Original Article
Ameliorating effects of low tidal volume ventilation with associated hypercapnia on pneumoperitoneum-induced lung injury by inhibition of Toll-like receptor 4

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Abstract: Background: Mechanical ventilation using lower tidal volume ventilation with associated hypercapnia is supported to avoid ventilator-induced lung injury, but the underlying mechanism is not clear. This study was intended to explore whether low tidal volume ventilation with associated hypercapnia would ameliorate pneumoperitoneum-induced lung injury and whether this protection strategy might work through mediating inflammation and oxidative stress via TLR 4 signaling pathway. Materials and methods: 50 anesthetized Wistar Rats were randomized to be mechanically ventilated for 4 h at 7 groups: Group A, ventilated with 12 ml/kg; Group B, similar to Group A but injected with LPS (Toll receptor 4 agonist); Group C, similar to Group A but injected with Pam3Cys (Toll receptor 2 agonist); Group D, ventilated with 12 ml/kg and subjected to pneumoperitoneum; Group E, ventilated with 6 ml/kg and subjected to pneumoperitoneum; Group F, similar to Group E but injected with LPS; Group G, similar to Group E but injected with Pam3Cys. After animals were killed, indices of lung Injury, inflammation markers and oxidative stress markes of the lungs tissues, bronchoalveolar lavage fluid and blood were assessed. Results: The group subjected to pneumoperitoneum (Group D) had elevated values of indices of lung Injury, inflammation oxidative stress markers compared with the controls (Group A). The low tidal volume ventilation group (Group E) had significantly decreased values of markers of lung Injury, inflammation and oxidative stress compared with the high tidal volume ventilation group (Group D). LPS treatment reversed all the results of Group E, while Pam3Cys treatment had no significant effect. Conclusions: Low tidal volume ventilation with associated hypercapnia ameliorated pneumoperitoneum-induced lung injury by reducing TLR 4-mediated inflammation and oxidative stress.

Keywords: Low tidal volume ventilation, hypercapnia, pneumoperitoneum, lung injury, Toll-like receptor 4

Introduction

Establishment of pneumoperitoneum is required in laparoscopic surgery, but it has an inherently detrimental effect on respiratory function. The pneumoperitoneum affects not only arterial oxygen partial pressure (PaO_2), arterial oxygen saturation (SaO_2), but lung compliance, tidal volume and alveolar ventilation [1-3]. Low tidal volume ventilation associated with hypercapnia has been recommended as one of lung protective mechanical ventilation strategies in recent years. A large multicenter trials showed that compared with a traditional tidal volume (12 ml per kilogram of predicted body weight), the use of a lower tidal volume (6 ml per kilogram of predicted body weight) would reduce mortality and increase the number of days without ventilator in patients with acute lung injury and the acute respiratory distress syndrome [4]. Sinclair et al [5] found that hypercapnic acidosis confers a protective effect against ventilator-induced lung injury (VILI) in an intact rabbit model. However, the cellular and biochemical underlying mechanism of this protective strategy is still needed to be elaborated.

Numerous researches showed that inappropriate mechanical ventilation produced mechanical injury, including barotraumas, volutrauma and atelectrauma, which likely developed to local inflammatory disequilibrium or even systemic inflammatory reaction [6, 7]. A significant increase of bronchoalveolar lavage fluid (BALF)

concentrations of interleukin (IL) 1b, IL-6, tumor necrosis factor (TNF)-α, TNF-α receptors and IL-1 receptor and a significant increase of plasma levels of TNF-α, IL-6 and TNF-α receptors were observed after conventional mechanical ventilation over 36 hours in Patients with acute respiratory distress syndrome [8]. These results suggested an important role of inflammatory mediators and cytokines in mechanical ventilation.

Previous studies have also shown that oxidative stress caused by the increased intra-abdominal pressure during pneumoperitoneum contributed to lung tissue injury [9, 10]. High tidal volume ventilation promoted the formation of reactive oxygen (ROS) and nitrogen species (RNS), resulting in vascular dysfunction associated with VILI [11]. Papaiahgari et al [12] showed that the redox imbalance involved in VILI and Nrf2-dependent transcriptional program played a critical protective role in VILI by reducing oxidative stress.

Vaneker et al [13] found that low-tidal-volume mechanical ventilation in healthy lungs increased the level of endogenous ligands for TLR4 in BALF and the mRNA level of TLR4 and TLR2 in lung tissue, suggesting that TLR4 and/or TLR2 receptor signaling was involved in the inflammatory response induced by mechanical ventilation. Moreover, TLR4 has been shown to contribute to the increase of ROS production involved in the subsequent inflammatory response [14, 15].

Based on the foregoing issues, using a classical rat model of VILI, we intended to explore whether low tidal volume ventilation with associated hypercapnia have a protective effect on pneumoperitoneum-induced lung injury. And we also studied the hypothesis that this protection strategy might work through mediating inflammation and oxidative stress via TLR 4 signaling pathway.

Materials and methods

Animals preparation and instrumentation

Care of the animals, techniques and procedures were approved by the Animal Care and Use Committee of Qianfo Mountain Hospital of Shandong University. SPF Wistar Rats weighing 300±50 g were obtained from Experimental Animal Center of Shandong University and were housed standardized with 12:12 h dark light circle with free access to water and food.

After anesthetized with an intraperitoneal injection of 3% phenobarbital (50 mg/kg), an endotracheal tube (2 mm internal diameter; Johnson and Johnson, New Brunswick, NJ) was inserted via a tracheostomy. The femoral artery was cannulated with a catheter (ED 0.96 mm; Intramedic, Clay Adams, Parsippany, NJ) to monitor systemic arterial pressure and collect blood, when the venous catheter was used for continuous infusion of 0.9% saline (10 ml/kg/h). Mechanical ventilation was initiated using a Stephanie infant ventilator (Stephan, GmbH, Medizintechnik, Gackenbach, Germany) with tidal volume (VT) of 12 ml/kg, fresh gas flow rate (FGFR) of 2.0 L/min, inspired oxygen fraction (FIO_2) of 0.50. The rate was adjusted to obtain a $PaCO_2$ in the target range (35-45 mm Hg). The animals were ventilated for 30 minutes to collect baseline data.

Experimental protocols

After recording baseline hemodynamic and gas exchange, 50 rats were randomly allocated into seven groups: Group A, ventilated with the above setting; Group B, premedication with LPS (2 mg/kg, i.p.) before ventilation with the same setting of group A; Group C, premedication with Pam3Cys (2 mg/kg, i.p.) before ventilation with the same setting of group A. Group D, ventilated with the above setting after establishing CO_2 pneumoperitoneum (pneumoperitoneum pressure of 12 mmHg); Group E, ventilated with VT of 6 ml/kg and the end-tidal carbon dioxide concentration ($ETco_2$) of 60 mmHg after establishing CO_2 pneumoperitoneum (pneumoperitoneum pressure of 12 mmHg); Group F, premedication with LPS (2 mg/kg, i.p.) before ventilation with the same setting of group E; Group G, premedication with Pam3Cys (2 mg/kg, i.p.) before ventilation with the same setting of group E. LPS and Pam3Cys were dissolved in saline. Arterial blood gases were measured at every half hour during the experiment. After 4 h ventilation the animals were sacrificed by exsanguinations. Blood was drawn for measurement of WBC concentration, which was tested using an automated hematology analyzer (Advia 2120; Siemens Diagnostic Solutions, Tarrytown, NY).

Gravimetric analysis

The middle lobe of right lung was gently wiped away the moisture on the surface, weighed to obtain wet weight (WW) and then placed in an oven at 80°C for 48 h to obtain the "dry" weight (DW). The wet to dry weight ratios (WW: DW) was calculated to assess tissue edema.

Histology

After rats were sacrificed, the lower lobe of right lung was fixed in 4% paraformaldehyde solution for 24 h, dehydrated, embedded in paraffin, sectioned and stained with hematoxylin and eosin according to the regular method. Slides were evaluated by a pathologist blinded to the experimental groups and scored using a scoring system developed by Simons et al [16] to grade the degree of lung injury. Briefly, lung injury was graded from 0 (normal) to 4 (severe) in four categories: interstitial inflammation, neutrophil infiltration, congestion, and edema. The total lung injury score (TLIS) was calculated by adding up the individual scores of each category.

Myeloperoxidase assay

The lung tissues were homogenized in phosphate buffer (50 mmol/l) at a pH of 6 containing 0.5% hexadecyltrimethylammonium bromide (100 mg of tissue per ml of buffer) and then sonicated for 10 s, with freezing and thawing at 20-30°C three times. After centrifuging at 18000 g for 25 min at 4°C, the supernatant was collected for myeloperoxidase (MPO) determination using the MPO Activity Assay kit (Nanjing Jiancheng Bioengineering Institute, China) according to the manufacturer's protocol. In brief, 250 µl of sample was incubated with 625 µl of phosphate buffer (50 mmol/l, pH = 6) containing 125 µl of hydrogen peroxide (0.0005%) and 0.167 mg/ml O-dianisidine dihydrochloride for 30 min. Then the absorbance at 460 nm was measured to determine the activity of MPO enzyme (U/g tissue).

Bronchoalveolar lavage fluid (BALF) total cell and PMN counting

Chest was opened via sternotomy, the right mainstem bronchus was clamped with a hemostat, the trachea was cannulated and bronchoalveolar lavage (BAL) of the left lung was performed by flushing lung and airways three with 5 ml cold (4°C) saline solution. Recovered BALF was centrifuged at 3000 rpm for 10 minutes at 4°C. The sediment cells were resuspended in 50 µl PBS and the supernatants were frozen at -80°C for TNF-α, IL-6, IL-8 and NO analysis. The total number of cells in BALF were counted double-blindly by using a standard hemocytometer. Cell differentiation was examined by counting a total of 200 cells/slide at 40× magnification on a cytospin smear prepared by using Wright-Giemsa staining.

Superoxide dismutase (SOD) activity

The SOD activity was detected as described before [17]. The samples were added in 3 ml of 0.05 M potassium phosphate buffer at pH 7.8 containing 10^{-4} M EDTA in a 1.0-cm cuvette thermostatted at 25°C. The reaction mixture contained 1×10^{-5} M ferricytochrome C, 5×10^{-5} M xanthine, and sufficient xanthine oxidase to produce a rate of reduction of ferricytochrome C at 550 nm of 0.025 absorbance unit per minute.

Malondialdehyde (MDA) level

MDA was measured by the colorimetric method using thiobarbituric acid as described earlier [18]. 2 ml of a mixture of 0.375% trichloroacetic acid, 15% thiobarbituric acid, and 0.25N HCl were added to 200 µl of erythrocytes and 800 µl of 0.15 M NaCl. The reaction mixture was then heated to 100°C for 15 min. After centrifugation, the absorbance of the supernatant was measured at 532 nm.

Real-time PCR

The upper lobe of right lung was homogenized with a micro-dismembrator II (Braun, Melsungen, Germany). Total RNA was extracted using Trizol reagent (Invitrogen, San Diego, CA, USA) according to the manufacturer's instructions. 1 µg of total RNA was reverse transcribed to single-strand cDNA using oligo dT primers and 200U MMLV reverse transcriptase (Invitrogen, San Diego, CA, USA) according to the manufacturer's directions. Subsequently, quantitative PCR was performed in a 20 µl reaction volume in triplicate using TransStar SYBR Green qPCR Supermix (TransGen Biotech, Beijing, China), according to the manufacturer's recommended protocol. And data were collected and analyzed
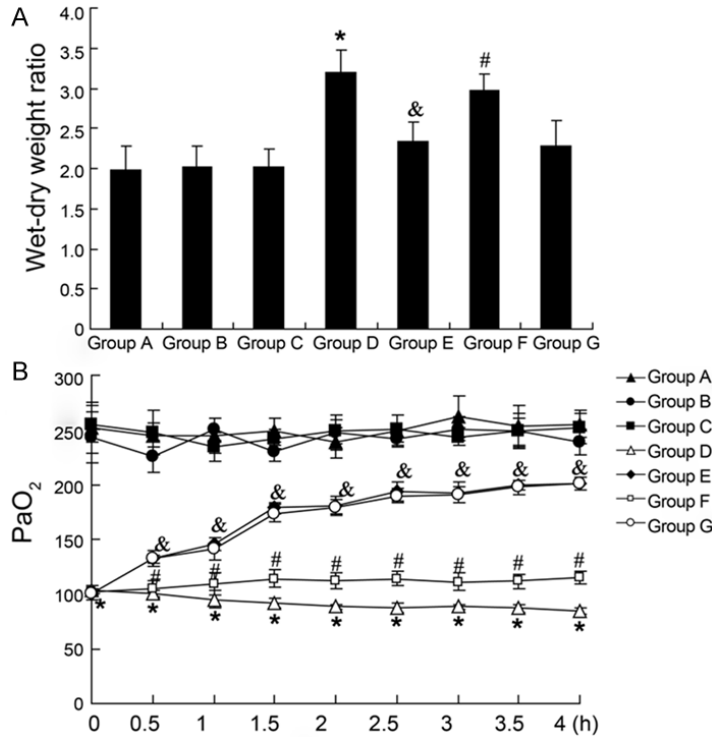
Figure 1. Indices of lung Injury. Wet to dry weight ratios (A) and PaO$_2$ (B) were used to estimate degree of lung injury. (A) The Wet to dry weight ratios were significantly increased in high tidal volume ventilation group (Group D) compared with the controls (Group A), whereas significantly decreased in low tidal volume ventilation group (Group E) compared with Group D. LPS treatment (Group F) improved the decrease in Group E, while Pam3Cys treatment (Group G) had no significant effect. (B) PaO$_2$ showed an opposite tendency. *P < 0.05 versus Group A; &P < 0.05 versus Group D; #P < 0.05 versus Group E.
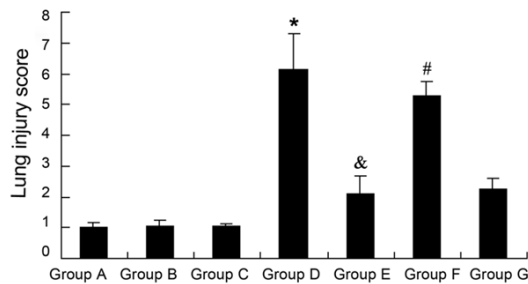

Figure 2. Semiquantitative analysis of lung histopathology by lung-injury score. High tidal volume ventilation group (Group D) had significantly greater total lung injury score (TLIS) compared with the controls (Group A), whereas low tidal volume ventilation group (Group E) had significantly reduced TLIS compared with Group D. In addition, TLIS was significantly greater in LPS-treated group (Group F) compared with Group E, but remained unchanged in Pam3Cys-treated group (Group G). *P < 0.05 versus Group A; &P < 0.05 versus Group D; #P < 0.05 versus Group E.

using an ABI Prism 7900 HT instrument (Applied Biosystems, Carlsbad, CA, USA). Relative quan-

titative measure of genes was evaluated using 2-ΔΔCt (where Ct is the threshold cycle). The target gene expression levels were normalized to the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH) values of the respective sample. The primers for iNOS, TNF-α and GAPDH were synthesized by Shanghai Sangon Company, Shanghai, China.

Cytokine analysis

The levels of TNF-α, IL-6, and IL-8 in BALF were quantified in duplication by the sandwich ELISA kit (RayBiotech Inc., Norcross, GA, USA) according to the manufacturer's instructions strictly.

Nitric oxide (NO) assay

The content of NO in the supernatants of the BALF was assayed using a commercially available NO assay kit (Pierce Biotechnology, Inc., Rockford, IL, USA) according to the manufacturer's instructions strictly.

Statistical analysis

Statistical analysis was carried out with SPSS 17.0 software (SPSS Inc, Chicago, IL, USA). One-or two-way analyses of variance (ANOVA) or students't-test, followed by the Bonferroni post hoc test, or Mann-Whitney nonparametric test was used to comparing the results between groups as appropriate.

Results

Indices of lung injury

Wet to dry weight ratios (WW: DW) and PaO$_2$ were used to estimate degree of lung injury. The WW: DW was significantly increased in high tidal volume ventilation group (Group D) compared with the controls (Group A), whereas significantly decreased in low tidal volume ventilation group (Group E) compared with Group D (**Figure 1**). In addition, LPS treatment (Group F) improved WW: DW in Group E, while Pam3Cys treatment (Group G) had no significant effect. PaO$_2$ was significantly lower in Group D than
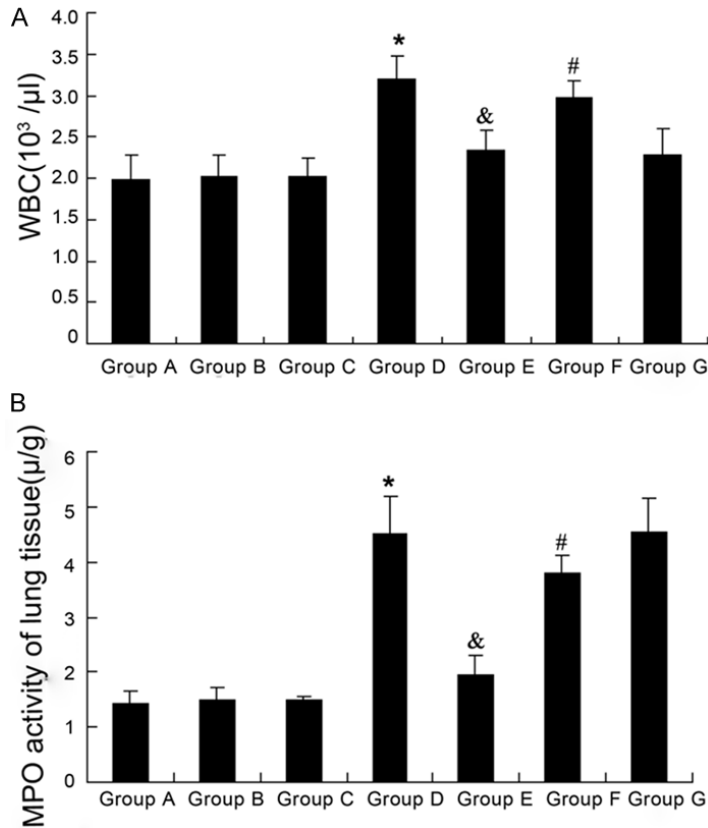
Figure 3. White blood cell (WBC) concentration (A) and myeloperoxidase (MPO) activity (B) in lung homogenate. MPO activity reflects the neutrophil infiltration in the lungs. Both the WBC concentration (A) and the myeloperoxidase (MPO) activity of lung tissues (B) were markedly higher in high tidal volume ventilation group (Group D) compared with the controls (Group A), lower in low tidal volume ventilation group (Group E) compared with Group D. Moreover, both of them were greatly increased after LPS treatment (Group F), but neither was significantly changed after Pam3Cys treatment (Group G). *P < 0.05 versus Group A; &P < 0.05 versus Group D; #P < 0.05 versus Group E.

White blood cell (WBC) concentration and myeloperoxidase (MPO) activity

Both the WBC concentration and the myeloperoxidase (MPO) activity of lung tissues were markedly higher in high tidal volume ventilation group (Group D) compared with the controls (Group A), lower in low tidal volume ventilation group (Group E) compared with Group D (**Figure 3**). Moreover, both of them were greatly increased after LPS treatment (Group F), but neither were significantly changed after Pam3Cys treatment (Group G) (**Figure 3**).

Bronchoalveolar lavage fluid (BALF) cell counts

The bronchoalveolar lavage fluid (BALF) total cell count, neutrophils count and lymphocytes count were all greatly higher in high tidal volume ventilation group (Group D) than the controls (Group A), and significantly lower in low tidal volume ventilation group (Group E) than Group D. All were greatly improved after LPS treatment (Group F), but neither were significantly changed after Pam3Cys administration (Group G) (**Figure 4**).

Group A, and significantly higher in Group E than Group D. Similarly, LPS treatment (Group F) reversed the results of Group E, while Pam-3Cys treatment (Group G) had no significant effect (**Figure 1**).

Lung histopathology

High tidal volume ventilation group (Group D) had significantly greater total lung injury score (TLIS) compared with the controls (Group A), whereas low tidal volume ventilation group (Group E) had significantly reduced TLIS compared with Group D. Moreover, lung injury was significantly more severe in LPS-treated group (Group F) compared with Group E and remained unchanged in Pam3Cys-treated group (Group G) (**Figure 2**).

iNOS, TNF-α, MDA and SOD levels in lung tissues

As illustrated in **Figure 5**, the mRNA expression of iNOS and TNF-α was found to be significantly increased in high tidal volume ventilation group (Group D) compared with the controls (Group A). And low tidal volume ventilation group (Group E) showed a remarkably lower mRNA expression of iNOS and TNF-α when compared with Group D. The decrease in Group E was significantly attenuated after LPS treatment (Group F), while there were no significant differences of both levels between Group E and the Pam3Cys treatment group (Group G). Similar profiles in MDA levels were observed, while SOD levels showed an opposite tendency.
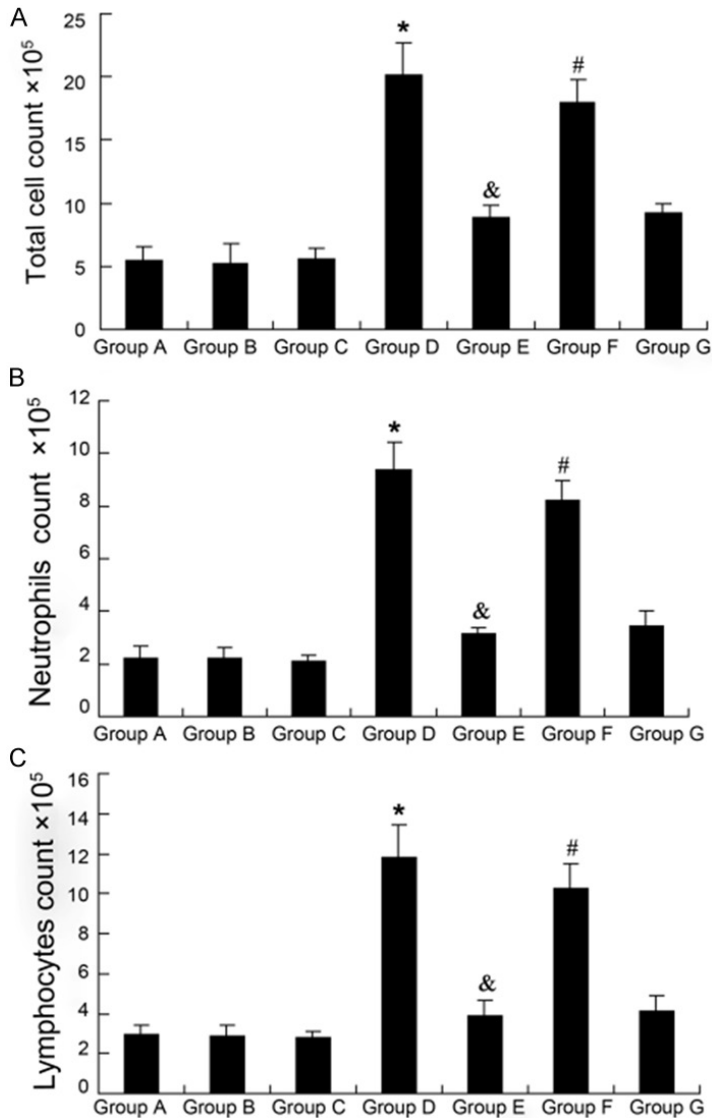
Figure 4. Numbers of total cells (A), neutrophils (B) and lymphocytes (C) in BALF. The BALF total cell count (A), neutrophils count (B) and lymphocytes count (C) were all greatly higher in high tidal volume ventilation group (Group D) than the controls (Group A), significantly lower in low tidal volume ventilation group (Group E) than Group D. All were greatly improved after LPS treatment (Group F), but neither were significantly changed after Pam3Cys administration (Group G). *P < 0.05 versus Group A; &P < 0.05 versus Group D; #P < 0.05 versus Group E.

BALF TNF-α, IL-6, IL-8 and NO concentrations

As shown in **Figure 6**, BALF concentrations of TNF-α, IL-6, IL-8 and NO were all significantly elevated in high tidal volume ventilation group (Group D) compared with the controls (Group A) and all markedly reduced in low tidal volume ventilation group (Group E) compared with Group D. Administration of LPS (Group F) suppressed the decrease of these cytokines and

NO levels in Group E, while treatment with Pam3Cys (Group G) did not work.

Discussion

Increasing evidence supports the protective effects of low tidal volume ventilation with associated hypercapnia on lung injury [19]. However, the exact role of this ventilatory strategy in protecting the lung remains to be determined. The results of the present study using a CO_2 pneumoperitoneum model in rats demonstrated that low volume pressure limited ventilation with permissive hypercapnia had a lung protective effect through reducing TLR 4-induced inflammation and oxidative stress.

It's reported that more than 3 hours of pneumoperitoneum induced lung injury in rabbits, which may be the result of large concentration of polymorphonuclear neutrophil (PMN) in the lungs [20]. 2 hours of ventilation using tidal volume of 20 ml/kg, respiratory rate of 85/min could cause permeability type pulmonary oedema in rats, which is one of the classical models of ventilator-induced lung injury (VILI) [21, 22]. In this study, we evaluated the severity of lung injury by several different markers, including gravimetric analysis (WW: DW), PaO_2 and histology. The significant changes of all these markers in group D and group E (**Figures 1, 2**) suggested that 4 hours of pneumoperitoneum did induce significant lung injury in rats and low tidal volume ventilation with associated hypercapnia reduced its severity. Low tidal volume ventilation with associated hypercapnia has been reported to reduce ventilator-induced lung injury and improve outcome in adult respiratory distress syndrome (ARDS) [23, 24]. Our results suggested that there was a need to see whether low tidal volume ventilation with associated hypercapnia could avoid pneumoperitoneum-induced lung injury in laparoscopic patients.
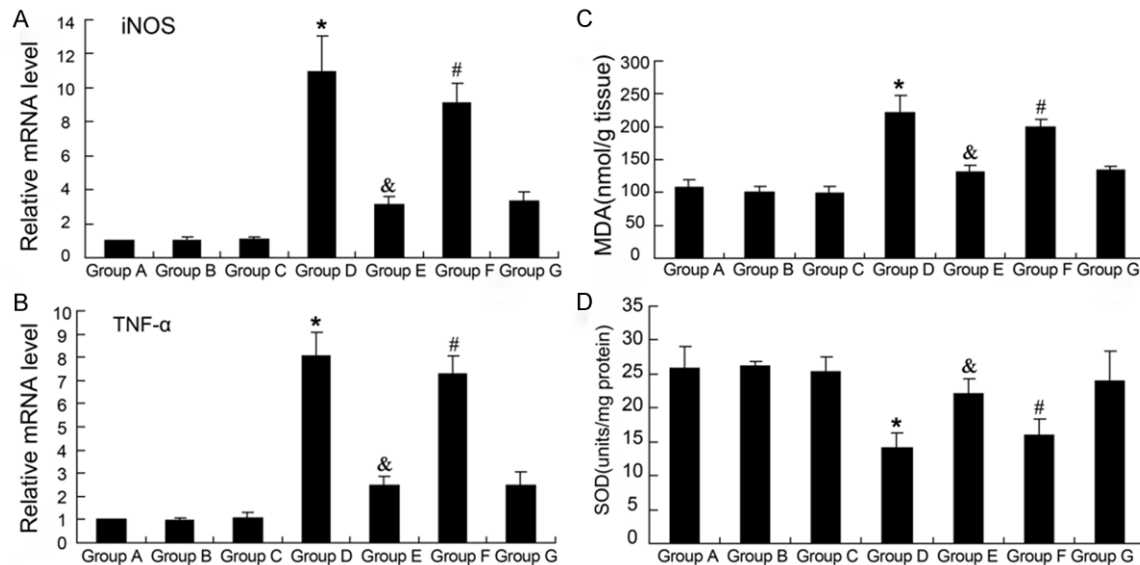
Figure 5. The mRNA expression of iNOS (A) and TNF-α (B), MDA levels (C) and SOD (D) activity in lung tissues. The iNOS mRNA level (A) and TNF-α mRNA level (B) were both significantly increased in high tidal volume ventilation group (Group D) compared with the controls (Group A), significantly decreased in low tidal volume ventilation group (Group E) when compared with group D. The decrease in Group E was significantly attenuated after LPS treatment (Group F), while there were no significant differences of both levels between group E and Pam3Cys treatment group (group G). (C) MDA levels showed similar profiles. (D) SOD levels showed an opposite tendency. *P < 0.05 versus Group A; &P < 0.05 versus Group D; #P < 0.05 versus Group E.

The ventilator-induced lung injury has been proved to result in the release of inflammatory mediators and cytokines. De Smet et al [25] reported that hypercapnic acidosis significantly reduced the levels of TNF-α and IL-6 in the lavage and perfusate in unstimulated and lipopolysaccharide (LPS)-stimulated isolated perfused rat lungs, indicating that hypercapnia had a protective effect by modulating inflammation response. We found an increase in WBC concentration, MPO activity, total cell count and differentiated cell count in BALF, TNF-α levels in lung tissues and TNF-α, IL-6, IL-8 concentrations in BALF after 4 hours of pneumoperitoneum with normal tidal volume, while using low tidal volume ventilation with associated hypercapnia in group E blocked the increase of all the above inflammatory markers (**Figures 3**-6), indicating that the protective effect of low tidal volume ventilation with associated hypercapnia may be associated with the anti-inflammatory response. Similar findings were made in clinical samples. Oliveira et al [26] showed that both TNF-α and IL-8 concentrations were increased with high VT but stable with low VT in the BALF of patients without lung disease, suggesting that use of lower VT may attenuate pulmonary inflammation response.

In addition, oxidative stress was also reported to contribute to the lung injury induced by mechanical ventilation [27]. In this study, reduction of iNOS, MDA and SOD levels in lung tissues and NO concentrations in BALF was observed in the presence of low tidal volume ventilation with associated hypercapnia, showing that oxidative stress played an important role in the mechanism of this lung protective mechanical ventilation strategy.

Our previous study with this CO_2 pneumoperitoneum model showed that both the TLR4 and TLR2 mRNA levels in lung tissues were significantly higher in group D compared with group A. But the mRNA expression of TLR4 in group E was markedly decreased compared with group D, while there was no difference of the TLR2 mRNA expression between group D and group E (Data not shown). Moreover, treatment with LPS, an agonist of TLR4, significantly weakened the protective action of low tidal volume ventilation with associated hypercapnia, while administration of Pam3Cys, an agonist of TLR2 had no significant effect. Meanwhile, neither 2 mg/kg LPS treatment nor 2 mg/kg Pam3Cys treatment resulted in significant change of PaO_2 levels and arterial blood gas (Data not shown).
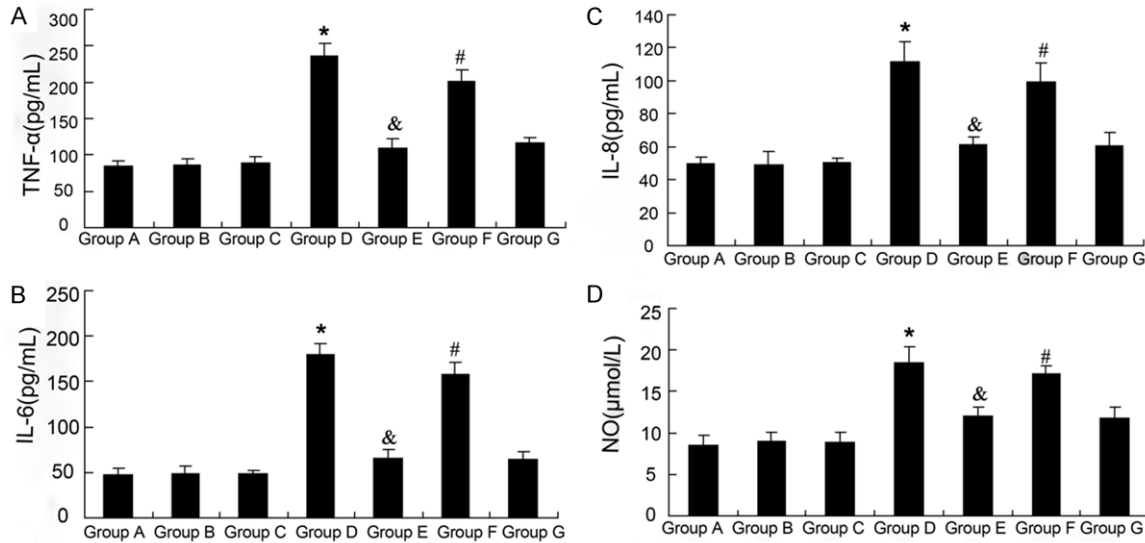
Figure 6. TNF-α (A), IL-6 (B), IL-8 (C) and NO (D) concentrations in BALF. BALF concentrations of TNF-α (A), IL-6 (B), IL-8 (C) and NO (D) were all significantly elevated in high tidal volume ventilation group (Group D) compared with the controls (Group A) and all markedly reduced in low tidal volume ventilation group (Group E) compared with Group D. Administration of LPS (Group F) suppressed the decrease of these cytokines and NO levels in Group E, while treatment with Pam3Cys (Group G) did not work. *P < 0.05 versus Group A; &P < 0.05 versus Group D; #P < 0.05 versus Group E.

All these data suggested that the TLR4, not TLR2 signaling was involved in the process of inhibiting inflammatory response and oxidative stress induced by low tidal volume ventilation with associated hypercapnia. These results are consistent with the findings of previous studies [28].

However, there are contradictory research results. Hong et al [29] found that mechanical ventilation with High tidal volume (VT)/low positive endexpiratory pressure (PEEP) resulted in less pulmonary inflammation and less histologic lung injury compared with low VT mechanical ventilation strategie. Feihl et al [30] showed that permissive hypercapnia had a negative effect on pulmonary gas exchange by increasing pulmonary shunt, which could be explained by the combined effects of increased and decreased alveolar ventilation in ARDS patients. Park et al [31] demonstrated there were no significant differences in oxygenation, BALF inflammatory markers, WW/DW and histologic scores between high pressure hypercapnic group and high pressure normocapnic group, implying that hypercapnic acidosis, induced by direct administration of CO_2, would not be protective effect against VILI in normal rabbit model. All these findings suggested that large and long-term clinical outcome data remain

necessary to elucidate the best use of tidal volume and/or therapeutic hypercapnia before the practical clinical application becomes even more widespread.

In summary, the ventilation protocol with low tidal volumes and associated hypercapnia ameliorated pneumoperitoneum-induced lung injury and the reduction of inflammation reaction and oxidative stress via inhibiting TLR 4 signal might contribute to this effect. These findings provided additional insight into the molecular mechanisms behind pneumoperitoneum-induced lung injury and suggested novel therapies targeted at inflammation reaction and oxidative stress for pneumoperitoneum-induced lung injury. It's also helpful in developing the best clinical application of tidal volume and/or therapeutic hypercapnia to improve patients' outcome. However, large and long-term clinical outcome data are still required.

Disclosure of conflict of interest

None.

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