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Original Article

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ABSTRACT

Objective: To investigate the effect of positive end-expiratory pressure (PEEP) on right heart function in mechanically ventilated patients using bedside ultrasonography

Design: Retrospective study

Setting: Department of Emergency Medicine, the First Affiliated Hospital of Anhui Medical University, Hefei, China

Subjects: Eighteen patients who received mechanical ventilation between December 2014 and May 2016

Interventions: Different levels of PEEP were applied to patients to achieve appropriate PaO2 levels.

Main outcome measures: Indices of right heart function was assessed at three different PEEP levels, ≤5 cm H2O, 5-10 cm H2O or ≥10 cm H2O. Indices included preload assessment by measurement of the area of the right atrium (RA), the diameter of the inferior vena cava (IVC) and measurement of the central venous pressure (CVP); afterload was assessed by estimation of the pulmonary vessel resistance (PVR); right ventricular systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE).

Results: The IVC diameter and the CVP increased as PEEP levels increased (14.5 ± 2.2 vs. 16.9 ± 1.4 vs. 22.6 ± 2.4; 7.1 ± 1.1 vs. 7.9 ± 1.3 vs. 13.2 ± 2.0); the RA area decreased at the same time (36.6 ± 2.9 vs. 32.1 ± 2.0 vs. 25.3 ± 3.8). These changes were statistically significant. PVR and TAPSE changed significantly at higher levels of PEEP (p <0.05). PEEP levels positively correlated with the IVC diameter and the PVR, and negatively correlated with TAPSE; coefficients of determination were 0.644, 0.759, and 0.628, respectively.

Conclusions: The application of PEEP decreased the preload and increased the afterload of the right heart. Right ventricular contractility decreased significantly at higher levels of PEEP.

KEYWORDS: PEEP, ultrasound, mechanical ventilation, heart function

INTRODUCTION

It is important to stabilize cardiopulmonary function in critically ill patients. Cardiopulmonary interactions may be influenced by intermittent positive pressure ventilation through alterations in intrathoracic pressure[1]. The effect of tide volume variation on intrathoracic pressure and cardiac function has been previously reported[2]. However, there are few reports on the effect of positive end-expiratory pressure (PEEP) on cardiac function, especially that of the right heart. PEEP is
widely used during mechanical ventilation (MV). Historically, the effect of PEEP on left heart function has been studied more than its effect on right heart function. The pathophysiology of right ventricular failure includes increased afterload and reduced right ventricular contractility\cite{3,4}. The venous return may decrease due to high intrathoracic pressures generated during positive pressure ventilation leading to a fall in right ventricular output\cite{5,6}. The application of PEEP may further reduce preload; however, it leads to an increase in the pulmonary vascular resistance (PVR) and increases afterload. Hence, it is important to assess the effect of PEEP on right heart function.

Ultrasound plays a key role in the evaluation of cardiac function. Historically, invasive techniques including the Swan-Ganz catheter were the main monitoring tools used to detect cardiac function in critically ill patients\cite{7}. However, being invasive, it carries potential risks, and cannot be applied in all critically ill patients. Recently, bedside-ultrasonography has been widely used in the assessment of critically ill patients, especially to evaluate cardiac function\cite{8,9}. Previous studies have demonstrated the accuracy of bedside-ultrasonography and shown good correlation with invasive monitoring\cite{10,11}.

There are few studies that focus on the effect of PEEP on right heart function. We aimed to assess the influence of different levels of PEEP on right heart function by bedside ultrasonographic evaluation.

**SUBJECTS AND METHODS**

**Patients**

We included 18 patients who received MV in our unit between December 2014 and May 2016. Twelve patients were diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin definition\cite{12}. The other six patients had respiratory failure due to poisoning with anticholinesterase insecticide. All patients had acute respiratory failure with no previous history of cardiovascular or pulmonary disease and required MV because of severe hypoxemia. Midazolam, sufentanil, and etomidate were administered for tracheal intubation and to attain ventilator synchrony as required. During the course of this study, all patients remained hemodynamically stable and did not need vasopressors. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Anhui Medical University. Written informed consent was obtained from all participants or their guardians.
Ventilator settings

MV was carried out in the synchronized intermittent mandatory ventilation (SIMV) mode initially using standard ventilators (Puritan Bennett 760, Covidien, USA); all patients were in the weaning phase.

We used PEEP with every mode, at a baseline level of 5 cm H\(_2\)O or less. For a sustained oxygen saturation greater than 90\%, the level of PEEP was increased step by step from a low (5 cm H\(_2\)O) to a sufficient level. The fractional inspired oxygen concentration (FiO\(_2\)), and the PEEP levels were selected according to a PEEP-FiO\(_2\) table (Table 1). Depending on the response, the PEEP level was increased gradually, to a maximum limit of 15 cm H\(_2\)O. The PEEP level was classified as \(\leq 5\) cm H\(_2\)O, 5 - 10 cm H\(_2\)O or \(\geq 10\) cm H\(_2\)O.

Ultrasonographic assessment

Echocardiographic evaluation was carried out in all patients prior to the initiation of MV and at different levels of PEEP using a Sonosite MAXX machine (Sonosite, Seattle, USA) equipped with 2.5- and 3.5-MHz transducers. Studies were carried out with the patient in the supine position. We evaluated right heart function based on three types of indices.

**The preload indexes:** The area of the right atrium (RA) was measured by echocardiographic imaging at end-diastole in the apical view. The diameter of inferior vena cava (IVC) was measured in the subcostal view to estimate RA pressure.

**The afterload indexes:** The PVR was estimated from the peak tricuspid regurgitant velocity (TRV) and the right ventricular outflow tract time-velocity integral (TVI\(_{RVOT}\)) in accordance with published guidelines\(^{[13]}\), using the equation, PVR = \((TRV/TVI_{RVOT}) \times 10^{+0.16}\). Color-flow Doppler examination was used to screen for the presence of valvular regurgitation in apical windows.

**The index of right heart systolic function:** We estimated tricuspid annular plane systolic excursion (TAPSE) in real time. On M-mode, the cursor was passed through the lateral tricuspid annulus in the apical 4-chamber view. TAPSE was estimated by measurement of the extent of longitudinal motion of the lateral tricuspid annulus at peak systole\(^{[14]}\).

Statistical analysis

Statistical analyses were performed by using the SPSS 16.0 statistical software. Data are expressed as means ± SD unless otherwise specified. Repeated measure analysis at different PEEP levels was done using the one-way ANOVA. The correlation of different PEEP levels with
IVC, PVR and TAPSE are shown as scatterplots. The coefficients of determination were analyzed. A p-value <0.05 was considered as statistically significant.

RESULTS

Baseline patient characteristics

We enrolled 18 patients in this study. Twelve patients underwent mechanical ventilation for ARDS secondary to pneumonia, severe acute pancreatitis, or severe sepsis. The other 6 patients were diagnosed with acute pulmonary edema or acute respiratory failure secondary to organophosphorus pesticide poisoning. The highest levels of PEEP ranged from 12 to 15 cm H$_2$O (13.1 ± 1.3). The duration of ventilation ranged from 6 to 20 days (9.8 ± 4.5). The Apache II scores ranged from 20 to 36 (26.1 ± 5.1). Table 2 shows baseline patient characteristics.

Arterial blood gas analysis and pulmonary mechanics

All patients had severe hypoxemia with a low PaO$_2$/FiO$_2$ ratio at baseline. The PaO$_2$ and PaO$_2$/FiO$_2$ ratios improved with increasing levels of PEEP. However, the peak inspiratory pressure (PIP) and the plateau pressure (Pplat) also increased as the PEEP levels increased (25.3 ± 8.2 vs. 28.9 ± 6.3 vs. 33.2 ± 5.6; 20.1 ± 3.8 vs. 25.4 ± 4.3 vs. 29.7 ± 4.6); these changes were statistically significant (p <0.05) (Table 3).

Preload indexes

The IVC diameter and the central venous pressure (CVP) increased with increasing PEEP levels (14.5 ± 2.2 vs. 16.9 ± 1.4 vs. 22.6 ± 2.4; 7.1 ± 1.1 vs. 7.9 ± 1.3 vs. 13.2 ± 2.0), and the RA area decreased with increasing PEEP (36.6 ± 2.9 vs. 32.1 ± 2.0 vs. 25.3 ± 3.8). The change in IVC diameter and the RA area were statistically significant (P <0.05).

Afterload index

The PVR increased from 2.4 ± 0.2 Wood units (WU) at baseline (PEEP ≤5 cm H$_2$O) to 2.6 ± 0.2 WU (PEEP 5–10 cm H$_2$O). The changes were not statistically significant. When the PEEP level reached >10 cm H$_2$O, the PVR was significantly higher by 3.7 ± 0.3 WU compared to baseline and lower PEEP levels.
Right ventricular function

TAPSE decreased with increasing levels of PEEP; however, there was no significant difference between baseline (PEEP ≤5 cm H2O) and lower levels of PEEP (5–10 cm H2O). TAPSE decreased significantly at PEEP levels of >10 cm H2O (17.2 ± 2.5 vs. 16.3 ± 2.5 vs. 11.1 ± 1.6), (P <0.01) (Table 4).

Correlation analysis

The correlation between IVC, PVR, TAPSE, and PEEP levels are shown as scatterplots. PEEP levels showed a positive correlation with IVC and PVR and a negative correlation with TAPSE. The central line in the scatterplot is the regression line, the two lines on either side of the regression line are 95% CI of individual predicted values. The coefficients of determination were 0.644, 0.759, and 0.628 respectively (Figure 1).

DISCUSSION

The patients in our study had ARDS and acute lung edema secondary to underlying disease. PEEP can prevent cyclic opening and collapse of alveoli by maintaining the alveolar pressure at end expiration[15]. PEEP may influence cardiac output, especially that of the left ventricle, through changes in intrathoracic pressure[16]. Due to its anatomical characteristics, right ventricular changes during positive pressure ventilation are less noticed compared with those of the left ventricle. As the output from the right ventricle flows into the pulmonary arteries, changes in intrathoracic pressure may influence right ventricular output through alterations in preload, afterload, and right ventricular systolic function. We used ultrasonography to verify this hypothesis.

Our patients were on MV for variable periods of time. The duration of ventilation in patients with poisoning was shorter than that in ARDS patients. There were more female patients with poisoning, which may be peculiar to China. PaO2 and PaO2/FiO2 ratios were significantly lower than normal in all patients. PIP and Pplat increased as the PEEP level increased, leading to high ventilation pressures.

CVP denotes the pressure within the RA, besides reflecting the volume status. A change in the CVP level can influence the diameter of the IVC[17]. In previous studies, the prognostic value of the IVC diameter was similar to that of RA pressure[18,19]. In our study, the CVP levels and the IVC diameter were significantly different in groups with different PEEP levels. The increase in
IVC diameter showed a positive correlation with the PEEP level. The mechanism of this phenomenon may be as reported by Jellinek et al.\textsuperscript{[20]} They demonstrated that positive airway pressure equally increases the mean systemic filling pressure and the RA pressure in humans and alters venous return without changes in the pressure gradient. In our opinion, the reduction in RA area may reduce the preload to the right heart. PEEP may increase the intrathoracic pressure, leading to compression of the RA and reduction of its area. The reduction in RA area was more obvious in the high PEEP group (>10 cm H\textsubscript{2}O). As reported previously\textsuperscript{[21]}, we noted a decrease in atrial volumes in systole and diastole with positive pressure ventilation, with atrial volumes decreasing relatively more than ventricular volumes. The absolute and relative decrease in RA volumes were higher compared to LA volumes. Therefore, the influence of PEEP on RA preload may be significant.

PVR is considered to constitute the right ventricular afterload. It is a concept that relates to the pressure needed to drive blood across the lungs to the pulmonary circulation. The resistances of large and small arteries, the pulmonary microcirculation, and the veins are the main contributors to PVR. Several factors can contribute to changes in PVR. In ARDS, PVR is elevated due to hypoxic vasoconstriction and tortuosity of the medium and large intrapulmonary blood vessels\textsuperscript{[22]}. PEEP affects PVR by compression of intra-alveolar capillaries by over expanded alveoli\textsuperscript{[23]}. The reservoir-wave model suggested that there was a small increase in microcirculatory resistance with the application of PEEP\textsuperscript{[24]}. The present study demonstrated that PVR increased significantly at PEEP levels of >10 cm H\textsubscript{2}O. However, the difference in PVR between PEEP levels of ≤5 cm H\textsubscript{2}O and 5–10 cm H\textsubscript{2}O was not significant. These results may indicate that compression of intra-alveolar capillaries and increase in microcirculatory resistance became significant at PEEP levels of >10 cm H\textsubscript{2}O.

The change in right ventricular function or contractility was less compared to preload and afterload changes of the right heart during mechanical ventilation. The right ventricular perfusion is dependent on the gradient between aortic pressure and the right ventricular systolic pressure; it is also influenced by the intrathoracic pressure. High levels of PEEP can worsen right ventricular ischemia\textsuperscript{[25]}. A previous study demonstrated that the right ventricular free wall showed dyssynchronous contraction at the highest PEEP level reached on assessment by speckle tracking echocardiography. TAPSE is a better, non-invasive index of right ventricular function. It provides information not only on the emptying of the right ventricle but also on the driving force which acts on the systemic venous column because systolic shortening of the right ventricle
occurs from base to apex. In our study, TAPSE decreased significantly at PEEP levels of >10 cm H$_2$O. The scatterplot revealed that the decrease in TAPSE correlated with increasing PEEP levels. This suggests that right ventricular contractility may be influenced by higher levels of PEEP.

Limitations

There are several limitations to our study. First, our study was limited to two main disease processes. Previous studies have shown that PVR may be higher than normal in the early stage of ARDS\cite{21}. Besides, organophosphorus pesticide poisoning could result in myocardial injury\cite{26}. These two factors could have contributed to the variability observed in the results. However, a clear correlation was observed between right heart function and the level of PEEP. A larger sample size is required to confirm our findings. Second, although bedside ultrasound is a convenient, non-invasive technique of hemodynamic assessment in critically ill patients, it has some limitations. A reliable ultrasonographic assessment depends on several factors including patient condition, the use of MV, and individual proficiency in carrying out the examination.

CONCLUSIONS

We demonstrated in our study that right heart function could be reliably assessed by bedside ultrasonography. The application of PEEP decreased the preload and increased the afterload of the right heart. Right ventricular contractility decreased significantly at higher levels of PEEP.

ACKNOWLEDGMENT

Conflicts of interest: The authors declare no conflict of interest.

REFERENCES


FIGURE LEGENDS

**Fig 1:** The PEEP correlations with IVC, PRV and TAPSE. (A) The correlation between PEEP with IVC (coefficient of determination=0.644); (B) The correlation between PEEP with PRV (coefficient of determination=0.759); (C) The correlation between PEEP with TAPSE (coefficient of determination=0.628)
### Table 1: PEEP-FiO₂ adjustment form

<table>
<thead>
<tr>
<th>Index</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP (cmH₂O)</td>
<td>5 5 8 8 10 10 12 14 14 14 16 18 18-24</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.3 0.4 0.4 0.5 0.5 0.6 0.7 0.7 0.8 0.9 0.9 0.9 1.0</td>
</tr>
</tbody>
</table>

Note: 1 cmH₂O = 0.098 kPa

### Table 2: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Gender / age</th>
<th>Diagnosis/reason for intubation</th>
<th>Highest level of PEEP (cmH₂O)</th>
<th>Time of MV</th>
<th>Apache II score</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/56</td>
<td>Pneumonia/ARDS</td>
<td>12</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>M/32</td>
<td>Pneumonia/ARDS</td>
<td>12</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>F/30</td>
<td>SAP/ARDS</td>
<td>15</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>M/45</td>
<td>Pneumonia/ARDS</td>
<td>14</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>F/28</td>
<td>SAP/ARDS</td>
<td>12</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>M/50</td>
<td>Severe sepsis/ARDS</td>
<td>12</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>F/62</td>
<td>Pneumonia/ARDS</td>
<td>15</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>M/48</td>
<td>SAP/ARDS</td>
<td>12</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>F/54</td>
<td>Pneumonia/ARDS</td>
<td>15</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>M/60</td>
<td>Severe sepsis/ARDS</td>
<td>14</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>F/40</td>
<td>SAP/ARDS</td>
<td>12</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>F/46</td>
<td>Pneumonia/ARDS</td>
<td>15</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>F/32</td>
<td>AOPP/acute pulmonary edema</td>
<td>12</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>F/40</td>
<td>AOPP/acute pulmonary edema</td>
<td>14</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>F/32</td>
<td>AOPP/acute pulmonary edema</td>
<td>12</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>M/38</td>
<td>AOPP/acute respiratory failure</td>
<td>14</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>F/35</td>
<td>AOPP/acute respiratory failure</td>
<td>12</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>M/50</td>
<td>AOPP/acute pulmonary edema</td>
<td>12</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

SAP: severe acute pancreatitis; AOPP: acute organophosphorus pesticide poisoning
### Table 3: Arterial blood gas and pulmonary mechanics at different PEEP levels (cmH_2O)

<table>
<thead>
<tr>
<th>Patients indexes</th>
<th>PEEP≤5</th>
<th>5&lt;PEEP≤10</th>
<th>10&lt;PEEP≤15</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO_2 (mmHg)</td>
<td>47 ± 12</td>
<td>55 ± 10’</td>
<td>66 ± 13#</td>
</tr>
<tr>
<td>PaCO_2 (mmHg)</td>
<td>42 ± 11</td>
<td>40 ± 12</td>
<td>41 ± 11</td>
</tr>
<tr>
<td>PaO_2/FiO_2</td>
<td>78 ± 10</td>
<td>112 ± 13’</td>
<td>180 ± 18#</td>
</tr>
<tr>
<td>PIP (cmH_2O)</td>
<td>25.3 ± 8.2</td>
<td>28.9 ± 6.3’</td>
<td>33.2 ± 5.6#</td>
</tr>
<tr>
<td>Pplat (cmH_2O)</td>
<td>20.1 ± 3.8</td>
<td>25.4 ± 4.3’</td>
<td>29.7 ± 4.6#</td>
</tr>
</tbody>
</table>

Compared with PEEP≤5, *P<0.05; #P<0.01

### Table 4: Right heart function at different PEEP levels (cmH_2O)

<table>
<thead>
<tr>
<th>Right heart indexes</th>
<th>PEEP≤5</th>
<th>5&lt;PEEP≤10</th>
<th>10&lt;PEEP≤15</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA area (cm^2)</td>
<td>36.6 ± 2.9</td>
<td>32.1 ± 2’</td>
<td>25.3 ± 3.8#</td>
</tr>
<tr>
<td>IVC (mm)</td>
<td>14.5 ± 2.2</td>
<td>16.9 ± 1.4’</td>
<td>22.6 ± 2.4#</td>
</tr>
<tr>
<td>CVP (cmH_2O)</td>
<td>7.1 ± 1.1</td>
<td>7.9 ± 1.3’</td>
<td>13.2 ± 2#</td>
</tr>
<tr>
<td>PVR</td>
<td>2.4 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>3.7 ± 0.3#</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>17.2 ± 2.5</td>
<td>16.3 ± 2.5</td>
<td>11.1 ± 1.6#</td>
</tr>
</tbody>
</table>

IVC: the diameter of inferior vena cava; CVP: center vessel pressure; PVR: pulmonary vessel pressure; TAPSE: tricuspid annular plane systolic excursion. Compared with PEEP≤5, *P<0.05; #P<0.01