Positive end-expiratory pressure increases strain in patients with ALI/ARDS

Pressão expiratória final positiva aumenta o estiramento em pacientes com LPA/SDRA

INTRODUCTION

Mechanical ventilation may induce or worsen lung injury by causing overdistension and by the cyclic recruitment and derecruitment (R/D) of unstable alveoli.\(^1\)\(^{-5}\) Experimental data have shown that using positive end-expiratory pressure (PEEP) and a low tidal volume may protect against ventilator-induced lung injury (VILI).\(^6\)\(^{-7}\) The protective role of a low tidal volume has been confirmed in large clinical trials of patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS).\(^8\)\(^{-11}\) However, while recent trials have demonstrated that high levels of PEEP decrease refractory hypoxemia, they have not demonstrated any mortality benefit.\(^3\)\(^{-14}\)

Recently, various authors have proposed that stress and strain on the lung

ABSTRACT

**Objective:** The objective of this study was to assess the effects of positive end-expiratory pressure on recruitment, cyclic recruitment and derecruitment and strain in patients with acute lung injury and acute respiratory distress syndrome using lung computed tomography.

**Methods:** This is an open, controlled, non-randomized interventional study of ten patients with acute lung injury and acute respiratory distress syndrome. Using computed tomography, single, basal slices of the lung were obtained during inspiratory and expiratory pauses at a tidal volume of 6 ml/kg and a positive end-expiratory pressure of 5, 10, 15 and 20 cmH\(_2\)O. The densities of the lung parenchyma were measured in Hounsfield units. The values for positive end-expiratory pressure-induced recruitment, cyclic recruitment and derecruitment and strain were then calculated.

**Results:** Increasing levels of positive end-expiratory pressure were correlated with increased recruitment and global strain (\(p < 0.01\)), which was significantly correlated with plateau pressure (\(r^2 = 0.97, p < 0.01\)). In addition, increasing levels of positive end-expiratory pressure systematically increased strain along the sternovertebral axis.

**Conclusion:** While strain is an adverse effect of positive end-expiratory pressure, the decision use positive end-expiratory pressure with any patient should be balanced against the potential benefits of recruitment. Due to the small number of patients in this study, the present data should be treated as hypothesis generating and is not intended to limit the clinical application of a high level of positive end-expiratory pressure in patients with severe hypoxemia.

**Keywords:** Positive end-expiratory pressure; Respiration, artificial; Respiratory distress syndrome, adult; Tomography, x-ray computed

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parenchyma is the ultimate cause of VILI.\(^{(4,15,16)}\) Stress is measured by transpulmonary pressures, which are largely heterogeneous along different lung regions. Strain refers to alveolar cell deformation that is induced by changes in transpulmonary pressures. Several approaches have been proposed to assess strain at a patient’s bedside. The group ofGattinoni defined strain as the relative difference between the gas volume at end inspiration and the resting volume of the lung.\(^{(15,17)}\) Although this definition does not account for alveolar surface area, which can vary depending on the degree of recruitment, it can be easily used in conjunction with computed tomography as a surrogate for clinical strain.

By recruiting unstable alveoli, high levels of PEEP improve oxygenation and may protect against cyclic R/D. However, high levels of PEEP can also increase strain across the lung parenchyma.\(^{(3,18,19)}\) The objective of the present study was to assess the effects of PEEP on strain, recruitment and cyclic R/D in patients with ALI/ARDS.

**METHODS**

This is an open, controlled, non-randomized, interventional CT-scan study of ten patients with ALI/ARDS who were mechanically ventilated. The institutional ethics committee approved the study protocol, and written informed consent was obtained from each patient’s next of kin. While under continuous infusions of midazolam and morphine, patients were transferred to the CT-scan facility room and connected to a Siemens 900-C ventilator (Siemens-Elema AB, Sweden). Pancuronium 0.1 mg/kg was administered before the procedure to avoid increased ventilatory efforts. Prior to initiating the protocol, gentle tracheal suctioning was followed by a short recruiting maneuver, which consisted of increasing the PEEP above 20 cmH\(_2\)O to obtain plateau pressures between 40 and 45 cmH\(_2\)O for a period of one minute. Continuous electrocardiogram monitoring was performed, and invasive blood pressure and oxygen saturation parameters were continuously measured with a portable monitor (LightSolo, Datex-Ohmeda, Helsinki, Finland).

**CT-scan protocol**

A conventional CT scan (GE Light Speed QX/I, GE Medical Systems, Wisconsin, USA) was performed from the neck to the lung bases and took 8-mm thick slices during an inspiratory pause. The matrix was 512 x 512, which gives a voxel size of approximately 2–3 mm\(^3\). A single CT slice approximately 2–3 cm above the diaphragmatic dome, arbitrarily selected by the corresponding author (GB) to avoid the appearance of the diaphragm even at the lowest pressures, was used for the entire protocol.

Patients were on volume-controlled ventilation throughout the study. Ideal body weight was calculated according to the ARDSnet study.\(^{(10)}\) Baseline parameters included a tidal volume of 6 ml/kg, a PEEP of 10 cmH\(_2\)O, a respiratory rate of 25 and a FiO\(_2\) set to obtain oxygen saturation greater than 92%. Single CT sections were taken both at expiratory and inspiratory pauses at a PEEP of 10, 5, 15 and 20 cmH\(_2\)O following the stabilization of mean airway pressures. This task was generally accomplished after 45 to 60 seconds, so each PEEP level was usually completed within two minutes. Mean airway pressure, plateau pressure (P\(_{pl}\)) and expiratory tidal volume (V\(_t\)) were measured by the ventilator at each PEEP level. Static compliance (C\(_{st}\)) was calculated at a PEEP of 10 cmH\(_2\)O, given that C\(_{st}\) = V\(_t\) / P\(_{pl}\) – PEEP.

**Image processing**

The CT images were downloaded to an optical disk and processed using the Maluna\(^{\circ}\) (Mannheim, Germany) software.\(^{(20)}\) We used methods similar to those of other CT studies, describing the lung parenchyma according to its density in Hounsfield units (HU).\(^{(21,22)}\) First, the lung contour on each image was traced, and then, the total CT volume (TV\(_{CT}\)) and average density (H\(_{CT}\)) were measured.

With these data, we obtained lung weight (W\(_{CT}\)) and gas volume (GV\(_{CT}\)) values for each lung slice:

\[
\begin{align*}
GV_{CT} & = TV_{CT} \times (H_{CT} / -1000) \\
W_{CT} & = TV_{CT} - GV_{CT}.
\end{align*}
\]

Hyperinflated tissue was defined as -1000 to -901 HU, normally aerated tissue as -900 to -501 HU, poorly aerated tissue (PAT) as -500 to -101 HU and non-aerated tissue (NAT) as -100 to +100 HU.\(^{(23)}\) For data analysis, we used the weight (expressed in grams) of each compartment.

Recruitment induced by the increase in PEEP was defined as the decrease in NAT at expiration compared with that at a PEEP of 5 cmH\(_2\)O. This value was expressed as a percentage of the lung slice weight:

\[
\text{Recruitment} = 100 \times \frac{(\text{NAT exp}_{\text{PEEP}5} - \text{NAT exp}_{\text{PEEP}x})}{\text{total weight exp}_{\text{PEEP}5}}
\]

Strain was calculated according to Valenza et al.:\(^{(23)}\)

\[
\text{Strain} = \frac{(GV_{CT \text{ end insp}_{\text{PEEP}5}} - GV_{CT \text{ end exp}_{\text{PEEP}x}})}{GV_{CT \text{ end-exp}_{\text{PEEP}5}}}
\]

Cyclic recruitment-derecruitment (R/D) was also calculated:
R/D = 100 x [(NAT end exp / total weight exp) – (NAT end insp / total weight insp)]

Recruitment, strain and cyclic R/D were calculated for each PEEP level both for the entire slice (referred to as global) and regionally by splitting the slice into ten compartments along the sternovertebral axis.

Statistical analysis
Clinical characteristics and ventilatory data are presented as the mean ± SD. Comparisons in the amount of gas and tissue at different levels of PEEP were evaluated by ANOVA for repeated measures or by paired t-test. Linear regression was used to correlate strain with airway pressures and recruitment with R/D. The level of statistical significance was set at p < 0.05.

RESULTS
Ten patients (4 M, 6 F, 51 ± 16 y.o.) with ALI/ARDS (Pa/FiO\textsubscript{2} 80–285) were included in the study. Clinical characteristics and baseline parameters are shown in table 1. The distribution of lung volumes and plateau and mean airway pressures at different levels of PEEP are shown in figure 1.

Recruitment and cyclic R/D
In all patients, recruitment increased significantly with increasing levels of PEEP (Table 2). However, cyclic R/D was highly variable with increasing levels of PEEP, though overall a decreasing trend with higher PEEP levels was observed (p = 0.056; Figure 2 and Table 2). Regional R/D was predominant in the middle levels and decreased when the PEEP level increased to 20 cmH\textsubscript{2}O (Figure 3).

We found no correlation between PEEP-induced

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Type of ARDS</th>
<th>APACHE II</th>
<th>Pa/FiO\textsubscript{2}</th>
<th>Day on MV</th>
<th>Oxygenation index</th>
<th>Static compliance (ml/cmH\textsubscript{2}O)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>52</td>
<td>Pneumonia</td>
<td>P</td>
<td>22</td>
<td>128</td>
<td>2</td>
<td>11.7</td>
<td>39.6</td>
<td>D</td>
</tr>
<tr>
<td>F</td>
<td>24</td>
<td>Pancreatitis</td>
<td>EP</td>
<td>15</td>
<td>84</td>
<td>1</td>
<td>27.5</td>
<td>18.9</td>
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<tr>
<td>F</td>
<td>72</td>
<td>Pneumonia</td>
<td>P</td>
<td>24</td>
<td>232</td>
<td>1</td>
<td>7.8</td>
<td>27.1</td>
<td>D</td>
</tr>
<tr>
<td>F</td>
<td>64</td>
<td>Postoperative pneumonia</td>
<td>P</td>
<td>15</td>
<td>285</td>
<td>5</td>
<td>6.3</td>
<td>21.7</td>
<td>S</td>
</tr>
<tr>
<td>F</td>
<td>37</td>
<td>Peritonitis</td>
<td>EP</td>
<td>18</td>
<td>183</td>
<td>3</td>
<td>8.6</td>
<td>16.9</td>
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<tr>
<td>F</td>
<td>60</td>
<td>Pneumonitis</td>
<td>P</td>
<td>18</td>
<td>80</td>
<td>5</td>
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<td>8</td>
<td>6.4</td>
<td>46.5</td>
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<tr>
<td>F</td>
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<td>EP</td>
<td>12</td>
<td>173</td>
<td>2</td>
<td>8.7</td>
<td>25.6</td>
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</tr>
<tr>
<td>M</td>
<td>67</td>
<td>Postoperative pneumonia</td>
<td>P</td>
<td>11</td>
<td>275</td>
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<td>5.8</td>
<td>38.1</td>
<td>S</td>
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<tr>
<td>M</td>
<td>51</td>
<td>Pneumonia</td>
<td>P</td>
<td>17</td>
<td>128</td>
<td>12</td>
<td>16.5</td>
<td>26.9</td>
<td>S</td>
</tr>
</tbody>
</table>

4M/6F 51 ± 16
16 ± 4 181 ± 80 4.0 ± 3.6 13.3 ± 4 29.2 ± 9.6


P- pulmonary; EP - extrapulmonary; ARDS - acute respiratory distress syndrome; APACHE II - acute lung injury/acute respiratory distress syndrome; Pa/FiO\textsubscript{2} - oxygen partial pressure/oxygen inspiratory fraction; MV- mechanical ventilation; S - survival; D - death. Values are given as the mean ± SD.
recruitment and changes in cyclic R/D (delta R/D) when increasing PEEP from 5 to 20 cmH\textsubscript{2}O (Figure 4).

**Strain**

Global strain increased with higher levels of PEEP \((p < 0.01)\). Global strain at various PEEP levels was highly correlated with plateau pressure \((r^2 = 0.97, p < 0.01)\) (Figure 5). Regional strain at a PEEP of 5 cmH\textsubscript{2}O was distributed evenly along the sternovertebral axis. Increasing PEEP levels systematically increased strain along the sternovertebral axis (Figure 6).

### Table 2 - Weight (g) of each lung compartment during expiration and inspiration at different positive end-expiratory pressure levels

<table>
<thead>
<tr>
<th>PEEP</th>
<th>Cycle</th>
<th>Hyperinflated (-1000 to -901)</th>
<th>Normal aeration (-900 to -501)</th>
<th>Poorly aerated (-500 to -101)</th>
<th>Non-aerated (-100 to +100)</th>
<th>Total weight</th>
<th>R/D\textsuperscript{a} (expiration-inspiration)</th>
<th>Recruitment\textsuperscript{b} (versus PEEP 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Expiration</td>
<td>0.10 ± 0.24</td>
<td>14.40 ± 7.04</td>
<td>10.75 ± 4.34</td>
<td>28.27 ± 14.32</td>
<td>53.52 ± 16.77</td>
<td>6.04 ± 5.83%</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Inspiration</td>
<td>0.16 ± 0.36</td>
<td>14.87 ± 7.48</td>
<td>12.63 ± 3.97</td>
<td>23.67 ± 11.26</td>
<td>51.33 ± 16.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Expiration</td>
<td>0.09 ± 0.23</td>
<td>14.56 ± 6.98</td>
<td>12.63 ± 4.16</td>
<td>24.15 ± 13.05*</td>
<td>51.44 ± 15.78</td>
<td>4.16 ± 4.84%</td>
<td>4.13 ± 3.46%</td>
</tr>
<tr>
<td></td>
<td>Inspiration</td>
<td>0.16 ± 0.24</td>
<td>14.06 ± 7.74</td>
<td>14.13 ± 3.97</td>
<td>20.65 ± 10.50</td>
<td>48.98 ± 15.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Expiration</td>
<td>0.15 ± 0.27</td>
<td>14.26 ± 7.88</td>
<td>13.46 ± 4.04</td>
<td>22.03 ± 12.45*</td>
<td>49.90 ± 15.69*</td>
<td>3.16 ± 6.04%</td>
<td>6.70 ± 6.29%*</td>
</tr>
<tr>
<td></td>
<td>Inspiration</td>
<td>0.35 ± 0.49</td>
<td>13.25 ± 8.57</td>
<td>14.22 ± 3.84</td>
<td>19.05 ± 10.66</td>
<td>46.87 ± 15.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Expiration</td>
<td>0.27 ± 0.44</td>
<td>14.50 ± 9.25</td>
<td>15.13 ± 3.13</td>
<td>20.43 ± 11.75*</td>
<td>50.33 ± 15.88</td>
<td>2.27 ± 2.75%</td>
<td>8.92 ± 9.18%*</td>
</tr>
<tr>
<td></td>
<td>Inspiration</td>
<td>0.53 ± 0.74*</td>
<td>13.32 ± 8.97</td>
<td>15.23 ± 2.92</td>
<td>18.16 ± 11.18</td>
<td>47.24 ± 16.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\) Recruitment and derecruitment (R/D) is the fractional decrease in non-aerated tissue between inspiration and expiration at each positive end-expiratory pressure level.

\(\textsuperscript{b}\) Recruitment is the decrease in non-aerated tissue at expiration compared to a positive end-expiratory pressure of 5 cmH\textsubscript{2}O.

\(* p < 0.05\) versus a positive end-expiratory pressure of 5. All data are given as the mean ± SD. Also shown are the mean ± SD values for opening and closing, and expiratory recruitment \(\textsuperscript{a,b}\).

PEEP - positive end-expiratory pressure.

**Figure 2** - Global cyclic recruitment and derecruitment at different positive end-expiratory pressure levels. There were no significant differences between the groups.

**Figure 3** - Regional distribution of cyclic recruitment and derecruitment at different positive end-expiratory pressure levels given a tidal volume of 6 ml/kg. \(^\# p < 0.05\) for differences between the positive end-expiratory pressure groups.
The main findings in the present study include the following: first, the potential benefits of PEEP recruitment are coupled with a consistent increase in strain; second, global strain, a physical measure of alveolar stretching, was closely related to plateau pressure. However, due to the small number of patients in the study, the present data should be treated as hypothesis generating and not intended to limit the clinical application of a high level of PEEP in patients with severe hypoxemia.
Current literature on ventilator-induced lung injury suggests that lung injury is primarily caused by overdistension and cyclic R/D.\(^2\)\(^3\)\(^4\)\(^5\) The role of PEEP in preventing VILI is controversial, as only tidal-volume reduction has demonstrated a clear impact on the survival of patients with ALI/ARDS.\(^10\)\(^13\)\(^14\) A recent meta-analysis suggested that higher levels of PEEP beyond those that are used to decrease refractory hypoxemia, might have a survival benefit in patients with ARDS.\(^24\)

In patients with ALI/ARDS, Caironi et al. demonstrated that high levels of PEEP decreased cyclic R/D in patients with highly recruitable lungs but increased strain independent of lung recruitment.\(^25\) In their study, cyclic R/D was not directly measured but estimated from hypothetical curves that were derived from previous studies.\(^26\) By measuring non-aerated tissue both at expiration and inspiration, we were able to directly measure recruitment, cyclic R/D, and strain. Thus, we demonstrated that, in all patients, an increase in the levels of PEEP decreases the amount of non-aerated tissue at end expiration (recruitment) but also increases strain. The effect of PEEP on cyclic R/D was very heterogeneous, although a trend toward less cyclic R/D with higher levels of PEEP levels was observed. The most likely explanation for this finding is type-II error due to our small sample size of non-selected ALI/ARDS patients.

Another important clinical finding derived from this protocol includes that global strain, a physical measure of alveolar stretching, was closely related to plateau pressure. We recognized that transpulmonary pressure, and not plateau pressure, is the distending force of the lung.\(^27\) However, as the measurement of transpulmonary pressures is complicated and is not routinely performed in most ICUs worldwide, plateau pressure may still have clinical value for assessing strain at the bedside. Although we cannot suggest a threshold value for plateau pressure, it appears logical, based on experimental and clinical studies, that it should be a highly controlled variable when ventilating patients with ALI/ARDS. Our data are consistent with the data from Hager et al., who utilized data from the ARDSnet trial, and demonstrated that mortality increased linearly with plateau pressure.\(^28\)

Several human studies have reported the simultaneous onset of alveolar recruitment and overdistension in patients with ALI/ARDS at PEEP levels ranging from 10 to 20 cmH\(_2\)O.\(^18\)\(^29\)\(^30\) The linear correlation we observed between strain and plateau pressure (Figure 5) might be due to another variable because recruitment and overdistension were not observed, and both phenomena occurred in the same proportion.\(^31\) However, given the small number of patients and values for plateau pressure, we are unable to generalize with regard to these data. Moreover, even in healthy lungs, the strain-pressure relationship is not linear.\(^32\)

Whether strain is more important than cyclic R/D in inducing further alveolar damage is a topic of debate.\(^25\) The demonstration that bullae are prevalent in dependent regions of the lung suggests that cyclic R/D also has a major impact on VILI.\(^33\) Recent trials comparing higher versus lower levels of PEEP in patients with ARDS demonstrated higher plateau pressures but a similar rate of mortality in patients with higher levels of PEEP.\(^12\)\(^14\)\(^24\) Once again, however, different rates of lung recruitment among patients may explain the confounding results of these trials.\(^20\)\(^25\)\(^34\)

**Limitations of our study**

First, our study included a small number of patients with ALI/ARDS who were mechanically ventilated for various periods of time, so these results should be treated as hypothesis generating and not intended to limit the clinical application of a high level of PEEP in patients with severe hypoxemia. Larger trials in patients with different types of ALI/ARDS,\(^34\) based on the measurement of inflammatory mediators, may help identify the real impact of PEEP on strain and lung function.

Second, although we did not perform a whole lung CT for every level of PEEP, it is widely accepted that a single, basal CT section adequately represents the whole lung.\(^21\)\(^35\) Several authors have used this approach to avoid excessive radiation exposure.\(^36\) As faster spiral-CT machines become available, whole-lung-CT clinical trials using different levels of airway pressure could be performed at acceptable radiation levels.\(^37\)

Third, we compared static end-expiratory and end-inspiratory CT results to infer changes in density distributions that occurred during mechanical ventilation. However, this approach may have some limitations. Experimental data suggest that recruitment and derecruitment are time dependent and therefore, static images taken after prolonged inspiratory and expiratory holds may not adequately reflect the lung during uninterrupted mechanical ventilation.\(^38\)\(^39\) Modern CT technology with improved time resolutions
has the potential to dynamically assess changes in density distribution during continuous mechanical ventilation.\(^{(40)}\)

Finally, as previously stated, strain does not refer to gas volumes but to changes in the linear dimension of alveolar cells. In a lung that is fully open, measures of strain and gas volume may have a near-perfect correlation. In contrast, in a heterogeneous lung—as in human ARDS—this may not be totally equivalent. It would be also interesting to evaluate the impact of a stronger recruitment maneuver prior to setting the PEEP level, which may favor recruitment and decrease strain.\(^{(41)}\)

**CONCLUSIONS**

Strain is systematically increased by increasing levels of PEEP and also correlates with plateau pressure. Thus, strain is clearly an adverse effect of PEEP, which for any patient should be balanced against the potential benefits of recruitment and prevention of cyclic R/D. Due to the small number of patients in this study, the present data should be treated as hypothesis generating and are not intended to limit the clinical application of a high level of PEEP in patients with severe hypoxemia.

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**REFERENCES**


**RESUMO**

**Objetivo:** O objetivo deste estudo foi avaliar os efeitos da pressão expiratória final positiva no estiramento, recrutamento e desrecrutamento cíclico avaliados por tomografia computadorizada pulmonar em pacientes com lesão pulmonar aguda/síndrome do desconforto respiratório agudo.

**Métodos:** Trata-se de um estudo aberto, controlado, não randomizado, de intervenção, em pacientes com lesão pulmonar aguda/síndrome do desconforto respiratório agudo. Foram realizados cortes simples de tomografia computadorizada durante pausas inspiratórias e expiratórias com um volume corrente de 6 ml/kg e níveis de pressão expiratória final positiva de 5, 10, 15 e 20 cmH2O. Medimos as densidades do parênquima pulmonar em unidades Hounsfield e calculamos o recrutamento, recrutamento e desrecrutamento cíclico induzidos pela pressão expiratória final positiva, assim como o estiramento.

**Resultados:** O aumento dos níveis de pressão expiratória final positiva aumenta de forma consistente o recrutamento e o estiramento globais (p<0,01), o que se correlacionou de forma significante com a pressão de platô \((r^2=0,97)\; p<0,01\). O aumento dos níveis de pressão expiratória final positiva aumentou sistematicamente a distensão alveolar em todo o eixo esterno-vertebral.

**Conclusão:** A distensão alveolar é um efeito adverso da pressão expiratória final positiva que deve ser ponderado em qualquer paciente em relação aos seus potenciais benefícios no recrutamento. Em razão do número reduzido de pacientes, estes dados devem ser considerados como geradores de hipótese e não limitar a aplicação de valores elevados de pressão expiratória final positiva em pacientes com hipoxemia grave.

**Descritores:** Respiração com pressão positiva; Respiração artificial; Síndrome do desconforto respiratório do adulto; Tomografia computadorizada por raios x


