Review Article Effects of dexmedetomidine on inflammatory cytokines and oxidative stress in pulmonary tissue of rats with ventilator-induced lung injury

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Abstract: To explore the role of dexmedetomidine on inflammatory cytokines and oxidative stress in pulmonary tissue of rats with ventilator-induced lung injury. Altogether 24 SD rats aged 6-8 weeks were selected and randomly divided into the control group (CG), the treatment group (TG) and the model group (MG), with 8 rats in each group. The CG rats were only treated with thoracotomy to expose left lung after mechanical ventilation. The TG and the MG groups were given mechanical ventilation to establish ventilator-induced lung injury model. The treatment group was injected with 200 mg/kg dexmedetomidine intraperitoneally to analyze the effects of dexmedetomidine on lung function index level, lung dry-wet ratio, lung injury score, alveolar ventilation index and PaO₂ expression of rats. The effects on serum inflammatory cytokines (IL-6, IL-1 β , TNF- α), oxidative stress indexes (MDA, SOD, MPO), apoptosis-related factors (Caspase 9, Caspase 3, Bax, Bcl-2), and lung cell apoptosis were also explored. Dexmedetomidine can improve lung function index of rats, inhibit serum IL-6, IL-1 β , TNF- α to reduce inflammatory state of rats, reduce MDA, MPO and increase SOD to inhibit oxidative stress, and reduce the apoptosis index, NFK-B activity and P65 protein expression level. Dexmedetomidine can reduce lung inflammatory reaction and oxidative stress reaction during mechanical ventilation in rats with lung injury, reduce cell apoptosis and improve lung injury.

Keywords: Dexmedetomidine, ventilator-induced lung injury, pulmonary tissue, inflammatory cytokines, oxidative stress reaction

Introduction

Mechanical ventilation is an irreplaceable therapeutic measure for some clinically severe patients [1, 2]. However, mechanical ventilation often leads to excessive expansion of the patient's lung, thus causing or aggravating lung injury [3, 4]. Especially under large tidal volume, mechanical ventilation will expose the lungs, especially alveoli, to excessive expansion, which will lead to traumatic injury, and then release inflammatory and vasoactive cytokines and prostaglandins, thus leading to pulmonary injury [5, 6]. Clinically, the morbidity and mortality of pulmonary injury patients induced by mechanical ventilation are still very high, and the clinical therapeutic effect is limited at present [7].

Clinically, patients with prolonged mechanical ventilation have longer hospitalization time and

higher mortality rate, and appropriate sedation measures can reduce anxiety and pressure caused by tracheal intubation [8]. Dexmedetomidine is a unique sedative agent, which can improve the pain tolerance ability of patients and also has a sedative effect, and can reduce the agitation of patients [9]. Studies have shown that dexmedetomidine has played a protective role in lung injury models both in vivo and in vitro, such as one-lung ventilation models, which can promote the production of many pro-inflammatory cytokines and activated carbon in patients' lungs, while dexmedetomidine can effectively reduce lung injury [10]. Clinical studies have shown that sedation drugs used after cardiovascular surgery can improve the tolerance of mechanical ventilation, and reduce metabolic requirements and hemodynamic instability in patients' respiratory process. Dexmedetomidine can reduce heart rate and blood pressure moderately, which is related to predictable stable hemodynamic changes and is also an ideal choice for management of patients with mechanical ventilation after cardiovascular surgery [11].

In this study, a mechanical ventilation lung injury rat model was established to observe the effects of dexmedetomidine on inflammatory cells, stress response and apoptosis of pulmonary tissue cells in rats, and to observe its protective mechanism.

Material and method

Experimental animal

Twenty-four SD rats aged 6-8 weeks were obtained from the Animal Experimental Center and kept in a clean environment with good ventilation. Before the experiment, all rats were kept in an environment with indoor humidity of 48-59% and temperature of 21-26°C for 1 week. The experiment was approved by the ethics committee [12].

Establishment of ventilator-induced lung injury rat model

Twenty-four rats were grouped into the control group (CG), the model group (MG) and the treatment group (TG) (8 rats in each group). All rats in the three groups were fasted for 12 h [13] at night before the experiment. They were given free drinking water and intraperitoneal injection of 40 mg/kg of 3% pelltobarbitalum natricum. After anesthesia, the organs were cut open, and the catheter was inserted into tracheal and fixed. The rats in the CG were given mechanical ventilation with a rodent ventilator (Syker Biotechnology Co., Ltd., Beijing, China, Rovent). The rats in the CG were given thoracotomy to expose the left lung after mechanical ventilation and given intraperitoneal injection of 1.5 mL/kg of 10% chloral hydrate (Lianshuo Biotechnology Co., Ltd., Shanghai, China. N/A-969) 5 minutes after thoracotomy. Rats in the TG were given intraperitoneal injection of 1.5 mL/kg of 10% chloral hydrate and 2 mL of saline (Chundu Biotechnology Co., Ltd., Wuhan, China, CD-10794-ML) 5 minutes after thoracotomy. In the treatment group, 200 mg/kg of dexmedetomidine was injected intraperitoneally (Shr Bio Co., Ltd., Nanjing, China, T2524). After 15 minutes, ventilator-controlled breathing and tracheal intubation were started according to the parameters of tidal volume of 40 mL/kg, frequency of 40-60/min, 1:E ratio of 1:1, and positive and negative expiratory pressure of 0. The proportion of oxygen supplied to the TG rats was about 40-50%. Blood samples were obtained from the femoral artery indwelling catheter. The pressure of carbon dioxide was applied to regulate the respiratory frequency of rats, and the respiratory frequency was kept between 35-45 mmHg. After 4 hours of mechanical ventilation, the left lung of the three groups of rats was ligated and the pulmonary artery blood was flushed with solution. Three groups of rats were executed by fast bleeding and the entire trachea, heart and lung were removed.

Outcome measures

(1) Pulmonary function index: Lung function indexes of the three groups of rats were detected by small animal lung function tester (Ranger Apparatus Co., Ltd., Shanghai, China, RZ-flexi), including respiratory peak expiratory flow (PEF), forced expiratory volume in the first second (FEV1) and FEV1/forced vital capacity (FVC).

(2) Lung dry-wet ratio: The rats were executed by fast bleeding and the whole trachea, heart and lung were removed. The collected pulmonary tissue was weighed on an electronic balance, and the wet weight of pulmonary tissue was measured. Then the tissue was placed in a drying oven at 80°C for 48 h to get dry weight. Finally, the wet weight/dry weight ratio of rat pulmonary tissue was obtained to evaluate pulmonary edema.

(3) Pulmonary injury score [14]: The pulmonary tissue was fixed in 4% paraformaldehyde PBS solution (Chreagen Biotechnology Co., Ltd., Beijing, China, 120832) at 4°C for 48 hours, embedded with conventional paraffin, cut to 4 μ m thickness, and dyed with HE (Nanjing Bosgene Biotech Co., Ltd, Nanjing, China) to observe the lung injury. The four indexes (pulmonary interstitial edema, neutrophil infiltration, alveolar edema and alveolar hyperemia) were observed, with no change or slight change as 0 point, mild as 1 point, moderate as 2 points, severe as 3 points and extremely severe as 4 points. The cumulative score of the four grades was the lung injury score.

(4) Determination of inflammatory cytokines and oxidative stress indexes: A total of 5 mL venous blood was collected from rats in the three groups after mechanical ventilation, centrifuged at 1500×g at 4°C for 10 min, and placed in a low temperature refrigerator at -70°C for later use. The expression level of indexes was tested by ELISA [15]. Interleukin-6 (IL-6), interleukin-1ß (IL-1ß), tumor necrosis factor- α (TNF- α), superoxide dismutase (SOD), malondialdehyde (MDA), catalase (CAT), and glutathione peroxidase (GSH-Px) were detected with reference to the instructions of IL-6 (Mu-ItiSciences (Lianke) Biotechnology Corporate Limited, Hangzhou, China, 70-EK106/2), IL-1β (Xi Yuan Biotechnology Co., Ltd., Shanghai, China, XY-JBS-PR-400), TNF-α (Hui Jia Biotechnology Co., Ltd., Xiamen, China, IQP-163R), SOD (Chreagen Biotechnology Co., Ltd., Beijing, China, 13800-1), MDA (Victory Biological Technology Co., Ltd., Sichuan, China, wkq-04658), MPO (Jingke Chemical Technology Co., Ltd., Shanghai, China, ENZ-074-5G), and GSH-Px (Jingkang Bioengineering Co., Ltd., Shanghai, China, JK-(a)-5138) kits.

(5) Cell apoptosis detection: pulmonary tissue was TUNEL stained according to cell apoptosis detection kit (Sanshu Biotechnology Co., Ltd., Shanghai, China, BYT0125) to evaluate cell apoptosis in pulmonary tissue. After incubation with proteinase K (Lianshuo Biological Technology Co., Ltd., Shanghai, China, 1245680100) for 30 minutes, The tissues were rinsed with phosphate buffered saline twice, the slices were incubated with TUNEL reaction mixture for 1 hour, and dyed with $1 \mu g/mL$ DAPI (Chreagen Biotechnology Co., Ltd., Beijing, China, 12632) in the dark for 30 minutes. Ten complete and non-overlapping high power fields (×400) in rat alveolar region were selected under microscope to observe apoptosis (apoptosis index = positive cells/total cells ×100%).

(6) Western blot (WB) detection: A total of 50 mg of pulmonary tissue was taken, and 500 μ L of lysis solution (G-Clone Biotechnology Co., Ltd., Beijing, China, EX6020-100 ml) was added for lysis. After homogenization in ice bath, centrifugation was carried out at 12,000×g, 4°C for 20 min. The supernatant was obtained and the protein concentration was measured by BCA kit. A 12% SDS-PAGE (Whiga Technology Co., Ltd., Guangzhou, China, P0672-250 ml)

was applied for electrophoresis separation, the tissues were then transfered to PVDF membrane after ionization. The transfer membrane was placed in 5% defatted milk powder (Lianshuo Biological Technology Co., Ltd., Shanghai, China, N/A-433) for sealing. The membrane was mixed with Caspase 9 (Biolab Technology Co., Ltd., Beijing, China, K12465), Caspase 3 (Xinyu Biotechnology Co., Ltd., Shanghai, China, XY-11504), Bax (Zhenyu Biotechnology Co., Ltd., Shanghai, China, K001435M), or Bcl-2 antibody (Biolab Technology Co., Ltd., Beijing, K11141) (the dilution ratio was 1:1000) and incubated at 4°C overnight. The membrane was washed to remove the primary antibody, and horseradish peroxidase labeled goat antirabbit secondary antibody (Xinyu Biotechnology Co., Ltd., Shanghai, China, XY0650) (the dilution ratio was 1:1000) was added, placed at 37°C for 1 hour, and washed with PBS for 3 times, 5 min each time. After completion, the ECL luminescent reagent was applied for developing and fixing, the image was taken by the Quantity One. The protein to be detected = gray value of the strip to be detected/gray value of the internal reference protein strip.

Statistical method

GraphPad 6 was used for data analysis and picture visualizing. All data were represented as mean \pm SD. Independent sample t test was applied for comparison between the two groups, and one-way ANOVA for comparison among multiple groups, which was represented by F. LSD-t test was applied for post-event comparison, and repeated measurement ANOVA for multi-time point expression, which was represented by F. Bonferroni was applied for post hoc testing. SPSS18.0 was used for data analysis. P<0.05 was regarded as statistically significant difference.

Result

Comparison of lung function among three groups of rats

The results of lung function tests of the three groups of rats showed that, compared with the CG, PEF, FEV1 and FEV1/FVC in the MG were evidently decreased (P<0.05), while those in the treatment group were evidently increased after dexmedetomidine intervention (P<0.05). See **Figure 1**.





Figure 1. Comparison of lung function of three groups of rats. A. Effects of dexmedetomidine on PEF in rats with lung injury induced by mechanical ventilation. B. Effect of dexmedetomidine on FEV1 in rats with lung injury induced by mechanical ventilation. C. Effect of dexmedetomidine on FEV1/FVC in rats with lung injury induced by mechanical ventilation. Note: compared with the CG or comparison between the two groups, * indicates P<0.05, ** indicates P<0.001.

Dry-wet ratio and lung injury score

We examined the lung indexes of the three groups of rats and found that compared with the CG, the lung dry-wet ratio, lung injury score and alveolar ventilation index of the rats in the MG were evidently enhanced, but PaO_2 was evidently decreased (P<0.05), while after dexmedetomidine intervention, the lung dry-wet ratio, lung injury score and alveolar ventilation index of the rats in the treatment group were evidently decreased, while PaO_2 index was evidently increased (P<0.05). See **Figure 2**.

Role of dexmedetomidine on inflammatory cytokines

We explored the effect of dexmedetomidine on inflammatory cytokines in rats with pulmonary injury induced by mechanical ventilation and found that IL-6, IL-1 β and TNF- α in the serum of rats in the MG were enhanced evidently (P<0.05), while those in the treatment group were decreased evidently after dexmedetomidine intervention (P<0.05). See **Figure 3**.

Effect of dexmedetomidine on oxidative stress in rats with mechanical ventilation lung injury

We explored the effect of dexmedetomidine on oxidative stress in rats with mechanical ventilation lung injury and found that, compared with the CG, SOD and GSH-Px in the serum of rats in the MG were evidently decreased, while MDA and MPO were evidently increased (P<0.05). After dexmedetomidine intervention, it was found that the expression levels of SOD and GSH-Px in the serum of rats in the treatment group were evidently increased, while the expression levels of MDA and MPO were evidently decreased (P<0.05). See **Figure 4**.

Effects of dexmedetomidine on apoptosis and related factors in ventilator-induced lung injury rats

The apoptosis of three groups of rats was observed. We conducted TUNEL analysis, and the results showed that compared with the CG, the apoptosis rate in the MG increased evident-



Figure 2. Lung dry-wet ratio and lung injury score. A. Effects of dexmedetomidine on dry-wet ratio of lung in rats with mechanical ventilation lung injury. B. Effect of dexmedetomidine on lung injury score of rats with mechanical ventilation lung injury. C. Effect of dexmedetomidine on alveolar ventilation index in rats with mechanical ventilation lung injury. D. Effects of dexmedetomidine on PaO₂ in rats with lung injury induced by mechanical ventilation. Note: compared with the CG or comparison between the two groups, * indicates P<0.05, ** indicates P<0.001.

ly (P<0.05), while after dexmedetomidine intervention, it was found that the occurrence of apoptosis in the TG was alleviated and the apoptosis rate was reduced (P<0.05). The level of apoptosis-related proteins in each group was detected. Compared with the CG, the expression and apoptosis rate of apoptosis-related proteins caspase-9, caspase-3, and Bax in the MG were evidently increased, while the expression and cell activity of apoptosis-related protein Bcl-2 were evidently decreased. Application of dexmedetomidine in the treatment group could evidently reverse the above situation. See **Figure 5**.

Discussion

Previous studies have shown that dexmedetomidine is widely used in patients undergoing mechanical ventilation and has anti-inflammatory effect in specific organs by inhibiting the release of inflammatory cytokines [16, 17]. However, there are few studies on the lung protective effect of dexmedetomidine on pulmonary injury caused by mechanical ventilation and its effect on apoptosis of pulmonary tissue. In order to explore the lung protective effect of dexmedetomidine on lung injury caused by mechanical ventilation, this experiment was designed. The results showed that dexmedetomidine can effectively reduce inflammatory cells in rat model, improve oxidative stress level and promote cell apoptosis.

Mechanical ventilation is the main treatment method for patients with respiratory failure and critical illness. It can improve the oxygen cooperation of patients, reduce respiratory function

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Figure 3. Effects of dexmedetomidine on inflammatory cytokines in rats with mechanical ventilation lung injury. A. Effect of dexmedetomidine on IL-6 concentration in rats with lung injury induced by mechanical ventilation. B. Effect of dexmedetomidine on IL-1 β concentration in rats with lung injury induced by mechanical ventilation. C. Effect of dexmedetomidine on TNF- α concentration in rats with lung injury induced by mechanical ventilation. Note: compared with the CG or comparison between the two groups, * indicates P<0.05, ** indicates P<0.001.

and prevent muscle fatigue [18, 19]. However, mechanical ventilation often aggravates pulmonary injury in patients. Although the strategy of mechanical ventilation (lower airway platform pressure, low tidal volume, optimal positive end-expiratory pressure) is widely used clinically, the mortality rate of patients with lung injury is still very high [20]. Moreover, studies have shown that dexmedetomidine can evidently reduce distortion, inflammatory reaction, pulmonary edema and macrophage infiltration caused by hyperoxia, indicating that dexmedetomidine may be a potential therapeutic agent for preventing infant lung injury caused by hyperoxia [21]. PEF, FEV1 and FEV1/FVC of lung function of rats after mechanical ventilation lung injury were evidently reduced, while PEF, FEV1 and FEV1/FVC of rats after mechanical ventilation lung injury were evidently increased after dexmedetomidine intervention. It showed that dexmedetomidine had the effects of anti-sympathetic and inhibiting catecholamine release, and it can effectively reduce the risk of respiratory depression and promote bronchodilation, thus improving the lung function of rats during mechanical ventilation. A previous research showed that airway resistance, lung dry-wet ratio and lung injury score of mechanical ventilation lung injury model were evidently reduced [22]. This finding was similar to that of the present study. Our results showed that after mechanical ventilation lung injury, the lung dry-wet ratio, lung injury score and alveolar ventilation index of rats were evidently increased, but PaO, was evidently decreased. After intervention with dexmedetomidine, the lung dry-wet ratio, lung injury score and alveolar ventilation index of rats with mechanical ventilation lung injury were evidently decreased, while PaO₂ was evidently increased, indicating that dexmedetomidine can gradually increase the dry-wet ratio of lung in rats with mechanical ventilation lung injury, and can obviously reduce the degree of pulmonary tis-



Figure 4. Effect of dexmedetomidine on oxidative stress in rats with lung injury induced by mechanical ventilation. A. Effect of dexmedetomidine on SOD concentration in rats with lung injury induced by mechanical ventilation. B. Effect of dexmedetomidine on MDA concentration in rats with lung injury induced by mechanical ventilation. C. Effect of dexmedetomidine on MPO concentration in rats with mechanical ventilation lung injury. D. Effect of dexmedetomidine on GSH-Px concentration in rats with lung injury induced by mechanical ventilation. Note: compared with the CG or comparison between the two groups, * indicates P<0.05, ** indicates P<0.001.

sue injury in rats with mechanical ventilation pulmonary injury.

Previous studies showed that imbalance of proinflammatory and anti-inflammatory cytokines acts in the pathogenesis of pulmonary injury caused by mechanical ventilation [23]. This study showed that IL-6, IL-1 β and TNF- α in rats with mechanical ventilation lung injury increased evidently, while IL-6, IL-1 β and TNF- α in rats with mechanical ventilation lung injury decreased evidently after dexmedetomidine intervention. This indicated that dexmedetomidine could reduce the release of inflammatory cytokines in rat lungs, thus reducing the level of inflammatory cytokines in vivo and protecting the lungs. Studies have shown that lung injury

during mechanical ventilation can make the lung continuously circulate and stretch, leading to tissue rupture and edema formation, thus stimulating the excessive production of reactive oxygen species, and eventually leading to the decline of antioxidant capacity in the body [24]. This study found that SOD and GSH-Px in rats with mechanical ventilation lung injury decreased evidently, while MDA and MPO enhanced evidently. SOD and GSH-Px in rats with mechanical ventilation lung injury increased evidently after dexmedetomidine intervention, while MDA and MPO decreased evidently. This indicated that dexmedetomidine could inhibit oxidative stress reaction in rats with lung injury induced by mechanical ventila-



Protective role of dexmedetomidine on ventilator-induced pulmonary injury in rats

Figure 5. Effects of dexmedetomidine on apoptosis and related factors in rats with mechanical ventilation lung injury. A. Effect of dexmedetomidine on apoptosis rate in rats with mechanical ventilation lung injury. B-E. Effects of dexmedetomidine on caspase-9, caspase-3, Bax and Bcl-2 in mechanically ventilated lung injury rats. F. Protein map. G. Flow chart of apoptosis. Note: compared with the CG or comparison between the two groups, * indicates P<0.05, ** indicates P<0.001.

tion, thus reducing lung injury. Studies have shown that the non-cell apoptosis rate of ventilator-induced lung injury patients was evidently increased [25]. However, we found through cell experiments that dexmedetomidine could alleviate cell injury and inhibit cell apoptosis in rats with mechanical ventilation lung injury, resulting in an evident decrease of caspase-3, caspase-9 and Bax transcription levels and an evident increase in anti-apoptotic gene Bcl-2.

To sum up, dexmedetomidine can reduce lung inflammatory reaction and oxidative stress reaction during mechanical ventilation in rats with lung injury, reduce cell apoptosis and improve lung injury. However, there is still room for improvement in this study. For example, the mediator of the protective effect of dexmedetomidine on the lung of rats with mechanical ventilation lung injury is not clear, and a dosedependent relationship between dexmedetomidine and its regulatory mechanism can be supplemented. We will gradually improve the study from the above perspective in the future.

Disclosure of conflict of interest

None.

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