

# Low Tidal Volume Ventilation in Patients Without Acute Lung Injury

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**Abstract** Acute respiratory distress syndrome is a life threatening respiratory condition characterized by breakdown of the alveolar-capillary barrier, leading to flooding of the alveolar space producing the classical chest radiograph of bilateral pulmonary infiltrates. In this study, we employed lung protective ventilation strategies in patients without acute lung injury (ALI) to determine whether mechanical ventilation with lower tidal volume would provide more clinical benefits to patients without ALI.

**Keywords** ARDS · Low tidal volume ventilation · Acute lung injury

## Introduction

Acute respiratory distress syndrome (ARDS) is a life threatening respiratory condition characterized by breakdown of the alveolar-capillary barrier, leading to flooding of the alveolar space producing the classical chest radiograph of bilateral pulmonary infiltrates [1]. Now, mechanical ventilation remains as the most common treatment. However, mechanical ventilation, particularly in the setting of lung injury, can exacerbate functional and structural alterations in the lung. Recent clinical evidence showed that lung protective ventilation strategies (LPVS) could provide clinical benefits to the patients with acute lung injury or acute respiratory distress syndrome (ALI or ARDS) [2]. In a NIH-sponsored multicenter study of patients with ARDS, patients randomized to receive a

lower tidal volume ( $V_t$ ) [4–6 ml/kg predict body weight (PBW) and maintenance of plateau pressure between 25 and 30 cmH<sub>2</sub>O] had a survival benefit [3]. Mortality was reduced from 40 % in the conventional arm to 31 % in the low  $V_t$  arm (CI 2.4–15.3 % difference between groups). The benefit in terms of mortality and ventilation free days did not appear to be related to the value of the lung compliance at baseline or to the underlying risk factor for ARDS. However, the survival benefit was associated with a reduction of plasma IL-6 concentration, indicating that a lung protective strategy limits the spread of inflammatory mediators into the systemic circulation of, which in turn may induce multiple system organ failure. Recent studies showed that the levels of variously inflammatory mediators were much lower in low tidal volume compared to high volume group in patients with non-ALI/ARDS who also need mechanical ventilations [4, 5]. However, little evidence supports the use of lower tidal volume in critically ill patients without ALI/ARDS. Therefore, whether or not to utilize LPVS in patients without ARDS who received ventilation remains a question [1].

In this study, we employed LPVS in patients without acute lung injury (ALI) to determine whether mechanical ventilation with lower tidal volume would provide more clinical benefit to patients without ALI.

## Study Design and Patients

### Study Population

From July 2011 until March 2012, patients were recruited in the intensive care departments of our hospital. Patients were eligible for the study, if they did not meet the consensus criteria for ALI/ARDS and needed mechanical

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ventilation for an anticipated duration of more than 72 h. The monitoring of patients started less than 36 h after the onset of mechanical ventilation. Exclusion criteria were younger than 18 years, participation in other clinical trials, pregnancy, increased uncontrollable intracranial pressure, chronic obstructive pulmonary disease (defined as a forced expiratory volume in 1 s to a forced vital capacity ratio less than 0.64 and daily medication), restrictive pulmonary disease (evidence of chronic interstitial infiltration on chest radiograph), use of immunosuppressive agents (100 mg hydrocortisone per day was allowed), pulmonary thromboembolism, previous pneumectomy or lobectomy, and previous randomization in this study. The study protocol was approved by the medical ethics committees of our hospital, and written informed consent was obtained from the patient or closest relatives before entry in the study.

### Ventilatory Management

Mechanical ventilation was conducted via volume-controlled mode. Predicted body weight was used to calculate tidal volume, as described. As routine practice, the target tidal volume in the conventional group was 10 ml/kg of predicted body weight. Patients in this study were ventilated at tidal volumes of 6 ml/kg of predicted body weight. In this study, the tidal volume was allowed to be elevated to 7–8 ml/kg, if patients had severe dyspnea, as identified by increased respiratory rate (more than 35–40 breaths/min) accompanied by increasing levels of discomfort (with or without need for more sedation). Levels of PEEP were set, as well as the level of inspired oxygen ( $\text{FiO}_2$ ) depending on the  $\text{PaO}_2$  according to a local protocol. Lung injury was diagnosed, if a patient met the consensus criteria.

### Objective and Outcomes

Cytokine levels in obtained bronchoalveolar lavage fluid and plasma were set as the primary outcome. Secondary outcomes were set as development of lung injury (according to consensus criteria for ALI/ARDS), duration of mechanical ventilation, and mortality.

### Data Collection and Statistical Analysis

Demographic data and ventilation parameters were recorded immediately after the ventilator settings were changed on day 0. On the day of enrollment and each second day until the patient was weaned from the ventilator, a bronchoalveolar minilavage was conducted to determine the levels of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and interleukin-6 (IL-6).

**Table 1** Demographic data

	Conventional-tidal-volume group ( <i>n</i> = 32)	Lower-tidal-volume group ( <i>n</i> = 31)	<i>P</i> value
Age (years, mean $\pm$ SD)	51.4 $\pm$ 5.4	53.6 $\pm$ 6.1	0.08
Male sex ( <i>n</i> , %)	33 (68)	20 (64)	0.59
Body weight (kg)	68.4 $\pm$ 10.4	65.3 $\pm$ 8.9	0.36
APACHE II score (mean $\pm$ SD)	23 $\pm$ 3	27 $\pm$ 2	0.26

**Table 2** Admission diagnosis

	Conventional-tidal-volume group ( <i>n</i> = 32)	Lower-tidal-volume group ( <i>n</i> = 31)
Cardiac arrest	9	13
Neurologic disease	10	6
Sepsis	3	2
Pneumonia	1	1
Trauma	5	4
Pancreatitis	–	1
Medical other	2	2
Cardiopulmonary	1	1
Other surgery	1	1

## Results

### Baseline Characteristics of Patients

Demographics and admission diagnosis were listed in Tables 1 and 2. Study groups were well balanced with *P/F* less than 40 kPa and unilateral chest radiographs abnormalities, the number of patients with bilateral chest radiographs abnormalities but *P/F* more than 40 kPa, and risk factors for ALI/ARDS. No significant differences were presented in demographics and admission diagnosis.

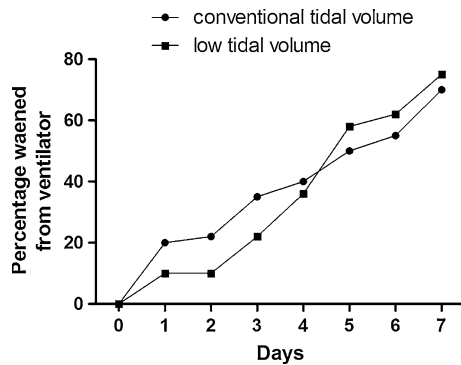
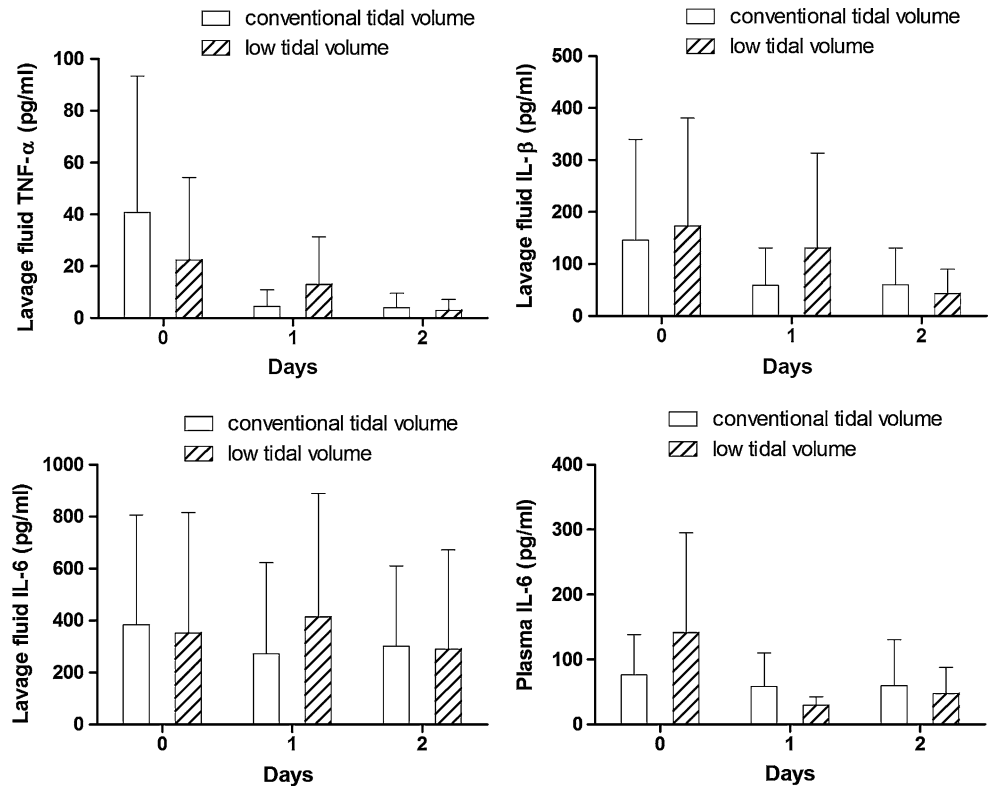
### Cytokine Level

Baseline lavage-fluid levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 as well as plasma IL-6 levels were comparable (Fig. 1). In the conventional-tidal-volume group, plasma IL-6 levels decreased after 4 days, but the decrease over time was more remarkable in the lower-tidal-volume group (*P* < 0.05).

### Clinical Outcomes

After 7 days, 9 (28 %) of the surviving patients from the conventional-tidal-volume group and 6 (18 %) from the

**Fig. 1** Effect of low tidal volume on inflammatory makers



**Fig. 2** Effect of low tidal volume on clinical outcome

lower-tidal-volume group were still on the ventilator ( $P = 0.41$ ). After 28 days, the number of ventilator-free days was not different between groups: 22.0 (19–27) days in the conventional-tidal-volume group and 23.0 (20–28) days in the lower-tidal-volume group ( $P = 0.68$ ). The curves are shown in Fig. 2.

**Discussion**

Recently, LPVS has been widely used in the treatment of ARDS, and the clinical benefit of using LPVS in ARDS has been confirmed in clinical settings. The application of

LPVS corresponds to the pathophysiological characteristics of ARDS. Patients with ARDS have significantly decreased lung volume because of the collapse of large amount of alveoli. Therefore, regular and large tidal volume ventilation often led to overexpansion of alveoli and high airway plateau pressure, resulting in injury of lung and distal organs. One of the key features of LPVS is low tidal volume ventilation (6–8 ml/kg) [6]. In the treatment of ARDS, regular or large volume ventilation (12–15 ml/kg) often led to overexpansion of alveoli and high airway plateau pressure, resulting in ventilator-induced lung injury (VILI). VILI refers to injury of healthy lung tissue or worsening of lung tissue injury due to mechanical ventilation, including barotraumas, volume trauma, atelectrauma, and biotrauma. To prevent and decrease the occurrence of VILI, high tidal volume ventilation and high plateau pressure should be avoided in mechanical ventilation. To reach a plateau pressure lower than 30 cmH<sub>2</sub>O, much lower tidal volume is needed sometimes [7]. When the low tidal volume ventilation is applied, arterial PaCO<sub>2</sub> may higher than normal, which is called “permissive hypercapnia, PHY”. Acute hypercapnia can lead to series pathological or physiological changes, including dilation of cerebral and peripheral blood vessels, increased heart rate, elevated blood pressure, and increased cardiac output. Intracranial hypertension is the contraindication of permissive hypercapnia. In addition, low tidal volume ventilation should be used with caution in patients with cardiac dysfunction, hypotension,

and severe metabolic acidosis. Furthermore, conscious patients cannot tolerate the low tidal volume ventilation, making the application of sedative or muscular relaxant necessary. Studies have proved that slight hypercapnia during LPVS is safe. However, intracranial hypertension and acidemia commonly limited the application of permissive hypercapnia. Moreover, limiting plateau pressure is also a key feature of LPVS. Plateau pressure can objectively reflect the alveolar pressure, and excessively elevated plateau pressure could result in VILI. Therefore, plateau pressure and tidal volume may be of same importance for VILI prevention [8]. Our study demonstrated that LPVS with low tidal volume could effectively prevent the occurrence of VILI without increase in plasma PaCO<sub>2</sub>. This could be explained by the corresponding adjustments of ventilation parameters according to the conditions of patients.

Acute respiratory distress syndrome (ARDS) is a life threatening respiratory condition characterized by breakdown of the alveolar-capillary barrier, leading to flooding of the alveolar space producing the classical chest radiograph of bilateral pulmonary infiltrates. The mortality could be as high as 50–70 %. Mechanical ventilation is the mainstream treatment of ARDS. Nowadays, LPVS has replaced the regular or large tidal volume ventilation. However, the clinical value of LPVS in patients without ARDS has never been discovered. Our study showed that LPVS has protective effect for patients without ARDS and could be used as a safe and effective protective measure.

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