

Protective effect of dexmedetomidine on perioperative myocardial injury in patients with Stanford type-A aortic dissection

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SUMMARY

OBJECTIVE: To investigate the protective effect and mechanism of dexmedetomidine (Dex) on perioperative myocardial injury in patients with Stanford type-A aortic dissection (AD).

METHODS: Eighty-six patients with Stanford type-A AD were randomly divided into Dex and control groups, with 43 cases in each group. During the surgery, the control group received the routine anesthesia, and the Dex group received Dex treatment based on routine anesthesia. The heart rate (HR) and mean arterial pressure (MAP) were recorded before Dex loading (t0), 10 min after Dex loading (t1), at the skin incision (t2), sternum sawing (t3), before cardiopulmonary bypass (t4), at the extubation (t5), and at end of surgery (t6). The blood indexes were determined before anesthesia induction (T0) and postoperatively after 12h (T1), 24h (T2), 48h (T3), and 72h (T4).

RESULTS: At t2 and t3, the HR and MAP in the Dex group were lower than in the control group ($P < 0.05$). Compared with the control group, in the Dex group at T1, T2, and T3, the serum creatine kinase-MB, cardiac troponin-I, C-reactive protein, and tumor necrosis factor- α levels were decreased, and the interleukin-10 level, the serum total superoxide dismutase, and total anti-oxidant capability increased, while the myeloperoxidase and malondialdehyde levels decreased (all $P < 0.05$).

CONCLUSIONS: Dex treatment may alleviate perioperative myocardial injury in patients with Stanford type-A AD by resisting inflammatory response and oxidative stress.

KEYWORDS: Dexmedetomidine. Aneurysm, dissecting. Myocardium. Oxidative stress. Inflammation/metabolism. Inflammation mediators/metabolism.

INTRODUCTION

Aortic dissection (AD) refers to the tearing of the aortic intima under the action of certain pathogenic factors. In this disease, the blood flows into the middle

layer of the aortic wall through the torn intimal orifice, which causes the intima to exfoliate along the aortic cavity to form a hematoma, i.e., pseudolumen.

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AD is a rare but fatal disease that is dangerous and progresses rapidly. Patients with AD often die from hematoma rupture, massive hemorrhage, and pericardial tamponade¹. The high-risk factors of AD include hypertension, Marfan's syndrome, aortic degeneration, cocaine abuse, atherosclerosis, and so on, and hypertension and Marfan's syndrome are the most common^{2,3}. According to the location of the primary rupture and the treatment methods, AD is classified as Stanford type A and B. Stanford type-A AD is more common, which involves the ascending aorta. In Stanford type-A AD, the period from the onset to the 14th day is the acute phase, during which the active drug treatment to control blood pressure and appropriate analgesia and sedation should be performed⁴. At present, surgery is the most effective method to treat Stanford type-A AD, but the operation process is complicated, with great trauma and bleeding, and the incidences of postoperative complications and mortality rate are high⁵. The acute myocardial infarction, pericardial tamponade, hypotension, shock, and old age are the main risk factors for early death after surgery in AD patients⁶. Therefore, strengthening the perioperative myocardial protection and blood pressure management are of great significance to improve the success rate of surgery and prognosis of patients. Dexmedetomidine (Dex) is an imidazole derivative that selectively activates the α_2 adrenergic receptors. It is widely used in clinical anesthesia assistance due to its sedative, analgesic, and sympathetic blockade effects⁷. Dex can reduce the number of other drugs to achieve the best intoxication effect while minimizing side effects. At present, there are many animal experiments on the protective effect of Dex on myocardium^{8,9}. Clinical studies mainly focus on cardio-protection of Dex during coronary artery bypass grafting^{10,11}, but the application of Dex for Stanford type-A AD is rarely reported. The aim of this study was to investigate the protective effect and mechanism of Dex on perioperative myocardial injury in patients with Stanford type-A AD, so as to provide a reference for its further clinical application.

SUBJECTS AND METHODS

Subjects

The clinical data of 86 patients with Stanford type-A AD receiving surgery in the Shengli Oilfield Central Hospital (Dongying, China) from July 2014 to December 2017 were selected. There were 56 males

and 30 females, aged 28-69 years, with an average age of 47.52 ± 8.31 years. The body mass index (BMI) was 23.11 ± 4.92 kg/m². There were 19 cases of smoking history, 50 cases of hypertension history, and 11 cases of diabetes mellitus history. The American Society of Anesthesiologists (ASA) grade was III (49 cases) or IV (37 cases). The anesthesia duration was 254.48 ± 55.04 min. The cardiopulmonary bypass (CPB) duration was 138.98 ± 28.12 min. The surgery duration was 275.28 ± 59.28 min. Eighty-six patients were randomly divided into Dex and control groups, 43 cases in each group. There was no significant difference in gender, age, BMI, smoking history, hypertension history, diabetes mellitus history, ASA grade, anesthesia duration, CPB duration, or surgery duration between Dex and control groups ($P > 0.05$). This study was in line with the medical ethics standards and was approved by the ethics committee of the Shengli Oilfield Central Hospital. Informed consent was obtained from all subjects.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 18-70 years old; Stanford type-A AD confirmed by clinical and imaging examinations, within 14 days of onset; normal liver and kidney function. The exclusion criteria were as follows: complicated with other cardiopulmonary diseases; neurological dysfunction; obvious severe tissue perfusion defects; a long-term history of sedative use.

Anesthesia and intraoperative monitoring

In the two groups, after admission, oxygen was inhaled by mask, and ECG and pulse oxygen saturation were monitored routinely. At the same time, a bispectral index monitor was used to monitor the depth of anesthesia. The peripheral venous access of one upper limb was opened and a compound sodium lactate Ringer solution was intravenously dripped. Left-radial-artery puncture catheterization was performed to monitor the arterial blood pressure. The induction and maintenance of anesthesia were the same in the two groups. An intravenous injection of midazolam (0.05-0.1 mg/kg), etomidate (0.10-0.30 mg/kg), rocuronium (1.00 mg/kg) and sufentanil (1.00-2.00 μ g/kg) was used for the induction of anesthesia. After endotracheal intubation, mechanical ventilation was performed. The oxygen concentration was 60%, with an oxygen flow rate of 0.5-1.0 L/min, a tidal volume of 8-10 ml/kg, I/E ratio of 1: 2, and a respiratory rate of 10-14 times/min. The end-expiratory partial pressure

of carbon dioxide was maintained at 35-45 mmHg. The right internal jugular vein was punctured, and a three-chamber 7F central venous catheter (depth 13-15 cm) was placed for infusion and monitoring of the central venous pressure. Intravenous infusion of sufentanil [0.5-1.5 $\mu\text{g}/(\text{kg}\cdot\text{h})$] and propofol [4-6 $\text{mg}/(\text{kg}\cdot\text{h})$] was used for anesthesia maintenance. Intermittent intravenous injection of pancuronium was performed to maintain muscle relaxation. The intraoperative bispectral index was maintained at 40-60. In the Dex group, after anesthesia induction, Dex was intravenously dripped (1 $\mu\text{g}/\text{kg}$) for 10 min, followed by intravenously dripping at a rate of 5 $\mu\text{g}/(\text{kg}\cdot\text{h})$ to the end of surgery. The control group received an intravenous drip of 0.9% sodium chloride after anesthesia, using the same volume and methods as in the Dex group. All surgical operations were performed under general anesthesia, deep hypothermic circulatory arrest, and selective cerebral perfusion, and were completed by the same group of surgeons.

Hemodynamic monitoring

The heart rate (HR) and mean arterial pressure (MAP) were recorded before Dex loading (t0), 10 min after Dex loading (t1), at the skin incision (t2), sternum sawing (t3), before cardiopulmonary bypass (t4), at the extubation (t5), and at the end of surgery (t6).

Determination of blood indexes

The peripheral venous blood samples were collected before anesthesia induction (T0), and postoperatively after 12h (T1), 24h (T2), 48h (T3), and 72h (T4). After centrifuging at 3000 rpm for 10 min, the serum was stored in a refrigerator at -70 °C. The serum levels of myocardial injury indexes, including creatine kinase-MB (CK-MB) and cardiac troponin-I (cTnI), inflammatory cytokines, including C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and IL-10 and oxidative stress indexes, including total superoxide dismutase (TSOD), total anti-oxidant capability (TAOC), myeloperoxidase (MPO) and malondialdehyde (MDA), were determined by enzyme-linked immunosorbent assay. The operations were carried out strictly according to the instructions of the kits (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA). The enumeration data were presented as number and rate, and the

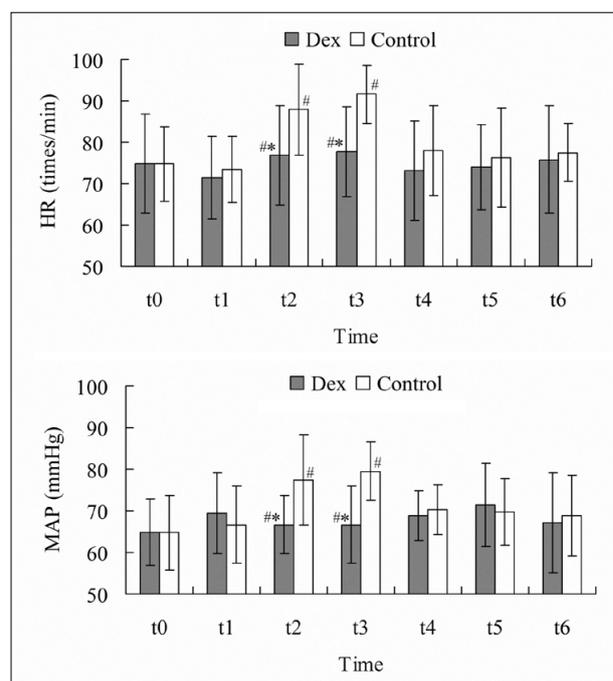
comparison between the two groups was performed using the χ^2 test. The measurement data were presented as mean \pm standard deviation, and the comparison between the two groups was performed using the t-test. Statistical significance was accepted at two-sided $P < 0.05$.

RESULTS

Comparison of HR and MAP between two groups

As shown in Figure 1, from t0 to t6, the HR and MAP in the control and Dex groups gradually increased, followed by a decrease. At t2 and t3, the HR and MAP in the Dex group were significantly lower than those in the control group ($P < 0.05$). At all the other time points, there was no significant difference in the indexes between the two groups ($P > 0.05$).

FIGURE 1. COMPARISON OF HR AND MAP BETWEEN THE DEX AND CONTROL GROUPS.



$P < 0.05$ compared with t0; * $P < 0.05$ compared with the control group. HR, heart rate; MAP, mean arterial pressure; Dex, dexmedetomidine.

Comparison of serum CK-MB and cTnI levels between two groups

At T0, T1, T2, T3, and T4, the serum CK-MB level in the Dex group was 2.92 \pm 0.41, 24.5 \pm 3.43, 16.83 \pm 2.36, 15.04 \pm 2.10, and 7.21 \pm 0.98 ng/ml, respectively; in the control group, it was 2.82 \pm 0.39, 29.7 \pm 4.16, 27.7 \pm 3.88, 17.21 \pm 2.38, and 8.03 \pm 1.12 ng/ml, respectively. At T0,

T1, T2, T3, and T4, the cTnI level in the Dex group was 0.33 ± 0.05 , 2.21 ± 0.31 , 1.63 ± 0.22 , 1.42 ± 0.20 , and 0.89 ± 0.12 ng/ml, respectively; in the control group, it was 0.31 ± 0.04 , 3.27 ± 0.45 , 2.35 ± 0.32 , 2.52 ± 0.35 , and 1.31 ± 0.18 ng/ml, respectively. From T0 to T4, the serum CK-MB and cTnI levels in the Dex and control groups increased, followed by a decrease. Each of them was the highest at T1. In addition, at T1, T2, and T3, the serum CK-MB level in the Dex group was significantly lower than that in the control group ($P < 0.05$). At T1, T2, T3, and T4, the serum cTnI level in the Dex group was significantly lower than that in the control group, respectively ($P < 0.05$).

Comparison of serum CRP, TNF- α , IL-6, and IL-10 levels between the two groups

With the time prolonging from T0 to T4, the serum CRP, TNF- α , and IL-6 levels in each group increased, followed by a decrease. Over time, the serum IL-10 level in each group decreased, followed by an increase. In each group, the serum CRP level at T2, TNF- α level at T2, and IL-6 level at T1 were the highest among the 5 time points, and the IL-10 level at T1 was the lowest among the 5 time points. In addition, compared with the control group, in the Dex group, the CRP level at T1, T2, and T3 and TNF- α and IL-6 levels at T1, T2, T3, and T4 were significantly decreased ($P < 0.05$), while the IL-10 level at T1, T2, T3, and T4 was significantly increased ($P < 0.05$) (Figure 2).

Comparison of serum TSOD, TAOC, MPO, and MDA levels between the two groups

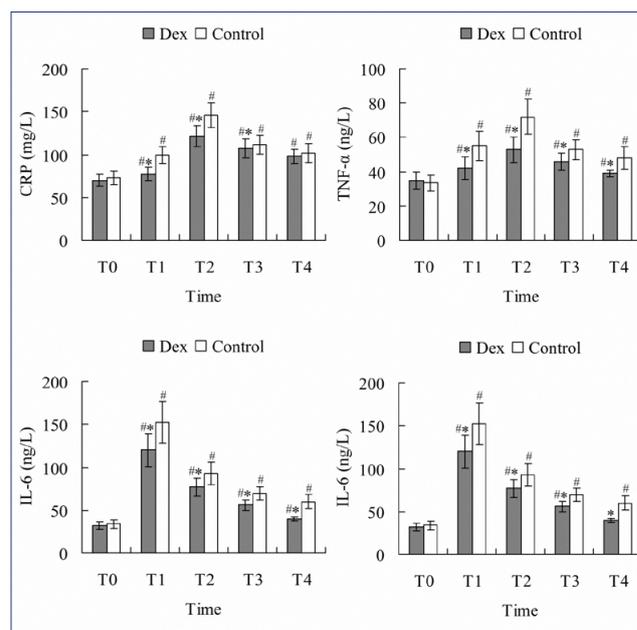
Figure 3 shows that, from T0 to T4, the serum TSOD and TAOC levels in each group decreased, followed by a gradual increase, and the serum MPO and MDA levels in each group increased, followed by a gradual decrease. In each group, the TSOD and TAOC levels at T1 were the highest among the 5 time points, and the MPO and MDA levels at T1 were the lowest among the 5 time points. In addition, compared with the control group, in the Dex group, the TSOD and TAOC levels at T1, T2, and T3 were significantly increased ($P < 0.05$), and the MPO level at T1, T2, and T3 and MDA level at T1, T2, T3, and T4 were significantly decreased ($P < 0.05$).

DISCUSSION

In AD, as the blood continuously flows into the middle layer through the torn intimal orifice, the aortic intima exfoliates to form a hematoma, which leads

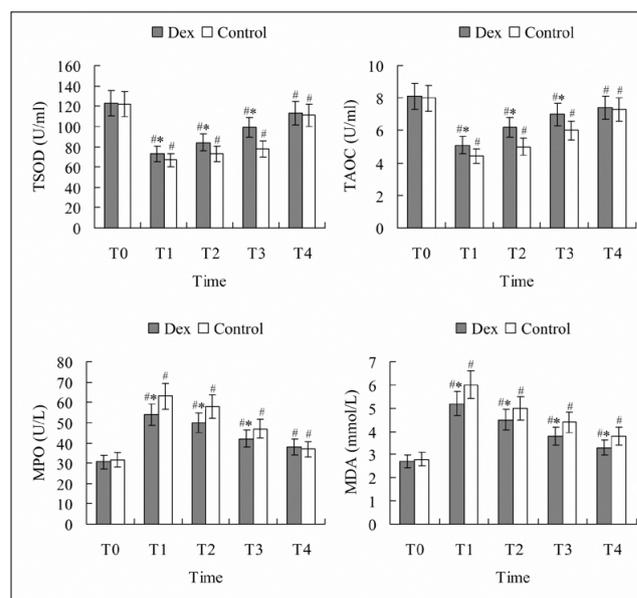
to the weakness of the aortic wall. The increase of blood pressure and tachycardia caused by any reason during the onset of AD may lead to an increase of shear force in the aortic wall and increase the risk of intimal rupture^{12,13}. Therefore, active sedation and

FIGURE 2. COMPARISON OF SERUM CRP, TNF- α , IL-6, AND IL-10 LEVELS BETWEEN THE DEX AND CONTROL GROUPS.



$P < 0.05$ compared with T0; * $P < 0.05$ compared with the control group. CRP, C-reactive protein; TNF- α , tumor necrosis factor- α ; IL, interleukin; Dex, dexmedetomidine.

FIGURE 3. COMPARISON OF SERUM CRP, TNF- α , IL-6, AND IL-10 LEVELS BETWEEN THE DEX AND CONTROL GROUPS.



$P < 0.05$ compared with T0; * $P < 0.05$ compared with the control group. TSOD, total superoxide dismutase; TAOC, total anti-oxidant capability; MPO, myeloperoxidase; MDA, malondialdehyde; Dex, dexmedetomidine.

analgesia, strict control of blood pressure, maintenance of hemodynamics, and reduction of shear force in the aortic wall are the basic principles for the perioperative management of patients with acute AD. This study investigated the protective effect of Dex on patients with Stanford type-A AD. Results showed that, compared with the patients using routine anesthesia, in patients additionally using Dex, the HR and MAP at t2 and t3 were significantly decreased. This indicates that the Dex treatment can further maintain hemodynamic stability during surgery in patients with Stanford type-A AD.

CK-MB is a specific myocardial isozyme, which is abundant in myocardial cells. Under normal circumstances, the serum CK-MB level is very low. When the myocardial cells are damaged, CK-MB is released into the blood in large quantities. It has high sensitivity in judging the myocardial damage and is often used in the clinical diagnosis of myocarditis and for evaluating its severity¹⁴. The cardiac troponin (cTn) molecule is spherical and consists of three subunits including cTnI, cTnT, and cTnC. cTnI in the myocardium is different from that in other muscle tissues. Meanwhile, the molecular weight of cTnI is small. In the early stage of myocardial injury, it can be rapidly released into the blood to increase its blood concentration. cTnI can be used as an early diagnostic index for myocardial injury¹⁵. Results of this study showed that, at T1, T2, and T3, the serum CK-MB level in the Dex group was significantly lower than that in the control group. At T1, T2, T3, and T4, the serum cTnI levels in the Dex group were significantly lower than those in the control group. This indicates that the Dex treatment can alleviate perioperative myocardial injury in patients with Stanford type-A AD.

The occurrence, development, and clinical manifestations of AD are significantly correlated with the inflammatory response¹⁶. CRP is a non-specific marker of inflammation. It is the most powerful predictor and risk factor of cardiovascular disease. Its level is increased rapidly in inflammation, injury, and infectious diseases. A previous study has shown that the serum level of CRP is increased significantly in patients with AD¹⁷. TNF- α is produced by mononuclear macrophages and plays a central role in the inflammatory response. It can promote the inflammatory response by injuring vascular endothelial cells, increasing the expression of endothelial cell-adhesion molecules and other inflammatory factors¹⁸. IL-6 is also a key component of inflammatory

response. It can induce hepatocytes to synthesize acute-phase proteins and regulate macrophages to increase the TNF- α level¹⁹. IL-10 is an endogenous anti-inflammatory factor, which can inhibit the expression of inflammatory mediators such as TNF- α and IL-6²⁰. In the present study, compared with the control group, in the Dex group, the CRP level at T1, T2, and T3 and TNF- α and IL-6 levels at T1, T2, T3, and T4 were significantly decreased, and the IL-10 levels at T1, T2, T3, and T4 were significantly increased. This suggests that the Dex treatment can reduce the inflammatory response in patients with Stanford type A AD, which may be related to its protective effect on myocardial injury.

During the formation of AD, the blockage of aortic branch vessels affects the blood flow, leads to ischemia and poor perfusion of corresponding tissues. The recanalization of vessels can lead to ischemia-reperfusion injury, which can cause a large number of neutrophils to accumulate in the lung, heart, and other organs. They activate degranulation and produce and release a large amount of oxygen free radicals, which cause oxidative stress damage²¹. Lipids in cells have a high affinity with oxygen free radicals. Oxygen free radicals attack lipids, which can damage cell structure and function and produce MDA²². MPO is the key enzyme catalyzing the generation of oxygen free radicals, and its content can also reflect the production of oxygen free radicals²³. SOD and other antioxidant catalytic enzymes can scavenge oxygen free radicals to a certain extent. However, when oxygen free radicals are generated in large quantities and exceed the body's antioxidant capacity, SOD will be continuously consumed and TAOC will be reduced²⁴. Results of this study showed that, compared with the control group, in the Dex group, the TSOD and TAOC levels at T1, T2, and T3 were significantly increased, and the MPO levels at T1, T2, and T3 and MDA levels at T1, T2, T3, and T4 were significantly decreased. This indicates that the Dex treatment can reduce oxidative stress, thus alleviating myocardial injury in patients with Stanford type-A AD.

CONCLUSION

The Dex treatment can alleviate perioperative myocardial injury in patients with Stanford type-A AD. Its mechanism may be related to resistance to inflammatory response and oxidative stress. This study has

provided a reference for further clinical application of Dex in AD surgery. However, the results of this study are obtained only from clinical manifestations and laboratory detections, and no myocardial pathological result has been found. In addition, the correlations among different indexes are not analyzed. These are the limitations of this study, which need to be solved in further studies.

Author's Contribution

Ke Liu and Quan Lin designed the study. Dalong Wang and Meiqing Du participated in data collection. Guanrong Zheng and Weimin Xu performed the statistical analyses. Dalong Wang drafted the manuscript. Ke Liu and Haishan Zhang critically revised the manuscript. All authors read and approved the final manuscript.

RESUMO

OBJETIVO: Investigar o efeito protetor e o mecanismo da dexmedetomidina (Dex) na lesão perioperativa do miocárdio em doentes com dissecação aórtica Tipo A de Stanford (AD).

MÉTODOS: Oitenta e seis pacientes com o Tipo A de Stanford foram aleatoriamente divididos em Dex e grupos de controle, 43 casos em cada grupo. Durante a cirurgia, o grupo de controle recebeu a anestesia de rotina, e o grupo Dex recebeu tratamento Dex baseado na anestesia de rotina. A frequência cardíaca (AR) e a pressão arterial média (MAP) foram registradas no momento anterior ao Dex carregar (t0), 10 minutos após o Dex carregar (t1), incisão cutânea (t2), serragem de esterno (t3), antes do bypass cardiopulmonar (t4), extubação (t5) e fim da cirurgia (t6). Os índices de sangue foram determinados no momento antes da indução da anestesia (T0) e no pós-operatório 12 horas (T1), 24 horas (T2), 48 horas (T3) e 72 horas (T4).

RESULTADOS: Em T2 e t3, o RH e o MAP do grupo Dex foram inferiores ao grupo de controle ($p < 0,05$). Em comparação com o grupo de controle, no grupo Dex em T1, T2 e T3, os níveis séricos de creatina quinase-MB, troponina-I, proteína C-reativa e necrose do fator- α do tumor diminuíram, o nível interleucina-10 aumentou, o desalinhamento total do superóxido sérico e a capacidade antioxidante total aumentaram e os níveis de mieloperoxidase e malondialdeído diminuíram (todos $p < 0,05$).

CONCLUSÃO: O tratamento com Dex pode aliviar a lesão do miocárdio perioperativo em doentes com o Tipo A de Stanford por resistência à resposta inflamatória e ao estresse oxidativo.

PALAVRAS-CHAVE: Dexmedetomidina. Aneurisma dissecante. Miocárdio. Estresse oxidativo. Inflamação/metabolismo. Mediadores da inflamação/metabolismo.

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