangrillo et al.\cite{13} and the present one may be attributed to different induction techniques, higher doses of sevoflurane was used in ours, lower-risk patients were included in Zangrillo et al.’s study.

The cardioprotective effects are related to the modalities and dosage of their administration.\cite{16} To translate the cardioprotective effect of volatile agents on clinical settings, myocardial ischemia has to be present in a constant, predictable, and reproducible manner, which is not the case in vascular surgery.\cite{17}

The results of the present study do not mean that the difference detected in postoperative cTnl levels is without significance. In patients undergoing vascular surgery, elevated troponin T levels were associated with an increased risk for cardiac events during a 6-month follow up period.\cite{18} Landesberg et al.\cite{19} and Godet et al.\cite{20} demonstrated that postoperative troponin elevations even at low cutoff levels are independent and complementary predictors of long-term mortality.

Several limitations should be considered when interpreting the results of the present study, such as the authors preferred to include in the study the lowest risk patients. No supported functional tests and with no long-term outcome follow up, it is not powerful enough to draw conclusion on the superiority of one anesthesia method over the other.

In conclusion, patients with CAD receiving sevoflurane for peripheral vascular surgery and experiencing myocardial ischemia had significantly lower postoperative release of troponin I than patients receiving propofol for the same procedure with significant decrease in the duration, cumulative duration of ischemic events, and degree of ST depression in each patient.

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