The Effect of the Pressure–Volume Curve for Positive End-Expiratory Pressure Titration on Clinical Outcomes in Acute Respiratory Distress Syndrome: A Systematic Review
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What is This?
The Effect of the Pressure–Volume Curve for Positive End-Expiratory Pressure Titration on Clinical Outcomes in Acute Respiratory Distress Syndrome: A Systematic Review

J. Steven Hata, MD, FCCP, MSc1,2,3,4, Kei Togashi, MD5, Avinash B. Kumar, MD6, Linda D. Hodges, DO7, Eric F. Kaiser, MD8, Paul B. Tessmann, MD9, Christopher A. Faust, DO10, and Daniel I. Sessler, MD11

Abstract

Purpose: Methods to optimize positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS) remain controversial despite decades of research. The pressure–volume curve (PVC), a graphical ventilator relationship, has been proposed for prescription of PEEP in ARDS. Whether the use of PVC’s improves survival remains unclear. Methods: In this systematic review, we assessed randomized controlled trials (RCTs) comparing PVC-guided treatment with conventional PEEP management on survival in ARDS based on the search of the National Library of Medicine from January 1, 1960, to January 1, 2010, and the Cochrane Central Register of Controlled Trials. Three RCTs were identified with a total of 185 patients, 97 with PVC-guided treatment and 88 with conventional PEEP management. Results: The PVC-guided PEEP was associated with an increased probability of 28-day or hospital survival (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.5, 4.9) using a random-effects model without significant heterogeneity (I² test: P = .75). The PVC-guided ventilator support was associated with reduced cumulative risk of mortality (0.24 (95% CI 0.38, 0.11). The PVC-managed patients received greater PEEP (standardized mean difference [SMD] 5.7 cm H2O, 95% CI 2.4, 9.0) and lower plateau pressures (SMD −1.2 cm H2O, 95% CI −2.2, −0.2), albeit with greater hypercapnia with increased arterial pCO₂ (SMD 8 mm Hg, 95% CI 2.14). Weight-adjusted tidal volumes were significantly lower in PVC-guided than conventional ventilator management (SMD 2.6 mL/kg, 95% CI −3.3, −2.0). Conclusion: This analysis supports an association that ventilator management guided by the PVC for PEEP management may augment survival in ARDS. Nonetheless, only 3 randomized trials have addressed the question, and the total number of patients remains low. Further outcomes studies appear required for the validation of this methodology.

Keywords

acute respiratory distress syndrome, mechanical ventilation, positive end expiratory pressure, systematic review
Introduction

Methods to limit ventilator-associated lung injury in patients with acute respiratory distress syndrome (ARDS) remain a major focus of critical care practice. In recent decades, lung protective strategies have become routine, including reduced tidal volumes and restricting ventilator plateau pressures. Positive end-expiratory pressure (PEEP) has been used to reverse atelectasis associated with ARDS, to improve refractory hypoxemia, and to limit progressive lung injury. Although PEEP has been considered fundamental to the management of ARDS, it reduces venous return, increases right ventricular afterload thereby impairing right ventricular function, and can contribute to barotrauma. Optimizing PEEP to individual patients may improve its efficacy while limiting toxicity. Various clinical strategies of PEEP titration have been used, but the effectiveness of PEEP and the ideal method to prescribe it as an intervention to limit mortality in ARDS remains controversial.

The pressure–volume curve (PVC) is a bedside diagnostic test for evaluating lung properties in mechanically ventilated patients, depicting the graphical relationship between airway pressure and lung volume. Although its theoretical constructs and clinical efficacy have been controversial, the PVC can identify patients whose oxygenation is likely to improve in response to PEEP therapy, mechanistically by reducing atelectasis and limiting lung injury associated with repetitive alveolar opening and closing. Several bedside methods to produce a PVC have been introduced, adaptable to intensive care unit (ICU) mechanical ventilators, with the low, constant flow method comparable to historical methods (eg, Figure 1). In patients with acute lung injury, the PVC typically shows a sigmoidal inspiratory and expiratory relationship of increasing airway pressures and lung volumes. The PVC may be additionally beneficial, albeit controversial, in identifying potentially injurious ventilator tidal volumes in patients with ARDS. The lower inflection point (LIP) is identified during the inspiratory phase of pressure–volume curve at the intersection of lines A and B. Plateau pressure, tidal volume, and arterial carbon dioxide (PaCO₂).

Materials and Methods

Data Sources and Searches

We used a prospective protocol to review the trials in which the effects of using the PVC to adjust PEEP were compared with routine PEEP management in patients with ARDS. We included published, randomized controlled trials (RCTs) in adults, which used a standard definition specified for ARDS and evaluated PEEP support directed by the interpretation of a PVC.

We performed a computer search in PubMed from January 1, 1960, to January 1, 2010, and the Cochrane Central Register of Controlled Trials (Figure 2). There were no restrictions based on language, size, or publication status. Search terms included the key words ARDS, acute lung injury, positive end expiratory pressure, PEEP, and PVC. Observational studies were excluded.

Two teams independently reviewed each candidate study to insure that inclusion and exclusion criteria were met. Data were obtained from the published articles, and the corresponding author was contacted when necessary for additional details. Individual studies were assessed for bias by the 2 reviewing teams. Disagreements about data and study quality were resolved by consensus.

Data Synthesis and Analysis

We compared the overall mortality of PVC-guided PEEP therapy versus the control groups within the identified RCTs to assess the primary mortality outcome. For the purposes of this meta-analysis, we combined both inhospital and 28-day mortality. Secondary comparisons included ventilator tidal volumes, inspiratory plateau airway pressures, arterial PaCO₂,
and PEEP levels. The quality of the RCTs was assessed with a standardized methodology, including study descriptions of randomization, double-blind conduct, withdrawals, and dropouts, requiring consensus of the reviewers.17

Statistical Analyses

For the analysis of the dichotomous primary outcome and differences in mortality, we quantified risk in terms of odds ratio (OR) with 95% confidence intervals (CIs). For the analyses of our secondary outcomes, we expressed continuous variables as standard mean differences (SMDs) with 95% CIs. A 2-sided z-test was performed to assess differences between the PVC guided and routine management of PEEP. Statistical significance was established at a P value of less than .05.

We examined heterogeneity using the I² test18 to assess the proportion of variation across trials that was not due to chance. We used the random-effects model when I² statistics was greater than 25%.18 We did not use funnel plots as a test of publication bias, because the number of studies in our analysis was small. Sensitivity analyses were performed to assess the effect of individual studies on the primary outcomes.19 The meta-analysis and forest plots were performed using Stata 10.1 (Stata Corporation, College Station, Texas).

Results

Trial Characteristics

Three RCTs were identified, which compared PVC-guided PEEP management to routine PEEP management in patients with ARDS.20-22 Of the 3 trials, 2 trials specified the American–European Consensus Criteria for the diagnosis of ARDS23 as part of their inclusion criteria. The study of Amato et al required the diagnosis of ARDS together with a lung injury score20 of ≥2.5. Combining all patients within these 3 trials, there were a total of 185 patients, with 97 assigned to PVC-guided ventilator management and 88 assigned to conventional management. Demographic characteristics, illness severity, factors associated with ARDS, and initial ventilator parameters are shown in Table 1. Pneumonia and sepsis were major factors associated with acute lung injury in all the 3 studies. Exclusion criteria among the studies were highly variable. All the 3 trials set PEEP levels in the interventional groups based upon the assessment of the LIP of the PVC.

Primary Outcomes: Mortality

Survival data from all 3 RCTs supported an overall reduction in mortality comparing PVC-guided versus routine ventilator care (Table 2). Use of the PVC was associated with a significantly increased OR of survival, based on 28-day mortality and hospital mortality statistics, in this high-risk patient population (OR 2.7, 95% CI 1.5, 4.9) as shown in Figure 3. The cumulative risk reduction was −0.24 (95% CI −0.38, −0.11). The I² test failed to show significant heterogeneity (P = .75) among the studies. None of the trials assessed 6-month or 1-year survival. Based on the mortality event rate of 0.60 for the control group and 0.36 for the PVC group within the overall sample, the number needed to treat was 4.1 patients. The estimated number of avoidable deaths was thus 244 per 1000 comparable patients (CI 98, 367).

Secondary Outcomes: Differences in Mechanical Ventilation Support

Use of the PVC appeared to affect several parameters in the prescription of mechanical ventilation in the respective patient populations. Patients exposed to the PVC were treated with increased levels of PEEP when compared to the conventional groups. The SMD in PEEP based upon the PVC was 5.7 cm H₂O (95% CI 2.4, 9.0) as shown in Figure 4. This analysis, however, was associated with significant heterogeneity (P < .001). As shown in Figure 5, the ventilator plateau pressure was decreased in the overall patient sample comparing those exposed to the PVC with the conventional group (P < .001). This difference, again, was associated with significant heterogeneity (P = .001).

The PVC-guided ventilator management was associated with significant hypercapnia; the pooled SMD in arterial PaCO₂ among the 3 RCTs between the PVC-guided versus conventional ventilator management was 8 mm Hg (95% CI
Table 1. The Patient Demographics and Respiratory Function Before Randomization in the 3 RCTs.a

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Amato</th>
<th>Ranieri</th>
<th>Villar</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP Management</td>
<td>Conventional</td>
<td>PVC</td>
<td>Conventional</td>
<td>PVC</td>
</tr>
<tr>
<td>Number of patients</td>
<td>24</td>
<td>29</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>NA</td>
<td>NA</td>
<td>9 (47)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>36 (14)</td>
<td>33 (13)</td>
<td>49 (18)</td>
<td>51 (18)</td>
</tr>
<tr>
<td>APACHE II (mean ± SD)</td>
<td>27 (6)</td>
<td>28 (7)</td>
<td>14 (3)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Lung injury score (mean ± SD)</td>
<td>3.2 (0.4)</td>
<td>3.4 (0.4)</td>
<td>2.5 (0.6)</td>
<td>2.5 (0.5)</td>
</tr>
<tr>
<td>PaO2 (mean ± SD)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>FiO2 (mean ± SD)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>134 (67)</td>
<td>112 (51)</td>
<td>142 (56)</td>
<td>149 (66)</td>
</tr>
<tr>
<td>Total</td>
<td>768 (13) mL²</td>
<td>348 (6) mL</td>
<td>11.1 (1.9) mL/kg</td>
<td>7.6 (1.1) mL/kg</td>
</tr>
</tbody>
</table>

Abbreviations: AECC, American European Consensus Conference; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; LIS, lung injury score; PaO2, not available; PaCO2; PEEP, positive end-expiratory pressure; Plat, plateau pressure; PVC, pressure–volume curve; RCT, randomized, controlled trial; SD, standard deviation; UIP, upper inflection point.

aThe ventilator tidal volumes performed within the PVC-guided groups are shown along with the tidal volumes of the conventional ventilation groups.

Table 2. The Proportion of Hospital Survivors Comparing Patients Exposed to the Pressure–Volume Curve When Compared With the Control Group in the 3 Identified RCTs of ARDS.a

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>PVC (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato et al20</td>
<td>1998</td>
<td>18 of 29 (62)</td>
<td>7 of 24 (29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ranieri et al22</td>
<td>1999</td>
<td>11 of 18 (61)</td>
<td>8 of 19 (42)</td>
<td>.19</td>
</tr>
<tr>
<td>Villar et al21</td>
<td>2006</td>
<td>33 of 50 (66)</td>
<td>20 of 45 (44)</td>
<td>.018</td>
</tr>
<tr>
<td>Total</td>
<td>1998-2006</td>
<td>62 of 97 (64)</td>
<td>35 of 88 (40)</td>
<td>.001b</td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; PVC, pressure–volume curve; RCT, randomized, controlled trial.

aThe Level of Significance is as Reported in the Original Studies.

Sensitivity Analysis

A sensitivity assessment was performed to evaluate the influence of each individual trial on overall survival outcome, systematically removing each of the 3 studies and repeating the meta-analysis to understand the effect of the pooled results. When the study of Amato et al was removed, analysis of the 2 remaining studies showed that PEEP adjustment based on the PVC increased the overall survival (OR 2.3, 95% CI 1.2, 4.7) without significant heterogeneity (P = .88). With the removal of Ranieri et al, PEEP adjustment based on the PVC similarly increased likelihood of survival (OR 2.9, 95% CI 1.5, 5.6) without significant heterogeneity (P = .497). Finally, exclusion of Villar et al showed that PVC-guided care increased survival (OR 3.0, 95% CI 1.3, 7.3) without significant heterogeneity (P = .495).

Discussion

The results of this systematic review support that exposure to a ventilator management strategy in which PEEP is titrated by the PVC is associated with enhanced survival in the...
management of ARDS. Our findings contrast the results of other studies evaluating other methods of prescribing PEEP with the primary outcome of mortality in ARDS. That ventilator tidal volume is an important determinant of ARDS outcome is well established by the ARDSNet trials.25-27 Those studies concluded that the use of higher levels of PEEP did not improve survival when comparing a low-versus high-PEEP support strategy while controlling for excessive ventilator plateau pressures.25 Importantly, the ARDSNet trial relied upon a nomogram based upon FiO₂ requirements to assign PEEP. Similarly, Meade et al evaluated an “open lung” approach that emphasized increased levels of PEEP, based upon a nomogram using FiO₂ requirements. The trial showed no differences in all-cause hospital mortality, 28-day mortality, ICU mortality, or death during mechanical ventilation. Patients within the high-PEEP group, however, showed less refractory hypoxemia and decreased need for rescue therapies, such as inhaled nitric oxide, prone ventilation, high-frequency oscillation,

Figure 3. This forest plot shows the increased odds ratio for survival when pressure–volume curves were used to guide positive end-expiratory pressure (PEEP) management in patients with acute respiratory distress syndrome (ARDS) compared with conventional ventilation management strategies.

Figure 4. As shown in this forest plot, the use of pressure–volume curves to guide positive end-expiratory pressure (PEEP) management significantly increased PEEP (cm H₂O) when compared with the conventional ventilation group.
high-frequency jet ventilation, or extracorporeal membrane oxygenation. Recently, a systematic review and meta-analysis assessed RCTs comparing high-to-low PEEP with controlled ventilator inspiratory plateau pressures in all the groups and found no differences in hospital mortality between the groups. Similarly, a systematic review, evaluating interactions of ventilator tidal volume and PEEP levels, concluded that in patient populations with ARDS or acute lung injury improved survival outcomes were associated with low-ventilator tidal volume strategies but not with strategies of high-PEEP ventilation. Subgroup analyses supported the role of higher PEEP in reducing the need for rescue therapies for refractory hypoxemia and death in this specific patient group. It is germane to state that the methods of PEEP titration in these prior investigations differed from our focus on PVC-guided therapy, as the previous investigations used largely empiric or nomogram-guided-based protocols.

Using PVCs to guide PEEP is not a new concept. It has been shown to facilitate management of otherwise refractory hypoxemia and appears to ameliorate the systemic and

Table 1: Comparison of Pressure–Volume Curve (PVC)-Guided Positive End-Expiratory Pressure (PEEP) with Conventional Ventilator Strategies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>SMD (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato</td>
<td>1998</td>
<td>-1.58 (-2.20, -0.96)</td>
<td>33.13</td>
</tr>
<tr>
<td>Ranieri</td>
<td>1999</td>
<td>-1.76 (-2.53, -1.00)</td>
<td>31.04</td>
</tr>
<tr>
<td>Villar</td>
<td>2006</td>
<td>-0.33 (-0.73, 0.08)</td>
<td>35.83</td>
</tr>
<tr>
<td>Overall (I-squared = 88.3%, p = 0.000)</td>
<td></td>
<td>-1.19 (-2.18, -0.20)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 5. This forest plot shows decreased standardized mean difference in ventilator plateau pressure (cm H2O) comparing pressure–volume curve (PVC)-guided positive end-expiratory pressure (PEEP) with conventional ventilator strategies.

Figure 6. This forest plot shows the increased standardized mean difference in PaCO2 (mm Hg) between pressure–volume curve (PVC)-guided and conventional ventilator management within the 3 identified randomized controlled trials.
bronchoalveolar inflammatory response in patients with ARDS. With advances in ventilator technology, these curves have been routinely displayed on critical care ventilators. The use of PVC-guided PEEP to conventional PEEP control has only been formally compared in 3 randomized trials. The results, compared in our meta-analysis, were reasonably homogeneous and strongly suggest that PVC-guided PEEP management in adults with ARDS is associated with a reduction in mortality, with a number needed to treat of only 4.

The biological effect of a diagnostic maneuver such as the PVC and the improvement in lung function and associated outcomes appear through optimization of PEEP. However, it does not follow that a simpler prescription of the type used in previous “low versus high” trials will improve outcome, since the optimal end-expiratory pressure probably differs substantially among the patients. Consistent with this theory, a recent systematic review evaluating low versus high PEEP showed no significant difference in short-term mortality or risk of barotrauma in ARDS. In contrast, our analysis suggests that a PVC through an optimal PEEP prescription can improve pulmonary function—recognizing that the optimal pressure may change substantially over time in an individual as underlying ARDS pathology waxes and wanes.

Although the focus of each study we reviewed is the LIP of the PVC, the upper inflection point may contribute to ventilator management by helping to avoid iatrogenic lung overdistention. We cannot exclude the possibility that positive results in each of the studies we evaluated resulted from the interactive effects of PVC-guided PEEP, with the overall reduction in ventilator tidal volumes or plateau pressures. Within the study of Ranieri et al, plateau pressures were set by protocol to less than the upper inflection point of the PVC unless it could not be determined. In the study by Amato et al, however, tidal volumes were maintained less than 6 mL/kg in the protective ventilation group by protocol. This investigation also included lung recruitment maneuvers and pressure-controlled, inverse ratio ventilator modes that may have contributed to improved outcomes in the treatment group. Within the lung protective group by Villar et al, ventilator tidal volumes were set at 5 to 8 mL/kg based on the patient’s body weight. In these latter trials, it remains unclear from the published protocols whether the upper inflection point of the PVC influenced management. Nonetheless, overall weight-based tidal volumes were significantly decreased in both Ranieri et al and Villar et al.

The PVC-guided care was associated with significant hypercapnia. Although this management strategy may be contraindicated in selected patients, permissive hypercapnia appears to offer a survival advantage in subsets of patients with ARDS. The potential for beneficial effects of permissive hypercapnia in the support of patients with ARDS is controversial from a mechanistic viewpoint. It may represent a passive finding related to protective mechanical ventilation limiting lung injury, with reduction in tidal volumes and excessive ventilator rates. Others have proposed that permissive hypercapnia may attenuate reperfusion injury, directly protecting against free radical-induced lung injury, and limit injury to other organs. Our results, within the context of the identified PVC-guided trials, are consistent with improved survival with a management strategy allowing permissive hypercapnia.

The validity of our findings, as with any systematic review, is limited by heterogeneity among the studies. Although our results of secondary analyses were heterogeneous, the primary survival outcome was homogeneous for beneficial effects of PVC-guided PEEP management. Major factors contributing to heterogeneity among the 3 trials could result from differences in inclusion and exclusion criteria, variations in patient characteristics, variations and timing of initiation of other parameters of ventilator management and supportive care, primary etiologies of ARDS, length of follow-up, and the range of years during which the studies were performed. Our analysis of survival required combining the end points of 28-day survival (Amato et al and Ranieri et al) and hospital mortality (Villar et al). This limitation could contribute to heterogeneity in survival outcomes to the extent of the proportional differences between these time periods.

A limitation of this analysis is that other factors in addition to PEEP could influence outcomes in this high-risk population. The effect of differences in tidal volume between the experimental and the control groups cannot be excluded, a contributing factor in the observed, survival differences. In the trial of Ranieri et al, the PVC directed the ventilator tidal volume prescription, using the upper inflection point as a marker of lung overdistention. In the studies by Villar and Ranieri, ventilator tidal volumes were determined using ideal body weight in both the interventional and the control groups. In contrast to the differences in PEEP prescriptions, the overall differences in ventilator plateau pressure were small (Figure 5). In our review, there were no published studies identified in ARDS trials comparing a low-tidal volume strategy with PEEP settings set by PVC with a control arm of PEEP set by other means. In all of the 3 investigations in this review, the PVC-directed groups used higher PEEP levels, lower ventilator plateau pressures, and smaller tidal volumes. It is plausible that additive effects of these interventions limited lung injury and contributed to the observed outcomes.

Although randomization was used in all the studies within this analysis, there is a potential that failure of concealment of methods of the ventilator prescription could have influenced findings. Furthermore, none of the studies used the specific ventilator tidal volume or PEEP prescription methods of the ARDSNet trial. Of the 3 studies, 2 (Amato and Ranieri) studies were performed before the year 2000. It is plausible that other improvements in supportive care have reduced mortality; however, there is no reason to believe that the observed treatment effect would differ. Furthermore, sensitivity analysis indicates that exposure to PVC-guided PEEP therapy was associated with greater survival benefits in analyses excluding each of the cited trials.

Conclusion
In summary, clinical studies addressing the best method to target optimal PEEP in mechanically ventilated patients with
ARDS have been conflicting. The plausible benefits of the PVC have been suggested for decades as a bedside tool to guide ventilator management. This meta-analysis supports that PVC-guided PEEP management appears associated with reduction in ARDS mortality with a number needed to treat of 4. The small number of randomized trials using the PVC to guide PEEP in ARDS and the confounding influence of tidal volume heterogeneity between the experimental and the control groups support the need for further investigation in lung protective strategies.

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