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A Trial of Two Anesthetic Regimes for Minimally Invasive Mitral Valve Repair

Marco Moscarelli[1], Nora Terrasini[2], Anna Nunziata[2], Prakash Punjabi[3], Gianni Angelini[4], Marco Solinas[5], Alba Buselli[6], Paolo Del Sarto[2], Dorela Haxhiademi[2]

[1] GVM Care & Research, Anthea Hospital, Bari, Italy

[2] Operative Unit of Anesthesiology, G. Pasquinucci Heart Hospital, Fondazione Toscana G. Monasterio, Massa, Italy

[3] Imperial College of London, Hammersmith Hospital, London, UK

[4] Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, United Kingdom

[5] Operative Unit of Cardiac Surgery, G. Pasquinucci Heart Hospital, Fondazione Toscana G. Monasterio, Massa, Italy

[6] Perfusion Department, G. Pasquinucci Heart Hospital, Fondazione Toscana G. Monasterio, Massa, Italy

Corresponding Author: Marco Moscarelli

Anthea Hospital

Via Camillo Rosalba 35/37 70124, Bari, Italy

Tel: +39 080 564 4111

Fax: +39 080 564 4678

Email: m.moscarelli@imperial.ac.uk

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Objective: Minimally invasive mitral valve repair may be associated with prolonged cardioplegic arrest times and ischemic reperfusion injury. Intravenous (propofol) and volatile (sevoflurane) anesthesia are routinely used during cardiac surgery and are thought to provide cardioprotection; however, the individual contribution of each regimen to cardioprotection is unknown. Thereby we sought to compare the cardioprotective effects of propofol and sevoflurane anesthesia in patients undergoing minimally invasive mitral valve repair.

Design: A single-center single blind randomized controlled trial.

Setting: A specialized regional cardiac surgery center in Italy.

Participant: The study enrolled 62 adults undergoing elective isolated minimally invasive mitral valve repair for degenerative disease. Exclusion criteria included secondary mitral regurgitation, previously treated coronary artery disease, diabetes mellitus, chronic renal failure requiring dialysis, atrial fibrillation, and documented allergy to either propofol or sevoflurane.

Intervention: All patients received video-assisted right minimally invasive minithoracotomy. Patients were randomized to receive propofol or sevoflurane anesthesia in a 1:1 ratio.

Measurements and main results: Cardiac troponin I release was measured over the first 72 h postoperatively. Operative, cross clamp, and total bypass times were similar between groups. Cardiac troponin I release was non-significantly reduced in the propofol group ($p = 0.62$) and peak troponin I release was correlated with cross clamp time in both groups. There were no differences in terms of intraoperative lactate release and blood pH in between groups.

Conclusions: Propofol and sevoflurane anesthesia were associated with similar degrees of myocardial injury, indicating comparable cardioprotection. Myocardial injury was directly related to the duration of cardioplegic arrest.

Key words: mitral valve; propofol; reperfusion injury; sevoflurane; troponin I.

Trial registry number: NCT02551328.

Introduction

The magnitude of cardiac damage resultant from ischemic-reperfusion injury during cardiac surgery is inversely related to both early and long-term survival.[1] Accordingly, there is significant interest in reducing ischemic-reperfusion injury to improve postoperative outcomes. To this end, both sevoflurane and propofol have demonstrated utility for pre-operative conditioning.[2-4] Sevoflurane is thought to reduce reperfusion injury by attenuating cellular Ca^{2+} overload,[5] whereas propofol exerts antioxidant effects that decrease oxidative myocardial injury secondary to the generation of reactive oxygen species.[6] Yet, it is unclear whether one of these agents is superior for preventing damage during cardiac surgery.[7]

A majority of previous studies examining the protective conditioning effects of sevoflurane and propofol were conducted in heterogeneous populations (e.g., different baseline cardiac diseases, different operative techniques) with several confounding morbidities (e.g. inclusion of patients with diabetes or previous ischemic episodes).[8] Patients with organic mitral regurgitation in the absence of coronary disease may represent an ideal substratum for investigating the utility of potential conditioning agents. Moreover, minimally invasive mitral valve repair is a procedure associated with prolonged durations of ischemia[9] and significant ischemic-reperfusion injury, such that strategies for decreasing troponin release in this context are needed.

The aim of this study was to determine whether propofol or sevoflurane anesthesia confers superior cardioprotection in patients undergoing isolated minimally invasive mitral valve repair.

Methods

Ethical approval

This trial was registered with ClinicalTrials.gov (NCT02551328). The study protocol was approved by the Area Vasta Toscana Ethics Committee (reference CEAVNO no. 452/14) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to study participation. All authors had access to the study data and reviewed and approved the final manuscript.

Trial design

The MINI-SEVO trial was a single-center, single blind, randomized controlled trial. Participants were randomly allocated to propofol or sevoflurane anesthetic conditioning regimens using a 1:1 ratio.

Participants

Adults (age >18 years) undergoing elective isolated minimally invasive mitral valve repair for degenerative disease were eligible for study participation. The exclusion criteria were secondary mitral regurgitation, previously treated coronary artery disease such as a history of coronary stenting or coronary artery bypass grafting, diabetes mellitus, chronic renal failure requiring dialysis, atrial fibrillation (AF), or documented allergy to either propofol or sevoflurane. The study was conducted at G. Pasquinucci Heart Hospital, Fondazione Toscana G. Monasterio, a specialized regional cardiac surgery center in Italy.

Intervention

Beta-adrenergic antagonists and other relevant medications were continued until the morning of surgery in all patients. In the operating room, patients were monitored with 5-lead

electrocardiography, left radial artery catheter, capnography, pulse oximetry, blood findings, and rectal/urine bladder temperatures. Transesophageal echocardiography was used in all patients.

In the group randomized to sevoflurane (Sevoflurane®, Abbott), anesthesia was induced with intravenous sufentanil (0.5–1 mcg kg $^{-1}$; Hameln Pharmaceuticals, Hameln, Germany) and midazolam (0.08–0.2 mg kg $^{-1}$; Mayrhofer Pharmazeutika, Linz, Austria). Tracheal intubation was facilitated with intravenous rocuronium (0.6–1 mg kg $^{-1}$; Pharmadox Healthcare, Malta). Anesthesia was maintained with sevoflurane at a minimum end-tidal concentration of at least 1 minimal alveolar concentration (MAC) throughout the entire procedure, including cardiopulmonary bypass (CPB) and endovenous sufentanil (0.01–0.02 mcg kg $^{-1}$ min). During CPB, sevoflurane was administered in the oxygenator circuit through a calibrated vaporizer and MAC was measured at the outlet of the oxygenator of the extracorporeal circulation. Patients of this group received no propofol: neither during surgery, nor during ICU stay.

In the group randomized to propofol (Diprivan, Astra-Zeneca, Stockholm, Sweden), anesthesia was induced with intravenous sufentanil (0.5–1 mcg kg $^{-1}$) and propofol (2 mg- kg $^{-1}$). Tracheal intubation was facilitated with intravenous rocuronium (0.6–1 mg kg $^{-1}$). Anesthesia was maintained with propofol (0.1 -0.5 mg kg $^{-1}$ min) and sufentanil (0.01–0.02 mcg kg $^{-1}$ min). No volatile anesthetic was used at any time during the procedure.

In both groups, depth of anesthesia was monitored with bispectral index (BIS XP ®, Aspect Medical System, Newton, MA); the dosage of propofol and sevoflurane (within the above ranges) was titrated to maintain BIS values from 40 to 60.

Postoperatively, the inspired oxygen fraction was set at 0.5 and the positive end expiratory pressure at 5 cm H20. Sedation in ICU was continued for 3-4 hours, propofol in the propofol group and boluses of midazolam if required in the sevoflurane group. After 3-4 hours, if

partial pressure of oxygen/fraction of inspired oxygen was above 200, PaCo2 between 35-45 mmHg and bleeding from chest tubes was < 1 mL/kg, sedation was stopped.
Extubation was then performed if patients' cardio-circulatory, respiratory (partial pressure of oxygen/FiO2 < 250, respiratory rate > 25/min, FiO2 40-50%) and neurological criteria were within range. Criteria for intensive care discharge were: hemodynamic stability with no inotropic support, spontaneous breathing and clear neurological status.

Surgical technique

The surgical approach used in this study has been previously described.[10] Briefly, a central aortic cannulation was performed and venous drainage was achieved by percutaneous cannulation of the right femoral vein. A small 5-cm incision was made at the level of the 4th intercostal space. Two ports were used for camera insertion, cardiotomy venting, CO_2 insufflation, and other pericardial stay sutures. After CPB, the aorta was clamped under direct supervision and cold crystalloid cardioplegia (CUSTODIOL® Bretschneider's HTK-Solution, DR. FRANZ KÖHLER CHEMIE, Bensheim, Germany) with single antegrade delivery (25 ml kg $^{-1}$) was used. The mitral valve was then exposed through a left para-septal atriotomy. Mitral repair was performed in accordance with the mechanism of regurgitation.

Outcomes

The primary outcome was myocardial injury as assessed by serum cardiac troponin I (cTnI) in blood samples collected preoperatively and at 1, 6, 12, 24, and 72 h after the end of the ischemic period. The institutional laboratory quantified cTnI by immunoassay (Cobas 6000 analyzer series, Roche Diagnostic USA). Secondary outcomes were systemic metabolic stress as assessed by blood pH, lactate, and serum creatinine level; mechanical ventilation time; length of intensive care unit/high dependency unit stay; and left ventricular function. Blood

samples for measuring lactate and pH were taken before CPB, during CPB (at 20 and 40 min), and at the end of surgery. Blood samples for measuring serum creatinine were taken at 6, 24, 48, and 72 h after surgery. Left ventricular function was assessed preoperatively and between days 4 and 6 postoperatively. Examinations were performed using the Philips Healthcare IE33 echocardiography system, and the biplane method of disks summation (modified Simpson's rule) was applied to quantify left ventricular function.

Sample size

Cardiac troponin was measured the day before surgery (baseline) and 6 times after exposure to the anesthetic conditioning stimulus; considering an average pre-post correlation of 0.3 and an average post-post correlation of 0.5, we calculated a sample size of 60 (30 patients in each group).[11] With analyses of variance and covariance, this sample size provided 90% power to detect a standardized difference in serum markers of 0.43 between groups providing there was no interaction between group and pathology. If there was an interaction, a sample size of 60 had 80% power to detect a standardized difference in serum markers of 0.55 between groups.

Randomization and blinding

Random allocations were generated by computer software. Treatment allocations were (a) blocked with varying block sizes to ensure approximate balance in the number of participants allocated to each group; (b) generated prior to the study; and (c) accessed using a secure, internet-based randomization system to guarantee concealment until each participant's identity and eligibility was confirmed and securely documented. A designated research nurse who was not involved in data collection performed patient randomization after acquiring written consent and as close as possible to the operation date. Participants were blinded to the

intervention given that all conditioning was performed in the operatory theatre and there were no visible signs of the anesthetic conditioning regimens. Operating staffs were not blinded to treatment given the nature of the study.

Statistical analysis

The assumption of normality of each variable distribution was tested with the Shapiro–Wilk test. Normally distributed variables are reported as the mean ± standard deviation or median and interquartile range (IQR). Categorical variables are reported as the percentage. Continuous outcomes are summarized and presented graphically as geometric means and standard errors; a natural logarithmic transformation was applied to the data to normalize distributions. Categorical data are summarized as the number (percentage). cTnI and other markers were analyzed by fitting multilevel mixed effect linear regression models (continuous variable measured at different time points). Model validity was checked and poor fit was addressed by exploring transformations. Outcomes analyzed on a logarithmic scale were transformed back to the original scale after the analysis and results were presented as geometric mean ratios (GMRs). Likelihood ratio tests were used to determine statistical significance. The effect of cross clamp time on cTnI release was explored with a Pearson's correlation analysis. No sub-group analyses were planned. The trial was not powered to detect differences in clinical outcomes; therefore, frequencies are tabulated descriptively. The threshold for statistical significance was $p < 0.05$. All analyses were performed using R-project (R Core Team 2013, Vienna, Austria; http://www.R-project.org/) (packages: 'stat', 'graph', 'ggplot2').

Results

Patient recruitment

Between March 2015 and December 2016, 225 patients were assessed for study inclusion; of these, 160 did not meet the inclusion/exclusion criteria and were excluded (see CONSORT diagram / figure 1. After randomization, 3 patients were excluded due to concomitant tricuspid surgery and AF ablation. There were 2 protocol violations: 1 patient allocated to the propofol group received sevoflurane and 1 patient allocated to the sevoflurane group received propofol. One patient in the sevoflurane group was converted to stenotomy and underwent mitral valve replacement for a failed repair. These patients were included in the intention-to-treat population. Therefore, 62 participants were included in the per-protocol analysis (Figure 1).

Baseline data

The mean age of the population was 64.7 ± 11.9 years and 28 of 62 patients (45.1%) were male. Patients allocated to propofol group were older than those allocated to the sevoflurane group (68.3 ± 9.5 years vs. 60.7 ± 12.5 years, respectively). The median Logistic European System for Cardiac Operative Risk Evaluation score was 3.7 (IQR, 5). Other baseline characteristics and mitral valve regurgitation values are summarized in Table 1.

Operative data

Total CPB times and cross clamp times were similar between the propofol and sevoflurane groups (CPB: 139.7 ± 40.5 min vs. 141.2 ± 38.7 min, cross clamp: 90.3 ± 31.5 min vs. 94.3 ± 28.5 min, respectively). All patients received cold crystalloid antegrade cardioplegia. The average sevoflurane MAC was 1.2 ± 0.2. The average propofol infusion was 2.6 ± 0.7 mg $^{-1}$ kg $^{-1}$. Except for 1 patient, mitral valve repair was successful in all cases with no residual

regurgitation on intraoperative trans-esophageal echocardiography. The type of rings implanted and repair techniques used are summarized in Table 2.

Postoperative outcomes

Time courses of cTnI values are shown in Figure 2A. Preoperative concentrations of cTnI were undetectable in both treatment groups (< 0.01 ng ml $^{-1}$). Concentrations of cTnI were increased postoperatively and peaked at 6 h after surgery; these values were, on average, 8% lower in the propofol group compared to the sevoflurane group, but this difference was not statistically significant (GMR 0.92; 95% confidence interval [CI] 0.63–1.27, p = 0.62). Peak cTnI release occurring at 6 and 12 h after surgery was positively correlated with cross clamp time in both groups (p < 0.001) (Fig. 3, 4).

Postoperative blood pH, lactate, and serum creatinine were marginally lower in the sevoflurane group compared to the propofol group (blood pH: mean difference [MD] 0.02, 95% CI −0.02–0.04, p = 0.19; lactate: GMR 1.12, 95% CI 0.92–1.23, p = 0.68; serum creatinine: GMR 1.13, 95% CI 1–1.19, p = 0.33) (Fig. 2B–D). Mechanical ventilation time was lower in the sevoflurane group compared to the propofol group (median 497 min [IQR, 460] vs. 589 min [285], respectively; p < 0.05), while intensive care unit stay and total length of stay durations were similar between the propofol and sevoflurane groups (intensive care unit stay: mean 1186 ± 176 vs. 1215 ± 122 min); total length of stay: median 8 days (IQR, 3) vs. 8 days (IQR, 2)) (Table 3). Mean pre- and postoperative left ventricle ejection fractions were 58.2 ± 6.8% and 50 ± 5.7% in the propofol group and 59 ± 7.9% and 50 ± 10.3% in the sevoflurane group, respectively.

Postoperative complications

There were no in-hospital deaths. One patient in the sevoflurane group was re-operated for bleeding but conversion to sternotomy was not necessary. Other event rates were similar between the 2 treatment groups (Table 3). All patients were discharged with no or negligible residual mitral regurgitation. No unexpected serious adverse events occurred.

Discussion

To the best of our knowledge, this is the first study to compare the effects of propofol and sevoflurane as conditioning agents in patients undergoing isolated minimally invasive mitral valve repair. Our study found that both conditioning regimens were associated with similar degrees of myocardial injury. Bignami and colleagues compared propofol and sevoflurane in terms of cardiac troponin release in patients with coronary disease undergoing mitral surgery,[12] and Landoni and colleagues investigated the effects of desflurane versus propofol in patients undergoing mitral surgery[13]; however, neither study clarified whether volatile anesthesia was superior to intravenous anesthesia for mitral valve repair. In the latter study, subjects with concomitant coronary disease were not excluded, and moreover desflurane was used only as preconditioning agent for 30 minutes. The vast majority of previous studies on anesthetic conditioning were conducted in the context of coronary bypass grafting, and very few investigations have focused on isolated valve repair.[8] Additionally, investigations performed in patients with coronary disease failed to control for several confounding factors including diabetes and related medication use, previous angina, hibernating myocardium, coronary micro-embolization, no-reflow, and hypercholesterolemia.[14] Accordingly, these studies have yielded inconsistent results.

We believe that patients with isolated valve disease such as degenerative mitral valve disease provide an ideal scenario for testing the abilities of potential conditioning agents to prevent myocardial damage. Furthermore, organic mitral valve disease has a lower association with

coronary disease than aortic valve disease, which is associated with hypertension, diabetes, and dyslipidemia.[15] It can be argued that different forms of anesthetic conditioning (e.g., remote ischemic, volatile, etc.) do not add additional protection against cardioplegic arrest in the context of bypass grafting, since patients with coronary disease may already be naturally preconditioned.

In the present study, we were unable to demonstrate superiority of one anesthetic regimen over another for decreasing cTnI release in patients who underwent isolated mitral valve repair; patients in the propofol group tended to have lower cTnI release, but this difference was not statistically significant. Moreover, postoperative left ventricular function assessed between days 4 and 6 was similar between the 2 treatment groups. Rather, we uncovered a positive correlation between cross clamp time and peak troponin release in both groups. Minimally invasive surgery may require longer operation times[9] and thus an increased likelihood of ischemic-reperfusion injury in cardiac settings, accounting for an association between operation time and troponin release.

With regard to secondary outcomes, mechanical ventilation time was significantly shorter in the sevoflurane group than in the propofol group. The duration of mechanical ventilation is influenced by the sedation regimen used in the intensive care unit; in this study, the suspension of continuous infusion of hypnotic agents before arrival in the intensive care unit in the sevoflurane group was likely the main cause of early extubation.

An important strength of the present study was that we did not include patients with combined coronary disease, ensuring no previous exposure to angina or other natural ischemic preconditioning. Additionally, we excluded diabetic patients so as to avoid the possible influence of diabetic medication. This study was conducted in a high-volume mitral reference center with surgeons performing more than 50 mitral repairs per year, so that there was no learning curve effect on the present results. Finally, pain stimuli may elicit

preconditioning as a confounding factor, such that the use of a minimally invasive procedure in this study reduced the contribution of nociceptive components.[16]

This study had some limitations. First, this research was a proof-of-concept analysis that was primarily based on troponin release. For practical reasons, participants but not physicians and medical staff were blinded to treatment group assignments. Second, this trial did not include a third arm to examine synergy between sevoflurane and propofol, nor were the dose-dependent effects of propofol and sevoflurane[6] investigated; instead, our study design corresponded with routine anesthetic practice and evaluated potential differences between 2 standard regimens. Third, our trial included relatively low-risk patients, which may limit its generalizability to larger patient populations. Notably, we did not follow-up patients in our study; however, only weak evidence supports the idea that anesthetic conditioning has effects on late post-surgical outcomes.[8] Another important consideration is that in the propofol group, propofol infusion was continued in the intensive care unit and may have provided post-conditioning, whereas sevoflurane was not. There is some evidence that the preconditioning effect of sevoflurane is enhanced when treatment is maintained during the first 6 h after surgery,[17] yet the most uniform cardioprotective effects are seen when sevoflurane is administered for the duration of the procedure.[18] Finally, sufentanil was used in both groups; opioids produce cardioprotection against ischemia-reperfusion injury in rodents in a manner potentially related to adenosine receptor cross-talk.[19] Future studies should address these important points in order to better inform the utility of different anesthetic preconditioning regimens in cardiac surgery.

Conclusions

Propofol and sevoflurane anesthesia were associated with similar degrees of myocardial injury in patients undergoing minimally invasive mitral valve repair for degenerative disease.

Notably, injury was directly related to the duration of cardioplegic arrest regardless of the preconditioning regimen.

Declaration of interest

None declared.

Author contributions

M.M, N.T., and D.H.: study design, data collection, and statistical analysis; P.P., G.A., and M.S: study design, writing the first draft of the paper, critical review; A.B., A.N. and P.D.S: patient recruitment and data collection; S.S: study design and statistical analysis.

References

1. Croal BL, Hillis GS, Gibson PH et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. *Circulation* 2006; **114** : 1468–75.

2. Rogers CA, Bryan AJ, Nash R et al. Propofol cardioplegia: A single-center, placebo-controlled, randomized controlled trial. *J Thorac Cardiovasc Surg* 2015; **150** : 1610-9 e13.

3. 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** : 477–83.

4. De Hert SG, ten Broecke PW, Mertens E et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. *Anesthesiology* 2002; **97** : 42–9.

5. Kojima A, Kitagawa H, Omatsu-Kanbe M, at al. Sevoflurane protects ventricular myocytes against oxidative stress-induced cellular Ca2+ overload and hypercontracture. *Anesthesiology* 2013; **119** : 606–20.

6. Ansley DM, Raedschelders K, Chen DD, et al. Rationale, design and baseline characteristics of the PRO-TECT II study: PROpofol CardioproTECTion for Type II diabetics: a randomized, controlled trial of high-dose propofol versus isoflurane preconditioning in patients undergoing on-pump coronary artery bypass graft surgery. *Contemp Clin Trials* 2009; **30** : 380–5.

7. Likhvantsev VV, Landoni G, Levikov DI, et al. Sevoflurane Versus Total Intravenous Anaesthesia for Isolated Coronary Artery Bypass Surgery With Cardiopulmonary Bypass: A Randomized Trial. *J Cardiothorac Vasc Anesth* 2016; **30** : 1221–7.

8. 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; **111** : 886–96.

9. Moscarelli M, Fattouch K, Casula R, at al. What Is the Role of Minimally Invasive Mitral Valve Surgery in High-Risk Patients? A Meta-Analysis of Observational Studies. *Ann Thorac Surg* 2016; **101** : 981–9.

10. Moscarelli M, Cerillo A, Athanasiou T al. Minimally invasive mitral valve surgery in high-risk patients: operating outside the boxplot. *Interact Cardiovasc Thorac Surg* 2016; **22** : 756–61.

11. Fiorentino F, Angelini GD, Suleiman MS et al. Investigating the effect of remote ischaemic preconditioning on biomarkers of stress and injury-related signalling in patients having isolated coronary artery bypass grafting or aortic valve replacement using cardiopulmonary bypass: study protocol for a randomized controlled trial. *Trials* 2015; **16** : 181.

12. 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** : 482–90.

13. Landoni G, Calabro MG, Marchetti C et al. Desflurane versus propofol in patients undergoing mitral valve surgery. *J Cardiothorac Vasc Anesth* 2007; **21** : 672–7.

14. Heusch G, Kleinbongard P, Skyschally A, et al. The coronary circulation in cardioprotection: more than just one confounder. *Cardiovasc Res* 2012; **94** : 237–45.

15. Yan AT, Koh M, Chan KK et al. Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. *J Am Coll Cardiol* 2017; **69** : 1523–32.

16. Gross ER, Hsu AK, Urban TJ, et al. Nociceptive-induced myocardial remote conditioning is mediated by neuronal gamma protein kinase C. *Basic Res Cardiol* 2013; **108** : 381.

17. Guerrero Orriach JL, Galan 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; **28** : 879 e13-8.

18. 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. *Anesthesiology* 2004; **101** : 299–310.

19. Lee YC, Jung J, Park SJ. Remifentanil-induced preconditioning has cross-talk with A1 and A2B adenosine receptors in ischemic-reperfused rat heart. *Bosn J Basic Med Sci* 2016; **16** : 64–70.

Figure legends

Figure 1. Flow of patient enrolment. AF, atrial fibrillation; MIMVR, minimally invasive mitral valve repair; PIL, patient information leaflet.

Figure 2. Changes in blood parameters over time. A. Cardiac troponin I. B: Lactate. C: Blood pH. C: Creatinine. Geometric means and 95% confidence intervals (CIs) are shown for different postoperative time points by group. Geometric mean ratios (GMRs) and 95% CIs for propofol versus sevoflurane are also shown. Data are expressed as the mean and standard deviation (SD) at each study time point by group and the mean difference (MD) and 95% CI for propofol versus sevoflurane. CPB, cardiopulmonary bypass. MV, mitral valve. There were no missing data.

Figure 3. Correlation between cross clamp time and troponin I concentration at 6 h post-surgery. Propofol (blue), adjusted R-squared value 0.43, correlation 0.67, $p < 0.001$; sevoflurane (red), adjusted R-squared value 0.34, correlation 0.6, $p < 0.001$.

Figure 4. Correlation between cross clamp time and troponin I concentration at 12 h post-surgery. Propofol (blue), adjusted R-squared value 0.35, correlation 0.61, $p < 0.001$; sevoflurane (red), adjusted R-squared value 0.34, correlation 0.61, $p < 0.001$.

TABLE 1. Baseline characteristics

	Randomized to propofol (n=31)	Randomized to sevoflurane (n=31)	p value	Overall (N=62)
Age (year)	68.3±9.5	60.7±12.5	0.03	64.7±11.9
Male %	15 (48.3)	13 (41.9)	0.9	28 (45.1)
Body mass index	24.7±3.5	24.9±3.3	0.52	25.2±3.4
Creatinine (mg dl $^{-1}$)	0.89±0.2	0.78±0.2	0.03	0.83±0.27
Logistic Euroscore (IQR)	3.5 (4.1)	3.2 (4.3)	0.07	3.7(5)
Smoker/Ex smoker (%)	1 (3.2)	1 (3.2)	-	2 (3.2)
Hypercholesterolemia (%)	4 (12.9)	6 (19.3)	0.8	10 (16.1)
Family history for CV disease (%)	6 (19.3)	4 (12.9)	0.8	10 (16.1)
Systemic Hypertension (%)	8 (25.8)	6 (19.3)	0.85	12 (19.3)
Previous Stroke/TIA (%)	1 (3.2)	0	1	1 (1.6)
Pulmonary Hypertension (%)	3 (9.6)	4 (12.9)	1	7 (11.2)

LV function <50% (%)	3 (9.6)	4 (12.9)	1	7 (11.2)
LV function >50% (%)	28 (90.3)	27 (87)	1	55 (88.8)
NYHA I-II (%)	25 (80.6)	27 (87)	0.98	52 (83.9)
NYHA III (%)	6 (19.3)	4 (12.9)	0.8	10 (16.1)
Degenerative mitral regurgitation				
Isolated posterior (%)	20 (64.5)	18 (58)	0.96	38 (61.3)
Isolated anterior (%)	5 (16.1)	4 (12.9)	1	9 (14.5)
Anterior and posterior (%)	6 (19.3)	8 (25.8)	0.85	14 (22.5)

Values are presented as median (interquartile range), mean ± standard deviation, or n (%). There were no missing data. CV, cardio vascular; LV, left ventricle; NYHA, New York Heart Association classification; TIA, transient ischemic attack.

TABLE 2. Intraoperative details

	Randomized to propofol (n=31)	Randomized to sevoflurane (n=31)	p-value	Overall (N=62)
Operation time (min)	320±50.6	322±41	0.88	321.1±45.5
Cross clamp time (min)	90.3±31.5	94.3±28.5	0.33	92.6±29.5
Bypass time (min)	139.7±40.5	141.2±38.7	0.55	140±39
Conversion to sternotomy (%)	0	1 (3.2)	1	1 (1.6)
Mitral repair techniques*♮				
Resection (%)	16 (51.6)	14 (45.2)	0.93	30 (48.3)
Neochord (%)	15 (48.3)	24 (77.4)	0.34	39 (62.9)
Sliding (%)	4 (12.9)	7 (22.5)	0.61	11 (17.7)
Other (%)	2 (6.4)	2 (6.4)	1	4 (6.4)
CE-Physio II ring (%)	11 (35.4)	15 (48.3)	0.67	26 (41.9)
Sorin Memo 3D ring (%)	20 (64.5)	16 (51.6)	0.74	36 (58)

Values are presented as median (interquartile range), mean ± standard deviation, or n (%). There were no missing data. * Patients may have more than one techniques.♮ One patient had mitral valve replacement with mechanical prosthesis.

TABLE 3. Postoperative details

	Randomized to propofol (n=31)	Randomized to sevoflurane (n=31)	p value	Overall (N=62)
Mechanical ventilation time (min) (IQR)	589(285)	497(460)	0.05	572 (367)
LOS ICU (min)	1186±176	1215±122	0.19	1200±120
LOS total (day) (IQR)	8 (3)	8 (2)	1	8 (2)
N of patients requiring inotrops/vasoconstrictors (%)	12 (38.7)	11 (35.4)	1	23 (37)
N of patients transfused (%)	3 (9.6)	5 (16.1)	0.77	8 (12.9)
In hospital death (%)	0	0	-	0
De novo Atrial Fibrillation (%)	3 (9.6)	5 (16.1)	0.77	8 (12.9)
AV block requiring temporary pace maker (%)	3 (9.6)	4 (12.9)	1	7 (11.2)
AV block requiring permanent pace -maker (%)	1 (3.2)	0	1	1 (1.6)
Post-operative MI (%)	0	0	-	0
Reopening for bleeding (%)	0	1 (3.2)	1	1 (1.6)
Stroke/TIA (%)	0	0	-	0

Delirium (%)	1 (3.2)	0	1	1 (1.6)
Pneumothorax or effusion requiring drain (%)	1 (3.2)	2 (6.4)	1	3 (4.8)
Wound dehiscence (%)	2 (6.4)	0	0.5	2 (3.2)
Groin access complication (%)	1 (3.2)	1 (3.2)	1	2 (3.2)

Values are presented as median (interquartile range), mean ± standard deviation, or n (%). AV, atrio-ventricular. ICU, Intensive care unit. LOS, Length of stay. MI, Myocardial infarction. TIA, transient ischemic attack.