Dose-response and mechanism of protective functions of selective alpha-2 agonist dexmedetomidine on acute lung injury in rats

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ABSTRACT

الأهداف: التحقق من الخصائص الوقائية التي يقوم بها ديكس ميد يتو ميدين ضد تضرر الرئة الحاد والذي تم تحفيزه من خلال متعددات السكريد الشحمي لدى عينة من الجرذان.

الطريقة: أُجريت هذه الدراسة في مستشفى زونغشان، شانغهاي، الصين خلال الفترة من مايو 2008م إلى ديسمبر 2009م. شملت الدراسة 40 جرذي من النوع سبراغو دوللي والذين قُسموا عشوائياً إلى المجموعات التالية: مجموعة الشاهد (NS)، ومجموعة متعددات السكريد الشحمي (LPS)، ومجموعة ديكس ميد يتو بجرعات عالية (HD)، ومجموعة ديكس ميد يتو بجرعات متوسطة (MD)، ومجموعة ديكس ميد يتو بجرعات متدنية (LD). وبعد أن قمنا بتحفيز تضرر الرئة بواسطة متعددات السكريد الشحمي قمنا بحقن LD، MD، HD بالجرعات التالية من ديكس ميد يتو ميدين 0.5، 1.5، 4.5 ميكروغرام/كلغ، أما مجموعة الشاهد فقد حُقنت بمحلول الملح فحسب. ولقد قمنا باستخدام الاختبارات الكيميائية المناعية للأنسجة واختبار تفاعل البلمرة المتسلسل المسبوق بالنسخ العكسي من أجل تحليل مدى تضرر أنسجة الرئة في كافة المجموعات.

النتائج: أشارت نتائج الدراسة إلى انخفاض عامل بيتا كابا ومستقبل تول 4 لمراسل الرنا في الأنسجة الرئوية للمجموعتين HD، MD مقارنة بالمجموعة LPS. كما قلت مستويات بيتا معامل تنخر الأورام، وبيتا 1 إنترلوكين، وإنترلوكين 6، بالإضافة إلى نسبة وزن الأنسجة الرئوية الجافة إلى الرطبة وذلك في المجموعتين HD، MD.

خاتمة: أظهرت الدراسة بأن التفاعلات الالتهابية في الأنسجة الرئوية قد قلت بشكل واضح عند تعاطي الجرعات التي تتراوح مابين 4.5–1.5 ميكروغرام/كلغ مما أدى إلى وقاية الأنسجة.

Objectives: To investigate the protective functions of dexmedetomidine on lipopolysaccharide-induced acute lung injury in the lung tissues of rats.

Methods: The experiment was conducted from May 2008 to December 2009 in Zhongshan Hospital, Shanghai, China. Forty Sprague Dawley rats were randomized into a normal group (NS group), a lipopolysaccharide model group (LPS group), and dexmedetomidine groups in high dosages (HD), moderate dosages (MD), and low dosages (LD). After the acute lung injury model was duplicated by lipopolysaccharide, the rats in the LD, MD, and HD groups were injected with 0.5 μg/kg, 1.5 μg/kg, and 4.5 μg/kg of dexmedetomidine. The rats in the NS group were injected with normal saline. Immuno-histochemical and reverse transcription polymerase chain reaction techniques were used to assess the damage of lung tissue in each group.

Results: The nuclear factor-KappaB and Toll-like receptor 4 messenger RNA expression in the lung tissues of the rats in the MD and HD groups were inhibited compared to the LPS group. The amount of tumor necrosis factor-beta, interleukin-1beta, and interleukin-6 as well as the lung tissue wet to dry weight ratio were also reduced in the MD and HD groups.

Conclusion: The inflammatory reactions in lung tissues can be effectively inhibited at doses ranging from 1.5-4.5 μg/kg, resulting in a protective effect on lung tissue.

Saudi Med J 2012; Vol. 33 (4): 375-381

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Received 10th November 2011. Accepted 27th February 2012.

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Acute lung injury (ALI) is the inflammatory reaction that is primarily characterized by injuries to the pulmonary capillary membrane, which are subsequently associated with an increase in permeability and inflammatory cell infiltration and severely interfere with gas exchange.[1] The etiological factors for ALI are varied and mortality rates are high. Elucidating the mechanism of pathogenesis and appropriate treatments are high priorities in the basic and clinical research environments. Dexmedetomidine (Dex) is a novel α2-adrenoceptor agonist that is primarily used in surgical anesthesia and conscious-sedation.[2] Recent investigations have reported that Dex alleviates systemic inflammatory reactions induced by lipopolysaccharide (LPS). The use of Dex to maintain sedation in patients with sepsis can decrease levels of TNF-α, IL-1ß and IL-6 and other inflammatory factors, suggesting that Dex plays an anti-inflammatory role.[3] These results have been instrumental in promoting clinically viable applications for Dex, such as treatment for patients with systemic inflammatory response syndrome (SIRS). Despite the potential clinical benefits of Dex, there is little information on the mechanism of inhibition of the inflammatory response, and it is not known whether Dex possesses any lung protective functions in patients with SIRS. Therefore, the aim of the present study was to determine whether Dex had protective effects on LPS induced ALI by establishing an ALI model in rats to provide the theoretical basis for further clinical investigations.

Methods. The experiment was conducted from May 2008 to December 2009 in The Zhongshan Hospital, Shanghai, China. The animals were cared for in accordance with the Guide for the Care and Use of Laboratory Animals. Our research was reviewed and approved by the Institution Review Board of Zhongshan Hospital of Fudan University (Approval No: ZS 2008-01004).

Experimental animals. Forty Sprague Dawley rats (20 male and 20 female) of clean grade that weighed between 180-220 g and 7-9 weeks of age were used in this study.

Disclosure. All the authors have no conflicts of interests and this study was not supported or funded by any drug company.

Animal grouping and model preparation. Rats were randomized into one of 5 groups: the normal group (NS group, normal saline 0.5 mL), the LPS model group (LPS group, LPS 4 mg/kg), or the high dosage (HD) group (Dex 4.5 μg/kg), moderate dosage (MD) group (1.5 μg/kg), and low dosage (LD) Dex groups (0.5μg/kg). There were 8 rats per group. After the rats were injected intraperitoneally with 30 mg/kg pentobarbital and vena femoralis injection with LPS to duplicate the ALI model, rats in the Dex intervention groups were immediately injected with the corresponding doses of Dex, while rats in the NS group were injected with the same volume of isotonic normal saline. Rats from the various groups were sacrificed by exsanguination via the abdominal aorta 6 hours following the experimental procedure.

Determination of the weight ratio (W/D) of lung tissue. After the lung tissue was removed, the wet weight of the right inferior pulmonary lobe (W) was measured. The tissues were then dried and the dry weight (D) was measured. The W/D ratio was calculated to evaluate the degree of pulmonary edema.

Determination of TNF-α, IL-1 ß, and IL-6 levels in lung tissue. The supernatant of the left lung tissue was assayed by the ELISA method in accordance with the manufacturer's instructions. The levels of the aforementioned inflammatory factors were determined using an automatic microplate reader after color development.

Pathological examination. The right superior pulmonary lobes of the rats were collected and subjected to hematoxylin and eosin staining. The pathological changes in the tissues from the groups were observed by light microscopy.

Immunohistochemistry. Two lung tissue sections were obtained from each mouse, one for staining and another for a blank control. Three percent of hydrogen peroxide was used to block endogenous hydrogen peroxidase. Normal goat serum was used to block non-specific binding. Then Nuclear Factor-KappaB (NF-κB) polyclonal antibody (1:200) was added to the sections for staining. The samples were stored at 4°C overnight and biotin-labeled secondary antibody was added, The sections were then incubated at 37°C for one hour. Finally, 3,3'-Diaminobenzidine (DAB) was used to stain the samples and the staining time was controlled under the microscope. After the sections were mounted, the semi-quantitative analyses of NF-κB proteins were performed.

Specific analysis method. Five non-overlapping fixed visual fields were randomly selected from each section (400x). These fields included approximately 12000 positive cells (yellow to brown granular cells were defined as positive cells). The Image-Pro Plus 5.0 software was used to determine the net gray scale values (the net gray scale values = gray scale value of blank control section - gray scale values of staining section). The mean value was calculated to reflect the relative NF-κB protein expression level.

The RT-PCR for Toll-like receptor 4 (TLR4) messenger RNA (mRNA) expression in lung tissue. The remaining parts of the left lung were used to determine total RNA. The same quantity of RNA was used for reverse transcription and synthesis of cDNA. The polymerase chain reaction (PCR) amplification was used to amplify the fragments of the TLR4 and ß-actin sequences, using the following primers: forward 5'GCCGGAAAGTTATTGTGGTGGT3'; reverse 5'ATGGGTTTTA GGCGCAGAGTTT3' and forward 5'AACCCTAAGGCCAACAGTGAAAAG3'; and reverse 5'TCATGAGGTAGTCTGTCAGGT3'. The PCR products were subjected to 2% agarose gel electrophoresis and the gel was scanned and photographed. The JEDA 80l Gel Imaging Analysis software (JEDA, Jiangshu, China) was used to analyze the optical density of the product. Semiquantitative analysis was conducted to indicate the expression level of TLR4 mRNA, using the ratio between the absorbance for the different groups and the optical density of ß-actin as the standard.

Statistical analysis. The Statistical Package for the Social Sciences version 11.5 (SPSS, Chicago, IL, USA) statistical software was used for processing. Data were represented as the mean±standard deviation. To compare between groups, the ANOVA test was used for normally distributed data and the Kruskal-Wallis test was used for the non-homogeneic data. Post-hoc testing was performed using the least significant difference or Mann-Whitney tests. A $p<0.05$ was indicative of statistical significance.

Results.

General observations of lung tissue. The surface of lung tissues from the NS group were smooth and pale pink, with no obvious abnormalities. Lung tissue from the LPS and LD groups was enlarged and a more intense red color. Congestion was obvious, and extensive points of bleeding were observed. Congestion and edema were improved in lung tissue from the MD and HD groups and associated injuries were reduced as the dose increased (**Figure 1**).

Pathological changes in lung tissue. Lung tissue structures in the NS group were intact under the light microscope. The alveolar space was distinct and interstitial matter was observed in the pulmonary alveoli. A large amount of effusion was observed in the alveolar space in the LPS and LD groups. These groups also demonstrated substantial thickening of the alveolar wall and congestion/bleeding were observed in the pulmonary alveoli, with obvious inflammatory cell infiltration. There was only a small amount of effusion in the MD and HD groups. These groups also

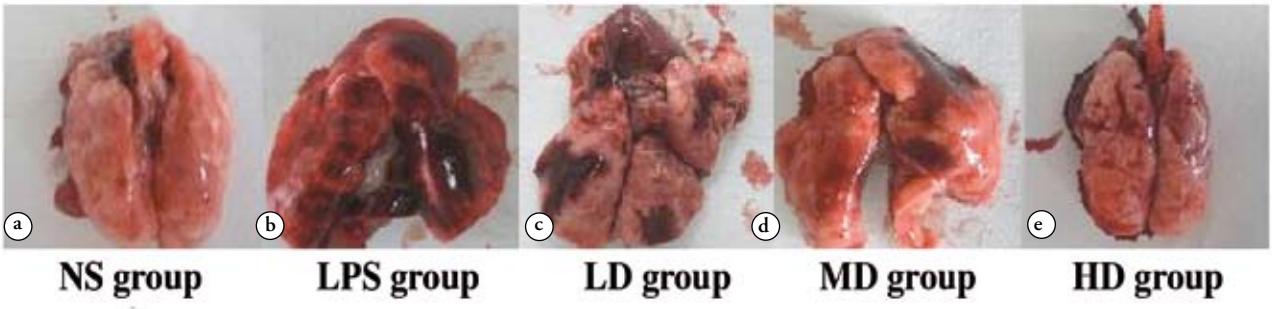

Figure 1 - General observations of lung tissues in different groups showing **a)** lung tissues in the NS group, the lung tissue was uniformly pink, and the capsule was smooth, soft, and flexible. **b) and c)** Lung tissue from the LPS and LD groups shows volume was increased and appeared dark red, showing significant congestion and points of extensive bleeding. **d) and e)** Lung tissue from the MD and HD groups shows swelling and congestion, but to a lesser extent. There were no large areas of hemorrhage present in these samples. NS group - normal group, LPS group - lipopolysaccharide model group, LD group - dexmedetomidine group in low dosage, MD group - dexmedetomidine group in moderate dosage, HD group - dexmedetomidine group in high dosage.

demonstrated a slight thickening of the alveolar wall and the blood capillaries were slightly elongated. Other structures appeared almost normal (**Figure 2**).

Changes in the W/D ratio in lung tissue. Compared to the NS group, the W/D ratios in lung tissue from the LPS and LD groups was significantly higher (p=0.006 and p=0.046). Compared to the LPS group, the W/D ratios in lung tissue from the MD and HD groups was significantly lower (p=0.002 and p=0.000) indicating that high and moderate dosages of Dex can alleviate pulmonary edema in the ALI model (**Table 1**).

NF-κB protein expression in lung tissue. NF-κB nuclear positive cells were mainly mucosal endothelial cells in the airways, infiltrative inflammatory corpuscles,

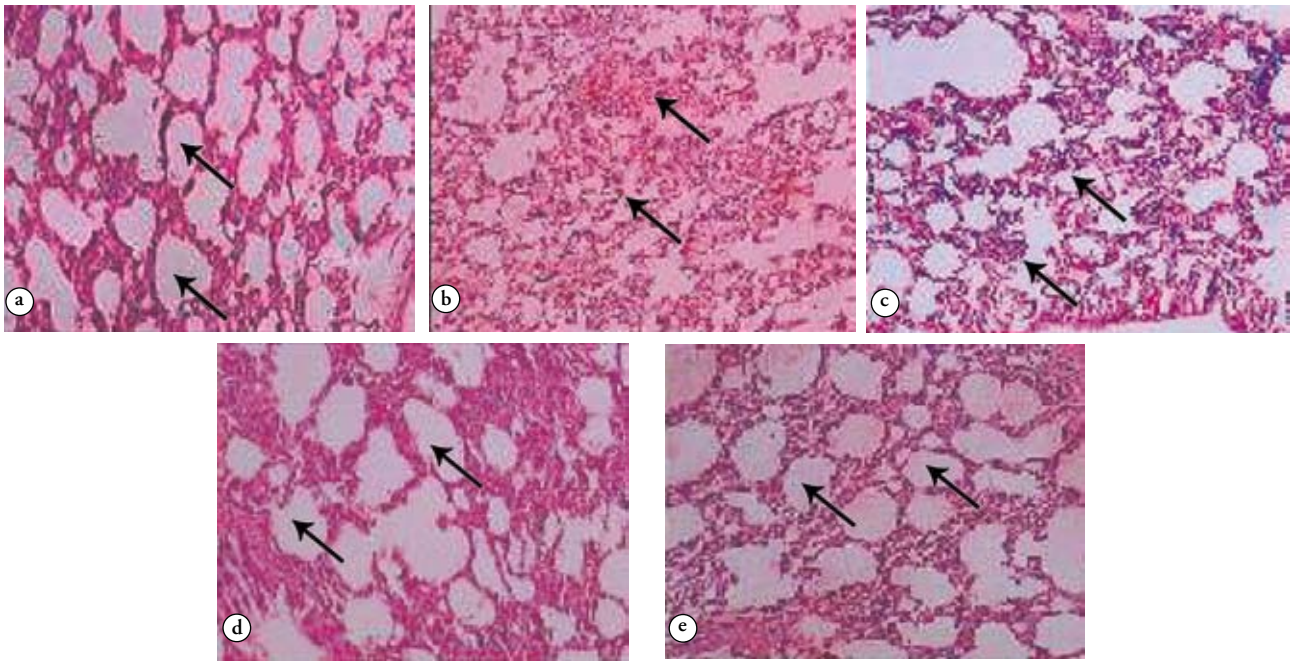

Figure 2 - Pathological changes in lung tissues showing **a)** shows pathological analysis of the NS group (x100), lung tissue structure was clear, and there was no neutrophil infiltration into the alveolar space. The alveolar walls were thin and there was no expansion of the interstitial capillaries (highlighted by the arrows). **b) and c)** Pathological analysis of the LPS and LD groups (x100) shows lung tissue demonstrated atelectasis, there was thickening of the alveolar septa, and the alveolar walls collapsed. There was interstitial telangiectasia, and red blood cell migration was apparent with infiltration into the alveolar spaces. The alveolar space showed a large area of pink exudate, infiltrated with inflammatory cells in part of the lung (highlighted by the arrows). **d) and e)** Results for the pathological analysis of the MD and HD groups (x100). Significant improvement of atelectasis was noted, with only a small amount of leakage, and slight thickening of the alveolar walls. Alveolar hemorrhage and inflammatory cell infiltration decreased while interstitial pulmonary edema was reduced (highlighted by the arrows).

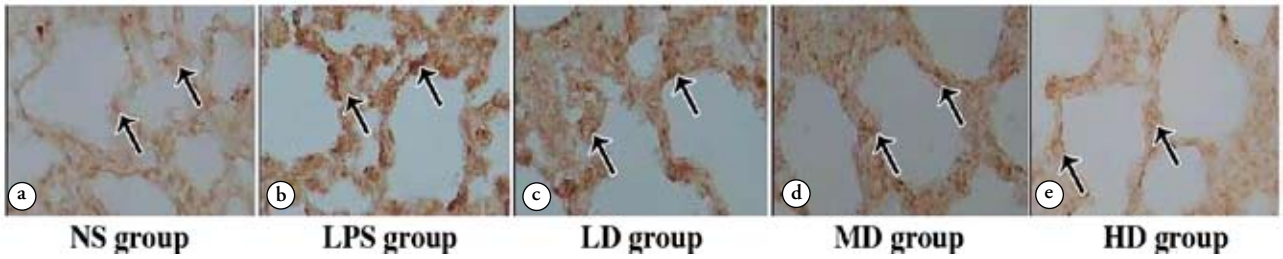

Figure 3 - Nuclear Factor-KappaB (NF-κB) protein expression in lung tissue showing **a) and c)** NF-κB protein expression in the NS group and LD group (x400), the expression of NF-κB in lung tissue was weak and expressed only in the airway epithelium and interstitial space. There were small amounts of scattered nuclear-positive cells (highlighted by the arrows). **b)** NF-κB expression in the LPS group (x400), NF-κB expression was significantly increased in lung tissue. The deep brown colored granules in the cell cytoplasm and nucleus was mainly in the bronchial epithelial cells and inflammatory cells. NF-κB was also expressed in alveolar epithelial cells, endothelial cells and pulmonary interstitial cells (highlighted by the arrows). **d) and e)** NF-κB expression in the MD and HD group (x400) - NF-κB expression was significantly decreased in lung tissues. The distribution of stained cells was similar to the LPS group, but their number and color depth were significantly reduced (highlighted by the arrows).

Table 1 - Comparison of weight ratio (W/D), Nuclear Factor-KappaB (NF-κB) and toll-like receptor 4 (TLR4) mRNA in lung tissues.

Group	Dose (mL) (μg/kg)	W/D ratio	NF-κB Gray scale value	TLR4 mRNA (TLR4/ß-actin optical density)
Normal group	0.5			
Mean±SD		4.71±0.40†	19.86±5.08†	0.38±0.02†
95% confidence interval		3.76-5.66	7.85-31.87	0.33-0.43
P-value		*p*=0.006	*p*=0.000	*p*=0.000
Lipopolysaccharide model group	4.0			
Mean±SD		5.46±0.75*	35.74±8.41*	0.60±0.04*
95% confidence interval		3.69-7.23	15.85-55.63	0.51-0.69
P-value		(*p*=0.006)	*p*=0.000	*p*=0.000
Dexmedetomidine group in low dosage	0.5			
Mean±SD		5.24±0.40*	32.58±6.64*	0.60±0.03*
95% confidence interval		4.29-6.19	16.88-48.28	0.53-0.67
P-value		*p*=0.046 and *p*=0.395	*p*=0.002 and *p*=0.412	*p*=0.000 and *p*=0.777
Dexmedetomidine group in moderate dosage	1.5			
Mean±SD		4.62±0.61†	25.24±4.37†	0.45±0.10*†
95% confidence interval		3.18-6.06	14.90-35.58	0.21-0.69
P-value		*p*=0.724 and *p*=0.002	*p*=0.166 and *p*=0.009	*p*=0.016 and *p*=0.000
Dexmedetomidine group in high dosage	4.5			
Mean±SD		4.38±0.54†	22.04±6.19†	0.38±0.03†
95% confidence interval		3.10-5.66	7.40-36.68	0.31-0.45
P-value		*p*=0.194 and *p*=0.000	*p*=0.571 and *p*=0.001	*p*=0.962 and *p*=0.000

Significance was considered at $p<0.05$, 95% confidence interval, the first *p* means NS groups compared with the other 4 groups (LPS, LD, MD, HD), the second *p* means LPS groups compared with the other 4 groups (NS, LD, MD, HD), *$p<0.05$ versus NS group; †$p<0.05$ versus LPS group.
NS group - normal group, LPS group - lipopolysaccharide model group, LD group - dexmedetomidine group in low dosage, MD group - dexmedetomidine group in moderate dosage, HD group - dexmedetomidine group in high dosage

Table 2 - Comparison of tumor necrosis factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interleukin-6 (IL-6) levels in lung homogenates.

Group	Dose mL (μg/kg)	TNF-alpha (pg/mg prot)	IL-1β (pg/mg prot)	IL-6 (pg/mg prot)
Normal group	0.5			
Mean±SD		167.42±28.82†	53.16±8.74†	42.89±12.64†
95% confidence interval		(99.26-235.58)	(32.49-73.83)	(13.00-72.78)
P-value		(*p*=0.000)	(*p*=0.001)	(*p*=0.001)
Lipopolysaccharide model group	4.0			
Mean±SD		399.57±39.02*	87.97±8.48*	72.83±15.55*
95% confidence interval		(307.29-491.85)	(67.91-108.03)	(36.05-109.61)
P-value		(*p*=0.000)	(*p*=0.001)	(*p*=0.001)
Dexmedetomidine group in low dosage	0.5			
Mean±SD		347.28±57.97*	90.08±16.08*	72.60±11.83*
95% confidence interval		(210.18-484.38)	(52.05-128.11)	(44.62-100.58)
P-value		(*p*=0.000 and *p*=0.411)	(*p*=0.000 and *p*=0.721)	(*p*=0.001 and *p*=0.978)
Dexmedetomidine group in moderate dosage	1.5			
Mean±SD		313.24±85.64*†	74.31±7.06*†	44.92±19.05†
95% confidence interval		(110.70-515.78)	(57.61-91.01)	(4.87-94.97)
P-value		(*p*=0.000 and *p*=0.045)	(*p*=0.000 and *p*=0.021)	(*p*=0.804 and *p*=0.001)
Dexmedetomidine group in high dosage	4.5			
Mean±SD		246.27±60.55*†	73.87±9.14*†	32.82±20.30†
95% confidence interval		(103.07-389.47)	(52.25-95.49)	(-15.19-80.83)
P-value		(*p*=0.025 and *p*=0.000)	(*p*=0.001 and *p*=0.017)	(*p*=0.222 and *p*=0.000)

Significance was considered at $p<0.05$, 95% confidence interval. The first *p*-value is the NS group compared with the other 4 groups (LPS, LD, MD, HD), the second *p*-values is the LPS group compared with the other 4 groups (NS, LD, MD, HD), *$p<0.05$ versus NS group, †$p<0.05$ versus LPS group, NS group - normal group, LPS group - lipopolysaccharide model group, LD group - dexmedetomidine group in low dosage, MD group - dexmedetomidine group in moderate dosage, HD group - dexmedetomidine group in high dosage

alveolar epithelial cells, and vascular endothelial cells (**Figure 3**). The net gray scale values for NF-κB in the LPS and LD groups were significantly greater than those in the NS group (p=0.000, p=0.002). The net gray scale values for NF-κB in the MD and HD group were decreased compared to the LPS group (p=0.009, p=0.001) (**Table 1**).

TLR4 mRNA expression in lung tissue. The TLR4 mRNA expression in the LPS group, the LD group, and the MD group were all significantly up-regulated compared to the NS group (p=0.000, p=0.000, p=0.016). The TLR4 mRNA expression in the MD group and the HD group were significantly lower than the LPS group (p=0.000, p=0.000) (**Table 1**).

NF-α, IL-1ß and IL-6 levels in lung homogenates. The TNF-α levels for all groups were significantly greater than the NS group (p=0.000, p=0.000, p=0.000, p=0.025). The TNF-α levels in the MD and HD groups were significantly lower than the LPS group (p=0.045, p=0.000). The IL-1ß levels for all groups were significantly higher than the values in the NS group (p=0.001, p=0.000, p=0.000, p=0.001). The IL-1ß levels in the MD and HD groups were significantly lower than the LPS group (p=0.021, p=0.017). For IL-6, the values were significantly higher in the LPS and LD groups compared to the NS group (p=0.001, p=0.001), while the levels in the MD and HD groups were significantly lower than the LPS group (p=0.001, p=0.000) (**Table 2**).

Discussion. Acute lung injury is a lung manifestation of systemic inflammatory disease that typically arises from pyemia-induced bacterial infection.[4] The major cell wall component of Gram-negative bacteria, LPS is one of major etiological factors of the disease. Therefore, intravenous injection of LPS is a conventional method for preparing an ALI model in rats.[5] The present study revealed that the pathological changes in the LPS treated group included thickening of the alveolar wall, inflammatory cell infiltration, extensive effusion, and hemorrhaging in the lung cavity following the intravenous injection of 4 mg/kg LPS. These findings, in addition to the increase in the W/D ratio, indicated that the ALI model was successfully prepared.[6-7] Our experimental results also showed that LPS can lead to increased effusion in the pulmonary alveoli, aggravation of pulmonary edema, and typical acute lung injuries.

The LPS can transmit signals into cells and trigger the signaling transduction system by interacting with the TLR4 receptor on the cell membrane, thus inducing NF-κB and further regulating the transcription of genes that are closely linked to the immunological responses of organisms. This can result in the release of large amounts of pre-inflammatory factors, including TNF-α, IL-1ß, IL-6, and others. These inflammatory factors can prevent alveolar cell perfusion and gas exchange by activating pulmonary endothelial cells and macrophages, promoting leukocyte migration, granulocyte degranulation, blood capillary leakage and other mechanisms, ultimately leading to pyemia and pulmonary injuries.[8] The Dex is a novel α2-adrenoceptor agonist, acting selectively in the excitation of the α2-adrenoceptor in comparison to clonidine. It can inhibit norepinephrine release and alleviate the signal transduction of pain by exciting presynaptic membrane receptors, and thus it has conscious-sedation and anxiety alleviation activity. Since Dex has excellent effects in conscious-sedation without inhibiting spontaneous breathing in patients, it can reduce the incidence rates of acute confusional states and coma in patients, and thus, is frequently used for mechanically ventilated patients in the intensive care unit (ICU).[9] The Dex was also used in surgical patients to reduce postoperative delirium and reduce the amount of opioids that were administered. Recent research has also revealed that Dex can reduce systemic inflammatory reactions induced by endotoxins. According to the results from our present study, Dex may play an important role in the regulation of inflammatory factor levels in serious cases of septicemia and may have a protective effect on internal organs. In the present study, we administered different doses of Dex to quantify its protective function on lung tissue. The application of 1.5-4.5 μg/kg Dex significantly reduced the expression of TLR4 and NF-κB in lung tissue, reduced the levels of TNF-α, IL-1ß, IL-6 and other inflammatory factors, and reduced the lung tissue W/D ratio. Taken collectively, these findings indicate that Dex can alleviate inflammatory reactions in lung tissue and pulmonary injuries. We also found that the animals treated with 0.5 μg/kg Dex had no significant change in the expression of pulmonary TLR4 and NF-κB in lung tissue, no change in TNF-α, IL-1ß, and IL-6 levels and no change in the W/D ratio. These results suggest that 0.5 μg/kg Dex had no therapeutic efficacy in this model.

This study is clinically significant because it evaluated the possible inhibitory effects of high doses of Dex on inflammatory reactions, as well as its protective effects in lung tissue. However, the recommended safe and effective clinical dosage range of Dex is only 0.5-1 μg/kg.[10,11] The results from our present study suggest that such a low dose cannot protect internal organs. Previous reports that have evaluated clinical dose of Dex in a small sample size determined that some patients require Dex administration at 5-10 times of the recommended clinical dosage to maintain sedation status.[10,11] Even at this does the cardiovascular responses were steady, particularly in pediatric patients.[10,11] High doses of Dex do not only provide satisfactory sedation status for these patients, but also inhibit inflammation and protect internal organs, thus widening the scope of clinical application. However, this treatment may lead to delayed pallanesthesia, over-sedation, or a range of other side effects, including hypothermia, apnoea and bradycardia. Thus, the safety of this treatment still requires further clinical trials with larger sample sizes. Dex has a dose-dependent effect on lung tissues and the underlying mechanisms are still not fully understood. It is currently thought that extensive Ca^{2+} influx into cells is required if NF-κB transcription activation is required in the inflammatory reaction signaling pathway.[12] Increased Ca^{2+} influx can be detected when low doses of Dex are administered, while Ca^{2+} influx can be inhibited when the Dex dosage is increased,[13] possibly leading to different inflammatory reactions. However, some investigations also revealed that the anti-inflammatory effects of Dex may be the result of interaction with the α2-adrenoceptor.[14]

In summary, the administration of 0.5 μg/kg Dex does not inhibit inflammatory reactions or protect lung tissue from damage. Dex can effectively inhibit inflammatory reactions in lung tissue and lead to protective effects when the dosage is increased to 1.5-4.5 μg/kg. Despite the important findings in this study, several limitations should be noted. During this study, we did not maintain a stable blood concentration. We also did not monitor the hemodynamics in the rats; therefore the safety of high doses of Dex cannot be assessed and controlled. Safety of higher doses will require additional clinical experiments. Future work should also elucidate the specific mechanisms and the pathways by genetic expression is altered.

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