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Lung-protective ventilation in intensive care unit and operation room
*Tidal volume size, level of positive end-expiratory pressure and driving pressure*

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Download date: 05 Mar 2020
Chapter 3

Dissipated energy is a key mediator of VILI: Rationale for using low driving pressures

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Introduction

Positive pressure ventilation should never be seen as a simple and safe intervention, either in patients under general anesthesia for surgery in whom ventilation usually lasts minutes to hours, or in critically ill patients who generally need invasive ventilation for days to weeks. Indeed, positive pressure ventilation is increasingly recognized as a potentially harmful intervention, with ventilator-induced lung injury (VILI) as one of its most important adverse effects.¹ So-called ‘lung-protective’ ventilation strategies, i.e., ventilation strategies aiming at prevention of VILI, have a strong potential to benefit patients with acute respiratory distress syndrome (ARDS) as well as patients with uninjured lungs.²

What is the best way to protect the lungs during positive pressure ventilation? Should ‘lung-protective’ mechanical ventilation always include the use of low tidal volumes, because clinical studies showed that tidal volume restriction improved outcome of ARDS patients³,⁴ and suggested benefit in patients with uninjured lungs?⁵-⁷ And should it always include higher levels of positive end-expiratory pressure (PEEP), because PEEP up-titration has been shown to improve outcome of ARDS patients?⁸

Recently, another ventilator setting has been suggested that could reduce harm from positive pressure ventilation. In a large cohort of patients with ARDS the “driving pressure”, defined as the plateau pressure or its equivalent minus the level of PEEP, appeared to be strongly and independently associated with mortality.⁹ This review focuses on the interaction between energy dissipated in the lung during positive pressure ventilation as a rationale for aiming for the lowest driving pressure by manipulating tidal volume size and the level of PEEP in individual patients.

History of Ventilator-Induced Lung Injury

Barotrauma versus Volutrauma

Shortly after its introduction, several investigators raised concerns that inflation of the lung with positive pressure ventilation could potentially damage the lungs and produce air leaks.¹⁰ These lesions, termed ‘barotrauma’, were for several years believed to be the most relevant
in the pathogenesis of VILI. Dreyfuss et al. explored whether it was the high airway pressure per se or the resulting tidal volume that led to VILI. The key finding of their landmark preclinical study in which animals were ventilated with various tidal volumes at similar airway pressures was that high tidal volumes, and not high airway pressures, produced VILI. This was called ‘volutrauma’ and from then on researchers considered this more important than barotrauma. Interestingly, the lungs of healthy animals without preceding lung injury also seemed sensitive to ventilation with high tidal volumes suggesting that volutrauma could not only be an entity in ARDS patients, but also in patients with uninjured lungs.

Atelectrauma and Biotrauma

Meanwhile, investigators started to be interested in the beneficial effects of PEEP in the prevention of lung injury. Use of too low levels of PEEP, or no PEEP, was associated with lung injury and lung dysfunction. This effect was thought to result from repetitive opening and closing of lung tissue that collapses at the end of expiration, a phenomenon called ‘atelectrauma’. Positive pressure ventilation was also found to increase pulmonary and systemic levels of inflammatory mediators, responsible for local injury through inflammation and multisystem organ failure, a phenomenon called ‘biotrauma’.

Clinical Evidence for Benefit of Tidal Volume Reduction and Up-Titration of PEEP

Tidal volume restriction

The harmful effects of high tidal volumes in patients with ARDS continued to be considered as unimportant until a series of randomized controlled trials (RCTs) showed mortality reduction with the use of low tidal volumes. Recent clinical studies have shown that tidal volume restriction also prevents pulmonary complications in critically ill patients with uninjured lungs and in surgical patients who receive short-lasting ventilation during general anesthesia.

Up-Titration of PEEP
Although individual RCTs in patients with ARDS showed no benefit from ventilation using higher levels of PEEP, one meta-analysis that used the individual patient data from these trials showed that up-titration of PEEP was associated with improved survival, though only in patients with severe forms of ARDS. The best-protective level of PEEP in critically ill patients with uninjured lungs has never been determined, although physicians have tended to use higher levels of PEEP in recent years. Recent studies suggest that PEEP does not protect against postoperative pulmonary complications in surgical patients ventilated during general anesthesia.

**A New Concept: Energy Transferred From the Ventilator to the Lung**

*Stretch and Strain*

Preclinical studies have shown that damage of lung cells or lung strips is closely related to the amplitude of cyclic stretch, rather than to the maximal or sustained level of maximum stretch. This seems related to the fact that lung cells can slowly adapt and expand their size, especially the size of their external cell membrane (anchored to the extracellular matrix), provided that the imposed stretch is performed in a slow or sustained manner. This process involves exocytosis and active traffic of lipids from the inner cell vesicles to the outer membrane. The inner vesicles rapidly fuse into a large ‘lipid patch’, in close vicinity to the newly formed gaps, resulting in the sealing of the membrane, with decreased wall tension. Extrapolation of these findings to the three-dimensional lung parenchyma predicts that a high, but sustained lung stretch is not necessarily deleterious, with epithelial lung cells preserving their integrity if the cyclic stretch is kept low, or if occurring at a slow pace.

*The Driving Pressure*

Translating these findings to the pressure domain, we should consider that a high plateau pressure or its equivalent does not necessarily represent an increased risk of cell damage, except if accompanied by a high cyclic driving pressure. Corroborating this concept, most of the *in vivo* experiments demonstrating the occurrence of VILI or the deleterious effects of...
cyclic alveolar recruitment consistently used high driving pressures. Similarly, some recent studies trying to prove the major role of absolute lung strain as a key factor for VILI had to conclude that the cyclic strain was, indeed, the most important factor. Moreover, studies in which high inspiratory pressures were associated with lower levels of PEEP, either at equivalent levels of inspiratory lung strain or equivalent levels of plateau pressure, were consistently deleterious, with all of them presenting extremely high levels of driving pressure, the difference between plateau pressure or its equivalent, and the level of PEEP.

‘Energytrauma’

From a physical perspective, the VILI process must be related to the energy transfer from the ventilator to the fragile lung. At each breath, the ventilator transfers some energy to the respiratory system, which must equal the integral of the proximal airway pressure (at the Y connection between the ventilator and the artificial airway) over the volume delivered. This energy is basically spent in four processes: 1) elastic storage of energy (stored in the lung tissue and chest wall); 2) airway resistive losses (energy wasted to move the tidal volume through the upper and lower airways); 3) acceleration of air molecules and masses involved in lung and chest wall deformation (a negligible component during low frequency ventilation); and 4) parenchymal losses, comprising a mixture of phenomena such as plastic tissue deformation, recruitment and de-recruitment of new lung units during the breath, viscous movements within liquid filled airways, stress relaxation of the lung scaffold, and dynamic changes in the surface tension forces due to the complex behavior of the surfactant system. All these latter phenomena are partially responsible for lung hysteresis, i.e., the phenomenon in which the lung conserves energy during one respiratory cycle, with the elastic recoil of the lung always returning less energy during exhalation than that absorbed during inspiration. In other words, there is considerable dissipation of energy, probably resulting in heat and lung tissue damage during each breath. In physical terms, the hysteresis area represents precisely this energy dissipated across the parenchyma (after discounting the energy loss along the airways) and should bear some correlation with VILI.
Interestingly, classical physiological studies have demonstrated that, provided the tidal volume does not vary too much, there is a strong, linear relationship between the hysteresis area and driving pressure, regardless of volume history and regardless of the end-expiratory lung volume. Typically, the hysteresis area represents 10–13% of the total energy transferred from the ventilator to the lung, irrespective of the lung condition. It is also interesting to note that, for a patient in whom the respiratory system compliance ($C_{RS}$) is known, the total energy transfer is proportional to $(\text{driving pressure})^2 \times C_{RS}$. Therefore, the hysteresis area and the total energy transferred are strongly determined by the driving pressure.

**Clinical Evidence for the Benefit of Low Driving Pressure**

Several studies have considered the impact of driving pressure on clinical outcomes (Table 1). In a landmark study in patients with ARDS in Brazil, Amato et al. showed that a protective strategy of ventilation with low tidal volume and high levels of PEEP with recruitment maneuvers decreased 28-day mortality compared to conventional ventilation with high tidal volume and low levels of PEEP without recruitment maneuvers. Since the effect of the protective strategy was observed in the context of many concomitant maneuvers the authors conducted an analysis to determine the key combination of ventilatory variables responsible for the ventilatory treatment effect on mortality. They found that the driving pressure during the first 36 h was independently associated with high mortality. This was the first time that a possible relationship between high driving pressure and worse outcomes had been found.

This finding was confirmed in an Argentinian study in patients with ARDS, in which a higher driving pressure was independently associated with in-hospital mortality. In a cohort of patients in which lung recruitability was studied using computed tomography, de Matos et al. showed that the only ventilatory parameter associated with higher in-hospital mortality was the driving pressure. By contrast, in a retrospective analysis of an RCT comparing ventilation with low tidal volumes versus high tidal volumes, Boussarsar et al. did not find...
an association between driving pressure and development of barotrauma, although this was rather a small study.40

The recent individual patient data meta-analysis by Amato et al.9 using data from several RCTs testing various strategies of positive pressure ventilation in patients with ARDS showed that, irrespective of the plateau pressure, tidal volume size and level of PEEP, the driving pressure was the key ventilatory parameter associated with mortality.9 This was confirmed in a causal mediation analysis, showing that although driving pressure was not an explicit target of the ventilation strategy tested, survival benefits were proportional to reductions in driving pressure driven by treatment group assignments rather than to reductions in tidal volume or increments in PEEP.

In a study focusing on the incidence of cor pulmonale in patients with ARDS undergoing lung-protective ventilation, Boissier et al.41 found that higher driving pressure was associated with development of cor pulmonale as well as increased 28-day mortality;41 these findings were, however, not confirmed in another study.42 More recently, in a subgroup of patients with severe ARDS treated with extracorporeal membrane oxygenation (ECMO) because of refractory hypoxemia, Schmidt et al.43 showed that non-survivors had higher driving pressure before and in the first three days of ECMO compared to survivors.43 Finally, Goligher et al.44 showed that a higher driving pressure was associated with a decrease in contractile activity and decrease in diaphragm thickness in critically ill patients receiving positive pressure ventilation.44

**How to Limit the Driving Pressure?**

It remains uncertain how to achieve a low driving pressure in an individual patient. One strategy that certainly makes sense is to aim for low tidal volumes, as this usually results in low driving pressures. On the other hand, in some patients, tidal volumes remain high, or become higher during the course of ventilation even at a low driving pressure. This suggests that a low tidal volume is not the sole key of protective ventilation.
Another strategy concerns a more adequate up- (or down-) titration of PEEP and the use of recruitment maneuvers. While PEEP up-titration, with or without the use of recruitment maneuvers usually focuses on the impact on oxygenation this may be, at least in part, wrong. For example, if PEEP up-titration, with or without the use of recruitment maneuvers, results in better oxygenation at the price of a higher driving pressure, it could be that the intervention not only resulted in recruitment of lung tissue, but also overdistension of other parts of the lung. Or if PEEP up-titration, with or without the use of recruitment maneuvers, does not affect oxygenation at all but results in a higher driving pressure, the intervention did recruit lung tissue but only caused overdistension. The best response to an up-titration of PEEP, with or without the use of recruitment maneuvers, is a decrease in the driving pressure, meaning that the intervention resulted in recruitment of lung tissue without causing overdistension. As such, energy delivered by or transferred from the ventilator to the lungs decreases, while there is sufficient gas-exchange. Thus PEEP up-titration, with or without recruitment maneuvers, should not be seen as a goal in itself, but as a way to achieve the lowest driving pressure. Of note, it is uncertain what the effects on driving pressures are of other interventions that could lead to recruitment of lung tissue, such as proning.

Limitations of Aiming at Low Driving Pressures

It is well established that VILI results from non-physiological lung stress (transpulmonary pressure) and strain (inflated volume to functional residual capacity ratio), and that transpulmonary pressure (the pressure difference from airway opening to pleural space) is the relevant distending pressure for the lung. This concept is often overlooked when practitioners focus on the plateau pressure without considering the effect of the chest wall in determining lung expansion and stress. The same plateau pressure produced largely variable transpulmonary pressure due to the variability of the lung elastance to respiratory system elastance ratio. This suggests that the plateau pressure is an inadequate surrogate for transpulmonary pressure and driving pressure could suffer from this limitation. Nevertheless, because lung compliance in patients with ARDS is much more affected than
chest wall compliance,\textsuperscript{47,48} approximately 80% of the driving pressure is typically attributable to the lung during inspiration, making it a reasonable surrogate for transpulmonary driving pressure. Moreover, although elevated pleural pressures occur frequently in critically ill patients, especially in the obese or those with large pleural effusions, they are seldom associated with changes in chest wall compliance. Commonly, there is an offset in pleural pressures, causing proportional increases in inspiratory and expiratory pleural pressures, thus not affecting the driving pressure.\textsuperscript{9} Finally, patients with spontaneous breathing activity have pleural pressure decreases during inspiration as a result of their own efforts to breathe, which result in high transpulmonary pressures without the possibility to control the driving pressure.\textsuperscript{48}

Because driving pressure is the tidal increase in static respiratory pressure, it is proportional to tidal volume, with respiratory system elastance being the constant of proportionality. Thus, the ability of driving pressure to predict outcome could be attributable to the fact that variables that define it are known to predict or affect mortality in ARDS.\textsuperscript{48} Finally, the studies reported above were not designed to assess driving pressure as an independent variable, and thus the findings should be considered hypothesis-generating: is it possible to aim for the lowest driving pressure during positive pressure ventilation, and if so, does this strategy truly benefit ventilated patients?

**Conclusion**

A high driving pressure results in more ‘energytrauma’, and as such is a key mediator of VILI in positive pressure ventilation. We are in need of clinical studies that show the best way to limit driving pressures and RCTs that test whether strategies aiming for low driving pressures truly affect the outcome of patients with ARDS, and maybe even those with uninjured lungs.

**Funding**

Support was provided solely from institutional and/or departmental sources.
Table 1 – Studies describing the impact of driving pressure on clinical outcome

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>Number of Patients</th>
<th>Comparison</th>
<th>Primary Outcome</th>
<th>Findings on driving pressure</th>
</tr>
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<tbody>
<tr>
<td>Amato MB, 1998&lt;sup&gt;37&lt;/sup&gt;</td>
<td>RCT</td>
<td>53</td>
<td>Protective vs. Conventional Ventilation</td>
<td>28-day Mortality</td>
<td>Driving pressure associated with high mortality in patients with ARDS (Cox proportional-hazard model)</td>
</tr>
<tr>
<td>Estenssoro, 2002&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Cohort</td>
<td>235</td>
<td>None</td>
<td>In-Hospital Mortality</td>
<td>Higher driving pressure associated with mortality in patients with ARDS (multivariate analysis)</td>
</tr>
<tr>
<td>Boussarsar M, 2002&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>116</td>
<td>None</td>
<td>Barotrauma</td>
<td>Driving pressure was not associated with the incidence of barotrauma in patients with ARDS (direct comparison)</td>
</tr>
<tr>
<td>de Matos GF, 2012&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Cohort</td>
<td>51</td>
<td>None</td>
<td>Lung Recruitability</td>
<td>Higher driving pressure associated with higher mortality in patients with ARDS (multivariate logistic regression)</td>
</tr>
<tr>
<td>Boissier F, 2013&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Cohort</td>
<td>226</td>
<td>None</td>
<td>Cor Pulmonale</td>
<td>Higher driving pressure associated with cor pulmonale and 28-day mortality in patients with ARDS (multivariate logistic regression)</td>
</tr>
<tr>
<td>Amato MB, 2015&lt;sup&gt;9&lt;/sup&gt;</td>
<td>IPD</td>
<td>3562</td>
<td>None</td>
<td>60-day Mortality</td>
<td>Higher driving pressure associated with mortality in patients with ARDS (causal mediation analysis)</td>
</tr>
<tr>
<td>Schmidt M, 2015&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Cohort</td>
<td>168</td>
<td>None</td>
<td>ICU Mortality</td>
<td>Higher driving pressure associated with mortality in patients with ARDS treated with ECMO (direct comparison)</td>
</tr>
<tr>
<td>Goligher EC, 2015&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Cohort</td>
<td>107</td>
<td>None</td>
<td>Diaphragm Thickness</td>
<td>Higher driving pressure associated with decreased contractile activity and decrease in diaphragm thickness in patients under mechanical ventilation</td>
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<tr>
<td>Legras A, 2015&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Cohort</td>
<td>195</td>
<td>None</td>
<td>ACP and PFO</td>
<td>No effect of driving pressure on cor pulmonale or patent foramen ovale in patients with ARDS</td>
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</table>

*RCT: randomized controlled trial; IPD: individual patient data meta-analysis; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; ACP: acute cor pulmonale; PFO: patent foramen ovale*
References


