Cervical sympathetic trunk transection alleviates acute lung injury caused by intestinal obstruction via inhibition of phospholipase A₂ in rats

Zhengfeng Gu*, Lian Xin, Huizhi Yu, Shunmei Lu, Jinbo Wu, Hui Wang, Dongxiao Huang and Chunxiao Hu

Abstract

Background: Intestinal obstruction can result in inflammatory injury to distant organs, especially the lungs. Stellate ganglion block (SGB) provides sympathetic nervous homeostasis and inhibits the systemic inflammatory response. This study aimed to investigate whether SGB can alleviate acute lung injury by inhibiting phospholipase A₂ expression in rats.

Methods: Thirty healthy male Sprague–Dawley rats were divided into three groups: C group (sham-operated); CLP group (cecal ligation and puncture with intestinal obstruction), and cervical sympathetic trunk transection (CSTT) group (transection of the cervical sympathetic trunk following CLP). Arterial blood samples were obtained to determine the ratio of partial arterial pressure of oxygen (PaO₂) to fraction of oxygen in inspired air (FiO₂). Venous blood samples were used to evaluate the serum concentrations of chemokines, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-10 using enzyme-linked immunosorbent assays. Following euthanasia, the lungs were isolated to estimate the wet/dry lung weight (W/D) ratio, evaluate the pathological damage to lung tissues on microscopy, and determine secretory-type phospholipase A₂ (sPLA₂) expression using western blotting.

Results: Rats in the CLP group showed increased fatigue, decreased activity levels, and coarse, gray hair. The levels of chemokines, TNF-α, and IL-6 in the CLP and CSTT groups were higher than those in the C group. However, the levels were lower in the CSTT group than those in the CLP group. IL-10 levels in the CLP and CSTT groups were higher than those in the C group, whereas these levels in the CSTT group were lower than those in the CLP group. No lung injury was noted in group C, and the lung injury scores were lower in the CSTT group than those in the CLP group.

Conclusions: sPLA₂ overexpression in the lungs may be a pathogenic factor in acute lung injury. CSTT alleviated acute lung injury by inhibiting sPLA₂ expression.

Keywords: Acute lung injury, Intestinal obstruction, Phospholipase A₂, Stellate ganglion block

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upregulated in multiple ALI models, and some isoforms play unique roles in the regulation of the pathophysiology of ALI [1]. Intestinal obstruction may result in bacterial translocation and the production of inflammatory factors, which may result in ALI. Stellate ganglion block (SGB) can regulate the sympathetic nervous system and inflammatory response [2, 3]. Therefore, in this study, we aimed to investigate whether cervical sympathetic trunk transaction (CSTT) can regulate inflammation via inhibition of sPLA_2 secretion.

**Methods**

**Ethics statement**

All animal experiments were approved by the Ethics Committee of the Wuxi People’s Hospital (approval number: MS201916).

**Animals**

Thirty healthy male Sprague–Dawley rats (270–320 g) were acquired from Changzhou Cavens Laboratory Animal Co., Ltd. (Changzhou, Jiangsu, China) and housed in specific pathogen-free conditions with animal service from the Laboratory Center of Jiangsu Lung Transplantation in Wuxi. The room temperature was set at 23–25 °C with a 12-h day/night cycle, and the rats (n = 5 per cage) were acclimatized for 7 days with ad libitum access to water and food before the experiments [4]. The rats were fed and cared for by a full-time technician, who coded the cages and rats. The rats were randomly assigned to three groups using a computer-based random order generator (n = 10 each): (1) C group, in which the rats underwent abdominal and cervical incisions and sutures; (2) cecal ligation and puncture (CLP) group, in which the rats underwent CLP; and (3) CSTT group, in which the rats underwent isolation and transection of the sympathetic nerve trunk following CLP. For each animal, five different investigators were involved and had the following roles. The first investigator performed the procedures including sample collection based on the randomization table. This investigator was the only person aware of the treatment group allocation. The second investigator was responsible for performing blood gas analysis and serum biochemical assay, and the third investigator performed the western blot analysis and histopathological test. Finally, the fourth investigator (also unaware of treatment) assessed the animals’ behavior, and the fifth investigator performed data analysis.

**Surgical procedures**

The rats were anesthetized using 5% sevoflurane on an anesthesia machine for small animals followed by intra-peritoneal injection of pentobarbital sodium (30 mg/kg) [5, 6]. All the rats in this trial maintained autonomous respiration and air inhalation during the whole procedure. They were maintained in a supine position on a heating table mat (AUX Group, Ningbo, Zhejiang, China) with the temperature set to 37 °C. Hair over the abdomen and around the neck was shaved using an electric haircutter. Anesthesia was verified by testing limb immobility via forceps clamping of the skin. The skin over the abdomen and neck was sterilized using 75% alcohol. Ophthalmic scissors were used for the incisions of the skin, abdominal muscles, and peritoneum along Hunter’s line of the lower abdomen at a width of 1.5–2.0 cm. An incision along Hunter’s line can prevent vascular injury and bleeding. The cecum, usually located in the right upper abdomen, was extracted using anatomical forceps. A 3–0 silk suture was passed through the mesoecum, and the cecum was ligated at its upper third adjacent to its root [7]. The cecum was then bilaterally punctured by inserting an 18-gauge needle through the cecal wall followed by cecal pressing with sterile cotton swabs and extrusion of the intestinal contents through the punctured openings. The cecum was returned to the abdominal cavity, and the peritoneal and skin incisions were sutured layer-by-layer using 3–0 absorbable sutures. Sham-operated mice in the C group underwent identical procedures except for CLP. All animals received an abdominal infusion of normal saline (1 mL) after closure of the abdominal wall.

The mice in the CSTT group underwent identical procedures for CLP with additional CSTT [8, 9]. The ventral neck was incised using ophthalmic microscissors to expose the platysma myoides and left sternocleidomastoid. The triangle of the left sternocleidomastoid was bluntly dissected using the ophthalmic microscissors until the carotid artery sheath was exposed. The carotid artery was isolated from the nerve trunk using ophthalmic microforceps. The top end of the forceps was arc-shaped with a diameter of 0.3 mm. With the vagus nerves isolated from the sympathetic nerve trunk using the ophthalmic microforceps, the sympathetic nerve trunk was transected using ophthalmic microscissors. The platysma myoides and skin were closed using 3–0 absorbable sutures. The index of a successful model establishment was the development of Horner’s syndrome, with features such as blepharoptosis, narrowing of the palpebral fissure, miosis, and canthus secretions. Conversely, the absence of Horner’s syndrome was considered an indication of a failed model, and another experiment was warranted. If the rats died during the procedure, another experiment was conducted until the desired number was achieved.

The rats were returned to their cages followed by care and ad libitum access to food and water in the laboratory for 24 h. The animals’ behavior; wet/dry lung weight ratio (W/D); oxygenation index (expressed as the ratio of
arterial partial pressure of oxygen \([\text{PaO}_2]\) to oxygen concentration \([\text{FiO}_2]\); lung injury scores assessed by histopathology analysis; serum concentrations of chemokines, tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-6, and IL-10; and sPLA\(_2\) levels were assessed.

**Blood gas analysis**
After 24 h, the rats were anesthetized, and the lower abdomen was opened through the original incision. The small intestine was extracted, and the mesentery was bluntly and gently isolated using sterilized cotton swabs. The abdominal aorta and inferior vena cava were then exposed. Blood from the aorta was obtained using a 1-mL syringe for arterial blood gas analysis. The oxygenation index was evaluated by dividing \(\text{PaO}_2\) by \(\text{FiO}_2\). We regarded \(\text{FiO}_2\) in the air as 21%. Venous blood was obtained from the inferior vena cava and stored in an anticoagulant-coated tube. Venous blood was centrifuged, and the serum was stored in a refrigerator for subsequent analysis.

**Histopathological analysis**
The rats were euthanized by cervical dislocation. The pulmonary artery was irrigated with normal saline until the absence of blood was noted from the lungs. With the superior lobe of the right lung isolated, water and blood were removed using a filter paper, and the wet weight was measured. Then, the sample was kept in a drying oven at 120 °C for 24 h; subsequently, the dry weight was estimated, and the W/D was calculated. The middle lobe of the right lung was dissected, fixed with 10% formaldehyde solution, embedded in paraffin, microtomed into slices, and stained with hematoxylin–eosin. The slides were observed under a light microscope (100× magnifications). Histological changes were evaluated by a pathologist blinded to the experimental conditions. The degree of lung injury was graded using a histological scoring system [10]. Edema, alveolar and interstitial inflammation and hemorrhage, atelectasis, necrosis, and hyaline membrane formation were scored on a 5-point scale as follows: 0, no injury; 1, injury in 25% of the viewing field; 2, injury in 50% of the viewing field; 3, injury in 75% of the viewing field; and 4, injury throughout the field. Three different viewing fields per slide were analyzed, and the mean score of the three viewing fields was considered the score of the slide. The final lung injury score was obtained by summing these scores [11].

**Serum biochemical indices**
The serum concentrations of chemokines, TNF-\(\alpha\), IL-6, and IL-10 were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Neobioscience, Nanjing Proteinbio Technology Co., Ltd., China) according to the manufacturer’s instructions [12]. The plates were read using a microplate reader at a wavelength of 450 nm [13].

**Western blotting**
sPLA\(_2\) levels were determined using western blotting according to the instructions of the Protein Assay Kit (Abcam, Cambridge, Univ Biotechnology Co., Ltd., Shanghai, China, ab139692) [14]. The left lung was dissected; 100 mg was cut into pieces before being placed into the centrifuge tube, and 1 mL of lysis solution was injected into the tube. A total of 50 μL of lysis solution included 40 μL of radioimmunoprecipitation assay, 5 μL of the protease inhibitor, 5 μL of the phosphatase inhibitor, and 0.5 μL of phenylmethanesulfonyl fluoride. Two 50-mL beakers were prepared. One beaker was filled with normal saline as a wash homogenizer, and another one was filled with ice to keep the centrifuge tube filled with lung tissue cool. Homogenization was performed for 2 s. The centrifuge was placed in a refrigerator at 4 °C for more than an hour before being used. The lysed tissue was centrifuged for 10 min at 15,000 rpm and 4 °C after being lysed for 30 min at 4 °C. About 800 μL of supernatants were obtained. Samples from the cell supernatants were subjected to 15% lauryl sodium sulfate–polyacrylamide gel electrophoresis followed by immunoblotting onto a polyvinylidene difluoride membrane. Nonspecific binding sites were blocked via incubation with 5% skim milk in Tris-buffered saline containing 0.1% Tween-20 (TBS-T) for 4 h at 4 °C. The membranes were then incubated overnight. After rinsing with TBS-T, the blots were incubated for 2 h at room temperature. The immunoreactive bands were visualized using an enhanced chemiluminescence detection kit, and the intensities were analyzed using an image processing program. Equal protein loading was confirmed using horseradish peroxidase-conjugated anti-mouse IgG (ab205719; Abcam, Cambridge, UK) as the secondary antibody.

**Statistical analysis**
Values are expressed as mean ± standard deviation of three experiments. Comparisons were assessed using repeated measurement variables (within-subjects factors) followed by an independent samples \(t\)-test. Data were tested using the D’Agostino–Pearson test for normal distribution. Data were analyzed using MedCalc (version 20.110–32-bit;MedCalc Software Ltd., Ostend, Belgium). The level of statistical significance was set at \(p < 0.05\).
Results

Behavioral alterations
The rats in the CLP group showed increased fatigue, reduced activity levels, and coarse, gray hair compared to those in the C and CSTT groups. The rats in the CSTT group demonstrated narrowing of the palpebral fissure in one eye and secreta at the canthus, which confirmed the successful establishment of the model.

Histopathological changes
We evaluated the profiles of the lung injuries caused by CLP. Lung tissues from the C group demonstrated normal structures without histological changes under a light microscope (100 × and 200 × magnifications; Fig. 1). The lung tissues in the CLP group showed severe histological lesions, including reduced alveolar cavities, increased area of the pulmonary interstitial space due to edema, interstitial hyperemia, hemorrhage, and evident infiltration of inflammatory cells, which demonstrated the successful establishment of the CLP-induced ALI model. However, the lung tissues in the CSTT group demonstrated mitigated interstitial edema, reduced pulmonary interstitial space, and decreased infiltration of inflammatory cells compared to those in the CLP group (Fig. 1). There were significant differences in the pathological scores between the CLP and CSTT groups (p < 0.001; Table 1).

W/D and PaO2/FiO2
The W/D and PaO2/FiO2 ratios in the CLP and CSTT groups were greater than those in the C group, whereas

Table 1  Wet/dry lung weight ratios (W/D), PaO2/FiO2 ratios, lung injury scores, and sPLA2 levels (n = 10)

| Group  | W/D    | PaO2/FiO2 | Lung injury scores | sPLA2 (ng/L) |
|--------|--------|-----------|--------------------|--------------|
| C      | 4.09 ± 0.19 | 275.5 ± 11.7 | 0                  | 1.08 ± 0.01  |
| CLP    | 5.11 ± 0.15 a | 213.4 ± 22.1 a | 7.01 ± 0.41       | 1.68 ± 0.04 a |
| CSTT   | 4.73 ± 0.22 ab | 264.5 ± 22.3 b | 4.53 ± 0.23 b     | 1.46 ± 0.02 ab |

Values represent mean ± standard deviation (n = 10)
PaO2, Partial arterial pressure of oxygen,FiO2, Fraction of oxygen in inspired air, sPLA2, Secretory-type phospholipase A2, C, Control, CLP, Cecal ligation and puncture, CSTT, Cervical sympathetic trunk transection

* p < 0.001 versus C group
b p < 0.001 versus CLP group

Fig. 1  Histopathological images of lung tissue samples from each experimental group (100 x and 200 x magnifications, hematoxylin & eosin staining)
the ratios in the CSTT group were lower than those in the CLP group ($p < 0.001$; Table 1).

**Chemokines, TNF-α, IL-6, and IL-10**
We determined the levels of inflammatory factors to assess the inflammatory reactions. The expression levels of chemokines, TNF-α, and IL-6 in the CLP and CSTT groups were higher than those in the C group ($p < 0.001$; Table 2), whereas these cytokine levels in the CSTT group were lower than those in the CLP group ($p < 0.001$; Table 2). IL-10 levels in the CLP group were higher than those in the C group. Furthermore, IL-10 levels in the CSTT group were higher than those in the CLP group ($p < 0.001$; Table 2).

**Western blotting of sPLA2**
Western blotting was performed to investigate whether CSTT affected the expression of sPLA2. The protein levels of sPLA2 in the lung tissues of the CLP group were higher than those in the C group, whereas the sPLA2 levels in the CSTT group were lower than those in the C group (Fig. 2A and B, Table 1).

**Discussion**
ALI is one of the commonest complications of intestinal obstruction and is associated with high morbidity and mortality [6]. Intestinal obstruction is a common disease of the digestive tract, particularly in children and elderly patients. The release of gut-derived detrimental factors into the circulation has been implicated in the development of ALI [5]. The ALI model induced using CLP in laboratory animals can perfectly imitate the clinical manifestations of intestinal obstruction, peritonitis, and ALI [5, 6]. The CLP-induced animal model is acknowledged as the standard model of sepsis, which justifies our employment of CLP in the establishment of a model of ALI.

Some pharmaceutical agents, such as ulinastatin and cucurbitacin, have been reported to have positive effects on the prevention and treatment of ALI. In recent years, SGB has been widely adopted in clinical therapeutics for various diseases for its inhibitory effects on inflammatory reactions caused by trauma, infection, shock, and major surgery [3, 15, 16]. CSTT also improves pulmonary function by regulating the homeostasis of the autonomic nervous system [17]. Our study identified that CSTT improved pulmonary oxygenation (improved $\text{PaO}_2/\text{FiO}_2$) and mitigated lung edema by decreasing pulmonary permeability and exudation (lower $W/D$ ratio and lung injury scores). Furthermore, SGB effectively inhibited the inflammatory factors by downregulating chemokines, TNF-α, and IL-6 levels, while upregulating the expression of IL-10, which inhibits the release of inflammatory factors, such as TNF-α, IL-1β, IL-6, and IL-8. IL-10 is a kind of anti-inflammatory mediator. Infection activates the sympathetic nervous system, and the latter downregulates or inhibits the expression of IL-10. CSTT relieves the inhibition of IL-10 expression by the sympathetic nervous system [18]. These results are supported by the findings of previous studies [3, 17]. Increased activity of the rats in CSTT group demonstrated the attenuation of inflammatory reactions.

| Table 2 | Serum concentrations of CK, TNF-α, IL-6, and IL-10 ($n = 10$) |
|---------|---------------------------------------------------------------|
| Group   | CK (ng/L) | TNF-α (ng/L) | IL-6 (ng/L) | IL-10 (ng/L) |
| C       | 23 ± 11   | 60 ± 12      | 66 ± 11     | 61 ± 13      |
| CLP     | 95 ± 14   | 223 ± 22     | 198 ± 14    | 99 ± 12      |
| CSTT    | 69 ± 12   | 152 ± 15     | 149 ± 12    | 139 ± 16     |

Values are presented as mean ± standard deviation ($n = 10$)

C Control, CLP Cecal ligation and puncture, CSTT Cervical sympathetic trunk transection, CK Chemokines, TNF-α Tumor necrosis factor α, IL-6 Interleukin-6, IL-10 Interleukin-10

* $p < 0.001$ versus C group

* $p < 0.001$ versus CLP group

Fig. 2 Protein levels of secretory-type phospholipase A$_2$ (sPLA$_2$) determined using western blotting. A Representative sPLA$_2$ bands (full-length blots are presented in Additional file 1). B Concentrations of sPLA$_2$ normalised to GAPDH expression. * and ** $p < 0.001$
The oxygenation index, calculated as PaO2/FiO2, is an important indicator of lung function. Lower values of PaO2/FiO2 in the CLP group compared with those in the C group confirm the CLP-induced impairment of lung oxygenation. Despite the decreased PaO2/FiO2 in the CSTT group (versus the CLP group), CSTT increased the oxygenation of the injured lung. Our pulmonary histopathological measurements revealed that CSTT alleviated alveolar epithelial edema, decreased the percolate in the alveolar cavity, and reversed the narrowing of alveolar walls. These findings suggest that CSTT can protect lung function by reducing the levels of cytokines, such as IL-6 and IL-8. Our results are consistent with prior findings by Chen et al. [3].

To date, more than 30 enzymes that possess PLA2 or related activities have been identified. Approximately one-third of these enzymes belong to the sPLA2 family, which comprises low molecular weight, Ca2+-requiring, secreted enzymes with a histidine/aspartate catalytic dyad and serve specialized biological roles [19]. To date, eleven sPLA2 isoforms (Iβ, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA, and XIIIB) have been identified in mammals and are subdivided into three major categories: one containing the conventional sPLA2 enzymes (I/II/V/X) and two groups of atypical sPLA2 enzymes (III and XII). Phospholipase A (PLA) comprises a supergroup of esterase enzymes present in all human cells and plays a key role in mediating the production of free fatty acids and lysophospholipids from glycerophospholipids. The isoforms of PLA fall into six main groups: cytosolic PLA, calcium-independent PLA, secretory PLA, lysosomal PLA, adipose-specific PLA, and platelet-activating factor acetylhydrolase [20]. The molecular structure of secretory PLA consists of 6–8 disulfide bonds and shares a histidine/aspartate active site with a calcium cofactor for catalysis. Secretory PLA has been demonstrated to have a wide variety of functions in the body. It possesses potent antiviral properties, as well as antibacterial activities against a wide spectrum of Gram-positive and Gram-negative bacteria. The mechanism involves the penetration of the peptidoglycan cell wall by the degradation of membrane phospholipids. The antiviral mechanism of secretory PLA involves inhibition of chemokine receptors, which ultimately prevents viral entry into host cells. ‘Sepsis’ is currently identified as ‘a life-threatening condition that arises when the body’s response to an infection injures its own tissues and organs’ [21]. Initiated by an invading pathogen, generally represented by bacteria and, less frequently, by viruses or fungi, sepsis results in an inflammatory process in which the body’s own response has a deleterious effect on itself [22]. Pathogen infection is the condition of ‘sepsis’ and activates sPLA2. Secretory PLA2 causes then the release of inflammatory factors. The tissue is damaged when the concentration of inflammatory factors in the body reaches a certain level. Secretory PLA2 is favorable for resisting viruses and bacteria, but it damages the normal cell membrane. Thus, attenuating the inflammatory process by decreasing sPLA2 expression protects the body. Although inflammation and tissue damage are hallmarks of sepsis, the specific mechanisms linking inflammation, injury, and outcomes remain unclear [23]. Our findings demonstrated that CSTT could inhibit the concentration of serum chemokines and, consequently, alleviate ALI via inhibition of chemokines. Nevertheless, the mechanism of inhibition of chemokine production by CSTT remains unclear and requires further research. Phospholipase A2 hydrolyzes phospholipids and initiates the production of inflammatory lipid mediators [24]. Secretory PLA2 contributes to pulmonary diseases [25, 26]. Moreover, sPLA2-V and sPLA2-X can potently hydrolyze phosphatidylcholine in vitro, which highlights that the mechanism of airway injury, at least partially, includes hydrolytic degradation of lung surfactants. Owing to the well-known significance of secretory PLA in the pathogenesis of several inflammatory diseases, attempts to synthesize inhibitors of the enzyme are underway for quite some time for the treatment of some of these diseases. Phosphodiesterase inhibitors exert a broad spectrum of favorable effects that are potentially beneficial in ALI [27]. Phospholipase A2 inhibitors are beneficial in the treatment of ALI associated with bacterial infections [28, 29], thus implying that inhibition of phospholipase A2 will produce advantageous results in ALI. Our findings demonstrated that CSTT may decrease sPLA2 concentrations in lung tissues. PLA2 acts as an acute-phase protein, and its serum concentration is related to the mortality of toxic shock and multiple organ failure, thus rendering it important in establishing the diagnosis and estimating the prognosis [30].

There are some limitations to this study. First, although this study demonstrated that CSTT inhibits sPLA2 expression, further studies are needed to clarify the mechanism underlying this observation. Second, this study was conducted in an animal model. Third, we did not evaluate the heart rate, blood pressure, and oxygen saturation. Therefore, our results should be clinically confirmed by SGB.

Conclusions
Due to the potent anti-inflammatory activity of CSTT, its supplementation can effectively improve pulmonary oxygenation, mitigate pulmonary edema, and inhibit inflammatory infiltration by reducing the production of sPLA2. These results reflect the beneficial effects of SGB in the clinical treatment of ALI.
Abbreviations
ALL: Acute lung injury; CLP: Cecal ligation and puncture; CSTT: Cervical sympathetic trunk transection; ELISA: Enzyme-linked immunosorbent assay; IL: Interleukin; PaO2/FiO2: Arterial partial pressure of oxygen to oxygen concentration ratio; PLA: Phospholipase A; SGb: Stellate ganglion block; sPLA2: Secretory-type phospholipase A2; TBS-T: Tris-buffered saline containing 0.1% Tween-20; TNF-α: Tumor necrosis factor-α; W/D: Wet/dry weight ratio.

Supplementary Information
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Additional file 1. Western blot images.

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Authors’ contributions
ZFG: conception of the trial design, experimental guidance, drafting of original manuscript; LX: performed experiments and major contributor in writing the manuscript; HZY: performed experiments; SML: interpretation of data, data processing, and software operation; HW: performed experiments; JMW: performed histological evaluations; DXH: reviewed the manuscript; CXH: reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
All animal experiments were approved by the Ethics Committee of the Wuxi People’s Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1.Letsiou E, Htwe YM, Dudek SM. Secretory phospholipase A2 enzymes in acute lung injury. Cell Biochem Biophys. 2021;79:609–17.
2. Liu MH, Tian J, Su YP, Wang T, Xiang Q, Wen L. Cervical sympathetic block regulates early systemic inflammatory response in severe trauma patients. Med Sci Monit. 2013;19:194–201.
3. Chen Y, Guo L, Lang H, Hu X, Jing S, Luo M, et al. Effect of a stellate ganglion block on acute lung injury in septic rats. Inflammation. 2018;41:1601–9.
4. Dai D, Zheng B, Yu Z, Lin S, Tang Y, Chen M, et al. Right stellate ganglion block improves learning and memory dysfunction and hippocampal injury in rats with sleep deprivation. BMC Anesthesiol. 2021;21:272.
5. Wang SY, Li ZJ, Wang X, Li WF, Lin ZF. Effect of ulinastatin on HMGBl expression in rats with acute lung injury induced by sepsis. Genet Mol Res. 2015;14:4344–53.
6. Hu B, Liu X, Lu S, Wang Z. Protective effects of cucurbitacin B on acute lung injury induced by sepsis in rats. Med Sci Monit. 2017;23:1355–62.
7. Hagiwara M, Yamada M, Motoda N, Yokota H. Intravenous immunoglobulin attenuates cecum ligation and puncture-induced acute lung injury by inhibiting apoptosis of alveolar epithelial cells. J Nippon Med Sch. 2020;87:129–37.
8. Ikeda T, Hirakawa H, Kuriyama T, Nishida Y, Kajzma T. Effect of cervical sympathetic trunk transection on renal sympathetic nerve activity in rats. Physiol Res. 2006;55:77–82.
9. Kizilay H, Caliç H, Kılıç E, Frat T, Kuru T, Sahin AA. Effects of stellate ganglion block on healing of fractures induced in rats. Biomed Res Int. 2020;2020:450363.
10. Wu X, Kong Q, Zhan L, Qiu Z, Huang Q, Song X. TIP2E ameliorates lipopolysaccharide-induced apoptosis and inflammation in acute lung injury. Inflamm Res. 2019;68:981–92.
11. Liu L, Qiu HB, Yang Y, Wang L, Ding HM, Li HP. Losartan, an antagonist of AT1 receptor for angiotensin II, attenuates lipopolysaccharide-induced acute lung injury in rats. Arch Biochem Biophys. 2009;481:131–6.
12. Marques CD, Diego LA, Macones-Machado J, Amarim OR, Carvalho LR, Módolo Ns, et al. Serum concentrations and renal expressions of IL-1 and TNF-α early after hemorrhage in rats under the effect of glibenclamide. Acta Cir Bras. 2016;31:434–41.
13. Tang Y, Kong J, Zhou B, Wang X, Liu X, Wang Y, et al. Mesenteric lymph duct ligation alleviates acute lung injury caused by severe acute pancreatitis through inhibition of high mobility group box 1-induced inflammation in rats. Dig Dis Sci. 2021;66:4344–53.
14. Krisiouli E, Antoniou G, Gotozou H, Karagiannopoulos M, Basagiannis D, Christoforidis S, et al. Effect of azithromycin on the LPS-induced production and secretion of phospholipase A2 in lung cells. Biochim Biophys Acta. 2015;1852:1288–97.
15. Yang X, Shi Z, Li X, Li J. Impacts of stellate ganglion block on plasma NF-κB and inflammatory factors of TBI patients. Int J Clin Exp Med. 2015;8:15630–8.
16. Zhang J, Lin XR, Zhang YP, Zhang LM, Du HB, Jiang LN, et al. Blockade of stellate ganglion mediates hemorrhagic shock-induced intestinal barrier dysfunction. J Surg Res. 2019;244:69–76.
17. Liu Y, Tao T, Li W, Bo Y. Regulating autonomic nervous system homeostasis improves pulmonary function in rabbits with acute lung injury. BMC Pulm Med. 2017;17:98.
18. Atti C, Guerfali FZ, Lacroix C. Role of human macrophage polarization in inflammation during infectious diseases. Int J Mol Sci. 2018;19:1801.
19. Murakami M, Takemoto Y, Sato H, Yamamoto K. Secreted phospholipase A2 revisited. J Biochem. 2011;150:233–55.
20. Casale J, Kacimi SEO, Varacallo M. Biochemistry, phospholipase A2. Treasure Island (Florida): StatPearls; 2022. p. 1–13.
21. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
22. Lazzaro A, De Girolamo G, Filippi V, Innocenti GP, Santinelli L, Ceccarelli G, et al. The interplay between host defense, infection, and clinical status in septic patients: a narrative review. Int J Mol Sci. 2022;23:803.
23. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of inflammation during infectious diseases. Int J Mol Sci. 2018;19:2653.
24. Lazzaro A, De Girolamo G, Filippi V, Innocenti GP, Santinelli L, Ceccarelli G, et al. The interplay between host defense, infection, and clinical status in septic patients: a narrative review. Int J Mol Sci. 2022;23:803.
25. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of sepsis: time for a reappraisal. Crit Care. 2020;24:287.
26. Mruwut R, Yedgar S, Lavon L, Ariel A, Krsnys M, Shosyev D. Phospholipase A2 in experimental allergic bronchitis: a lesson from mouse and rat models. PLoS One. 2013;8:e76641.
27. Toussi A, Alouei-Er-Azher M. Mammalian secreted phospholipases A2 and their pathophysiological significance in inflammatory diseases. Curr Mol Med. 2001;1:739–54.
28. Furue S, Mikawa K, Nishina K, Shiga M, Ueno M, Tomita Y, et al. Therapeutic effect of a group IIa phospholipase A2 inhibitor in rabbit acute lung injury: Correlation with lung surfactant protection. Crit Care Med. 2001;29:719–27.
27. Mokra D, Mokry J. Phosphodiesterase inhibitors in acute lung injury: what are the perspectives? Int J Mol Sci. 2021;22:1929.
28. Fisher AB, Dodia C, Tao JQ, Feinstein SI, Chatterjee S. Inhibition of peroxiredoxin 6 PLA2 activity decreases oxidative stress and the severity of acute lung injury in the mouse cecal ligation and puncture model. Antioxidants (Basel). 2021;10:1676.
29. Htwe YM, Wang H, Belvitch P, Meliton L, Bandela M, Letsiou E, et al. Group V phospholipase A2 mediates endothelial dysfunction and acute lung injury caused by methicillin-resistant Staphylococcus aureus. Cells. 2021;10:1731.
30. Kaiser E. Phospholipase A2: its usefulness in laboratory diagnostics. Crit Rev Clin Lab Sci. 1999;36:65–163.

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