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*Original Article*

# Protective effect of dexmedetomidine on the brain of patients receiving heart valve replacement and its influence on inflammatory response

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**Abstract:** *Objective:* This study was to investigate the protective effect of dexmedetomidine (Dex) on brain tissues of patients receiving heart valve replacement and its influence on the inflammatory response in brain tissues. *Methods:* A total of 70 patients with heart disease were selected and underwent the heart valve replacement in vitro, and they were divided equally into observation group and control group. Patients in control group were anesthetized via propofol, while those in observation group were anesthetized via propofol + dexmedetomidine. The cognitive function of patients in both groups was evaluated before operation and at 3 d after operation, and the peripheral blood was collected at different time points (before CPB (T0), immediately after CPB (T1), immediately after operation (T2), at 6 h after operation (T3) and at 24 h after operation (T4)) to detect expressions of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasma S-100β and neuron-specific enolase (NSE). *Results:* The levels of plasma TNF-α and IL-6 in patients of both groups were gradually increased at T1-T4, and they were significantly lower in observation group than those in control group (P<0.05). The S-100β protein levels in both groups were increased to different degrees at different time points after operation, displaying statistically significant differences compared with those before operation (P<0.05). The NSE concentration at T2-T4 was increased compared with that at T0 (P<0.05), and it was significantly higher in control group at T1-T4 compared with that at T0 (P<0.05), while it was obviously lower at T1 and T2 in observation group compared with that in control group (P<0.05). *Conclusion:* Dexmedetomidine can significantly reduce the cerebral oxygen metabolic rate, alleviate the brain tissue damage and relieve the inflammatory response during heart valve replacement.

**Keywords:** Dexmedetomidine, heart valve replacement, brain protection, inflammatory response

## Introduction

Cardiopulmonary bypass (CPB) is a kind of auxiliary surgical method. Oxidative stress and inflammatory response possibly occur in patients in the process of heart valve replacement due to various uncertain factors, leading to the release of a large number of oxygen free radicals and inflammatory factors. It even causes damage to a variety of organs in the patient's body, such as the heart, lung and brain [1, 2]. Brain tissues of patients are in an ischemic-hypoxic state during CPB, and the brain nerve of patients is easily prone to damage in case of insufficient blood supply to brain tissues, thus threatening the patient's life safety. Therefore, the necessary protection on tissues and organs, such as the heart and brain, during CPB, is of extreme importance. Dexmedetomidine is a kind of highly-selective α2 adrenergic receptor agonist newly discovered in recent years [3]. When dexmedetomidine binds to the α2 receptor in the spinal cord, it can significantly inhibit the synthesis and secretion of epinephrine. It thereby reduces the synthesis of catecholamine and the neural excitation, while ultimately blocks the pain signal transduction process [4]. It has been reported that this α2 adrenergic receptor agonist can protect brain tissues from ischemia and hypoxia [5]. Engels M et al [6] found that the application of dexmedetomidine can reduce the pain in patients after operation and assist patients maintain deep sleep without side effects on the patient's

breath. This study aims to investigate the protective effect of dexmedetomidine on brain tissues of patients receiving heart valve replacement and its influence on the inflammatory response in brain tissues.

## Materials and methods

### *General data*

A total of 70 patients with heart disease diagnosed and treated in our hospital were selected, and they all underwent heart valve replacement in vitro. There were 35 males and 35 females aged 40-71 years old with the body weight of 42-78 kg, left ventricular ejection fraction (LVEF) ≥35% and mini-mental state examination (MMSE) score ≥24 points in the American Society of Anesthesiologists (ASA) grade II or III. All patients enrolled were randomly and equally divided into observation group (dexmedetomidine) and control group according to the random number table. Exclusion criteria: patients with atrioventricular block, sinus bradycardia, a history of chronic inflammation or central nervous system diseases or taking anti-inflammatory drugs; those with severe diseases affecting cognitive function or mental state after operation; those with other brain diseases or allergy to anesthetics; or those with LVEF <40% or MMSE score <23 points. All patients and their families had signed the informed consent, and this study was approved by the Ethics Committee of Zhejiang Putuo Hospital. There were no statistically significant differences in general clinical data (gender, age, height, weight, LVEF and aortic occlusion time) among patients ($p$>0.05).

### *Methods*

After fasting for solids and liquids at 12 h and 6 h before heart valve replacement, respectively, patients in observation group were injected with 0.4 μg/kg dexmedetomidine solution, while those in control group were injected with 0.01 mg/kg atropine. Vital signs of patients in both groups were monitored using the monitor, and the anesthesia was induced using 0.2 g/kg cisatracurium, 0.2 μg/kg etomidate and 0.5 μg/kg sufentanil. During operation, patients in control group were injected with 2 mg/kg propofol, while those in observation group were injected with 2 mg/kg propofol + 0.4 μg/kg dexmedetomidine for anesthesia till the end of the operation. During CPB, normal saline was injected continuously into patients in control group, while 0.4 μg/kg dexmedetomidine was injected continuously into patients in observation group.

### *Evaluation of therapeutic effects*

The cognitive function of patients in observation group and control group was evaluated using the MMSE score before operation and at 3 d after operation. The total MMSE score was 30 points and the MMSE score ≥24 points in patients educated for more than 6 years indicates the normal cognitive function.

After anesthesia, 2 mL jugular bulb blood and 2 mL radial artery blood were drawn from patients. The jugular venous oxygen saturation ($SjvO_2$), cerebral artery-jugular venous oxygen content difference ($Ca\text{-}jvO_2$) [$Ca\text{-}jvO_2$ = Hb × 1.34 × ($SaO_2$-$SjvO_2$) + 0.003 ($PaO_2$-$PjvO_2$)] and cerebral oxygen extraction rate ($ERO_2$) [$ERO_2$ = ($SaO_2$-$SjvO_2$)/$SaO_2$ × 100%] were detected. Radial arterial oxygen saturation and partial pressure of oxygen were detected and represented the internal carotid arterial oxygen saturation and partial pressure of oxygen, respectively.

Before CPB (T0), immediately after CPB (T1), immediately after operation (T2), at 6 h after operation (T3) and at 24 h after operation (T4), 5 mL peripheral venous blood was collected from patients in observation group and control group, and the supernatant was obtained. Then expression levels of plasma tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), S-100β and neuron-specific enolase (NSE) were detected via enzyme-linked immunosorbent assay (ELISA).

Postoperative recovery: The postoperative recovery (cured, effective and ineffective) of patients in both groups was evaluated according to the symptom evaluation criteria for heart failure of the New York Heart Association [7]. Effective rate of treatment = (cured cases + effective cases)/total cases × 100%.

### *Statistical analysis*

Statistical Product and Service Solutions (SPSS) 19.0 software was used for data analysis. Measurement data were presented as

**Table 1.** MMSE score of patients in both groups before and after operation ($\bar{x} \pm sd$)

| | n | Before operation | 3 d after operation | Incidence rate of cognitive dysfunction |
|---|---|---|---|---|
| Control group | 35 | 27.98±1.22 | 25.99±1.64[a] | 12 (34.29%) |
| Observation group | 35 | 28.04±1.31 | 28.25±1.63[b] | 7 (20.00%) |

[a]P<0.05 vs. before operation, [b]P<0.05 vs. control group at 3 d after operation.

mean ± standard deviation ($\bar{x} \pm sd$). *t* test was used for the significance analysis between groups. Chi-square test was adopted for the significance analysis of enumeration data, and Radit analysis was used for ranked data. P<0.05 was the statistical test level.

## Results

*Evaluation of cognitive function of patients in both groups*

In control group, the MMSE score of patients at 3 d after operation was significantly lower than that before operation ($t = 6.133$, P<0.05). The MMSE score of patients in observation group was significantly higher than that in control group at 3 d after operation ($t = 5.902$, P<0.05). There was no statistically significant difference in the incidence rate of cognitive dysfunction between control group and observation group (34.29% vs. 20.00%) ($\chi^2 = 1.895$, P>0.05) (**Table 1**).

*Expressions of inflammatory factors in plasma of patients in both groups*

The levels of TNF-α in patients in control group and observation group at T1-T4 were significantly higher than those at T0 (P<0.05). At T1-T4, the expressions of plasma TNF-α in observation group were significantly lower than those in control group (P<0.05) (**Table 2**).

The levels of IL-6 in patients of control group and observation group at T1-T4 were significantly higher than those at T0 (P<0.05). At T2-T4, the expressions of plasma IL-6 in observation group were significantly lower than those in control group (P<0.05) (**Table 3**).

*Brain protection indexes of patients in both groups*

The levels of S-100β protein in patients of control group and observation group at T1-T4 were obviously higher than those at T0 (P<0.05). At T3, the level of plasma S-100β protein in observation group were significantly lower than that in control group (P<0.05) (**Table 4**).

The levels of NSE in patients of control group and observation group at T2-T4 were statistically higher than those at T0 (P<0.05). At T1-T2, the expressions of NSE in observation group were significantly lower than those in control group (P<0.05) (**Table 5**).

$SjvO_2$ in observation group and control group at T1 was remarkably higher than that at T0 (P<0.05). $SjvO_2$ in observation group at T1 was statistically higher than that in control group (P<0.05) (**Table 6**).

$Ca\text{-}jvO_2$ in observation group and control group at T1 was statistically lower than that at T0 (P<0.05). $Ca\text{-}jvO_2$ in observation group at T1 was statistically lower than that in control group (P<0.05) (**Table 7**).

$PaO_2$ in observation group and control group at T1-T4 was remarkably higher than that at T0 (P<0.05). $PaO_2$ in observation group at T1 was statistically higher than that in control group (P<0.05) (**Table 8**).

$ERO_2$ in observation group and control group at T1-T2 was apparently lower than that at T0 (P<0.05). $ERO_2$ in observation group at T1 was evidently lower than that in control group (P<0.05) (**Table 9**).

*Clinical efficacy of patients in both groups*

After treatment, the overall effective rate in observation group was 97.14% (34/35), which was significantly higher than that in control group (71.43%, 25/35) (P<0.05) (**Table 10**).

## Discussion

At present, CPB has been widely applied in the operation of heart disease, but there are various uncertain factors affecting the operation results in the process of CPB. For example, ischemia-reperfusion injury of organs, immediate contact between blood and non-physiological vessels and mechanical shearing may cause damage to the lungs, thereby leading to inflammatory response in the body. Systemic

**Table 2.** Plasma TNF-α levels in patients in both groups at different time points ($\bar{x}$ ± sd)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 350±246 | 439±55[a] | 852±124[a] | 1025±112[a] | 859±37[a] |
| Observation group | 35 | 347±214 | 394±40[a,b] | 729±68[a,b] | 934±97[a,b] | 794±66[a,b] |
| *t* | | 0.019 | 4.482 | 5.317 | 3.958 | 6.274 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at each time point.

**Table 3.** Plasma IL-6 levels in patients in both groups at different time points ($\bar{x}$ ± sd)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 34.1±4.3 | 42.9±4.5[a] | 107.2±8.9[a] | 155.8±15.7[a] | 117.3±12.9[a] |
| Observation group | 35 | 33.6±3.5 | 40.2±4.1[a] | 92.3±9.1[a,b] | 140.6±16.3[a,b] | 100.5±8.7[a,b] |
| *t* | | 2.301 | 2.016 | 6.795 | 4.572 | 6.356 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at each time point.

**Table 4.** S-100β protein expression levels in patients in both groups at different time points ($\bar{x}$ ± sd, pg/mL)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 103.7±9.2 | 122.4±7.5[a] | 335±27[a] | 427±22[a] | 389±40[a] |
| Observation group | 35 | 102.8±7.4 | 120.7±3.3[a] | 328±23[a] | 370±44[a,b] | 391±36[a] |
| *t* | | 0.359 | 1.148 | 1.167 | 6.352 | 0.137 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at T3.

**Table 5.** NSE expression levels in patients in both groups at different time points ($\bar{x}$ ± sd, ng/mL)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 12.6±1.5 | 17.9±1.3[a] | 20.8±1.9[a] | 24.1±2.1[a] | 22.5±1.5[a] |
| Observation group | 35 | 12.4±1.7 | 14.4±1.9[b] | 18.9±1.7[a,b] | 23.4±2.5[a] | 21.9±1.4[a] |
| *t* | | 0.489 | 9.482 | 5.831 | 1.038 | 0.941 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at T1-T2.

inflammatory response syndrome (SIRS) may occur in severe cases, resulting in death of patients [8]. It has been reported that the selective α2 adrenergic receptor agonist has a favorable inhibitory effect on TNF-α produced during inflammatory response and attenuates inflammatory response [9]. According to animal experiments, dexmedetomidine can relieve the myocardial ischemia in rats, and thus significantly reduce the incidence rate of nerve injury after transient cerebral ischemia [10]. However, there is little research on whether dexmedetomidine has a similar anti-inflammatory and protective effect on the brain during heart valve replacement under CPB.

Dexmedetomidine can reduce the plasma TNF-α and IL-6 expressions in rats and remarkably decrease the mortality rate of rats with sepsis [11]. It has been found that dexmedetomidine can activate the complement system in the body, leading to the excessive synthesis and release of cytokines. It further results in endotoxemia and stimulates a variety of cells to synthesize and release such inflammatory factors as TNF-α, IL-6 and IL-10 during heart valve replacement [12]. In this study, it was indicated that the levels of plasma TNF-α and IL-6 in patients of observation group and control group were significantly increased after CPB and reached the peak at T3, but they were significantly lower in observation group than those in control group, indicating that dexmedetomidine can effectively alleviate the inflammatory response in patients after operation. However, little is known concerning the related mecha-

**Table 6.** Comparison of $SjvO_2$ between the two groups of patents at different time points ($\bar{x}$ ± sd, %)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 65±5 | 72±6[a] | 66±7 | 65±6 | 64±7 |
| Observation group | 35 | 66±6 | 81±8[a,b] | 67±6 | 66±7 | 65±6 |
| *t* | | 0.642 | 3.952 | 1.947 | 0.431 | 0.585 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at T1.

**Table 7.** Comparison of Ca-$jvO_2$ between the two groups of patents at different time points ($\bar{x}$ ± sd, mmol/L)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 49±8 | 31±7[a] | 47±9 | 57±8 | 56±7 |
| Observation group | 35 | 50±7 | 23±8[a,b] | 46±8 | 58±7 | 57±8 |
| *t* | | 0.503 | 4.286 | 1.382 | 0.741 | 0.575 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at T1.

**Table 8.** Comparison of $PaO_2$ between the two groups of patents at different time points ($\bar{x}$ ± sd, mmHg)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 134±53 | 209±36[a] | 178±38[a] | 199±56[a] | 203±51[a] |
| Observation group | 35 | 135±65 | 230±45[a,b] | 189±36[a] | 201±54[a] | 203±50[a] |
| *t* | | 0.140 | 2.265 | 1.284 | 0.083 | 0 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at T1.

**Table 9.** Comparison of $ERO_2$ between the two groups of patents at different time points ($\bar{x}$ ± sd, %)

| | n | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| Control group | 35 | 38±7 | 26±8[a] | 32±7[a] | 41±8 | 40±7 |
| Observation group | 35 | 36±8 | 17±10[a,b] | 29±8[a] | 39±9 | 39±8 |
| *t* | | 0.915 | 2.895 | 1.718 | 1.375 | 1.052 |

[a]P<0.05 vs. T0, [b]P<0.05 vs. control group at T1.

**Table 10.** Comparison of clinical efficacy between the two groups of patients [n (%)]

| | n | Cured | Effective | Ineffective | Effective rate |
|---|---|---|---|---|---|
| Control group | 35 | 19 (54.29) | 6 (17.14) | 10 (28.57) | 25 (71.43) |
| Observation group | 35 | 29 (82.86) | 5 (14.29) | 1 (2.9) | 34 (97.14)[a] |

[a]P<0.05 vs. control group.

nism. Previous study illustrated that the incidence rate of cognitive dysfunction was 15% at 1 week after joint replacement, but it was increased to 45% after coronary artery bypass grafting [13]. Results of this study revealed that there was no significant difference in the MMSE score between the two groups before operation, but the MMSE score of patients in observation group was significantly higher than that in control group at 3 d after operation, suggesting that dexmedetomidine can improve the cognitive function of patients after operation.

The S-100β protein is one of the members of calcium-binding protein, which can produce great influence on the growth, differentiation and proliferation of neuroglial cells [14]. It has been demonstrated that the S-100β protein expression can be used to evaluate the brain injury in patients receiving heart operation under CPB [15]. NSE is a kind of special acidic protease expressed in the cytoplasm, which can be released out of cells in case of neuronal damage [16]. Therefore, both S-100β protein and NSE are commonly-used clinical indexes for evaluating the brain injury after CPB, as well as sensitive indexes for detecting mild brain injury [17, 18]. In this study, consistently, we found that the S-100β protein expression was increased at T1-T4, and it was significantly higher at T3 in observation group than that in control group. The NSE level was increased at T2-T4 compared with that at T0, and it was higher in control group at T1-T4 than that at T0, while it was significantly lower at T1-T2 in observation group than that in control group, indicating that dexmedetomidine can relieve the NSE release after CPB during administration, but the plasma NSE level is not affected after drug withdrawal. The clinical detection of $SjvO_2$, Ca-$jvO_2$, $PaO_2$ and $ERO_2$ can reflect the metabolic status of brain tissues, in

which the decline in $SjvO_2$ indicates increased oxygen consumption or decreased oxygen supply in the brain [19]. It was found in this study that $SjvO_2$ and $PaO_2$ in observation group at T1 were obviously higher than those in control group, while Ca-$jvO_2$ and $ERO_2$ in observation group were obviously lower than those in control group. $PaO_2$ was remarkably increased and $ERO_2$ was extraordinarily decreased in both groups, suggesting that the brain metabolic rate and oxygen consumption of patients in observation group were decreased, the tolerance ability of brain tissues to hypoxia was increased, and the brain injury was alleviated. At the same time, $SjvO_2$ was higher than 50% in both groups of patients at each time point, indicating that no significant imbalance of cerebral oxygen supply and demand occurred in both groups during anesthesia [20]. After treatment, the overall effective rate in observation group (97.14%) was significantly higher than that in control group (71.43%), suggesting that dexmedetomidine presents good protective effect on the brain of patients and improves the patient's quality of life.

## Conclusion

In conclusion, dexmedetomidine can significantly reduce the cerebral oxygen metabolic rate, alleviate the brain tissue damage and relieve the inflammatory response during heart valve replacement, which finding provides new insights into an auxiliary mean for the heart valve replacement.

## Disclosure of conflict of interest

None.

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