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Original Article

The effects of dexmedetomidine on inflammatory responses in patients undergoing valve replacement surgery with cardiopulmonary bypass

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Abstract: Objective: This prospective study was designed to research the effect of dexmedetomidine (DEX) on reducing the inflammation responses of valve replacement surgery patients under cardiopulmonary bypass (CPB) and explore the safety, efficacy and clinical significance of DEX used in this kind of cardiac surgery. Method: 30 patients were randomly divided into two groups: patients in one group (Group D, n=15) received dexmedetomidine 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ before incision and 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intra-operatively, while the control group (Group C, n=15) received the same volume of saline. Venous blood was collected at several time points for the serum content detection of TNF-α, IL-6, SOD and MDA. Results: Compared with group C, the content of TNF-α in group D declined significantly at time point T_2, T_3, T_4, T_5. The content of serum IL-6 in group D declined significantly at time point T_4 and T_5. Meanwhile, the serum SOD content in group D was obviously elevated with a significant difference at time point T_2, T_3, T_4 ($P<0.05$) and the content of MDA in group D declined significantly at time point T_3, T_4 and T_5 ($P<0.05$). Furthermore, the extubation time and the ICU care duration of group D were both significantly shorten compared with group C ($P<0.05$). Conclusion: The continuous administration of dexmedetomidine during valve replacement surgery with CPB suppressed intraoperative and post-operative cytokine secretion, and improved post-operative inflammatory response indices in the present study. These results can be attributed to the anti-inflammatory effects of dexmedetomidine.

Keywords: Dexmedetomidine, inflammatory reaction, CPB, valve replacement

Introduction

After the first operation using cardiopulmonary bypass (CPB) in the early 1950s, the operative mortality for open heart surgery rapidly decreased each year. Better oxygenators, better surgical techniques, better cardiology, and many other improvements brought the risk of death down to single-digit levels [1]. However, cardiac surgery with cardiopulmonary bypass provoked severe complications, including respiratory failure, renal failure, or multiple organ dysfunction syndrome (MODS). The most common one is the systemic inflammatory response syndrome (SIRS), which can often lead to dysfunction of major organs [2-7].

Surgical trauma, contact with foreign materials, abnormal shear stress, ischemia, reperfusion, hypothermia and pathological situations may cause SIRS in cardiac surgery under CPB. It is reported that SIRS occurring after cardiac surgery is always accompanied by superfluous synthesis of cytokines [8, 9]. Furthermore, these conditions could contribute to complicated inflammatory response, including complement activation and the production of oxygen free radical. If necessary medical care is lacked, these inflammatory cascade response can even cause serious postoperative complications, including respiratory failure, renal failure and even the multi-organ dysfunction syndrome (MODS) [10].

Dexmedetomidine, the highly selective α2-adrenergic agonist, has been used for sedative and analgesic purposes in intensive care units. In recent years, its anti-inflammatory effects have been highlighted. In in-vitro studies, α2-adrenoceptor treatment inhibited the release of cytokines with endotoxaemia [11, 12]. Dexmedetomidine can reduce cytokine secretion,

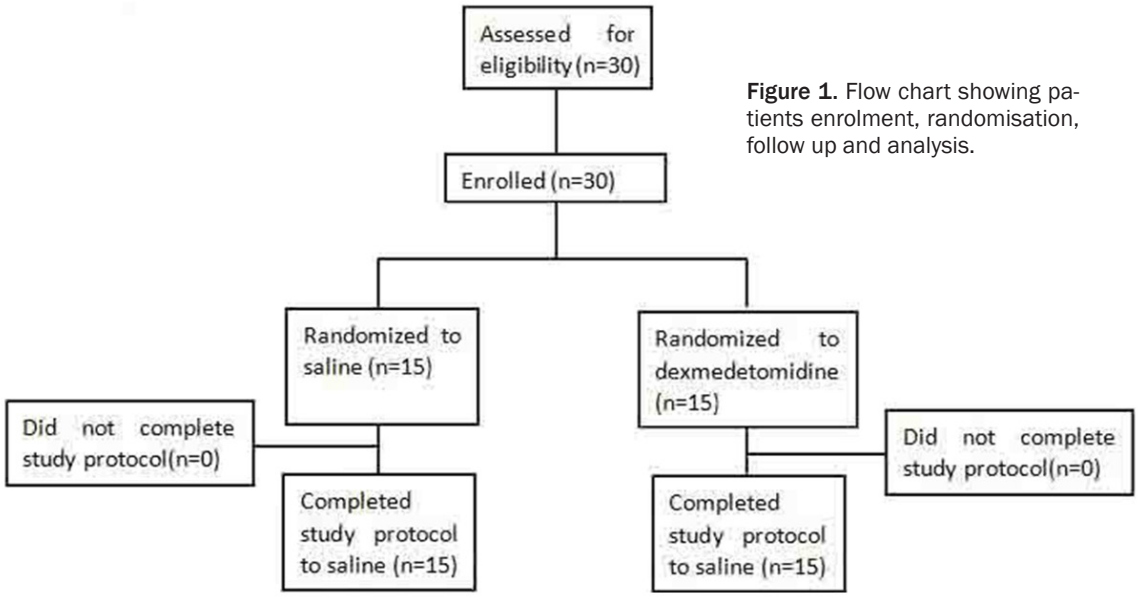

Figure 1. Flow chart showing patients enrolment, randomisation, follow up and analysis.

which subsequently alleviates inflammation and reduces mortality [11, 13]. It was thought that excessive activation of the sympathetic nervous system and inflammation caused by cytokine secretion secondary to immune system interactions were alleviated by central sympatholytic effects of dexmedetomidine. This evidence suggested that harmful inflammatory responses can be suppressed by dexmedetomidine administration in patients who were stressed and have enhanced inflammatory reactions due to surgery and anaesthesia. In addition, dexmedetomidine had organ-protective effects and could inhibit apoptotic cell death that played a pivotal role in the pathogenesis of sepsis [11]. However, the effects of dexmedetomidine, which was commonly used during cardiac surgery, on the systemic inflammation induced by CPB in valve replacement surgery had not been reported.

This study was conducted to determine the effects of dexmedetomidine on inflammatory responses in patients undergoing valve replacement surgery with CPB.

Patients and methods

This was a double-blind, randomized, parallel-group study designed to research the effect of DEX on reducing the inflammation responses of valve replacement surgery patients under cardiopulmonary bypass. Altogether 30 patients were screened and randomized to receive the study treatment in study center (**Figure 1**). The study was performed according to Helsinki Declaration and standards of Good Clinical Practise. The protocol and amendments were reviewed and approved by separate Ethics Committees of the Institutional Review Board of The First Affiliated Hospital of Nanchang University. Informed consent was obtained from all the patients to obtain blood samples for the purpose of this study.

The inclusion criteria

The inclusion criteria were as follows: (1) A patient who complied with surgical indications for valve replacement; (2) Sex is not limited and the patient age is between 24-65 years old; (3) The patient's weight in 40~71 kg and less than 15% of the standard weight fluctuations; (4) A patient with American Society of Anesthesiologists (ASA) grade II~III and without abnormal anesthesia operation history, liver and renal function were not abnormal; (5) A patient without cardiac conduction block and other serious medical complications and have normal left ventricular ejection fraction; (6) Understanding and signed informed consent in clinical trials.

The exclusion criteria

The exclusion criteria were as follows: (1) A patient with Inflammation in the respiratory tract and fever before surgery; (2) A patient

Table 1. Clinical characteristics of the 30 patients (P>0.05)

Groups	Sex ratio (Male/Female)	Age (x±s)	Weight (kg, $\bar{x}$±s)	LVEF (%, $\bar{x}$±s)	Time of CPB (min, $\bar{x}$±s)	Aortic clamping time (min, $\bar{x}$±s)
Group C	7/8	50.37±10.26	48.12±7.19	57.81±7.10	112.62±20.99	71.50±21.46
Group D	7/8	50.23±10.47	50.38±7.27	59.92±8.26	124.15±33.19	83.38±27.02

Note: LVEF: Left ventricular ejection fraction; CPB: Cardiopulmonary bypass.

Table 2. Number of neutrophils in serum ($\times 10^9$/L)

Groups	NO. of neutrophils before the surgery	NO. of neutrophils 24 h after the surgery
Group C	3.36±0.72	16.09±2.93$^{\Delta}$
Group D	2.83±0.81	12.13±1.75$^{\Delta,*}$

Compared with the NO of neutrophils before the surgery, $^{\Delta}$P<0.05; Compared with group C, *P<0.05.

with liver function, renal function, lung function abnormalities; (3) A patient with any grade of heart block or left ventricular ejection fraction of 40% or less; (4) A patient with severe hypertension (SBP/DBP≥180/110), severe anemia and hypoproteinemia; (5) A long-term smoker; (6) A patient with severe respiratory diseases or immune system diseases or mental illness.

Cardiopulmonary bypass

30 Patients (14 males, 16 females) undergoing valve replacement surgery with CPB were randomly assigned (by sealed envelopes) into two groups. Patients in one group (Group D, n=15) received dexmedetomidine 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ before incision and 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intra-operatively, while the control group (Group C, n=15) received the same volume of saline. The randomization was done by the pharmacy, and the code was broken only after data accumulation was complete. Induction of anaesthesia consisted of midazolam (0.1 mg/kg), vecuronium (0.12 mg/kg), sufentanil (1 to 2 g/kg) and propofol (0.5 to 1.0 mg/kg) by intravenous infusion. Anaesthesia was maintained during the operation using propofol, sufentanil, vecuronium bromide and intermittent inhalation of small doses of sevoflurane.

Laboratory tests

Venous blood was collected before anesthesia induction (T_1) and 10 min after the CPB (T_2), 6 h after the CPB (T_3), 12 h after the CPB (T_4) and 24 h after the CPB (T_5). The blood samples were immediately centrifuged at 1000 r/min for 15 min and the serum was stored at -80°C until analysis. After finishing the blood collection, the content of TNF-α, IL-6, SOD and MDA in serum were examined by ELISA method.

Statistical analysis

SPSS 12.0 (USA) was used for data analysis. All data were presented as the mean ± standard deviation and analyzed by two-tailed unpaired Student's t test. P<0.05 was considered statistically significant.

Results

Demographics and clinical characteristics of patients

In total, 30 patients were recruited for the study. The characteristics of patients are summarized in **Table 1**. The groups were similar in sex, age, weight, LVEF, CPB time, aortic clamping time (P>0.05). In both groups, no postoperative major complications (death, myocardial infarction or stroke) occurred up to discharge from hospital, and no patients had adverse events related to dexmedetomidine administration.

Number of neutrophils

As indicated in **Table 2**, the neutrophils content was increased 24 h after the surgery in both group C and group D (P<0.05). Compared with group C, the neutrophils content of group D decreased significantly 24 h after the surgery, while the contents before the surgery were comparable (P<0.05).

The content of serum TNF-α and IL-6

There were no significant differences in baseline (T_1) cytokine concentrations before surgery between the two groups. Compared with T_1 time point, the serum levels of the prionflammatory cytokines - IL-6 and TNF-α, were significantly increased at time points T_2, T_3, T_4, and T_5 in all patients of the two groups (**Figures 2**, **3**).

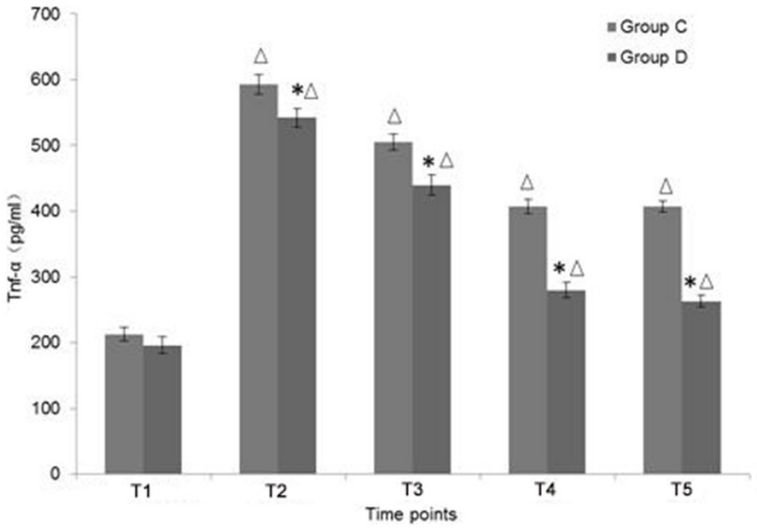

Figure 2. Mean serum levels of TNF-α of patients in Group C and Group D (pg/ml). There were no significant differences in baseline (T_1) cytokine concentrations before surgery between the two groups. Compared with T_1 time point, the serum levels of TNF-α was significantly increased at time points T_2, T_3, T_4, and T_5 in all patients of the two groups. The TNF-α concentrations were significantly lower in group D compared with group C. *P<0.05, compared with group C; ΔP<0.05, compared with T_1.

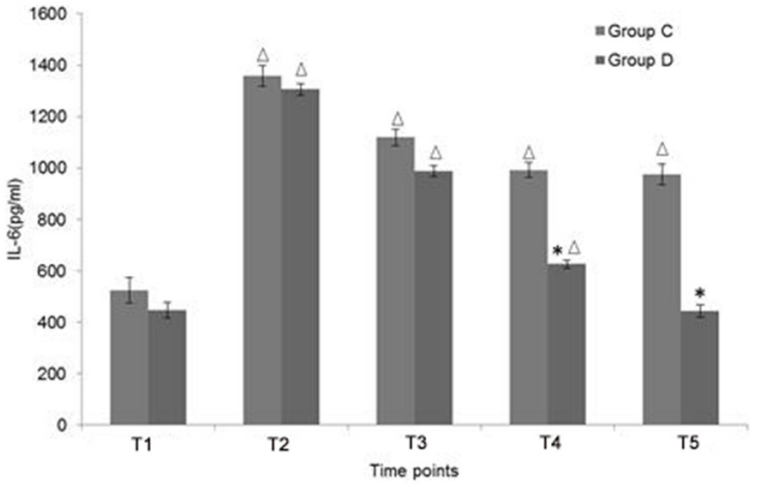

Figure 3. Mean serum levels of IL-6 of patients in Group C and Group D (pg/ml). There were no significant differences in baseline (T_1) cytokine concentrations before surgery between the two groups. Compared with T_1 time point, the serum levels of IL-6 was significantly increased at time points T_2, T_3, T_4, and T_5 in all patients of the two groups. The concentrations of IL-6 showed similar patterns, but the differences were not significant at time points T_2 and T_3. *P<0.05, compared with group C; ΔP<0.05, compared with T_1.

At time points T_2, T_3, T_4 and T_5, the TNF-α concentrations were significantly lower in group D compared with group C (**Figure 2**). The concentrations of IL-6 showed similar patterns, but the differences were not significant at time points T_2 and T_3 (**Figure 3**).

The content of serum SOD and MAD

Figure 4 showed the changes in serum SOD level, which increased significantly over time in group D and returned to normal values at time point T_5. The content of serum SOD in group C showed no significant change at all the other time points compared to time point T_1. Compared with group C, the content of serum SOD in group D increased significantly at time points T_2, T_3, T_4.

Compared to time point T_1, the content of serum MDA at time points T_2, T_3, T_5 changed significantly in group D (P< 0.05), and reached to the peak value at time point T_2. However, the content of serum MDA showed significant difference at all the other time points in group C (P< 0.05). Compared with group C, the serum MDA content of group D reduced significantly at time points T_3, T_4, T_5, but showed no significant difference at time points T_1 and T_2 (P<0.05) (**Figure 5**).

Extubation time, ICU care duration and the dosage of sufentanil comparisons of the two groups

As shown in **Table 3**, compared with group C, the extubation time and ICU care duration of group D were significantly shortened, and the dosage of sufentanil reduced obviously (P<0.05).

Discussion

Surgical trauma leads to profound physiological changes that involve metabolic, inflammatory, immune reactions, and brings about extensive changes in organ functions. During CPB, blood contracts with large areas of foreign materials for a long time could activate the synthesis and

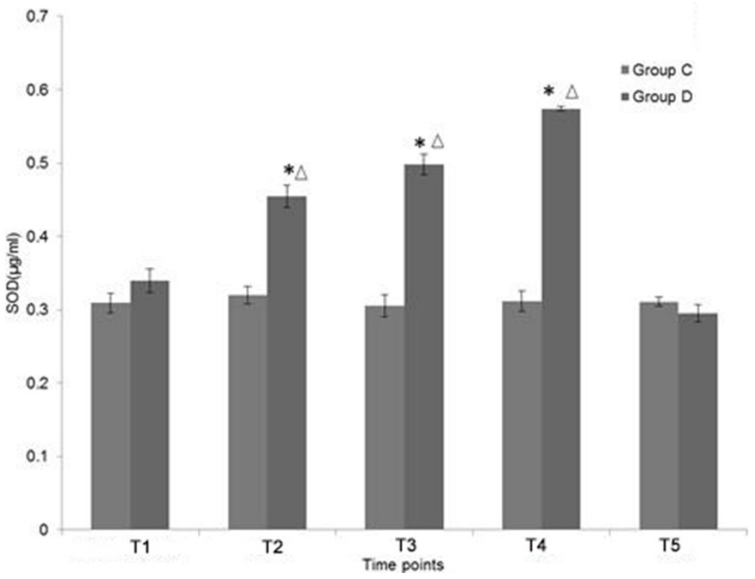

Figure 4. Mean serum levels of SOD in Group C and Group D (μg/ml). The levels of SOD increased significantly over time in group D and returned to normal values at time point T_5. The content of serum SOD in group C showed no significant change at all the other time points compared to time point T_1. Compared with group C, the content of serum SOD in group D increased significantly at time points T_2, T_3, T_4. $^*P<0.05$, compared with group C; $^\Delta P<0.05$, compared with T_1.

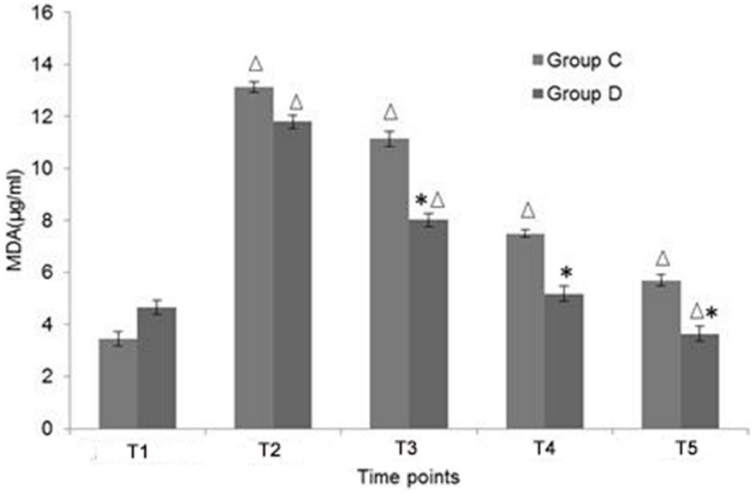

Figure 5. Mean serum levels of MDA in Group C and Group D (μg/ml). Compared to time point T_1, the content of serum MDA at time points T_2, T_3, T_5 changed significantly in group D ($P<0.05$), and reached to the peak value at time point T_2. However, the content of serum MDA showed significant difference at all the other time points in group C ($P<0.05$). Compared with group C, the serum MDA content of group D reduced significantly at time points T_3, T_4, T_5, but showed no significant difference at time points T_1 and T_2 ($P<0.05$). $^*P<0.05$, compared with group C; $^\Delta P<0.05$, compared with T_1.

secretion of inflammatory mediators [14, 15]. The release of these cytotoxic and vasoactive substances could cause multiple organ injury, increasing morbidity and mortality. These endogenous mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8 and IL-6 were related to the degree of tissue injury, as these cytokines was adopted as markers of intensity of the inflammatory reaction, and the measurements of these cytokine is reliable [16, 17].

Prevention measures of the inflammatory response caused by CPB had been attempted using various pharmacological agents and perfusion techniques, but little success had been obtained. Several studies had reported that the alpha-2 receptor agonist dexmedetomidine had many desirable effects in clinical practice [18-22].

In this study, we demonstrated that injection of dexmedetomidine during cardiac surgery under CPB can reduce the content of serum TNF-α and the myocardial damage inducer IL-6. TNF-α, which was an essential mediator responsible for the pathogenesis of myocardial ischemia-reperfusion injury, could causing hypotension and the decrease of systemic vascular resistance and biventricular dilatation via reducing myocardial contractility and ejection fraction [23, 24]. IL-6 produced by monocytes, lymphocytes, and endothelial cells, was thought to have the function of stimulating the interaction between adhesive neutrophil-cardiac myocytes and inducing myocardial damage after CPB [25]. In in-vitro studies, dexmedetomidine had been shown that it could inhibit

Table 3. Extubation time/ICU care duration and the dosage of sufentanil comparisons of the two groups

Groups	Extubation time (h, $\bar{x}\pm s$)	ICU care duration (h, $\bar{x}\pm s$)	The dosage of sufentanil (μg, $\bar{x}\pm s$)
Group C (n=15)	21.7±4.5	34.1±6.6	233.6±75.3
Group D (n=15)	17.8±2.5$^{\Delta}$	28.9±7.0$^{\Delta}$	143.1±39.9$^{\Delta}$

Compared with group C, $^{\Delta}P<0.05$. Note: ICU: Intensive care unit.

TNF-α and IL-6 production in peripheral blood mononuclear cells stimulated by lipopolysaccharides [18, 19]. In a clinical study, dexmedetomidine attenuated IL-6 elevation in postoperative patients [25]. Tasdogan showed that intravenous dexmedetomidine infusion decreases serum cytokine levels (TNF-α, IL-1 and IL-6) after abdominal surgery [26].

The patients in our study were under stress related to surgery and anaesthesia, and dexmedetomidine significantly reduced the concentrations of TNF-α, and IL-6 during and after surgery compared with the levels in the control group. Furthermore, the TNF-α and IL-6 concentrations were reduced by dexmedetomidine during and after surgery compared with the concentrations before surgery despite the presence of stress sources. Our results suggested that the anti-inflammatory effect of dexmedetomidine may be useful in various clinical contexts.

MDA was one of the products of lipid peroxide, the content of which in serum reflects the injury degree of cells by oxygen radical. SOD had already been demonstrated to remove oxygen free radicals and protect the injured cells. The free radical scavenging capacity could be reflected by the content of SOD [26]. Combined with these two indexes, the lipid peroxidation and the reperfusion injury degree could be analyzed. We found that the DEX could improve the concentration of SOD and reduce the MDA concentration. It was indicted that DEX could enhance the free radical scavenging capacity and reduce the generation of free radicals.

Furthermore, we found that the neutrophils of all the patients after the 24 hours extracorporeal circulation were significantly higher compared with before the surgery. Compared with the control group, the neutrophils of the DEX group decreased significantly ($P<0.05$) 24 h after CPB. This illustrated that the inflammatory response of the DEX group was reduced. It had been reported that DEX could reduce neutrophil infiltration and pulmonary edema in the lung and reduce the inflammatory response of patients [27]. However, the anti-inflammatory effect of DEX could be inverted by the α2-adrenaline receptor blockers atipamezole, indicated that the anti-inflammatory effects of DEX were related to the α2-adrenaline receptor dependent and independent pathway [28].

In summary, this study demonstrated that the continuous administration of dexmedetomidine during valve replacement surgery with CPB suppressed intraoperative and post-operative cytokine secretion, and improved post-operative inflammatory response indices in the present study. These results could be attributed to the anti-inflammatory effects of dexmedetomidine.

Disclosure of conflict of interest

None.

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