International Journal of Pharmacology

ISSN 1811-7775

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OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2023.574.584

Research Article
Myocardial Protection of Dexmedetomidine and Sevoflurane Pretreatment in Patients Undergoing Valve Replacement

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Abstract

Background and Objective: Surgical trauma stimulation during aortic valve replacement (AVR) with cardiopulmonary bypass (CPB) can induce inflammatory response, which causes myocardial ischemia-reperfusion and induces myocardial injury. This study aims to elucidate the involvement of the Toll-Like Receptor 4 (TLR4)/Nuclear Transcription Factor-κB (NF-κB) signaling pathway in regulating the inflammatory response and myocardial protection in patients undergoing AVR after dexmedetomidine combined with sevoflurane pretreatment. **Materials and Methods:** A retrospective analysis was conducted on the clinical data of 60 patients who underwent AVR with CPB at Nanchong Central Hospital. Based on their anesthetic regimen, 28 patients pretreated solely with sevoflurane were included in the control group, while 32 patients received a combined pretreatment of dexmedetomidine and sevoflurane were included in the experimental group. **Results:** At 24 hrs postoperatively, myocardial injury markers (creatine kinase isoenzyme, cardiac troponin I, N-terminal pro-brain natriuretic peptide), Partial Pressure of Carbon Dioxide ($PaCO_2$), TLR4, NF-κB, inflammatory response markers (interleukin-6, interleukin-8, tumor necrosis factor-α, C-reactive protein) levels were significantly increased compared to preoperative values in both groups. However, these increases were less pronounced in the experimental group than in the control group. In contrast, oxygen index (OI) and Partial Pressure of Oxygen (PaO_2) were significantly reduced postoperatively but were higher in the experimental group than in the control group ($p<0.05$). **Conclusion:** The combined pretreatment with dexmedetomidine and sevoflurane effectively enhances myocardial protection in patients undergoing AVR.

Key words: Aortic valve replacement, dexmedetomidine, sevoflurane, TLR4/NF-κB signaling pathway, inflammatory response

Citation: Xie, D., B. Dong, D. Lv, H. Xiang and H. Feng, 2023. Myocardial protection of dexmedetomidine and sevoflurane pretreatment in patients undergoing valve replacement. Int. J. Pharmacol., 19: 574-584.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cardiac valve disease is a prevalent clinical pathology with an escalating incidence rate, particularly with the advent of an aging population in China. Concomitantly, the occurrence of valve lesions induced by senile valve disease, coronary artery disease and myocardial infarction is on the rise[1]. Initial stages of heart valve disease often go unnoticed in patients and as the disease advances, symptoms such as angina, dyspnea, vertigo and hemoptysis may ensue, thereby posing a substantial threat to the patient's well-being and survival[2].

Currently, aortic valve replacement (AVR) employing cardiopulmonary bypass (CPB) is a widely adopted therapeutic approach with proven efficacy for treating heart valve disease[3]. However, the surgical intervention can incite an inflammatory response, amplified by the necessity for cardiac arrest during the procedure. The resulting myocardial ischemia-reperfusion injury, experienced during cardiac resuscitation, further exacerbates myocardial damage[4,5]. Consequently, devising effective strategies for myocardial protection in patients undergoing AVR under CPB is an area of intense clinical interest.

Sevoflurane pretreatment is frequently utilized with the intention of ameliorating myocardial injury in patients undergoing AVR under CPB. However, the overall impact of this strategy remains unsatisfactory[6,7]. Hence, the exploration of superior anesthetic alternatives is necessitated. Dexmedetomidine, an α2-adrenoceptor agonist, is renowned for its diverse effects, including anti-sympathetic, anxiolytic, analgesic and sedative properties, making it a common adjunct in clinical anesthesia[8]. Recently, its application in AVR under CPB has gained momentum and preliminary studies indicate a potential myocardial protective effect. However, the underlying mechanism remains to be fully elucidated[9].

Considering these factors, the present study aims to elucidate the involvement of the Toll-Like Receptor 4 (TLR4)/Nuclear Transcription Factor-κB (NF-κB) signaling pathway in regulating the inflammatory response and its connection to the myocardial protection of dexmedetomidine combined with sevoflurane pretreatment in patients undergoing AVR.

MATERIALS AND METHODS

Patient selection and data collection: A retrospective analysis was performed on the clinical data of 60 patients who underwent AVR under CPB in Affiliated Hospital of North Sichuan Medical College from January to December, 2022. Patients comprised 35 males and 25 females, aged between 32 and 69 years with a mean age of (45.69±3.95) years. According to the New York Heart Association (NYHA) classification, there were 29 patients in grade II and 31 in grade III. As per the American Society of Anesthesiologists (ASA) classification, there were 33 patients in grade II and 27 in grade III. The average body mass index was (22.43±2.03) kg m^{-2}. The primary indications for surgery were rheumatic heart disease (42 cases), mitral stenosis with concurrent closure (9 cases) and aortic septal stenosis (9 cases). Based on the anesthetic protocol utilized, patients were categorized into a control group (n = 28) and a study group (n = 32). This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College. The research objects were informed and they signed a fully-informed consent form.

Inclusion and exclusion criteria: Patients were eligible for the study if they were diagnosed with heart valve disease in accordance with established criteria[10], were between 30-70 years of age, undergoing their first elective AVR under CPB and had complete clinical data. NYHA classification of II-III and ASA classification of II-III were required.

Patients were excluded if they had a left ventricular ejection fraction <45%, were allergic to dexmedetomidine, sevoflurane, or other drugs utilized in this study, had severe preoperative dysfunction of the brain, liver, kidney, or lung and malignant tumors. A history of cardiac surgery, recent heart failure, myocardial infarction and CPB shutdown failure necessitating re-CPB also led to exclusion.

Anesthesia procedure: Upon entering the operating room, patients were subjected to standard cardiac monitoring. A left radial artery puncture was performed under local anesthesia to facilitate blood pressure and arterial blood gas monitoring. Anesthesia was induced using midazolam (0.1-0.2 mg kg^{-1}, Jiangsu Enhua Pharmaceutical Group Co. Ltd., State Pharmacopoeia H20031037), etomidate (0.2-0.3 mg kg^{-1}, Jiangsu Yuanheng Pharmaceutical Co. Ltd., State Pharmacopoeia H20233206), sufentanil (0.2-0.4 μg kg^{-1}, Yichang Renfu Pharmaceutical Co. Ltd., State Drug Registration H20030197) and cis-atracurium (0.15-0.3 mg kg^{-1}, Guangdong Zhongsheng Pharmaceutical Co. Ltd., Drug Registration H20203524) followed by mechanical ventilation via tracheal intubation. Cardiac function and hemodynamics were monitored using esophageal cardiac ultrasound and central venous catheterization.

In the study group, a loading dose of dexmedetomidine (0.5 μg kg^{-1}, Yunnan Longhai Natural Plant Pharmaceutical Co., Ltd., State Drug Administration H20223161) was administered over 10 min, followed by a continuous infusion at 0.5 μg/(kg-hr) until aortic blockade. The control group received a similar volume of saline. Both groups received inhaled sevoflurane (Hebei Yipin Biomedical Co. Ltd., State Pharmacopoeia H20223617) at a concentration of 2% after mechanical ventilation, which was maintained for 30 min before CPB. Anesthesia was maintained intraoperatively with propofol (Jiangsu Yingke Biopharmaceutical Co. Ltd., State Drug Pharmacopoeia H20223914) and sufentanil, aiming for bispectral index (BIS) values between 40 and 60. Elevated blood pressure was managed by increasing the dose of propofol or sufentanil and if necessary, nitroglycerin was used. Hypotension was managed with norepinephrine and vasoactive drugs were administered as needed to maintain circulatory stability.

Outcome measures:

- **Perioperative metrics:** The duration of cardiac resuscitation, time to postoperative awakening and extubation and length of ICU and overall hospital stay were recorded for comparison between the two groups
- **Hemodynamic parameters:** Mean arterial pressure (MAP) and heart rate (HR) were recorded and compared prior to anesthesia induction (T0), after tracheal intubation (T1), post-sternotomy (T2), pre-CPB (T3) and 10 min post-CPB cessation (T4)
- **Myocardial injury markers:** Central venous blood (3 mL) was collected preoperatively and 24 hrs postoperatively. Serum was separated by centrifugation and analyzed for Creatine Kinase Isoenzyme (CK-MB), Cardiac Troponin I (cTnI) and N-terminal pro-brain Natriuretic Peptide (NT-proBNP) using immunosuppression, chemiluminescence and radioimmunoassay techniques, respectively. The kits were supplied by Beijing Yita Biotechnology Co. Ltd. (Beijing, China)
- **Pulmonary function parameters:** Oxygenation index (OI), Arterial Partial Pressure of Oxygen (PaO_2) and Arterial Partial Pressure of Carbon Dioxide ($PaCO_2$) were measured preoperatively and 24 hrs postoperatively using GEM Premier 4000 blood gas analyzer (Instrumentation Laboratory Co. Bedford, Massachusetts, USA)
- **Inflammatory pathway components:** As TLR4 and NF-κB levels were measured in fasting venous blood samples collected preoperatively and 24 hrs postoperatively. The serum samples were analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA), with the kits supplied by Eiaab Science Inc., Wuhan (Wuhan, China)
- **Inflammatory response markers:** Interleukin levels (IL-6, IL-8), Tumor Necrosis Factor-α (TNF-α) and C-reactive protein (CRP) levels were measured preoperatively and 24 hrs postoperatively. The assays were performed using ELISA and immunoturbidimetric methods, respectively. The kits were supplied by Shenzhen HSA Biotech Co. Ltd. (Shenzhen, China)
- **Adverse effects:** The occurrence of adverse anesthetic reactions such as chills, nausea, bradycardia and hypotension were compared between the two groups

Statistical analysis: Statistical analysis was performed using SPSS 23.0. Continuous data, including perioperative indicators, hemodynamics, myocardial injury markers, lungs function parameters, TLR4 and NF-κB levels and inflammatory response markers, were presented as Mean±Standard deviation. The independent sample t-test and paired sample t-test were used to compare between-group and within-group differences, respectively. Repeated measures were analyzed by ANOVA. Categorical data, such as adverse reactions, were presented as percentages and analyzed using the χ^2 test. A $p<0.05$ was considered statistically significant.

RESULTS

Comparison of demographic and clinical data: There was no significant difference in demographic and clinical variables, including NYHA classification, gender, age, ASA classification, body mass index and indications for surgery, between the control and study groups ($p>0.05$). These data were presented in Table 1.

Perioperative parameters: The study group exhibited shorter durations for cardiac resuscitation (Fig. 1a), postoperative awakening (Fig. 1b), extubation (Fig. 1c), ICU stay (Fig. 1d) and overall hospitalization (Fig. 1e) compared to the control group ($p<0.05$) (Fig. 1).

Table 1: Comparison of clinical data between the two groups n/($\bar{\chi}\pm S$)

Group	Sex (male/female)	Age (years)	NYHA classification (grade II/III)	ASA classification (grade II/III)	Body mass index (kg m^{-2})	Reason for surgery (rheumatic heart disease/mitral stenosis combined with closure/aortic septal stenosis)
Control group (n = 28)	15/13	45.32±5.12	11/17	14/14	22.58±2.14	17/4/7
Study group (n = 32)	20/12	45.89±5.23	18/14	19/13	22.31±2.21	25/5/2

NYHA: New York Heart Association and ASA: American Society of Anesthesiologists

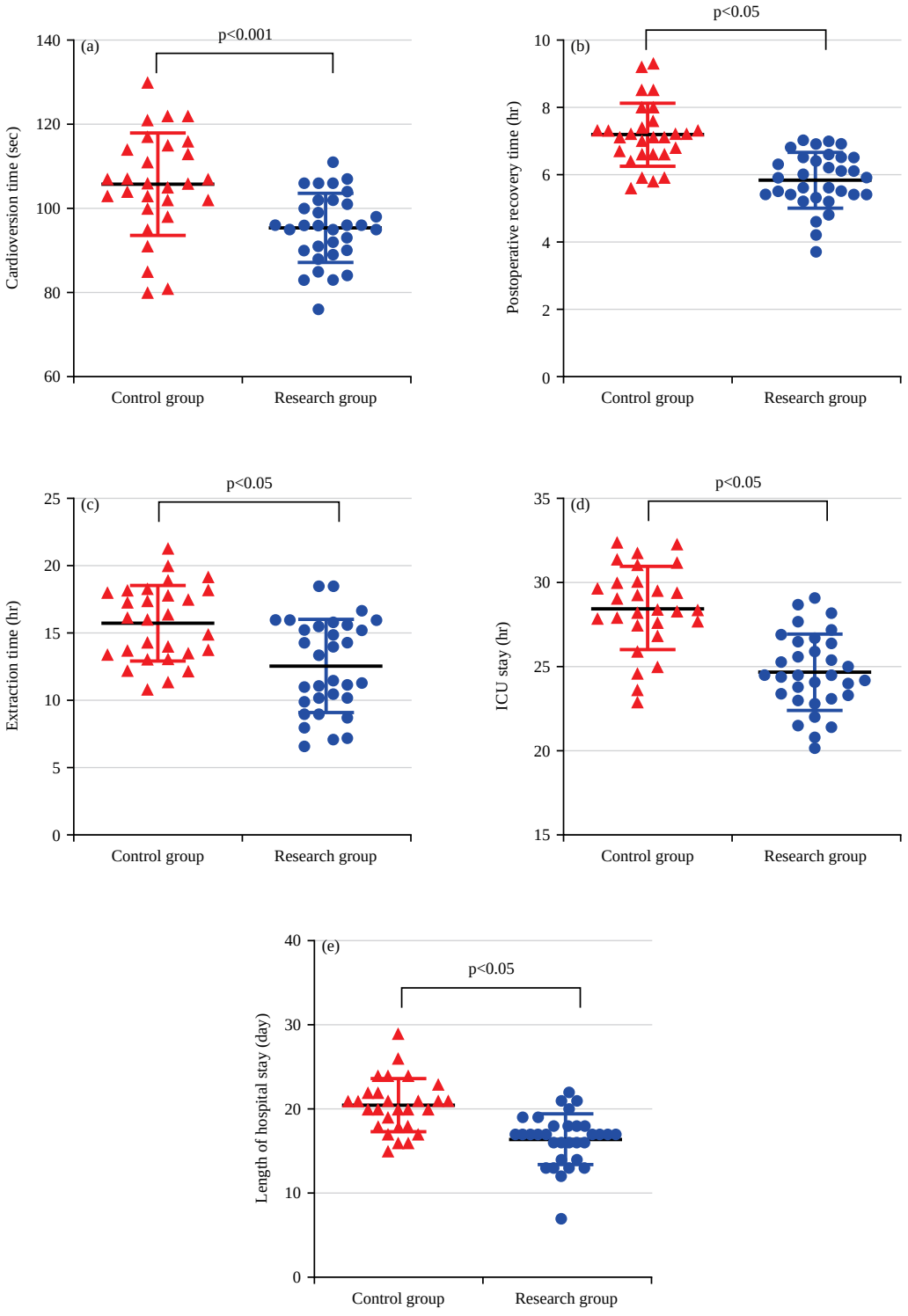

Fig. 1(a-e): Influence of dexmedetomidine and sevoflurane pretreatment on perioperative indices in aortic valve replacement patients, administration of dexmedetomidine in conjunction with sevoflurane pretreatment noticeably curtails, (a) Duration of cardiac resuscitation, (b) Interval to postoperative awakening, (c) Extubation time, (d) Length of intensive care unit (ICU) stay and (e) Overall hospitalization duration in patients undergoing aortic valve replacement
p<0.05 indicates significant difference

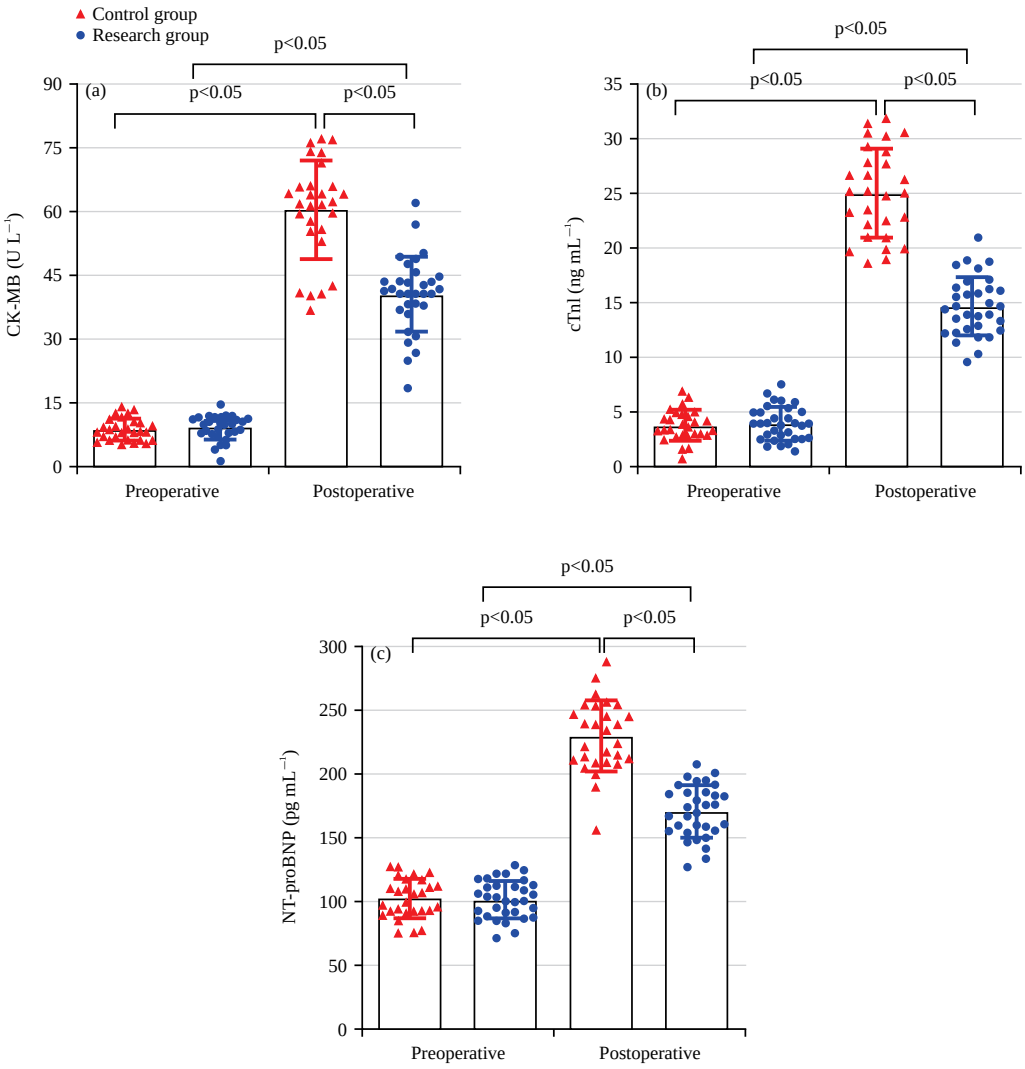

Fig. 2(a-c): Effect of dexmedetomidine and sevoflurane pretreatment on myocardial injury indices in patients undergoing aortic valve replacement, dexmedetomidine combined with sevoflurane pretreatment markedly attenuates the escalation of myocardial injury indices, specifically, (a) Creatine kinase MB (CK-MB), (b) Cardiac troponin I (cTnI) and (c) N-terminal pro b-type natriuretic peptide (NT-proBNP), in patients undergoing aortic valve replacement
p<0.05 indicates significant difference

Hemodynamic assessment: At baseline (T0), no significant difference in heart rate (HR) and mean arterial pressure (MAP) was observed between the groups (p>0.05). At T1-T3, both groups exhibited a higher HR and a lower MAP compared to baseline, with the study group demonstrating lower HR and higher MAP compared to the control group (p<0.05). At T4, no significant difference in HR and MAP was observed between the groups (p>0.05) (Table 2).

Myocardial injury markers: Preoperatively, no significant difference in the levels of myocardial injury markers CK-MB (Fig. 2a), cTnI (Fig. 2b) and NT-proBNP (Fig. 2c) was observed between the groups (p>0.05). At 24 hrs postoperatively, these markers significantly increased in both groups compared to preoperative levels, but the study group demonstrated lower levels compared to the control group (p<0.05) (Fig. 2).

Pulmonary function parameters: At baseline, no significant difference in oxygenation index (OI) (Fig. 3a), Arterial Partial Pressure of Oxygen (PaO_2) (Fig. 3b) and Arterial Partial Pressure Of Carbon Dioxide ($PaCO_2$)

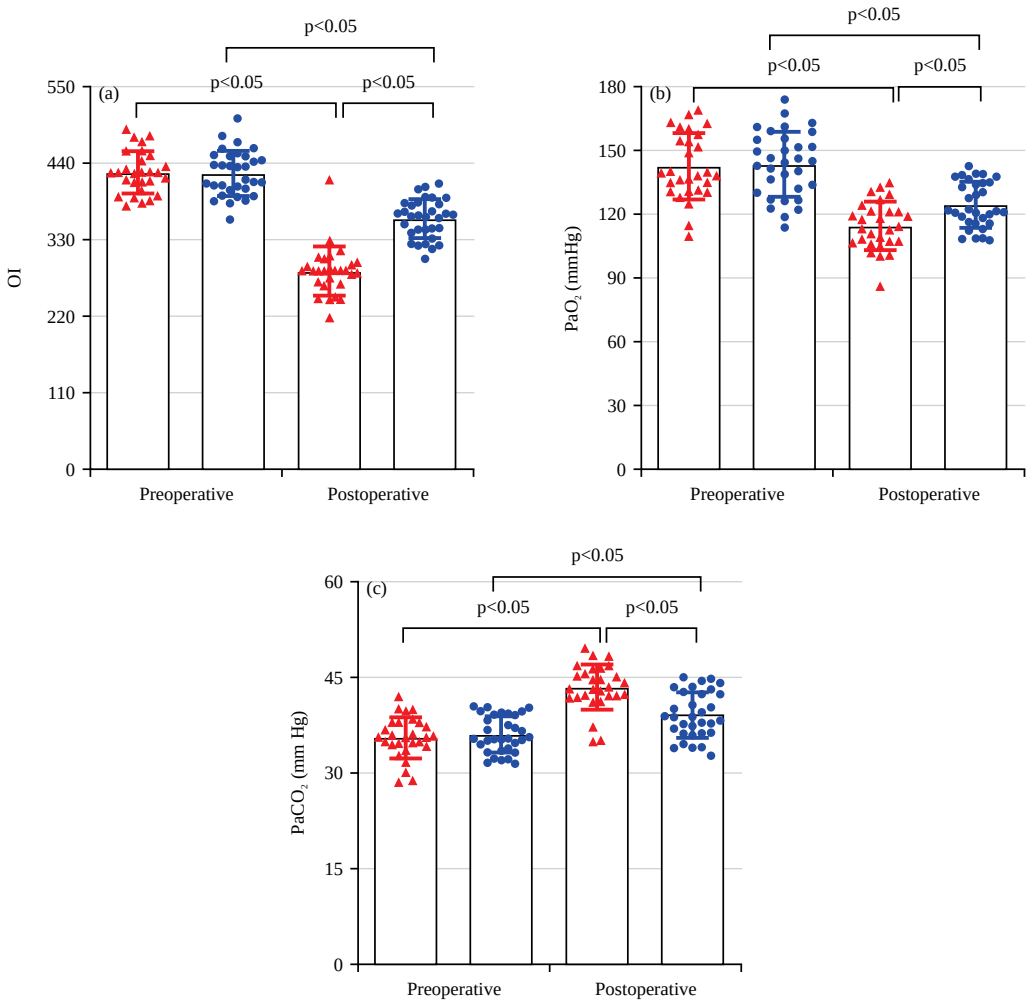

Fig. 3(a-c): Impact of dexmedetomidine and sevoflurane pretreatment on pulmonary function parameters in aortic valve replacement patients, dexmedetomidine co-administered with sevoflurane pretreatment significantly enhances the levels of pulmonary function parameters, specifically, (a) Oxygen index (OI), (b) Arterial oxygen tension (PaO_2) and (c) Arterial carbon dioxide tension ($PaCO_2$), in patients undergoing aortic valve replacement

p<0.05 indicates significant difference

Table 2: Comparison of hemodynamic-related indicators ($\bar{\chi}\pm S$)

Indicators	Group	T0	T1	T2	T3	T4
HR (times min^{-1})	Control group (n = 28)	73.69±2.36	88.96±3.54#	84.26±3.18#	79.52±4.02#	76.25±3.15
	Study group (n = 32)	73.82±2.51	83.58±3.25#*	80.52±3.05#*	76.02±3.02#*	75.91±3.22
MAP (mm Hg)	Control group (n = 28)	88.76±5.25	72.52±2.98#	76.25±3.29#	80.77±4.21#	89.16±4.06
	Study group (n = 32)	89.26±4.87	78.91±3.06#*	80.56±3.57#*	85.54±3.09#*	88.74±3.44

HR: Heart rate, MAP: Mean arterial pressure, T0: Prior to anesthesia induction, T1: After tracheal intubation, T2: Post-sternotomy, T3: Pre-CPB, T4: 10 min post-CPB cessation, #p<0.05 compared to T_0 and *p<0.05 compared to control group

(Fig. 3c) was found between the groups (p>0.05). At 24 hrs postoperatively, OI (Fig. 3a) and PaO_2 (Fig. 3b) were significantly lower and $PaCO_2$ (Fig. 3c) was significantly higher in both groups compared to baseline, with the study group demonstrating higher OI and PaO_2 and lower $PaCO_2$ compared to the control group (p<0.05) (Fig. 3).

TLR4 and NF-κB Levels: Preoperatively, both groups exhibited no marked differences in serum TLR4 (Fig. 4a) and NF-κB (Fig. 4b) levels (p>0.05). At 24 hrs postoperatively, both groups exhibited markedly elevated levels of serum TLR4 (Fig. 4a) and NF-κB (Fig. 4b) compared with preoperative levels, with the study group showing lower levels in contrast to the control group (p<0.05) (Fig. 4).

Inflammatory response markers: At baseline, no significant difference in serum IL-6 (Fig. 5a), IL-8 (Fig. 5b), TNF-α (Fig. 5c) and CRP (Fig. 5d) levels was observed between the groups (p>0.05). At 24 hrs postoperatively, these markers significantly increased in both groups compared to preoperative levels, but were lower in the study group compared to the control group (p<0.05) (Fig. 5).

Adverse reactions: In the control group, there were 1 (3.57) case of chills, 0 case of nausea, 1 (3.57) case of bradycardia and 1 (3.57) case of hypotension, with the incidence of adverse reactions of 10.71%. In the study group, there were 1 (3.13) case of chills, 1 (3.13) case of nausea, 0 case of bradycardia and 2 (6.25) cases of hypotension, with the incidence of adverse reactions

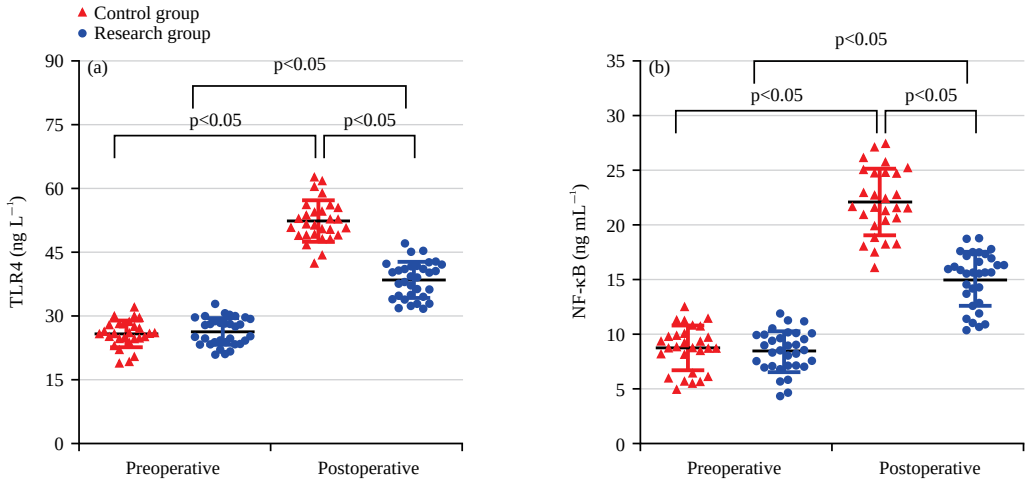

Fig. 4(a-b): Impact of dexmedetomidine and sevoflurane pretreatment on TLR4 and NF-κB levels in aortic valve replacement patients, dexmedetomidine combined with sevoflurane pretreatment appreciably diminishes serum, (a) Toll-Like Receptor 4 (TLR4) and (n) Nuclear Factor-Kappa B (NF-κB) levels in patients undergoing aortic valve replacement, as assessed 24 hrs, postoperatively

p<0.05 indicates significant difference

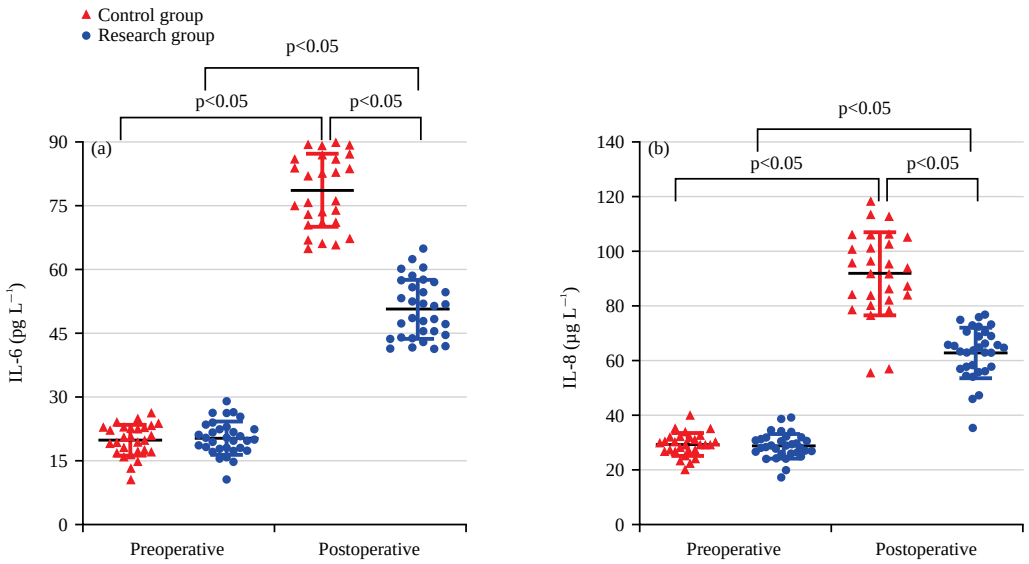

Fig. 5(a-d): Continue

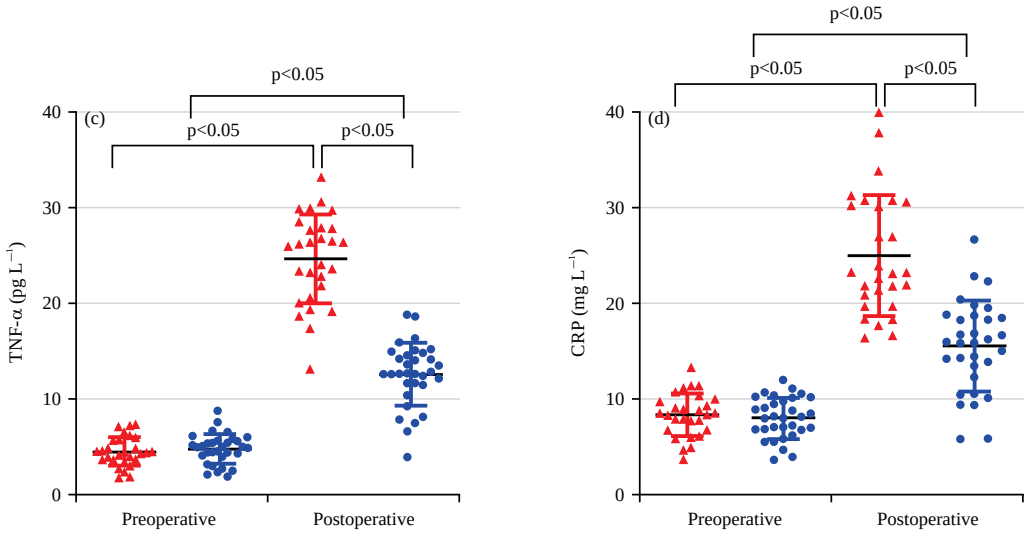

Fig. 5(a-d): Influence of dexmedetomidine and sevoflurane pretreatment on various inflammatory response indicators in aortic valve replacement patients, dexmedetomidine in conjunction with sevoflurane pretreatment significantly reduces serum (a) Interleukin 6 (IL-6), (b) Interleukin 8 (IL-8), (c) Tumor Necrosis Factor Alpha (TNF-α) and (d) C-reactive protein (CRP) levels at 24 hrs, postoperatively in patients undergoing aortic valve replacement
p<0.05 indicates significant difference

of 12.50%. There was no significant difference in the incidence of adverse reactions between the control and study groups (p>0.05).

DISCUSSION

The AVR serves as the primary therapeutic intervention for heart valve disease, fundamentally employing either a synthetic mechanical valve fabricated from specialized materials or a biological valve derived from unique biological tissues[11,12]. Although effective, the procedure's complexity invariably precipitates perturbations in hemodynamics, provoking an imbalance in cardiac blood supply, which may subsequently impair myocardial function[13,14]. Additionally, during cardiopulmonary bypass (CPB), the patient's internal milieu interacts with foreign surfaces, such as oxygenators and tubes, thereby stimulating mononuclear macrophages and the complement system. This interaction instigates the production and release of a vast array of inflammatory cytokines, which, coupled with the necessity of ascending aortic occlusion during CPB, diminishes target organ perfusion and provokes ischemia-reperfusion injury. These factors collectively compromise myocardial function and adversely impact prognosis[15]. Hence, it is crucial to devise effective strategies for myocardial protection to optimize surgical outcomes and hasten postoperative recovery.

Sevoflurane, a widely utilized inhalational anesthetic, is renowned for its rapid induction and ease of depth control, however, its myocardial protective effects, while present, could be augmented[5]. Dexmedetomidine, a prevalent adjunct in clinical anesthesia, has gained significant attention in recent years for its application in cardiac surgery performed under CPB[16]. Tang *et al.*[17] discerned that dexmedetomidine effectively mitigated inflammatory response, ameliorated myocardial injury and curtailed the incidence of adverse cardiac events in patients undergoing AVR under CPB. Mei *et al.*[18] established that perioperative dexmedetomidine use effectively attenuated the damage inflicted by anesthesia, surgery and CPB on the patient's vital organs, thereby reducing the incidence of perioperative complications.

In this study, a regimen comprising dexmedetomidine combined with sevoflurane was implemented, exhibiting reduced cardiac resuscitation, postoperative awakening, extubation, ICU stay and hospitalization duration in the study group relative to the control group. Interestingly, both groups displayed elevated heart rate (HR) at T1-3 compared to T0, alongside a lower mean arterial pressure (MAP) relative to T0, yet the MAP in both groups exceeded that of the control group. Furthermore, the 24 hrs postoperative pulmonary function indices, oxygen index (OI) and arterial oxygen tension (PaO_2) were considerably diminished in both

groups, albeit higher in the study group relative to the control group. Conversely, levels of Arterial Carbon Dioxide Tension ($PaCO_2$), Creatine Kinase MB (CK-MB), Cardiac Troponin I (cTnI) and N-terminal Pro b-type Natriuretic Peptide (NT-proBNP) were substantially elevated, yet lower in the study group compared to the control group. These findings suggested that the combination of dexmedetomidine and sevoflurane yields significant anesthetic effects and can efficiently stabilize hemodynamics while preserving myocardial and pulmonary function in patients undergoing AVR under CPB.

The plausible mechanism behind these effects could be dexmedetomidine's function as a highly selective α2 adrenergic receptor agonist. Dexmedetomidine not only binds to α2 adrenergic receptors in the locus coeruleus of the brainstem but also inhibits norepinephrine release from postganglionic sympathetic nerves, thereby tempering sympathetic excitability and achieving analgesia and sedation[19,20]. Moreover, dexmedetomidine may enhance cardiac vagal tone, diminish myocardial oxygen consumption and boost myocardial reserve capacity, consequently safeguarding myocardial function[21]. Furthermore, dexmedetomidine could potentially diminish the release of inflammatory cytokines, ameliorate the myocardial inflammatory response, minimize inflammatory injury and consequently protect myocardial function, potentially through the activation of cholinergic anti-inflammatory pathways[22].

The AVR, a stressor, incites an inflammatory response in the body, engaging the Toll-Like Receptor 4/Nuclear Factor-Kappa B (TLR4/NF-κB) signaling pathway and encouraging the secretion of a profusion of inflammatory cytokines such as Interleukin 6 (IL-6), Interleukin 8 (IL-8), Tumor Necrosis Factor Alpha (TNF-α) and C-reactive protein (CRP). This sequence exacerbates the inflammatory response and consequently impairs cardiomyocyte function[23]. As a quintessential inflammatory response signaling pathway, TLR4/NF-κB can intensify the inflammatory response in the organism by participating in processes such as immune regulation and oxidative stress, thereby promoting histamine factors and inflammatory cytokines[24]. In this study, serum TLR4, NF-κB, IL-6, IL-8, TNF-α and CRP levels 24 hrs, postoperatively were significantly elevated in both groups, but were relatively lower in the study group compared to the control group. These results suggest that the protective effects of dexmedetomidine combined with sevoflurane on myocardial function in patients undergoing AVR could be associated with the inhibition of the TLR4/NF-κB signaling pathway-regulated inflammatory response.

Further, current study found comparable incidence rates of adverse reactions between the two groups (10.71% vs 12.50%), suggesting that dexmedetomidine combined with sevoflurane does not significantly augment adverse reactions, hence implying a superior safety profile. Nonetheless, the retrospective nature of this study, the relatively small sample size and the single source of cases are limitations that necessitate further investigation. The mechanisms underlying the protective effects of dexmedetomidine combined with sevoflurane pretreatment on myocardial function in patients undergoing AVR warrant exploration in a larger, multicenter, prospective study.

CONCLUSION

The dexmedetomidine combined with sevoflurane pretreatment can effectively protect myocardial function, stabilize hemodynamics and safeguard pulmonary function in patients undergoing AVR, presumably by inhibiting the TLR4/NF-κB signaling pathway-regulated inflammatory response. Furthermore, this regimen presents an encouraging safety profile.

SIGNIFICANCE STATEMENT

Surgical trauma stimulation during aortic valve replacement with cardiopulmonary bypass can induce inflammatory response, which can cause myocardial ischemia-reperfusion and induce myocardial injury. Dexmedetomidine has been gradually applied in aortic valve replacement under cardiopulmonary bypass, which has a potential myocardial protective effect, but its underlying mechanism remains to be fully elucidated. This study aimed to elucidate the involvement of TLR4/NF-κB signaling pathway in regulating the inflammatory response and its connection to the myocardial protection of dexmedetomidine combined with sevoflurane pretreatment in patients undergoing aortic valve replacement. The results found that dexmedetomidine combined with sevoflurane pretreatment effectively enhances myocardial protection, stabilizes hemodynamics and protests lung function in patients undergoing aortic valve replacement by inhibiting the inflammatory response regulated by TLR4/NF-κB signaling pathway.

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