

## Does the use of a volatile anesthetic regimen attenuate the incidence of cardiac events after vascular surgery ?

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**Abstract :** *Objective :* To compare the effects of a volatile anesthetic to a non-volatile anesthetic regimen on the incidence of postoperative cardiac events, including the postoperative elevation of troponin I values after arterial vascular surgery in high risk patients.

*Design :* Retrospective analysis of data of a phase II study that compared the Na<sup>+</sup>/H<sup>+</sup> exchanger type I inhibitor, zonisiporide to placebo on the occurrence of cardiac events.

*Setting :* Multicenter study conducted in 105 sites throughout the United States, South America, Europe and Asia

*Participants :* 784 subjects scheduled for urgent or elective major arterial vascular surgery and a history of at least 3 of the following : age  $\geq$  65 years, hypertension, documented stroke or transient ischemic attack, previous myocardial infarction, active angina pectoris diabetes mellitus, congestive heart failure, or symptomatic cardiac arrhythmia.

*Interventions :* Type of anesthesia was retrospectively retrieved from the database and patients were subdivided in two groups : inhalational (group A) vs non-inhalational anesthetic regimen (group B). Incidence of postoperative cardiac events was compared between the two groups.

*Measurements and Main Results :* The incidence of postoperative cardiac events was not different between the two groups. Maximum postoperative troponin I levels was not different between the two groups in the total population and in the patients undergoing peripheral arterial surgery. In patients undergoing aortic surgery the incidence of elevated troponin levels higher than 1.5 and 4 ng.mL<sup>-1</sup> tended to be lower in group A than in group B in the aortic surgery (28% vs 18% and 30% vs 20% respectively) but this difference did not reach statistical significance.

*Conclusion :* The results of this hypothesis-generating study suggest that potential beneficial effects on extent of postoperative myocardial damage in high risk patients undergoing arterial surgery will probably be more apparent in abdominal aortic surgery than in peripheral vascular surgery. Further sufficiently powered studies using a standardized protocol should now be performed to definitively address this question.

**Key words :** Vascular surgery ; myocardial protection ; troponin I ; volatile anaesthetics ; intravenous anaesthetics.

### INTRODUCTION

Cardiac complications are a major cause of perioperative morbidity and mortality after major vascular surgery (1). Preoperative cardiac evaluation may help to identify those patients that are at increased risk for developing postoperative cardiac events (2). However, recent data have indicated that even in these patients coronary revascularization did not result in improved outcome after vascular surgery (3, 4). Alternatively, perioperative pharmacological strategies have been proposed to decrease postoperative cardiac adverse events after vascular surgery (5). Over the years different strategies have been developed to decrease the rate of postoperative myocardial complications and evidence suggests that the perioperative use of  $\beta$ -blocking drugs,  $\alpha_2$ -adrenergic drugs and statins appear to be effective in reducing postoperative cardiac complications in vascular surgery patients (6-10). Other therapies such as the perioperative administration of Na<sup>+</sup>/H<sup>+</sup> exchange inhibitors have until now not been proven to significantly decrease postoperative cardiac complications (11).

Experimental evidence increasingly indicates that volatile anesthetic agents may have cardioprotective effects that occur independently from their beneficial effects on the myocardial oxygen

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balance. Indeed, volatile agents have been shown to decrease the extent of myocardial infarction area or the magnitude of myocardial dysfunction after myocardial ischemia (12, 13). A number of recent studies in coronary surgery patients have suggested that the choice of a volatile anesthetic regimen might also prove to be cardioprotective in the perioperative clinical setting. These cardioprotective effects were evident from a lower postoperative release of troponin I, improved early postoperative recovery of myocardial function, and decreased requirements for postoperative positive inotropic support (14-20). In addition, the intensive care unit length of stay and the probability of cardiac event-free survival appeared to be favorably influenced by the perioperative use of a volatile anesthetic regimen.

Based on these data it was suggested that the use of a volatile anesthetic regimen might constitute an additional therapeutic tool in the perioperative period to decrease perioperative myocardial complications (21). Until now, no data have been published on a potential cardioprotective effect of a volatile anesthetic regimen in vascular surgery patients. The present study analyzed retrospectively from a multicenter data base of patients undergoing arterial vascular surgery whether the choice of a volatile anesthetic regimen might affect the incidence of postoperative cardiac events.

## MATERIAL AND METHODS

Data were obtained from the database of a phase II study that compared the Na<sup>+</sup> / H<sup>+</sup> exchanger type I inhibitor zoniporide to placebo on the occurrence of perioperative mortality and cardiac events within the first 30 postoperative days in subjects at high risk undergoing noncardiac vascular surgery. The results of this study have been published previously, and no significant difference in cardiac outcomes was detected between the placebo and the different zoniporide groups. Therefore, all of the original treatment groups were combined for the present analysis (7). The randomized double-blind multicenter study was conducted in sites throughout the United States, South America, Europe and Asia. The study was approved by the local Ethical Committees and all patients gave written informed consent. The study population consisted of subjects with peripheral vascular atherosclerotic disease and a history of at least three of the following : age  $\geq$  65 years, hypertension, documented stroke or transient ischemic attack, previous

myocardial infarction, medically managed coronary artery disease with active angina pectoris (Canadian Class II or higher), diabetes mellitus, congestive heart failure (New York Heart Association class II or higher), symptomatic cardiac arrhythmia, or a history of one of these risk factors and either radionuclide, echocardiographic, or electrocardiographic (ECG) evidence of reversible ischemia in response to exercise or pharmacologic stress, or evidence of clinically significant coronary artery disease at coronary angiography. All patients were scheduled for urgent or elective major arterial vascular surgery involving revascularization using aortic or proximal lower extremity vascular cross-clamping or infrainguinal lower extremity vascular reconstruction. Subjects were excluded if they had coronary artery disease requiring immediate revascularization, current history of liver disease or renal disease requiring dialysis.

Type of anesthesia was retrospectively retrieved from the database and patients were subdivided in two groups : inhalational (group A) vs non-inhalational (group B) anesthetic regimen. Patients were allocated to the inhalational anesthetic regimen when they had received halothane, enflurane, isoflurane, desflurane or sevoflurane in the intraoperative period. When no volatile anesthetics had been administered intraoperatively, the patients were allocated to the non-inhalational group.

Surveillance of cardiac events consisted of ECGs, creatine kinase isoenzymes, and troponin I, beginning preoperatively, daily for the first three days, and additional measurements if the patient had symptoms. Biomarkers and ECGs were measured and reviewed in a central laboratory. Final determination of events was made by consensus of an Endpoint Classification Committee consisting of anesthesiologists, cardiologists and vascular surgeons, blinded to treatment groups. A cardiac event was defined as cardiac death, myocardial infarction, congestive heart failure, or serious cardiac arrhythmia. Cardiac death included sudden death, postresuscitation, procedural, or other cardiac death. A new myocardial infarction was defined with biomarker criteria of myocardial necrosis (creatine phosphokinase index  $>$  5% or troponin I  $>$  4 ng/mL) and one of the following : presence of left bundle-branch block, paced rhythm or non-specific ECG changes, or symptoms consistent with acute myocardial ischemia or acute coronary revascularization procedure. New or progressive congestive heart failure was defined as the presence of a syndrome characterized clinically by breathlessness,

pulmonary congestion, effort intolerance, fluid retention, and peripheral hypoperfusion secondary to declining myocardial performance. Serious cardiac arrhythmia was defined as the presence of a sustained cardiac rhythm disturbance that resulted in either hemodynamic compromise, syncope, cardiac arrest, cerebral vascular event, or altered mental status, and requiring urgent medical intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker. In addition, we evaluated the extent of myocardial damage as assessed by maximum postoperative troponin I levels in the two groups. A maximum postoperative troponin I level  $> 4 \text{ ng.mL}^{-1}$  was considered indicative of a peri-operative myocardial infarction as defined by the Endpoint Classification Committee of the Zoniporide phase II study (see above). A maximum postoperative troponin I level  $> 1.5 \text{ ng.mL}^{-1}$  was considered as indicative of major perioperative myocardial damage (22). Finally, a maximum postoperative troponin I level between 0.5 and  $1.5 \text{ ng.mL}^{-1}$  was considered as indicative of minor myocardial damage.

For categorical variables, a chi-square test was used for testing differences between patients using inhaled anesthetics and patients using non-inhaled anesthetics, and for patients with aortic surgery versus patients with peripheral surgery. For continuous variables, a Wilcoxon rank sum test was used. Logistic regression for dichotomous response was used to assess the effect of inhaled anesthetics versus non-inhaled anesthetics on peak troponin cut at 0.5, 1.5 and 4 in patients with aortic surgery versus patients with peripheral surgery. Maximum likelihood estimates were obtained. Wald chi-square test which takes the form of the squared value ratio for the estimate to its standard error was applied to indicate the significance of the estimates. The covariates used to adjust the effect are treatment, age, gender, weight, height, loop diuretic, sympathomimetics, and selective adrenoceptor stimulants.

## RESULTS

A total of 784 patients with atherosclerotic vascular disease from 105 centers in the United States, South America, Europe and India operated between November 2001 and May 2003 were included in the present analysis. Of these 319 had an inhalational based anesthesia whereas 465 patients received no inhalational anesthetic agent at all. Demographic and intraoperative data of

Table 1

Demographic, and intraoperative data

	Volatile anesthetic regimen (n = 319)	Non-volatile anesthetic regimen (n = 465)
demographic data		
male / female	230 / 89	330 / 135
age (years)	70 $\pm$ 10	71 $\pm$ 10
height (cm)	171 $\pm$ 10	168 $\pm$ 10
weight (kg)	77 $\pm$ 15	73 $\pm$ 16
intraoperative data		
aortic / peripheral surgery	99 / 220	71 / 394
duration of anesthesia (hrs)	5.0 $\pm$ 2.1	4.6 $\pm$ 1.8
clamping time (min)	57 $\pm$ 37	56 $\pm$ 42
blood loss (mL)	836 $\pm$ 949	554 $\pm$ 672

Table 2

Cardiac outcome data

	Volatile anesthetic regimen (n = 319)	Non-volatile anesthetic regimen (n = 465)
all surgery		
n	n = 319	n = 465
mortality	17 (5%)	24 (5%)
myocardial infarction	36 (11%)	52 (12%)
congestive heart failure	24 (8%)	35 (8%)
arrhythmias	30 (9%)	27 (6%)
composite endpoint	70 (22%)	84 (18%)
aortic surgery		
n	n = 62	n = 43
mortality	3 (5%)	2 (5%)
myocardial infarction	13 (21%)	10 (23%)
congestive heart failure	7 (11%)	6 (14%)
arrhythmias	8 (13%)	3 (7%)
composite endpoint	18 (29%)	12 (28%)
infra inguinal surgery		
n	n = 257	n = 422
mortality	14 (5%)	22 (5%)
myocardial infarction	23 (9%)	42 (10%)
congestive heart failure	17 (7%)	29 (7%)
arrhythmias	22 (9%)	24 (6%)
composite endpoint	52 (20%)	72 (17%)

the patients are summarized in Table 1. There were no differences in male/female ratio, age, height and weight between the two groups. Preoperative medication was similar in both groups except for the use of  $\beta$ -blocking medication and loop diuretics, which was higher in the volatile anesthetic group (82% vs 69% ( $p < 0.001$ ) and 80% vs 63% ( $p < 0.001$ ) respectively). The percentage of patients that underwent aortic surgery was higher in the volatile anesthetic group (31% vs 15% ( $p < 0.001$ )) and blood loss was also higher ( $p < 0.001$ ). Duration of anesthesia and crossclamp time were similar in the volatile vs the non-volatile anesthetic groups.

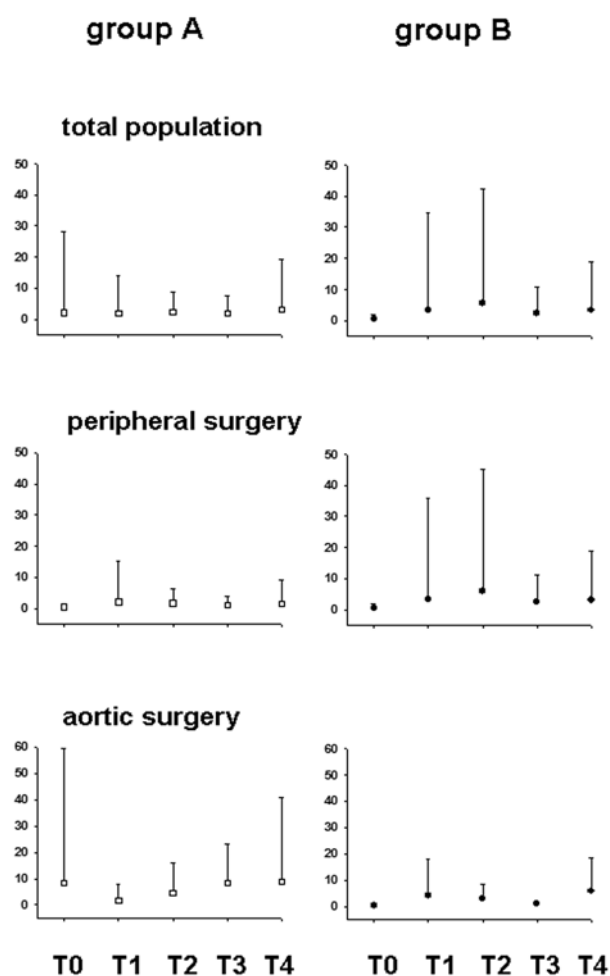


Fig. 1. — Serial postoperative troponin I levels (ng.mL<sup>-1</sup>). T0 = baseline, T1 = 24 hours, T2 = 72 hours, T3 = 120 hours, and T4 = 168 hours postoperatively. Group A = volatile anesthetic regimen, group B = non-volatile anesthetic regimen. For the sake of clarity, the standard deviation (SD) bars have been presented in only 1 direction. Data are means and SD.

Table 2 summarizes the incidence of the different cardiac adverse events. There appeared to be no differences in occurrence of postoperative cardiac events with regard to the anesthetic technique used in either the total population or in the subgroups of aortic and peripheral vascular surgery. Multivariate logistic regression analysis indicated that the choice between a volatile and a non-volatile based anesthetic regimen did not affect the incidence of postoperative cardiac events.

Postoperative troponin I levels are displayed in Figure 1. There was a transient increase in troponin I levels, which was more pronounced in the aortic surgery group than in the peripheral surgery group. Figure 2 shows the incidence of postoperative troponin I elevation for the three different cut-off values. The incidence of maximum postoperative troponin I levels was not different between the two

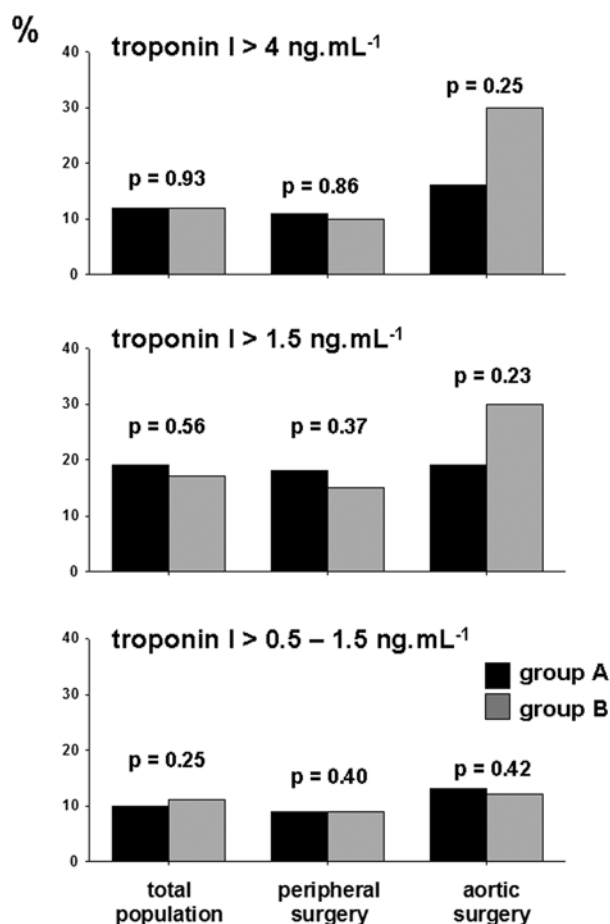


Fig. 2. — Incidence (%) of elevated maximum postoperative troponin I levels (ng.mL<sup>-1</sup>). Group A = volatile anesthetic regimen, group B = non-volatile anesthetic regimen.

groups in the total population and in the patients undergoing peripheral arterial surgery. In the patients undergoing aortic surgery, the incidence of elevated troponin levels greater than 1.5 and 4 ng.mL<sup>-1</sup> tended to be lower in group A than in group B.

## DISCUSSION

The present results did not show a statistically significant relationship between the use of a volatile anesthetic regimen and a lower incidence of postoperative cardiac events. However, in the setting of abdominal aortic surgery, a trend was apparent suggesting that in these high risk patients, the use of a volatile anesthetic regimen may help to reduce the incidence of postoperative elevated troponin I values.

Patients undergoing major vascular surgery are at increased risk to develop perioperative cardiac complications (1). Since preoperative coronary

revascularization did not seem to improve outcome after vascular surgery (3, 4), a number of perioperative pharmacological strategies have been proposed to decrease postoperative cardiac adverse events (5).  $\beta$ -blocking drugs,  $\alpha_2$ -adrenergic drugs and statins have been shown to be effective in reducing postoperative cardiac complications in vascular surgery patients (6-10). Another type of drugs that may have beneficial effects are the  $\text{Na}^+/\text{H}^+$  exchange type I inhibitors. The  $\text{Na}^+/\text{H}^+$  type I exchanger is involved in the regulation of the intracellular pH by exchanging intracellular protons for external sodium (24). In the presence of myocardial ischemia, the anaerobic glucose metabolism will reduce intracellular pH, which will activate the  $\text{Na}^+/\text{H}^+$  exchanger. This will result in an accumulation of intracellular sodium which in turn will activate the  $\text{Na}^+/\text{K}^+$  adenosine triphosphatase, leading to an increase in adenosine triphosphate consumption and depletion of cellular energy stores. Inhibition of the  $\text{Na}^+/\text{H}^+$  type I exchanger minimizes these changes and has been shown to reduce infarct size in animal models of ischemia-reperfusion injury (25, 26). However, despite this beneficial pharmacological profile and the promising experimental data, clinical studies failed to demonstrate a clinically relevant protection with this type of drugs against postoperative cardiac events in cardiac and vascular surgery patients (11, 27, 28).

Outcome after major vascular surgery has also been related to the anesthetic techniques used. Several studies have suggested that epidural anesthesia and analgesia may improve the outcome of major noncardiac surgery (29, 30). However, other studies have failed to demonstrate any efficacy for epidural anesthesia for the prevention of myocardial ischemia, myocardial infarction, and mortality (31, 32). It has been demonstrated in a cardiac surgical population that the use of a volatile anesthetic regimen might have cardioprotective effects. These cardioprotective effects were evident from a lower postoperative release of troponin I, improved early postoperative recovery of myocardial function, and decreased requirements for postoperative positive inotropic support (14-20). In addition, the intensive care unit length of stay and the probability of cardiac event-free survival appeared to be favorably influenced by the perioperative use of a volatile anesthetic regimen. No such data are available for other types of surgery in patients at risk for developing perioperative myocardial ischemia. Patients undergoing arterial vascular surgery are at particular risk for developing postoperative cardiac com-

plications (1), suggesting that these patients may benefit from potential cardioprotective properties of a volatile anesthetic regimen. Although the results of the present study were not indicative for such an effect, a trend was apparent suggesting that in these high risk patients, the use of a volatile anesthetic regimen may help to reduce the incidence of postoperative elevated troponin I values. Since several studies have related postoperative troponin levels to outcome and found that elevated troponin levels are associated with an increased incidence of adverse postoperative cardiac events (33-37), it might be interesting to explore this phenomenon further in sufficiently powered studies.

The data of the present study are in contrast to the more clear-cut cardioprotective effects of volatile anesthetic agents observed in the cardiac surgical setting. Several reasons can be invoked for this disparity. Cardiac surgery involves a constant and reproducible period of myocardial ischemia, resulting in a standardized ischemic insult. During vascular surgery, the occurrence and the possible extent of perioperative myocardial ischemia is unpredictable and therefore possible effects of cardioprotective strategies may be less straightforward. Several limitations of this study should indeed be considered when interpreting the results. The data were retrieved from the database of a phase II study that compared the  $\text{Na}^+/\text{H}^+$  exchanger type I inhibitor zonisipride to placebo on the occurrence of perioperative mortality and cardiac events within the first 30 postoperative days in subjects at high risk undergoing noncardiac vascular surgery. Accordingly, the methodology was designed to address that particular experimental question and not the issue of potential cardioprotective properties of different anesthetic regimens. One of the consequences is that the anesthetic regimens were not standardized, resulting in an important variability in the choice of the volatile and intravenous anesthetic drug used (halothane, enflurane, isoflurane, desflurane, sevoflurane, thiopental, etomidate, propofol, diazepam, midazolam) and in the modalities of administration (e.g. combined with locoregional techniques, co-administration of nitrous oxide), all of which may influence the extent of potential cardioprotective properties. In coronary surgery patients, the extent of cardioprotection with volatile anesthetic agents has been shown to be related to the modalities of their administration (17). Different dosage schemes and modalities of administration may thus affect the importance of the cardioprotective effects. Particularly, the fact that in many instances combined general and epidural

anesthetic techniques were used may have had an influence. It has indeed been suggested that the intraoperative combination of general and epidural anesthesia with continuing postoperative epidural analgesia might be beneficial in high risk patients undergoing major non-cardiac surgery (38). Finally, cardiac effects differ among the various volatile anesthetics, with the newer agents desflurane and sevoflurane having a better profile. The fact that a number of patients in the present study were anesthetized with older agents such as halothane and enflurane may also have affected the extent of possible cardioprotection. Another limitation is that the study was not powered to address issues related to potential cardioprotective properties of anesthetic agents; for instance, the group of abdominal aortic surgery only included 104 patients (62 in group A and 43 in group B). Despite these limitations, this study constitutes the first report on the occurrence of adverse cardiac events related to the choice of the anesthetic regimen in a larger population of arterial vascular surgery patients. The results of the present study should therefore primarily be interpreted as hypothesis-generating.

In conclusion, the results of this study suggest that potential beneficial effects on extent of postoperative myocardial damage in high risk patients undergoing arterial surgery will probably be more apparent in abdominal aortic surgery than in peripheral vascular surgery. Further sufficiently powered studies using a standardized anesthetic protocol should now be performed to definitively address this question.

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