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Efficacy of Lung Recruitment Maneuver with High-Level Positive End-Expiratory Pressure in Patients with Influenza-Associated Acute Respiratory Distress: A Single-Center Prospective Study☆

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ABSTRACT

Background: The latest data released to the public from the Chinese Ministry of Health reported 120,940 confirmed H1N1 cases and 659 deaths on the Chinese mainland.
Objective: We performed a prospective, single-center study to investigate the efficacy of lung recruitment maneuver (RM) with high-level positive end-expiratory pressure (PEEP) in patients with the 2009 influenza A (H1N1)-associated acute respiratory distress syndrome (ARDS).
Methods: Eighty-four patients with H1N1-associated ARDS were admitted to emergency intensive care units between October 2009 and February 2012. During pressure control ventilation, if arterial oxygen saturation (SpO_2) is consistently $< 88\%$ for > 30 minutes, an RM with high-level PEEP is performed to normalize lung volume at 30 cmH_2O for 60 seconds. The RM was considered initially a responder if SpO_2 increased $> 3\%$ within 15 minutes; otherwise, an SpO_2 increase $< 3\%$ would be considered initially a nonresponder. Variations on oxygen metabolism and hemodynamic parameters were also measured before and after initial RM with high-level PEEP.
Results: After the initial RM, 40 patients (47.6%) with influenza-associated ARDS displayed an increase ($\geq 3\%$) in SpO_2 (the responder group), and 44 patients (52.4%) had no significant improvement ($< 3\%$) in SpO_2 (the nonresponder group). Among 84 patients with influenza-associated ARDS, 56 patients survived and 28 patients died. There was significant difference in mortality rate between the responder group and the nonresponder group (7 out of 40 vs 18 out of 44; $P = 0.019$). The initial PEEP level in the responder group was lower than that of the nonresponder group ($P = 0.028$). The initial mean duration of mechanical ventilation in the responder group was also shorter than that of the nonresponder group ($P = 0.011$). Furthermore, the initial dynamic lung-thorax compliance was obviously higher in the initially responder group than in the nonresponder group ($P = 0.038$).
Conclusions: Initial response of lung RM with high-level PEEP may be associated with good clinical outcome of patients with influenza-associated ARDS. The initial PEEP level, duration of mechanical ventilation, and dynamic lung-thorax compliance dynamic lung-thorax compliance may be potential factors in influencing the initial response to RM.

Introduction

The novel swine-origin influenza virus pandemic A (H1N1), which first emerged in Mexico in April 2009, had spread globally and resulted in $> 130{,}000$ laboratory-confirmed cases and 800 deaths in > 100 countries by July 2009.[1] The latest data released to the public from the Chinese Ministry of Health reported 120,940 confirmed H1N1 cases and 659 deaths on the Chinese mainland.[2] Patients with H1N1 infection had greater risk of developing critical and fatal illnesses, such as severe pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, renal failure, and multiorgan failure.[3] Approximately 10% to 30% of hospitalized patients required intensive care, and 60% to 88% of intensive care patients required mechanical ventilation.[4] However, several animal and clinical studies have shown that mechanical ventilation can worsen pre-existing lung injury and produce ventilator-induced lung injury.[5] Emerging evidence indicates that the use of lung-protective mechanical ventilation strategies, such as

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volume- and pressure-limited ventilation, could minimize ventilator-induced lung injury and decrease short-term mortality in patients with ARDS.[6,7] Therefore, in recent years, lung recruitment maneuver (RM) and optimal positive end-expiratory pressure (PEEP) during lung-protective mechanical ventilation have been widely applied to reduce lung injuries and improve outcomes in this situation. Badet et al[8] confirmed that lung RM with optimal PEEP could improve oxygenation and dynamic lung-thorax compliance (C_{dyn}) in patients with early ARDS. Although the critical care community has generally endorsed the strategy of using lower tidal volumes and airway pressures, the optimal level of PEEP remains controversial. Several studies suggested that lung RM with higher PEEP levels could be more effective compared with lower PEEP levels,[9] whereas some other studies came to the conclusion that lung RM with low-level PEEP would be more favorable.[10,11] Additionally, a recent meta-analysis concluded that lung-protective mechanical ventilation with higher levels of PEEP was associated with improved survival in patients with ARDS.[12] It was hypothesized that lung RM and high levels of PEEP might be therapeutic for patients with influenza-associated ARDS. Therefore, we performed a prospective, single-center study to investigate the efficacy of lung RM with high-level PEEP in patients with influenza-associated ARDS. We also attempted to point out clinical factors influencing the initial validity of RM. Our preliminary study may provide the basis for treatment plans against influenza-associated ARDS in the future, as well as help improve the lung-protective mechanical ventilation strategy.

Methods

Ethics statement

The study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University. Informed consent was obtained in written form from all participants using procedures approved by institutional review boards. Next of kin, caregivers, or guardians consented on the behalf of participants whose capacity to consent was reduced. The study was conducted in the emergency intensive care unit (EICU) at the First Affiliated Hospital of China Medical University. The EICU is also a medical intensive care unit, which mainly cares for general medical or surgical patients, respiratory care patients, cardiovascular care patients, gastroenterology care patients, neurology care patients, trauma care patients, and burn care patients, for example.

Study design and subjects

This was a single-center prospective study of patients with influenza-associated ARDS admitted to the EICU from October 2009 to February 2012. Patients must meet certain criteria to be enrolled in this study. First, the patients must meet the clinical diagnosis of the 2009 H1N1 virus, which is in accordance with the revised 2009 national guidelines from the Ministry of Health of the People's Republic of China. That is, H1N1 infection was confirmed by real-time polymerase chain reaction of nasopharyngeal swabs or bronchoalveolar lavage fluid. Patients with strongly suspected infection had a diagnosis of influenza pneumonia without further determination of the subtype. Second, the diagnosis of ARDS was based on the American-European Consensus Conference criteria.[13] All patients were managed under a standard and uniform treatment protocol, which involves oral oseltamivir treatment, intravenous antibiotics to prevent infection, early short-term glucocorticoid treatment, multiple organ support therapy, intensive insulin therapy, the correction of metabolic acid–base disturbances, and mechanical ventilation.

Protocol

All patients underwent pressure control ventilation through orotracheal intubation using a protective ventilatory strategy. The inspiratory plateau pressure (PIEP) was consistently < 35 cmH_2O with a tidal volume of 6∼8 mL/kg. PEEP levels and inspired oxygen concentration were set according to different values of continuous arterial oxygen saturation (SpO_2) monitoring. If SpO_2 was consistently $< 88\%$ for > 30 minutes, an initial RM with high-level PEEP (> 40 cmH_2O) was performed to normalize the lung volume at 30 cmH_2O for 60 seconds. The ventilator mode and settings were unchanged within 15 minutes after an RM. After the initial RM, PEEP was maintained at 20 cmH_2O. According to individual patient needs, PEEP levels could be modified. Variations in gas exchange, ventilator settings, and vital signs were recorded for each patient. The RM was initially a responder if SpO_2 increased $> 3\%$ within 15 minutes; otherwise, an SpO_2 increase $< 3\%$ would be considered an initial nonresponder.[14,15] Variations in oxygen metabolism and hemodynamic parameters were also measured before and after an RM with high-level PEEP. Total lung-thorax compliance was calculated using the relationship $\Delta V/(PIEP - PEEP)$; where ΔV was the inspired volume minus the compressible volume ($V_{comp} = PIEP \times 4.5$ mL using standard tubing and humidifier).[14] Dynamic lung-thorax compliance (C_{dyn}) was calculated as the ratio of tidal volume to transpulmonary pressure change at points of zero flow.[16] The in-hospital mortality rates for influenza-associated ARDS patients were analyzed after mechanical ventilation.

Statistical analysis

Data were presented as mean (SD), median with interquartile ranges, or frequencies. A χ^2 test was used to compare frequencies. One-way ANOVA and Student t test were used for normally distributed variables, whereas the Mann-Whitney U test was used for non-normal distributed variables. Comparisons between 2 groups for nominal variables were made by the Fisher exact test. A probability value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18.0 software (IBM-SPSS, Inc, Armonk, NY).

Results

Baseline characteristics of patients

Among a total of 119 patients with clinical diagnosis of 2009 H1N1 infection from October 2009 to February 2012, 84 patients (70.6%) with influenza-associated ARDS were assessed in our study. The other 35 patients were excluded for the following reasons: 5 patients did not meet the diagnostic criteria for H1N1 pneumonia because they did not have chest radiographic and computed tomography findings, 25 patients did not fulfill the criteria for ARDS, and 5 patients refused invasive/noninvasive mechanical ventilation. The flowchart of patient selection and assessment process is shown in Figure 1. All 84 patients (52 men and 32 women) included in our study met the criteria for influenza-associated ARDS. The mean age was 36.3 (16.4) years (range 19–62 years). The median duration of mechanical ventilation in the EICU was 5.5 days (range 3.5–12.0 days). The overall mortality was 29.8% (25 out of 84). There were no significant differences in Acute Physiology and Chronic Health Evaluation II score and Simplified Acute Physiology Score result between the responder and nonresponder groups (all Ps > 0.05). Demographic characteristics of patients in the responder and nonresponder groups are summarized in **Table I**.

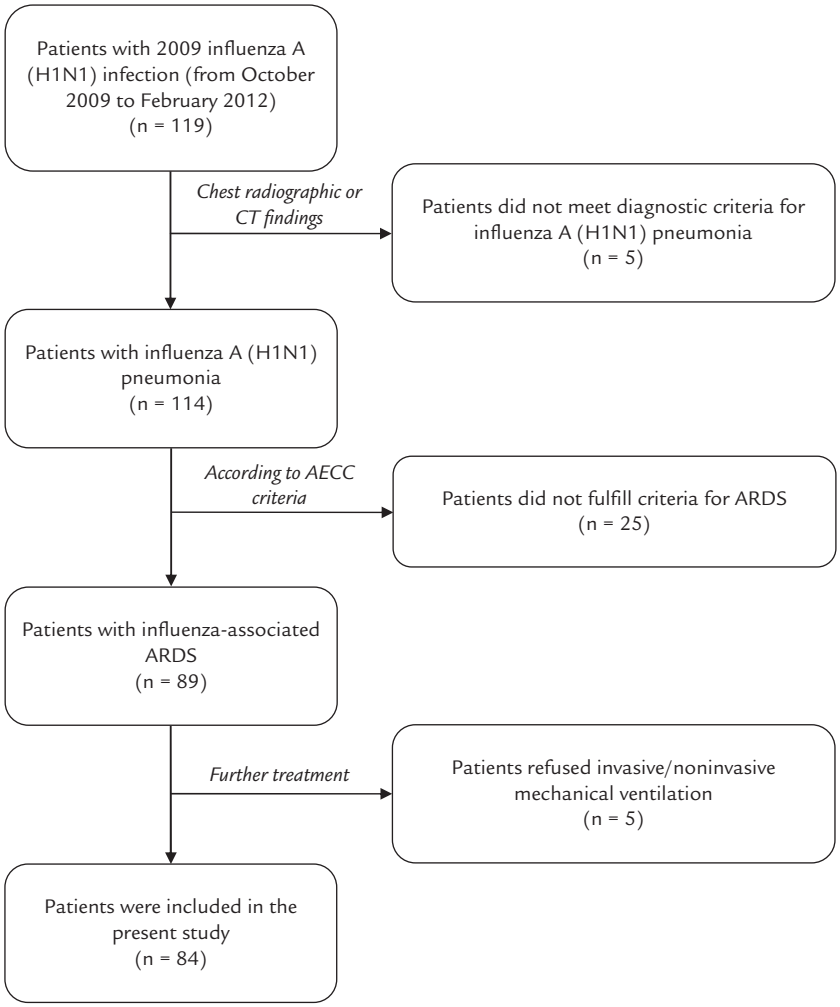

Figure 1. Flowchart of the patient selection and assessment process. CT = computed tomography; AECC = American-European Consensus Conference; ARDS = acute respiratory distress syndrome.

Table I
Differences in ventilator settings and hemodynamic parameters before recruitment maneuver.

Parameter	Responder group (n = 40)	Nonresponder group (n = 46)	*t*	*P*
	Mean (SD)			
IP, cmH_2O	24.3 (4.1)	28.2 (3.4)	1.88	0.066
RR, min^{-1}	17.8 (4.7)	19.2 (5.1)	−1.57	0.135
TV, mL	484.3 (32.7)	440.5 (31.4)	1.90	0.063
FiO_2, %	66.5 (8.2)	69.6 (9.0)	1.34	0.223
PEEP level, cmH_2O	8.6 (3.4)	11.3 (4.2)	2.24	0.028
SpO_2, %	86.7 (7.6)	87.1 (6.4)	0.85	0.422
HR, min^{-1}	72.4 (12.9)	73.6 (13.1)	0.92	0.398
MAP, mm Hg	71.6 (10.6)	76.0 (11.2)	1.04	0.348
PaO_2/FiO_2, mm Hg	82.8 (9.1)	79.9 (8.4)	1.60	0.129
$P_{A\text{-}a}DO_2$, mm Hg	102.4 (38.6)	117.9 (40.1)	0.90	0.395
C_{dyn}, mL/cmH_2O	30.8 (6.2)	26.1 (5.1)	2.12	0.038
DMV, d	4.1 (3.1)	5.8 (2.5)	2.58	0.011
APACHE II score	21.3 (6.4)	20.9 (5.9)	0.26	0.811
SAPS	37.2 (11.7)	36.5 (10.9)	0.11	0.922

IP = inspiratory pressure; RR = respiratory rate; TV = tidal volume; FiO_2 = inspired oxygen concentration; PEEP = positive end-expiratory pressure; SpO_2 = arterial oxygen saturation; HR = heart rate; MAP = mean arterial pressure; PaO_2/FiO_2 = oxygenation index; $P_{A\text{-}a}DO_2$ = alveolar-arterial oxygen tension difference; C_{dyn} = dynamic lung-thorax compliance; DMV = duration of mechanical ventilation; APACHE II = Acute Physiology and Chronic Health Evaluation II; SAPS = Simplified Acute Physiology Score.

Beneficial effects of RM with high-level PEEP on prognosis of patients

After the initial RM, 40 patients (47.6%) with influenza-associated ARDS showed an increase ($\geq 3\%$) in SpO_2 (the responder group), and 44 patients (52.4%) had no significant improvement ($< 3\%$) in SpO_2 (the nonresponder group). Among 84 patients with influenza-associated ARDS, 56 patients survived and 28 patients died. There was a significant difference in mortality rate between the responder group and the nonresponder group (7 out of 40 vs 18 out of 44; $P = 0.019$).

Clinical factors influencing the efficacy of RM with high-level PEEP

Before the initial RM, the initial PEEP level in the responder group was lower than that of the nonresponder group (8.6 [3.4] vs 11.3 [4.2] cmH_2O; $P = 0.028$). The mean duration of mechanical ventilation in the responder group was also shorter than in the nonresponder group (4.1 [3.1] vs 5.8 [2.5] days; $P = 0.011$). Furthermore, C_{dyn} was obviously higher in the responder group when compared with that of the nonresponder group (30.8 [6.2] vs 26.1 [5.1] mL/cmH_2O; $P = 0.038$). Differences in ventilator settings and hemodynamic parameters between the responder group and the nonresponder group were summarized in **Table II**.

At 15 minutes after the initial RM, there was no significant difference in the mean inspiration pressure between the responder

Table II
Differences in ventilator settings and hemodynamic parameters at 15 minutes after recruitment maneuver with high-level positive end-expiratory pressure.

Parameter	Responder group (n = 40)	Nonresponder group (n = 46)	*t*	*P*
	Mean (SD)			
IP, cmH_2O	21.2 (3.5)	27.8 (4.8)	1.90	0.063
Change, %	−12.8 (4.3)	−1.4 (3.8)	2.16	0.035
RR, min^{-1}	18.3 (4.8)	20.4 (4.3)	1.56	0.138
Change, %	2.8 (3.4)	6.3 (5.2)	1.88	0.066
TV, mL	495.2 (36.7)	462.4 (31.2)	1.82	0.075
Change, %	2.3 (3.6)	5.0 (4.9)	1.53	0.149
SpO_2, %	91.6 (6.5)	89.3 (7.1)	−1.46	0.177
Change, %	5.7 (4.2)	2.5 (3.1)	0.92	0.061
HR, min^{-1}	72.4 (8.0)	75.1 (9.3)	1.28	0.246
Change, %	−1.4 (2.3)	0.4 (1.8)	0.72	0.452
MAP, mm Hg	72.1 (10.8)	73.8 (11.6)	1.46	0.177
Change, %	0.7 (1.4)	−1.1 (1.6)	0.85	0.422
PaO_2/FiO_2, mm Hg	84.6 (11.7)	82.4 (10.1)	1.37	0.208
Change, %	2.2 (1.9)	3.1 (2.4)	1.12	0.316
$P_{A\text{-}a}DO_2$, mm Hg	72.5 (28.3)	97.4 (31.2)	2.25	0.028
Change, %	27.6 (9.5)	7.3 (6.1)	2.12	0.038
C_{dyn}, mL/cmH_2O	39.3 (7.4)	28.0 (8.2)	2.08	0.042
Change (%)	27.6 (9.5)	7.3 (6.1)	2.41	0.017

IP = inspiratory pressure; RR = respiratory rate; TV = tidal volume; SpO_2 = arterial oxygen saturation; HR = heart rate; MAP = mean arterial pressure; PaO_2/FiO_2 = oxygenation index; $P_{A\text{-}a}DO_2$ = alveolar-arterial oxygen tension difference; C_{dyn} = dynamic lung-thorax compliance.

group and the nonresponder group ($P = 0.063$). But the responder group had a greater reduction in inspiration pressure than the nonresponder group (−12.8% [4.3%] vs −1.4% [3.8%]; $P = 0.035$). The mean C_{dyn} in the responder group was higher than the nonresponder group (39.3 [7.4] vs 28.0 [8.2] mL/cmH_2O; $P = 0.042$); and the change in C_{dyn} was also greater in the responder group than in the nonresponder group (27.6% [9.5%] vs 7.3% [6.1%]; $P = 0.017$). Furthermore, the mean alveolar-arterial oxygen tension difference in the responder group was lower than that of the nonresponder group (72.5 [28.3] vs 97.4 [31.2] mm Hg; $P = 0.028$). There was also a significant difference in the changes in mean alveolar-arterial oxygen tension difference between the responder group and the nonresponder group (27.6% [9.5%] vs 7.3% [6.1%]; $P = 0.038$).

After the initial RM, the minimal SpO_2 occurred at 2.1 [0.6] minutes, and the maximal SpO_2 occurred at 12.7 [2.6] minutes (Figure 2). Compared with the initial level before RM, a significant increase in SpO_2 was observed in the responder group at 30 minutes after RM (90.4% [4.4%] vs 86.7% [7.6%]; $P = 0.047$). However, no significant increase in SpO_2 was observed in the nonresponder group at 30 minutes after RM compared with SpO_2 before RM (88.2% [5.3%] vs 87.1% [6.4%]; $P = 0.082$). There was a significant increase in SpO_2 at 30 minutes after RM between the responder group and the nonresponder group (4.3% [4.4%] vs 1.4% [3.3%]; $P = 0.044$). Furthermore, compared with the initial values before RM, heart rate increased significantly at the end of RM ($P = 0.038$), whereas the mean arterial pressure decreased significantly at the end of RM ($P = 0.049$). The responder group had higher heart rate and lower mean arterial pressure than the nonresponder group at the end of RM and 1 minute after RM (all $Ps < 0.05$).

Discussion

H1N1 appeared in Mexico during spring 2009 and caused an epidemic that led to several patients developing severe ARDS.[17] Mechanical ventilation is essential for patients with influenza-associated ARDS. However, it has become evident over the past 2 decades that mechanical ventilation itself can augment or cause acute lung injury.[18] Recently, lung RM with optimal PEEP has been introduced for the treatment of ARDS as an adjunctive modality, along with lung protective strategies. However, compared with lower PEEP levels, higher PEEP levels may improve oxygenation and reduce ventilator-induced lung injuries, but may also cause circulatory depression and lung injuries from overdistention.[19]

A recent meta-analysis on individual data of 3 studies showed that hospital mortality was significantly lower in the higher PEEP groups than in the lower PEEP groups; higher PEEP should be used in patients with severely hypoxemic ARDS and this technique should also be monitored at the bedside.[12,20] Therefore, we hypothesize that early application of lung RM with high-level PEEP may improve clinical outcomes of patients with influenza-associated ARDS. In this study, we evaluated the efficacy of lung RM with high-level PEEP in patients with influenza-associated ARDS. Our results indicated that influenza-associated ARDS patients with initial lung RM response may have more recruitable lung units and, therefore, benefit from higher levels of PEEP. A total of 84 patients with influenza-associated ARDS who met clinical

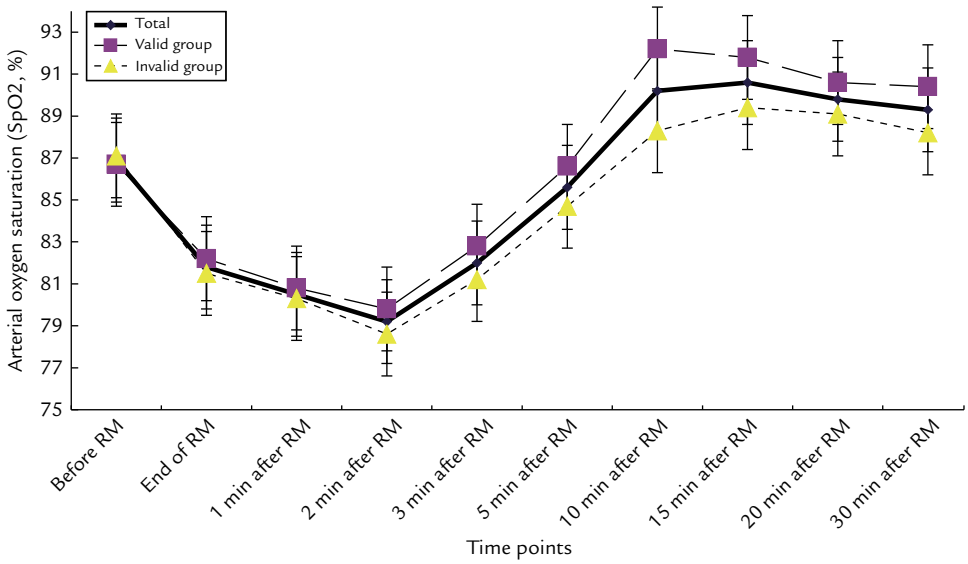

Figure 2. Dynamic changes in arterial oxygen saturation level after the initial recruitment maneuver (RM) with high-level positive end-expiratory pressure.

criteria were included. The overall mortality rate was 29.8% (25 out of 84). After the initial RM, 40 patients showed a significant increase ($\geq 3\%$) in SpO_2, but 44 patients exhibited no response ($< 3\%$). The mortality rate in the responder group was significantly lower than in the nonresponder group (17.5% vs 40.9%), indicating that RM with high-level PEEP has beneficial effects on the prognosis of patients with influenza-associated ARDS.

Our observations also revealed that significant differences in the initial PEEP level, mean duration of mechanical ventilation, and C_{dyn} between the responder group and the nonresponder group, which may suggest that these clinical factors can influence the initial efficacy of RM with high-level PEEP. There was also a significant difference in SpO_2 at 30 minutes after the initial RM between the responder group and the nonresponder group, which demonstrated that the beneficial effects of PEEP are associated with an increase in functional residual capacity that recruits previously collapsed alveoli for useful gas exchange. An experimental study also indicated that combined functional residual capacity and static lung compliance measurements may help in identifying the optimal level of PEEP.[21] At 15 minutes after the initial RM, there were also significant differences in the mean values and changes in mean alveolar-arterial oxygen tension difference between the responder group and the nonresponder group. These results provide supporting evidence for the beneficial effects of RM with high-level PEEP on oxygen metabolism in patients with influenza-associated ARDS.

Conclusions

Our results suggest that initial response of lung RM with high-level PEEP may be associated with good clinical outcome of patients with influenza-associated ARDS. Patients with influenza-associated ARDS in the responder group may have more recruitable lung units and therefore benefit from higher levels of PEEP. Lung RM may be able to better serve less severe patients with more recruitable units of lung. The beneficial effects of lung RM with high-level PEEP on oxygen metabolism may improve clinical outcomes in patients with influenza-associated ARDS. The initial PEEP level, duration of mechanical ventilation, and C_{dyn} may be potential factors influencing the efficacy of lung RM with high-level PEEP. Because a control group is lacking in our study, the true effects of lung RM with high-level PEEP in the treatment of patients with influenza-associated ARDS are still controversial. Therefore, further studies are needed to determine if lung RM with high-level PEEP can influence the clinical outcomes in patients with influenza-associated ARDS.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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