Cardiac Troponins and Volatile Anesthetics in Coronary Artery Bypass Graft Surgery: A Systematic Review, Meta-Analysis and Trial Sequential Analysis.

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ABSTRACT

**Background:** Volatile anesthetics are reported in experimental animal studies to protect the myocardium against the effects of acute ischemia-reperfusion injury (IRI) by reducing infarct size. The cardioprotective effect in the clinical setting of coronary artery bypass graft (CABG) surgery, where the heart is subjected to global IRI, remains controversial.

**Objective:** To demonstrate that clinical studies investigating the cardioprotective effect of volatile anesthetics on cardiac troponins in CABG are no longer warranted. Secondly we investigated the effect of volatile anesthetics on cardiac enzymes in off-pump cardiac surgery.

**Design:** Systematic review of randomized clinical trials, meta-analyses and trial sequential analysis.

**Data Sources:** Trials between January 1985 and March 2015 were obtained from electronic databases (Medline, Embase), Cochrane Controlled Trial Register, abstracts from major anesthesiology and cardiology journals and reference lists of relevant randomized trials and review articles.

**Eligibility Criteria:** Relevant randomized clinical trials were included. We investigated the effect of volatile anesthetics both in off-pump CABG and on-pump surgery with respect to troponin release (peak-postoperative, both cTnI and cTnT) and performed two separate meta-analyses. Trial sequential analysis was made to overcome the weakness of type-1 error associated with repeated meta-analyses.

**Results:** In 29 studies, 2496 patients were pooled for the meta-analysis. Outcome significantly favors volatile anesthetics peroperative use over non-volatile anesthetics during on-pump CABG surgery in regard to peak-postoperative cTnI: -1.028 μg/L (standard mean difference, 95%CI: -1.362 to -0.695 μg/L; \( p < 0.001 \)). Meta-analysis of 10 off-pump studies showed no difference in peak-postoperative cTnI: -0.370 μg/L (standard mean difference, 95% CI: -0.876 to 0.135 μg/L; \( p = 0.151 \)). TSA showed a required information size in on-pump surgery of 1062 patients. For off-pump surgery it is 1697 and has not yet been reached.
Conclusion: Volatile anesthesia in elective CABG surgery reduces peak-postoperative troponin level when compared to non-volatile anesthesia. The effect is not seen in off-pump surgery.
INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of death and disability worldwide. For patients with multi-vessel CAD, the treatment of choice is coronary revascularization by coronary artery bypass graft (CABG) surgery. Due to several factors including the aging population, an increase in co-morbidities such as diabetes, hypertension and renal failure, and the growing need for concomitant valve surgery, higher-risk patients are undergoing CABG surgery. The consequence of this is an increased risk of perioperative myocardial injury (PMI) and worse clinical outcomes. The process of reperfusion can itself cause myocardial injury. Currently there is no effective therapeutic intervention to protect the heart against ischemia-reperfusion injury (IRI). Novel cardioprotective therapies are therefore required to protect the heart against acute global IRI in order to limit the extent of PMI, preserve cardiac function, and improve morbidity and mortality in this patient group. In this regard, volatile anesthetics such as isoflurane, sevoflurane, and desflurane, have been reported in experimental animal studies to protect the myocardium against acute IRI as evidenced by reductions in myocardial infarct size. However, whether volatile anesthetics are cardioprotective in the clinical setting of CABG surgery, during which the heart is subjected to acute global IRI, has not been resolved. A substantial number of these clinical trials have used surrogate markers of cardioprotection such as serum cardiac enzymes (CK-MB and Troponin T/I, cTnT/cTnI) to quantify the extent of PMI sustained during surgery. The magnitude of PMI can be quantified by measuring perioperative levels of serum cardiac enzymes such CK-MB, Troponin-T, or Troponin-I - the release of which has been associated with worse clinical outcomes following CABG surgery. Newall et al found that a rise in serum CK-MB isoenzyme of 3-6 times upper reference limit (URL) (hazard ratio, HR 2.1) a rise of six or more times the URL (HR 5.0) were independently associated with increased one-year mortality. Croal et al found that 24 hour serum levels of Troponin-I were independently predictive of mortality at 30 days (odds ratio 1.14 per 10 g/L), 1 year (odds ratio 1.14 per 10 g/L), and at 3 years (odds ratio 1.07 per 10 g/L). Soraas et al reported that serum levels of Troponin-T measured at 7, 20, 44 hours were independently predictive of long-term mortality (HR 1.31). Finally, Wang et al found that an increase in high-sensitive Troponin-T at 12-24 hours of more than 10-times the
99th percentile URL with ECG and/or echocardiographic criteria of MI predicted 30-day (HR, 4.92) and medium-term mortality (HR 3.44).

The majority of these studies have shown volatile anesthetics to attenuate PMI when compared to non-volatile anesthesia. A number of meta-analyses have confirmed this cardioprotective effect of volatile anesthetics though they are likely insufficiently powered and the effect of volatile anesthetics on clinical outcomes has been inconclusive. A large adequately powered prospective randomized control trial is required to conclude whether volatile anesthetics when compared to non-volatile anesthesia can improve clinical outcomes in patients undergoing CABG surgery. In this study we have undertaken a systematic review of peak serum cardiac Troponin levels in clinical studies, which have investigated the cardioprotective effect of volatile anesthetics in elective CABG surgery using PMI as the endpoint. Troponin was chosen as a surrogate marker because it is a sensitive marker of myocardial damage. Moreover whether off-pump coronary artery surgery poses a different myocardial ischemic profile to on-pump intraoperatively is unclear [9], and has not previously been assessed with respect to volatile anesthetics effect on PMI.

There is an increased risk of a type 1-error arising from repetitive testing and analysis of sparse data in the substantial number of meta-analyses that have been performed[10]. We undertook a trial sequential analysis (TSA) to overcome the problem of the repeated meta-analyses [11].

The overall objective of our study was to demonstrate that clinical studies investigating the cardioprotective effect of volatile anesthetics on serum cardiac enzymes in CABG patients are no longer warranted. Secondly we investigated the cardioprotective effect of volatile anesthetics on serum cardiac enzymes in off-pump cardiac surgery (OPCAB/MIDCAB) as a subpopulation.

**METHODS**

**Systematic search**

We conducted a systematic literature search for all relevant randomized clinical trials, in all languages. Relevant trials between January 1985 and March 2015 were obtained from the following sources: electronic databases (Medline and EMBASE), the Cochrane
Controlled Trial Register, abstracts in major journals related to anesthesia and cardiac surgery, and reference lists of relevant randomized trials and review articles. The following medical subject headings (MeSH) electronic search was conducted in Medline using a search string, modified from Bignami, et al. \cite{12} (see supplementary).

**Inclusion and exclusion criteria**

We included all trials of adult cardiac patients undergoing: CABG surgery including both on-pump and off-pump; CABG in combination with valve replacement/repair; and one congenital heart surgery trial. All three authors independently screened all of the abstracts produced by the searches to identify eligible studies. Trials not using the cardio-pulmonary bypass machine (i.e. OPCAB or MIDCAB procedures) were selected for a separate meta-analysis and were not included in the meta-analysis of volatile anesthetics in peak postoperative troponin-release after CABG.

Studies were included irrespective of the timing or interval of the volatile anesthetic used for cardioprotection. No subgroup-analysis of volatile administration were made. Previously it has been shown that there were no significant difference between administration of volatile anesthetics pre- per- or postoperative and endpoints as myocardial ischemia, troponin-I level and ICU length of stay \cite{1}. Halothane and enflurane studies were excluded because they were considered not to reflect the current clinical pattern of use, thus restricting the included studies to isoflurane, desflurane and sevoflurane. Studies that did not include both a volatile anesthetic group and a non-volatile control group were excluded. Valve surgery alone was omitted since this group is heterogeneous with regard to myocardial ischemia. Remote ischemic preconditioning (‘RIPC’) as a comparator was excluded. We excluded trials not reporting data in English language after direct communication. In studies in which there was more than one volatile or non-volatile group, these groups were combined for the pooled analyses.

**Quality scoring**

The Jadad scale\cite{13} was used to quantify individual study quality (validity) using five criteria (one point each): (i) proper randomization, (ii) double blind, (iii) withdrawals documented, (iv) randomization adequately described, (v) blinding adequately described. The Jadad score is an instrument to assess the quality of reports of RCT’s
and it was used to assess the risk of high or low probability of bias, which in turn was used to meet the requirements for the Trial Sequential Analysis.

**Data analyses**

This study focused entirely on examining the peak post-operative release of cardiac troponins (both cTnI and cTnT) as this reflects the extent of PMI and the clinical presentation of ischemia shows considerable heterogeneity in the surrogate markers (clinical signs, ST-segment change, etc.). For studies where the median and range were reported, the mean and standard deviation (SD) were estimated by using the O’Rourke method\(^{[14]}\) whereby the median was used as the estimate of the mean, and the SD was a quarter of the range (SD equals the interquartile range multiplied by 1.35). In order to standardize cTnT and cTnI measurements to allow pooling, cardiac troponin-T concentration was converted to troponin-I concentration using a conversion factor of 2/0.65, based on the ratio of the upper limit of their respective reference ranges, as has previously been used\(^{[1]}\). A Forest plot was performed using the pooled troponin means and SD to form an estimate of standardized mean difference.

Under the fixed effects model, it is assumed that the studies share a common true effect, and the summary effect is an estimate of the common effect size. Under the random effects model, the true effects in the studies are assumed to vary between studies and the summary effect is the weighted average of the effects reported in the different studies\(^{[15]}\). The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree when there is no heterogeneity. When heterogeneity is present (see later) the random effects model is the preferred model.

\(I^2\) is the percentage of observed total variation across studies that is due to real heterogeneity rather than chance. It was calculated as \(I^2 = 100 \% \times (Q - df)/Q\), where \(Q\) is Cochran's heterogeneity statistic, and \(df\) the degrees of freedom. Negative values of \(I^2\) are put equal to zero so that \(I^2\) lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity\(^{[16]}\). We used MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium; [http://www.medcalc.org; 2014](http://www.medcalc.org)) in the collation, analysis, interpretation and presentation of data.
**Trial Sequential Analysis (TSA)**

Repeated updates (sequential multiplicity) and sparse data increase the risk of random error [17]. TSA is a method of meta-analysis that aims to correct for this increased risk [18–21]. Similar to monitoring boundaries for interim analyses in single trials, TSA provides an estimate of the required information size (RIS) for meta-analysis combined with monitoring boundaries used as thresholds for statistical significance.

The less data that have accumulated, the more conservative the TSA boundaries, making it less likely to declare statistical significance before the RIS has been reached. Similar to a sample size calculation for a single trial, estimating RIS involves a calculation that includes both type 1-error, type 2-error, the control event proportion, and the effect size. The calculation for RIS also requires an estimate of heterogeneity; if more heterogeneity is present, RIS increases [22]. In the current TSA, we estimated the RIS using 0.05 for type 1-error, 0.20 for type 2-error, the control event proportions calculated from the non-volatile anesthetic groups in all included trials. The effect size was estimated from the included trials with a low risk of bias, derived from the Jadad scale evaluation.

We used the $D^2$ (diversity) [23] present in the included trials as the estimate for heterogeneity. The TSA is interpreted by examining the boundaries and whether the cumulative meta-analysis (Z-score line) has crossed them. Web-based free TSA analysis software used in the current study was obtained from the Copenhagen Trials Unit. ([http://www.ctu.dk/tools-and-links/trial-sequential-analysis.aspx](http://www.ctu.dk/tools-and-links/trial-sequential-analysis.aspx))

**RESULTS**

**Retrieved and analyzed trials**

Our literature search from January 1985 - March 2015 combined with the studies included in Symons and Myles’ original meta-analysis [1] identified 75 studies eligible for inclusion and detailed assessment. Of these, 7 were excluded, as they were non-human studies, yielding 67. Of these, a further 7 were not randomized clinical trials, leaving 60 RCTs. OPCAB/MIDCAB was used in 11 trials [24–34] (obs + conzen et al evt. + Bein et al), which were then isolated for a separate meta-analysis, one of these were
excluded due to missing mean/median\cite{25}. Further we excluded 1 (congenital heart disease\cite{35}), 4 heart valve replacement (2 AVR + 2 MVR)\cite{36-39}, 6 non-cardiac\cite{40-45}, 2 PCI stenting procedure\cite{46-47} and 1 trial was a direct comparison (isoflurane vs. sevoflurane) with no non-volatile comparator\cite{48}. Of the remaining 36 studies, 3 had no English language data after direct communication (Russian\cite{49-50}, Turkish\cite{51}), 4 had RIPC or no nonvolatile comparator, or no relevant cardiac troponin outcomes were reported\cite{52-55}, and this left 29 studies\cite{56-84}(obs – Conzen et al. evt – Xu et al, evt. + Bein et al), comprising 2496 patients included in the meta-analysis. A flow chart illustrating this process is given in figure 1.

[Fig. 1] Flow diagram of the inclusion/exclusion of randomized clinical trials retrieved from database search.

The Jadad scores evaluating validity of the included trials are given in Table 1a and 1b.

[Table 1a and 1b] Description of the studies included in the two meta-analyses. (Standard Deviation (SD))

Trials with a Jadad score 3 or above were included in the Trial Sequential Analysis of on-pump CABG surgery, whilst scores < 3 were excluded from the TSA.

**Volatile Anesthetics during on-pump CABG: Meta-analysis**

The meta-analysis (Fig. 2 and table 2) resulted in a significant outcome favoring volatile anesthetic use (at all times; iso- sevo- and desflurane) over non-volatile anesthetic during on-pump CABG surgery with respect to peak post-operative cardiac troponin-I serum levels (Fixed Effects -0.557 $\mu$g/L standardized mean difference (95% CI: -0.640 to -0.473 $\mu$g/L) P<0.001; Random Effects -1.028 $\mu$g/L standardized mean difference (95%CI: -1.362 to -0.695 $\mu$g/L) P<0.001). Back conversion to troponin-T\cite{1}, this corresponds to -334.1 ng/L (95%CI: -442.65 to – 225.88 ng/L). The test for heterogeneity ($I^2$) showed significant inconsistency in the 29 analyzed randomized clinical trials (92.66%) (95%CI: 90.54 to 94.30), implicating that the Random Effects result above should be chosen over the Fixed Effects model when interpreting the results.
Meta-analysis of Cardiac Troponin in on-pump CABG surgery in 2496 patients in 29 RCTs.

Meta-analysis: continuous measure

Volatile Anesthetics during off-pump CABG: Meta-analysis

Eleven RCTs were separately analyzed from the main meta-analysis, because they consisted of an intervention-control comparison of peak postoperative troponin levels after off-pump (OPCAB) or minimally invasive direct angioplasty coronary procedures (MIDCAB). One was excluded because no standard deviation was present. The test for heterogeneity ($I^2$) showed significant inconsistency in the 10 analyzed randomized clinical trials (87.01%) (95%CI: 78.09 to 92.30) implicating that the Random Effects result should be chosen over Fixed Effects model. The meta-analysis did not reach a statistical significance level favoring either nonvolatile (control), or volatile anesthetic (intervention) with respect to peak post-operative cardiac troponin-I serum levels. Random Effects $-0.370 \, \square\text{g/L}$ standardized mean difference (95% CI: $-0.876$ to $0.135 \, \square\text{g/L}$) (Fig. 3)

Meta-analysis of Cardiac Troponin in OPCAB/MIDCAB.

Meta-analysis: continuous measure, OPCAB/MIDCAB

Trial Sequential Analysis

Seven trials were ignored in Interim Looks by the software application due to low information use ($<0.1\%$) in the Futility analysis: Belhomme et al. (1999) $^{[56]}$, De Hert et al. (2002) $^{[59]}$, Conzen et al. (2003) $^{[61]}$, Nader et al. (2004) $^{[63]}$, Kawamura et al. (2006) $^{[70]}$, Amr et al. (2010) $^{[79]}$ and Sirvinskas et al. (2015) $^{[84]}$. The cumulated Z-score shows, that the required information size (RIS) was 1062 patients, the point at which the Z-line crosses the 0.05% significance boundary for accumulated test results under due alpha-spending limitations (Fig. 4A). The Futility boundary for the current study is achieved in 3018 patients.
DISCUSSION

The major findings of our study are:

(1) By meta-analysis we find volatile anesthetics used in elective coronary artery bypass graft surgery reduces post-operative peak serum cardiac troponin enzyme levels by approximately 8% when compared to non-volatile anesthesia. The effect is seen in on-pump but not in off-pump bypass surgery. The novel aspect of this report is the analysis of the results of 10 OPCAB/MIDCAB studies (total n=573 subjects). However, data in this meta-analysis were not sufficiently powered to assess the influence of volatile anesthetics on peak postoperative cTnI/TnT.

(2) The pooled Trial Sequential Analysis of on-pump CABG shows conclusively that no further trials that evaluate surrogate markers of ischemia are necessary because the required information size (RIS) is approximately 1000 patients, and this was reached in late 2006. Thus further studies on precisely this question appear unnecessary, as the current level of clinical evidence has almost attained futility. However, further investigations appear warranted for volatile anesthetics in off-pump CABG surgery where RIS is estimated to 1697, a higher number of patients due to inconsistency in the findings of present studies.
Volatile anesthetic conditioning (VAC) is repeatedly proposed to hold clinical potential to mitigate the irreversible myocardial injury sustained by acute ischemia- and reperfusion injury. The anti-ischemic effects of volatile anesthetics were first proposed by Bland & Lowenstein (1976)[85], who found evidence that experimental myocardial ischemia in canine hearts was decreased by halothane. In 1997, two independent groups first proposed the pharmacologic induction of preconditioning with the volatile anesthetic, isoflurane independently of each other[86-87]. Volatile anesthetics appear to be consistently superior to intravenous anesthetics with regard to experimental myocardial protection, but clinical VAC remains divisive several decades after it was first proposed. Ultimately, a large adequately powered prospective randomized control trial is still required to determine whether volatile anesthetics when compared to non-volatile anesthesia can improve clinical outcomes in patients undergoing CABG surgery. The relative reduction in peak postoperative enzyme release carries with it no immediate clinical consequence; however, it is a surrogate marker for morbidity and mortality in patients undergoing open heart surgery[88-91].

Volatile anesthetics have not been sufficiently investigated in conjunction with coronary stenting procedures. A recent study found that sevoflurane administration during primary PCI did not reduce infarct size but there was a trend towards a reduction in infarct size among patients with anterior myocardial ischemia and sevoflurane was associated with improvement in ST-segment resolution[47].

Increased postoperative troponins occur after virtually all open-heart surgery, it not only reflects myocardial infarction but also myocardial cell injury caused by reperfusion, surgical trauma, defibrillation, operation time. Lehrke et al.[88] found a TnT-concentration > 0.46 μg/L 48 h postoperatively was associated with a 6.7-fold higher long term risk for subsequent cardiac death and a 11-fold higher risk for severe postoperative heart failure requiring mechanical support. Further Fellahi et al.[90] found that a high postoperative peak TnI (23.8 ng/ml; range, 13.4-174.6) was associated with increased long-term mortality and mortality from cardiac cause.

A lower peak troponin-T level by 350 ng/L would therefore be expected relevant in reducing morbidity and mortality. Still factors as cardiac function, clinical signs and
length of ICU-stay should be considered as relevant parameters in the overall evaluation of VAC.

Some researchers argue that the true VAC effect results in 30-40% reductions if enzyme release is plotted over time (area-under-the-curve, AUC) and that this is a better estimate, because it better quantifies the extent of PMI over that particular period[92]. No attempt was made to compare volatile anesthetics within-group; for that, the pooled data remain too sparse. There could be differences between anesthetics used to prevent irreversible myocardial injury; e.g., isoflurane may be more effective than sevoflurane as some experimental results point to. This is despite differences in relative potency. Further comparative trials would be needed to resolve this and other relevant issues, e.g. the question of dose-response, timing and duration of volatile anesthetic exposure. The result of the meta-analysis did not take into account the considerable heterogeneity associated with these factors. Conversely, experimental VAC indicates that even low doses can have an effect. [93-94].

A recent Bayesian network meta-analysis supports the hypothesis that volatile anesthetics are superior to TIVA-based anesthesia to improve survival in cardiac surgery but data could not support the theory that one volatile agent was more beneficial than another[95]. The overall results of this meta-analysis are statistically fragile as there were only 68 deaths and statistical significance is reached only when combining all volatile agents and comparing them with total intravenous anesthesia.

This study has potential weaknesses inherent in meta-analysis. Being able to pool many smaller studies increases the power of the analyses, but varied clinical practices and lack of uniformity of definition and reporting of endpoints limit the certainty of our findings. The TSA-analysis is an attempt to adjust this using a more conservative estimate.

The results need to be interpreted taking into account the different practices with regard to anesthesia, surgery and ICU-management of CABG patients between various institutions and development in methods over time. Much has changed since 1985 in regard to surgical technique, intraoperative and postoperative care. A more modern technique probably decreases the amount of total troponin thereby minimizing the difference between groups. This uncertainty is best dealt with by a large prospective randomized trial in order to establish the true role of volatile anesthetic agents in
myocardial protection. We believe such a trial is warranted, and recommend that common endpoint definitions should be established. A most relevant multicentre Randomized Controlled Trial is ongoing\cite{96}. In terms of statistical power it looks good. As for the estimate of the gains with expected outcome, our estimate is about a 10 per cent troponin reduction, so a 2 to 3 per cent mortality reduction does not seem unlikely in the ongoing trial. This statement is based on the consequence of a reduction of 2-300 ng/L (cTnt) relative to the control group, so in conclusion, a reduction in both morbidity and mortality could surely be expected in a trial of over 1000 patients.

The result of the current investigation cannot freely be extrapolated from elective CABG to valve surgery or to emergency bypass surgery, since Jakobsen \textit{et al.}\cite{97} found in a retrospective study in 10,535 patients that overall mortality was reduced by volatile anesthetics in elective surgery, but not in emergency surgery, probably due to hemodynamic instability.

The relative reduction is less than the 50-60\% reduction in myocardial infarct size often reported in experimental studies\cite{98-99} and could be due to several factors: for instance, the effects of age, comorbidity and ECC. Guidelines have been made to improve the lack of animal disease models that considers these factors (Translating novel strategies for cardioprotection: the Hatter Workshop Recommendations, Hausenloy \textit{et al.})\cite{100}.

Although the mechanisms of action remain unclear, volatile anesthetics act in similar ways to ischemic preconditioning by activating a number of known mechanisms including intracellular salvage kinase pathways, endothelial NO production, modulation of calcium homeostasis and prevention of mitochondrial permeability transition pore opening\cite{98}. Overall, the effects of volatile anesthetics in preconditioning are triggered by multiple pathways and has been reviewed detailed elsewhere\cite{93-94,101}.

There is an overlap between our meta-analysis and Symons and Myles of 10 studies. 15 of our included studies are published in 2006 or thereafter. Further we made separate analysis for OPCAB/MIDCAB procedures and excluded studies with combined CABG and valve surgery and with halotane and enflurane. The present study is larger and more adequately powered concerning troponin than Symons and Myles 2006 analysis. This is what they enquired back then.

In conclusion, we demonstrated that a systematic review, meta-analysis and trial sequential analysis of all existing clinical CABG trials point unquestionably towards
volatile anesthetics reduce the level of serum markers of myocardial injury. Moreover, the total volume of existing evidence supporting this result goes beyond adequacy, and further studies will be bound futile.

The overall objective of our study was to demonstrate that clinical studies investigating the cardioprotective effect of volatile anesthetics on serum cardiac enzymes in CABG patients are no longer warranted; thereby supporting the notion that a prospective investigation of volatile anesthetics in a large clinical outcome randomized clinical trial should be the priority. Further, a potential effect of volatile anesthetics in OPCAB/MIDCAB still needs to be clarified.

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References

5. Croal BL, Hillis GS, Gibson PH et al. Relationship between postoperative cardiac troponin I levels and outcome


42. Lurati Buse GA, Schumacher P, Seeberger E, et al. Randomized Comparison Of Sevoflurane Versus Propofol To Reduce Perioperative Myocardial Ischemia In Patients


