Clinical efficacy and safety of recruitment maneuver in patients with acute respiratory distress syndrome using low tidal volume ventilation: a multicenter randomized controlled clinical trial

XI Xiu-ming, JIANG Li, ZHU Bo and the RM group

Keywords: respiratory distress syndrome, adult; respiration, artificial; recruitment maneuver; positive-pressure respiration; randomized controlled trial

Background The recruitment maneuver (RM) has been shown to improve oxygenation in some patients with acute respiratory distress syndrome. But there is a lack of standardization and lack of clinical studies to prove the improvement on clinical outcome. We conducted this study to evaluate the clinical efficacy and safety of the RM in patients with acute respiratory distress syndrome (ARDS) using low tidal volume ventilation.

Methods We randomly assigned 110 patients with ARDS from 14 Chinese intensive care units (ICUs) at the tertiary teaching hospitals. Patients with PaO2 ≤200 mmHg at FiO2 1.0 and PEEP ≥10 cmH2O were included in the study. Patients were randomized into two groups: control group and RM group. The tidal volume was set to 6–8 ml per kilogram of predicted body weight (PBW) in both groups. RM was performed by continuous positive airway pressure (CPAP) of 40 cmH2O maintained for 40 seconds. RMs was conducted every eight hours for the first five days, or stopped within five days if the patient reached the weaning standard.

Results One hundred and ten patients had completed the requirements for the primary study goals, 55 from the RM group and 55 control patients. Baseline characteristics remained similar in the two groups. In the RM group the PaO2/FiO2 was significantly increased compared to baseline at 120 minutes after RM on day one and day two (P=0.007 and P=0.001). There were no significant differences between the RM and control group in hospital mortality (41.8% vs. 56.4%, P=0.13), 28-day mortality (29.1% vs. 43.6%, P=0.11) and ventilator-free days at day 28 (10.8±10.1 vs. 7.4±10.0, P=0.08). ICU mortality (32.7% vs. 52.7%, P=0.03), the rate of survival with unassisted breathing for at least 48 consecutive hours at day 28 (58.2% vs. 36.2%, P=0.02), and nonpulmonary organ failure-free days at day 28 (17.4±11.1 vs. 13.0±12.0, P=0.03) favored the RM group. There was no significant difference in mean blood pressure and heart rate before RM and at 30, 60, 120 minutes after RM. There was no incidence of barotraumas.

Conclusions RM was safe and useful for improving oxygenation in patients with ARDS who were ventilated with a low tidal volume, with a beneficial impact on their clinical outcome.

Methods

Patients and definitions

The study protocol was approved by the institutional review board of the ethics committee, and informed consent was obtained from each patient or next of kin. All patients admitted to the 14 Intensive Care Units (ICU) at tertiary teaching hospitals in China from March 2003 to September 2006 were screened for entry into the study.

Patients who were intubated and received mechanical ventilation were eligible for the study if they had an acute decrease in arterial oxygen (PaO2) to 200 mmHg or less (PEEP 10 cmH2O, FiO2 1.0, after 30 minutes), bilateral pulmonary infiltrates on a chest radiograph consistent with the presence of edema, and no clinical evidence of left atrial hypertension or (if measured) a pulmonary-capillary wedge pressure of 18 mmHg or less, age >18 years, and stable hemodynamics. Patients with history of acute myocardial infarction within the preceding week,
preexisting chronic respiratory insufficiency (chronic obstructive pulmonary disease, asthma, restrictive respiratory insufficiency), anatomic chest wall abnormalities, chest tube with persistent air leak, pneumothorax or bronchopleural fistula, a gross barotrauma in any form (subcutaneous emphysema, pneumomediastinum), pregnancy, malignant disease or end-stage chronic diseases, anatomical lobectomy within two weeks, bone marrow transplant or lung transplantation, chronic liver disease (as defined by Child-Pugh class C), intracranial pressure or neuromuscular disease that could impair spontaneous breathing, having been included in the same study, or participation in other studies were excluded from the study.

Randomization was achieved from computer-generated random numbers, which were then stored in sealed envelopes. The patients were randomly assigned to either the group treated with the RM and low tidal volume (RM group) or the group treated with a low tidal volume without RM (control group).

Ventilation protocol
The volume-controlled or pressure-controlled mode was requested to be used in the first 24 hours. Another ventilation mode could be chosen in the following days, but pressure support ventilation (PSV) was preferred. The tidal volume was set to 6–8 ml per kilogram of predicted body weight (PBW) to maintain plateau pressure at a level of no more than 30 cmH2O. The minimal tidal volume was 4 ml PBW. The level of PEEP were based on the patient’s underlying clinical condition to obtain an arterial oxygen saturation (SaO2) value of 90%–95% or PaO2 of 60–80 mmHg or both, with nontoxic FiO2 values of ≤0.60. The highest respiratory rate was less than 35/min allowing maintenance of partial pressure of arterial carbon dioxide (PaCO2) at a level of mild permissive hypercapnia between 45–50 mmHg or an arterial pH of 7.30–7.45.

RM
All patients were adequately sedated (Ramsay 4–5) with stable hemodynamics (systolic blood pressure 100–200 mmHg, heart rate 70–140/min) before RM. Neuromuscular blocking drugs could be used if needed. The FiO2 was set at 1.0 for five minutes. RM was performed by changing the ventilator mode to continuous positive airway pressure (CPAP) and gradually increasing the CPAP over 10 seconds to 40 cmH2O which was maintained for 40 seconds. The CPAP level then was decreased over 5 seconds and returned to the initial ventilator settings (mode, PEEP, and FiO2). RM were conducted every eight hours for the first five successive days, or stopped within five days if the patient reached the weaning standard. RM were stopped if any of the following events occurred: heart rate increased to ≥140/min or by >20/min, systolic blood pressure decreased to ≤90 mmHg or by >30 mmHg, oxyhemoglobin saturation measured by pulse oximetry (SpO2) was <90% and had decreased by >5%, or barotrauma of any form was detected by chest radiography.

Serum interleukin (IL)-6
Blood samples were obtained before randomization (day 0) and on days 3 and 5 for the measurement of serum IL-6 concentration by enzyme-linked immunosorbent assay.

Data collection
Data compiled from each patient included the followings: demographic information, clinical conditions associated with the development of ARDS, routine laboratory measurements, pulmonary physiologic and ventilatory measurements (including arterial blood gas, ventilator mode, tidal volume, PEEP, plateau pressure, peak pressure, and FiO2), chest radiographic, cardiovascular data, the number of extrapulmonary organ failures before and after randomization, complications and adverse events. Physiologic, radiographic and respiratory data were recorded from day 1 to day 5.

The primary outcome was ICU mortality. Secondary outcome variables included the number of ventilator-free days, nonpulmonary organ-dysfunction-free days from day 1 to day 28, 28-day mortality, the percentage of unassisted breathing hours for at least 48 consecutive hours, the incidence of barotrauma (defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema), or a pneumatocele that was more than 2 cm in diameter.

Statistical analysis
Statistical analysis was performed using the SAS version 8.0 (SAS Institution). The values for the IL-6 concentrations were not normally distributed so we performed log10 transformations to normalize the data to permit the application of parametric statistics. All continuous data are presented as mean ± standard deviation (SD) or median (25th–75th percentile) as appropriate. The statistical significance of the values at different time points after RM in the two groups was evaluated by repeated-measures analysis of variance models. To evaluate differences between the two groups, the Fisher exact test for categorical variables, the t test with equal variance for continuous variables, and the Mann-Whitney rank sum test for ordinal variables were used. The difference of hospital survival rate between the RM group and control group was compared by Kaplan-Meier survival analysis methods with the log-rank test. A P <0.05 was considered statistically significant.

RESULTS
One hundred and twenty-five patients were enrolled in the study; 110 patients completed data forms for the primary study goals, 55 in the RM group and 55 in the control group, 15 patients were withdrawn from the study (Figure 1). The baseline characteristics of the 110 patients were similar (Table 1).
There were no significant differences in the ventilator parameters and arterial blood gas between the two groups in the first five days (Tables 2 and 3). The PaO$_2$/FiO$_2$ ratio and PaO$_2$ showed a consistent and significant increase in both groups. The PaO$_2$/FiO$_2$ increased significantly at 120 minutes after RM on days one and two compared to baseline ($P=0.007$, $P=0.001$, respectively), but the differences became gradually smaller in the following three days (Figure 2). The mean log-transformed serum IL-6 concentration decreased from day one to day five in both groups. Serum IL-6 concentrations of inflammatory cytokines and mediators were significantly higher (17.4±11.1 vs 13.0±12.0, $P=0.03$) in the RM group compared with the control group. Slutsky et al.$^{11}$ explored the hypothesis that mechanical ventilation may play a pivotal role in the initiation and/or propagation of a systemic inflammatory response leading to multiorgan dysfunction syndrome (MODS) and have a significant effect on mortality. The improvement of organ function may play an important role in survival in ARDS patients. In addition, the data showed that the RM group had more ventilator-free days (10.8±10.1 vs. 7.4±10.0, $P=0.08$) and a significantly higher rate of survival with unassisted breathing for at least 48 consecutive hours at day 28 (58.2% vs. 36.4%, $P=0.02$). Those who were weaned may accrue an additional benefit from avoiding mechanical ventilation-induced lung injury and infection and other complications.

Recruitment is a dynamic process that refers to the opening of previously collapsed lung units that is forced by an increase in transpulmonary pressure. It avoids shear stress at the epithelium of the alveolar walls caused by the cyclic opening and closing of unstable lung units.$^{12-14}$ Other investigators have shown that lung protective ventilation strategies are associated with lower concentrations of inflammatory cytokines and mediators.

**Table 1.** Comparison of baseline characteristics between the two groups (mean ± SD or median (25th–75th percentile))

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RM group ($n=55$)</th>
<th>Control group ($n=55$)</th>
<th>$P$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>62.2±16.0</td>
<td>65.5±15.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Male ($n$ (%))</td>
<td>38 (69.1)</td>
<td>40 (72.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.5±6.7</td>
<td>23.1±8.6</td>
<td>0.28</td>
</tr>
<tr>
<td>Tidal volume (ml/kg of PBW)</td>
<td>6.6±0.9</td>
<td>6.8±1.1</td>
<td>0.39</td>
</tr>
<tr>
<td>PEEP (cmH$_2$O)</td>
<td>10.5±3.2</td>
<td>9.7±2.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Ppeak (cmH$_2$O)</td>
<td>28.0±5.9</td>
<td>27.9±6.8</td>
<td>0.94</td>
</tr>
<tr>
<td>Pplat (cmH$_2$O)</td>
<td>24.2±5.3</td>
<td>23.4±5.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>27.3±8.0</td>
<td>26.5±9.1</td>
<td>0.39</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>93.8 (68.7–150.0)</td>
<td>120.0 (88.3–140.0)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Causes of ARDS ($n$ (%))**

- Pneumonia: 19 (34.5) vs. 17 (30.9)
- Aspiration: 6 (10.9) vs. 4 (7.3)
- Sepsis: 7 (12.7) vs. 16 (29.1)
- Trauma: 2 (3.6) vs. 3 (5.5)
- Others: 21 (38.2) vs. 15 (27.3)

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Changes in mean blood pressure and heart rate were not significantly different before RM and at 30, 60, and 120 minutes after RM. RM was terminated early in only one case because of hypotension, which was transient and self-limiting after RM. No barotrauma was reported.

**DISCUSSION**

This trial did not show a significant benefit in hospital mortality and 28-day mortality. We think that this was partly due to the heterogeneity of the patients, lower post-RM PEEP level, small sample number, and for some patients, perhaps the CPAP level of RM was not high enough to open the collapsed alveolar. However, we found that the use of low tidal volume plus periodic RM improved the survival with unassisted breathing and decreased ICU mortality in ARDS patients. We ascribe the better outcome to the higher rates of weaning from the ventilator and lower rates of organ dysfunction.

The severity of organ dysfunction is an important factor in prognosis and the leading cause of death in patients with ARDS.$^{10,11}$ This trial showed that the number of days without nonpulmonary organ failure were significantly higher (17.4±11.1 vs 13.0±12.0, $P=0.03$) in the RM group compared with the control group. Slutsky et al.$^{11}$ explored the hypothesis that mechanical ventilation may play a pivotal role in the initiation and/or propagation of a systemic inflammatory response leading to multiorgan dysfunction syndrome (MODS) and have a significant effect on mortality. The improvement of organ function may play an important role in survival in ARDS patients. In addition, the data showed that the RM group had more ventilator-free days (10.8±10.1 vs. 7.4±10.0, $P=0.08$) and a significantly higher rate of survival with unassisted breathing for at least 48 consecutive hours at day 28 (58.2% vs. 36.4%, $P=0.02$). Those who were weaned may accrue an additional benefit from avoiding mechanical ventilation-induced lung injury and infection and other complications.
The table below shows the comparison of PaCO2, PaO2, PaO2/FiO2, Pplat, PEEP, and PEEP (cm H2O) between the two groups (mean ± SD). The study also shows that RM clearly improves oxygenation in some patients with ARDS, as has been demonstrated in animal models. This study shows an improvement in oxygenation two hours after RM on days 1 and 2, which demonstrated RM could improve oxygenation early in the course of treatment for patients with ARDS.

A sufficiently high level of PEEP is required to prevent lung volume loss after the recruitment maneuver. Several studies have suggested that an appropriate PEEP setting after RM should be in the range of 15–25 cmH2O to maintain the open lung. Controversy exists regarding the optimal level of PEEP. Some of the tools that have been used to define optimal PEEP levels include pressure-volume curve analysis and CT scan. However, these tests are difficult to perform at the bedside due to their complexity. In our study, the PEEP level was not specifically set and was only based on the oxygenation condition. The mean PEEP level did not seem too high. The lower post-RM PEEP level, as previously discussed, was one of the potential reasons for no improvement in hospital mortality and 28-day mortality. We think that lung compliance may have changed after RM; therefore, post-RM PEEP needs to be individualized and should not be decreased to the pre-RM PEEP level too quickly.

RM can be performed either by sustained inflation, intermittent sighs, or intermittent high levels of pressure-controlled ventilation methods. The best way to perform RM remains undetermined. The optimal pressure, length of time and periodicity may all be important parameters of RM. The method using high CPAP levels (40 cmH2O for 40 seconds) applied in this study has been demonstrated to be efficient. In some severe cases, however, CPAP with 40 cmH2O was not enough to open the collapsed lung units. They need higher pressure and longer time to get better oxygenation, perhaps with a better outcome.

It is essential to avoid potential adverse effects on cardiac function, specifically set and was only based on the oxygenation condition. The mean PEEP level did not seem too high. The lower post-RM PEEP level, as previously discussed, was one of the potential reasons for no improvement in hospital mortality and 28-day mortality. We think that lung compliance may have changed after RM; therefore, post-RM PEEP needs to be individualized and should not be decreased to the pre-RM PEEP level too quickly.

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In the blood and attenuated local and systemic cytokine response in ARDS patients. This study has shown that patients in the RM group had a reduction in plasma concentration of IL-6, although there was no significant difference between the two groups. As a consequence, we speculate that use of low tidal volume and RM may hold advantages by reducing pulmonary and systemic inflammatory responses, improving multiple organ failure, decrease the length of ventilation and reduce mortality.

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output and barotraumas caused by short periods of high intrathoracic pressures. The previous studies have demonstrated that there was a low incidence of adverse effects, moreover these effects were self-limiting and without apparent long-term sequelae.\textsuperscript{5,13,14} Although there was no occurrence of pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele, the patients should be monitored carefully in the course of RM.

In conclusion, it was safe and useful to increase oxygenation and it improved the clinical outcome for ARDS patients ventilated with a low tidal volume and RMs. In the near future, RM may be the optimal mechanical ventilation to improve the treatment of ARDS patients.

**Appendix:** The participants of the RM Group include: Dr. XI Xiu-ming (Beijing Fuxing Hospital), Dr. HANG Li (Beijing Fuxing Hospital), Dr. ZHU Bo (Beijing Fuxing Hospital), Dr. AN You-zhong (Peking University People’s Hospital), Dr. LIU Fang (Peking University People’s Hospital), Dr. WANG Chen (Beijing Chaoyang Hospital), Dr. ZHAN Qing-yuan (Beijing Chaoyang Hospital), Dr. ZHOU Jian-xin (Beijing Tiantan Hospital), Dr. QIN Ying-zhi (Tianjin Third Central Hospital), Dr. ZHANG Na-xin (Tianjin Third Central Hospital), Dr. WANG Ke-fu (Qilu Hospital of Shandong University), Dr. CHEN Xiao-mei (Qilu Hospital of Shandong University), Dr. SUN Yun-bo (Affiliated Hospital of Qingdao University Medical College), Dr. XING Jin-yan (Affiliated Hospital of Qingdao University Medical College), Dr. SONG Qing (General Hospital of Chinese People’s Liberation Army), Dr. PAN Liang (General Hospital of Chinese People’s Liberation Army), Dr. LIN Hong-yuan (First Affiliated Hospital of General Hospital of Chinese People’s Liberation Army), Dr. GUO Xu-sheng (First Affiliated Hospital of General Hospital of Chinese People’s Liberation Army), Dr. HU Zhen-jie (Forth Hospital of Hebei Medical University), Dr. ZHANG Yu-xiang (Forth Hospital of Hebei Medical University), Dr. XIU Yuan (Beijing Tongren Hospital), Dr. TIAN Zhuo-min (Tianjin People’s Hospital), Dr. JIN Tao (Tianjin People’s Hospital), Dr. LI Yuan-zhong (Dalian Municipal Central Hospital), Dr. HAN Shi-juan (Dalian Municipal Central Hospital), Dr. LIU Liu (Dalian Municipal Central Hospital), Dr. LI Gang (China-Japan Friendship Hospital), Dr. YI Li (China-Japan Friendship Hospital)

**REFERENCES**


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