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ORIGINAL ARTICLE

Cardioprotective Efficacy of Sevoflurane in Patients With Rheumatic Heart Disease Undergoing Heart Valve Surgery Under Cardiopulmonary Bypass

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Abstract

Objectives: **In this study, we investigated whether cardioprotective properties of sevoflurane were expressed in patients with rheumatic heart disease undergoing heart valve surgery under cardiopulmonary bypass (CPB).**

Methods: **Fifty patients with rheumatic heart disease undergoing heart valve surgery under CPB were randomly assigned to receive total anesthesia with sevoflurane or propofol during surgery. Except for this, anesthetic and surgical management was the same in all patients. The primary outcomes were postoperative high-sensitive cardiac troponin T (hs-cTnT) and creatine kinase-myocardial band (CK-MB) release. The secondary outcomes were hemodynamic events and short-term clinical outcomes (within 30 days after surgery).**

Results: **The plasma concentrations of hs-cTnT at 24-hour and CK-MB from 6-hour to 48-hour in the sevoflurane group were lower than those in the control group (the propofol group). After aortic unclamping, heartbeat recovery was faster and the rate of sinus rhythm was higher in the sevoflurane group than in the control group. Moreover, a lower proportion of pacemaker use and the need for intraoperative and postoperative inotropes were also found in the sevoflurane group. Nevertheless, there were no differences between the two groups regarding short-term clinical outcomes (durations of mechanical ventilation, intensive care unit stay, hospital stay, morbidity, and mortality rates).**

Conclusion: **Sevoflurane administered during the entire anesthetic procedure had a myocardial protective effect with less evidence of myocardial damage in the first 48-hour postoperatively but short-term clinical outcomes were not significantly different when compared with the control group in patients with rheumatic heart disease undergoing heart valve surgery under CPB.**

Keywords: Myocardial protective, Sevoflurane, Propofol, Heart valve surgery, Cardiopulmonary bypass

1. Background

Rheumatic heart disease (RHD) is quite common in developing countries, including Vietnam [1,2]. Heart valve surgery under cardiopulmonary bypass is an important treatment modality for patients with severe forms of RHD [2]. However, this type of surgery is associated with myocardial cell injury, which may originate from pre-existing heart disease, cardiac surgical manipulation, ischemia-reperfusion injury due to aortic cross-clamp and aortic unclamping, and cardiopulmonary bypass (CPB) [3–6]. Volatile anesthetics (such as sevoflurane, desflurane, or isoflurane) have been shown to protect against myocardial ischemia and reperfusion injury in animals [7–11]. However, the clinical data in cardiac surgery patients have shown variable results, depending on the protocol used intraoperatively, and cardioprotective effects of volatile anesthetics are clinically most evident when anesthetics are administered over the course of the entire

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anesthesia or surgical procedure [5,12–25]. On the other hand, these studies were performed mainly in patients undergoing coronary artery surgery [12,15,20,25–27]. Meawhile, some other studies were conducted in patients undergoing heart valve surgery under CPB but the damage was due to degeneration, unlike in Vietnam which was mainly due to rheumatic heart disease [5,16,28].

There are currently no studies mentioning the cardioprotective effects of sevoflurane used during the entire anesthesia process in patients with rheumatic heart disease undergoing heart valve surgery under CPB. We therefore designed a randomized controlled clinical intervention study to check whether the myocardial protective effects of sevoflurane administered during the entire anesthetic procedure were observed in patients with rheumatic heart disease undergoing heart valve surgery under CPB. The main objective of the present study was to determine whether, compared with propofol, total anesthesia with sevoflurane (induction and maintenance of anesthesia before, during, and after CPB) lowers postoperative plasma levels of high-sensitive cardiac troponin T (hs-cTnT) and creatine kinase-myocardial band (CK-MB). The secondary objectives were to assess the effect of sevoflurane on hemodynamic events and short-term clinical outcomes (≤30 days after surgery).

2. Materials and methods

2.1. Patient population

This randomized controlled clinical intervention study was approved by the ethics committee of the 108 Military Central Hospital (**No. 275/QD-V108**). The study was conducted following the Declaration of Helsinki. The written informed consents were obtained from 55 patients with rheumatic heart disease, aged 18 years or older who were scheduled for elective heart valve surgery under CPB between October 2017 and August 2019. Exclusion criteria included history of cardiac surgery, unstable angina, occurrence of coronary stenosis on coronary angiography, myocardial infarction <6 weeks, active congestive heart failure, preoperative inotropic or vasopressor or balloon therapy, severe chronic obstructive pulmonary disease (forced expired volume in 1 s < 0.8 L), altered liver (serum aspartate transaminase or serum glutamate pyruvate transaminase concentration >150 IU L^{-1}), renal insufficiency (serum creatinine concentration >130 μmol L^{-1}), history of nervous system diseases or psychiatric disturbance, pregnancy, reintervention and withdrawal of consent.

Abbreviations

BIS	Bispectral index
CK-MB	Creatine kinase-myocardial band
CPB	Cardiopulmonary bypass
hs-cTnT	High-sensitive cardiac troponin T
MAC	Minimum alveolar concentration
MAP	Mean arterial blood pressure
RHD	Rheumatic heart disease
SD	Standard deviation
TCI	Target-controlled infusion

2.2. Study groups

The patients were randomly assigned to the sevoflurane group (intervention group) or the propofol group (control group) with equal size according to computer-generated randomization. The sevoflurane group and the propofol group were anesthetized by inhaled sevoflurane or by infusion of propofol during the entire anesthetic process, respectively. A computer-generated random code determined which anesthetic protocol was identified by each treatment number. Subjects were assigned the treatment numbers in ascending chronological order of admission in the study. The participant randomization assignment was concealed in an envelope until the start of anesthesia. The surgeons, research assistants, and medical and nursing staff in the intensive care unit and the ward were blinded to the group assignments.

2.3. Anesthetic protocols

All preoperative cardiac medication was continued until the morning of surgery, except for the angiotensin-converting enzyme inhibitors. All patients received standard premedication of 0.04 mg kg^{-1} intravenous midazolam 30 minutes before induction of anesthesia. In the sevoflurane group, anesthesia was induced with a target-controlled infusion (TCI) of fentanyl at 2 ng mL^{-1}; sevoflurane was initially started at 8%, and when the patient was asleep, it was lowered and maintained at 1 ± 0.2 minimum alveolar concentration (MAC). In the propofol group, anesthesia was induced with a TCI of fentanyl at 2 ng mL^{-1} and of propofol at 1.5 μg mL^{-1}, increased by 0.5 μg mL^{-1} every 2 minutes if patients had not lose consciousness). In both groups, muscle paralysis was obtained with 0.1 mg kg^{-1} pipecuronium bromide to facilitate tracheal intubation. Mechanical ventilation was adjusted in assist-control mode with a tidal volume of 6–8 mL kg^{-1} body weight, respiratory frequency was adjusted to obtain an end-tidal carbon dioxide pressure of 35–45 mmHg, inspired oxygen

fraction was set at 0.5 and positive end-expiratory pressure of 5 cmH_2O was set as default. According to group allocation, anesthesia was maintained with TCI of fentanyl at 2 ng mL^{-1}, sevoflurane 1 ± 0.2 MAC and pipecuronium bromide 0.04 mg kg^{-1} every 2 hour (intervention group) or TCI of fentanyl at 2 ng mL^{-1}, TCI of propofol at 3−4 μg mL^{-1} and pipecuronium bromide 0.04 mg kg^{-1} every 2 hour (control group). During CPB, sevoflurane was administered through the oxygenator. In both groups, the depth of anesthesia before, during, and after CPB was controlled at bispectral index (BIS) 40−60 by adjusting the inhaled sevoflurane concentration or the infusion rate of propofol, respectively.

2.4. Perioperative procedure

In the operating room, all patients received routine monitoring including five-lead electrocardiography, invasive radial arterial pressure, central venous pressure, pulse oxygen saturation, end-tidal carbon dioxide pressure, esophageal temperature monitoring, and BIS monitoring to measure the depth of anesthesia. Hemodynamic monitoring was carried out with the FloTrac/EV1000 platform. Transesophageal echocardiography and urine output were also monitored.

Routine surgical and CPB techniques were used in all patients of two groups by the same group of cardiac surgeons. After systemic heparinization (300 IU kg^{-1}, activated clotting time >400 s), the ascending aorta and right atrium were cannulated. A standard CPB with a disposable hollow-fiber membrane oxygenator was started with a target output of 2.4 L min^{-1} m^{-2} of body surface area. The mean arterial blood pressure (MAP) was maintained at more than 65 mmHg by increasing the pump flow rate or a bolus of phenylephrine (100 μg) or norepinephrine (5 μg). Surgery was performed under normal body temperature (36−37 °C). After aortic cross-clamping, cardioplegia was achieved with the warm blood solution administered into the aortic root every 30 minutes, according to a standard protocol. After aortic unclamping, the heart was defibrillated if sinus rhythm did not resume spontaneously. Normoglycemia (arterial blood glycemia <10 mmol) was maintained with intravenous insulin (intravenous bolus of 5−10 UI) if necessary. Patients with a hemoglobin value below 8 g dL^{-1} received homologous red blood cell transfusions. Heparin was reversed with protamine at a ratio of 1 mg protamine for 100 IU heparin. Patients were transferred to the intensive care unit (ICU) where they were sedated with midazolam/fentanyl and extubated when pressure support ventilation was tolerated.

In this study, hypotension was defined as a mean arterial blood pressure <65 mmHg. Glyceryl trinitrate, dobutamine, or noradrenaline was administered by continuous infusion if CI was low (<2.4 L min^{-1} m^{-2}), depending on whether afterload was high, normal, or low (normal SVRI 1700−2400 dyn s cm^{-5} m^{-2}) [29].

2.5. Hemodynamic data

Global hemodynamic data (heart rate, mean arterial blood pressure, central venous pressure, cardiac index, systemic vascular resistance index) were recorded just before the start of induction, before the start of CPB, 15 minutes after the end of CPB, at the end of the operation, 6 hour and 24 hour after the operation.

2.6. Biochemical analysis

In all patients, blood was sampled for determination of hs-cTnT, CK-MB. Blood samples measuring hs-cTnT, and CK-MB were obtained before the start of surgery (base), after surgery 6 hour (H6), 24 hour (H24), and 48 hour (H48). Hs-cTnT and CK-MB were quantified by the sandwich immunity method using electrochemiluminescence technology. The detection limit for hs-cTnT was 0.003 ng mL^{-1} and CK-MB was 0.1 ng mL^{-1}.

2.7. Primary and secondary endpoints

The primary endpoints were the changes in hs-cTnT and CK-MB values from the beginning of anesthesia to 48 hour after operation. Secondary endpoints included hemodynamic events (characteristics of the heart beating again after aortic unclamping such as the proportions of patients with the heart beats again on its own and defibrillation after aortic unclamping, duration of the heart beating again after aortic unclamping, the rates of patients with sinus rhythm, using a pacemaker after aortic unclamping; hemodynamic variables and need for vasoactive or inotropic support during and after surgery) and short-term clinical outcomes (durations of mechanical ventilation, ICU stay and hospital stay, left ventricular ejection fraction before hospital discharge, morbidity and mortality rates within 30 days after surgery).

2.8. Statistical analysis

The sample size of the study was calculated based on cardiac troponin concentration as the primary outcome variable. A minimum detected difference

of 2 ng mL^{-1} between the intervention group and control group was considered clinically significant [5,16]. For a power of 0.8 and $\alpha = 0.05$, based on the formula estimating sample size for the comparison of two means, a sample size of at least 23 patients in each group was calculated to be appropriate.

Qualitative variables were described by frequency and percentage, and were compared using the χ^2 test or Fisher exact test as appropriate. Quantitative variables were presented as mean ± standard deviation (SD) or median (25–75%, interquartile range) and were compared by Student's test or Mann-Whitney test as appropriate. All data were analyzed by medical statistics algorithm with SPSS 26.0 software (SPSS Inc, Chicago, IL, USA) and statistical significance was accepted at $P < 0.05$. All reported P values were two-tailed.

3. Results

A total of 55 patients were randomized. Three were excluded because surgery was not carried out and two withdrew consent. Of the remaining 50 patients, 25 had been allocated to the sevoflurane group (intervention group) and 25 to the propofol group (control group). The flow diagram is shown in Fig. 1. The characteristics of the two groups were similar (Table 1). No significant differences were seen between groups in any of the preoperative and intraoperative patient characteristics.

3.1. Primary study endpoint

Plasma CK-MB and hs-troponin T levels increased in all patients throughout the observation period. However, plasma concentrations of CK-MB after surgery 6 hour (H6), 24 hour (H24), 48 hour (H48), and hs-troponin T after surgery 24 hour (H24) of the sevoflurane group were lower than those of the control group (propofol group) ($P < 0.05$) (Table 2).

3.2. Secondary study endpoints

Hemodynamic parameters (heart rate, mean arterial blood pressure, central venous pressure, cardiac index, systemic vascular resistance index) were kept stable throughout the observation period. However, mean arterial pressure during surgery immediately before CPB (Pre-CPB), 15 minutes after CPB (Post-CPB), and at the end of surgery (End) of the propofol group were lower than those of the sevoflurane group ($P < 0.05$). Cardiac index (CI) at 15 minutes after CPB (Post-CPB) and the end of surgery (End) of the propofol group were also lower than those of the sevoflurane group ($P < 0.05$) (Table 2).

The heartbeat recovery time after aortic unclamping of the sevoflurane group was shorter, the proportion of patients with sinus rhythm after aortic unclamping of the sevoflurane group was higher, and the percentage of patients who had to use a pacemaker after aortic unclamping of the sevoflurane group were lower than those of the propofol group ($P < 0.05$) (Table 3).

The need for inotropic support was significantly different between groups. The proportion of patients who required inotropic support with dobutamine during the observation period was 80.0 % in the propofol group and 32.0 % in the sevoflurane group ($P = 0.001$). The median amount of dobutamine used was 449.7 ± 424.4 mg in the propofol group and 187.8 ± 426.9 mg in the sevoflurane group ($P = 0.035$). The need for vasoconstrictive therapy

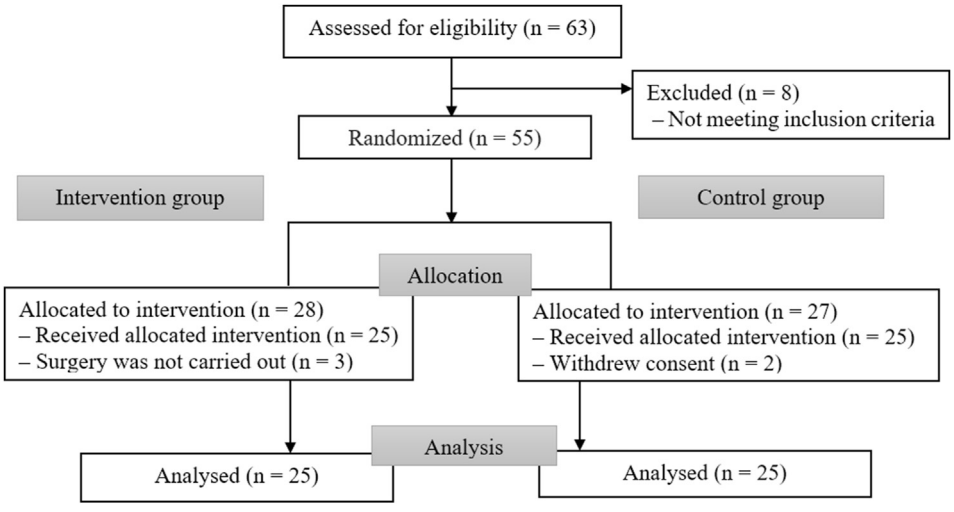

Fig. 1. CONSORT flow diagram.

Table 1. Patient characteristics.

Patient characteristics	Sevoflurane ($n = 25$)	Propofol ($n = 25$)	P value
Preoperative data			
Age (year)	50.6 ± 11.8	49.6 ± 14.5	0.799
Sex (M/F)	14/11	16/9	0.564
BMI (kg/m^2)	20.4 ± 2.0	20.7 ± 2.2	0.634
ASA class (II/III/IV)	7/17/1	8/17/0	1.000
NYHA (I/II/III)	2/16/7	1/19/5	0.630
EF (%)	63.6 ± 12.3	63.0 ± 8.9	0.865
Euro SCORE II	1.4 ± 0.6	1.5 ± 1.2	0.655
History of RHD (n, %)	25 (100)	25 (100)	NA
Types of surgery (n, %)			
Replace/repair the mitral valve	12 (48.0)	15 (60.0)	0.395
Replace the aortic valve	2 (8.0)	2 (8.0)	1.000
Replace/repair the mitral valve and replace the aortic valve	5 (20.0)	3 (12.0)	0.702
Replace/repair the mitral valve and shaping of tricuspid valve	6 (24.0)	5 (20.0)	0.733
Intraoperative data			
Anesthesia time (min)	240.0 ± 32.7	246.0 ± 36.1	0.541
Operating time (min)	199.8 ± 33.9	207.2 ± 35.5	0.457
CPB time (min)	93.4 ± 28.6	102.0 ± 27.8	0.284
Aortic clamp time (min)	72.6 ± 23.1	78.2 ± 25.0	0.421
Incidence of intraoperative awareness (%)	0	0	NA

Data are presented as mean ± SD, unless noted otherwise.
BMI = Body mass index; ASA class = American Society of Anesthesiologists physical status classification; NYHA = New York Heart Association; EF = Ejection fraction; SPAP = Systolic pulmonary artery pressure; EuroSCORE = European System for Cardiac Operative Risk Evaluation; COPD = Chronic obstructive pulmonary disease; CPB = Cardiopulmonary bypass.

was not statistically different between groups in this study design.

Short-term clinical outcomes such as the durations of mechanical ventilation, ICU stay, hospital stay, EF before hospital discharge, morbidity and mortality rates within 30 days after surgery of the two groups were not significantly different with $P > 0.05$. The proportion of patients with atrial fibrillation was 40.0% in the propofol group and 36% in the sevoflurane group ($P = 0.771$). Myocardial ischemia occurred in 8.0% of patients in the propofol group and 4.0% of patients in the sevoflurane group ($P = 1.000$). In particular, we did not encounter any patient who died during the study period.

4. Discussion

To the best of our knowledge, this is the first study investigating the cardioprotective effects of sevoflurane administered throughout the anesthetic procedure in patients with rheumatic heart disease undergoing heart valve surgery under CPB. The results of the current study indicated that in patients with rheumatic heart disease undergoing heart valve surgery under CPB, total anesthesia with sevoflurane had a myocardial protective effect as demonstrated by the plasma concentrations of hs-cTnT after surgery 24 hour and CK-MB after surgery 6–48 hour (the main objectives) of the sevoflurane group were lower than those of the control group (the propofol group). Besides, the proportion of pacemaker use and the heartbeat recovery time after aortic unclamping, the requirement of using inotropes agents during and after surgery (the secondary objectives) was also lower in the sevoflurane group.

There are many factors that determine the occurrence of myocardial damage and outcome after cardiac surgery under CPB. Of these, patient characteristics and surgery-related events are the most common causes of potential complications. Characteristics of study patients, surgery, CPB, and other characteristics of anesthesia and resuscitation during and after surgery were similar in both groups. This suggested that the sevoflurane group had lower postoperative plasma concentrations of hs-cTnT and CK-MB, better characteristics of the heart beating again after aortic unclamping, less requirement of using inotropes agents during and after surgery than those in the control group were not caused by differences in patient characteristics and intraoperative events but seemed instead to be related to the use of sevoflurane.

The cardioprotective mechanism of sevoflurane seems to be similar to the protective mechanism of repeated ischemia events (preconditioning) and during the reperfusion period after ischemia

Table 2. Perioperative markers of myocardial injury and hemodynamic data.

Parameters	Sevoflurane ($n = 25$)	Propofol ($n = 25$)	P value
Hs-cTnT (ng mL^{-1})			
Base	0.01 ± 0.01	0.01 ± 0.01	0.711
H6	1.20 ± 1.27	1.73 ± 1.55	0.193
H24	0.82 ± 0.87	1.51 ± 1.41	0.046
H48	0.59 ± 0.61	0.94 ± 0.82	0.092
CK-MB (ng mL^{-1})			
Base	1.54 ± 0.90	1.63 ± 0.63	0.705
H6	54.35 ± 29.92	76.21 ± 36.60	0.025
H24	23.98 ± 12.91	35.20 ± 17.66	0.013
H48	6.21 ± 3.40	8.54 ± 4.66	0.049
MAP (mmHg)			
Base	82 ± 10	86 ± 14	0.304
Pre-CPB	75 ± 6	69 ± 6	0.001
Post-CPB	80 ± 6	72 ± 7	0.000
End	83 ± 6	78 ± 7	0.008
ICU H6	86 ± 10	82 ± 10	0.272
ICU H24	85 ± 9	89 ± 10	0.242
CI (L min^{-1} m^{-2})			
Base	2.6 ± 0.8	2.7 ± 0.9	0.919
Pre-CPB	2.6 ± 0.7	2.6 ± 0.8	0.805
Post-CPB	2.7 ± 0.6	2.4 ± 0.6	0.048
End	2.9 ± 0.6	2.6 ± 0.5	0.049
ICU H6	2.9 ± 0.6	2.7 ± 0.5	0.176
ICU H24	2.9 ± 0.7	2.8 ± 0.6	0.395

Data are presented as mean ± SD.
H6 = 6 h after surgery; H24 = 24 h after surgery; H48 = 48 h after surgery.
CPB = Cardiopulmonary bypass; ICU = Intensive care unit; HR = Heart rate; MAP = Mean arterial pressure; CVP = Central venous pressure; CI = Cardiac index; SVRI = Systemic vascular resistance index.

Table 3. Characteristics of the heart beating again after aortic unclamping.

Characteristics	Sevoflurane ($n = 25$)	Propofol ($n = 25$)	P value
Sinus rhythm (n, %)	21 (84.0)	13 (52.0)	0.015
Using a pacemaker (n, %)	7 (28.0)	15 (60.0)	0.023
The heart beat recovery time (second)	83.0 ± 70.6	163.9 ± 130.4	0.010

Data are presented as mean ± SD, unless noted otherwise.

(postconditioning) [12,15,16]. The results of our study were similar to previous studies of De Hert et al. in coronary surgery patients, Cromheecke et al. in aortic valve replacement patients, and Yang et al. in heart valve replacement surgery under CPB [5,12,13,15,16]. These authors also used sevoflurane during the entire anesthesia or surgical procedure, but the study population was different from our study as mentioned above. Besides, our study results were different from Bignami et al. when studying patients with coronary artery disease undergoing mitral valve surgery and Jovic et al. when studying in patients undergoing aortic valve replacement surgery under CPB [18,19]. In these studies, the authors did not find myocardial protective effects of sevoflurane when compared with the control group (the propofol group). The reason may be that the authors did not use sevoflurane during the induction of anesthesia and CPB in the inhalation anesthesia group, so it may affect the ischemic conditioning. On the contrary, in our present study, sevoflurane was administered throughout the entire anesthetic procedure to combine a preconditioning effect (from induction of anesthesia until the start of CPB) and a postconditioning effect (after CPB, from declamping of the aorta), which may provide an optimal cardioprotection.

In addition, the myocardial protection effect of sevoflurane may be related to the used drug concentrations. Laboratory investigations reported that 1.0 MAC of inhaled anesthetics had a beneficial effect on myocardial injury, lower concentrations of less than 0.75 MAC often showed no effect, whereas higher concentrations of more than 1.5 MAC did not result in further protective effect [8,30]. In this study, we maintained sevoflurane at MAC 0.8 to 1.2 (intervention group) and propofol at Ce 3–4 μg mL^{-1} (the control group). No intraoperative awareness occurred in the two groups implying that the use of sevoflurane at MAC 0.8–1.2 and propofol at Ce 3–4 μg mL^{-1} was reasonable.

In spite of this, short-term clinical outcomes such as the durations of mechanical ventilation, ICU stay, hospital stay, EF before hospital discharge, morbidity, and mortality rates within 30 days after surgery of the sevoflurane groups were not significantly different when compared with the control group. The results of our study were also similar to those of Bignami et al. as well as Jovic et al. in the study population described above [18,19]. However, De Hert et al. and Yang et al. found that sevoflurane anesthesia reduced the durations of mechanical ventilation, ICU stay, and hospital stay [5,15]. Further larger studies will therefore have to elucidate whether the long-term clinical outcome may be influenced by the choice of the anesthetic agent in patients with rheumatic heart disease undergoing heart valve surgery under CPB.

Our study has several limitations. Firstly, it was a single-center study because multicenter studies reduced the effect of the special characteristics of a single institution. Secondly, we calculated the study sample size based on historical recordings of plasma cTnI concentrations from a previous study and not on a specific pilot study. Therefore, different reference values for plasma cTnI concentration could produce a different sample size which may leave our study underpowered. Nevertheless, the sample

size was still relatively small which urged a study with a larger and adequate sample size to have more valid results. Even so, our study contributed as a first-stage investigation that could be a reference of trends of variables for further studies. Thirdly, although patients were randomly assigned to each study group, anesthesiologists could not be blind to the anesthetic technique used in each group. Nevertheless, the surgeon, cardiologist, and clinical data manager were blind to group allocation. Additionally, we were not able to demonstrate a significant difference in short-term clinical outcomes. The reason may be that the sample size was not sufficient to adequately address this issue or the myocardial protective properties of sevoflurane are weaker in patients with rheumatic heart disease undergoing heart valve surgery under cardiopulmonary bypass. Consequently, research with a larger sample size based on clinical results is needed to clarify this issue.

5. Conclusions

In conclusion, in patients with rheumatic heart disease undergoing heart valve surgery under cardiopulmonary bypass, sevoflurane administered during the entire anesthetic procedure had a myocardial protective effect with less postoperative release of hs-cTnT and CK-MB but short-term clinical outcomes were not significantly different when compared with the control group.

Ethics information

This study was approved by the ethics committee of the 108 Military Central Hospital (No. 275/QD-V108). The study was conducted following the Declaration of Helsinki. The written informed consents were obtained from all patients participated in the study.

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Author contributions

Conception and design of Study, Revising and editing the manuscript critically for important intellectual contents: VTL, NQK. Literature review, Research investigation and analysis, Data collection, Drafting of manuscript: VTL, NML. Acquisition of data, Data preparation and presentation: VTL, NQK, NML. Analysis and interpretation of data: VTL. Supervision of the research, Research coordination and management: NQK.

Conflicts of interest

All authors have no conflict of interest to declare.

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