Hemodynamic and Respiratory Effects of Positive End-expiratory Pressure during a Pulmonary Distress Model in Isoflurane Anesthetized Swine

Ruben Lundgren Cavalcanti, Priscila Beatriz da Silva Serpa, & Cláudio Corrêa Natalini

ABSTRACT

Background: Several pulmonary and hemodynamic complications may occur during mechanical ventilation of the lungs. The use of a positive end-expiratory pressure (PEEP) can improve oxygenation and prevent atelectasis, although this method can cause important hemodynamic side effects. Mostly, these hemodynamic effects are due to increased airway pressure that is transferred to the intrapleural space, increasing the intrathoracic pressure, which decreases venous return to the heart. Cardiac output is significantly reduced with high PEEP levels which in turn precludes the improvement effects on blood oxygenation. The aim of this study was to evaluate hemodynamic and respiratory effects of different levels of carbon dioxide insufflations associated with different levels of PEEP under conventional two-lung ventilation in isoflurane anesthetized pigs.

Materials, Methods & Results: Twelve juvenile pigs were anesthetized with ketamine and midazolam, and end tidal isoflurane 2.0 V% for maintenance. Animals were submitted to tension pneumothorax through an acute intrathoracic insufflation with carbon dioxide at 0, 5, and 10 mmHg. Mechanical lung ventilation with 100% oxygen was started with zero PEEP then increased to 5 and 10 cmH₂O. Ventilatory, respiratory and hemodynamic parameters were measured, as well as blood gases. Tension pneumothorax of 10 mmHg, with both PEEP levels, induced a significant decrease in cardiac index, stroke volume, right ventricular stroke work index, dynamic compliance, arterial pH, arteriovenous oxygen difference, arterial blood pressure, in addition to significance increase in heart rate. Moreover, tension pneumothorax of 5 or 10 mmHg combined with 5 or 10 cmH₂O PEEP produced a significant increase in alveolar-arterial oxygen difference, a significant decrease in arterial oxygen content, and arterial partial pressure of O₂. Central venous pressure, mean pulmonary arterial pressure, physiologic dead space, and arterial partial pressure of CO₂ significantly increased with tension pneumothorax of 5 or 10 cmH₂O when 5 or 10 mmHg PEEP was used. Arterial oxygenation improved significantly when 10 cmH₂O PEEP was applied to 5 or 10 mmHg tension pneumothorax.

Discussion: In this study, a thoracoscopic trocar was used to produce the acute respiratory function impairment. All animals showed the hemodynamic effects of an increased intrapleural pressure (IPP), such as hypotension and decreased SpO₂. The major change observed was the increased shunt fraction, due to increased physiologic dead space. The hemodynamic changes observed were mainly due to compression of the large thoracic vessels as well as lung compression. When PEEP was applied without increased IPP, the hemodynamic depressive effects were less important. Levels of ETCO₂ in our study did not present a significant increase, demonstrating that recruitment maneuvers are not always effective when there is a concomitant increased IPP. Dead space and V/Q mismatch significantly increased, demonstrating an important respiratory depressant effect. We have demonstrated in this study that while arterial oxygenation and tissue oxygen extraction is improved when high PEEP strategy is used in a swine tension pneumothorax model, the mechanical ventilation of the lungs with low PEEP or high PEEP strategy produced significant depression of the hemodynamic function during tension pneumothorax.

Keywords: PEEP, ventilation, pigs, intrapleural pressure, pneumothorax.
INTRODUCTION

Mechanical ventilation is a therapeutic support for the patient which is aimed to produce ventilation of the lungs without micro structural pulmonary lesions [12]. The mode of ventilation is selected according to patient necessities in order to prevent trauma to the lungs. While low tidal volume ventilation is believed to improve arterial oxygenation, conventional tidal volumes combined with other strategies such as positive end-expiratory pressure (PEEP) is still not completely studied.

When PEEP is used in variable expiratory pressure, different degrees of hemodynamic impairment occur. High PEEP strategy, when used in tension pneumothorax such as in thoracoscopy procedures, may produce deleterious effects on blood oxygenation [1,11,22]. High PEEP may also reduce mortality in comparison to low PEEP in acute respiratory distress syndrome (ARDS) [9,16], but it is not associated with improved outcome in acute lung injury (ALI) [8].

Concerning pulmonary injuries and respiratory impairment studies, several animal models are available. Pulmonary injury model is different from respiratory impairment model, being the former more related to primary ARDS, which involves increment in permeability of the alveolar-capillary membrane, and the latter more related to chest trauma [22].

In order to produce a model similar to chest trauma to investigate the effects of thoracic insufflations and the benefits of positive end-expiratory pressure, we did compare the effects of two PEEP levels with zero PEEP in a tension pneumothorax swine model. We hypothesized that high PEEP would improve blood oxygenation as compared to low PEEP or zero PEEP when a tension pneumothorax is produced.

MATERIALS AND METHODS

Experimental protocol

Twelve juvenile (mean body weight 19.83 ± 1.13 kg) domestic pigs (Sus scrofa domestica) were anesthetized with ketamine (10 mg/kg) and midazolam (2 mg/kg) intramuscularly, and end tidal isoflurane 2.0 V% for maintenance. Mechanical lung ventilation was used and animals were instrumented after anesthesia was stabilized for 20 min. Depth of anesthesia was monitored continuously by arterial blood pressure and heart rate. Baseline measurements (T0) were then obtained with zero PEEP (ZEEP) and no tension pneumothorax with zero intrapleural pressure (ZIPP). Positive end-expiratory pressure at 5 cmH2O was initiated and after a stabilization period of 10 min measurements were obtained (T1). For T2, PEEP of 10 cmH2O was established and data collected after 10 min of stabilization.

In order to produce the experimental lung mechanics impairment and respiratory dysfunction the region of the eighth right intercostal space was blocked with 2% lidocaine and punctured with a 12 mm thoracoscope trocar. After the trocar insertion, 5 mmHg tension pneumothorax was produced, and after 10 min of stabilization measurements were taken with PEEP set to 5 cmH2O (T3). These events were repeated sequentially until all treatments were applied: PEEP 10 cmH2O + IPP 5 mmHg (T4), PEEP 5 cmH2O + IPP 10 mmHg (T5), and PEEP 10 cmH2O + IPP 10 mmHg (T6).

Instrumentation

Animals were kept in supine position throughout the study. After orotracheal intubation, with a 7.0 ID tracheal tube, podal artery, and external jugular vein were surgically exposed and a 5 Fr sheath was inserted in the artery and a 7.5 Fr sheath in the vein. A pediatric 5 Fr Swan-Ganz pulmonary artery catheter was advanced through the central access and positioned in the pulmonary artery. Correct positioning of the catheter tip was confirmed by typical waveforms of the pressure tracings. Ventilatory parameters and airway pressures and flows were measured with a spirometry monitor. Respiratory gases and respiratory parameters were monitored with an anesthesia gas monitor. Blood gas analysis was done with a digital monitor and calculated parameters were obtained automatically with the same equipment. Mean arterial and pulmonary arterial blood pressures (MAP, MPAP) and heart rate (HR) were measured continuously using the hemodynamic monitor system of the anesthesia monitor. Cardiac output (CO) measurements were performed by conventional thermodilution method.

Statistical analysis

Functional variables are presented as mean (± SD). Two-way repeated-measures analysis of variance was used for comparison between treatment and time x treatment effects. All tests were performed using SPSS. Corrections for multiple measurements were performed by Bonferroni post-tests. Statistical significance was accepted if P < 0.05.
Table 1. Mean ± standard deviation for hemodynamic parameters in swine submitted to zero end-expiratory pressure (ZEEP), positive end-expiratory pressure (PEEP) from 5 to 10 cmH₂O, and intrapulmonary pressure (IPP) from 0 (ZIPP) to 10 mmHg in the seven times studied (T0 to T6). Systolic blood pressure (SAP), diastolic blood pressure (DAP), mean blood pressure (MAP), central venous pressure (CVP), heart rate (HR), cardiac index (CI), Stroke volume index (SVI), Mean pulmonary arterial pressure (MPAP).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEEP</td>
<td>PEEP 5</td>
<td>PEEP 10</td>
<td>PEEP 5</td>
<td>PEEP 10</td>
<td>PEEP 5</td>
<td>PEEP 10</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>90±5</td>
<td>85±10</td>
<td>72±12</td>
<td>80±15</td>
<td>82±14</td>
<td>64±6</td>
<td>68±5</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>46±5</td>
<td>44±5</td>
<td>46±9</td>
<td>45±9</td>
<td>47±9</td>
<td>43±7</td>
<td>46±6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>60±5</td>
<td>57±9</td>
<td>55±8</td>
<td>57±12</td>
<td>60±12</td>
<td>51±6</td>
<td>53±5</td>
</tr>
<tr>
<td>CVP (cmH₂O)</td>
<td>8±1A</td>
<td>10±3ABC</td>
<td>10±1AB</td>
<td>11±2AB</td>
<td>12±1BC</td>
<td>16±2CD</td>
<td>17±1D</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>105±8A</td>
<td>102±7A</td>
<td>106±14A</td>
<td>115±29A</td>
<td>130±24ABC</td>
<td>179±42BCD</td>
<td>193±35C</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>5±0.5A</td>
<td>5±0.3A</td>
<td>4.6±0.4AB</td>
<td>4.5±0.6AB</td>
<td>5±0.5A</td>
<td>3±0.6BC</td>
<td>2±0.3C</td>
</tr>
<tr>
<td>SVI (mL/beat/m²)</td>
<td>51±6A</td>
<td>52±5A</td>
<td>44±3.5A</td>
<td>42±9A</td>
<td>41±8A</td>
<td>19±6B</td>
<td>12±3B</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>18±4A</td>
<td>24±8AB</td>
<td>23±5AB</td>
<td>26±6B</td>
<td>29±3B</td>
<td>28±5B</td>
<td></td>
</tr>
</tbody>
</table>

Different capital letters in the same line indicates statistically significant differences (P < 0.05).

Table 2. Mean ± standard deviation for respiratory parameters in swine submitted to zero end-expiratory pressure (ZEEP), positive end-expiratory pressure (PEEP) from 5 to 10 cmH₂O, and intrapulmonary pressure (IPP) from 0 (ZIPP) to 10 mmHg in the seven times studied (T0 to T6). Arterial partial pressure of oxygen (PaO₂), arterial oxygen saturation (SaO₂), arterial oxygen content (CaO₂), arterio-venous difference in oxygen content (a-vDO₂), oxygen delivery (DO₂), alveolar-arterial oxygen difference (A-aDO₂), dynamic compliance (Cdyn), dead space, minute ventilation (VE), tidal volume (VT), respiratory rate (RR), pH, bicarbonate (HCO₃⁻), end tidal carbon dioxide (ETCO₂), and arterial partial pressure of carbon dioxide (PaCO₂).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEEP</td>
<td>NIPP</td>
<td>PEEP 5</td>
<td>NIPP</td>
<td>PEEP 10</td>
<td>NIPP</td>
<td>PEEP 5</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>233±74AB</td>
<td>264±37A</td>
<td>320±96A</td>
<td>103±30CD</td>
<td>137±17ABD</td>
<td>72±15C</td>
<td>96±32CD</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>100±0.3A</td>
<td>100±0.2A</td>
<td>100±0.2A</td>
<td>97±1.8AB</td>
<td>99±1AB</td>
<td>92±7AB</td>
<td>96±3B</td>
</tr>
<tr>
<td>CaO₂ (mL/dL)</td>
<td>20±0.3A</td>
<td>20.27±0.41AB</td>
<td>20.54±0.42A</td>
<td>19.35±0.54BCD</td>
<td>20.01±0.55ABD</td>
<td>18.76±0.64C</td>
<td>19.04±0.79CD</td>
</tr>
<tr>
<td>a-vDO₂ (mL/dL)</td>
<td>3.3±0.8A</td>
<td>2.8±0.5A</td>
<td>3±0.3A</td>
<td>2±1A</td>
<td>4.0±0.5A</td>
<td>6±3B</td>
<td>5±2B</td>
</tr>
<tr>
<td>DO₂ (mL/min)</td>
<td>700±81A</td>
<td>690±5A</td>
<td>620±7A</td>
<td>564±6AB</td>
<td>645±6A</td>
<td>368±7B</td>
<td>275±2B</td>
</tr>
<tr>
<td>A-aDO₂ (mmHg)</td>
<td>321±185AB</td>
<td>370±124AB</td>
<td>280±130A</td>
<td>515±80ABC</td>
<td>469±135ABC</td>
<td>543±49C</td>
<td>505±82B</td>
</tr>
<tr>
<td>Cₐv (mL/cmH₂O)</td>
<td>56±15A</td>
<td>50±9A</td>
<td>49±5AB</td>
<td>40±7AB</td>
<td>43±10AB</td>
<td>28±6B</td>
<td>30±6B</td>
</tr>
<tr>
<td>Dead space (%)</td>
<td>12±4A</td>
<td>15±4A</td>
<td>14±5A</td>
<td>22±5AB</td>
<td>24±4B</td>
<td>33±2B</td>
<td>31±8B</td>
</tr>
<tr>
<td>V̇e (L/min)</td>
<td>4.2±1.4A</td>
<td>3.6±1.2A</td>
<td>4.0±0.4A</td>
<td>3.6±0.6A</td>
<td>3.7±1.0A</td>
<td>3.4±0.6A</td>
<td>3.0±0.5A</td>
</tr>
<tr>
<td>V̇T (mL/kg)</td>
<td>220±69A</td>
<td>156±5.6A</td>
<td>145±28AB</td>
<td>152±30AB</td>
<td>123±38ABC</td>
<td>111±13BC</td>
<td>96±21C</td>
</tr>
<tr>
<td>RR (bpm)</td>
<td>22±4A</td>
<td>26±7AB</td>
<td>32±2B</td>
<td>27±3A</td>
<td>37±9B</td>
<td>33±4B</td>
<td>36±4B</td>
</tr>
<tr>
<td>pH</td>
<td>7.45±0.04A</td>
<td>7.42±0.03AB</td>
<td>7.42±0.02AB</td>
<td>7.37±0.04BC</td>
<td>7.36±0.06BC</td>
<td>7.31±0.04C</td>
<td>7.29±0.05C</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>31±1</td>
<td>31±1</td>
<td>32±1</td>
<td>30±1</td>
<td>30±1</td>
<td>31±0.5</td>
<td>29±1</td>
</tr>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>39±2</td>
<td>42±4</td>
<td>43±1</td>
<td>42±5</td>
<td>42±4</td>
<td>42±3</td>
<td>44±2</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>45±4A</td>
<td>50±4A</td>
<td>50±3A</td>
<td>54±5B</td>
<td>55±7AB</td>
<td>62±7B</td>
<td>63±11B</td>
</tr>
</tbody>
</table>

Different capital letters in the same line indicates statistically significant differences (P < 0.05).
RESULTS

Tension pneumothorax of 10 mmHg, with both PEEP levels, induced a significant decrease in cardiac index, stroke volume, dynamic compliance, arterial pH, arterial blood pressure, in addition to significant increase in heart rate (Table 1). Moreover, tension pneumothorax of 5 or 10 mmHg combined with 5 or 10 cmH2O PEEP produced a significant increase in alveolar-arterial oxygen difference, a significant increase in arterial oxygen content, and arterial partial pressure of O2 (Table 2). Central venous pressure, arterio-venous pressure decrease in oxygen content, mean pulmonary arterial pressure, and decreased cardiac output [7,14,18,19,28].

In our study, a thoracoscopic trocar was used to produce the acute respiratory function impairment. Tension pneumothorax model in pigs has been described before, produced through insertion of an intrathoracic balloon occlusion catheter, surgically placed into the right pleural space [7]. The major change observed was the increased shunt fraction, due to increased physiologic dead space. In our study the effects of increased shunt fraction was demonstrated as the PaO2 decreased significantly after an increased intrathoracic pressure of 10 mmHg. Studies in sheep and swine have demonstrated progressive hypoxia as the earliest sign of increased intrapleural pressure [7].

Hemodynamic studies showing the effects of raised IPP in ventilated animal models demonstrated an early rise in central venous pressure [7]. We have demonstrated in this study that when IPP is not increased, PEEP will not impact the CVP. However, an increased IPP from 0 to 10 mmHg will produce a significant increase in CVP. When PEEP from 0 to 10 cmH2O is applied to ZIPP, no significant change in CVP was observed in our study. Similar effects were described before [17,20,21,25].

Central venous pressure, mean pulmonary arterial pressure, physiologic dead space, and arterial partial pressure of CO2 significantly increased with tension pneumothorax of 5 or 10 cmH2O when 5 or 10 mmHg PEEP was used. Arterial oxygenation improved significantly when 10 cmH2O PEEP was applied to 5 or 10 mmHg tension pneumothorax (Tables 1 and 2).

DISCUSSION

Mechanical ventilation is a strategic approach when patient needs respiratory support in acute or chronic pulmonary disease. Since mechanical ventilation involves several mechanisms in which the patient may have a better outcome when the proper modality is chosen, several ventilation modes have been described [12]. The techniques involved are well established and the complication as well as the benefits is known to increase the survival rate during ALI/ARDS in man [2,10]. Positive end-expiratory pressure (PEEP) is a technique used when hypoxemia in acute lung injury/acute respiratory stress syndrome occurs. This phenomenon occurs when a high shunt fraction is formed due to non-aerated areas in the lungs [1,11,23].

In order to investigate the effects of PEEP in a tension pneumothorax model it would be important to investigate the different modes of ventilation. In this study, a pressure controlled mode of ventilation was the only model investigated combined or not with PEEP. All animals showed the hemodynamic effects of an increased intrapleural pressure (IPP) such as hypotension and decreased SpO2. Hemodynamic function would deteriorate in patients under mechanical ventilation which produces an increased alveolar pressure, and when tension pneumothorax develops, the increased alveolar pressure above pulmonary venous or arterial pressure decreases cardiac output [7,14,18,19,28].
In order for the recruitment maneuvers to be effective, a sudden increase in ETCO$_2$ should indicate a signal of recruitment [4]. Levels of ETCO$_2$ in our study did not present a significant increase, demonstrating that recruitment maneuvers are not always effective when there is a concomitant increased IPP. The resulting significant decreased dynamic complacency, probably explains the lack of efficacy of our recruitment maneuvers [7,14].

In our study, tension pneumothorax of 5 or 10 mmHg combined with 5 or 10 cmH$_2$O PEEP in ventilated pigs, produced a significant increase in alveolar-arterial oxygen difference, a significant decrease in arterial oxygen content, and arterial partial pressure of O$_2$. Arterial oxygenation improved significantly when 10 cmH2O PEEP was applied to 5 or 10 mmHg tension pneumothorax, although important hemodynamic depressive effects do occur. Following those changes, the PaCO$_2$ levels, before IPP increase were lower than during and after IPP increase. Therefore, dead space and V/Q mismatch significantly increased, demonstrating an important respiratory depressant effect.

Improving tissue oxygenation is the main goal when PEEP strategies are used. The results of our study demonstrated that when SaO$_2$ decreased, CaO$_2$ also decreased which is physiologically expected [28]. Interestingly, the a-vDO$_2$ was significantly higher when PEEP of 5 or 10 cmH$_2$O was combined with IPP of 10 mmHg (T5 and T6), showing an increased tissue oxygen extraction. A possible explanation is the significant increase in heart rate, with a significant decrease in cardiac index and systolic index, which leads to decreased blood flow to peripheral tissues. Thus, even significant increase in cardiac workload did not produce an increase in blood flow. The significant reduction in CO observed in this study, in addition to the increased a-vDO$_2$, probably was also the cause of the reduction in systemic venous oxygen saturation (SvO2, data not showed but used to calculate a-vDO$_2$) presented. According to Karzai & Schwarzkopf [15], oxygenation during video thoracoscopic surgeries depends not only on the magnitude of the shunt fraction, but also the oxygenation of the shunted blood because there is a dependence of SaO$_2$ by SvO$_2$ at different levels of shunt. Thus, factors that lead to reduced oxygenation of the shunted venous blood, e.g. cases of increased oxygen extraction by tissues, as observed in our study, or low hemoglobin levels, can directly affect arterial oxygenation (PaO$_2$) [15].

**CONCLUSION**

Positive end-expiratory pressure of 5 or 10 cmH2O improve arterial oxygenation during mechanical ventilation. When tension pneumothorax 5 or 10 mmHg is used the effects of recruitment maneuvers are not efficient enough to prevent an increase in tissue oxygen extraction. Hemodynamic depressive effects of PEEP during IPP are extremely deleterious.

**ACKNOWLEDGEMENTS**

The authors thank Hospital de Clínicas de Porto Alegre and its Animal Experimental Unit for financial (Research Foundation of the Hospital de Clínicas de Porto Alegre -Fipe - Universidade Federal do Rio Grande do Sul) and infrastructure support.

**Ethical Approval.** The complete study proposal was approved by the Institutional Animal Care Committee (N° 07.288) and Brazilian Federal regulation for care and use of laboratory animals of the Hospital de Clínicas de Porto Alegre (HCPA-UFRGS), Porto Alegre, RS, Brazil.

**Declaration of Interest.** None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

**REFERENCES**


