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A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery

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Summary

A randomised study of 414 patients undergoing coronary artery surgery with cardiopulmonary bypass was conducted to compare the effects of a volatile anaesthetic regimen with either deesflurane or sevoflurane, and a total intravenous anaesthesia (TIVA) regimen on postoperative troponin T release. The primary outcome variable was postoperative troponin T release, secondary outcome variables were hospital length of stay and 1-year mortality. Maximal postoperative troponin T values did not differ between groups (TIVA: 0.30 [0.00–4.79] $ng.ml^{-1}$ (median [range]), sevoflurane: 0.33 [0.02–3.68] $ng.ml^{-1}$, and desflurane: 0.39 [0.08–3.74] $ng.ml^{-1}$). The independent predictors of hospital length of stay were the EuroSCORE ($p < 0.001$), female gender ($p = 0.042$) and the group assignment ($p < 0.001$). The one-year mortality was 12.3% in the TIVA group, 3.3% in the sevoflurane group, and 6.7% in the desflurane group. The EuroSCORE ($p = 0.003$) was the only significant independent predictor of 1-year mortality.

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Although experimental data have provided convincing evidence that volatile anaesthetics offer protection against the consequences of reversible myocardial ischaemia and reperfusion injury, the results from clinical studies in coronary surgery patients however, have been less consistent. When volatile anaesthetics were administered before a planned myocardial ischaemic event (preconditioning protocols) some studies indicated protective effects, as evidenced by a better preservation of postoperative myocardial function and/or less release of biochemical markers of myocardial damage, whereas others failed to confirm this [1]. A more consistent result with preservation of myocardial function and a lower postoperative release of markers of myocardial damage was only found in studies where the volatile agent was administered throughout the entire surgical procedure [2–9].

Whether such cardioprotective properties ultimately result in a better patient outcome still remains to be determined. While data from some studies have suggested a shorter hospitalisation period [10] and even a lower 1-year postoperative cardiovascular morbidity [11], this issue remains largely unresolved. Recently, three meta-analyses have been published including randomised trials comparing volatile with non-volatile anaesthesia in coronary surgery. Two of these grouped studies on all volatile anaesthetics including the older agents such as halothane, enflurane and isoflurane [12, 13]. Both meta-analyses indicated a better preservation of postoperative myocardial function and a lower postoperative troponin release with a volatile anaesthetic agent but no differences were observed in the incidence of postoperative mortality or myocardial infarction. The third meta-analysis included only studies using the newer volatile anaesthetic agents desflurane and sevoflurane [14]. Data from 22 studies in 1922 patients were reviewed. This meta-analysis demonstrated a reduced mortality and incidence of postoperative myocardial infarction with a volatile anaesthetic regimen, in addition to the beneficial on

postoperative myocardial function and troponin release. In contrast, data from a retrospective Danish database analysis, including 10 535 patients operated in three cardiac centers did not show any difference in overall postoperative mortality or myocardial infarction [15].

Taking into account the possible methodological limitations of meta-analyses of studies including a limited number of patients and of those with a retrospective design, the clinical implication of cardioprotection with a volatile anaesthetic regimen remains an unresolved issue, and is probably related to the multifactorial nature of the phenomenon of cardioprotection. To address this question we undertook a multicentre study in patients undergoing coronary artery surgery with cardiopulmonary bypass (CPB) anaesthetised with either a total intravenous anaesthetic regimen or a volatile anaesthetic based regimen. We hypothesised that the use of a volatile anaesthetic regimen is associated with less postoperative myocardial damage, as evidenced by a lower troponin T release. Secondary outcome variables were hospital length of stay and 1-year mortality.

Methods

The study was approved by all institutional ethical committees of the participating centres (see Appendix) and written informed consent was obtained. Patients scheduled to undergo elective isolated coronary artery bypass grafting with CPB were included unless there was documented evidence for a recent (< 7 days) or ongoing myocardial infarction. Patients with combined surgical procedures or redo operations were also excluded.

A computerised block randomisation in each centre was used to assign patients to one of the following three groups. A control group receiving total intravenous anaesthesia and analgesia throughout the operation (TIVA). The selection of intravenous anaesthetic drugs and doses was left entirely at the discretion of the attending clinician. The only absolute criterion for this group was that no volatile anaesthetic was used at any time during the procedure. The other two groups were subjected to treatment with either sevoflurane (SEVO) or desflurane (DES). There was no control over the selection of primary drugs used for induction and maintenance of anaesthesia. However, administration of volatile anaesthetic was strictly controlled according to the following regimen: starting at least 30 min before the initiation of myocardial ischaemia (aortic cross-clamping) all patients received the designated volatile anaesthetic at a minimum end-tidal concentration of 0.5 minimal alveolar concentration (MAC) (0.5 MAC measured at the outlet of the oxygenator of the extracorporeal circulation, when on CPB). This was continued over the entire ischemic period until at least 10 min after the beginning of reperfusion (release of the aortic cross-clamp). Thereafter, continuation of anaesthesia was left again to the preference of the attending anaesthesiologist. The responsible anaesthesiologist was allowed to make dose adjustments of baseline anaesthetic drugs to accommodate for the potential haemodynamic effects related to the additional use of volatile anaesthetics. With this experimental design, the primary characteristic difference of treatment vs control was the addition of a volatile anaesthetic at a dose of at least 0.5 MAC (sevoflurane or desflurane) to cover the pre- and intra-ischaemic episode, as well as the early reperfusion phase.

In principle, established institutional policies with regard to preoperative preparation and monitoring were respected. It was agreed however that according to the prevailing evidence for good clinical practice, beta-blockers and aspirin ought to be continued until the morning of surgery in all patients and that sulfonylureas had to be stopped and replaced by insulin when needed at the time of hospital admission. No attempts were made to control the choice of surgical technique, CPB management, type of cardioplegia technique or use of adjuvant cardioprotective drugs such as lidoflazine. Also the use of aprotinin was left to the discretion of the clinical teams.

The primary end-point of the study was myocardial cell damage quantified by the maximal postoperative troponin T release and the area under the curve of the cardiac troponin T blood concentrations over the first 24 h ($AUC_{24\ h}$). Blood samples were taken preoperatively and 0, 6, 12, 24, and 48 h following arrival on the intensive care unit for analysis of troponin T. Samples were centrifuged and frozen at −80 °C to be analysed at a central laboratory (Department of Biochemistry, Catholic University Leuven, method: Elecsys, Roche Basel, Switserland: normal range < 0.01 mg.l^{-1}, sensitivity > 0.01 mg.l^{-1}, intra- and inter-assay coefficient of variation < 5%). Secondary end-points were length of hospital stay and 1-year mortality.

Sample size estimation was based on previously published values for troponin T concentrations after coronary surgery [16]. Assuming a standard deviation of 2.5 μg.l^{-1} it was calculated that at least 120 patients were needed in each group to detect a 1 μg.l^{-1} difference in troponin T with a power of 0.8 and alpha set at 0.05.

Data were analysed on an intention-to-treat basis. Data between groups were compared using chi-squared or analysis of variance where appropriate. The independent risk factors for the different outcome variables (elevated troponin T level > 0.3 μg.l^{-1} [17], hospital length of stay longer than the median value of 10 days in the present study population, and 1-year mortality) were identified. For all patients the presence of the following variables was

noted: age > 70 years, EuroSCORE [18] > 2, female gender, body mass index > 30 kg.m^{-2}, ejection fraction < 50%, the presence of diabetes mellitus, daily intake of β-blockers, the intra-operative use of aprotinin, number of distal grafts > 2, and the group allocation. The relative risks for each of these independent variables on the different outcome variables were calculated. All the significant variables ($p < 0.05$) for each outcome variable were then included in a backward stepwise regression analysis to identify the independent risk factors for each of the different outcome variables. Survival curves were compared using the Logrank Test. Data were analysed using the SIGMASTAT 3.5 software package (Systat Software Inc, Richmond, CA and the GRAPHPAD PRISM™ software version 2.0 (Graphpad PRISM™, San Diego, CA). Data are expressed as mean (SD) or median [range] as appropriate. Statistical significance was accepted at $p < 0.05$.

Results

A total of 414 patients were recruited from two university hospitals and six large community hospitals within the Flemish Community and Brussels between August 2002 and April 2004. From these 145 subjects were randomised to receive TIVA, 132 received sevoflurane (SEVO) and 137 received desflurane (DES). No differences were observed between the three groups with regard to patient demographics or the most relevant peri-operative characteristics (Table 1). No protocol break was reported in any of the participating centres.

Table 1 Demographic data.

	TIVA group *n* = 145	SEVO group *n* = 132	DES group *n* = 137
Pre-operative data			
Gender; male/female %	117/28 81/19	108/24 82/18	112/25 82/18
Age; years	68 (9)	66 (9)	68 (9)
Weight; kg	77 (14)	78 (11)	79 (12)
Length; cm	169 (9)	171 (7)	172 (8)
Body mass index; kg.m^{-2}	27 (5)	27 (3)	27 (4)
Diabetes mellitus: *n*; %	34 (23)	31 (23)	32 (23)
Ejection fraction; %	67 (13)	67 (14)	67 (13)
Additive Euroscore; median [range]	4 [0–15]	3 [0–16]	4 [0–12]
Beta-blocking therapy: *n*; %	101 (70)	80 (61)	85 (62)
Intra-operative data			
Distal grafts; median [range]	3 [1–7]	3 [1–6]	3 [1–7]
Aprotinin	74 (51)	64 (48)	64 (47)

Data are mean (SD) unless noted otherwise.

Maximal postoperative troponin T values did not differ between groups (TIVA: 0.30 [0.00–4.79] ng.ml^{-1} (median [range]), SEVO: 0.33 [0.02–3.68] ng.ml^{-1}, and DES: 0.39 (0.08–3.74) ng.ml^{-1}). Area under the curve of troponin T release at 24 and 48 h are displayed in Fig. 1 (upper panel) and troponin T data at the different times of measurement are shown in Fig. 1 (middle panel). There was no statistically significant difference between groups for any of these variables. The lower panel of Fig. 1 depicts the individual maximal troponin T values for all patients in the different groups. It is apparent from this panel that the great majority of patients in this study population had troponin T levels below 1 ng.ml^{-1}. The relative risks for the different variables are summarised in Table 2. The only variable associated with an increased risk for an elevated postoperative troponin T value > 0.3 ng.ml^{-1} was more than two distal anastomoses.

The incidence of peri-operative myocardial infarction and new onset atrial fibrillation was not significantly different between the groups (peri-operative myocardial infarction: TIVA: 5.5%, SEVO: 2.2%, and DES: 2.2%; atrial fibrillation: TIVA: 17.9%, SEVO: 15.2%, and DES: 20.4%).

The median hospital length of stay was 12 days (range 7–87 days) for the TIVA group, 9 days (range 4–21 days) for the SEVO group and 9 days (range 4–30 days) for the DES group. The risk factors for an increased hospital length of stay (defined as an increased hospital length of stay longer than 10 days, which was the median length of stay in the present study population) are summarised in Table 3. The independent risk factors for an increased hospital length of stay identified by backward stepwise regression analysis were: an EuroSCORE > 2 ($p < 0.001$), female gender ($p = 0.042$) and the group assignment (TIVA, sevoflurane, desflurane) ($p < 0.001$).

One-year mortality was 12.3% in the TIVA group, 3.3% in the SEVO group and 6.9% in DES group. Mortalities at 1, 3, and 12 months are shown in Fig. 2. Comparison of mortality curves showed a different pattern between groups ($p = 0.034$). The relative risks of the different variables for 1-year mortality are summarised in Table 4. Backward stepwise regression analysis identified the presence of a EuroSCORE > 2 ($p = 0.003$) as the only significant independent predictor of 1-year mortality.

Discussion

We hypothesised that the use of the volatile anaesthetic agents sevoflurane and desflurane would be associated with less postoperative myocardial damage as assessed by postoperative troponin T values. This was not confirmed by our findings since postoperative troponin T values

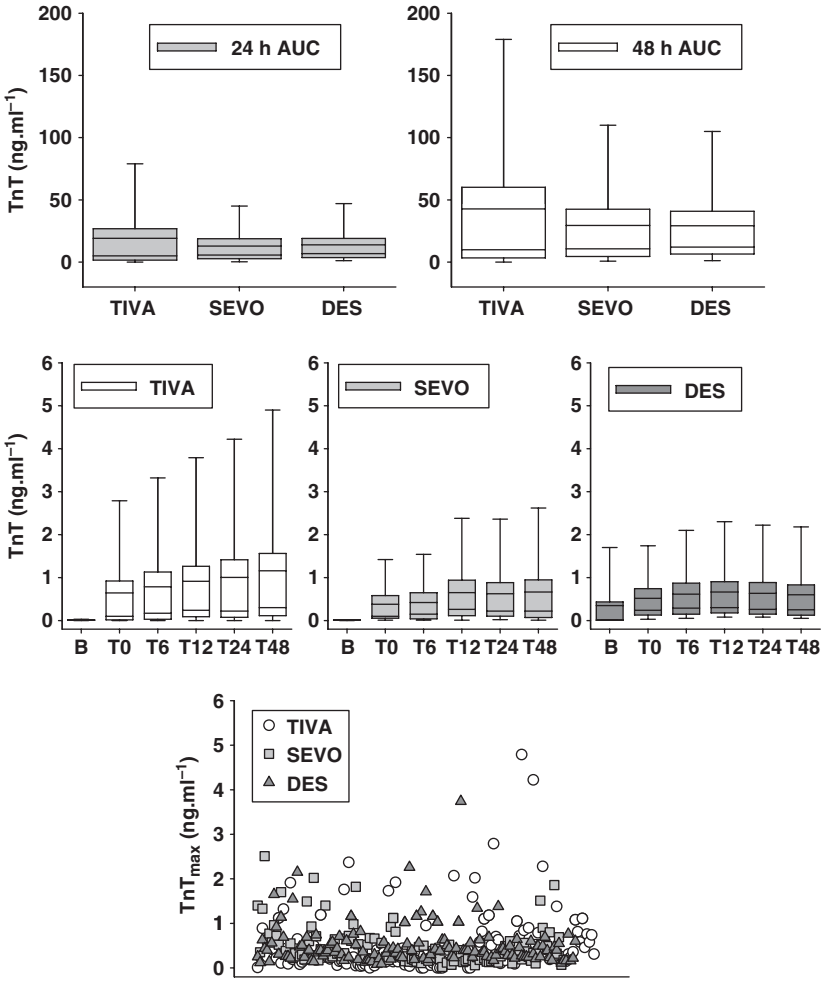

Figure 1 Upper panel: 24 and 48 h area under the curve (AUC) of the troponin T (TnT) values (median with 25% and 75% intervals and minimum and maximum values) in the three study groups (TIVA, total intravenous, SEVO, sevoflurane, DES, desflurane). Middle panel: Troponin T values ($ng.ml^{-1}$) (median with 25% and 75% intervals and minimum and maximum values) at the different sampling points in the three study groups. Lower panel: Maximal postoperative troponin T values ($ng.ml^{-1}$) of each individual patient included in the study.

Table 2 Relative risk of different variables for the occurrence of an elevated maximal postoperative troponin T value > 0.3 $ng.ml^{-1}$.

Variable	RR	95% CI	p
Age > 70 years	1.01	0.84–1.19	1
EuroSCORE > 2%	1.24	0.97–1.59	0.074
Ejection fraction < 50%	1.02	0.71–1.48	1
Female gender	1.03	0.83–1.28	0.796
Diabetes mellitus	1.18	0.98–1.42	0.109
BMI > 30 $kg.m^{-2}$	1.16	0.96–1.41	0.195
Chronic β-blocking therapy	0.97	0.82–1.16	0.831
Aprotinin	1.0	0.85–1.18	1
# distal grafts > 2	1.68	1.23–2.31	< 0.001
Volatile anaesthetic regimen	0.94	0.76–1.26	0.540

RR, relative risk; CI, confidence interval; p, statistical significance; BMI, body mass index; #, number.

Table 3 Relative risk of different variables for a median hospital length of stay longer than 10 days.

Variable	RR	95% CI	p
Age > 70 years	1.51	1.27–1.80	< 0.001
EuroSCORE > 2%	1.49	1.30–1.70	< 0.001
Ejection fraction < 50%	1.05	0.82–1.34	0.750
Female gender	1.54	1.17–2.03	< 0.001
Diabetes mellitus	1.01	0.84–1.21	1
BMI > 30 $kg.m^{-2}$	1.23	0.97–1.54	0.065
Chronic β-blocking therapy	0.95	0.81–1.13	0.585
Aprotinin	0.92	0.79–1.07	0.267
# distal grafts > 2	1.06	0.86–1.29	0.591
Volatile anaesthetic regimen	0.54	0.45–0.65	< 0.001

RR, relative risk; CI, confidence interval; p, statistical significance; BMI, body mass index; #, number.

were not significantly different between groups. These postoperative troponin T results appear contrary to previous reports that have observed a decreased postoperative troponin release when using a volatile anesthetic regimen [2–10]. The reason for these different findings remains to established. A striking observation is that the vast majority of patients displayed very low postoperative

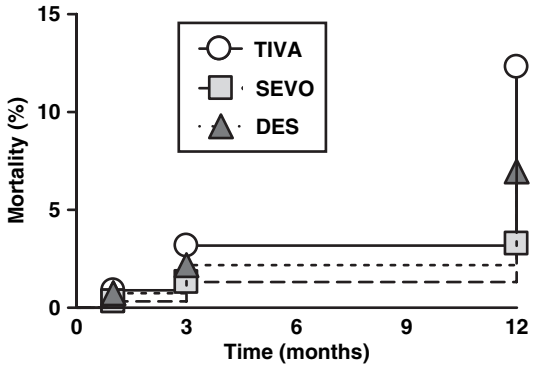

Figure 2 Mortality curves of the patients in the three different study groups.

Table 4 Relative risk of different variables for the 1-year post-operative mortality.

Variable	RR	95% CI	p
Age > 70 years	1.05	1.01–1.11	0.021
EuroSCORE > 2%	1.06	1.03–1.09	0.016
Ejection fraction < 50%	1.07	0.97–1.18	0.081
Female gender	1.07	0.99–1.16	0.018
Diabetes mellitus	1.02	0.97–1.08	0.375
BMI > 30 kg.m^{-2}	1.04	0.97–1.12	0.177
chronic β-blocking therapy	0.94	0.89–0.99	0.016
Aprotinin	0.97	0.93–1.02	0.137
# distal grafts > 2	1.62	0.38–6.94	0.748
Volatile anaesthetic regimen	0.95	0.90–0.99	0.018

RR, relative risk; CI, confidence interval; p, statistical significance; BMI, body mass index; #, number.

troponin T values (Fig. 2, lower panel). It is likely that in the absence of signs of major myocardial damage, the potential beneficial effects of a therapeutic action will be very difficult to demonstrate.

It is also apparent that the degree of cardioprotection offered by anaesthetic agents appears to be critically dependent on the modalities of administration. This is most obvious from the analysis of data of the different clinical preconditioning protocols. Indeed in these studies various results have been observed with some studies showing a protective action [19–27], whereas others failed to demonstrate such effect [28–30]. This is nicely demonstrated in a recent study by Fräβdorf et al. who demonstrated that one 5-min preconditioning period with 1 MAC sevoflurane did not decrease postoperatieve troponin I release compared to a control group without sevoflurane, but that two episodes of a 5-min sevoflurane 1 MAC preconditioning period significantly decreased postoperative troponin I release [31]. Bein et al. [32] recently reported that in patients undergoing coronary artery surgery, cardiac function was better preserved and myocardial damage was reduced in those who received sevoflurane in an interrupted manner before CPB, compared to patients who were treated before CPB with propofol and sevoflurane continuously. With regard to the effects of the administration of a volatile anaesthetic regimen during the CPB period, different results have been reported. While Nader et al. [33, 34] observed in coronary artery surgery patients, an inhibition of the inflammatory response, less evidence of postoperative myocardial dysfunction and lower troponin I values when sevoflurane 2% was added to the cardioplegia solution, Xia et al. [35] reported a lower oxidative stress response and lower postoperative troponin T values with a high dose propofol (120 μg.kg^{-1}.min^{-1}) scheme compared to a low dose propofol (60 μg.kg^{-1}.min^{-1}) scheme or isoflurane (1–1.5% end-tidal concentration) on CPB. Finally, De Hert et al. [6] observed that the cardioprotective properties of a volatile anesthetic regimen were most pronounced when administered throughout the entire procedure (before, during and after CPB).

Damage of myocardial cells results in the release of cardiac troponin I and T into the circulation. These cardiac troponins differ from troponins present in the skeletal muscles and in physiological conditions they are not detectable in the blood. Thus when measured in the plasma, both troponin I and T reflect myocardial damage with higher sensitivities and specificities compared to creatine kinase isoenzyme MB. It is considered that there is no discernible threshold below which an elevated value of cardiac troponin would be harmless and any amount of myocardial damage implies an impaired clinical outcome for the patients [36]. It is important to note that after cardiac surgery there is always some unavoidable tissue damage. Therefore troponins may be increased after reperfusion of the heart over values seen before surgery, and in those patients without any postoperative complications. Postoperative troponin release appears to be lower following off-pump compared to on-pump coronary surgery. Despite the controversy over the significance of troponin elevations after clinically uncomplicated and successful procedures, it is probable that less myocardial damage as detected by troponin release is beneficial for the patient. After elective percutaneous coronary interventions, only troponin increases more than eight times the upper reference limit seem to be associated with increased mortality in long-term follow-up. In patients who have a final diagnosis of peri-operative myocardial infarction, both troponin I and T values are significantly increased. Troponin T values tend to be less than 1 ng ml^{-1} in normal patients, however in patients who had a peri-operative myocardial infarction, the level seems to be invariably over 1, usually over 3, and occasionally over 10 ng ml^{-1} [37, 38]. It is difficult to

define an absolute cut off level. Carrier et al. [16] found troponin T levels higher than 3.4 $\mu g\,l^{-1}$ 48 h after CABG to show the best correlation with the diagnosis of peri-operative myocardial infarction whereas Bonnefoy et al. [17] defined the presence of a postoperative cardiac troponin T value of 0.3 $\mu g\,l^{-1}$ as the best cutoff value to discriminate between patients with and without major myocardial damage (new Q-waves on ECG) after coronary surgery with cardiopulmonary bypass. This latter value was also used in the present study as cutoff value to identify important postoperative myocardial damage.

In the design of the present study, a fixed minimal administration of the volatile anaesthetic agent was required, starting the agent (at least 0.5 MAC) at least 30 min before the initiation of myocardial ischaemia until at least 10 min after the start of reperfusion. However, there was no control over the selection and use of other anaesthetic drugs used for induction and maintenance of anaesthesia, before, during, and after CPB. This implies that a variety of baseline anaesthetic techniques (different associations intravenous – volatile agents vs total volatile) were present. Since, the extent of cardioprotection with volatile anaesthetic agents after coronary surgery seems related to the modalities of its administration, it is very possible that the lack of a real homogenous cardioprotective protocol (i.e. volatile anaesthetic throughout vs total intravenous throughout) could have masked potential protective effects. On the other hand, this is the first multicentre study including a large number of patients in whom a strict minimal protocol of administration of the volatile anaesthetic was applied within the normal daily clinical practice of cardiac anaesthesia in each participating centre. These results therefore underscore that the extent of cardioprotection may critically depend on the options in global peri-operative care of the cardiac patient.

The results of the present study should also be interpreted within the constraints of other methodological issues. In order to recruit sufficient patients and participating centres, the study was designed to interfere as little as possible with the routine procedures in each centre. This implies that surgical techniques (intermittent aortic cross-clamping vs. continuous cross-clamping) and additional peri-operative measures (choice of the cardioplegic solution, use of corticosteroids, aprotinin, lidoflazine, and others) were left at the discretion of the individual anaesthesiologist and surgeon. It is possible that this variability in individual techniques introduced a number of confounding factors that influenced the results. Some intravenous drugs may interfere with some of the mechanisms involved in anaesthetic cardioprotection. Another point relates to the risk factors included in the present analysis. We focused on those variables that have been shown to potentially influence myocardial damage and outcome after cardiac surgery and that were routinely collected in all participating centres. This implies that potential influences of other variables such as concomitant medication (statins, calcium channel blockers, α_2-agonists and others) or local peri- and postoperative protective strategies may have remained undetected. However, the primary goal of the present study was to determine whether the use of a volatile anaesthetic in the course of coronary surgery with CPB would affect postoperative troponin T release and hospital length of stay, independent of other local strategies.

We used the EuroSCORE [18] to quantify the degree of comorbidity and to estimate the peri-operative risk. The EuroSCORE is one of the most frequently used scores for assessing the peri-operative risk during cardiac surgery but it is known to overestimate the peri-operative risk [39, 40].

In conclusion, we were unable to demonstrate a lower postoperative troponin T release when using a volatile anaesthetic regimen according to the protocol of a minimal administration of 0.5 MAC started at least 30 min before the initiation of myocardial ischaemia until at least 10 min after the start of reperfusion. Hospital length of stay however was reduced and mortality curves differed between groups. Further studies are necessary to address the potential influence of choices of anaesthetic regimens on long-term postoperative outcome.

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Appendix

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