A Protective Tidal Volume Adapted To Lung Compliance and The PEEP Level With Lowest Transpulmonary Driving Pressure May Be Determined By a Rapid PEEP-Step Procedure

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A protective tidal volume adapted to lung compliance and the PEEP level with lowest transpulmonary driving pressure may be determined by a rapid PEEP-step procedure

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OS took part in planning the original study and did the post hoc analysis for the present study, and did the mathematical derivation of the method. OS drafted the manuscript.

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Abstract 348 words

Background: A protective ventilation strategy should be based on lung mechanics and transpulmonary pressure, as this is the pressure that directly “hits” the lung. Esophageal pressure has been used for this purpose but has not gained widespread clinical acceptance. Instead, respiratory system mechanics and airway driving pressure have been used as surrogate measures. We have shown that the lung pressure/volume (P/V) curve coincides with the line connecting the end-expiratory airway P/V points of a PEEP trial. Consequently, transpulmonary pressure increases as much as PEEP and lung compliance (CL) can be determined as ΔEELV/ΔPEEP and transpulmonary driving pressure (ΔPTP) as tidal volume divided by ΔEELV/ΔPEEP.

Methods: In ten patients with acute respiratory failure, ΔEELV was measured during each 4 cmH₂O PEEP-step from 0 to 16 cmH₂O and CL for each PEEP interval calculated as ΔEELV/ΔPEEP giving a lung P/V curve for the whole PEEP trial. Similarly, a lung P/V curve was obtained also for the PEEP levels 8, 12, and 16 cmH₂O only.

Results: A two-step PEEP procedure starting from a clinical PEEP level of 8 cmH₂O gave almost identical lung P/V curves as the four PEEP-step procedure.

The lung P/V curves showed a marked individual variation with an over-all CL (CLoa) 50-137 ml/cmH₂O. ΔPTP of a tidal volume of 6-7 ml/kg ideal body weight divided by CLoa ranged from 8.6-2.8 cmH₂O, while ΔPTP of tidal volume adapted to CLoa ranged from 3.3 in the patient with lowest to 4.3 cmH₂O in the patient with highest CLoa.

The ratio of airway driving pressure to transpulmonary driving pressure (ΔPTP/ΔPAW) varied between patients and changed with PEEP, reducing the value of ΔPAW as surrogate for ΔPTP in individual patients.

Conclusion: Only a two PEEP-step procedure is required for obtaining a lung P/V curve from baseline clinical PEEP to end-inspiration at the highest PEEP level, i.e. without esophageal pressure.
measurements. The best-fit equation for the curve can be used to determine a tidal volume related to lung compliance instead of ideal body weight and the PEEP level where transpulmonary driving pressure is lowest and possibly least injurious for any given tidal volume.
**Introduction**

Inadequately applied mechanical ventilation may cause injury to lung tissue and multi-organ failure, ventilator induced lung injury (VILI) [1-5]. Decreasing tidal volume was shown to be effective in decreasing mortality in ARDS [6, 7] and it was concluded that a protective ventilation strategy included tidal volumes of 6 ml per kg ideal body weight (kgIBW) [8], where ideal body weight was assumed to reflect the “true” size of the lung. Recent studies indicate that the tidal volume should be titrated according to the functional status of the respiratory system, respiratory system compliance, and that the complete energy load on lung tissue (the power concept) has to be considered [9-16]. However, it is acknowledged by the scientific community that it would be preferable to target tidal volume according to lung compliance instead of respiratory system compliance, as it is the transpulmonary driving pressure that “hits” the lung tissue directly [10, 17-23]. A prerequisite for separation of lung and chest wall mechanics has hitherto been esophageal pressure measurements, which are both time-consuming and cumbersome and has not gained wide-spread acceptance as a routine procedure for all patients during mechanical ventilation.

We have developed and validated an esophageal pressure-free method for lung compliance and transpulmonary pressure in both lung healthy patients and in patients with acute respiratory failure, the PEEP step method (PSM) [24-28]. PSM is based on the fundamental effect of the chest wall striving towards a higher volume until 70 – 80 % of total lung capacity is reached [29-32]. This means that the chest wall complex does not lean on the lung at end-expiration if end-expiratory lung volume (EELV) is increased by increasing end-expiratory airway pressure (PEEP). Thus, the increase in EELV is related to the elastic properties of the lung only. Consequently, lung compliance can be calculated as $CL = \frac{\Delta EELV}{\Delta PEEP}$ if $\Delta EELV$ is measured [33, 34].

The aim of the study is to evaluate the possibility to establish a complete lung P/V curve by a two PEEP-step procedure and to determine a protective tidal volume related to lung compliance, and the
PEEP level, where the transpulmonary driving pressure of such a lung compliance adapted tidal volume is lowest.

**Patients and Methods**

The study was performed in a mixed ICU of a university hospital and approved by the Local Ethics Committee of Gothenburg, Sweden, Box 100, S-405 30 Gothenburg, protocol number: 112-08. Informed consent was obtained from next of kin. Twelve mechanically ventilated patients with acute respiratory failure were included in the original study, where conventionally measured transpulmonary pressure by esophageal pressure was compared to transpulmonary pressure calculated on the basis of lung compliance determined as ΔEELV/ΔPEEP [25]. In the present study, ten of the patients could be used for analysis, while two of the patients had to be excluded from the analysis because of cuff leakage (Table 1).

**Table 1. Patient baseline characteristics.** Patient number according to over-all lung compliance (lowest – highest). F = female; M = male; BMI = Body mass index; P/F ratio = PaO\(_2\)/FiO\(_2\); PEEP cmH\(_2\)O, clinical baseline. AAA: abdominal aortic aneurysm.

| Patient | Sex | Age | BMI | P/F, kPa | PEEP | Intr. PEEP | X-ray infilt. | Diagnosis               |
|---------|-----|-----|-----|----------|-------|------------|---------------|-------------------------|
| 5       | F   | 78  | 27  | 33       | 10    | 3          | 2, 4          | Pneumonia               |
| 1       | M   | 65  | 28  | 29       | 12    | 4          | 2, 4          | Pancreatitis            |
| 10      | F   | 70  | 21  | 29       | 6     | 0          | 2, 4          | AAA, pleural exudate    |
| 2       | M   | 86  | 26  | 37       | 12    | 0          | 2, 4          | Abdominal sepsis        |
| 8       | F   | 29  | 18  | 46       | 10    | 0          | 2, 4          | Status epilepticus      |
| 3       | M   | 64  | 29  | 20       | 14    | 1          | 2, 4          | AAA, ischemic colitis   |
| 9       | M   | 57  | 31  | 41       | 5     | 3          | 0, 4          | Hepatic failure         |
| 6       | F   | 64  | 27  | 39       | 10    | 0          | 1, 4          | Polytrauma              |
| 4       | M   | 60  | 23  | 23       | 10    | 4          | 2, 4          | Traumatic brain injury  |
| 7       | F   | 45  | 35  | 35       | 10    | 4          | 2, 4          | Urosepsis               |

**Study protocol**

Patients were ventilated in a volume-control mode with a breathing rate of 20 breaths/min, with tidal volumes of 6–7 ml/kg ideal body weight in supine position. Before the start of protocol, sedation was deepened and muscle relaxant (rocuronium 40–50 mg) given.
The trial was performed with PEEP-steps of 0-4-8-12-16-0 cmH₂O.

**Pressure and volume measurements**

Ventilatory flow, volume and pressure were measured at the Y-piece with a D-lite side-stream spirometer connected to an AS/3 multi-module monitor (GE Healthcare, Helsinki, Finland).

**End-expiratory lung volume change, ΔEELV**

End-expiratory lung volume increase was determined as the cumulative expiratory tidal volume difference between PEEP levels with a precision of ± 3.5% [26] (*Measurement precision details in e-supplement, fig. S8*). ΔEELV was also traced for the whole PEEP trial by inspiratory tidal volume calibrated EIT (Dräger Medical, Lübeck, Germany) for analysis of regional lung elastance and transpulmonary pressure (not reported in the present study), using a 16-electrode belt placed around the chest wall at the 5th intercostal space [26, 35-37][Fig. 1]. Total ΔEELV was calculated as the sum of ΔEELV between ZEEP and PEEP 16 cmH₂O. For the two PEEP-step procedure, total ΔEELV was also calculated as the sum of ΔEELV between 8, 12 and 16 cmH₂O, plus the volume between ZEEP and 8 cmH₂O extrapolated from the best-fit lung P/V curve between 8, 12 and 16 cmH₂O of PEEP.

**The increase in transpulmonary pressure during PEEP inflation**

At functional residual capacity and zero positive end-expiratory airway pressure (FRC/ZEEP), transpulmonary pressure (PTP) is positive, 5-10 cmH₂O, because the expansive chest wall has inflated the lung from Residual Volume to FRC and the pleural pressure (PPL) becomes equally negative, PTP = PAW - PPL [29, 30, 32, 38-40]. At FRC/ZEEP there is a balance between the expansive chest wall and the recoil of the lung. The expansive chest wall cannot pull the lung to a higher volume. However, the chest wall would move outwards until it reaches its resting volume at 70 – 80% of total lung capacity (TLC) if not prevented by the lung recoil [30, 38, 40, 41]. Thus, if end-expiratory lung volume (EELV) is increased by PEEP, the chest wall will move out equally much at end-expiration.
Consequently, the chest wall complex does not impede end-expiratory lung volume change by PEEP and the increase in end-expiratory lung volume will be related to lung elastance only,

$$\Delta EELV = \Delta PEEP/EL \quad (\Delta EELV = \Delta PEEP \times CL)$$

[24-28, 33](Fig. 1).

During the first expiration after increasing PEEP (VFexp), EELV increases with a volume equal to the change in PEEP divided by respiratory system elastance:

$$VFexp = \Delta PEEP/ERS$$

when the expiratory valve of the ventilator closes at the new PEEP level [42, 43](Fig. 1). This is the highest volume increase that can be achieved, unless the chest wall yields to further lung inflation. During the second multi-breath phase of PEEP inflation (Vsec) [43], the increase in EELV is equal to the difference between $\Delta EELV$ and the first expiration volume

$$Vsec = \Delta PEEP/EL - \Delta PEEP/ERS = (\Delta PEEP \times ECW)/(ERS \times EL)$$

(Fig.1).
Fig. 1. A PEEP increase of 10 cmH\textsubscript{2}O, where airway driving pressure is just above, 11 cmH\textsubscript{2}O at baseline PEEP. Upper panel: airway pressure. Mid panel: esophageal pressure. Lower panel: lung volume by electric impedance tomography. Red bars indicate breath-by-breath increase in end-expiratory lung volume. During the first expiration after the PEEP increase (VF\textsubscript{exp}), EELV increases with a volume equal to the tidal volume, \(\Delta PEEP/ERS\), when the expiratory valve closes at the new PEEP level. After that, during the second phase of PEEP inflation, end-expiratory lung volume increases further until the new steady state PEEP/EELV is reached. The second phase (Vsec), multi-breath EELV build-up is equal to the difference between \(\Delta EELV\) and the first expiration volume increase, \(\Delta PEEP \times ECW/ERS \times EL\) and cannot occur unless the chest wall yields, i.e. does not squeeze the lung at end-expiration.
Table below figure: increase in end-expiratory transpulmonary and pleural pressure according to the mathematical derivation (above), during the first expiration after increasing PEEP (VFexp), during the second, multi-breath increase in end-expiratory lung volume pressure and for the whole increase in end-expiratory lung volume following a change in PEEP.

End-expiratory esophageal pressure increases only during the first expiration after increasing PEEP, in agreement with end-expiratory pleural pressure (PPLEE) of the mathematical derivation. During the second phase multi-breath inflation, end-expiratory pleural pressure remains at the first expiration level as the exterior surface of the lung and the interior surface of the thoracic cage moves in parallel to a higher end-expiratory volume and the chest wall strives outwards at end-expiration. Thus, end-expiratory transpulmonary pressure also remains at the level reached during the first expiration, as if no second phase multi-breath PEEP inflation occurs (Fig.2).

During inflation, the transpulmonary pressure increases in relation to the inflated volume and the elastic properties of the lung, V x EL. Consequently, during the first expiration after increasing PEEP, end-expiratory transpulmonary pressure increases with lung elastance times the first expiration volume:

\[ \Delta P_{TP_{EE}}^{V_{exp}} = EL \times \Delta PEEP/ERS \]  \hspace{1cm} (1)

and end-expiratory pleural pressure increases with chest wall elastance times the first expiration volume:

\[ \Delta P_{PLEE}^{V_{exp}} = ECW \times \Delta PEEP/ERS \]  \hspace{1cm} (2)

During the second phase inflation, the transpulmonary pressure increase is equal to EL times Vsec:

\[ \Delta P_{TP_{EE}}^{V_{sec}} = EL \times \Delta PEEP \times ECW/(EL \times ERS) = \Delta PEEP \times ECW/ERS \]  \hspace{1cm} (2)
Thus, during the second phase volume increase, the increase in transpulmonary pressure is equal to the increase in pleural pressure during the first expiration volume increase after increasing PEEP. The second phase multi-breath end-expiratory lung volume increase is a result of the chest wall complex yielding to lung inflation by PEEP, as all the pressure needed to hold the chest wall complex away during the first expiration, is used to inflate the lung during the second phase PEEP inflation (eq. 2). The total increase in transpulmonary pressure during PEEP inflation is the sum of the increase of phase 1 and 2:

\[ \Delta P_{L}^{\text{PEELV}} = E_\text{L} \times \Delta P_{\text{PEEP}/ERS} + E_\text{CW} \times \Delta P_{\text{PEEP}/ERS} = \Delta P_{\text{PEEP}} \]
Fig. 2. The recording of fig. 1, where only plateau pressures are shown and cardiac artefacts have been removed. **Left panels** show airway and absolute esophageal and transpulmonary pressure and in addition calculated lung volume. Transpulmonary pressure was calculated breath-by-breath as the direct difference between the airway and absolute esophageal pressure, resulting in a one-step increase in transpulmonary pressure. This indicates that the lung volume seemingly does not increase further after the first expiration after increasing PEEP, as depicted in the lower left panel, where the change in EELV is calculated as the change in absolute transpulmonary pressure divided by lung elastance. In fact EELV increases breath by breath also after the first expiration increase as seen in the recording in the right lower panel [43].

**Right panels** show airway, esophageal and transpulmonary pressure corresponding to the left panels. In the lower panel breath-by-breath EELV changes measured by the ventilator is depicted. Transpulmonary pressure increases in relation to the breath-by-breath increase in end-expiratory lung volume and the elastic properties of the lung, $\Delta EELV \times EL$ and are depicted in right mid lower panel. Note that PTPEE increases with 5.1 cmH$_2$O during the first expiration after increasing PEEP and then 4.9 cmH$_2$O during the second phase inflation, which is equal to the increase in esophageal pressure during the first expiration. The total increase in PTPEE is 10 cmH$_2$O, which confirms that PTPEE increases as much as PEEP is increased. Thus, end-expiratory esophageal pressure calculated as the end-expiratory airway pressure minus the EELV corrected end-expiratory transpulmonary pressure, subsidies back to baseline level after the first expiration increase. This confirms that during the second phase inflation, the chest wall yields to the lung volume increase, as a result of the rib cage spring out force.

As end-expiratory transpulmonary pressure increases as much as PEEP is increased, lung elastance is

$$EL = \frac{\Delta PEEP}{\Delta EELV}$$
Lung elastance is conventionally calculated by esophageal pressure as transpulmonary driving pressure divided by the tidal volume:

\[ EL = \frac{\Delta PTP}{VT} \]

Thus,

\[ \frac{\Delta PEEP}{\Delta EEV} = \frac{\Delta PTP}{VT} \]

and when tidal volume and increase in end-expiratory lung volume are equal

\[ \Delta PEEP = \Delta PTP \]

and as end-expiratory transpulmonary pressure increases as much as PEEP is increased

\[ \Delta PEEP = \Delta PTP = \Delta PTEE \]

(Mathematical proof of \( \Delta PEEP = \Delta PTP = \Delta PTEE \) and full mathematical derivation of PEEP inflation in e-supplement)

The mathematical derivation and the modelling show that respiratory mechanics can be defined by three equations when the tidal volume is equal to the change in end-expiratory lung volume:

\[ ERS = \frac{\Delta PAW}{\Delta EEV_{VT}} \]

\[ EL = \frac{\Delta PEEP}{\Delta EEV_{VT}} \]

\[ ECW = \frac{(\Delta PAW - \Delta PEEP)}{\Delta EEV_{VT}} \]

(Fig. 3)
Fig. 3. Principal graph of PEEP inflation, where $\Delta EELV$ is equal to the tidal volume (with permission from Br J Anaesthesia, Elsevier. Modified from [26]). Red arrows: tidal airway (respiratory system) $P/V$ curves. Blue arrows: tidal transpulmonary (lung) $P/V$ curves. Green arrows: tidal pleural (chest wall) $P/V$ curves. Note that end-expiratory transpulmonary pressure increases as much as PEEP is increased and that consequently, end-expiratory pleural pressure does not change when PEEP is increased (dashed green line), i.e. end-expiratory chest wall elastance is zero. This means that the chest wall complex does not press on the lung at end-expiration. The transpulmonary driving pressure of a $VT = \Delta EELV$ is equal to $\Delta PEEP$. Also note that tidal pleural pressure variation of a $VT = \Delta EELV$ is equal to the difference between airway driving pressure and $\Delta PEEP$. Also note that the end-inspiratory transpulmonary pressure from the low PEE id equal to end-expiratory transpulmonary pressure of the high PEEP. This means that transpulmonary pressure at a certain lung volume is independent of whether this volume has been reached by tidal or PEEP inflation.

Calculation of the lung $P/V$ curve

As the transpulmonary pressure increases as much as PEEP is increased, the lung $P/V$ curve between the end-expiratory $P/V$ points was obtained by plotting the end-expiratory transpulmonary pressure (PEEP) versus the end-expiratory lung volume at each PEEP level. It is an inherent feature of the PEEP
A step method that end-inspiratory transpulmonary pressure at the highest PEEP level (16 cmH$_2$O) cannot be determined, and the curve from end-expiration to end-inspiration at PEEP 16 has to be estimated. Tidal variations of pleural pressure (ΔPPL) reflect the pressure needed to displace a weight, the abdomen, rather than expanding an elastic entity, and are consequently mainly constant when PEEP is increased [20, 26, 28, 44], but shows slight changes in individual patients. Thus, ΔPPL at the highest PEEP level was extrapolated from the PEEP levels of 8 and 12 cmH$_2$O and end-inspiratory transpulmonary pressure (PTPEi) at PEEP 16 cmH$_2$O was calculated as end-inspiratory airway pressure minus extrapolated tidal pleural pressure variation. Finally, a best-fit lung P/V curve was calculated from end-expiration at the lowest PEEP level to end-inspiration at the highest PEEP level and the third degree equation for the curve used for determining the PEEP level where transpulmonary driving pressure was lowest. (Fig. 4). (For details measurement precision of the PEEP-step method compared to esophageal pressure, see e-supplement, figure S7).

![Diagram](image)

**Fig. 4.** The lung P/V curve is obtained by plotting the end-expiratory airway pressure vs end-expiratory lung volume for all PEEP levels. Red arrows: tidal airway P/V curves at ZEEP, PEEP 4, 8, 12 and 16 cmH$_2$O. Blue line: lung P/V curve. Blue circles: End-inspiratory transpulmonary P/V points. Blue circles filled red: End-expiratory transpulmonary (lung) P/V points and end-expiratory airway (respiratory system) P/V points. Note that the lung P/V curve and end-expiratory airway (respiratory system) P/V curve coincide, as the transpulmonary pressure increases as much as PEEP is increased. The end-
inspiratory transpulmonary pressure at PEEP 8 and 12 is calculated from the equation for the best-fit lung P/V curve and tidal pleural pressure variation (ΔPPL, black arrows) is then calculated as the difference between end-inspiratory airway and transpulmonary pressure. The end-inspiratory transpulmonary pressure at the highest PEEP level is estimated by extrapolation of ΔPPL at PEEP 16 cmH\textsubscript{2}O from the ΔPPL at the two lower PEEP levels and end-inspiratory transpulmonary pressure at PEEP 16 cmH\textsubscript{2}O is calculated as airway plateau pressure (PAWEI) minus extrapolated ΔPPL. Digits in italics identify estimated data.

**Over-all lung compliance** (CL\textsubscript{oa}) was calculated as the lung volume at end-inspiration (ΔEELV 0-16 + VT) divided by the end-inspiratory transpulmonary pressure at PEEP 16 cmH\textsubscript{2}O.

**Statistics**

Results are mainly reported for the individual patients, but when results are given for the group, they are reported as mean ± SD.
Results

The lung P/V curve

End-expiratory and end-inspiratory transpulmonary pressure/volume points are aligned on a common single P/V curve from end-expiration at ZEEP to end-inspiration at the highest PEEP level. Average CL was 86 ml/cmH₂O, ranging from 50 to 137 ml/cmH₂O (fig. 4). There are significant differences in the shape of the P/V curves in patients with almost the same CL. In all patients, the lung P/V curves show a lower inflection point (LIP), or rather a lower inflection zone, as lung compliance increases with PEEP increase from 0 to 8 – 12 cmH₂O (Fig. 5).
Fig. 5. Tidal airway P/V curves (red line) at PEEP 0, 4, 8, 12 and 16 cmH₂O. Lung best fit curves (according to a third degree equation) in ten patients with lung compliance ranging from 50 to 137 ml/cmH₂O.

Note that end-expiratory (blue circles filled red) and end-inspiratory transpulmonary pressure/volume points (blue circles) are aligned on a common single lung P/V curve, which coincides with the end-expiratory airway P/V curve. Also note, that in patients with almost equal compliance, patient 2 and 3, and patient 8 and 9, lung compliance increases at the highest PEEP level in patient 3 and 8, and decreases in patient 2 and 9. Thus, in patient 2 and 9 there is an unfavorable response to high PEEP and in patient 3 and 8 there is a positive response to high PEEP.

Transpulmonary versus airway driving pressure

Transpulmonary driving pressure is highest at ZEEP and decreases in all patients when PEEP is increased stepwise to 4 and 8 cmH₂O, which is expected as there is a lower inflection zone below a PEEP of 8 cmH₂O. The ratio of transpulmonary to airway driving press, ∆PTP/∆PAW (= EL/ERS) was 0.48 ± 0.13 varying between 0.28 and 0.76 in different patients at different PEEP. ∆PTP/∆PAW changes with changes in PEEP. ∆PTP/∆PAW changes with changes in PEEP. The PEEP level with lowest transpulmonary driving pressure coincided in three patients with the PEEP level where airway driving pressure was lowest. In the other patients, the PEEP level with lowest ∆PTP was 4-8 cmH₂O higher than for ∆PAW. When changing from PEEP 12 cmH₂O to 16 cmH₂O, ∆PTP and ∆PAW may even change in opposite direction (Fig. 6).
Fig. 6. Airway and transpulmonary driving pressure at PEEP levels 0 - 4 - 8 - 12 – 16 (and 20 in patient 1). Patients are ranked according to over-all lung compliance from lowest value, 50 ml/cmH\(_2\)O, in patient 1 and highest, 137 ml/cmH\(_2\)O, in patient 10.

**PEEP response**

Lung compliance increases with increasing PEEP in PEEP responders and is associated with higher CL\(^{oa}\), than in non-responders, where over-all lung compliance is low, as seen in the two most non-responsive patients (pat. 1 and 2) with CL\(^{oa}\) around 50 ml/cmH\(_2\)O, which is half the lung compliance seen in lung healthy [26, 44]. The PEEP non-responders are characterized by decreasing lung compliance with an upper deflection point on the lung P/V curve at higher PEEP levels (Fig. 7).
Fig. 7. Implementation of a short two-PEEP step procedure in two patients with the same respiratory system compliance at a baseline clinical PEEP of 8 cmH₂O (upper panels). PEEP is increased stepwise from 8 to 12 and 16 cmH₂O and the lung P/V curve (blue line) is determined from end-expiration of PEEP 8 to end-inspiration at PEEP 16 cmH₂O (mid panels). As the tidal lung P/V curve lies on the lung P/V curve, transpulmonary plateau and driving pressure (PTPplat, ΔPTP) can be calculated for any combination of PEEP and tidal volume. In this case PTPplat and ΔPTP is determined for a tidal volume of 400 ml at PEEP 8 and 15 cmH₂O, revealing that in patient 2 (right panels) this PEEP increase leads to a significant increase in ΔPTP and a high and possibly risky level of PTPplat. In patient 3 (left panels), the increase in PEEP from 8 to 15 cmH₂O results in a decrease in ΔPTP from 6.5 to 4.4 cmH₂O and a transpulmonary plateau pressure, which is well below VILI levels.
CL\textsuperscript{oa} calculated during the two PEEP-step procedure was 22 % higher than CL\textsuperscript{oa} calculated for the complete four PEEP-step procedure and correlated well with CL\textsuperscript{oa} of the complete four PEEP-step procedure, $y = 1.22x$, $r^2 = 0.96$.

**Optimal “physical power to the lung” PEEP**

Optimal PEEP level for the IBW and CL\textsuperscript{oa} related tidal volumes was very similar, 12.4 ± 2.3 and 12.4 ± 2.9 cmH\textsubscript{2}O, in both cases between 9 and 16 cmH\textsubscript{2}O, $y = 1.00x$, $r^2 = 0.79$ (Fig. 8).
Fig. 8. Lung P/V curves by a two PEEP step up-down procedure (black line). Black circles indicate transpulmonary P/V points at PEEP levels of 8, 12 and 16 cmH₂O which were used together with the estimated end-inspiratory transpulmonary P/V point (black filled circle) at the highest PEEP level for calculation of a best-fit lung P/V curve. The end-inspiratory transpulmonary pressure is, except for patient 1 and 2, who are PEEP non-responders, 18-21 cmH₂O. The red arrows show the tidal lung P/V curves with the lowest transpulmonary driving pressure for the tidal volume used clinically (optimal “mechanical” PEEP level. The highest optimal PEEP levels, 15 – 16 cmH₂O, are seen in patients with continuously increasing lung compliance when increasing PEEP, while lower optimal PEEP levels are seen in patients with an upper deflection zone.

The clinically used tidal volume of 6 – 7 ml/kg IBW was 410 ml (310 – 520) and did not correlate to CL\textsuperscript{oa}. The transpulmonary driving pressure calculated as the clinically used IBW related tidal volume divided by CL\textsuperscript{oa} was 5.2 cmH₂O (3.5 – 8.6). Transpulmonary driving pressure at optimal PEEP was 3.8 cmH₂O (2.8 – 6.7). A tidal volume adapted to the elastic properties of the lung, calculated as the mean transpulmonary driving pressure related to CL\textsuperscript{oa}, 5.2 cmH₂O, was 447 ml, ranging from 258 to 718 ml. The optimal transpulmonary driving pressure for such a tidal volume, adapted to CL\textsuperscript{oa}, was 3.8 cmH₂O, ranging only from 3.3 to 4.3 cmH₂O (Fig. 9).
Fig. 9. Dashed line indicates mean value of parameter. **Upper left panel**: Over-all lung compliance. **Mid left panel**: Tidal volume of 6-7 ml/kg IBW. **Lower left panel**: Tidal volume of a transpulmonary driving pressure of 5.2 cmH$_2$O, i.e. inversely correlated to the lung elastic properties, over-all lung compliance. **Upper right panel**: Transpulmonary driving pressure of tidal volume of 6-7 ml/kg IBW (VT$_6$IBW/CLOVER-ALL). **Mid right panel**: Optimal (lowest) transpulmonary driving pressure of tidal volume of 6 ml/kg IBW. **Lower right panel**: Optimal (lowest) transpulmonary driving pressure of a tidal volume adapted to over-all lung compliance.
Discussion

In patients with acute respiratory failure, we could show that it was possible to obtain precise lung P/V curves and determine the PEEP level where transpulmonary driving pressure was lowest for any given tidal volume by a two PEEP-step measurement procedure, i.e. without esophageal pressure measurements. Lung mechanics showed marked individual variation, with over-all lung compliance between 137 and 50 ml/cmH\textsubscript{2}O. Transpulmonary driving pressure for a 6-7 ml/kg IBW tidal volume ranged from 3.5 to 8.6 cmH\textsubscript{2}O, while ΔPTP of a tidal volume adapted to over-all lung compliance was around 4 cmH\textsubscript{2}O in all patients. The PEEP level with lowest airway driving pressure did not coincide with the PEEP level where transpulmonary driving pressure was lowest, in seven of ten patients.

Protective tidal volume related to ideal body weight

The baby lung concept is based on the fact that the open lung in the non-dependent region has normal elastic properties for its size [45]. After the ARDSnet study in 2000 [6], a tidal volume of 6 ml/kg IBW has been adopted for protective ventilation [46]. In the ARDSnet study the mean IBW was 71 kg, and the tidal volume 450 ml. In a typical ARDS patient with a respiratory system compliance of \(\approx 40\) ml/cmH\textsubscript{2}O [20, 44, 47], a tidal volume of 450 ml results in an airway driving pressure of \(\approx 12\) cmH\textsubscript{2}O, close to the upper limit for safe airway driving pressure of 15 cmH\textsubscript{2}O [48]. Recent studies have shown that the baby lung is partially inflamed and consequently, has a lower compliance than a normal lung of the same size [49-51]. Therefore, it was proposed that a protective tidal volume should be titrated according to the baby lung size instead of according to ideal body weight, as the risk of ventilator induced lung injury increases markedly, when respiratory system elastance is above 20 cmH\textsubscript{2}O/L (= compliance below 50 ml/cmH\textsubscript{2}O) [10, 51].

PEEP titration is commonly used to find the PEEP level where respiratory system compliance is highest for the 6 ml/kgIBW tidal volume [52-56] and consequently airway driving pressure lowest [48], which supposedly is the PEEP level where also the risk of VILI is lowest. However, the PEEP level with lowest airway driving pressure does not necessarily coincide with the PEEP level where
transpulmonary driving pressure is lowest, as the ratio of ΔPTP/ΔPAW changes unpredictably in individual patients with changes in PEEP (Fig.4). The safe limits for ΔPTP is not known, but can be estimated from the upper limit for airway driving pressure at 15 cmH₂O [22, 48] and the average ratio of lung to airway elastance, EL/ERS, of ≈ 0.70, to be ≈ 10 cmH₂O [20, 48, 57]. In the present study, the average transpulmonary driving pressure, calculated as the IBW tidal volume divided by two-point CL<sub>oa</sub>, was 5.2 ± 1.6 cmH₂O, ranging from a risky 8.6 cmH₂O in the patient with least lung compliance, to a low 3.5 cmH₂O in the most lung compliant patient. Optimal PEEP level, i.e. the PEEP level where transpulmonary driving pressure is lowest for the IBW tidal volume, was 3.8 cmH₂O, which was 26 ± 7 % lower than the average ΔPTP of 5.2 cmH₂O, indicating the possible benefit of determining “optimal PEEP”. ΔPTP at optimal PEEP was more than twice as high, 6.6 cmH₂O in the patient with lung compliance 50 ml/cmH₂O, similar to severe ARDS, as in the patient with lung compliance of 137 ml/cmH₂O. This confirms that targeting tidal volume to IBW is not optimal for adequate protective ventilation in the individual patient [11, 58, 59].

**Protective tidal volume related to lung compliance**

End-inspiratory and end-expiratory transpulmonary P/V points are aligned in a common single lung P/V curve (Fig. 2, 3, 5, 6) and, consequently, optimal PEEP can be calculated for any chosen tidal volume as any tidal lung P/V curve is positioned somewhere on the total lung P/V curve (Fig. 5). Thus, we calculated the tidal volume adapted to individual CL<sub>oa</sub> as CL<sub>oa</sub> times the average ΔPTP of 5.2 cmH₂O. ΔPTP in the patient with least CL<sub>oa</sub> was 40% lower than for the IBW tidal volume, indicating that adapting the tidal volume to lung compliance, instead of ideal body weight, would minimize the risk of transpulmonary driving pressure causing ventilation induced lung injury (VILI) in patients with low lung compliance. In the five patients with lowest over-all lung compliance and therefore the highest risk of VILI, ΔPTP at optimal PEEP level was 35 % (17 – 55) lower than the average ΔPTP of 5.2 cmH₂O, strongly underlining the favourable effect of titrating PEEP to the level where transpulmonary pressure is lowest.
Identifying “under-treatment”

As important it is to minimize VILI, it is to identify, where it is possible to increase tidal volume and PEEP to improve oxygenation and carbon dioxide removal without risk of VILI in patients where lung compliance is high. This has previously been shown by Grasso and coworkers, who managed to avoid ECMO treatment in half of the patients with influenza A (H1N1)[60], when they determined transpulmonary pressure and found that in half the patients, PEEP could be further increased without reaching the upper limit for transpulmonary plateau pressure, 25 cmH\(_2\)O [61-63]. In the present study, two patients had the same respiratory system compliance and airway driving pressure at 8 cmH\(_2\)O of PEEP. Assessment of the effects of a virtual increase of PEEP to 15 cmH\(_2\)O, showed in one of the patients, that transpulmonary driving pressure decreased around 30%, while in the other, transpulmonary driving pressure increased with 30 % and plateau pressure reached a dangerous level, 23.2 cmH\(_2\)O (Fig. 5).

Early lung property and VILI risk assessment

Preventive measures to avoid worsening of lung condition with consolidation of atelectasis should be taken early in the course of ventilator treatment [64-66]. The PEEP-step method provides easy assessment of lung mechanics and a rational basis for applying a protective PEEP and tidal volume strategy directly after the patient is connected to the ventilator. Also, the power concept assessment of VILI risk can be done using data of lung elastance and transpulmonary driving and plateau pressure as in the original publication, instead of respiratory system elastance and airway driving and plateau pressure [67-69].

Transpulmonary driving pressure monitoring

The two PEEP step measurement procedure can be regarded as a diagnostic procedure, which forms the basis for breath-by-breath monitoring of transpulmonary driving pressure. When changes in
respiratory system compliance are seen, and when patient position is changed or suctioning performed, a single PEEP-step up and down procedure can be done to check for changes in lung mechanics and update the diagnostic procedure.

Study limitations

In this analysis, we have only access to PEEP trials up to 16 cmH$_2$O. As it is an inherent feature of the PEEP step method, that the transpulmonary end-inspiratory pressure at the highest PEEP level always has to be estimated by extrapolation, it has not been possible to determine how precise estimated transpulmonary plateau pressure at 16 cmH$_2$O of PEEP is. Ideally, from a measurement precision point of view, PEEP steps up to 25 cmH$_2$O should be used, as this is the upper limit for safe transpulmonary plateau pressure [61-63]. In most cases however, it is probably sufficient if the highest PEEP level of the measurement procedure is 16-18 cmH$_2$O, because the plateau pressure at such PEEP levels will reach levels close to the upper safety limit. The estimation of end-inspiratory transpulmonary plateau pressure at the highest PEEP level will be validated in a coming feasibility study, ClinicalTrials.gov. NCT04484727.

Conclusion

The PEEP-step measurement procedure is non-invasive, and does not require calibration. It takes less than five minutes to perform. A two PEEP-step manoeuvre, where the change in end-expiratory lung volume is determined, gives a complete and precise assessment of the lung elastic properties, i.e. lung compliance, transpulmonary driving pressure and plateau pressure. The PEEP level where transpulmonary driving pressure is lowest (least injurious, “optimal PEEP”), for any chosen tidal volume and a protective tidal volume adapted to lung compliance, minimizing the risk of VILI, can be determined.
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