Effects of different ventilation strategies on exhaled nitric oxide in geriatric abdominal surgery

Yinghua Cui, Xin Pi, Changsong Wang, Shujuan Liu, Yulei Gong, Yang Wang, Fan Zhang, Jinghui, Shi, Ziwei Lin, Xin Zhang and Enyou Li

Department of Anesthesiology, the First Affiliated Hospital of Harbin Medical University, Harbin, People’s Republic of China

E-mail: haotian321@163.com

Keywords: mechanical ventilation, nitric oxide, small airway injury, inflammatory cytokines

Abstract

Exhaled nitric oxide (eNO) has been suggested to be a marker of small airway injury. We investigated the effects of different ventilation strategies on eNO. Sixty-nine patients who received elective open abdominal surgery under general anesthesia with more than 2 h of surgery duration were randomly divided into three groups: high tidal volume of 10–12 ml kg\(^{-1}\) predicted body weight (PBW) with zero end-expiratory pressure (ZEEP) (high \(V_T\) + ZEEP group); low tidal volume of 6–8 ml kg\(^{-1}\) PBW with 8 cm H\(_2\)O positive end-expiratory pressure (PEEP) (low \(V_T\) + PEEP group); and low tidal volume of 6–8 ml kg\(^{-1}\) PBW with 8 cm H\(_2\)O PEEP and recruitment maneuvers (low \(V_T\) + PEEP + RMs group). eNO, respiratory system compliance (Crs), oxygenation index, inflammatory mediators tumor necrosis factor-alpha (TNF-\(\alpha\)), interleukin-1\(\beta\) (IL-1\(\beta\)), IL-8, prostaglandin E2 (PGE2) and PGF2\(\alpha\) as well as pulmonary function were measured during the perioperative period. The postoperative eNO decreased in 78.3% of patients in the high \(V_T\) + ZEEP group and low \(V_T\) + PEEP group, and increased in 56.5% of patients in the low \(V_T\) + PEEP + RMs group \((P = 0.016)\). The Crs level in the high \(V_T\) + ZEEP group significantly decreased with time but significantly increased in the low \(V_T\) + PEEP + RMs group \((P < 0.05)\). The oxygenation index, inflammatory mediators and pulmonary function did not statistically differ among the three groups. Compared with the low \(V_T\) + PEEP + RMs group, the decreasing rate of postoperative eNO in the high \(V_T\) + ZEEP and low \(V_T\) + PEEP groups was higher, which may imply small airway injury during geriatric abdominal surgery.

1. Introduction

Mechanical ventilation can cause acute lung injury resulting in mechanical injury with subsequent immune cascade reactions (i.e. biological injury) [1]. The resultant systemic inflammatory responses and oxidative stress increase the risk of complications and multiple organ failure in patients; furthermore, these factors affect prognosis and mortality in elderly patients who receive major abdominal surgery and have existing lung diseases [2].

Nearly 230 million people worldwide require surgery under general anesthesia and mechanical ventilation every year; thus, there is an urgent need for effective intervention measures to minimize injury [3]. The appropriate use of ventilators and ventilation modes can prevent ventilator-induced lung injury [4]. Currently, many advocate using a protective ventilation strategy with low tidal volume (\(V_T\)), positive end-expiratory pressure (PEEP) and recruitment maneuvers (RMs), which can reduce the clinical signs of pulmonary infection [5] and yield fewer postoperative complications in major abdominal surgery [6]. Retrospective and prospective studies have shown that lower tidal volumes may avoid overdistending non-injured lungs. PEEP may alleviate atelectasis and prevent repetitive collapse/reopening of the small airways. Notably, RMs to open the lungs have also been found to improve the effectiveness of PEEP with regard to gas exchange during general anesthesia [7, 8]. However, these conclusions are still controversial [9, 10]. To date, there is no clear evidence of the additional benefit of these ventilation strategies in routine anesthesia.

Elevated levels of exhaled nitric oxide (eNO) are detectable in the exhaled breath of patients suffering from a number of inflammatory lung diseases, including asthma and bronchiectasis [11, 12]. eNO has been proposed as a useful biomarker in patients with...
asthma and a potential indicator of airway inflammation [13]. Moreover, an experimental study suggested that eNO can also be taken as a sign of peripheral airway injury [14]. Because most of the eNO from the lungs is produced by the small airway epithelium, a reduction in eNO levels may be a useful marker of the extent of the mechanical injury of the peripheral airways due to their cyclic opening and closing during tidal ventilation [15, 16]. We aimed to clarify the impact of tidal volume, PEEP and RMs on small airways by measuring eNO.

2. Methods

The present experiments were conducted in accordance with the Declaration of Helsinki. The protocol in this study was approved by the Ethics Committee of Harbin Medical University (no. 201314), and written informed consent was obtained from the patients prior to study enrollment.

Patients older than 60 years of age who were due to undergo major open abdominal surgery under general anesthesia at the First Affiliated Hospital of Harbin Medical University between October 20, 2012 and April 20, 2013 were selected. Patient baseline characteristics (i.e. age, height, body weight, cardiac function test, neck circumference, smoking history, drinking history, chronic obstructive pulmonary disease history, preoperative basal levels of eNO, and type of surgery and anesthesia), which were the factors affecting the eNO levels, were recorded (Table 1).

We used the following inclusion criteria: 1. All adult patients older than 60 years; 2. Patients scheduled for planned non-laparoscopic major abdominal surgery; 3. An expected surgery duration of ≥2 h; 4. A preoperative risk index for postoperative pulmonary complications of 2–3 [17]; and 5. Compliance with the online measurement method of the NO analyzer. We used the following exclusion criteria: 1. Past history of asthma; 2. Recent upper respiratory tract infection (within

| Table 1. Baseline Characteristics of the Patients. |
|-----------------------------------------------|
|                                  | High $V_t$  | Low $V_t$  | Low $V_t$  |
|                                  | + ZEEP     | + PEEP    | + PEEP + RMs |
|                                  | ($N = 23$) | ($N = 23$) | ($N = 23$) |
| Age, yr (mean ± SD)             | 65.1 ± 7.1 | 62.1 ± 8.7 | 67.0 ± 9.3 | 0.15 |
| Male sex, n(%)                 | 18(78.3)   | 18(78.3)  | 15(65.2)   | 0.45 |
| Height, cm (mean ± SD)         | 166.2 ± 8.8| 168.2 ± 7.6| 164.1 ± 7.2| 0.23 |
| Body Weigh, kg Actual          | 64.0 ± 11.0| 60.3 ± 10.5| 61.0 ± 9.6 | 0.45 |
| Predicted                      | 61.6 ± 9.3 | 63.6 ± 8.4 | 58.1 ± 8.3 | 0.11 |
| BMI, kg m$^{-2}$ (mean ± SD)    | 23.2 ± 3.7 | 21.6 ± 3.2 | 22.6 ± 3.2 | 0.26 |
| Neck circumference, cm (mean ± SD) | 38.8 ± 4.3 | 38.5 ± 4.4 | 38.2 ± 3.8 | 0.9 |
| Preoperative risk index for POPcs, n(%)   | 13(56.5)   | 12(52.2)  | 10(43.5)   | 0.67 |
| Risk class 2                    | 10(43.5)   | 11(47.8)  | 13(56.5)   | 0.38 |
| Preoperative exhaled nitric oxide levels, ppb(mean ± SD) | 18.2 ± 9.3 | 14.5 ± 6.1 | 16.4 ± 10.3 | 0.38 |
| Coexisting condition, n(%)      |            |            |            | 0.61 |
| Smoking history                 | 11(47.8)   | 10(43.5)  | 12(52.2)   | 0.84 |
| Drinking history                | 14(60.9)   | 11(47.8)  | 12(52.2)   | 0.67 |
| Chronic obstructive pulmonary disease | 6(26.1)   | 4(17.4)   | 5(21.7)    | 0.78 |
| Loss of >10% of weight in previous 6 months | 5(21.7)   | 5(21.7)   | 5(21.7)    | 1    |
| Type of surgery, n(%)           |            |            |            | 0.61 |
| Gastrectomy                     | 9(39.1)    | 10(43.5)  | 8(34.8)    | 0.83 |
| Colorectal resection            | 12(52.2)   | 10(43.5)  | 10(43.5)   | 0.98 |
| Pancreatoduodenectomy            | 2(8.7)     | 1(4.4)    | 4(17.4)    | 0.95 |
| Other procedure                 | 0(0)       | 2(8.7)    | 1(4.4)     | 0.59 |
| Cardiac echocardiogram test (mean ± SD) | 60.9 ± 2.7 | 61.5 ± 3.5 | 60.8 ± 3.2 | 0.83 |
| LVEF (%)                        | 48.0 ± 27.4| 48.2 ± 24.7| 50.1 ± 29.1| 0.98 |
| A peak (cm s$^{-1}$)             | 63.1 ± 36.7| 67.5 ± 33.3| 65.2 ± 37.2| 0.95 |
| E/A                             | 0.78 ± 0.21| 0.72 ± 0.15| 0.71 ± 0.16| 0.59 |

* The preoperative risk index for pulmonary complications (POPCs) [17] used risk classes that ranges from 1 to 5, the higher risk classes indicated a higher risk of postoperative complications. Patients with a risk class of 2 or 3 were eligible for participation in the study.
3 Specific reaction history (symptoms of allergic rhinitis, urticaria, recurrent rhinitis or skin allergies diagnosed by internal medicine); 4. Consumption of nitrogen-rich foods (such as lettuce, radish, spinach, sausage and offal), strenuous exercise within 2 h prior to the examination or active or passive smoking or drinking within 4 h; 5. Use of bronchodilators and corticosteroids or the intraoperative application of epinephrine and ester nitrates; 6. History of surgery, endotracheal intubation and mechanical ventilation, respiratory failure or systemic inflammatory response within 2 weeks; 7. Body mass index (BMI) \( \geq 35 \). Ultimately, 69 patients were included for analysis (figure 1).

### 2.1. Standard procedures

Patients were randomly divided into three groups, comprising a high \( V_T \) + zero end-expiratory pressure (ZEEP) group with a \( V_T = 10\text{–}12 \text{ ml kg}^{-1} \text{ PBW} \) predicted body weight (PBW), PEEP \( = 0 \text{ cm H}_2\text{O} \); a low \( V_T \) + PEEP group with \( V_T = 6\text{–}8 \text{ ml kg}^{-1} \text{ PBW}, \text{PEEP} = 8 \text{ cm H}_2\text{O} \); and a low \( V_T \) + PEEP + RMs group with \( V_T = 6\text{–}8 \text{ ml kg}^{-1} \text{ PBW}, \text{PEEP} = 8 \text{ cm H}_2\text{O} \) and RMs.

Patients were assigned to receive volume-controlled mechanical ventilation (Drager Fabius GS premium; Drager Medical AG, Lubeck, Germany) at an inspired oxygen fraction (FiO\(_2\)) of 0.50, an inspiratory to expiratory ratio of 1:2 and a respiratory rate adjusted to normocapnia (PETCO\(_2\) 30 and 40 mmHg). RMs were implemented just after intubation and repeated every 30 min according to the previous experimental methods [5]. For episodes of arterial desaturation (defined as SPO\(_2\) \( \leq 92\% \)), a transient increase in FiO\(_2\) to 100% was permitted.

A NO analyzer (NIOX; Aerocrine, Solna, Sweden) applied a continuous flow of breath. The measurement procedure met the standards of the American Thoracic Society and the European Respiratory Society. The patient first exhaled as much air as possible in
from the lungs, then inhaled NO-free air through his/ her mouth to the total capacity of the lung and finally closed the velopharyngeal aperture to exclude NO from the nose. Next, the patient exhaled slowly at a constant rate of 50 ml s⁻¹ through a filter for approximately 10 s to record a constant steady-state concentration of eNO for at least 3 s. eNO was recorded on-line using the NO analyzer when the patient entered the operation room, and 10 min after postoperative removal of the endotracheal tube. Blood samples for inflammatory mediators and blood gas analysis were collected immediately before surgery to maintain analgesia.

Respiratory system compliance (Crs) was recorded at the beginning of the mechanical ventilation and before extubation. The oxygenation index (partial pressure of O₂ in arterial blood/fraction of inspired oxygen, \( \text{PaO}_2/\text{FiO}_2 \)) was calculated based on the blood gas. The levels of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), IL-8, prostaglandin E2 (PGE2) and PGF2α in plasma samples were measured using a quantitative enzyme-linked immunosorbent assay kit (USCN Life Science Inc, Houston, TX, USA). Plasma samples were appropriately diluted to be within the detection range of each assay. The forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were measured twice at the bedside using a portable spirometer (Master-Screen GE; CareFusion, San Diego, CA) on the first days of preoperative and postoperative follow-up, respectively.

2.2. Anesthesia management

Epidural catheterization: Before the use of general anesthesia, patients underwent epidural anesthesia at the T8–T12 level when not contraindicated. Intraoperative maintenance included an additional 3–5 ml of local epidural anesthetics every hour (1% lidocaine + 0.5% ropivacaine). Approximately 30 min before the end of surgery, an epidural injection of 0.04 mg kg⁻¹ morphine and 1 mg droperidol was administered. Epidural catheters were retained after surgery to maintain analgesia.

General anesthesia: General anesthesia was induced using 0.02 mg kg⁻¹ midazolam, 0.3 μg kg⁻¹ sufentanil, 1–2 mg kg⁻¹ propofol and 0.2 mg kg⁻¹ cis-atracurium for endotracheal intubation. Anesthesia was maintained by inhalation of sevoflurane (end tidal concentration ≥0.7 MAC) and intermittent application of 0.05 mg kg⁻¹ cis-aatracurium every 40 min during the surgery until 1 h prior to the end of surgery. The intraoperative bispectral index was maintained at 40–60. Before endotracheal intubation, patients inhaled oxygen at FiO₂ = 1.0, and the partial pressure of carbon dioxide in the end-expiratory gas was monitored. A side stream spirometer (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) and a D-lite transmitter were connected to monitor the peak airway pressure (Ppeak), plateau inspiratory pressures (Pplat), compliance (Compl) and tidal volume (V₁) (Table 2).

### Table 2. Intraoperative Procedures.

|                                     | High V₁ + ZEEP (N = 23) | Low V₁ + PEEP (N = 23) | Low V₁ + PEEP + RM (N = 23) | P Value |
|-------------------------------------|-------------------------|------------------------|----------------------------|---------|
| Tidal volume, ml (mean ± SD)        | 544.7 ± 82.0*           | 414.7 ± 76             | 381.5 ± 66.4               | <0.0001 |
| Tidal volume, ml kg⁻¹ of PBW, median [IQR] | 11.2[9.6–11.9]¹         | 6.2[5.3–6.9]           | 6.5[6.1–6.9]               | <0.0001 |
| Respiratory rate, Breaths/min (mean ± SD) | 12 ± 2.3*               | 13.6 ± 1.5             | 14.1 ± 2.1                 | <0.0001 |
| PEEP, cm H₂O (mean ± SD)            | 1.7 ± 0.5*              | 7.8 ± 0.9              | 7.9 ± 0.4                  | <0.0001 |
| Peak pressure, cm H₂O (mean ± SD)   | 15.1 ± 2.0*             | 16.9 ± 2.0             | 16.9 ± 1.9                 | <0.01   |
| Plateau pressure, cm H₂O (mean ± SD)| 13.4 ± 2.0*             | 15.5 ± 2.0             | 15.5 ± 1.4                 | <0.0001 |
| SpO₂, % (mean ± SD)                 | 98.7 ± 0.8              | 99.0 ± 0.8             | 98.7 ± 1.4                 | 0.61    |
| ETCO₂, mm Hg (mean ± SD)            | 30.5 ± 2.2*             | 34.0 ± 3.1             | 32.7 ± 1.9                 | <0.0001 |
| HR, beats/min (mean ± SD)           | 72.1 ± 7.2              | 72.9 ± 6.5             | 75.2 ± 8.6                 | 0.39    |
| MAP, mm Hg (mean ± SD)              | 86.0 ± 8.1              | 83.9 ± 7.7             | 85.8 ± 8.0                 | 0.7     |
| Volume of fluids administered, liters (mean ± SD) |                       |                        |                            |         |
| Intraoperative fluid administration  | 2.1 ± 0.6               | 2.2 ± 0.4              | 2.4 ± 0.7                  | 0.68    |
| Intraoperative blood loss, ml, median [IQR] | 100[50–150]            | 100[50–100]            | 100[50–300]                | 0.41    |
| Intraoperative urine output, liters (mean ± SD) | 0.7 ± 0.3               | 0.6 ± 0.3              | 0.5 ± 0.4                  | 0.62    |
| Patients receiving blood packed cells, n (%) | 1(4.4)                | 2(8.7)                 | 0(0)                       | 0.77    |
| Duration of mechanical ventilation, h (mean ± SD) | 3.6 ± 1.5              | 3.9 ± 1.5              | 3.5 ± 1.3                  | 0.27    |
| Duration of surgery, h (mean ± SD)   | 3.2 ± 1.5               | 3.6 ± 1.3              | 3.2 ± 1.2                  | 0.64    |

* There were significant difference between High V₁ + ZEEP group and Low V₁ + PEEP, and High V₁ + ZEEP and Low V₁ + PEEP + RM, respectively (P < 0.05).

|                                     | (N = 23) |
|-------------------------------------|---------|
| Tidal volume, ml (mean ± SD)        | 544.7 ± 82.0* |
| Tidal volume, ml kg⁻¹ of PBW, median [IQR] | 11.2[9.6–11.9]¹ |
| Respiratory rate, Breaths/min (mean ± SD) | 12 ± 2.3* |
| PEEP, cm H₂O (mean ± SD)            | 1.7 ± 0.5* |
| Peak pressure, cm H₂O (mean ± SD)   | 15.1 ± 2.0* |
| Plateau pressure, cm H₂O (mean ± SD)| 13.4 ± 2.0* |
| SpO₂, % (mean ± SD)                 | 98.7 ± 0.8 |
| ETCO₂, mm Hg (mean ± SD)            | 30.5 ± 2.2* |
| HR, beats/min (mean ± SD)           | 72.1 ± 7.2 |
| MAP, mm Hg (mean ± SD)              | 86.0 ± 8.1 |

2.3. Statistical analysis

The normality of the data distribution was tested with the Kolmogorov–Smirnov test. The homogeneity of variance was tested by Levene's test. The data are expressed as the mean ± SD or median and interquartile range (25–75%), as appropriate. Comparisons of the normally distributed variables were performed with a one-way ANOVA or paired t-test, as appropriate.
increased from 54.0 ± 14.0 to 62.1 ± 14.4 ml cm⁻¹ H₂O.

V accounted for 78.3% of all patients. By contrast, the low level in the low Vₚ + PEEP + RMs group was significantly less than in the other two groups.

Postoperative eNO levels showed a decreasing trend in the high Vₚ + ZEEP and low Vₚ + PEEP groups, which accounted for 78.3% of all patients. By contrast, the low Vₚ + PEEP + RMs group showed an increasing trend of 56.5%. These group differences were statistically significant (P = 0.016; table 3). SNK revealed that the percentage decrease in the low Vₚ + PEEP + RMs group was significantly less than in the other two groups (P < 0.05).

The Crs level in the high Vₚ + ZEEP group significantly decreased from 56.9 ± 18.6 to 53.0 ± 16.3 ml cm⁻¹ H₂O (P < 0.05), by contrast, the level in the low Vₚ + PEEP + RMs group significantly increased from 54.0 ± 14.0 to 62.1 ± 14.4 ml cm⁻¹ H₂O (P < 0.05). The change in the low Vₚ + PEEP group did not reach statistical significance (figure 2). There was no correlation between the changes in Crs and eNO (ΔCrs–ΔeNO) (r = 0.261; P = 0.160).

The oxygenation index exhibited no statistically significant differences between groups (P > 0.05). The plasma levels of inflammatory mediators (TNFα, IL-1β, IL-8, PGE2 and PGF2α) at the early stage of inflammation did not statistically differ between the groups (P > 0.05; table 4). The postoperative FEV1 and FVC both significantly decreased; however, there was no difference among the groups (table 5).

### 4. Discussion

In our study, a post-hoc test (SNK) of the preoperative and postoperative changes in eNO revealed that the rates of decrease in the high Vₚ + ZEEP and low Vₚ + PEEP groups were higher than in the low Vₚ + PEEP + RMs group. Previously, several studies were conducted to assess the influence of ventilation on eNO production, as follows: Gerd Schmalisch et al. [18] reported that intubation and mechanical ventilation may reduce eNO in low-weight infants. Tornberg Daniel et al. [19] studied the NO concentration during tidal breathing with mechanical ventilation compared with flow-independent parameters and analyzed this at different PEEP levels during laparoscopic gynecologic surgery. The experiment of D’Angelo et al. confirmed that the eNO concentration decreases during open-chest procedures in rabbits with prolonged mechanical ventilation at a low lung volume and ZEEP [14]. Persson Magnus et al. [20] concluded that PEEP ventilation elicits increases in endogenously formed NO as detected in air exhaled by rabbits. Furthermore, the amplitude pressure, mean airway pressure and inspiratory time ratio were positively correlated with the level of eNO, and the frequency was negatively correlated with the level of eNO in the experiments of Yuh and Hua [21]. Artlich Andreas et al. also concluded from experimentation that high-frequency oscillatory ventilation increases pulmonary NO production in healthy rabbits [22]. To our knowledge, the present investigation is the first to probe the effects of three different common ventilation strategies on eNO during spontaneous ventilation in elderly patients before and after abdominal surgery. Our results indicated that low Vₚ and PEEP combined with RMs can reduce the occurrence of postoperative eNO decline. There may be similar mechanisms involved in our experiment and those of the abovementioned studies.

eNO is mainly generated by the small airways, and previous studies have suggested that eNO can be used as a small airway indicator [14]. Traditionally, many theories have postulated that eNO is produced by the induction of nitric oxide synthase by inflammatory mediators during the inflammatory response; thus, eNO levels increase after an injury [23]. However, we found that the eNO levels of patients mainly decreased after surgery in the high Vₚ + ZEEP and low Vₚ + PEEP groups in our study, indicating that other biological processes may occur during short-term mechanical ventilation [1, 24]. A possible explanation for the decrease in eNO is the repeated opening and closing of peripheral small airways induced by mechanical

---

**Table 3.** The postoperative change of expiratory nitric oxide.

|                  | High Vₚ + ZEEP (N = 23) | Low Vₚ + PEEP (N = 23) | Low Vₚ + PEEP + RMs (N = 23) | P       |
|------------------|-------------------------|-----------------------|-----------------------------|---------|
| Increase n(%)    | 18(78.3)^a              | 18(78.3)^a            | 10(43.5)                    | 0.016   |
| Decrease n(%)    | 5(21.7)                 | 5(21.7)               | 13(56.5)                    |         |

^a P < 0.05 versus Low Vₚ + PEEP + RMs group
ventilation, which can cause abnormal shear stress [15, 16], depletion and inactivation of surfactant and changes in the epithelial cell morphology and mechanics; thus, injury and detachment of epithelial cells may decrease the number of eNO-producing cells [25]. The degree of eNO decrease is associated with the number of injured airway epithelial cells below the bronchioles [14]. Indeed, compared with low \( V_T + PEEP + RMs \), the rate of postoperative eNO decrease with high \( V_T + ZEEP \) or low \( V_T + PEEP \) was higher, which may imply more serious small airway injury in these two groups.

Delgado et al [26] proposed that PGE2 and PGF2\(\alpha\) have a significantly potent inhibitory effect on eNO production. Detachment of injured airway epithelial cells with exposure of nerve endings, fibroblasts and collagen cells may release bradykinin and upregulate PGE2 and PGF2\(\alpha\) levels [27, 28]. In addition, the activation of alveolar epithelial cells and granulocytes also produces PGE2 and PGF2\(\alpha\). All of these upstream markers can decrease eNO production. Nevertheless, D’Angelo et al [14] has repeatedly confirmed that eNO is not associated with cytokines in the bronchoalveolar lavage fluid, but is associated with the bronchiolar injured score. In our study, the inflammatory mediators TNF-\(\alpha\), IL-1\(\beta\), IL-8, PGE2 and PGF2\(\alpha\) were also measured. The plasma levels of inflammatory mediators at the early stage did not statistically differ among groups, which supported the hypothesis of D’Angelo et al with respect to plasma. Thus, the eNO decrease occurs in the absence of an inflammatory reaction and is most likely attributable to small airway epithelial damage.

Our study is consistent with reports suggesting that mechanical ventilation can cause a 50–75% loss of postoperative pulmonary function in patients undergoing abdominal surgery. Through clinical and animal studies, scholars have shown that a ventilation mode with low \( V_T + PEEP + RMs \) can improve postoperative pulmonary function compared with high \( V_T + ZEEP \) [5]. However, these conclusions are still controversial. Another study demonstrated that the effects of high \( V_T + ZEEP \) and low \( V_T + PEEP \) (without RMs) on postoperative pulmonary function did not statistically differ [9], which is consistent with the results of our study. We found that Crs significantly decreased in the high \( V_T + ZEEP \) group and significantly increased in the low \( V_T + PEEP + RMs \) group. The change in the low \( V_T + PEEP \) group was not significant. These results indicate that \( V_T + PEEP + RMs \) influence Crs and that we should not ignore the effect of RMs.

In conclusion, compared with low \( V_T + PEEP + RMs \), the decreasing rate of postoperative eNO at high \( V_T + ZEEP \) or low \( V_T + PEEP \) is greater, which may imply small airway injury in elderly patients undergoing abdominal surgery.
Conflict of interest statements
The authors of this manuscript declare there are no conflicts of interest.

Funding
This work is partly supported by the Foundation of the Heilongjiang Educational Committee (no. 12541284) and the Health and Family Planning Commission Project of Heilongjiang Province (no. 2014–281).

Acknowledgments
We thank all the volunteers in the study. We also convey our sincere gratitude to the Foundation of the Heilongjiang Educational Committee (no. 12541284) and the Health and Family Planning Commission Project of Heilongjiang Province (no. 2014–281) for their financial support.

References
[1] Dos Santos C C and Slutsky A S 2000 Invited review: mechanisms of ventilator-induced lung injury: a perspective J. Appl. Physiol. (1985) 89 1645–55
[2] Shander A, Fleisher L A, Barie P S, Biglione L M, Sladen R N and Watson C B 2011 Clinical and economic burden of postoperative pulmonary complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies Crit. Care Med. 39 2163–72
[3] Weiser T R, Regenbogen S E, Thompson K D, Haynes A B, Lipsitz S R, Berry W R and Gawande A A 2008 An estimation of the global volume of surgery: a modelling strategy based on available data Lancet 372 139–44
[4] Tusman G, Bohm S H, Warner D O and Sprung J 2012 Atelectasis and perioperative pulmonary complications in high-risk patients Curr. Opin. Anaesthesiol. 25 1–10
[5] Severgnini P et al 2013 Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function Anesthesiology 118 1307–21
[6] Futie E et al 2013 Improve study group: a trial of intraoperative low-tidal-volume ventilation in abdominal surgery New Engl. J. Med. 369 428–37
[7] Girgis K, Hamed H, Khater Y and Kacmarek R M 2006 A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment Respir. Care 51 1132–9
[8] Maisch S, Keissmann H, Fuellekrug R, Weismann D, Rutkowski T, Tusman G and Bohm S H 2008 Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients Anesth. Analg. 106 175–81
[9] Treschon T et al 2012 Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function Br. J. Anaesth. 109 1993–140
[10] Hong C M et al 2010 Low tidal volume and high positive end-expiratory pressure mechanical ventilation results in increased inflammation and ventilator-associated lung injury in normal lungs Anesth. Analg. 110 1652–60
[11] Persson M G, Zetterström O, Agrenius V, lhre E and Gustafsson I E 1994 Single-breath nitric oxide measurements in asthmatic patients and smokers Lancet 343 146–7
[12] Khaitinov S A, Wells A U, O’Connor B J, Cole P J, Hansell D M, Logan-Sinclair R B and Barnes P J 1999 Logan-sinclair RR, Barnes P J; elevated levels of exhaled nitric oxide in bronchiectasis Am. J. Respir. Crit. Care Med. 151 1889–93
[13] Payne D N, Adcock I M, Wilson N M, Oates T, Scallan M and Bush A 2001 Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone Am. J. Respir. Crit. Care Med. 164 1376–81
[14] D’Angelo E, Koulouris N G, Della Valle P, Gentile G and Pecchiari M 2008 The fall in exhaled nitric oxide with ventilation at low lung volumes in rabbits: an index of small airway injury Respir. Physiol. Neurobiol. 160 215–23
[15] D’Angelo E, Pecchiari M, Baraggia P, Saetta M, Balestro E and Milic-Emili J 2002 Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits J. Appl. Physiol. 92 949–56
[16] D’Angelo E, Pecchiari M, Della Valle P, Koutsoukou A and Milic-Emili J 2005 Effects of mechanical ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits J. Appl. Physiol. (1985) 99 433–44
[17] Arozullah A M, Khuri S E, Henderson W G and Daley J 2001 Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery Ann. Intern. Med. 135 847–57
[18] Schmalsch G, Wilzicki S, Fischer H S and Bührer C 2014 Effect of intubation and mechanical ventilation on exhaled nitric oxide in preterm infants with and without bronchopulmonary dysplasia measured at a median postmenstrual age of 49 weeks BMC Res. Notes 7 389
[19] Tornberg D C, Bjorne H, Lundberg J O and Weitzberg E 2003 Multiple single-breath measurements of nitric oxide in the intubated patient Am. J. Respir. Crit. Care Med. 168 1210–5
[20] Persson M G, Lonnqvist P A and Gustafsson L E 1995 Positive end-expiratory pressure ventilation elicits increases in endogenously formed nitric oxide as detected in air exhaled by rabbits Anesthesiology 82 969–74
[21] Yuh Y S and Hua Y M 2009 Influence of ventilatory settings on exhaled nitric oxide during high frequency oscillatory ventilation Pediatr. Pulmonol. 44 800–5
[22] Artlich A, Adding C, Aragvald P, Persson M G, Lonnqvist P A and Gustafsson L E 1999 Exhaled nitric oxide increases during high frequency oscillatory ventilation in rabbits Exp. Physiol. 84 959–69
[23] Barnes P J and Belvisi M G 1993 Nitric oxide and lung disease Thorax 48 1034–143
[24] Ricard J D, Dreyfuss D and Saumon G 2001 Production of inflammatory cytokines in ventilator-induced lung injury: a reappraisal Am. J. Respir. Crit. Care Med. 163 1176–80
[25] D’Angelo E, Pecchiari M and Gentile G 2007 Dependence of lung injury on surface tension during low-volume ventilation in normal open chest rabbits J. Appl. Physiol. 102 174–82
[26] Delgado M, Munoz-Elia E J, Gomariz R P and Ganea D 1999 Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide prevent inducible nitric oxide synthase transcription in macrophages by inhibiting NF-kappa B and JNK regulatory factor 1 activation J. Immunol. 162 685–96
[27] Khaitinov S A, Sapienza M M, Chung K F and Barnes P J 1999 Prostaglandins mediate bradykinin-induced reduction of exhaled nitric oxide in asthma Eur. Respir. J. 14 1023–7
[28] Proud D 1997 Kinins as mediators of lung disease The Lung ed R G Crystal (New York: Lippincott-Raven) pp 89–101