The Anesthesia in Abdominal Aortic Surgery (ABSENT) Study

A Prospective, Randomized, Controlled Trial Comparing Troponin T Release with Fentanyl–Sevoflurane and Propofol–Remifentanil Anesthesia in Major Vascular Surgery

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ABSTRACT

Background: On the basis of data indicating that volatile anesthetics induce cardioprotection in cardiac surgery, current guidelines recommend volatile anesthetics for maintenance of general anesthesia during noncardiac surgery in hemodynamic stable patients at risk for perioperative myocardial ischemia. The aim of the current study was to compare increased troponin T (TnT) values in patients receiving sevoflurane-based anesthesia or total intravenous anesthesia in elective abdominal aortic surgery.

Methods: A prospective, randomized, open, parallel-group trial comparing sevoflurane-based anesthesia (group S) and total intravenous anesthesia (group T) with regard to cardioprotection in 193 patients scheduled for elective abdominal aortic surgery. Increased TnT level on the first postoperative day was the primary endpoint. Secondary endpoints were postoperative complications, nonfatal coronary events and mortality.

Results: On the first postoperative day increased TnT values (>13 ng/l) were found in 43 (44%) patients in group S *versus* 41 (43%) in group T ($P = 0.999$), with no significant differences in TnT levels between the groups at any time point. Although underpowered, the authors found no differences in postoperative complications, nonfatal coronary events or mortality between the groups.

Conclusions: In elective abdominal aortic surgery sevoflurane-based anesthesia did not reduce myocardial injury, evaluated by TnT release, compared with total intravenous anesthesia. These data indicate that potential cardioprotective effects of volatile anesthetics found in cardiac surgery are less obvious in major vascular surgery.

What We Already Know about This Topic

- Previous studies have demonstrated that volatile anesthetics may induce cardioprotection during cardiac surgery
- This study compared troponin T values in patients receiving volatile *versus* total intravenous anesthesia during elective abdominal aortic surgery

What This Article Tells Us That Is New

- No significant differences in troponin levels were observed between patients receiving volatile *versus* total intravenous anesthesia after elective abdominal aortic surgery
- These prospective randomized data suggest that volatile anesthesia is no more protective than total intravenous anesthesia

MYOCARDIAL ischemia and myocardial infarction (MI) are serious complications in cardiac and major noncardiac surgery.[1] Cardiac troponins have high tissue specificity and are sensitive markers of myocardial necrosis.[2] Troponin increase relates directly to magnitude of injury[3,4] and predicts short- and long-term outcomes after major surgery.[5,6] In cardiac surgery there are studies supporting that volatile anesthetics reduce postoperative complications including MI and mortality.[7–11] There is increased use of total intravenous anesthesia (TIVA) in major surgery[12,13] and propofol has been suggested to be cardioprotective in cardiac surgery.[13] The American College of Cardiology/American

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Heart Association 2007 guidelines[14] recommend the use of volatile anesthetics for maintenance of general anesthesia during noncardiac surgery in hemodynamic stable patients at risk for perioperative myocardial ischemia. Presently, there are limited data on cardioprotection by volatile anesthetics in major noncardiac surgery, and the recommendation is solely based on data from cardiac surgery.

Abdominal aortic aneurysm (AAA) is a common disease. Depending on aneurysm size and other factors,[15] untreated annual mortality rate varies from 0 to 50%. Patients with atherosclerosis in lower extremities often have coexisting coronary and cerebrovascular diseases and increased risk of MI, stroke, and cardiovascular death.[16] In this study (the ABSENT study: Anesthesia in *ab*domi*n*al aor*t*ic *s*urg*e*ry) consecutive patients with AAA and/or arteriosclerosis obliterans scheduled for elective surgery were included. We hypothesized that sevoflurane-based anesthesia is cardioprotective compared with TIVA also in elective abdominal aortic surgery. Cardioprotection is often primarily related to troponin levels.[17] Increased TnT level on the first postoperative day was the primary endpoint as a marker of myocardial damage. Secondary endpoints were postoperative complications, nonfatal coronary events, and mortality.

Materials and Methods

Study Design

This prospective, randomized, open, parallel-group trial was conducted at a central hospital in Norway, from February 2008 to February 2012, according to the Declaration of Helsinki principles. The necessary health authorities in Norway and at the hospital accepted initiation of the study, which was registered in Clinical Trials.gov (NCT00538421). Consecutive patients with AAA and/or aortic arteriosclerosis obliterans scheduled for open abdominal aortic surgery were screened for exclusion criteria (table 1). One hundred ninety-three patients were included and randomized (1:1) to sevoflurane-based anesthesia (group S) or TIVA (group T), illustrated in figure 1. After informed consent was given, patients selected a blank envelope with the randomization code inside from a box containing envelopes for all remaining patients to be included. Time from informed consent to surgery was 7 (2–9) days. Biochemical analysis and postoperative care were blinded with regard to randomization. A preoperative cardiological examination was performed by a doctor not involved in the ABSENT study. At time of inclusion, all patients were in a stable clinical condition, without evidence of acute coronary syndrome, uncontrolled heart failure, arrhythmia, or severe valvular disease.

Medication, Anesthesia, and Monitoring

Premedication was paracetamol (1.5 g <60 and 2.0 g >60 kg body weight). Concurrent medication like β-blockers, aspirin, and statins were continued through the perioperative period. Patients discontinued sulfonylurea, nonsteroid antiinflammatory drugs, xanthine derivatives, angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonists, and cyclooxygenase 2 inhibitors at least 24 h before surgery.

Patients were intra- and postoperatively monitored by a 5-lead electrocardiogram. A 12-lead electrocardiogram was recorded preoperatively, 30 min postoperatively, first-, second- and 30th-postoperative day, and more frequently if indicated. Invasive systemic blood pressure, central venous pressure, peripheral arterial oxygen saturation, and cardiac output (Vigileo/FloTrac system, Edwards Lifescience, Irvine, CA) were monitored. Patients were treated according to goal-directed hemodynamic management and fluid optimization (fig. 2). After hemodynamic measurements with volume adjustments, dopamine (1–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or noradrenaline (0.01–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was given intravenously (iv) at the discretion of the attending anesthesiologist to maintain a mean arterial blood pressure (MAP) of 65–90 mmHg. Transfusions were given at hemoglobin level less than 8.0 g/dl. Before induction of anesthesia an epidural catheter was introduced (thoracic level 6–10). Epidural analgesia started after opening of the aortic cross-clamp. An arterial line (a. radialis) and a 2–3 lumen venous catheter (v. jugularis int.) were introduced after induction of anesthesia.

All patients received general anesthesia and were ventilated by volume-controlled ventilation with tidal volume of approximately 8 ml/kg predicted body weight and respiratory frequency 10–18 beats/min. Predicted body weight was estimated as follows: men: predicted body weight (kg) = 50 + 0.91 (height [cm] – 152.2); women: predicted body weight (kg) = 45.5 + 0.91 (height [cm] – 152.2). Bispectral index (Philips Medical Systems, Eindhoven, The Netherlands) was used to monitor depth of anesthesia (level: 40–60). Group S (n = 97) received a balanced anesthesia with sevoflurane at 0.7–1.5 minimal alveolar concentration and repeated doses of fentanyl 0.05–0.1 mg iv. Group T (n = 96) received TIVA with propofol 1–10 $mg \cdot kg^{-1} \cdot h^{-1}$ iv and remifentanil 0.1–0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv. For induction of anesthesia, fentanyl 0.1–0.3 mg iv and thiopental sodium 3–6 mg/kg iv were given in group S, and fentanyl 0.1–0.3 mg iv and propofol 1–2 mg/kg iv in group T. Vecuronium 0.1 mg/kg iv was used for neuromuscular blockade, and 0.01–0.02 mg/kg was given based on train-of-four (TOF Watch S acceleromyograph; Organon Ltd., Dublin, Ireland). Patients were not extubated if train-of-four was less than 90%. Maintenance of anesthesia was adjusted according to bispectral index and MAP values. If bispectral index was less than 40, the propofol infusion was reduced in group T and the inspiratory sevoflurane concentration lowered in group S. If MAP was less than 65 mmHg and hypovolemia could be excluded, the remifentanil infusion was reduced in group T and planned injections of fentanyl temporarily postponed in group S. Opposite alterations were performed if bispectral index was more than 60 or MAP was more than 90 mmHg.

Postoperative analgesia consisted of oral paracetamol 1 g four times a day combined with epidural analgesia 3–12 ml/h

Table 1. Exclusion Criteria for Patients in the ABSENT Study

- Patients <18 yr of age
- Patients who were included in other pharmaceutical studies
- Abuse of opioids, benzodiazepines, antiepileptic drugs, alcohol, and α2-agonists
- Pregnant and breastfeeding women
- Patients with familiar history of malignant hyperthermia
- Patients with known hypersensitivity for opioids, propofol, or volatile anesthetics
- Patients with serious arrhythmias; ventricular fibrillation/tachycardia or tachycardia >100 beats/min (atrial fibrillation/flutter <100 beats/min was acceptable)
- Patients with severe valvular diseases requiring surgical repair before major noncardiac surgery
- Uncontrolled hypertension, serious psychiatric disease
- Patients with unstable angina pectoris or myocardial infarction 30 days before inclusion
- Acute abdominal aortic surgery (acute dissection or rupture)
- Planned laparoscopic abdominal aortic aneurysm surgery

(bupivacaine 1 mg/ml, fentanyl 2 μg/ml, and adrenaline 2 μg/ml). Morphine hydrochloride 1–10 mg iv was used as rescue pain medication.

Data Collection and Blood Samples

The primary endpoint was increased troponin T (TnT) levels (>13 ng/l) on the first postoperative day. Absolute values of TnT were also evaluated. Secondary endpoints were postoperative complications, nonfatal coronary events including postoperative acute MI, nonthrombotic troponin increase (NTTE), and mortality. Use of inotropic-, vasodilator-, and anesthetic drugs, bleeding, urine output, tachycardia (heart rate [HR] >20 beats/min above preoperative value lasting >2 min), and bradycardia episodes (HR <40 beats/min lasting >2 min), hypotensive (MAP <65 mmHg or <15 mmHg of preoperative value lasting >2 min), and hypertensive episodes (MAP >15 mmHg of preoperative value lasting >2 min) during surgery, ischemic events and arrhythmias, fluids and

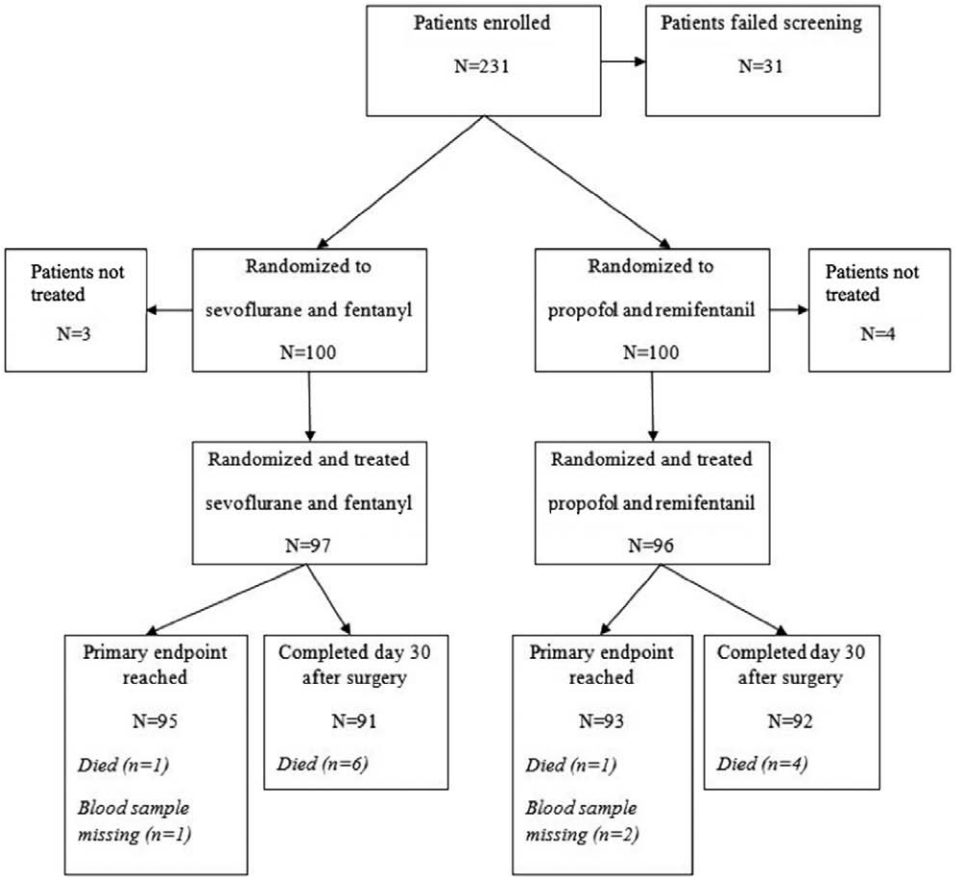

Fig. 1. Flow diagram of patient distribution showing number of patients enrolled, screened, randomized, treated, and reaching primary endpoint.

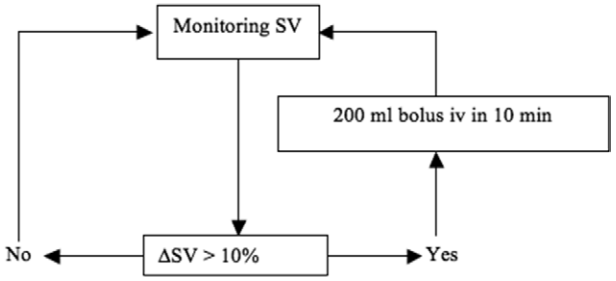

Fig. 2. Perioperative goal-directed hemodynamic fluid optimization management. iv = intravenous; SV = stroke volume; ΔSV = difference between stroke volumes.

transfusions administered, postoperative pain (Visual Analog Pain Score), and postoperative nausea and vomiting 24 h after surgery were registered. Sequential Organ Failure Assessment score was recorded 8 h, on the first (8:00 AM) and second (8:00 AM) days after surgery if the patient was still in the postoperative ward.

Length of postoperative ward/intensive care unit and hospital stay, complications and mortality were recorded at a follow-up visit 30 days after surgery. Discharge criteria from postoperative ward/intensive care unit were: adequate communication/obey commands, respiratory rate of 10 min^{-1} or more, peripheral arterial oxygen saturation of 93% or more without supplemental oxygen for minimum 5 min, no diaphoresis, HR less than 100 beats/min, adequate pain relief with Visual Analog Pain Scale less than 5. Values were accepted if equivalent to preoperative status. Data on long-term mortality were collected from the Norwegian National Population Register (vital status per September 7, 2012 for all patients included). Due to regulatory restrictions, cause of death was not available.

A high-sensitivity fifth-generation immunoassay to measure serum TnT was used (Cobas e411; Roche Diagnostics GmbH, Mannheim, Germany) with a variation coefficient less than 10% at a TnT value of 10. Plasma was kept frozen at −80°C and analyzed after completion of the study. A value more than 13 ng/l was considered abnormal.[18]

Diagnostic Criteria

Preoperative Coronary Artery Disease. A diagnosis of preexisting coronary artery disease (CAD) was based on one or more of the following: sustained acute MI verified from hospital records, previous percutaneous coronary intervention and/or coronary artery bypass grafting, angiographically verified coronary artery stenosis of 50% or more or a positive exercise test combined with a history of typical angina pectoris, as in the ACTION study.[19]

History of Stroke/Transient Ischemic Attack. Diagnosis verified by hospital records including findings of computer tomography and/or magnetic resonance imaging.

Peripheral Artery Disease. Diagnosis verified by angiographic findings of one or more significant stenoses (≥50%) of aortoiliac and infrainguinal arteries.

Carotid Artery Stenosis. Angiographic or ultrasonographic evidence of one or more significant stenosis (≥50%).

Atherosclerotic Disease. Presence of one or more of the diagnoses listed above.

Postoperative MI. To diagnose an acute MI a rise in TnT to more than 30 ng/l postoperatively and at least one of the following additional criteria had to be fulfilled[20]: symptoms of ischemia, new electrocardiogram changes indicative of ischemia (ST and/or T changes or left bundle branch block presumed to be of recent onset), development of pathological Q waves in the electrocardiogram. In absence of any of these concomitant criteria, the patient was categorized as having NTTE.[21]

Statistical Analysis

All tests were two-sided, with a 5% significance level. Continuous data, if near normally distributed, are expressed as mean and SD and analyzed with independent and paired samples *t* tests. The Kolmogorov–Smirnov test was used to test normality. Categorical data are presented as proportions, n (%), and analyzed with Fisher exact test. Data with skewed distributions, which included our primary endpoint TnT, are presented as median (25, 75% percentile) and analyzed with the Mann–Whitney U test or the Wilcoxon signed-rank test. To compare biochemical variables in blood samples pre-, intra-, and postoperatively we used the Friedman test. All analyses were performed by using SPSS 17 (SPSS Inc., Chicago, IL).

The current study included 193 patients scheduled for elective abdominal aortic surgery. To our knowledge, the only data on troponin release in patients anesthetized with volatile anesthetics or TIVA in elective open abdominal aortic surgery, which existed when the ABSENT study was planned and designed were data in an Abstract presented at the American Society of Anesthesiologist congress in 2004. Prestudy sample size calculations were based on these preliminary data from the study by De Hert *et al.* where they found increased postoperative troponin I levels in 27.9% of patients in the TIVA group, compared with 10.9% in the sevoflurane group (approximately 60% relative risk reduction). To be able to detect the same relative risk reduction (approximately 60%) for increased postoperative TnT levels, assuming 28% of patients with increased TnT levels in group T, α of 0.05 and power of 80%, 96 patients had to be randomized to each group. No power calculations were performed for comparison of secondary outcomes.

Results

Preoperative Characteristics and Baseline Demographics

Preoperative characteristics and baseline demographics are given in table 2. Mean age of the study population was 68 (range 43–84) yr. The study included 123 patients (64%) in American Society of Anesthesiologist class 3 and 4. Coexistent CAD was present in 70 patients (36%). Except for slightly higher HR and lower use of aspirin in group S,

the groups were well balanced for all remaining variables. In group S, 76 patients (78%) were subjected to AAA surgery *versus* 74 (77%) in group T. Remaining patients had to undergo surgery for other conditions in the infrarenal aorta or iliac arteries, requiring abdominal aortic surgery either with a tube graft or bifurcated graft (table 3).

TnT Release

There were no significant group differences between the two groups in TnT levels pre- or postoperatively. In group S, 22 patients (23%) had preoperative TnT values more than 13 ng/l *versus* 15 (16%) in group T ($P = 0.202$). Preoperative median TnT value was less than 10 ng/l (<10, 13) in group S *versus* less than 10 (<10, 10) in group T ($P = 0.345$). On the first postoperative day TnT values were more than 13 ng/l in 43 patients (44%) in group S *versus* 41 (43%) in group T ($P = 0.999$). In group S, 19 patients (20%) had a rise of TnT to more than 30 ng/l *versus* 15 (16%) in group T ($P = 0.579$). Median TnT value on the first postoperative day was 12 ng/l (<10, 26) in group S *versus* 12 (<10, 22) in group T ($P = 0.662$).

Intra- and Postoperative Characteristics

There were no significant differences between the two groups regarding intra- and postoperative characteristics (table 4), except that more patients in group T were bleeding the first day after surgery ($P = 0.037$) and patients in group T had higher intraoperative diuresis ($P = 0.002$) compared with group S. More patients were given dopamine in group T compared with group S ($P = 0.003$). On the basis of *post hoc* analysis of paper anesthesia records there were no differences between the two groups in number of episodes of brady-/tachycardia and hyper-/hypotension lasting more than 2 min (table 4). Two patients did not receive an epidural catheter (one in each group). The first postoperative day at 8:00 AM, 11 patients (7 in group S and 4 in group T) had epidural analgesia that was not optimal.

Postoperative Complications

Postoperative complications assessed from end of surgery to 30 days follow-up are given in table 5. Six of 34 patients with a rise in TnT to more than 30 ng/l on the first postoperative day qualified for a diagnosis of acute MI. Another two patients had acute MI (one with normal TnT the first postoperative day) with a rise in TnT to more than 30 ng/l at a later stage during hospitalization. Total incidence of postoperative acute MI was 8 (4.1%); 5 (5.2%) in group S *versus* 3 (3.1%) in group T. All patients with acute MI were categorized to have non-ST segment increase MI and none of them had evidence of new left ventricular dysfunction, as shown by a postoperative echocardiogram.

Mortality Rates

Total 30-day mortality was 8/193 (4.1%), 6/84 (7%) in patients with increased TnT more than 13 ng/l *versus* 2/109 (2%) among patients with normal TnT. The mortality rate was 3/8 (37.5%) in patients with acute MI *versus* 2/27 (7.4%) in the NTTE group. Total study group mortality rates were 11 (5.7%) at 3 months and 12 (6.2%) at 6 months (fig. 3). Median long-term follow-up was 1,064 (range 221–1,649) days. During this period 23 patients (11.9%) died, 10 in group S (10.3%) *versus* 13 (13.5%) in group T.

Time of Hospitalization

Median hours of stay at the postoperative ward/intensive care unit were 28 (25, 62) in group S *versus* 27 (25, 50) in group T, and median days of hospital stay were 9 (8, 12) in group S *versus* 9 (8, 12) in group T.

Discussion

In elective abdominal aortic surgery we found no significant differences between patients receiving sevoflurane-based anesthesia compared with TIVA in increased TnT levels (>13 ng/l) on the first postoperative day or in TnT levels at any time.

In different models and species it has been shown that volatile anesthetics and opioids can induce cardioprotection.[22–26] Data from cardiac surgery have shown a cardioprotective effect of volatile anesthetics[8–11] and is supported by two meta-analyses.[7,27] Also, propofol has been suggested to have protective effects[28,29] and has been indicated in clinical studies.[13,30]

There are limited data on cardioprotection by volatile anesthetics in noncardiac surgery. In a retrospective, nonrandomized study, De Hert *et al.*[31] found a nonsignificant trend toward lower troponin I release with volatile agents *versus* nonvolatile anesthetic regimen in patients undergoing aortic surgery. To the best of our knowledge, there are only two prospective randomized studies comparing volatile anesthetics and TIVA with regard to cardioprotection in major noncardiac surgery.[32,33] Zangrillo *et al.*[32] randomized 88 patients to sevoflurane-based anesthesia or TIVA. They found no significant difference in number of patients with troponin release after surgery and no differences in complications between the two groups. On the basis of American Society of Anesthesiologist classification, the populations in the two studies seem to be quite similar. In both studies coexistent CAD was present in 36% of the patients. An important aspect separating the two studies is that peripheral vascular surgery was included in the study by Zangrillo *et al.*,[32] as opposed to open abdominal aortic surgery. In the study by Zangrillo *et al.*[32] no perioperative MI or ischemia occurred after 30 days, and the incidence of cardiac events after 1 yr was limited, reflecting that their heterogeneous study population was not optimal for detecting cardioprotection. Additionally, intraoperative hemodynamic assessment and management were not described in their study.

In a study by Lurati Buse *et al.*,[33] 385 patients subjected to noncardiac surgery were randomized to sevoflurane or propofol. The sample-size calculation in their study was based on myocardial ischemia on a 3-lead electrocardiogram and

Table 2. Baseline Demographics and Clinical Preoperative Characteristics for Patients Receiving Volatile Anesthetics (Group S, n = 97) or TIVA (Group T, n = 96)

Variable	Group S	Group T
Number of patients included (men/women)	97 (73/24)	96 (72/24)
Age, yr	69 ± 9	67 ± 9
Body mass index, kg/m^2	25 ± 4	26 ± 4
ASA classification		
II	36 (37)	34 (35)
III	47 (48)	49 (51)
IV	14 (14)	13 (13)
Current smoker	39 (40)	50 (52)
Preoperative medication		
Statins	66 (68)	71 (74)
β-Blockers	38 (39)	46 (48)
ACEI/A2RB	37 (38)	35 (36)
Acetylsalicylic acid	60 (62)	73 (76)*
Heart rate before induction of anesthesia, beats/min	71 ± 12	66 ± 12*
Systolic blood pressure before induction of anesthesia, mmHg	154 ± 23	154 ± 27
Number of patients, %		
Diabetes mellitus	10 (10)	7 (7)
Hypertension	58 (60)	53 (55)
CHD	35 (36)	35 (37)
Previous acute MI	26 (27)	32 (33)
Previous coronary artery bypass grafting	15 (15)	12 (12)
Previous percutaneous coronary intervention	16 (16)	12 (12)
Atherosclerotic disease	63 (65)	61 (64)
Heart failure	5 (5)	4 (4)
Supraventricular arrhythmias	13 (13)	13 (13)
Renal failure	10 (10)	8 (8)

Values are mean ± SD or numbers of patients (men/women) or number (% of group).

* $P < 0.05$.

A2RB = angiotensin II receptor blocker; ACEI = angiotensin-converting enzyme inhibitor; ASA = American Society of Anesthesiologists; CHD = coronary heart disease; MI = myocardial infarction; TIVA = total intravenous anesthesia.

not on TnT increase. The primary endpoint was a composite of any ischemic episode, detected by 3-lead electrocardiogram and/or by TnT increase. They found that sevoflurane did not reduce the incidence of ischemia compared with propofol. Details regarding intraoperative hemodynamic management were not given. Only 58% of their patients were subjected to major vascular surgery. The study population had either established CAD or two or more risk factors for CAD, resulting in a higher prevalence of CAD and ongoing chronic β-blockade than in our study. β-Blockade could theoretically diminish potential cardioprotective effects of anesthetic drugs. TnT increase in their study was based on two assays with different cutoff values, with the majority based at more than 30 ng/l. This may explain why the incidence

Table 3. Type of Surgery for the 193 Patients Receiving Either Volatile Anesthetics (n = 97) or TIVA (n = 96)

Variable	Volatile Anesthetics	TIVA	*P* Value
ASO surgery (men/women)	19 (6/13)	20 (10/10)	0.86
AAA and combined arteria iliaca aneurysm surgery (men/women)	76 (65/11)	74 (62/12)	0.86
Combined AAA and ASO (men/women)	1 (1/0)	1 (1/0)	0.99
Aneurysm size (cm; n = 152)	5.8 ± 1.1	5.7 ± 0.9	0.86
Arteria iliaca aneurysms surgery (men/women)	1 (1/0)	0	0.99
Chronic abdominal aortic dissection (men/women)	0	1(1/0)	0.99
Tube graft (men/women)	44 (37/7)	41 (32/9)	0.66
Bifurcated graft (men/women)	53 (36/17)	55 (41/15)	0.77

Values are mean ± SD or numbers of patients (men/women).

AAA = abdominal aortic aneurysm; ASO = arteriosclerosis obliterans; TIVA = total intravenous anesthesia.

Table 4. Perioperative Characteristics for Patients Receiving Volatile Anesthetics (Group S, n = 97) or TIVA (Group T, n = 96)

Variable	Group S	Group T	*P* Value
Anesthetic time, min	209 (177, 246)	220 (183, 277)	0.10
Surgery time, min	181 (138, 213)	189 (144, 243)	0.15
Aorta cross-clamp time, min	76 ± 29	81 ± 33	0.22
Hemodynamic alterations during surgery (lasting >2 min)			
Bradycardia	0 (0, 0)	0 (0, 1)	0.20
Tachycardia	0 (0, 2)	0 (0, 1)	0.10
Hypertension	1 (0, 2)	0 (0, 1)	0.10
Hypotension	5 (2, 6)	4 (2, 6)	0.16
Bleeding during surgery, ml	930 (690, 1,600)	1,260 (830, 1,880)	0.08
Bleeding first day, n/%	11 (11)	22 (23)	0.04
Bleeding first day, ml (n = 11/22)	140 (120, 200)	195 (130, 380)	0.35
Intravenous fluid during surgery, ml	4,600 (3,630, 6,130)	4,670 (4,100, 6,660)	0.15
Crystalloids, ml	3,500 (2,700, 4,450)	3,700 (3,050, 4,800)	0.17
Colloids, ml	500 (500, 1,000)	750 (500, 1,000)	0.38
Allogeneic transfusion, n/%	30 (31)	38 (40)	0.23
(ml) (n = 30/38)	750 (440, 1,060)	500 (250, 1,000)	0.22
Autologous transfusion, n/%	21 (22)	14 (15)	0.26
(ml) (n = 21/14)	620 (480, 830)	730 (470, 1,030)	0.33
Intravenous fluid first day, ml	2,440 (1,580, 3,200)	2,060 (1,480, 3,070)	0.41
Crystalloids, ml	1,800 (1,070, 2,400)	1,530 (1,040, 2,390)	0.30
Colloids, ml	100 (0, 500)	0 (0, 500)	0.57
Allogeneic transfusion, n/%	27 (28)	21 (22)	0.29
(ml) (n = 27/21)	250 (250, 500)	250 (250, 500)	0.47
Intraoperative diuresis, ml	300 (190, 450)	375 (260, 650)	<0.01
Diuresis first day, ml	1,290 (980, 1,700)	1,410 (1,020, 1,730)	0.39
Fluid by mouth on first day, ml	450 (200, 750)	450 (150, 710)	0.61

Values are median (25%, 75% percentile), mean ± SD or numbers of patients (%). First day = time from arriving at postoperative ward until next morning 8:00 AM. All autologous transfusions were performed with a Cell Saver® 5+ (Haemonetics Corporation, Braintree, MA). TIVA = total intravenous anesthesia.

of TnT increase in the two groups was lower compared with that in our study.

In a large-cohort study of patients aged more than 65 yr, Newman *et al.*[34] found that AAA patients had increased risk for other cardiovascular diseases and cardiovascular death, and the risk increased with size of the aneurism. In that survey 41% of individuals with AAA had a history of cardiovascular disease, compared with 36% in the current study. These aspects may explain the relative high incidence of cardiovascular complications in the current study.

The incidence of acute MI is comparable with that in other studies.[35,36] Although this study was not powered to evaluate mortality or other secondary outcomes, mortality in patients with acute MI tended to be higher than in patients with NTTE. This is contradictory to mortality in patients hospitalized with chest pain and troponin increase.[21] All patients with acute MI in our study were without ST-segment increase. We found no significant difference in TnT levels among patients with acute MI *versus* NTTE.

When we initiated inclusion, the only data that existed on troponin release in patients anesthetized with volatile anesthetics or TIVA in elective open-abdominal aortic surgery was an Abstract presented at the American Society of Anesthesiologist annual meeting in 2004. We used these data for our prestudy sample-size analysis. Calculations regarding the primary endpoint assumed an approximately 60% relative risk reduction. We cannot exclude that smaller differences in TnT release do exist between the two groups. Another assumption was that increased TnT levels occurred in minimum 28% of patients anesthetized with TIVA. We observed increased TnT levels in 43% of the patients, a fact that further increases power of the primary endpoint of the study. With the relatively high number of NTTE and noncardiac complications observed, it seems unlikely that one anesthetic method is associated with substantial clinical benefit *versus* the other. To evaluate myocardial injury based on the rise of troponins, the cutoff values applied are essential. Different results may occur by using different cutoff values. Differences between the two anesthetic regimens were not detectable using either TnT more than 13 ng/l or more than 30 ng/l as cutoff values. When TnT of more than 13 ng/l was used, a higher number of patients inevitably had TnT

Table 5. Postoperative Complications Assessed from End of Surgery to 30 Days after Surgery

Complications	Group S	Group T
Acute myocardial infarction	5 (5)	3 (3)
Cerebral embolism/thrombosis	1 (1)	1 (1)
Ischemic lower extremity	4 (4)	5 (5)
Renal failure	3 (3)	4 (4)
Pulmonary failure	9 (9)	6 (6)
Pneumonia	13 (13)	9 (9)
Gastrointestinal failure	2 (2)	4 (4)
Peptic ulcer	2 (2)	3 (3)
Cognitive dysfunction	6 (6)	4 (6)
Atrial fibrillation/-flutter	9 (9)	9 (9)
Other minor complications	21 (22)	18 (19)
Reoperation	10 (10)	10 (10)
Ileus	2 (2)	5 (5)
Wound rupture	2 (2)	0 (0)
Peripheral embolism/rhabdomyolysis	5 (5)	3 (3)
Graft infection	1 (1)	0 (0)
Ischemic colon	1 (1)	3 (3)
Bleeding	1 (1)	1 (1)
Explorative lapratomy	2 (2)	0 (0)
Death, 30 day	4 (4)	4 (4)

Patients received volatile anesthetics (group S, n = 97) or TIVA (group T, n = 96). Values are numbers (%). Note that some patients had more than one complication. Other minor complications consisted of urinary tract infection, urinary retention, urinary incontinence, hematuria, retrograde ejaculation, wound infection, atelectasis, upper airway infection, chronic obstructive pulmonary disease exacerbation, pneumothorax, prolonged vomiting and nausea, esophagitis, hematemesis, erosive gastritis, gastroenteritis, obstipation, diarrhea, duodenitis, increased expression of liver enzymes, cholecystitis, back pain, pain in limbs, gout, chest pain of unknown origin, loss of pacemaker function, fatigue, fever of unknown origin.

TIVA = total intravenous anesthesia.

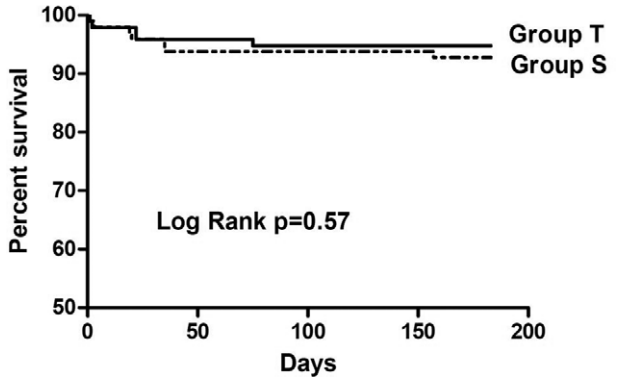

Fig. 3. Kaplan–Meier curve for the survival of patients in group S (n = 97) and group T (n = 96).

increase, representing a higher power to detect possible differences. We did not observe any differences between the groups in postoperative complications, length of stay at intensive care unit/hospital, or mortality. These observations, however, must be interpreted with caution because the study was not powered to detect a difference in these secondary outcomes.

For induction of anesthesia thiopental was used in group S and propofol in group T. Cardioprotective effect of thiopental is controversial.[37,38] In the current study fentanyl was used for induction of anesthesia in both groups. Thereafter, fentanyl was used to potentiate sevoflurane anesthesia in group S, whereas remifentanil was used in group T. It has been shown that opioids, especially remifentanil, have cardioprotective effects.[39] Thus, the use of opioids and choice of induction agents might have influenced the results and made the results harder to interpret. Another important aspect is that minimum alveolar concentration of sevoflurane used in the current study should be high enough to achieve cardioprotection.[40,41]

Before accepting our results it is mandatory to exclude potential differences between the two groups. We used goal-directed hemodynamic management intra- and postoperatively. The protocol was followed rigorously. There was no difference in amount of iv fluid, hemodynamic alterations, or use of epidural analgesia perioperatively between the two groups. The groups were well balanced for coexisting CAD and other important prognostic variables. However, significantly more patients used aspirin in group T compared with group S. Aspirin has shown to be protective during surgery.[42] Thus, this could have improved the results in group T. Patients in group S also had slightly higher resting HR than in group T. We also found a higher urine output during surgery in group T, which might be explained by more use of dopamine in this group. We consider these differences too small to explain the neutral finding in our study.

Another possible confounder may be a selection bias in patients with too few complications to detect differences in cardioprotection. The prevalence of preexisting CAD, however, was identical to that reported by Young *et al.*[43] and increase of TnT above the discriminator level for myocardial necrosis was comparable with that in a study by Abraham *et al.*[44] Thirty-day mortality for elective AAA surgery has been reported from 1.6 to 7.8%,[45,46] indicating that our study group did not represent a low-risk group, as reflected from the 30-day and 6-month mortality rates of 4.1% and 6.2% respectively. Although we did not include predefined high-risk cardiovascular patients, included patients had substantial morbidity and mortality. Due to regulatory rules, data on long-term total mortality could only be obtained without the possibility of subdividing between cardiovascular and noncardiovascular death. Therefore, it cannot be excluded that the number of deaths unrelated to the surgically treated aortic disease may have been different in the two groups.

A factor that could diminish differences between the groups is remote ischemic preconditioning.[47,48] During abdominal aortic surgery, aorta is cross-clamped and both limbs made ischemic. We found no significant difference in

cross-clamp time ($P = 0.218$) between the groups, but cannot exclude that remote protection may have masked anesthetic cardioprotective differences.

The proportion of increased TnT is considerably higher than in previous reports and is probably related to the use of highly sensitive assay with low levels for normality. The value of 13 ng/l was chosen as cutoff point because even small postoperative TnT increases are associated with higher long-term risks of subsequent cardiovascular events and all-cause mortality.[6,49,50]

Current guidelines[14] recommend use of volatile anesthetics during noncardiac surgery in high-risk patients for the maintenance of general anesthesia in hemodynamically stable patients at risk for perioperative myocardial ischemia. Data from the ABSENT study together with data from the studies by Zangrillo *et al.*[32] and Lurati Buse *et al.*[33] do not support these recommendations.

We conclude that there were no differences in number of patients and levels of increased postoperative TnT values between the two anesthetic regimens. Our data indicate that cardioprotective effects of volatile anesthetics found in cardiac surgery are less obvious in unselected patients undergoing elective major vascular abdominal surgery. Further larger-scaled studies are needed to clarify potential anesthetic cardioprotection in different types of noncardiac surgery.

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