

# Sevoflurane attenuates pulmonary inflammation and ventilator-induced lung injury by upregulation of HO-1 mRNA expression in mice

Xiang-qing Xiong

Li-na Lin

Liang-rong Wang

Li-da Jin

Department of Anesthesiology, the First Affiliated Hospital of Wenzhou Medical College, Wenzhou, People's Republic of China

**Background:** Mechanical ventilation has been documented to paradoxically cause lung injury. As a commonly used volatile anesthetic, sevoflurane has been proven to possess antiinflammatory and antioxidative properties. This study aims to investigate the protective effects of sevoflurane on inflammation and ventilator-induced lung injury during mechanical ventilation in healthy mice.

**Methods:** The adult healthy mice were divided into four groups, each consisting of ten subjects: mice in group Con- $L_{VT}$  and group Sev- $L_{VT}$  were ventilated with tidal volumes of 8 mL/kg for 4 hours, while those in group Con- $H_{VT}$  and group Sev- $H_{VT}$  were ventilated with tidal volumes of 16 mL/kg instead. Control mice (group Con- $L_{VT}$  and Con- $H_{VT}$ ) were subjected to fresh air, while sevoflurane-treated mice (groups Sev- $L_{VT}$  and Sev- $H_{VT}$ ) were subjected to air mixed with 1 vol% sevoflurane. After 4 hours of ventilation, the bronchoalveolar lavage (BAL) fluid was collected and analyzed for the levels of tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-10. Lung homogenates were harvested to detect the expression of nuclear factor-kappa B (NF- $\kappa$ B) and heme oxygenase (HO)-1 mRNA by reverse transcription-polymerase chain reaction method. Lung damage was evaluated using the modified Ventilator-Induced Lung Injury histological scoring system.

**Results:** Compared to group Con- $L_{VT}$ , the levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 in BAL fluid, mRNA expressions of NF- $\kappa$ B and HO-1 in lung tissue, and lung injury scores were significantly increased in group Con- $H_{VT}$ ; compared to group Con- $H_{VT}$ , group Sev- $H_{VT}$  BAL samples showed decreased levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6; they also showed increased levels of IL-10, the downregulation of NF- $\kappa$ B mRNA, and HO-1 mRNA upregulation; the lung injury scores were significantly lower in group Sev- $H_{VT}$  than group Con- $H_{VT}$ .

**Conclusion:** Mechanical ventilation with high tidal volume might lead to lung injury, which could be significantly, but not completely, attenuated by sevoflurane inhalation by inhibiting the NF- $\kappa$ B-mediated proinflammatory cytokine generation and upregulating HO-1 expression.

**Keywords:** mechanical ventilation, sevoflurane, inflammation, lung injury

## Introduction

Mechanical ventilation is an essential respiratory support approach during general anesthesia and provides a lifesaving intervention in acute respiratory failure therapy.<sup>1</sup> However, excessive alveolar distension can lead to lung injury due to increased pulmonary vascular permeability, alteration in lung mechanics, and increased production of inflammatory mediators.<sup>2,3</sup> Although modulation of ventilator settings such as applying low tidal volumes and low plateau pressure may help to relieve lung injury,<sup>4</sup> ventilator-induced lung injury (VILI) remains a major problem in the long-term use of mechanical ventilation with an unacceptably high rate of

Correspondence: Li-na Lin  
Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou 325000, Zhejiang Province, People's Republic of China  
Tel +86 1390 663 1675  
Fax +86 0577 8806 9458  
Email lin201199@sina.com

morbidity and mortality.<sup>5</sup> The underlying mechanisms of VILI are incompletely understood, but a large body of investigation indicates that proinflammatory cytokines and heme oxygenase (HO)-1 play an important role in the development of VILI.<sup>6,7</sup> Therefore, alternative therapeutic antiinflammatory strategies to further minimize the risk of VILI need to be developed.

Sevoflurane is a widely used volatile anesthetic whose antiinflammation properties have recently gained increasing attention.<sup>8-10</sup> Many studies have demonstrated that sevoflurane can modulate inflammatory cascades and has protective effects against ischemia/reperfusion injury.<sup>11-13</sup> Studies by Suter et al<sup>11</sup> demonstrated a decrease in the production of inflammatory proteins in alveolar epithelial cells with sevoflurane preconditioning in endotoxin-induced lung injury. However, as a widely used anesthetic in general anesthesia, whether sevoflurane is capable of attenuating VILI remains unknown.

Based on these recent findings, the aim of the current study was to verify the hypothesis that sevoflurane may attenuate pulmonary inflammation and VILI by upregulating HO-1 expression and inhibiting the nuclear factor-kappa B (NF- $\kappa$ B) mediated proinflammatory cytokine generation in an in vivo model of VILI.

## Materials and methods

### Animal preparation

The study strictly abided by the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All experimental procedures were approved by the Animal Ethics Committee of Wenzhou Medical College.

Adult healthy male C57BL/6N mice weighing 30 g to 35 g were obtained from the Animal Experimental Center of Wenzhou Medical College. All mice were anesthetized with 90 mg/kg of ketamine and 1 mg/kg of acepromazine intraperitoneally and placed in the supine position. Muscular relaxation was achieved by applying an intraperitoneal injection of 1.5 mg/kg of vecuronium. Anesthesia was maintained by continuous intraperitoneal administration of ketamine (45 mg/kg/hour), acepromazine (0.5 mg/kg/hour), and vecuronium (0.75 mg/kg/hour) as needed. Adequacy of anesthesia during maintenance was assessed based on hemodynamic responses. Tracheotomy was established using a 15-gauge catheter, and a polyethylene catheter was inserted into the left carotid artery for direct blood pressure monitoring and blood gas sampling. An ear vein was cannulated with a 7-gauge intravenous catheter for receiving an intravenous infusion of Ringer's solution ( $5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ).

## Experimental design

The 40 mice were divided into four groups: (1) group Con- $L_{VT}$  ( $n = 10$ ): the mice were ventilated with fresh air at a tidal volume of 8 mL/kg; (2) group Con- $H_{VT}$  ( $n = 10$ ): the mice were ventilated with synthetic air at a tidal volume of 16 mL/kg; (3) group Sev- $L_{VT}$  ( $n = 10$ ): the mice were ventilated with synthetic air supplemented with 1 vol% minimum alveolar concentration (MAC) sevoflurane at a tidal volume of 8 mL/kg; (4) group Sev- $H_{VT}$  ( $n = 10$ ): ventilated with synthetic air supplemented with 1 vol% MAC sevoflurane at a tidal volume of 16 mL/kg. The inspiratory/expiratory ratio was 1:2, the respiratory rate was 16 bpm, the total gas flow was 1.5 L/minute, and the fraction of inspired oxygen ( $\text{FiO}_2$ ) was maintained for all animals and no positive end-expiratory pressure was applied. Oxygen saturation, arterial blood pressure, and electrocardiography were monitored continuously and recorded every 15 minutes. Mean airway pressure and peak inspiratory pressure were monitored continuously and recorded every 30 minutes. Arterial blood gases were analyzed hourly. The above monitoring instruments came from Hewlett-Packard Co, Ltd (Palo Alto, CA, USA).

## Bronchoalveolar lavage and cytokine measurements

Mice were put to death after 4 hours of continuous mechanical ventilation, and bronchoalveolar lavage (BAL) was performed via the tracheal catheter in the right lung lobes using 0.8 mL of phosphate buffered saline; the withdrawn fluid was centrifuged, and the supernatant was snap frozen and stored at  $-80^\circ\text{C}$  for further use. Aliquots of BAL fluid were detected in duplicate with enzyme-linked immunosorbent assay (ELISA kit offered by Glory Science Co, Ltd, Del Rio, TX, USA) kits for tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-6, and IL-10 according to the manufacturer's instructions. The minimum detection limits for these kits were 3.5 pg/mL for TNF- $\alpha$ , 3.0 pg/mL for IL-1 $\beta$ , 15 pg/mL for IL-6, and 20 pg/mL for IL-10.

## Measurement of NF- $\kappa$ B and HO-1 mRNA by RT-PCR

The left lung tissues were homogenized and total RNA was extracted using TRIzol reagent (Shanghai Sangon Biological Engineering Technology and Service Co, Ltd, Shanghai, People's Republic of China) according to the manufacturer's instructions. For reverse transcription-polymerase chain reaction (RT-PCR), 1  $\mu\text{g}$  of total RNA from each sample was resuspended in 25  $\mu\text{L}$  final volume of reaction buffer.

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal control. The following primers were used for PCR: HO-1 forward primer 5'-TCC TCA ATG CTG TAC TGG TCC-3', reverse primer 5'-ATG TTC TTC CTT TCC AGG TC-3'; NF- $\kappa$ B forward primer 5'-AGT TGA GGG GAC TTT CCC AGG C-3', reverse primer 5'-GCC TGG GAA AGT CCC CTC AAC T-3'; and GAPDH forward primer 5'-AAT GCA TCC TGC ACC ACC AA-3', and reverse primer 5'-GTA GCC ATA TTC ATT GTC ATA-3'.

## Assessment of lung histopathology

The left lung lobe was fixed in 4% buffered formalin solution overnight at room temperature, dehydrated, embedded in paraplast, and then 4  $\mu$ m-thick sections were obtained. Lung histopathology was assessed under a light microscope after hematoxylin and eosin staining. The degree of lung damage was assessed using a modified VILI histological scoring system:<sup>14</sup> (1) thickness of the alveolar walls; (2) infiltration or aggregation of inflammatory cells; and (3) hemorrhage. Each item was graded according to the following five-point scale: 0, minimal damage; 1, mild damage; 2, moderate damage; 3, severe damage; 4, maximal damage. The degree of lung damage was assessed by the sum of scores ranging from 0 to 12.

## Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences version 15.0 (SPSS, IBM Corporation, Armonk, NY, USA). Data were analyzed for normality using the Kolmogorov–Smirnov method, and the normally distributed data were expressed as mean  $\pm$  standard deviation. To compare normally distributed data between each group, one-way analysis of variance followed by the Student–Newman–Keuls post hoc test was employed. A *P*-value of less than 0.05 was considered significant.

## Results

### The change in hemodynamics and respiratory function

No significant differences were observed in heart rate and mean arterial pressure between or within groups (*P* > 0.05). Mean airway pressures and peak airway pressure were higher in group Con- $H_{VT}$  and Sev- $H_{VT}$  compared with groups Con- $L_{VT}$  and Sev- $L_{VT}$  respectively, and there were no significant differences between the two  $H_{VT}$  groups or  $L_{VT}$  groups (Table 1).

Arterial pH in all animals was kept within the range of 7.3–7.5 during the protocol.  $H_{VT}$  groups had significantly higher arterial pH than  $L_{VT}$  groups (Table 1). Partial pressure of carbon

**Table 1** Parameters for ventilation strategies and blood gas

	Con- $H_{VT}$	Sev- $H_{VT}$	Con- $L_{VT}$	Sev- $L_{VT}$
<b>Hemodynamics</b>				
MAP (mmHg)	55.6 $\pm$ 3.1	54.4 $\pm$ 3.3	56.2 $\pm$ 3.5	55.7 $\pm$ 2.8
HR	126 $\pm$ 4.6	128 $\pm$ 5.6	124 $\pm$ 4.0	127 $\pm$ 5.2
<b>Respiratory pressure</b>				
$P_{mean}$ (cm $H_2O$ )	14.5 $\pm$ 0.6*	15.1 $\pm$ 0.3*	8.9 $\pm$ 0.4	8.7 $\pm$ 0.5
$P_{peak}$ (cm $H_2O$ )	25.7 $\pm$ 1.2*	26.8 $\pm$ 1.8*	12.4 $\pm$ 0.9	12.4 $\pm$ 0.6
<b>Blood gas</b>				
pH	7.48 $\pm$ 0.05*	7.47 $\pm$ 0.04*	7.31 $\pm$ 0.03	7.32 $\pm$ 0.04
$HCO_3$ (mmol/L)	23.5 $\pm$ 1.2	24.2 $\pm$ 0.8	25.6 $\pm$ 1.4	25.7 $\pm$ 1.3
$PO_2$ (mmHg)	125 $\pm$ 5.4	128 $\pm$ 7.9	124 $\pm$ 4.3	126 $\pm$ 6.7
$PCO_2$ (mmHg)	35.4 $\pm$ 1.5*	36.2 $\pm$ 1.3*	48.7 $\pm$ 2.6	47.7 $\pm$ 3.1

**Note:** \**P* < 0.05, compared with Con- $L_{VT}$  or Sev- $L_{VT}$ .

**Abbreviations:** Con- $H_{VT}$ , high tidal volume of synthetic air ventilation; Sev- $H_{VT}$ , high tidal volume of air ventilation supplemented with sevoflurane; Con- $L_{VT}$ , low tidal volume of synthetic air ventilation; Sev- $L_{VT}$ , low tidal volume of air ventilation supplemented with sevoflurane; MAP, mean arterial pressure; HR, heart rate;  $P_{mean}$ , mean airway pressures;  $P_{peak}$ , peak airway pressures.

dioxide ( $PaCO_2$ ) was within its normal range of 35–50 mmHg in all mice. Compared to the  $L_{VT}$  groups,  $PaCO_2$  levels in  $H_{VT}$  groups were significantly higher (Table 1). Partial pressure of arterial oxygen ( $PaO_2$ ) differed between any two groups.

### The measurement of inflammatory cytokines in BAL fluid

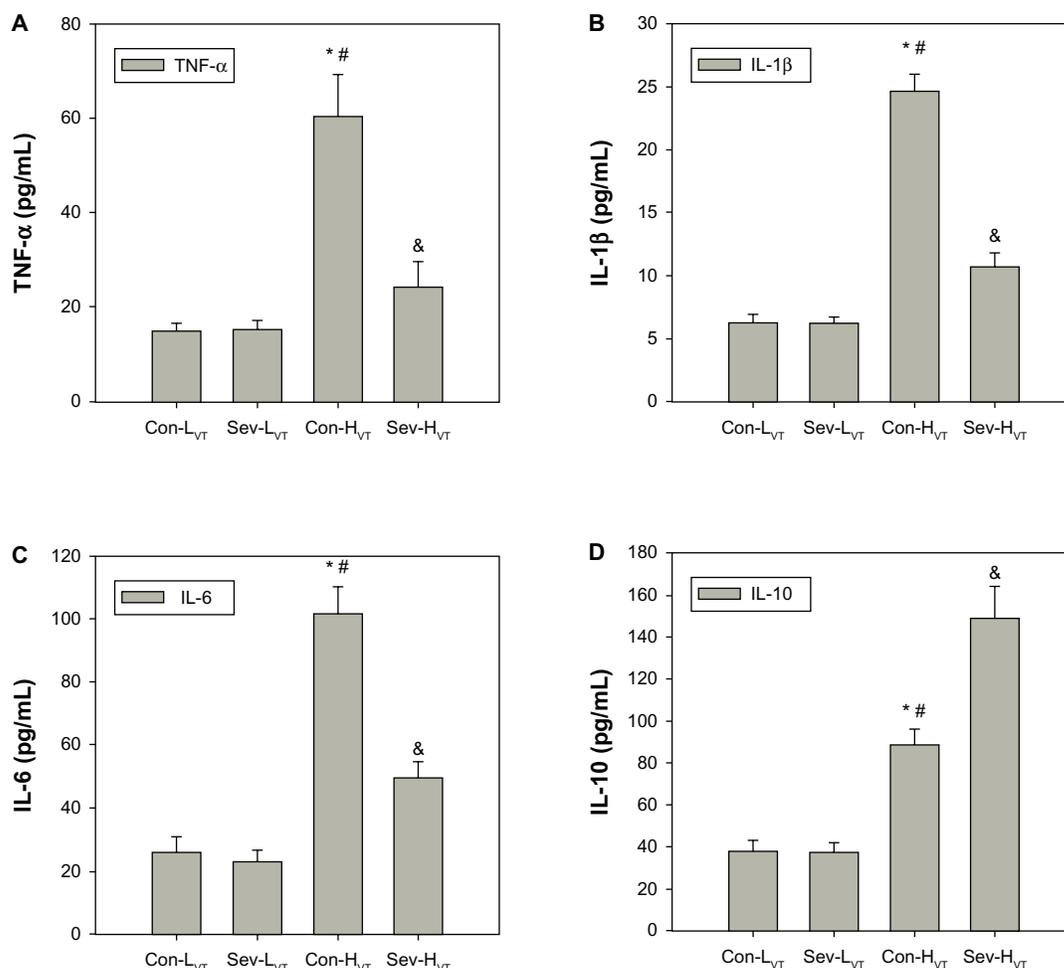
The levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 in BAL fluid in the  $H_{VT}$  groups were significantly higher than those in the  $L_{VT}$  groups (Figure 1). The levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in BAL fluid were significantly decreased, and IL-10 levels were increased in the Sev- $H_{VT}$  group as compared with the Con- $H_{VT}$  group (Figure 1).

### The expressions of NF- $\kappa$ B and HO-1 mRNA in the lung homogenates

In the lung homogenates, the expressions of NF- $\kappa$ B and HO-1 were found to be significantly regulated in the  $H_{VT}$  group as compared to the  $L_{VT}$  group (Figure 2). The mRNA expression levels of NF- $\kappa$ B were lower, and the expression of HO-1 mRNA were higher in group Sev- $H_{VT}$  than group Con- $H_{VT}$  (Figure 2).

### The assessment of lung histopathological changes

Normal histology in lung tissue was observed in the Con- $L_{VT}$  and Sev- $L_{VT}$  groups, while the lung presented severe lesions in the Con- $H_{VT}$  group, manifested as lung interstitial edema, inflammatory cell infiltration, pulmonary alveolus rupture, and hemorrhage. These histopathological changes were markedly attenuated in the group Sev- $H_{VT}$  (Figure 3). The lung injury scores were significantly lower in group



**Figure 1** All mice were ventilated for 4 hours with low tidal volume (8 mL/kg, group Con-L<sub>VT</sub> and group Sev-L<sub>VT</sub>) or high tidal volume (16 mL/kg, group Con-H<sub>VT</sub> and group Sev-H<sub>VT</sub>). The BAL fluid was obtained from the right lung lobes and analyzed for the concentration of TNF-α (A), IL-1β (B), IL-6 (C), and IL-10 (D) by ELISA.

**Notes:** \* $P < 0.05$ , group Con-H<sub>VT</sub> versus Con-L<sub>VT</sub>; # $P < 0.05$ , group Con-H<sub>VT</sub> versus Sev-L<sub>VT</sub>; & $P < 0.05$ , group Sev-H<sub>VT</sub> versus Con-H<sub>VT</sub>.

**Abbreviations:** Con-L<sub>VT</sub>, low tidal volume of synthetic air ventilation; Sev-L<sub>VT</sub>, low tidal volume of air ventilation supplemented with sevoflurane; Con-H<sub>VT</sub>, high tidal volume of synthetic air ventilation; Sev-H<sub>VT</sub>, high tidal volume of air ventilation supplemented with sevoflurane; BAL, bronchoalveolar lavage; TNF, tumor necrosis factor; IL, interleukin; ELISA, enzyme-linked immunosorbent assay.

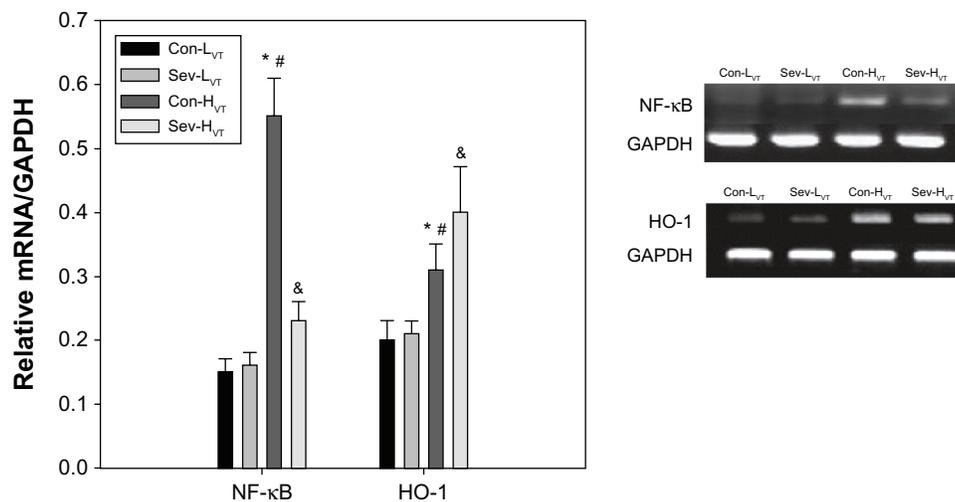
Sev-H<sub>VT</sub> ( $2.32 \pm 0.18$ ) versus group Con-H<sub>VT</sub> ( $5.20 \pm 0.34$ ) (Figure 3).

## Discussion

The main findings of our study were that sevoflurane inhalation was shown to attenuate VILI by upregulating HO-1 expression and inhibiting the NF-κB-mediated proinflammatory cytokine generation.

Many studies have shown that severe lung injury is provoked by ventilation with high tidal volumes.<sup>15–17</sup> Although the exact underlying mechanisms of VILI remain undefined, several potential pathways have been proposed, with barotrauma appearing to be the generally accepted one. In our study, significant infiltration of neutrophils was observed on pathological examination of the lung tissue exposed to high tidal volume ventilation.

Studies showed that NF-κB signaling can be rapidly induced by a large number of stimuli, which trigger the transcription of inflammatory cytokines.<sup>18,19</sup> During the process of positive pressure ventilation with high tidal volume, baroreceptors on lung epithelial cells and alveolar macrophages are stimulated by excessive alveolar stretching, leading to serial biochemical events via a mechanical transduction mechanism, which would cause the modulation of the NF-κB signal pathway, the activation of inflammatory cells, and formation of chemical chemoattractants. With the action of chemotactic stimuli and expression of adhesion molecules, the infiltration of activated neutrophils into the lung tissue may initiate an inflammatory cascade that unavoidably results in the generation of its down-flow cytokines (eg, TNF-α, IL-1β, IL-6).<sup>20</sup> Our study demonstrated that increased airway



**Figure 2** All mice were ventilated for 4 hours with low tidal volumes (8 mL/kg, group Con-L<sub>VT</sub> and group Sev-L<sub>VT</sub>) or high tidal volumes (16 mL/kg, group Con-H<sub>VT</sub> and group Sev-H<sub>VT</sub>).

**Notes:** The left lung was homogenized and RNA was extracted, followed by the measurement of the expression of NF-κB and HO-1 mRNA using RT-PCR. \**P* < 0.05, group Con-H<sub>VT</sub> versus Con-L<sub>VT</sub>; #*P* < 0.05, group Con-H<sub>VT</sub> versus Sev-L<sub>VT</sub>; &*P* < 0.05, group Sev-H<sub>VT</sub> versus Con-H<sub>VT</sub>.

**Abbreviations:** Con-L<sub>VT</sub>, low tidal volume of synthetic air ventilation; Sev-L<sub>VT</sub>, low tidal volume of air ventilation supplemented with sevoflurane; Con-H<sub>VT</sub>, high tidal volume of synthetic air ventilation; Sev-H<sub>VT</sub>, high tidal volume of air ventilation supplemented with sevoflurane; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; NF-κB, nuclear factor-kappa B; HO-1, heme oxygenase-1; RT-PCR, reverse transcription polymerase chain reaction.

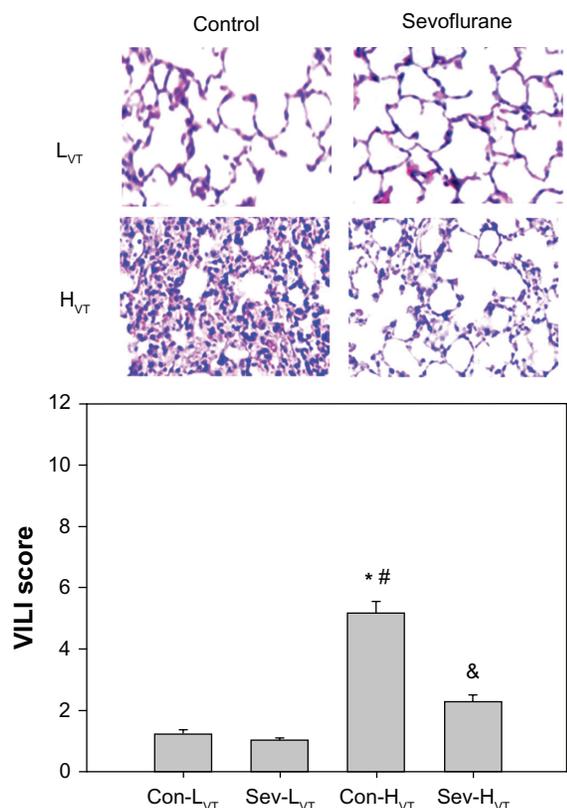
pressure and inflammatory cytokine release are associated with H<sub>VT</sub> mechanical ventilation. Similar results have been obtained by Chu et al.<sup>21</sup>

To avoid the influence of systemic hemodynamics, we applied 1 vol% sevoflurane. There was no significant difference among the four groups with regard to mean arterial pressure during ventilation. Lee et al<sup>12</sup> demonstrated that volatile anesthetics reduced necrosis and inflammation. Schilling et al<sup>22</sup> recently reported that sevoflurane suppressed local alveolar inflammatory responses during one-lung ventilation. Our studies showed that sevoflurane administration significantly attenuated the lung injury by the inhibition of TNF-α, IL-1β, IL-6, and the augmentation of IL-10. At the same time, the protein expression of the proinflammatory cytokine induction of NF-κB was also remarkably inhibited in the groups with sevoflurane. NF-κB is a pivotal inducible transcription factor that regulates the expression of many genes of inflammation, so we deduce that sevoflurane administration results in a proinflammatory shift by down-regulating the mRNA expression of NF-κB. Consistent with this finding, Zhong et al<sup>23</sup> reported that sevoflurane protected the lung from ischemia/reperfusion injury by suppressing the expression of NF-κB.

HO – the rate-limiting enzyme in heme degradation to carbon monoxide (CO), free iron, and biliverdin – is normally expressed at low levels in tissues. In the previous study, it was found that HO-1 expression could be induced by heavy metals, glutathione depletors, immunostimulants,

and a variety of stressful conditions.<sup>24,25</sup> In our studies, HO-1 expression is induced by ventilation with a tidal volume of 16 mL/kg, indicating that HO-1 expression is sensitive to induction by mechanical stimulation. The increase in HO-1 expression has been considered to be an inducible defense and a beneficial response to acute lung injury;<sup>26–28</sup> however, the underlying mechanisms are still poorly understood. An et al<sup>29</sup> reported the beneficial effect of HO-1 to ventilator-induced lung injury. Park et al<sup>30</sup> found that the overexpression of HO-1 mediated the antiinflammatory response through Nrf-2, PI3K/Akt, and ERK activation. During those downstream products of HO-1, CO has been demonstrated to modulate the inflammatory pathway in a variety of experimental models, reducing the production of inflammatory cytokines, while increasing the production of antiinflammatory cytokines through interaction with the MAPK pathways.<sup>31</sup> CO might be able to depress leukocyte adhesion through the modulation of platelet dynamics,<sup>32</sup> but the studies of Maulik et al<sup>33</sup> indicate that the antiinflammatory function of CO contributes to the production of nitric oxide, resulting in the indirect modulation of adhesive interaction.

Although Schwer et al<sup>6</sup> had reported that the augmentation of HO-1 could be induced by sevoflurane in the rat liver, we provided the first proof that 1% MAC sevoflurane administration upregulated the mRNA expression of HO-1 in the lung tissue during ventilation, which reduced proinflammatory cytokine generation. We presume that this could be the underlying mechanism of sevoflurane



**Figure 3** All mice were ventilated for 4 hours with low tidal volumes (8 mL/kg, group Con-L<sub>VT</sub> and group Sev-L<sub>VT</sub>) or high tidal volumes (16 mL/kg, group Con-H<sub>VT</sub> and group Sev-H<sub>VT</sub>).

**Notes:** The sections from the right lung lobe were hematoxylin and eosin stained. Representative pictures were shown for each experimental group (magnification  $\times 400$ ). The lung tissue in the H<sub>VT</sub> group demonstrated histological changes with lung interstitial mesenchymal edema, inflammatory cell infiltration, pulmonary alveolus rupture, bursts, and hemorrhage. These changes were markedly attenuated by sevoflurane administration. Lung injury scores were calculated using modified VILI scoring. \* $P < 0.05$ , group Con-H<sub>VT</sub> versus Con-L<sub>VT</sub>; # $P < 0.05$ , group Con-H<sub>VT</sub> versus Sev-L<sub>VT</sub>; & $P < 0.05$ , group Sev-H<sub>VT</sub> versus Con-H<sub>VT</sub>.

**Abbreviations:** Con-L<sub>VT</sub>, low tidal volume of synthetic air ventilation; Sev-L<sub>VT</sub>, low tidal volume of air ventilation supplemented with sevoflurane; Con-H<sub>VT</sub>, high tidal volume of synthetic air ventilation; Sev-H<sub>VT</sub>, high tidal volume of air ventilation supplemented with sevoflurane; H<sub>VT</sub>, high tidal volume; VILI, ventilator-induced lung injury.

attenuating VILI. Whether this beneficial effect is threshold or dose-dependent still remains unanswered.

## Conclusion

Mechanical ventilation with high tidal volume could probably lead to lung injury, which could be significantly attenuated by sevoflurane inhalation by upregulating HO-1 expression and inhibiting the NF- $\kappa$ B-mediated proinflammatory cytokine generation.

## Disclosure

The authors report no conflicts of interest in this work.

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