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

Therese S. Straarup,
Department of Anesthesia, Viborg, and Department of Anesthesia, Aarhus University Hospital Denmark (Corresponding author. Contact: therese.straarup@gmail.com)

Derek J. Hausenloy
The Hatter Cardiovascular Institute, University College London, United Kingdom

Jens K. Rolighed Larsen
Institute of Clinical Medicine, Aarhus University Hospital and Department of Anesthesia, Viborg and Silkeborg, Denmark

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 □g/L (standard mean difference, 95%CI: -1.362 to -0.695 □g/L) $p<0.001$). Meta-analysis of 10 off-pump studies showed no difference in peak-postoperative cTnI; -0.370 □g/L (standard mean difference, 95% CI: -0.876 to 0.135 □g/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[1]. 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[2], Troponin-T[3], [4] or Troponin-I [5], [6] - the release of which has been associated with worse clinical outcomes following CABG surgery. Newall et al[7] found that a rise in serum CK-MB isoenzyme of 3-6 times upper reference limit (URL0 (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 [5] 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[8] 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[4] 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.* [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 [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[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*) 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*)

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[25]. Further we excluded 1 (congenital heart disease[35]), 4 heart valve replacement (2 AVR + 2 MVR)[36-39], 6 non-cardiac[40-45], 2 PCI stenting procedure[46-47] and 1 trial was a direct comparison (isoflurane vs. sevoflurane) with no non-volatile comparator[48]. Of the remaining 36 studies, 3 had no English language data after direct communication (Russian[49-50], Turkish[51]), 4 had RIPC or no nonvolatile comparator, or no relevant cardiac troponin outcomes were reported[52-55], and this left 29 studies[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 □g/L standardized mean difference (95% CI: -0.640 to -0.473 □g/L) P<0.001; Random Effects -1.028 □g/L standardized mean difference (95%CI: -1.362 to -0.695 □g/L) P<0.001). Back conversion to troponin-T[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.

[Fig. 2] ***Meta-analysis of Cardiac Troponin in on-pump CABG surgery in 2496 patients in 29 RCTs.***

[Table 2] ***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[33]. 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 □g/L standardized mean difference (95% CI: -0.876 to 0.135 □g/L) (Fig. 3)

[Fig. 3] ***Meta-analysis of Cardiac Troponin in OPCAB/MIDCAB.***

[Table 3] ***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.

[Fig. 4] ***Trial Sequential Analysis of the meta-analyzed data. The cumulative meta-result (Z-curve, blue) is viewed over the course of patient inclusion. The 0.05 continuous alpha-spending boundaries (solid, red) is crossed by the Z-curve near 1000 included patients. The projected Futility boundary is shown (broken line, red) and includes possible no-result near the zero***

Trial Sequential Analysis, OPCAB/MIDCAB

No trials were ignored in Interim Looks by the software application due to low information use (<0.1%) in the Futility analysis. The required information size was estimated to 1697 patients. Conzen *et al.* (2003) [61]???

[Fig. 5] ***Trial Sequential Analysis of the meta-analyzed OPCAB-data.***

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 asses 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[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 *et al.*[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[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 *et al.*)[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[98]. Overall, the effects of volatile anesthetics in preconditioning are triggered by multiple pathways and has been reviewed detailed elsewhere[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 futility.

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.

ACKNOWLEDGEMENTS

1. Assistance with the article: None declared.

2. Financial support and sponsorship: None declared.

3. Conflicts of interest: None declared.

4. Presentation: Preliminary data was presented as a poster and a oral presentation at the annual meeting of DASAIM (Danish Association of Anesthesiology and Intensive Care Medicine) in 2014.

References

1. Symons JA, Myles PS. Myocardial Protection With Volatile Anesthetic Agents During Coronary Artery Bypass Surgery: A Meta-Analysis. BJA 2006; 97(2): 127–36.
2. Brener SJ, Lytle BW, Schneider JP et al. Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. J Am Coll Cardiol 2002;40(11):1961-1967.
3. Mohammed AA, Agnihotri AK, van Kimmenade RR et al. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. Circulation 2009;120(10):843-850.
4. Wang TK, Stewart RA, Ramanathan T, Kang N, Gamble G, White HD. Diagnosis of MI after CABG with high-sensitivity troponin T and new ECG or echocardiogram changes: relationship with mortality and validation of the universal definition of MI. Eur Heart J Acute Cardiovasc Care 2013;2(4):323-333.
5. Croal BL, Hillis GS, Gibson PH et al. Relationship between postoperative cardiac troponin I levels and outcome

of cardiac surgery. Circulation 2006;114(14):1468-1475.

6. Muehlschlegel JD, Perry TE, Liu KY et al. Troponin is superior to electrocardiogram and creatinine kinase MB for predicting clinically significant myocardial injury after coronary artery bypass grafting. Eur Heart J 2009;30(13):1574-1583
7. Newall N, Oo AY, Palmer ND et al. Intermediate and high peri-operative cardiac enzyme release following isolated coronary artery bypass surgery are independently associated with higher one-year mortality. J Cardiothorac Surg 2006;1:20
8. Soraas CL, Friis C, Engebretsen KV et al. Troponin T is a better predictor than creatine kinase-MB of long-term mortality after coronary artery bypass graft surgery. Am Heart J 2012;164(5):779-785.
9. Møller CH, Penninga L, Wetterslev J, et al. Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. Cochrane Database Syst Rev. 2012 Mar.
10. Apple FS, Wu AHB, Jaffe AS. European Society Of Cardiology And American College Of Cardiology Guidelines For Redefinition Of Myocardial Infarction: How To Use Existing Assays Clinically And For Clinical Trials. Am Heart J 2002; 144(6): 981–6.
11. Mcpherson K. Statistics: The Problem Of Examining Accumulating Data More Than Once. N Engl J Med 1974; 290: 501-2.
12. Bignami E, Greco T, Barile L, et al. The Effect Of Isoflurane On Survival And Myocardial Infarction: A Meta-Analysis Of Randomized Controlled Studies. J Cardiothorac Vasc Anesth 2013; 27(1): 50-8.
13. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12.
14. O'Rourke K. Mixed Means And Medians: A Unified Approach To Deal With Disparate Outcome Summaries. In: Proceedings Of The Symposium On Systematic Reviews: Pushing The Boundaries. Oxford: 2002; 49
15. Wetterslev J, Thorlund K, Brok J, et al. Estimating requiredinformation size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol 2009; 9: 86
16. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003 327:557-560.
17. Borenstein M, Hedges LV, Higgins JPT, et al. (2009) Introduction to meta-analysis. Chichester, UK: Wiley.
18. Brok J, Thorlund K, Gluud C, et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008; 61: 763–9
19. Thorlund K, Imberger G,Walsh M, et al. The number of patients and events required to limit the risk of overestimation of intervention effects

in meta-analysis–a simulation study. PLoS One 2011; 6: e25491

20. Brok J, Thorlund K, Wetterslev J, et al. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulatingdata in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009; 38: 287–98
21. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008; 61: 64–75
22. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009; 38: 276–86
23. Thorlund K, Engstrøm J,Wetterslev J, et al. User Manual for Trial Sequential Analysis (TSA). Copenhagen, Denmark: Copenhagen Trial Unit, Centre for Clinical Intervention Research, 2011; 1–115. Available fromwww.ctu.dk/tsa (accessed 30 May 2014)
24. Kendall JB1, Russell GN, Scawn ND, et al. A prospective, randomised, single-blind pilot study to determine the effect of anesthetic technique on troponin T release after off-pump coronary artery surgery. Anesthesia. 2004 Jun;59(6):545-9.
25. Law-Koune JD, Raynaud C, Liu N, et al. Sevoflurane-remifentanil versus propofol-remifentanil anesthesia at a similar bispectral level for off-pump coronary artery surgery: no evidence of reduced myocardial ischemia. J Cardiothorac Vasc Anesth. 2006 Aug;20(4):484-92. Epub 2006 Feb 2.
26. Guarracino F, Landoni G, Tritapepe L, et al. Myocardial Damage Prevented By Volatile Anesthetics: A Multicenter Randomized Controlled Study. J Cardiothorac Vasc Anesth. 2006; 20(4): 477-83.
27. Lucchinetti E, Hofer C, Bestmann L, et al. Gene Regulatory Control Of Myocardial Energy Metabolism Predicts Postoperative Cardiac Function In Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery: Inhalational Versus Intravenous
28. Xu ZD, Jin M, He WX, et al. [Remifentanil preconditioning lowers cardiac troponin I levels in patients undergoing off-pump coronary artery bypass graft surgery]. [Article in Chinese] Nan Fang Yi Ke Da Xue Xue Bao. 2009 Aug;29(8):1554-6.
29. Tempe DK, Dutta D, Garg M, et al. Myocardial Protection With Isoflurane During Off-Pump Coronary Artery Bypass Grafting: A Randomized Trial. Cardiothorac Vasc Anesth. 2011; 25(1): 59-65.
30. Kim TY, Kim DK, Yoon TG, et al. Myocardial injury in remifentanil-based anesthesia for off-pump coronary artery bypass surgery: an equipotent dose of sevoflurane versus propofol. Anaesth Intensive Care. 2011 May;39(3):418-25.

31. Suryaprakash S, Chakravarthy M, Muniraju G, et al. Myocardial Protection During Off Pump Coronary Artery Bypass Surgery: A Comparison Of Inhalational Anesthesia With Sevoflurane Or Desflurane And Total Intravenous Anesthesia. Ann Card Anaesth. 2013;16(1): 4-8.
32. Guerrero Orriach JL, Galán Ortega M, Ramirez Aliaga M, et al. Prolonged sevoflurane administration in the off-pump coronary artery bypass graft surgery: beneficial effects. J Crit Care. 2013 Oct;28(5):879.e13-8.
33. Bein B, Renner J, Caliebe D, et al. Sevoflurane But Not Propofol Preserves Myocardial Function During Minimally Invasive Direct Coronary Artery Bypass Surgery. Anesth Analg 2005; 100(3): 610-6.
34. Mroziński P, Lango R, Biedrzycka A, et al. Comparison of haemodynamics and myocardial injury markers under desflurane vs. propofol anaesthesia for off-pump coronary surgery. A prospective randomised trial. Anaesthesiol Intensive Ther. 2014 Jan-Mar;46(1):4-13.
35. Malagon I, Hogenbirk K, Van Pelt J, et al. Effect Of Three Different Anesthetic Agents On The Postoperative Production Of Cardiac Troponin T In Paediatric Cardiac Surgery. Br J Anaesth. 2005; 94(6): 805-9.
36. Cromheecke S, Pepermans V, Hendrickx E, et al. Cardioprotective Properties Of Sevoflurane In Patients Undergoing Aortic Valve Replacement With Cardiopulmonary Bypass. Anesth Analg 2006; 103(2): 289-96
37. Landoni G, Calabrò MG, Marchetti C, et al. Desflurane Versus Propofol In Patients Undergoing Mitral Valve Surgery. J Cardiothorac Vasc Anesth. 2007; 21(5): 672-7.
38. Jovic M, Stancic A, Nenadic D, et al. Mitochondrial Molecular Basis Of Sevoflurane And Propofol Cardioprotection In Patients Undergoing Aortic Valve Replacement With Cardiopulmonary Bypass. Cell Physiol Biochem. 2012; 29(1-2): 131-42.
39. Bignami E, Landoni G, Gerli C, et al. Sevoflurane Vs. Propofol In Patients With Coronary Disease Undergoing Mitral Surgery: A Randomised Study. Acta Anaesthesiol Scand. 2012; 56(4): 482-90.
40. Erol DD, Ozen I. Is General Anesthesia A Risk For Myocardium? Effect Of Anesthesia On Myocardial Function As Assessed By Cardiac Troponin-I In Two Different Groups (Isofluran+N2o Inhalation And Propofol+Fentanyl Iv Anesthesia). Vasc Health Risk Manag. 2007;3(5):755-8.
41. Zhang Yl, Guan CY, Hu SF, et al. [Effect Of Long-Term Sevoflurane Anesthesia On Markers Of Myocardial Damage]. Zhonghua Yi Xue Za Zhi. 2009 Jul 21;89(27):1916-8. Chinese.
42. Lurati Buse GA, Schumacher P, Seeberger E, et al. Randomized Comparison Of Sevoflurane Versus Propofol To Reduce Perioperative Myocardial Ischemia In Patients

Undergoing Noncardiac Surgery. Circulation. 2012;126(23): 2696-704.

43. Zangrillo A, Testa V, Aldrovandi V, et al. Volatile Agents For Cardiac Protection In Noncardiac Surgery: A Randomized Controlled Study. J Cardiothorac Vasc Anesth. 2011; 25(6): 902-7.
44. Yu JB, Gong LR, Wang J, et al. Effect Of Sevoflurane Combination With Epidural Anesthesia On Myocardial Injury In Patients With Coronary Artery Disease Undergoing Non-Cardiac Surgery. Saudi Med J. 2011 Oct;32(10):1009-16.
45. Barbagallo M, Casati A, Spadini E, et al. Early Increases In Cardiac Troponin Levels After Major Vascular Surgery Is Associated With An Increased Frequency Of Delayed Cardiac Complications. J Clin Anesth. 2006 Jun;18(4):280-5.
46. Landoni G, Zangrillo A, Fochi O, et al. Cardiac Protection With Volatile Anesthetics In Stenting Procedures. J Cardiothorac Vasc Anesth. 2008 Aug;22(4):543-7.
47. Lavi S, Bainbridge D, D'Alfonso S, et al. Sevoflurane in acute myocardial infarction: a pilot randomized study. Am Heart J. 2014 Nov;168(5):776-83.
48. Delphin E, Jackson D, Gubenko Y, et al. Sevoflurane provides earlier tracheal extubation and assessment of cognitive recovery than isoflurane in patients undergoing off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2007 Oct;21(5):690-5.
49. Omitted: [No Authors Listed] [Cardioprotective Properties of Sevoflurane In Coronary Bypass Surgery With Extracorporeal Circulation]. Anesteziol Reanimatol. 2011 Nov-Dec ;(6):13-6. Russian.
50. Omitted:Zadorozhnyĭ MV, Iavorovskiĭ AG, Ziuliaeva TP, et al. Method of Pharmacological Myocardial Preconditioning With Halogen-Containing Anesthetics In Cardiosurgical Patients]. Anesteziol Reanimatol. 2008 Sep-Oct;(5):4-8. Russian.
51. Omitted: Ceyhan D, Tanrıverdi B, Bilir A. Comparison Of The Effects Of Sevoflurane And Isoflurane On Myocardial Protection In Coronary Bypass Surgery. Anadolu Kardiyol Derg. 2011 May;11(3):257-62.
52. Karuppasamy P, Chaubey S, Dew T, et al. Remote Intermittent Ischemia Before Coronary Artery Bypass Graft Surgery: A Strategy To Reduce Injury And Inflammation? Basic Res Cardiol. 2011 Jun;106(4):511-9.
53. Hemmerling T, Olivier JF, Le N, et al. Myocardial Protection By Isoflurane Vs. Sevoflurane In Ultra-Fast-Track Anesthesia For Off-Pump Aortocoronary Bypass Grafting. Eur J Anaesthesiol. 2008 Mar;25(3):230-6.
54. Hong DM, Mint JJ, Kim JH, et al. The Effect Of Remote Ischaemic Preconditioning On Myocardial Injury In Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery.

Anaesth Intensive Care. 2010 Sep;38(5):924-9.

55. Lucchinetti E, Bestmann L, Feng J, et al. Remote Ischemic Preconditioning Applied During Isoflurane Inhalation Provides No Benefit To The Myocardium Of Patients Undergoing On-Pump Coronary Artery Bypass Graft Surgery: Lack Of Synergy Or Evidence Of Antagonism In Cardioprotection? Anesthesiology. 2012;116(2): 296-310.
56. Belhomme D, Peynet J, Louzy M, et al. Evidence for preconditioning by isoflurane in coronary artery bypass graft surgery. Circulation. 1999 Nov 9;100(19 Suppl):II340-4.
57. Tomai F, De Paulis R, Penta De Peppo A, et al. Beneficial Impact Of Isoflurane During Coronary Bypass Surgery On Troponin I Release. G Ital Cardiol 1999; 29(9): 1007-14.
58. Pouzet B, Lecharny Jb, Dehoux M, et al. Is There A Place For Preconditioning During Cardiac Operations In Humans? Ann Thorac Surg 2002; 73(3): 843-8.
59. De Hert SG, ten Broecke PW, Mertens E, et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology. 2002 Jul;97(1):42-9.
60. De Hert SG, Cromheecke S, ten Broecke PW, et al. Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. Anesthesiology. 2003 Aug;99(2):314-23.
61. Conzen PF, Fischer S, Detter C, et al. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. Anesthesiology. 2003 Oct;99(4):826-33.
62. Julier K, Da Silva R, Garcia C, et al. Preconditioning By Sevoflurane Decreases Biochemical Markers For Myocardial And Renal Dysfunction In Coronary Artery Bypass Graft Surgery: A Double-Blinded, Placebo-Controlled, Multicenter Study. Anesthesiology. 2003; 98(6): 1315-27.
63. Nader ND, Li CM, Khadra WZ, et al. Anesthetic myocardial protection with sevoflurane. J Cardiothorac Vasc Anesth. 2004 Jun;18(3):269-74.
64. De Hert SG, Van Der Linden PJ, Cromheecke S, et al. Cardioprotective Properties Of Sevoflurane In Patients Undergoing Coronary Surgery With Cardiopulmonary Bypass Are Related To The Modalities Of Its Administration. Anesthesiol 2004; 101(2): 299-310.
65. De Hert SG, Van der Linden PJ, Cromheecke S, et al. Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. Anesthesiology. 2004 Jul;101(1):9-20.
66. Forlani S, Tomai F, De Paulis R, et al. Preoperative shift from glibenclamide to insulin is cardioprotective in diabetic patients undergoing coronary artery bypass surgery. J Cardiovasc Surg (Torino). 2004 Apr;45(2):117-22.

67. Wang X, Järvinen O, Kuukasjärvi P, et al. Isoflurane produces only minor preconditioning in coronary artery bypass grafting. Scand Cardiovasc J. 2004 Oct;38(5):287-92.
68. Xia Z, Huang Z, Ansley DM. Large-Dose Propofol during Cardiopulmonary Bypass Decreases Biochemical Markers Of Myocardial Injury In Coronary Surgery Patients: A Comparison With Isoflurane. Anesth Analg. 2006; 103(3): 527-32.
69. Lee MC, Chen CH, Kuo MC, et al. Isoflurane Preconditioning-Induced Cardio-Protection In Patients Undergoing Coronary Artery Bypass Grafting. Eur J Anaesthesiol. 2006 ; 23(10): 841-7.
70. Kawamura T, Kadosaki M, Nara N, et al. Effects Of Sevoflurane On Cytokine Balance In Patients Undergoing Coronary Artery Bypass Graft Surgery. J Cardiothorac Vasc Anesth. 2006; 20(4): 503-8.
71. Piriou V, Mantz J, Goldfarb G, et al. Sevoflurane Preconditioning At 1 Mac Only Provides Limited Protection In Patients Undergoing Coronary Artery Bypass Surgery: A Randomized Bi-Centre Trial. Br J Anaesth. 2007; 99(5): 624-31.
72. Ndoko SK, Tual L, Ait Mamar B, et al. Isoflurane, 0.5 Minimum Alveolar Concentration Administered Through The Precardiopulmonary Bypass Period, Reduces Postoperative Dobutamine Requirements Of Cardiac Surgery Patients: A Randomized Study. J Cardiothorac Vasc Anesth. 2007; 21(5): 683-9.
73. Meco M, Cirri S, Gallazzi C, et al. Desflurane Preconditioning In Coronary Artery Bypass Graft Surgery: A Double-Blinded, Randomised And Placebo-Controlled Study. Eur J Cardiothorac Surg. 2007; 32(2): 319-25.
74. Tritapepe L, Landoni G, Guarracino F, et al. Cardiac Protection By Volatile Anesthetics: A Multicentre Randomized Controlled Study In Patients Undergoing Coronary Artery Bypass Grafting With Cardiopulmonary Bypass.
Eur J Anaesthesiol. 2007; 24(4): 323-31.
75. De Hert S, Vlasselaers D, Barbé R, et al. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia. 2009 Sep;64(9):953-60.
76. Frässdorf J, Borowski A, Ebel D, et al. Impact Of Preconditioning Protocol On Anesthetic-Induced Cardioprotection In Patients Having Coronary Artery Bypass Surgery. J Thorac Cardiovasc Surg. 2009; 137(6): 1436-42.
77. Yildirim V, Doganci S, Aydin A, et al. Cardioprotective Effects Of Sevoflurane, Isoflurane, And Propofol In Coronary Surgery Patients: A Randomized Controlled Study. Heart Surg Forum. 2009; 12(1): E1-9.
78. Flier S, Post J, Concepcion AN, et al. Influence Of Propofol-Opioid Vs Isoflurane-Opioid Anesthesia On Postoperative Troponin Release In

Patients Undergoing Coronary Artery Bypass Grafting. Br J Anaesth. 2010; 105(2): 122-30.

79. Amr YM, Yassin IM. Cardiac Protection During On-Pump Coronary Artery Bypass Grafting: Ischemic Versus Isoflurane Preconditioning. Semin Cardiothorac Vasc Anesth. 2010; 14(3): 205-11.
80. Huang Z, Zhong X, Irwin Mg, et al. Synergy Of Isoflurane Preconditioning And Propofol Postconditioning Reduces Myocardial Reperfusion Injury In Patients. Clin Sci (Lond). 2011; 121(2): 57-69.
81. Hellström J, Öwall A, Bergström J, et al. Cardiac Outcome After Sevoflurane Versus Propofol Sedation Following Coronary Bypass Surgery: A Pilot Study. Acta Anaesthesiol Scand 2011; 55(4): 460-7.
82. Kottenberg E, Thielmann M, Bergmann L, et al. Protection By Remote Ischemic Preconditioning During Coronary Artery Bypass Graft Surgery With Isoflurane But Not Propofol - A Clinical Trial. Acta Anaesthesiol Scand. 2012; 56(1): 30-8.
83. Soro M, Gallego L, Silva V, et al. Cardioprotective Effect Of Sevoflurane And Propofol During Anesthesia And The Postoperative Period In Coronary Bypass Graft Surgery: A Double-Blind Randomised Study. Eur J Anaesthesiol. 2012; 29(12): 561-9.
84. Sirvinskas E, Kinderyte A, Trumbeckaite S, et al. Effects of sevoflurane vs. propofol on mitochondrial functional activity after ischemia-reperfusion injury and the influence on clinical parameters in patients undergoing CABG surgery with cardiopulmonary bypass. Perfusion. 2015 Feb 16.
85. Bland JHL and Lowenstein E. Halothane-induced Decrease in Experimental Myocardial Ischemia in the Non-failing Canine Heart. Anesthesiol 1976; 45: 287-93.
86. Kersten JR, Schmeling TJ, Pagel PS, et al. Isoflurane Mimics Ischemic Preconditioning Via Activation Of $_K$(Atp) Channels: Reduction Of Myocardial Infarct Size With An Acute Memory Phase. Anesthesiol 1997; 87(2): 361-70.
87. Cason B, Gamperl A, Slocum RE, Hickey RF. Anesthetic-Induced Preconditioning: Previous Administration Of Isoflurane Decreases Myocardial Infarct Size In Rabbits. Anesthesiol 1997; 87(5): 1182-90.
88. Lehrke S, Steen H, Sievers HH, Peters H, et al. Cardiac Troponin T for Prediction of Short- and Long-Term Morbidity and Mortality after Elective Open Heart Surgery Clinical Chemistry 50:91560 –1567 (2004)
89. Greenson N, Macoviak J, Krishnaswamy P, et al. Usefulness of cardiac troponin I in patients undergoing open heart surgery. Am Heart J. 2001 Mar;141(3):447-55.
90. Fellahi JL, Gué X, Richomme X, et al. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing

coronary artery bypass grafting.. Anesthesiology. 2003 Aug;99(2):270-4.

91. Kathiresan S, Servoss SJ, Newell JB, et al. Cardiac troponin T elevation after coronary artery bypass grafting is associated with increased one-year mortality. Am J Cardiol. 2004 Oct 1;94(7):879-81
92. Hausenloy DJ, Mwamure PK, Venugopal V, et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. Lancet. 2007 Aug 18;370(9587):575-9.
93. Swyers T, Redford D, Larson DF. Volatile anesthetic-induced preconditioning. Perfusion. 2014 Jan;29(1):10-5. Review.
94. Tanaka K, Ludwig LM, Kersten JR, et al. Mechanisms of cardioprotection by volatile anesthetics. Anesthesiology. 2004 Mar;100(3):707-21. Review
95. Landoni G, Greco T, Biondi-Zoccai G et al. Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery. Br J Anaesth. 2013 Dec;111(6):886-96.
96. Landoni G, Volatile anesthetics to reduce mortality in cardiac surgery *https://clinicaltrials.gov/ct2/show/NCT02105610?term=NCT02105610&rank=1*
97. Jakobsen CJ, Berg H, Hindsholm KB, et al. The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. J Cardiothorac Vasc Anesth. 2007 Oct;21(5):664-71.
98. Larsen JR, Aagaard S, Lie RH, et al. Sevoflurane improves myocardial ischaemic tolerance in a closed-chest porcine model. Acta Anaesthesiol Scand. 2008 Nov;52(10):1400-10.
99. Hausenloy DJ, Tsang A, Mocanu MM, et al. Ischemic preconditioning protects by activating prosurvival kinases at reperfusion.
Am J Physiol Heart Circ Physiol. 2005 Feb;288(2):H971-6.
100. Hausenloy DJ, Baxter G, Bell R, et al. Translating novel strategies for cardioprotection: the Hatter Workshop Recommendations. Basic Res Cardiol. 2010 Nov;105(6):677-86.
101. Zaugg M, Lucchinetti E, Uecker M, et al. Anaesthetics and cardiac preconditioning. Part I. Signalling and cytoprotective mechanisms. Br J Anaesth. 2003 Oct;91(4):551-65. Review.