Effects of Pre–Cardiopulmonary Bypass Administration of Dexmedetomidine on Cardiac Injuries and the Inflammatory Response in Valve Replacement Surgery With a Sevoflurane Postconditioning Protocol: A Pilot Study

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Background: Preventing myocardial ischemia–reperfusion injury in on-pump cardiac surgeries remains an enormous challenge. Sevoflurane postconditioning has been effective at overcoming this challenge by modulating inflammatory mediators and ameliorating antioxidative stress. Dexmedetomidine (DEX) is a commonly used medication for cardiac patients with organ-protective properties that lead to positive outcomes. Whether DEX also has cardiac-protective properties and the associated mechanism in sevoflurane postconditioning–based valve replacement surgeries are unknown.

Objective: This study was conducted to observe the effect of DEX administration before cardiopulmonary bypass (CPB) on myocardial injury, oxidative stress, and inflammatory response indicators in the peripheral blood.

Methods: Twenty-eight eligible cardiac patients who underwent valve replacement surgery with standard sevoflurane postconditioning were included in the study. The patients were randomly divided into a DEX group and a non-DEX group according to whether DEX (0.5–m g/kg overload dose for 10 minutes and a 0.5–m g/kg/h maintenance dose) or saline was administered from induction to the beginning of CPB. The primary outcome was the cardiac troponin I concentration (cTnI) in the blood 24 hours after CPB. The levels of malondialdehyde (MDA), superoxide dismutase, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) were also measured.

Results: The mean cTnI at 24 hours after CPB was clearly decreased in the DEX group compared with that in the non-DEX group (4.16 ± 1.58 vs. 6.90 ± 3.73, P < 0.05). TNF-α levels were lower in the DEX group after CPB (T1–T5), with a significant difference found at 1–6 hours after CPB (1 hour, 19.03 vs. 28.09; 6 hours, 20.74 vs. 30.94, P < 0.05). The IL-6 and IL-8 concentrations in the DEX group were dramatically increased at 6 hours after CPB (P < 0.05). The MDA content and superoxide dismutase activity were comparable between the 2 groups. A lower proportion of anemia cases were noted after CPB in the DEX group than in the non-DEX group (non-DEX, 10% vs. DEX, 5%, P < 0.05).

Conclusions: In valve replacement surgery with sevoflurane postconditioning, pre-CPB administration of DEX can reduce the cTnI level at 24 hours after CPB and brings synergic benefits of the inflammatory response.

Key Words: dexmedetomidine, sevoflurane, postconditioning, cardiopulmonary bypass

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INTRODUCTION

The incidence of morbidity after revascularization in cardiopulmonary bypass (CPB) has been reported to be approximately 20%–40% in cardiac patients. Along with surgical interference and numerous fundamental contributions, such as systemic inflammatory responses and oxidative stress reactions, reperfusion injury, which closely follows myocardial ischemia, can increase myocardial damage and even lead to myocardial apoptosis or worsened clinical outcomes. The search continues for ideal solutions to prevent ischemia–reperfusion injury (IRI) in postoperative patients. Volatile anesthetics are known to significantly reduce cardiac mortality and complications in cardiac patients compared with i.v. anesthesia. Furthermore, some studies have concluded that prolonged inhalation of volatile anesthetics by cardiac patients can result in better outcomes. Based on these conclusions, an increasing number of clinical trials have emerged that include preconditioning and postconditioning methods. Regarding postconditioning with sevoflurane, the well-known mechanisms of action include inhibition of apoptosis and inflammatory mediators, alleviation of anti-oxidative stress, activation of mitochondrial adenosine-triphosphate-sensitive potassium channels, and stimulation of the IP3K-Akt and MEK-ERK 1/2 cascades. However, the beneficial effect that has been verified in large fundamental experiments has been less consistent in the clinical setting, partly because of the elemental diversity of studies. But, a few
studies have attempted to demonstrate the positive impact of postconditioning with sevoflurane in cardiac patients when IRI happened. Therefore, complete translation of these mechanisms from bench to bedside is still in the early stages. More and more clinical studies were needed.

Dexmedetomidine (DEX), a highly selective α2-adrenoreceptor agonist, has been confirmed as another agent suitable for pharmacological conditioning to prevent IRI and exhibits numerous protective functions in various organs, including the lungs, spinal cord, brain, liver, kidneys, and heart. The experimental mechanisms described previously were partly attributable to sevoflurane postconditioning. To precisely illustrate the protective mechanisms of sevoflurane postconditioning against IRI and to observe the enhanced cardioprotective effect, we applied DEX preconditioning based on the standard sevoflurane postconditioning protocol to evaluate the outcomes.

**METHODS**

The ethics committee of the Second Affiliated Hospital of Jiaxing University approved this prospective, randomized, and controlled study (JXEY-20180718H01). Written informed consent was signed by all eligible patients or their families. From August 20 to October 30, 2018, 35 patients scheduled for elective valve replacement surgery under CPB were enrolled in this RCT at the Second Affiliated Hospital of Jiaxing University. The exclusion criteria were as follows: emergency surgery; younger than 18 years; NYHA Cardiac Function Classification greater than grade IV; severe chronic obstructive pulmonary disease; coronary heart disease, myocardial infarction, or a high cardiac troponin I concentration (cTnI > 0.2 ng/mL); renal insufficiency (creatinine > 41.6 mg/dL); hypotension [mean arterial pressure (MAP) < 60 mm Hg]; and bradycardia [heart rate (HR) < 50 beats/min] in the past 3 days.

This was a placebo-controlled, single-center, and double-blinded study performed to compare the effects of DEX on the characteristics of myocardial injury occurring during cardiac surgery with those of saline. Seven patients were excluded from this study for various reasons (Fig. 1). Before the start of the study, 28 patients were randomly assigned to either the DEX group or the non-DEX group (1:1) using programmed block randomization software with a fixed block size of 4, and the group designations were not revealed to any assistants to avoid bias. The experimental solutions of DEX or saline were unlabeled and diluted by pharmacists in the central pharmacy and were not known to the investigators. Syringes containing the respective solutions were obtained from the pharmacists immediately before the start of the operation. All of the participating patients and the central laboratory members were unaware of the solutions used in each case. Blind-breaking occurred only in emergency situations of patient instability. The patients were premedicated with 0.1 mg/kg of morphine 30 minutes before admission. Upon entering the operating room, routine monitoring of the patient was initiated, including pulse oximetry, 5-lead standard electrocardiography, core temperature monitoring, and radial arterial pressure monitoring. General anesthesia was induced with 0.1–0.2 mg/kg of midazolam, 0.2–0.3 mg/kg of etomidate, lidocaine (in some cases), 0.2–0.3 μg/kg of sufentanil, and 0.6–0.9 mg/kg of rocuronium. Phenylephrine was used intermittently to address fluctuations in blood pressure. After the induction of anesthesia, a central venous catheter and transesophageal echocardiography were applied for hemodynamic and cardiac function monitoring. Infusion of the experimental solutions started with a 0.5–μg/kg overload dose for 10 minutes followed by a 0.5–μg/kg/h maintenance dose. Ventilation parameters were adjusted to an end-tidal CO2 of 35–45 mm Hg. During surgery, the vasoactive drugs used included adrenaline, nitroglycerin, norepinephrine, and dopamine. All of the solutions were stopped at the beginning of CPB. The CPB apparatus used included MAQUET oxygenators and a MAQUET circuit filled with cold blood crystalloid cardioplegia. The acid–base balance was guaranteed under medium hypothermia CBP. Sevoflurane inhalation was provided through a Dräger vaporizer attached to the oxygenator and was started at the time of aortic declamping and lasted for approximately 20 minutes. A 1.5 minimum alveolar concentration of sevoflurane was maintained during postconditioning. Anesthesia was maintained using a combination of propofol and sufentanil, with the goal of maintaining the bispectral index between 40 and 60. Hypertension was treated by increasing the dose of sufentanil or propofol or by administration of nitroglycerin if necessary. Hypotension was corrected using phenylephrine as clinically indicated. Inotropic support was provided by infusion of dobutamine or dopamine (both at > 5 mg/kg/min). Adrenaline was added if these medications were insufficient. After surgery, the

**FIGURE 1.** Flow diagram of the patients included in this prospective study. DEX, dexmedetomidine; Non-DEX, without dexmedetomidine; NYHA, New York Heart Association.
patients were transferred to the intensive care unit (ICU) and sedated with propofol, sufentanil, or a combination of both as required (the dosage was controlled by the ICU physician). Vasoactive drugs were administered in the ICU based on the physician’s standard care.

Central venous blood samples were collected at several time points (immediately after induction and 1, 6, 12, and 24 hours after CPB) and centrifuged immediately at 3000 rpm for 10 minutes. Serum was stored at −80°C for analysis. The primary endpoint of this study was the cTnI measured at 24 hours after cessation of CPB. To support this endpoint, we analyzed the cTnI at multiple time points after CPB. The secondary endpoints were the levels of CK-MB, superoxide dismutase (SOD), malondialdehyde (MDA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-8, which were analyzed by the laboratory with respect to the safety and prognosis of patients.

Troponin I levels were measured with an enzyme immunoassay (MyBioSource, San Diego, CA) in the central laboratory. Inflammation and oxidation–reduction markers were measured using standard diagnostic kits purchased from Jiancheng Biotechnology Co, Ltd (Nanjing, China). Renal dysfunction was defined as serum creatinine concentrations greater than 200 μmol/L. Hypotension was defined as a MAP <60 mm Hg, and bradycardia was defined as an HR <80 beats/min when patients presented in the ICU. Anemia and hypoalbuminemia were defined as a hematocrit <24% and an albumin level <30 g/L in the ICU, respectively. Coagulopathy was defined as a prothrombin time longer than 14.8 seconds.

Hemodynamic data, including systolic arterial pressure, diastolic pressure, MAP, HR, and central venous pressure (CVP), were recorded before and after induction of anesthesia, during sternotomy, before and after CPB, during sternum closure, and at the end of the operation. Throughout the perioperative period, the use of several major medications was recorded, including propofol and sufentanil during surgery, as well as inotropic drugs in the ICU. The average dosage and the ratio (%) of each drug used during anesthesia, during sternotomy, before and after CPB, during sternum closure, and at the end of the operation.

Statistical Analysis
Continuous variables are expressed as the mean ± SD or the median (interquartile range), and categorical and rank variables are expressed as counts (%). SPSS (version 17.0, Chicago, IL) was used to conduct independent t-tests or χ² tests for continuous or categorical variables when appropriate, and the Mann–Whitney U test was applied for continuous variables with non-normal distributions. Variance analysis of repeated measurements was used for comparisons of the cTnI, IL-6, IL-8, and TNF-α values at different time points. IL-6 and IL-8 levels were transformed into log values due to their non-normal distributions. All reported P values were 2-sided, and P values <0.05 were considered significant.

RESULTS

Study Populations
Between August 20 and October 30, 2018, 35 patients scheduled for elective on-pump valve replacement surgery were considered eligible for recruitment. Of these patients, 28 (intention to treat population) were included and randomized to the treatment protocols after various medical evaluations and acquisition of consent. Two patients (1 from each group) failed to undergo the follow-up because of their families’ unwillingness to continue participation. These dropouts occurred during hospitalization in the ICU. In total, 13 patients in each group (per-protocol populations) completed follow-up (Fig. 1).

Baseline Characteristics of the Patients
The demographic and intraoperative data were well balanced between the 2 groups and are summarized in Table 1. No significant differences were found in age, height, body weight, body surface area, sex, diabetes mellitus, hypertension, ejection fraction, hemoglobin level, and smoking history between the 2 groups. The baseline hemoglobin levels were comparable between the 2 groups (12.3 ± 2.7 vs. 11.9 ± 2.4 g/dL).

Differences in cTnI Levels Between the 2 Groups
The mean cTnI at 24 hours after CPB was obviously decreased in the DEX group compared with that in the non-DEX group at the same time point (4.16 ± 1.58 vs. 6.90 ± 3.73, P < 0.05, Fig. 2). The same trend in cTnI values at T1, T2, T3, and T4 was shared by all patients; however, the appearance of the peak cTnI value was delayed in the DEX group (the peak cTnI values appeared at T2 and T3 in the non-DEX and DEX groups, respectively), and eventually, no difference was observed in the measurements across time points between the 2 groups (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/JCVP/A390). The same trend was also found for CK-MB levels, with no difference found between the 2 groups at any time points (see Figure 2, Supplemental Digital Content 2, http://links.lww.com/JCVP/A391).

Differences in Inflammatory Indicators Between the 2 Groups
The TNF-α levels were lower in the DEX group at the time points after CPB (T1–T5), and a significant difference was found at 1–6 hours after CPB (1 hour, 19.03 ± 6.83 vs. 28.09 ± 8.13; 12 hours, 20.74 ± 7.58 vs. 30.94 ± 19.09, P < 0.05, compared with the non-DEX group, Fig. 3). IL-6 and IL-8 concentrations were dramatically increased in the DEX group from 6 hours after CPB compared with those in the non-DEX group. The greatest statistical increase in IL-6 was found at 6–24 hours after CPB (logIL-6 at 6 hours, 2.41 ± 0.25 vs. 2.12 ± 0.33; logIL-6 at 12 hours, 2.40 ± 0.39 vs. 2.13 ± 0.20; logIL-6 at 24 hours, 2.23 ± 0.36 vs. 1.99 ± 0.22, P < 0.05, compared with the non-DEX group, Fig. 4). The greatest increase in IL-8 was found at 6–12 hours after CPB (logIL-8 at 6 hours, 1.50 ± 0.22 vs. 1.29 ± 0.28;
TABLE 1. Demographic and Intraoperative Data for Both Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-DEX Group (n = 14)</th>
<th>DEX Group (n = 14)</th>
<th>P</th>
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<td>Age, y</td>
<td>Mean ± SD</td>
<td>58.6 ± 8.9</td>
<td>57.4 ± 9.3</td>
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<td>Sex</td>
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<td>22.0 (3.0)</td>
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<td>Hemoglobin (g/dL)</td>
<td>Mean ± SD</td>
<td>12.3 ± 2.7</td>
<td>11.9 ± 2.4</td>
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<td>Coexisting diseases, n, %</td>
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<tr>
<td>Hypertension</td>
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<td>3 (21.4)</td>
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<tr>
<td>Diabetes</td>
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<td>1 (7.1)</td>
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<td>Renal failure</td>
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<td>Mitral + tricuspid surgery</td>
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<td>1 (7.1)</td>
<td>0.596</td>
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<tr>
<td>Mitral + aortic surgery</td>
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<td>Cardiotoxic drugs</td>
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<td>Antiplatelet drugs</td>
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<tr>
<td>Cardiotoxic drugs</td>
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<td>Sulfentanil (μg)</td>
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<td>159.3 ± 28.1</td>
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<td>Propolol (mg)</td>
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<tr>
<td>Operation time</td>
<td>208 (45)</td>
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<td>0.392</td>
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Values of continuous variables are presented with a median with interquartile range [median (IQR)] or mean ± SD if appropriate. Categorical data are presented with percentages (n, %). The P values were obtained from the Student t-test, Mann-Whitney U test, χ² test, or Fisher exact test, as appropriate.

*ACEI, angiotensin-converting enzyme inhibitors; BMI, body mass index; DEX, dexmedetomidine; LVEF, left ventricular ejection fraction; NYHA, the New York Heart Association.*


dexmedetomidine; LVEF, left ventricular ejection fraction; NYHA, the New York Heart Association.

FIGURE 2. The mean cTnI detected in the peripheral blood at 24 hours after CPB in the 2 groups. Bars represent mean ± SD (n = 13 for each group). cTnI, troponin I; DEX, dexmedetomidine; Non-DEX, without dexmedetomidine, saline instead. *P < 0.05, compared with the non-DEX group.


Hemodynamic and Recovery Characteristics of All Patients

Hemodynamic data, including the systolic arterial pressure, diastolic pressure, MAP, HR, and CVP, were recorded at several time points for both groups and showed identical trends during the procedure. Although DEX can increase the CVP to a certain degree (approximately 2 cmH₂O), no statistically significant hemodynamic difference was found between the 2 groups (see Figures 4–8, Supplemental Digital Contents 4–8, http://links.lww.com/JCVP/A393, http://links.lww.com/JCVP/A394, http://links.lww.com/JCVP/A395, http://links.lww.com/JCVP/A396, and http://links.lww.com/JCVP/A397, respectively).

The postoperative data during hospitalization indicated that comparable amounts of vasoactive drugs were used, and a comparable incidence of adverse events in the ICU was observed in the 2 groups, except for a lower anemia incidence in the DEX group (non-DEX, 10% vs. DEX, 5%, P < 0.05). Regarding recovery parameters, such as ICU stay durations, extubation times, and postoperative hospitalization times, no statistical significance was found between the 2 groups, although the patients in the DEX group exhibited a slightly faster recovery than those in the non-DEX group (see Table 1, Supplemental Digital Content 9, http://links.lww.com/JCVP/A399). The comparison of 5-month survival after the operation between the 2 groups is shown in Supplemental Digital Content 10 (see Figure 9, http://links.lww.com/JCVP/A398). No difference in the median survival time was observed, with only 1 patient death in the non-DEX group (log rank, P = 0.155, see Figure 9, Supplemental Digital Content 10, http://links.lww.com/JCVP/A398).

DISCUSSION

In this prospective, double-blind, randomized, controlled study conducted to examine pre-CBP DEX infusion logIL-8 at 12 hours, 1.44 ± 0.45 vs. 1.07 ± 0.19, P < 0.05, compared with the non-DEX group, Fig. 5). No differences were found in the MDA content and SOD activity between the 2 groups at 24 hours after CPB (see Figure 3, Supplemental Digital Content 4, http://links.lww.com/JCVP/A393, http://links.lww.com/JCVP/A394, http://links.lww.com/JCVP/A395, http://links.lww.com/JCVP/A396, and http://links.lww.com/JCVP/A397, respectively).

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in valve replacement surgery compared with standard sevo-
fluurane postconditioning, our data suggest that DEX can help
reduce the cTnI at 24 hours after CPB and provide 2-way
regulation of the in-
fl
ammatory response.

The application of CPB is recognized as a potent source
of inflammatory mediators, IRI, and cardiac dysfunction.
Sevo
fluurane postconditioning has been extensively used in
cardiac procedures, particularly for myocardial IRI. The
protective mechanisms reported by numerous experimental
and clinical studies include anti-apoptotic, anti-in
fl
ammatory,
and anti-
–
endoplasmic reticulum stress mechanisms. Although
Lemoine et al recommended in 2016 that additional clinical
studies should be conducted,7 few studies have reported
positive effects of sevo
fluurane postconditioning in cardiac
surgery until recently. One reason for the lack of studies may
be due to the subtle effect of sevo
fluurane postconditioning,
although the use of sevo
fluurane for cardioprotection during
procedures was strongly recommended by De Hert.16 How-
ever, the outcomes from cardiac studies concerning sevo-
fluurane conditioning indicated an obviously inhibited
inflammatory response.17,18 Thus, in this study, the sevo-
fluurane postconditioning group was selected as the control
group.

DEX has well-established protective effects against IRI
in multiple organs,14 such as the heart, liver, brain, and kid-
ney. Most of the mechanisms noted in experimental studies
involved inflammatory response suppression19,20,24 or were
related to TLR signaling pathways such as the TLR4 path-
way.20,22,23 Since the first clinical study concerning the
cardioprotective effect of DEX began,25 the search for ideal
strategies for cardiac patients has continued. Zeynep’s study25
found a decreased cTnI in the DEX group after CPB; how-
ever, this effect was diminished possibly because DEX was
infused during the entire procedure, which led to unstable
blood pressures or prolonged surgery times in the DEX
group. In the current study, the baseline variables were well
balanced between the 2 groups, and the DEX infusion

FIGURE 3. The mean TNF-α values detected in the peripheral
blood of the 2 groups were recorded after induction (1) and at
1 hour (2), 6 hours (3), 12 hours (4), and 24 hours (5) after
CPB. The non-DEX group was applied for a standard sevo-
fluurane postconditioning. The DEX group was applied an ex-
tra DEX infusion after induction until the beginning of cardio-
pulmonary bypass. TNF-α, tumor necrosis factor-α; DEX,
dexmedetomidine; Non-DEX, without dexmedetomidine,
saline instead. Values are expressed as mean ± SD (n = 13
for each group). *P < 0.05, compared with the non-DEX group.

FIGURE 4. The mean IL-6 values detected in the peripheral
blood of the 2 groups were recorded after induction (1) and at
1 hour (2), 6 hours (3), 12 hours (4), and 24 hours (5) after
CPB. The non-DEX group was applied for a standard sevo-
fluurane postconditioning. The DEX group was applied an extra
DEX infusion after induction until the beginning of cardio-
pulmonary bypass. Values are expressed as mean ± SD (n = 13
for each group). *P < 0.05, compared with the non-DEX group.

FIGURE 5. The mean IL-8 values detected in the peripheral
blood of the 2 groups were recorded after induction (1) and at
1 hour (2), 6 hours (3), 12 hours (4), and 24 hours (5) after
CPB. Values are expressed as mean ± SD (n = 13 for each
group). *P < 0.05, compared with the non-DEX group.
strategy mitigated the negative side effects of DEX. The combined effect of DEX and sevoflurane showed a fluctuating trend comparable with that observed in the control group. Finally, an obviously decreased cTnI value was found at 24 hours after CPB.

Regarding inflammatory response indicators, TNF-α, IL-6, and IL-8 are the most prominent inflammatory cytokines studied in various research fields. The most well-recognized mechanisms by which DEX mitigates the inflammatory response include inhibition of the NF-kB pathway, Toll-like receptors, or several inflammatory mediators.26–30 Li’s meta-analysis of the anti-inflammatory effects of DEX treatment during routine general anesthesia indicated significantly decreased IL-6, IL-8, and TNF-α levels.31 Chen’s research30 investigating the effect of DEX infusion throughout entire procedures on myocardial IRI illustrated the anti-inflammatory effects of DEX in CABG surgeries under CPB. To the best of our knowledge, this study is the first to present the combined use of DEX preconditioning and sevoflurane postconditioning without DEX infusion throughout the entire procedure. Our study also found increasing levels of proinflammatory indicators in the peripheral blood after CPB, which indicated a dramatic inflammatory response. Although the DEX group may have had a decreased level of TNF-α, similar to that found in other studies,32 obvious upregulation of IL-6 and IL-8 was detected at 6 hours after CPB, unlike other reports,26,33,34 which contributed to 2-way regulation of the inflammatory response. The most likely reason for these increases in IL-6 and IL-8 may be the greater negative influence of DEX on IL-6 and IL-8 when standard sevoflurane postconditioning is applied; otherwise, downstream regulation of the TLR4 or NF-kB pathway may be involved; however, whether the TLR4 or NF-kB level was inhibited in the present context is unclear. Therefore, the related mechanisms warrant further study.

Based on the transfusion standard after cardiac surgery used in a study by Hajjar,15 we found that DEX pretreatment with sevoflurane postconditioning could reduce blood transfusion requirements in cardiac surgery by 5% according to the same anemia standard. It is more likely that the anemia was interfered by DEX with coagulation function or due to some interaction happened between DEX and different medications. The mechanism of this result needs further research. The MDA content and SOD activity were comparable among all patients.

We acknowledge that this study has several limitations. (1) This pilot study was performed on a small sample size in a single hospital; therefore, the data should be interpreted with caution. (2) The study period stopped at 24 hours after CPB, which is not sufficient for an adequate explanation of the impact of the intervention on the conclusions. (3) Blood loss was not recorded, causing difficulty in determining the reasons for the difference in the anemia incidence between the 2 groups. (4) The distribution of the inflammatory marker data was non-normal, possibly because of the small sample size. The corresponding results should be interpreted with caution, and a large-scale study is warranted in the future.

CONCLUSIONS

In valve replacement surgery with sevoflurane post-conditioning, pre-CPB administration of DEX can reduce the cTnI at 24 hours after CPB, decrease the need for post-operative blood transfusion, and provide 2-way regulation of the inflammatory response.

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