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Effect of protective lung ventilation strategy combined with lung recruitment maneuver in patients with acute respiratory distress syndrome (ARDS)

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ABSTRACT

Objective: To evaluate the efficacy and safety of protective lung ventilation strategy combined with lung recruitment maneuver (RM) in the treatment patients with acute respiratory distress syndrome (ARDS). **Methods:** Totally 74 patients with ARDS admitted to the Department of Intensive Care Unit, Changshu Second People's Hospital in Jiangsu Province between September 2010 and June 2013 were selected and randomly divided into lung recruitment group and non-recruitment group, and the initial ventilation mode for both groups was synchronized intermittent mandatory ventilation (SIMV). Lung recruitment was performed in condition of SIMV mode (pressure control and pressure support). Positive end expiratory pressure (PEEP) was increased by 5 cm H_2O every time and maintained for 40-50 s before entering the next increasing circle, and the peak airway pressure was always kept below 45 cm H_2O. After PEEP reached the maximum value, it was gradually reduced by 5 cm H_2O every time and finally maintained at 15 cm H_2O for 10 min. **Results:** A total of 74 patients with mean age of (49.0±18.6) years old were enrolled, 36 patients were enrolled in lung recruitment maneuver (RM) group and 38 patients were enrolled into non-lung recruitment maneuver (non-RM) group. 44 were male and accounted for 59.5% of all the patients. For the indicators such as PEEP, pressure support (PS), plateau airway pressure (P_{plat}), peak airway pressure (P_{peak}), vital capacity (VC) and fraction of inspired oxygen (FiO_2), no statistical differences in the indicators were found between the RM group and non-RM group on D1, D3 and D7 (P>0.05), except that only FiO_2 of RM group on D7 was significantly lower than that of non-RM group [(47.2±10.0) vs. (52.2±10.5), P<0.05]. For the indicators of blood gas analysis, including pH, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and oxygenation index (PaO_2/FiO_2), PaO_2 and PaO_2/FiO_2 of RM group were significantly higher than those of non-RM group on D7, and the values were [(90.2±16.1) mmHg vs. (76.4±11.3) mmHg, P<0.05] and [(196.5±40.7) mmHg vs. (151.7±37.3) mmHg, P<0.05] respectively. There was no statistical difference in heart rate (HR), cardiac index (CI), central venous pressure (CVP) or mean arterial pressure (MAP) between RM group and non-RM group on D1, D3 and D7 (P>0.05). 28-day mortality, ICU mortality and in-hospital mortality were 25% vs. 28.9%, 25% vs. 26.3% and 36.1% vs. 39.5% respectively between RM group and non-RM group (all P>0.05). **Conclusion:** Protective lung ventilation strategy combined with lung recruitment maneuver can improve the indicators such as PaO_2, FiO_2 and PaO_2/FiO_2 on D7, but failed to improve the final outcomes such as 28-day mortality, ICU mortality and in-hospital mortality.

1. Introduction

Acute respiratory distress syndrome (ARDS) is one of the common critical diseases in the emergency department and ICU, and mechanical ventilation is an important therapy for respiratory support in patients with ARDS [1-3]. In recent years, researches have shown that small tidal volume ventilation (6 vs. 12 mL/Kg) of protective lung ventilation strategy can significantly increase the survival rate in patients with ARDS, because this strategy can reduce the shearing injury caused by persistent alveolar opening and closing [4,5]. However, small tidal volume ventilation can also

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cause some unexpected consequences, and the most severe adverse consequence is the alveolar collapse and atelectasis caused by insufficient ventilation [6,7]. Animal experiments has shown that lung recruitment maneuver (RM) can reduce the alveolar collapse caused by small tidal volume ventilation strategy, and improve the oxygenation and respiratory parameters [8]. However, it remains controversial whether RM can improve clinical outcomes in patients with ARDS [9,10]. Therefore, we sought to explore whether protective lung ventilation strategy combined with lung recruitment maneuver technique (PEEP increment method) can improve the outcomes of respiratory parameters, blood gas analysis indices, hemodynamic indices, and clinical prognosis in patients with ARDS.

2. Materials and methods

2.1. Study population

Patients with ARDS admitted to the Department of Intensive Care Unit, Changshu Second People's Hospital in Jiangsu Province between September 2010 and June 2013 were considered potentially eligible. The research was approved by the ethics committee of Changshu Second People's Hospital, and in accordance with the ethics standard of clinical research. All patients or their clients signed written informed consent.

2.2. Inclusion criteria

Inclusion criteria was according to the ARDS Berlin standard [1]: patients with factors for ARDS; acute onset, high respiratory frequency and (or) respiratory distress; X ray showes bilateral infiltrates; cardiac pulmonary edema was eliminated; hypoxemia during mechanical ventilation ($PaO_2/FiO_2 \leq 300$ mmHg).

2.3. Exclusion criteria

Less than 18 years old; pregnant; the expected hospital stay less than 48 h; with end-stage chronic disease or malignant disease; with intracranial hypertension or neuromuscular disorders; patients with lobectomy; patients without autonomous respiration.

2.4. Grouping scheme

A stratified randomized controlled method was used. The enrolled patients were first classified according to the pathogenies of ARDS, and then each type of the patients was randomly assigned to the RM or non-RM group. Random assignment was achieved by computer-generated random number, and sealed envelope was used for allocation concealment.

2.5. Mechanical ventilation

Initial ventilation mode was synchronized intermittent mandatory ventilation (SIMV), and the capacity control + pressure support or pressure control + pressure support scheme were prescribed according to patients' conditions. Parameter settings: suitable positive end-expiratory pressure (PEEP) levels were selected, namely the minimum PEEP level to maintain the target oxygenation with the fraction of inspired oxygen (FiO_2) less than 60%, restricted platform pressure less than 30 cm H_2O and tidal volume 6–7 mL/kg [11,12]; the target parameters: blood gas analysis pH 7.30–7.45, PaO_2 60–80 mmHg or SaO_2 90%–95%, $PaCO_2$ 35–55 mmHg [11,12].

2.6. Lung RM process

Patients were fully sedated (Ramsay score 4-5 grade) before initiation of lung recruitment. Patients received pure oxygen inspiration for 5 min before lung RM to ensure adequate oxygenation. For RM, ventilators were set as SIMV mode (pressure control + pressure support), and PEEP increment method was applied. PEEP was increased by 5 cm H_2O every time from baseline and maintained for 40–50 s before entering into the next PEEP increasing circle. During PEEP incremental process, in order to control the peak airway pressure always below 45 cm H_2O, when the P_{peak} was equal to 45 cm H_2O, PS was decreased by 5 cm H_2O as PEEP increased. After PEEP reached the peak value, it was then reduced by 5 cm H_2O every time, and maintained at 15 cm H_2O for 10 min. Finally, PEEP and other respiratory parameters were set to the initial levels before lung recruitment. Lung RM flow chart is shown in Figure 1, and each RM lasted for about 17 min and repeated every 8 h [13].

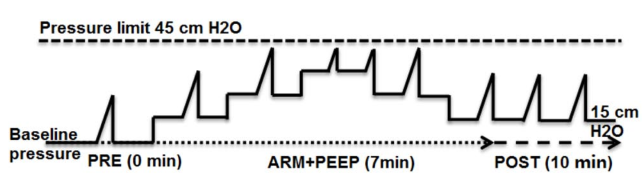

Figure 1. Lung recruitment flow chart.

2.7. Observations

The general information, respirator conditions and ARDS causes of the enrolled patients; dynamic changes of respirator parameters such as PEEP, pressure support (PS), plateau airway pressure (P_{plat}), peak airway pressure (P_{peak}), vital capacity (VC) and fraction of inspired oxygen (FiO_2) of RM group and non-RM group on D1, D3 and D7; blood gas analysis results such as pH, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and oxygenation index (PaO_2/FiO_2) of RM group and non-RM group on D1, D3 and D7; dynamic change of hemodynamic parameters such as heart rate (HR), cardiac index (CI), central venous pressure (CVP) or mean arterial pressure (MAP) of RM group and non-RM group on D1, D3 and D7; prognostic indicators such as 28-day mortality, ICU mortality, in-hospital mortality and incidence of complications.

2.8. Statistical analysis

Normally distributed data were expressed as mean (standard deviation), and compared with independent *t*-test; non-normally distributed data were expressed as median (interquartile range), and compared with Wilcoxon-Mann-Whitney test; enumeration data were expressed as number (percentage), and compared by *Chi*-square test or the Fisher's exact test. Survival curves were built by Kaplan-Meier method, and compared by the Log-rank test. All statistical analysis was performed by SPSS 20.0. $P<0.05$ indicated that the difference was statistically significant.

3. Results

3.1. Study population

Clinical general data of two groups of patients are shown in Table 1. A total of 74 patients with ARDS were enrolled (36 cases in RM group and 38 cases in non-RM group). 44 patients were male and accounted for 59.5% of the total amount. The average age was (49.0±18.6) years old. The common causes of ARDS were lung infections (20 cases), sepsis or septic shock (13 cases), drowning and aspiration (9 cases), acute pancreatitis (9 cases), pulmonary contusion (8 cases), etc in turn. RM group and non-RM group were not statistically different in age, gender, APACHEII score and ARDS causes on admission ($P>0.05$), and the clinical data of two groups of patients were comparable.

Table 1

Clinical characteristics of RM group and non-RM group on admission.

Clinical characteristics	RM group	Non-RM group	*P*
Number of people	36	38	0.879
Age	46.9±15.0	51.1±21.5	0.394
Male (*n*,%)	21(58.3%)	23(60.5%)	0.848
Mechanical ventilation time before inclusion	1(1–3)	1(1–3)	0.757
APACHEII score	16.6±5.0	17.6±4.8	0.809
Number of extra-pulmonary organ failure	2.1±1.3	2.0±1.2	0.732
Oxygenation index	173.5±41.2	172.9±39.0	0.949
Main causes of acute lung injury			
Lung infections	9	11	0.702
Sepsis or septic shock	7	6	0.680
Drowning and aspiration	5	4	0.658
Acute pancreatitis	4	5	0.788
Pulmonary contusion	4	4	0.936
Burn	3	2	0.599
Acute pulmonary embolism	1	1	0.969
Poisoning	1	2	0.587
Others	2	3	0.689

3.2. Respirator parameters of RM group and non–RM group on D1, D3 and D7

Respirator parameters of two groups of patients on D1, D3 and D7 are shown in Table 2. For the indicators such as PEEP, PS, P_{plat}, P_{peak}, vital capacity (VC) and fraction of inspired oxygen (FiO_2) in RM group and non-RM group, no statistical differences in the indicators were found between the RM group and non-RM group on D1, D3 and D7 ($P>0.05$), except that only FiO_2 of RM group on D7 was significantly lower than that of non-RM group [(47.2±10.0) vs. (52.2±10.5), $P<0.05$].

3.3. Blood gas analysis results of RM group and non–RM group on D1, D3 and D7

Blood gas analysis results of two groups of patients on D1, D3 and D7 are shown in Table 3. For all the gas analysis results [pH, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and PaO_2/FiO_2], only PaO_2 and PaO_2/FiO_2 of RM group were significantly higher than those of non-RM

Table 2

Comparison of respirator parameters between RM group and non-RM group on D1, D3 and D7.

Time	Group	PEEP(cm H_2O)	PS (cm H_2O)	Plateau airway pressure (cm H_2O)	Peak airway pressure (cm H_2O)	Vital capacity (mL/kg)	Fraction of inspired oxygen (*n*, %)
D1	RM group	8.3±2.4	15.9±4.1	24.2±5.9	33.9±4.8	6.6±1.1	67.9(11.6)
	Non-RM group	8.2±2.3	16.6±3.8	24.8±5.6	34.8±5.6	6.5±0.9	62.5(10.5)
D3	RM group	7.8±2.2	15.0±3.7	22.8±5.1	32.7±4.6	6.4±1.0	57.8(11.3)
	Non-RM group	7.6±1.7	15.5±3.4	23.1±4.7	33.2±5.9	6.4±0.9	57.6(10.9)
D7	RM group	7.4±1.6	14.2±3.3	21.6±4.3	31.1±5.0	6.2±1.0	47.2(10.0)
	Non-RM group	7.1±1.8	14.8±3.5	21.9±5.0	32.2±6.2	6.3±0.9	52.2(10.5)$^{\#}$

$^{\#}$ comparison between RM group and non-RM group, $P<0.05$.

group on D7 (P<0.05).

3.4. Hemodynamic parameters of RM group and non–RM group on D1, D3 and D7

Hemodynamic parameters of two groups of patients on D1, D3 and D7 are shown in Table 4. There was no statistical difference in HR, CI, CVP or MAP between RM group and non-RM group on D1, D3 and D7 (P>0.05).

3.5. Prognosis and complications of patients in RM group and non–RM group

Prognosis and complications of patients in the two groups are shown in Table 5. 28-day mortality of RM group and non-RM group were 25.0% and 28.9% (P>0.05) respectively, and the survival curve (Figure 2) was not statistically different between two groups of patients (P>0.05). Furthermore, ICU mortality (25.0% vs. 26.3%) and in-hospital mortality (36.1% vs. 39.5%) were not statistically different between RM group and non-RM group (P>0.05). Duration of mechanical ventilation, length of ICU stay and length of in-hospital stay for RM group and non-RM group were 10(6–18.75) vs. 14.5(7–23.25), 10(9.25–25.25) vs. 16.5(11–26.25) and 16(12–28.5) vs. 26(16–32.5) respectively and not statistically different (P>0.05). The incidence of common ARDS complications, including refractory hypoxemia (11.1% vs. 10.5%), refractory acidosis (13.9% vs. 10.5%) and barotraumas or pneumothorax (11.1% vs. 13.2%) were not statistically different between RM group and non-RM group (P>0.05).

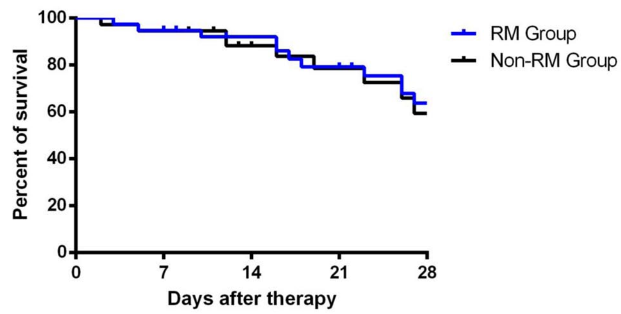

Figure 2. 28 d survival curve of RM group and non-RM group.

Table 3

Comparison of blood gas analysis results between RM group and non-RM group on D1, D3 and D7.

Time	Group	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	PaO_2/FiO_2 (mmHg)
D1	RM group	7.38±0.07	85.1±17.5	41.9±6.1	129.5±37.3
	Non-RM group	7.38±0.07	79.1±12.5	43.5±6.7	131.9±37.4
D3	RM group	7.39±0.04	81.9±15.0	43.1±4.0	146.9±37.7
	Non-RM group	7.40±0.04	76.0±10.9	41.9±4.8	137.4±36.4
D7	RM group	7.39±0.03	90.2±16.1	41.9±4.2	196.5±40.7
	Non-RM group	7.41±0.03	76.4±11.3#	42.8±6.2	151.7±37.3#

comparison between RM group and non-RM group, P<0.05.

Table 4

Comparison of hemodynamic parameters between RM group and non-RM group on D1, D3 and D7.

Time	Group	Heart rate (times/min)	Cardiac index (L/min/M^2)	Central venous pressure (cm H_2O)	Mean arterial pressure (mmHg)
D1	RM group	96.3(19.2)	3.6(0.5)	9.9(4.1)	86.8(13.2)
	Non-RM group	95.3(19.8)	3.6(0.5)	10.0(4.3)	90.0(18.2)
D3	RM group	92.2(16.7)	3.6(0.6)	9.7(3.7)	85.2(11.4)
	Non-RM group	90.6(17.4)	3.6(0.5)	9.7(2.9)	89.1(12.1)
D7	RM group	88.2(13.6)	3.6(0.5)	8.9(4.3)	80.9(7.8)
	Non-RM group	86.7(14.0)	3.6(0.5)	9.0(1.9)	84.1(12.1)

Table 5

Comparison of clinical results between RM group and non-RM group.

Clinical characteristics	RM group	Non-RM group	P value
28d mortality (n, %)	9(25.0%)	11(28.9%)	0.702
ICU mortality (n,%)	9(25.0%)	10(26.3%)	0.897
In-hospital mortality (n, %)	13(36.1%)	15(39.5%)	0.766
Duration of mechanical ventilation (days)	10(6-18.75)	14.5(7-23.25)	0.338
Length of ICU stay (d)	10(9.25-25.25)	16.5(11-26.25)	0.433
Length of in-hospital stay (d)	16(12-28.5)	26(16-32.5)	0.119
Refractory hypoxemia incidence (n, %)	4(11.1%)	4(10.5%)	0.936
Refractory acidosis (n, %)	5(13.9%)	4(10.5%)	0.658
Barotraumas or pneumothorax (n, %)	4(11.1%)	5(13.2%)	0.788

4. Discussion

In this study, we found that protective lung ventilation strategy combined with lung RM (compared with no implementation of lung RM), can significantly improve patients' oxygenation index on D7, but failed to improve the 28-day mortality, length of hospital stay, incidence of complications and other prognostic indicators.

One of the important pathophysiological characteristics of ARDS is the massive collapse of alveolar, which results in less effective ventilatory volume [1,14]. The protective lung ventilation strategy of small tidal volume ventilation can reduce platform pressure and decrease the ventilator-associated lung injury and ARDS mortality, but it goes against the re-expansion of collapsed alveoli in patients with ARDS. Therefore, application of a certain maneuver for lung RM may promote the recruitment of collapsed alveoli, improve oxygenation, reduce intrapulmonary shunt, and even reduce mortality [14-19]. There are many common clinical types of lung RMs, including sustained inflation, sighing respiration, high-frequency oscillatory ventilation, PEEP incremental method, etc., the principles are not the same, but the ultimate goal is re-expansion of collapsed alveoli [20].

It has been more than 20 years since Lanchman first proposed the lung RM concept and applied it in clinical practice in 1992 [21]. During two decades, the lung RMs emerge in endlessly, but it is still inconclusive in both animal experiments and clinical research whether lung recruitment can improve the prognosis of patients with ARDS. In this study, lung recruitment failed to improve the patient's primary and secondary outcomes. The conclusions of previous clinical studies are also different, some studies show that lung recruitment can improve patients' clinical outcomes, such as reducing mortality in patients with ARDS and shortening hospitalization time, but another part of the studies indicate that lung recruitment can not improve the prognosis of patients with ARDS [9,10,22]. The reasons of contradictory results may be related to a variety of factors such as the different ARDS causes, severity, ventilation strategies, respirator parameter setting and the lung RMs in different studies [3,22]. Therefore, the reaction of different patients with ARDS shows high heterogeneity to lung recruitment, a certain kind of lung RM may benefit some patients, but cause excessive alveolar expansion in another part of patients and aggravate the ARDS, thus counteract the possible benefits from lung recruitment [23].

In addition, with the increasing understanding of pathophysiological mechanisms of ARDS, the researchers have found that different types of ARDS patients have different response to mechanical ventilation and drug intervention. At present, one universal classification is to divide the ARDS into pulmonary ARDS and extrapulmonary ARDS [24]. The main pathological mechanism of pulmonary ARDS is primary alveolar damage; and the main mechanism of extrapulmonary ARDS is the pulmonary capillary endothelial injury caused by extrapulmonary factors [25,26]. However, a series of studies based the classification system failed to achieve consistent conclusion in radiological manifestations, the degree of lung inflammation, reactivity to respiratory therapy, in-hospital mortality, and so on in the two subtypes of ARDS patients [27,28]. Most scholars believe that the response of extrapulmonary ARDS to lung recruitment is much better than pulmonary ARDS [29,30], and a multi-center study in 2007 shows that the pulmonary ARDS and extrapulmonary ARDS reactivity to lung recruitment are similar [31]. In this study, it was found that the inducing factors of ARDS in some patients include both pulmonary factors and extrapulmonary factors, so it is difficult to further define what subtype of ARDS patients can benefit more from lung recruitment strategy.

Although it is found in this study that the lung recruitment strategy cannot improve clinical outcomes in patients with ARDS, it is found that the lung recruitment can improve the oxygenation in patients with ARDS. PaO_2 of lung recruitment group rises gradually from D1 to D7 when compared with PaO_2 of non-lung recruitment group. And as far as the PaO_2/FiO_2 is concerned, this trend is more obvious, and the PaO_2/FiO_2 of lung recruitment group on D7 is significantly higher than that of non-lung recruitment group. This is because that in order to prevent the oxygen toxicity and pulmonary atelectasis caused by continuous high-concentration of oxygen inspiration, FiO_2 is prompt to be reduced if enough oxygenation can be maintained. Thus, the improvement of oxygenation is not necessarily embodied in the rise of PaO_2, and may also be in the reduction of FiO_2. Therefore, PaO_2/FiO_2 can more comprehensively reflect the oxygenation improvement during mechanical ventilation in patients with ARDS. A similar situation is also reported in abroad study, high PEEP, persistent lung expansion, CPAP and other lung recruitment strategies can all improve the patient's PaO_2 and improve oxygenation, and this effect is most apparent within 30 min-2 h after lung recruitment, and then gradually falls back to the levels before recruitment [8,10,32-33].

Lung recruitment not only influences the patient's oxygenation, but also has certain influence on the patients' hemodynamics. The study of Lim and others shows that implementation of lung RM can lead to real-time drop of cardiac output and mean arterial pressure, but they can return to normal after 5–15 min [34]. As the immediate effect of the lung recruitment influence on hemodynamics has been explored in foreign articles, our research focused on whether the lung recruitment has continuous influence on hemodynamics, and the results showed that 2 h after the lung RM in lung recruitment group, the hemodynamic indices were not significantly different from those of non-lung recruitment group, which indicates that the lung recruitment influence on the hemodynamics is temporary. This temporary hemodynamic change may be related to the returned blood volume decrease caused by transient intrathoracic pressure increase during lung recruitment.

To sum up, protective lung ventilation strategy combined with lung RM can improve the indicators such as PaO_2, FiO_2 and PaO_2/FiO_2 on D7, but failed to improve the final outcomes such as 28-day mortality, ICU mortality and in-hospital mortality.

Conflict of interest statement

We declare that we have no conflict of interest.

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