Using exhalation dynamics to evaluate PEEP levels in COVID-19 related ARDS

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Research

Keywords: expiratory time constant, COVID-19, acute respiratory distress syndrome, positive end-expiration pressure, PEEP titration

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Abstract

Background

We hypothesized that measured expiratory time constant (TauE) could be a bedside parameter for evaluation of PEEP settings in mechanically ventilated COVID-19 patients during pressure-controlled ventilation (PCV) mode. TauE is an easily measured parameter to assess lung physiology, even in non-homogeneous lungs including COVID-19 ARDS.

Methods

A prospective study was conducted including consecutively admitted adults (n = 16) with COVID-19 related ARDS requiring mechanical ventilation. Ventilator settings for all patients included: PCV, RR 18/min, constant inspiratory pressure 14 cmH_2O, I:E ratio 1:1.5 and FiO_2 1.0. Escalating levels of PEEP (0 to 18 cmH_2O) were applied and measured TauE and expiratory tidal volume (Vte) recorded. Next, a new parameter, TauE Index (TEI) was calculated (TEI = TauE * Vte) at each PEEP level in prone (n = 29) or supine (n = 24) positions. TEI maps were created to graphically show changes in individual physiology with PEEP. The PEEP setting with the highest TEI corresponded to the highest product of TauE and Vte and was considered the most suitable PEEP. Most suitable PEEP range was calculated as ± 10% from highest TEI.

Results

Two groups of patterns were observed in the TEI maps, recruitable (R) (75%) and non-recruitable (NR) (25%). In R group, the most suitable PEEP and PEEP range was 9±3 cmH_2O and 6-12 cmH_2O for prone position and 11±3 cmH_2O and 7-13 cmH_2O for supine position. In NR group, the most suitable PEEP and PEEP range was 7±3 cmH_2O and 0-8 cmH_2O for prone position and 4±2 cmH_2O and 0-7 cmH_2O for supine position, respectively. The R group showed significantly higher suitable PEEP (p<0.01) and PEEP ranges (p<0.01) than NR group. 45% of measurements resulted in most suitable PEEP being significantly different between the positions (p < 0.01).

Conclusions

Based on TEI mapping, responses to PEEP were easily measured. There was wide variation in patient responses to PEEP that indicate the need for personalized evaluation.

Introduction
Mechanical ventilation has been an integral method used in ICU care for decades [1]. Although it can be a life-supporting intervention including with COVID-19, it can also contribute to lung injury through stress and strain, referred to as ventilator induced lung injury (VILI), even in previously healthy lungs [2]. The impact may be worse when significant lung non-homogeneity is present as with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Therefore, the ultimate goal of protective ventilation is the preservation of function of healthy areas (e.g. prevention of overdistension) and to decrease ventilation inhomogeneity (e.g. increased lung aeration). In the conventional protective ventilation strategy, which combines low tidal volume (Vt) with sufficient positive end-expiratory pressure (PEEP), the selection of the optimal PEEP level to balance recruitment and avoid overdistension for an individual patient is still heavily-debated in clinical practice [3, 4, 5]. Therefore, a personalized approach to mechanical ventilation is deemed necessary. Studies expressing best recruitment with highest lung compliance, or other methods during inspiration, might be biased as inspiratory mechanics (or lung response to Vt delivered) are modified by set inspiratory parameters (e.g. modes of ventilation, inspiratory flows, pressures and times) [6, 7].

Contrary to previous work that evaluated recruitment during inspiration, we decided to assess lung mechanics during exhalation as it is presumed to be a passive process, even in mechanically ventilated patients. To do so, we used pulmonary mechanics and the expiratory time constant (TauE). The TauE determines the rate of change in the volume of the lung. There is a 63% change in expiratory tidal volume during the first TauE [8]. The TauE determines the rate of change in the volume of the lung and is comprised of static compliance (Cst) and airway resistance (Raw) [9]. Measured TauE is significantly different from calculated due to the non-homogeneity of the lung and difficulties associated with measuring an accurate single measurement of Raw and Cst.

In contrast to calculated time constants, measured TauE reflects changes of the whole respiratory system including artificial airways, breathing circuits, humidification devices and mechanical ventilator [10]. Due to dynamics of lung mechanics during non-homogenous lung ventilation, TauE changes frequently, and therefore the term ‘constant’ should be referred to only at the particular time of the measurement (e.g TauE of 0.6 seconds at PEEP of 8 cm H2O might differ significantly after a few hours with the same ventilator settings in the same patient). Changes in TauE reflect not only changes in lung physiology (compliance and resistance) but also changes in tidal volume. Increases in TauE due to increases in PEEP are likely due to recruitment (increased tidal volume and increased compliance) while decreases in TauE are likely due to overstretching the alveoli. There is a complex balance between these two phenomena in nonhomogeneous lungs. Multiplying expiratory volume (Vte) and speed through which 63% of that volume was exhaled (TauE) creates a new parameter called TauE Index (TEI).

The purpose of this study was to evaluate the impact of multiple PEEP levels using passive elastic recoil of the lungs by measuring Vte and its corresponding exhalation time (TauE). Measuring TauE and creating TEI may allow for simple evaluation of the previously mentioned competing issues.

Materials And Methods
Study design and participants

This prospective study was performed in the COVID ICU department in a tertiary center (East Slovak Institute for Cardiovascular Diseases, Slovakia). Approval was obtained by the Institutional Ethics Committee. Because of critical illness and the generally recognized PEEP titration method, informed consent was waived. Consecutively admitted patients (n = 16) diagnosed with COVID-19 pneumonia confirmed by PCR test were enrolled in the study. Oxygenation in these patients did not improve (SpO$_2$ < 85%) using either non-invasive ventilation (NIV, PEEP > 5 with FiO$_2$ > 0.8) or high-flow nasal cannula (HFNC) (flow = 60 lpm, FiO$_2$ = 0.8) and therefore intubation and mechanical ventilation was required. Patients fulfilled the criteria of moderate or severe ARDS according to Berlin definition (PaO$_2$:FiO$_2$ ratio < 150 with PEEP > 5 cmH$_2$O) [11]. As part of clinical care, all subjects were sedated using continuous infusion of propofol and sufentanyl and received neuromuscular blockade with either atracurium or rocuronium. All patients were lying flat with zero-degree head elevation at the time of measurement, in either supine or prone position.

TauE was measured using a mechanical ventilator (Aura V, Chirana Medical, Stará Turá, Slovakia). The following ventilation parameters were used for all patients: pressure-controlled ventilation mode (PCV), frequency of 18 breaths/min, I:E ratio was 1:1.5, maximal inspiratory flow was set to 60 lpm. Tube compensation (TC) on the ventilator was set to 0%. Before measurements, patients were preoxygenated with 100% oxygen for 5 minutes. Then an end-expiratory pause with zero end-expiratory pressure (ZEEP) was applied for 6 seconds to achieve full exhalation. An inspiratory pressure of 14 cmH$_2$O was applied on top of each PEEP. PEEP levels were in escalating order of 0, 5, 8, 10, 12, 15 and 18 cmH$_2$O. Values recorded at each PEEP level included: Vte and TauE. TauE was recorded as an average value from the last 10 of 15 consecutive breaths at each PEEP level. TauE required approximately 5 breaths to equilibrate after each change in PEEP level, therefore the TauE average included only the last 10 breaths of each level where TauE showed minimal variation (± 0.01 sec).

Method of TauE measurement (Iteration method)

The first expiratory time constant (TauE) is the time required for deflation of an end-inspiratory volume by 63%, during the passive exhalation (Figure 1).

The mechanical ventilator measured the time required to exhale 63% of the Vte in the previous breath. Measured TauE was then displayed on the ventilator and recorded. Based on TauE and Vte, a TauE Index (TEI) at each PEEP level was created (Equation 1).

$$\text{TEI} = \text{TauE} \times \text{Vte}$$ (1)

Outcome Measurements

The primary outcome of this study was to identify an appropriate PEEP and/or PEEP range for each patient. Most suitable PEEP was defined as the PEEP level where the highest TEI was found on the map.
of PEEP vs. TEI, and the optimal PEEP range was identified as the PEEP levels with TEI within 10% of its peak value. Secondary outcomes were to compare differences in most suitable PEEP in prone vs. supine position and comparing single most suitable PEEP and/or PEEP range using Vt. Because PEEP titration was performed using constant pressure during PCV, Vt was used as a surrogate for $C_{st}$. Finally, patterns found were analyzed and grouped according to the lung recruitability.

**Statistical Analysis**

Categorical data are expressed as n (%), continuous data were expressed as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data for continuous variables. Data were analyzed using statistical software (MATLAB, version R2018a, The MathWorks Inc, Natick, MA, USA).

**Results**

Fifty-three PEEP titrations were performed in prone (n = 29) and supine (n = 24) position. 12 patients were measured in supine and prone position within 15 min of position change and 6 patients were measured repeatedly in intervals of 12 hours to 5 days after admission during their course of COVID-19. Baseline patient characteristics are shown in Table 1.
### Table 1 - Demographic and clinical characteristics of patients in the first 24 hours of ICU admission due to COVID-19.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>58 [46,66]</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), median (IQR)</td>
<td>33 [28,38]</td>
</tr>
<tr>
<td><strong>Scoring systems on admission</strong></td>
<td></td>
</tr>
<tr>
<td>APACHE II score, median (IQR)</td>
<td>13 [12,19]</td>
</tr>
<tr>
<td>SOFA score, median (IQR)</td>
<td>7 [5,9]</td>
</tr>
<tr>
<td>P/F ratio, mean (SD)</td>
<td>74 (±31)</td>
</tr>
<tr>
<td><strong>Medical History, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (62%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Cardiovascular disease (^a)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>COPD/Asthma</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (30%)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Others (^b)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td><strong>Adjunctive therapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Prone position</td>
<td>14 (87%)</td>
</tr>
<tr>
<td>NMBA</td>
<td>15 (94%)</td>
</tr>
<tr>
<td>Corticosteroids for COVID-19 (^c)</td>
<td>16 (100%)</td>
</tr>
<tr>
<td>VV-ECMO</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>CRRT</td>
<td>7 (43%)</td>
</tr>
<tr>
<td><strong>Outcomes, median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Duration of MV (days)</td>
<td>11 [7,36]</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>14 [9,47]</td>
</tr>
</tbody>
</table>

\(^a\)Cardiovascular disease includes chronic heart failure, \(^b\)Other includes endocrine disorders, neurologic disorders, chronic liver disease, \(^c\)dexamethasone 8 mg/day while on mechanical ventilation

From 53 TEI maps obtained, recruitable (R) (75%) and non-recruitable (NR) (25%) patterns were observed (Table 2). Within the recruitable group, two additional patterns emerged, termed the ‘hill’ pattern (67%) and the ‘flat’ pattern (8%). Non-recruitable patterns showed a decreasing curve with increasing PEEP and
therefore all non-recruitable TEI maps were termed ‘descending’ (25%). PEEP values within 10% from the peak TEI were considered suitable PEEPs and are indicated by colored boxes on the maps.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEANING</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECRUITABLE (R)</td>
<td>TEI shows evidence of recruitment</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>‘hill’ pattern</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>TEI increased significantly across PEEP range (Fig. 2a)</td>
<td>(67%)</td>
</tr>
<tr>
<td></td>
<td>‘flat’ pattern</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>TEI did not increase or decrease significantly across PEEP range (Fig. 2b)</td>
<td>(8%)</td>
</tr>
<tr>
<td>NON-RECRUITABLE (NR)</td>
<td>TEI did not show evidence of recruitment</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>‘descending’ pattern</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TEI decreased significantly across PEEP range (Fig. 2c)</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 2 – Pattern groups and shapes based on TEI mapping

Three categories of TEI maps and the regions (colored boxes) where TEI is within 10% of the peak are shown in Figure 2. The ‘Hill’ pattern (Figure 2a) was most common (67% of PEEP titrations) in our cohort and showed a rising and then falling TEI pattern. With increasing Vte and TauE during PEEP titration there is recruitment that increases TEI until overdistension begins to dominate as PEEP increases further (lower Vte and shorter TauE, and thus lower TEI, indicating higher speed of elastic recoil). The ‘Flat’ pattern (Figure 2b) was found in 7% of the PEEP titrations. In these patients, TEI did not change by more than 10% across a broad range of PEEPs (very similar Vte and TauE), indicating that any recruitment was balanced by increased stretch of the alveoli that were recruited at lower PEEPs. The ‘descending’ pattern (Figure 2c) was found in 25% of PEEP titrations and showed that either Vte and/or TauE (and therefore also TEI) decreased with increasing PEEP. Overdistension likely dominated recruitment in these patients.

Statistics regarding most suitable PEEP and PEEP range for both, the Recruitable and Non-recruitable groups in both prone and supine positions are shown in Table 3. It can be seen that the recruitable group showed significantly higher suitable PEEP and PEEP ranges than non-recruitable group (p < 0.01). With the non-recruitable group, best recruitment was shown with very low PEEP levels.
### PEEP Analysis Using TEI (n = 53)

<table>
<thead>
<tr>
<th></th>
<th>PRONE POSITION</th>
<th>SUPINE POSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 29</td>
<td>n = 24</td>
</tr>
<tr>
<td></td>
<td>Recruitable</td>
<td>Non-recruitable</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Vte (ml/kg/PBW)</td>
<td>9.2 (1.3)</td>
<td>7.9 (1.2)</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>9 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>PEEP Range (cmH₂O) **</td>
<td>6 - 12</td>
<td>0 - 8</td>
</tr>
</tbody>
</table>

**Table 3** - Analysis of all 53 PEEP titrations showing most suitable PEEP and PEEP range using TauE Index (TEI). Standard deviations are shown in parenthesis. * most suitable PEEP based on highest TEI value, ** most suitable PEEP range based on highest TEI ± 10%, Vte – expiratory tidal volume, PBW – predicted body weight

### Prone vs. Supine Analysis

In a subset of subjects, TEI was also used to compare PEEP titrations in prone and supine positions measured within 15 minutes of each other. Summary statistics for these 40 PEEP titrations are shown in Table 4. Although there are differences between recruitable and non-recruitable most suitable PEEP and PEEP ranges, there was little difference in the mean values between prone and supine positions.

<table>
<thead>
<tr>
<th></th>
<th>PRONE POSITION</th>
<th>SUPINE POSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 20</td>
</tr>
<tr>
<td></td>
<td>Recruitable</td>
<td>Non-recruitable</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Vte (ml/kg/PBW)</td>
<td>7.9 (1.1)</td>
<td>7.9 (1.2)</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>8 (1)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>PEEP Range (cmH₂O) **</td>
<td>6 - 12</td>
<td>0 - 8</td>
</tr>
</tbody>
</table>

**Table 4** - Analysis of 40 PEEP titrations comparing prone vs. supine positions (each patient measured in both positions 15 minutes apart), showing most suitable PEEP and PEEP range using TauE Index (TEI). Standard deviations are shown in parenthesis. * most suitable PEEP based on highest TEI value, ** most suitable PEEP range based on highest TEI ± 10%, Vte – expiratory tidal volume, PBW – predicted body weight

However, in some cases there were significant differences between the measurements in prone and supine position on the same patient. Figure 3 shows two examples of patients where supine and prone measurements indicated very different values of most suitable PEEP and PEEP range as well as differences between recruitability.
Figure 4 shows a combined plot of 40 PEEP titrations (20 pairs) performed where both prone and supine measurements were made in succession (15 minutes apart). There were 18 (45%) PEEP titrations where the most suitable PEEP in supine vs prone position was different by at least 4 cmH\textsubscript{2}O in this cohort. In addition, in 6 PEEP titrations (15%) the most suitable PEEP ranges did not overlap at all. In 20 PEEP titrations (50%) the most suitable PEEP was the same. In 10 PEEP titrations (25%) prone position showed superior TEI at all PEEP levels and in 10 PEEP titrations (25%) supine position showed superior TEI at all PEEP levels. In 16 measurements (40%) best overall TEI was found in the prone position and in 16 measurements (40%) the best overall TEI was found in the supine position (in the remaining 8 PEEP titrations (20%) the best TEI was essentially the same between prone and supine positions).

**TEI vs Vte Comparison**

For comparison, we calculated most suitable PEEP and PEEP range using Vte in the same way as obtained using TEI (Table 5). Comparing the most suitable PEEP range as dictated by TEI vs. Vt differed significantly in Recruitable group for both, prone (p = 0.016) and supine (p<0.02) position (Table 5). The smaller PEEP range obtained by TEI was attributed mainly to shorter time constants at different PEEP levels. In the Non-recruitable group, the difference in PEEP range was not significant in prone (p=0.19) or supine position (p=0.24).

<table>
<thead>
<tr>
<th>PRONE POSITION</th>
<th>SUPINE POSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 29</strong></td>
<td><strong>n = 24</strong></td>
</tr>
<tr>
<td><strong>Recruitable</strong></td>
<td><strong>Non-recruitable</strong></td>
</tr>
<tr>
<td>PEEP TEI (cmH\textsubscript{2}O)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>PEEP Vte (cmH\textsubscript{2}O)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>PEEP Range TEI (cmH\textsubscript{2}O)</td>
<td>6 - 12</td>
</tr>
<tr>
<td>PEEP Range Vte (cmH\textsubscript{2}O)</td>
<td>5 - 14</td>
</tr>
</tbody>
</table>

**Table 5** - Comparison of the most suitable PEEP and PEEP range using highest TEI vs highest Vt in all 53 PEEP titrations. PEEP range was identified as highest TEI or Vte ± 10%. Standard deviations are shown in parenthesis.

**Discussion**

The main finding of this study was that TauE and its related TEI were able to assess physiologic responses to changes in PEEP, including recruitability in non-homogenously affected lungs. Secondly, when similar TEI is obtained at various PEEP levels (e.g. 5-10 cmH\textsubscript{2}O or 8-15 cmH\textsubscript{2}O), a range of PEEP values were identified that yielded similar lung mechanics.
Measuring TEI may be used to determine suitable PEEP for multiple reasons: First, a higher compliance produces higher TauE, resulting in a larger TEI. Also, studies have shown that $R_{aw}$ changes during PEEP titration, showing a decrease with increasing PEEP [12,13]. Because $C_{st}$ and $R_{aw}$ vary with Vt, time constants differ between inspiration and exhalation and also within different lung regions [14]. Second, PEEP levels that increase Vt due to recruitment will create a larger TEI. Third, a Vt exhaled over longer TauE will result in a larger TEI (e.g. if 63% of 500 ml tidal volume is exhaled in 0.8 seconds at low-to-moderate PEEP, or 0.4 seconds is needed for the same amount of gas to be exhaled at higher PEEP levels, or vice-versa). Because of the aforementioned reasons, TauE and TEI may also prove superior for determining the suitable PEEP due to integrating changes of compliance, resistance and therefore also changes in Vt.

Larger values of TEI indicated greater product of Vte and TauE and greater time necessary to reach complete exhalation. This observation also led to the conclusion that maximum recruitment was usually associated with highest TauE and therefore TEI. Conversely, if Vte or TauE and therefore TEI were not changing significantly during ascending PEEP levels or were decreasing, the increased force of elastic recoil associated with higher PEEP was overshadowing any potential recruitment. This finding demonstrates that not only Vt, but also time through which particular Vt is exhaled, should be considered important when assessing optimal PEEP.

In the limited and existing evidence regarding TauE, no study has used TauE to assess changes in physiology associated with PEEP titration. The value of TEI lies in an integration of all aspects of lung emptying during passive exhalation, namely emptying of different areas of the non-homogenous lungs (short and long TauE compartments) and different regional compliances and resistances (laminar or turbulent flows in a different TauE areas of the ARDS lung).

It has been shown that aerated and ventilatable parenchyma in severe ARDS is markedly reduced [15,16]. Knowing the potential for recruitability may provide important information about the functional concept of ‘baby lungs’. It can be assumed that the ‘hill’ pattern shows recruitment, the ‘flat’ pattern shows an almost equal trade off of recruitment and overdistension, and the ‘descending’ pattern shows lungs that cannot be recruited even at high PEEP values. Using these patterns, various degrees of baby lungs may be identified. With the ‘flat’ pattern where TEI does not change significantly across the PEEP range, higher PEEP levels might not be that harmful in terms of VILI (same Vte exhaled over the same TauE across the whole range of PEEPs). With the ‘descending’ pattern, we assume that higher PEEP levels will be harmful due to overdistention of relatively healthy areas of the ‘baby lung’ as there is no evidence of recruitability. Exposing non-homogenous lungs to diagnostic PEEP titration may therefore be well justified.

Studies have shown that using universally higher vs. lower PEEP for ventilating ARDS patients did not prove to be beneficial in terms of mortality [17,18]. On the other hand, it has been shown that utilization of higher PEEP has improved mortality in a subgroup of ARDS patients who responded to increased PEEP by improved oxygenation [19] or have been hypothesized to show recruitability [20]. Obtaining TEI maps
and patterns that show recruitability might be beneficial in selecting those patients who may benefit from higher PEEPs.

The use of prone positioning has been well described in patients with COVID-19 ARDS [21,22]. Our measurements suggest that we may be able to identify more favorable pulmonary mechanics in terms of recruitment and PEEP levels in supine and prone position and therefore predicting those patients benefiting from either position (Figure 4).

From the TEI maps constructed in the sequential study of the same patients, pulmonary mechanics shifted as ARDS was changing over time. Therefore, ventilation and PEEP optimization may be required more frequently than previously thought, and TEI maps may be an efficient method of assessing these changes quickly.

Expiratory time constant and constructed TEI maps to find a suitable PEEP range can be performed at the bedside, it is fast, practical, repeatable, non-invasive, does not pose any radiation risk, nor does it require patient transport to other hospital locations (e.g. CT). Taking these findings into account, individual PEEP optimization settings based on assessing TauE and TEI may be easily performed, allowing for increasing PEEP where recruitment is found and avoiding higher PEEP levels where recruitment is not expected.

Our study suggests that if multiple PEEP levels would be beneficial in terms of lung recruitment and increased aeration, then using multiple alternating PEEP levels during mechanical ventilation warrants further clinical research. Using this approach to look at not only ARDS, but ALI or even healthy lungs may reveal additional useful information for clinicians.

**LIMITATIONS**

Our study includes a relatively small group of patients who present with moderate to severe COVID-19 related ARDS, and therefore further studies are required to validate TauE and TEI mapping usability with other etiologies causing ARDS.

Another possible limitation is that of equilibration time needed for proper recruitment at each PEEP level varies from patient to patient. Our study was designed to obtain results quickly at bedside due to critical illness connected with hypoxemia in ARDS patients. Thus, TauE at each PEEP level was evaluated during 15 breaths. Time spent at each PEEP could have therefore been relatively short for recruitment to manifest fully.

**Conclusion**

Applied physiology and assessing real measured time constants could comprise another approach to personalized mechanical ventilation for each individual patient. Based on TEI mapping, most suitable PEEP may be viewed as more of a range than a particular value in inhomogeneous ARDS lungs. By
avoiding inappropriately high PEEP that does not lead to recruitment or overdistention, higher mechanical energy impact on the lung and VILI may be prevented. Repeated measurements are likely beneficial and personalized optimization of ventilation should be done frequently during initial stages of ARDS to assure the most protective ventilation. Additional clinical studies evaluating the usefulness of TEI mapping are warranted to assess utility and validity in various degrees of ALI and ARDS.

**Abbreviations**

**ALI**: acute lung injury

**APACHE II**: acute physiology and chronic health evaluation

**ARDS**: acute respiratory distress syndrome

**COPD**: chronic obstructive pulmonary disease

**COVID-19**: coronavirus disease

**CRRT**: continuous renal replacement therapy

**VV-ECMO**: veno-venous extracorporeal membrane oxygenation

**IQR**: interquartile range

**LOS**: length of stay

**MV**: mechanical ventilation

**NMBA**: neuromuscular blocking agents

**P/F ratio**: PaO\(_2\):FiO\(_2\) ratio

**PBW**: predicted body weight

**PCV**: pressure-controlled ventilation

**PEEP**: positive end-expiratory pressure

**RRT**: renal replacement therapy

**SD**: standard deviation

**SOFA score**: sequential organ failure assessment score

**TauE**: first expiratory time constant
TEI: TauE Index

VILI: ventilator induced lung injury

Vte: expiratory tidal volume

ZEEP: zero end-expiratory pressure

References


**Declarations**

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

The study was approved by the institutional ethics committee

**CONSENT FOR PUBLICATION**

Informed consent was waived due to the nature of critical illness

**AVAILABILITY OF DATA AND MATERIALS**

Any data related questions should be directed to the corresponding author

**COMPETING INTERESTS**

FD and MG disclose research funding from IPM Chirana Inc. Other authors have no conflict of interest to disclose

**FUNDING**

None to declare

**AUTHORS CONTRIBUTIONS**
FD conceived the idea, collected the data and drafted the manuscript, PT supervised the study, NE and MG conducted data analysis, provided critical revision and editing, all authors reviewed the manuscript for important intellectual content and approved the final manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

none

CORRESPONDING AUTHOR

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Figures

**Figure 1**

Flow vs. time (Q/t curve) and volume vs. time (Vt/t curve) during PCV showing how TauE is measured. Time constant (TauE (s)) represents the time for which 63% of the Vte is exhaled (Qi – inspiratory flow, Qe – expiratory flow, Vti – inspiratory tidal volume, Vte – expiratory tidal volume).

![Figure 1](image_url)
Figure 2

TEI maps showing examples of the (a) ‘hill’ pattern, (b) ‘flat’ pattern, and (c) ‘descending’ pattern. In (a), the maximum TEI occurs around PEEP of 8 cmH2O and the suitable PEEP range (where TEI is within 10% of peak) is between 4 and 10 cmH2O. Similarly, the suitable PEEP range in (b) is between 7 and 18 cmH2O indicating similar lung mechanics across wide PEEEP range. In (c) the suitable PEEP range is between 0 and 7 cmH2O, likely indicating no significant recruitment is occurring.

Figure 3

Example of different patterns of the TEI map in two different patients in supine and prone positions. The recruitable ‘hill’ pattern in supine position at higher PEEPs (12 – 18 cmH2O) with limited recruitment in prone position (A). Different findings are shown (B) in prone position being preferential to supine in terms of recruitment at higher PEEP levels.
Figure 4

Prone vs. supine plots showing suitable PEEP range according to the highest TEI ± 10% (colored boxes). R – recruitable pattern, NR – non-recruitable pattern.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- GraphAbsTEI.jpg