A novel insight in exploring the positive end expiratory pressure for sustained ventilation after lung recruitment in a porcine model of acute respiratory distress syndrome

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Received June 23, 2015; Accepted August 8, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: The aim of the present study was to explore a novel insight to determine the positive end expiratory pressure (PEEP) for sustained ventilation after lung recruitment in an acute respiratory distress syndrome (ARDS) model. Continuous infusion of oleic acid was performed to establish an ARDS model. Pressure control ventilation (PCV) was applied for lung recruitment with PEEP of 20 cm H₂O. After lung recruitment, maneuver was changed to volume-controlled ventilation and PEEP titration were performed by decreasing PEEP gradually starting from the level of 20 cm H₂O. The optimal level of PEEP for sustained ventilation was set as the lowest PEEP until oxygen partial pressure (PaO₂) plus carbon dioxide partial pressure (PaCO₂) ≥400 mmHg. Hemodynamic and respiratory parameters at basal level, ARDS state and different levels of PEEP around the optimal PEEP were recorded. The defined optimal PEEP was 13.14 ± 1.35 cm H₂O. Respiratory parameters including intrapulmonary shunt (Qs/Qt) and arterial oxygen saturation (SaO₂) were significantly improved by various levels of PEEP for sustained ventilation after lung recruitment (P<0.05). Static compliance (Cst) and dynamic compliance (Cdyn) were also significantly increased after application of different levels of PEEP after lung recruitment (P<0.05). There was no significant statistic difference on most hemodynamic parameters (P>0.05) between various levels of PEEP. The application of different PEEP levels around the defined optimal PEEP had an obvious improvement on respiratory mechanics and gas exchange for collapsed lung tissue without influencing the hemodynamics.

Keywords: Acute respiratory distress syndrome, positive end expiratory pressure, hemodynamics, gas exchange, respiratory mechanics

Introduction

Acute respiratory distress syndrome (ARDS) has become a severe public health issue owing to its high mortality of approximately 40% [1]. Pulmonary exudative change which is the early pathological characteristic of ARDS could result in atelectasis, increased intrapulmonary shunt, gas exchange impairment and reduced lung compliance [2-4], thus positively correlated with the poor prognosis of ARDS [5]. The mechanical ventilation is a common approach to re-expand collapsed alveoli and keep it inflated for normal gas exchange, during which maintaining the optimal level of positive end expiratory pressure (PEEP) is important [6, 7]. Effective lung recruitment and sustained ventilation with the optimal PEEP after lung recruitment could improve the respiratory system by opening small airway, keeping collapsed alveoli inflated with a certain extent, increasing functional residual capacity and aerial exchange area, reducing work of breath (WOB) as well as promoting oxygenated function, pulmonary compliance and ventilation-perfusion ratio [8-11].

While the optimal PEEP for both effective lung recruitment and sustained ventilation in ARDS is still an intensively debated topic. According to the previous description, PEEP levels could be selected using the methods of the maximum
pressure-volume slope during a decremental PEEP trial after a recruitment maneuver according to the mathematical model of ARDS [12]. Following this opinion, Tugrul et al [13] displayed an easy technique to identify the best PEEP for keeping lung open after lung recruitment with stepwise decrements of 1 cm H$_2$O starting from a level of 20 cm H$_2$O PEEP in accordance with peripheral oxygen saturation. In our study we also conducted PEEP titration in volume-controlled ventilation for sustained ventilation. Previous animal study demonstrated that maximum PaO$_2$+PaCO$_2$ yielded similar values for open-lung PEEP compared to that of dynamic tidal respiratory compliance and minimum shunt. In addition, Borges et al proposed that the index PaO$_2$+PaCO$_2$ ≥400 mmHg (at 100% oxygen) was a reliable indicator for maximum lung recruitment in early ALI/ARDS [14, 15]. So we defined the PEEP level at the sum of PaO$_2$ and PaCO$_2$ ≥400 mmHg as the optimal PEEP for sustained ventilation after lung recruitment. Furthermore, we also investigated the effects of several PEEP levels around the optimal PEEP including itself on the hemodynamic and respiratory functions. The present study tried to provide a novel insight in exploring the best PEEP for keeping lung open after lung recruitment and discuss the impact of lung-recruitment maneuvers on respiratory and hemodynamics. We hope our study would provide theoretical and experimental basis for clinical treatment of ARDS.

Materials and methods

Animals

Eleven healthy male pigs with average weight of 40.19 ± 5.86 kg were provided by the animal center of Pinggu Hospital of Capital Medical University (License No.: SYXK(B) 2010-0016). Seven individuals completed the whole process while the other four animals were eliminated due to death or failure to establish the porcine ARDS model. This experiment was approved by the animal ethics committee of Beijing Shijitan Hospital which is affiliated to Capital Medical University. The care and use of experimental animals strictly followed the guidelines of the National Institute of Health (NIH).

Mechanical ventilation model

Animals were anaesthetized by intramuscular (i.m.) injection of a mixture of 3% sodium pento-barbital (30 mg/kg), ketamine (35 mg/kg) and diazepam (1.5 mg/kg) and then fixed in a supine position. Then pigs were ventilated mechanically using a capacity control model (Servo-I, Siemens, Munich, Germany) after tracheotomy, with a tidal volume ($V_t$) of 8 ml/kg, inspired fraction in oxygen (FiO$_2$) of 100%, a PEEP of 5 cm H$_2$O (1 cm H$_2$O = 0.098 kPa), a respiratory rate (f) of 40 breaths/min, the inspiratory time of 25%, inspiratory apnea of 5% and inhalation/exhalation ratio ($I:E$) of 1:2. The maintenance of anesthesia during ventilation was performed by intravenous injection with continuous infusion of pipe curium bromide (0.03 mg/kg/h), pentobarbital sodium (2 mg/kg/h) and ketamine (3 mg/kg/h). The central venous catheter (Edwards, Irvine, California, USA) and the continuous cardiac output system with pulse contour (PICCO, Pulsion Medical Systems catheter, Munich, Germany) was respectively placed into the right carotid artery and the left femoral artery. After stabilization for 30 min, the parameters both in respiratory system [PaCO$_2$, PO$_2$, oxygen delivery (DO$_2$), oxygenation index (Oi), arterial oxygen saturation (SaO$_2$), mixed venous oxygen saturation (SvO$_2$), intrapulmonary shunt (Qs/Qt), plateau airway pressure (Pplat), dynamic compliance (Cdyn), static compliance (Cst) and alveolar tidal volume (Valv)] and blood circulation system [central venous pressure (CVP), CO, intrathoracic blood volume (ITBV), global end diastolic volume (GEDV), extravascular lung water (EVLW) and systemic vascular resistance (SVR)] were recorded from the ventilator to serve as the baseline.

ARDS model

ARDS model in pigs was established by continuous infusion of oleic acid (Sigma-Aldrich inc. St. Louis, MO, USA) (0.2 ml/kg/h) that was diluted 10-folds in 0.9% normal saline into the central vein for 15 min. Arterial blood gas was analyzed by blood gas analyzer (GEM PREMIER 3000, Lexington MA, USA) at 15, 30, 60, and 90 min after infusion. When the PaO$_2$/FiO$_2$ ratio (P/F ratio) was less than 200 mmHg (1 mmHg = 0.133 kPa), the model was considered to be successfully constructed [16]. Subsequently, PaCO$_2$, PO$_2$, DO$_2$, OI, SaO$_2$, SvO$_2$, Qs/Qt, Pplat, Cdyn, Cst, Valv, CVP, CO, GEDV, ITBV, EVLW and SVR were recorded from the ventilator to serve as the ARDS state.
### Table 1. Effects of PEEP on gas exchange of ARDS models

<table>
<thead>
<tr>
<th></th>
<th>Basal value</th>
<th>ARDS state</th>
<th>Optimal P+4</th>
<th>Optimal P+2</th>
<th>Optimal P</th>
<th>Optimal P-2</th>
<th>Optimal P-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>35.31 ± 6.85</td>
<td>43.71 ± 8.49</td>
<td>46.59 ± 12.64</td>
<td>47.39 ± 11.79&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48.80 ± 11.38&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49.05 ± 13.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47.22 ± 12.03</td>
</tr>
<tr>
<td>OI (mmHg)</td>
<td>564.37 ± 158.85</td>
<td>78.71 ± 23.22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>310.83 ± 170.82&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>372.00 ± 136.00&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>338.26 ± 141.33&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>290.95 ± 65.50&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>179.20 ± 121.78&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>SaO₂ (%)</td>
<td>99.9 ± 0.053</td>
<td>88.8 ± 10.83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57.40 ± 13.70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61.30 ± 12.70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62.50 ± 12.80&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>61.80 ± 15.90&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55.00 ± 11.80&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>78.1 ± 11.8</td>
<td>48.80 ± 9.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.01 ± 5.78&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.42 ± 2.82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.28 ± 6.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.19 ± 0.38&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.78 ± 4.70&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>2.00 ± 1.32</td>
<td>21.04 ± 15.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40.1 ± 13.70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61.30 ± 12.70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62.50 ± 12.80&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>61.80 ± 15.90&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55.00 ± 11.80&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DO₂ (ml/min)</td>
<td>817.40 ± 327.87</td>
<td>424.10 ± 162.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>554.67 ± 264.24</td>
<td>562.96 ± 302.81&lt;sup&gt;a&lt;/sup&gt;</td>
<td>551.86 ± 311.92</td>
<td>460.64 ± 237.43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>427.69 ± 234.91&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

Note: PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome; OI, oxygenation index; Qs/Qt, intrapulmonary shunt; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation; DO₂, oxygen delivery. *Indicates comparing with that of basal value (P<0.05). **Indicates comparing with that of the ARDS state (P<0.05). Optimal P+4, optimal P+2, optimal P, optimal P-4 and optimal P-2 indicate different PEEP levels (optimal P+4 cm H₂O, optimal P+2 cm H₂O, optimal P, optimal P+2 cm H₂O and optimal P+4 cm H₂O).

### Table 3. Effects of PEEP on hemodynamics of ARDS models

<table>
<thead>
<tr>
<th></th>
<th>Basal value</th>
<th>ARDS state</th>
<th>Optimal P+4</th>
<th>Optimal P+2</th>
<th>Optimal P</th>
<th>Optimal P-2</th>
<th>Optimal P-4</th>
</tr>
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<tbody>
<tr>
<td>CVP (mm Hg)</td>
<td>6.57 ± 1.99</td>
<td>8.43 ± 2.82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.86 ± 1.77&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>11.57 ± 2.23&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>11.14 ± 3.08&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>10.83 ± 2.79&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.60 ± 2.07&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>CO (l/min)</td>
<td>5.21 ± 2.62</td>
<td>4.46 ± 2.57</td>
<td>3.76 ± 2.52</td>
<td>3.49 ± 2.32</td>
<td>4.06 ± 2.75</td>
<td>3.78 ± 2.57</td>
<td>3.29 ± 2.13</td>
</tr>
<tr>
<td>ITBV (ml)</td>
<td>742.57 ± 258.02</td>
<td>716 ± 252.37</td>
<td>617.29 ± 173.88</td>
<td>626.29 ± 245.93</td>
<td>643.71 ± 250.27</td>
<td>723.33 ± 287.48</td>
<td>609.40 ± 297.16</td>
</tr>
<tr>
<td>GEDV (ml)</td>
<td>594.00 ± 206.19</td>
<td>573.29 ± 202.07</td>
<td>494.14 ± 139.27</td>
<td>501.57 ± 196.52</td>
<td>514.43 ± 201.04</td>
<td>579.00 ± 229.82</td>
<td>488.00 ± 237.71</td>
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<tr>
<td>EVLW (ml)</td>
<td>421.86 ± 156.28</td>
<td>692.57 ± 252.78&lt;sup&gt;a&lt;/sup&gt;</td>
<td>687.00 ± 210.45&lt;sup&gt;a&lt;/sup&gt;</td>
<td>677.00 ± 225.44&lt;sup&gt;a&lt;/sup&gt;</td>
<td>680.29 ± 285.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>684.00 ± 359.29&lt;sup&gt;a&lt;/sup&gt;</td>
<td>600.40 ± 141.52&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SVR (dyn • s • cm⁻³)</td>
<td>1341 ± 638</td>
<td>1933 ± 1033</td>
<td>1936 ± 1178</td>
<td>2136 ± 1470</td>
<td>2170 ± 1408</td>
<td>2506 ± 1459</td>
<td>2513 ± 1440</td>
</tr>
</tbody>
</table>

Note: PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome; CVP, central venous pressure; CO, cardiac output; GEDV, global end diastolic volume; ITBV, intrathoracic blood volume; EVLW, extravascular lung water; SVR, systemic vascular resistance. *Indicates comparing with that of basal value (P<0.05). **Indicates comparing with that of the ARDS state (P<0.05). Optimal P+4, optimal P+2, optimal P, optimal P-4 and optimal P-2 indicate different PEEP levels (optimal P+4 cm H₂O, optimal P+2 cm H₂O, optimal P, optimal P+2 cm H₂O and optimal P+4 cm H₂O).
Table 2. Effects of PEEP on respiratory mechanics of ARDS models

<table>
<thead>
<tr>
<th></th>
<th>Basal value</th>
<th>ARDS state</th>
<th>Optimal P+4</th>
<th>Optimal P+2</th>
<th>Optimal P</th>
<th>Optimal P-2</th>
<th>Optimal P-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP (cm H(_2)O)</td>
<td>5.00 ± 0.00</td>
<td>5.00 ± 0.00</td>
<td>17.29 ± 1.38</td>
<td>15.29 ± 1.38</td>
<td>13.14 ± 1.35</td>
<td>11.33 ± 1.37</td>
<td>9.40 ± 1.52</td>
</tr>
<tr>
<td>Pplat (cm H(_2)O)</td>
<td>13.47 ± 1.13</td>
<td>21.86 ± 6.96(^a)</td>
<td>33.71 ± 3.68(^b)</td>
<td>30.86 ± 3.34(^ab)</td>
<td>28.14 ± 3.24(^a)</td>
<td>26.83 ± 4.22(^b)</td>
<td>23.80 ± 1.64(^*)</td>
</tr>
<tr>
<td>Cdyn (ml/cm H(_2)O)</td>
<td>38.14 ± 6.72</td>
<td>14.43 ± 5.50(^*)</td>
<td>17.43 ± 3.30(^*)</td>
<td>19.14 ± 4.45(^*)</td>
<td>20.57 ± 5.59(^*)</td>
<td>18.00 ± 5.22(^*)</td>
<td>17.00 ± 4.30(^*)</td>
</tr>
<tr>
<td>Cst (ml/cm H(_2)O)</td>
<td>38.89 ± 7.81</td>
<td>16.64 ± 2.37(^*)</td>
<td>21.07 ± 5.94(^*)</td>
<td>22.00 ± 6.12(^*)</td>
<td>24.13 ± 7.18(^*)</td>
<td>21.95 ± 5.20(^*)</td>
<td>20.74 ± 3.08(^*)</td>
</tr>
<tr>
<td>Valv (ml)</td>
<td>146.11 ± 45.43</td>
<td>92.06 ± 35.22(^*)</td>
<td>98.23 ± 37.51(^*)</td>
<td>111.79 ± 42.63(^*)</td>
<td>109.86 ± 44.06(^*)</td>
<td>99.3 ± 38.82(^*)</td>
<td>98.76 ± 41.59(^*)</td>
</tr>
</tbody>
</table>

Note: PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome; Pplat, plateau airway pressure; Cst, static compliance; Cdyn, dynamic compliance; Valv, alveolar tidal volume. * indicates comparing with that of basal value (P<0.05). \(^a\) indicates comparing with that of the ARDS state (P<0.05). optimal P+4, optimal P-2, optimal P, optimal P+4 and optimal P-2 indicate different PEEP levels (optimal P+4 cm H\(_2\)O, optimal P-2 cm H\(_2\)O, optimal P, optimal P+2 cm H\(_2\)O and optimal P+4 cm H\(_2\)O).

Recruitment maneuvers

After establishing ARDS state, animals were stabilized for 15 minutes on the following settings before recruitment maneuvers: pressure control ventilation (PCV), peak inspiratory pressure (PIP) of 35 cm H\(_2\)O, PEEP of 20 cm H\(_2\)O, inspiratory time of 0.6 s, respiratory frequency of 40 breaths/min, and FiO\(_2\) of 100%. Then the lung recruitment strategy was performed on all the animals following the previous description [17]. Briefly, PEEP was set to 20 cm H\(_2\)O and pressure control set to a PIP of 40 cm H\(_2\)O, and then the full lung recruitment was defined as PaO\(_2\) + PaCO\(_2\) > 400 mmHg. However, if the sum of PaO\(_2\) and PaCO\(_2\) was less than 400 mmHg, the PEEP level was kept unchanged and the airway pressure was increased with 5 cm H\(_2\)O each time while not exceeded 50 cm H\(_2\)O until the sum of PaO\(_2\) and PaCO\(_2\) were above 400 mmHg.

PEEP titration

After lung recruitment, mechanical ventilation mode was changed to volume-controlled ventilation with a \(V\_i\) of 8 ml/kg and respiratory frequency of 40 breaths/min. PEEP titration were performed by decreasing PEEP gradually starting from the level of 20 cm H\(_2\)O to 0 cm H\(_2\)O with a decrement of 2 cm H\(_2\)O for 10 min in each step. The optimal PEEP (optimal P) was defined as the lowest PEEP maintaining the sum of PaO\(_2\) and PaCO\(_2\) ≥ 400 mmHg.

Measurements

After setting the optimal PEEP, several hemodynamic and respiratory parameters including CO, GEDV, ITBV, PaCO\(_2\), PO\(_2\), Qs/Qt, Pplat, Cdyn, Cst and other parameters were recorded at the optimal PEEP level, 2 cm H\(_2\)O above optimal P level (optimal P+2 level), 4 cm H\(_2\)O above optimal P level (optimal P+4 level), 2 cm H\(_2\)O below optimal P level (optimal P-2 level) and 4 cm H\(_2\)O below optimal P level (optimal P-4 level), respectively.

Statistical analysis

Data were presented as mean ± standard deviation (SD). Statistical comparisons were conducted by a one-way analysis of variance (ANOVA), followed by a Student-Newman-Keuls multiple comparison test using SPSS 19.0 software (IBM-SPSS, Inc, Armonk, NY, USA). A P<0.05 indicated that the difference was significant.

Results

PEEP levels

After PEEP titration, the defined optimal PEEP was 13.14 ± 1.35 cm H\(_2\)O and the level in other four conditions around optimal P were 15.29 ± 1.38 cm H\(_2\)O (optimal P+2 level), 17.29 ± 1.38 cm H\(_2\)O (optimal P+4 level), 11.33 ± 1.37 cm H\(_2\)O (optimal P-2 level) and 9.40 ± 1.52 cm H\(_2\)O (optimal P-4 level), respectively.

Effects of different levels of PEEP on gas exchange

The effects of different PEEP levels around optimal PEEP on gas exchange in ARDS model were exhibited in Table 1. \(\Omega_l\), SaO\(_2\), SvO\(_2\), Qs/Qt and DO\(_2\) in ARDS state were deteriorated significantly compared to the baseline (P<0.05). PaCO\(_2\) showed an indistinctive increase between the ARDS state and the baseline, after application with different levels of PEEP it still continuously increased and showed a statistical difference at optimal P, optimal P+2 and optimal P-2 level compared to the baseline (P<0.05).
SaO$_2$ and Qs/Qt were greatly improved by PEEP titration ($P<0.05$) compared to ARDS state and both of them returned to the baseline. There was also an obvious improvement of OI compared to ARDS state by PEEP ventilation ($P<0.05$), while it was still significantly lower than that of the baseline ($P<0.05$). Furthermore, it seemed that the application with PEEP had no obvious effects on DO$_2$ following the results. A significant improvement in SvO$_2$ was only observed at the optimal P level ($P<0.05$).

**Effects of different levels of PEEP on respiratory mechanics**

The results of different PEEP levels on respiratory mechanics were presented in Table 2. Cdyn, Cst and Valv in ARDS state were deteriorated significantly than the baseline ($P<0.05$). After ventilation with different levels of PEEP, Cdyn and Cst increased compared to ARDS state, while the obvious improvement only occurred at the optimal P level ($P>0.05$). Valv was also improved by application of the PEEP, moreover in optimal P+2 and optimal P levels it showed no significant difference with the baseline ($P>0.05$).

Pplat in ARDS state was obviously higher than that of the baseline ($P<0.05$). However, it also increased after PEEP ventilation and showed a dramatic increment in the optimal P+2 and optimal P+4 level ($P<0.05$).

**Effects of different levels of PEEP on hemodynamics**

As illustrated in Table 3, most parameters in blood circulation system including GEDV, ITBV, CO and SVR changed indistinctively during the whole process ($P>0.05$). While there was a statistical difference in CVP between the baseline and the ARDS state ($P<0.05$). Even though after application of PEEP ventilation, CVP was still significantly higher than that of the basal value and the ARDS state ($P<0.05$). In addition, EVLW in the ARDS state was dramatically higher than that of the baseline, even if various PEEP levels were applied afterward ($P<0.05$).

**Discussion**

The application of recruitment maneuvers is considered an effective strategy to open collapsed lung units, but the open state of lung units should be kept with high PEEP levels to avoid excessive stretching and hemodynamic impairment [18]. Due to the great importance of selecting an appropriate PEEP level after lung recruitment, several studies have concentrated on these issues and gained numerous achievements. Tugrul et al [13] displayed an easy technique to identify the optimal PEEP for sustained inflation after lung recruitment with performing a PEEP titration of 1 cm H$_2$O stepwise decrements starting from a level of 20 cm H$_2$O PEEP. In the present study the optimal PEEP was selected using this strategy in volume-controlled ventilation. In addition, previous study showed that PaO$_2$+PaCO$_2$ ≥400 mmHg could be set as an indicator for maximum lung recruitment in early ARDS [15]. Then we defined the optimal P for keeping the lung open after lung recruitment as the sum of PaO$_2$ and PaCO$_2$ ≥400 mmHg. Furthermore, we detected the effects of the optimal P and other different PEEP levels around the optimal P on hemodynamics, gas change and respiratory mechanics.

ARDS is always involved in the deterioration on gas exchange arising from the alveolar collapse and alveolar recruitment while PEEP has positive effects on gas exchange and lung mechanics [2]. Following the results in the present study, lower Qs/Qt, higher SaO$_2$, SvO$_2$ and OI after application of the PEEP levels around the optimal PEEP compared to ARDS state were observed. Studies have indicated that it is essential to maintain adequate dissolved oxygen in blood circulation to the peripheral tissues in ARDS patients [19] and the lower oxygen saturation was related with low survival rate in the clinical practice [20]. The increase of SaO$_2$, SvO$_2$ and OI showed the improvement on oxygen delivery with the post inflation PEEP levels around the optimal PEEP in ARDS. Furthermore, the decrease of Qs/Qt is an indicative of the reduction of intrapulmonary shunt, while the development of ARDS is always associated with increased intrapulmonary shunt [21, 22]. All these results indicated the improvement on gas exchange after application of the PEEP levels around the optimal PEEP for keeping the lung open after lung recruitment. There was also an increase in PaCO$_2$ after PEEP ventilation, the elevation of PaCO$_2$ level is always considered as a direct sign of alveolar over inflation, however, the effects of metabolic CO$_2$.
Hemodynamic and respiratory effects of PEEP

production could not be excluded in our study [23].

As it was noted previously, the respiratory compliance is an essential indicator for monitoring the recruitment of collapsed lung units [24] and an increase in compliance is tightly associated with the improvement of lung collapse [25]. Numerous studies reported that the appropriate PEEP level for sustained inflation after lung recruitment should effectively increase the compliance, thus the selection of PEEP level has been widely used based on the optimum compliance in clinical practice [13, 26-30]. Our study showed that PEEP ventilation after lung recruitment around the optimal PEEP could benefit the respiratory mechanics because both Cst and Cdyn increased significantly after PEEP application compared to ARDS state. However, Cst and Cdyn did not recover to the baseline. The lower level of Cst and Cdyn might be involved in the change of lung elasticity caused by several factors such as surfactant inactivation [31].

Since the impact of lung-recruitment maneuvers on hemodynamics remains controversial, we also detected the effects of different PEEP levels for post inflation around the optimal PEEP on hemodynamics. Several studies [13, 32, 33] showed that there were few hemodynamic side effects caused by recruitment maneuvers, while Nielsen et al [34] indicated that lung recruitment maneuvers in ARDS significantly decreased left-ventricular end-diastolic volume and cardiac output (CO) at hypovolemia, meanwhile during the maneuver a marked right-ventricular dysfunction also be found. Though there was an abnormal increase of CVP which might be caused by increased pressure within the chest cavity and resistance to venous return with high level of PEEP [35], most of hemodynamic parameters including CO, ITBV, GEDV and SVR showed indistinctive changes during the whole experiment. These results indicated PEEP ventilation seemed to have no influence on hemodynamics which were consistent with previous studies [13, 36, 37]. Moreover, there was not PEEP induced ventricular dysfunction since there were few changes of CO. During a disease such as ARDS, EVLW would increase [28] that was also observed in the ARDS state of our study. This increase could cause the airway and lung parenchyma collapse and lead to deterioration in gas exchange which is indicated by the low oxygenation index (PaO$_2$/FiO$_2$) [28]. There were inconsistent results of the PEEP influencing on the EVLW. Slutsky et al showed that PEEP could open part of collapsed lung and significantly reduce EVLW in the patients with high permeability pulmonary edema [18]. However, our study displayed that the application of PEEP (less than 20 cm H$_2$O) did not affect EVLW induced by ARDS. These contradictory results may be caused by the heterogeneity of ARDS.

There were several limitations in the present study. Firstly, our strategy for defining the optimal P for sustained inflation after lung recruitment is not deduced by the mathematic model but based on the previous description. Moreover, the PEEP titration was conducted only within 20 cm H$_2$O PEEP. Secondly, the number of experimental animals was relatively small and the study duration was insufficient. However, the present study provided a novel insight in exploring the best PEEP for keeping lung open after lung recruitment and the effects on gas exchange and respiratory mechanics would provide a definite evidence for the improvement of the ARDS with the application of PEEP levels around the optimal PEEP after lung recruitment. Certainly, more and deeper explorations on recruitment maneuver should be conducted in the future.

In conclusion, the application of different PEEP levels around the defined optimal PEEP had an obvious improvement on respiratory mechanics and gas exchange for collapsed lung tissue without influencing the hemodynamics. Our study would provide a novel insight in exploring the best PEEP for keeping lung open after lung recruitment.

Acknowledgements

This study was supported by National Natural Science Foundation of China (No. 81372043).

Disclosure of conflict of interest

None.

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Hemodynamic and respiratory effects of PEEP


