Protective PEEP and Lung Capacity May Be Determined by a Rapid PEEP-step Procedure

Christina Grivans
University of Gothenburg Institute of Clinical Sciences: Goteborgs universitet Institutionen for kliniska vetenskaper
Ola Stenqvist (ola.stenqvist@aniv.gu.se)
University of Gothenburg Institute of Clinical Sciences: Goteborgs universitet Institutionen for kliniska vetenskaper https://orcid.org/0000-0002-9879-0914

Research Article

Keywords: Protective PEEP, lung capacity, rapid PEEP-step procedure, lung mechanics, end-expiratory lung volume (ΔEELV)

Posted Date: May 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-495708/v1

Protective PEEP and lung capacity may be determined by a rapid PEEP-step procedure

Christina Grivans[1], Ola Stenqvist[2]

1.Kungälvs hospital, Västra Götalandsregionen, Sweden. 2. Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden.

Corresponding author: Ola Stenqvist, Blockgatan 8, SE-26361 Viken, Sweden.

ola.stenqvist@aniv.gu.se

3841 words, 9 figures, 3 tables and 62 references

Abstract 349 words

Background: A protective ventilation strategy should be based on assessment of ***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 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 is increased. If the change in end-expiratory lung volume (ΔEELV) is determined, lung compliance (CL) can be determined as ΔEELV/ΔPEEP and ΔPTP as tidal volume times ΔPEEP/ΔEELV.

Methods: In ten patients with acute respiratory failure, ΔEELV was measured during each 4 cmH_2O PEEP-step from 0 to 16 cmH_2O and CL for each PEEP interval calculated as ΔEELV/ΔPEEP giving a lung P/V curve for the whole PEEP trial.

Results: Lung P/V curves showed a marked individual variation with an overall lung compliance of 43 – 143 ml/cmH_2O (total inspiratory volume divided by end-inspiratory transpulmonary plateau pressure at PEEP 16 cmH_2O). The two patients with lowest lung compliance were non-responders to PEEP with decreasing lung compliance at high PEEP levels, indicating over-distension. Patients with higher lung compliance had a positive response to PEEP with successively higher lung compliance when increasing PEEP. A two-step PEEP procedure starting from a clinical PEEP level of 8 cmH_2O gave almost identical lung P/V curves as the four PEEP-step procedure.

The ratio of airway driving pressure (ΔPAW) 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: Separation of lung and chest wall mechanics can be achieved without esophageal pressure measurements if ΔEELV is determined when PEEP is changed**.** Only a two-step PEEP

procedure is required for obtaining a lung P/V curve from baseline clinical PEEP to end-inspiration at the highest PEEP level, which can be used to determine the PEEP level where transpulmonary driving pressure is lowest and possibly least injurious for any given tidal volume.

Trial registration: ClinicalTrials.gov, NCT04484727. Registered 24 July 2020 – Retrospectively registered,
https://clinicaltrials.gov/ct2/show/NCT04484727?term=Lindgren%2C+Sophie&cntry=SE&draw=2&rank=1

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 [8]. In spite of the fact that experimental studies showed that increasing PEEP led to a decrease of VILI [9-11], large multi-centre studies failed to show significant positive effect of high PEEP on mortality [12-14]. A large multi-centre study with a recruitment manoeuvre and PEEP titration, where PEEP was set two cmH_2O above the PEEP level with best respiratory system compliance, showed even increase in mortality in the study group compared to the control group, which was managed with low tidal volume/low PEEP according to ARDSnet [6, 15]. This was a setback as the PEEP level with the highest respiratory system compliance also has the lowest airway driving pressure, which is strongly correlated to reduced mortality [16, 17]. But, as VILI is a *lung* problem, it would be rational to individualize according to best lung compliance and transpulmonary driving pressure instead [18, 19], especially so, as there is no correlation in individual patients between airway and transpulmonary driving pressure [20]. However, adding esophageal pressure measurements to a standard multi-step PEEP titration makes the procedure even more time consuming and cumbersome and is still not a standard procedure in every patient.

We have found that the size of the end-expiratory lung volume change after a PEEP change is determined by the size of the PEEP change and the elastic properties of the lung, $\Delta EELV = \Delta PEEP \times CL$ [20-26], which indicates that the chest wall does not affect lung mechanics during end-expiratory zero-flow conditions. The data from a study by Yoshida using esophageal pressure measurement during a PEEP-trial 0-24 cmH_2O confirms our findings. In that study, ΔEELV is not determined [27], but lung compliance (CL) can be calculated at each PEEP level by data retrieved from figures of the study. Consequently, ΔEELV can be determined for each PEEP step and tidal airway- and lung P/V curves can be displayed at respective end-expiratory lung volume level. This reveals that end-expiratory- and end-inspiratory transpulmonary P/V points are positioned along a single, common lung P/V curve coinciding with the end-expiratory airway P/V curve (Fig. 1).

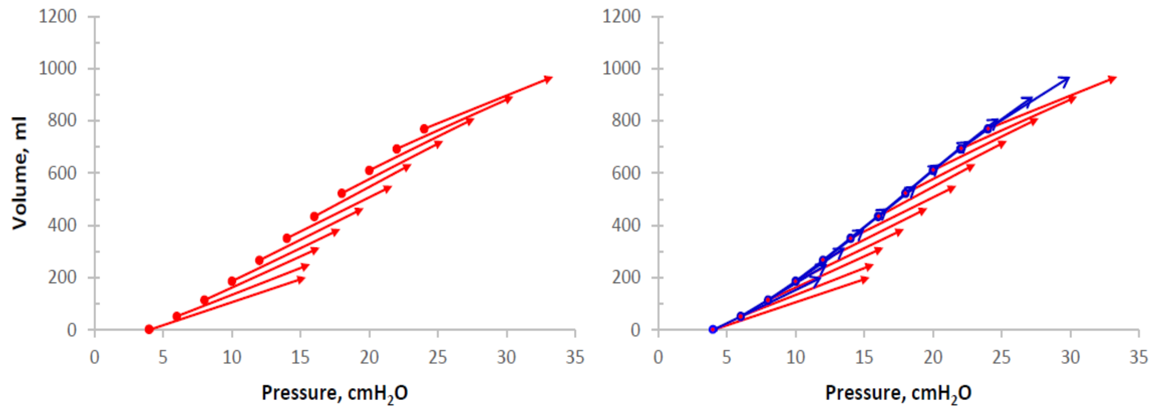

Fig. 1. Tidal airway (red arrows) and lung P/V curves (blue arrows) calculated from end-expiratory and end-inspiratory esophageal and transpulmonary pressure data at each PEEP (ΔPAW/VT, (ΔPAW - ΔPES)/VT) level of the Yoshida et al study 2018 [27]. This makes it possible to determine transpulmonary and chest wall driving pressure and lung and chest wall elastance (EL, ECW) and respiratory system elastance (ERS) as the sum of tidal lung and chest wall elastance at each PEEP level. Also, ΔEELV between PEEP levels can be calculated as ΔPEEP/EL (ΔPEEP x CL).

Left panel: *Tidal airway P/V curves at PEEP 4 to 24 cmH_2O with tidal volume of 200 ml from Yoshida et al [27] where ΔEELV was determined for each 2 cmH_2O PEEP step as ΔPEEP/EL, and EL calculated as ΔPTP/VT.*

Right panel: *Tidal airway and lung P/V curves are plotted in the same diagram, showing that the lung P/V curve coincides with the end-expiratory airway P/V curve, which confirms that lung elastance can be determined as ΔPEEP/ΔEELV (lung compliance, CL = ΔEELV/ΔPEEP).*

Even if transpulmonary driving pressure is the dominating factor, also the PEEP level, minute ventilation, flow and respiratory rate are important factors of VILI, as described by the “Power” concept [28-30]. However, transpulmonary pressure is difficult to determine by esophageal pressure. To make the concept work for a majority of ventilator patients, airway driving pressure has been introduced in the concept as a surrogate of transpulmonary driving pressure [31, 32], but there is no correlation between the two in individual patients [20].

The aim of the study is to demonstrate that the lung P/V curve can be measured without esophageal pressure measurements with a two PEEP-step procedure and to determine the PEEP level, where the transpulmonary driving pressure of any chosen 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 [33]. 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 incomplete EIT data and cuff leakage (Table 1).

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

Table 1. Patient characteristics. PEEP cmH_2O, clinical baseline. AAA: abdominal aortic aneurysm.

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 cmH_2O.

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 and traced for the whole PEEP trial by inspiratory tidal volume calibrated EIT (Dräger Medical, Lübeck, Germany) using a 16-electrode belt placed around the chest wall at the 5th intercostal space (Fig. 2) [34-37]. An additional paragraph provides detailed information on the tidal volume calibration by EIT process [see Additional file 1].

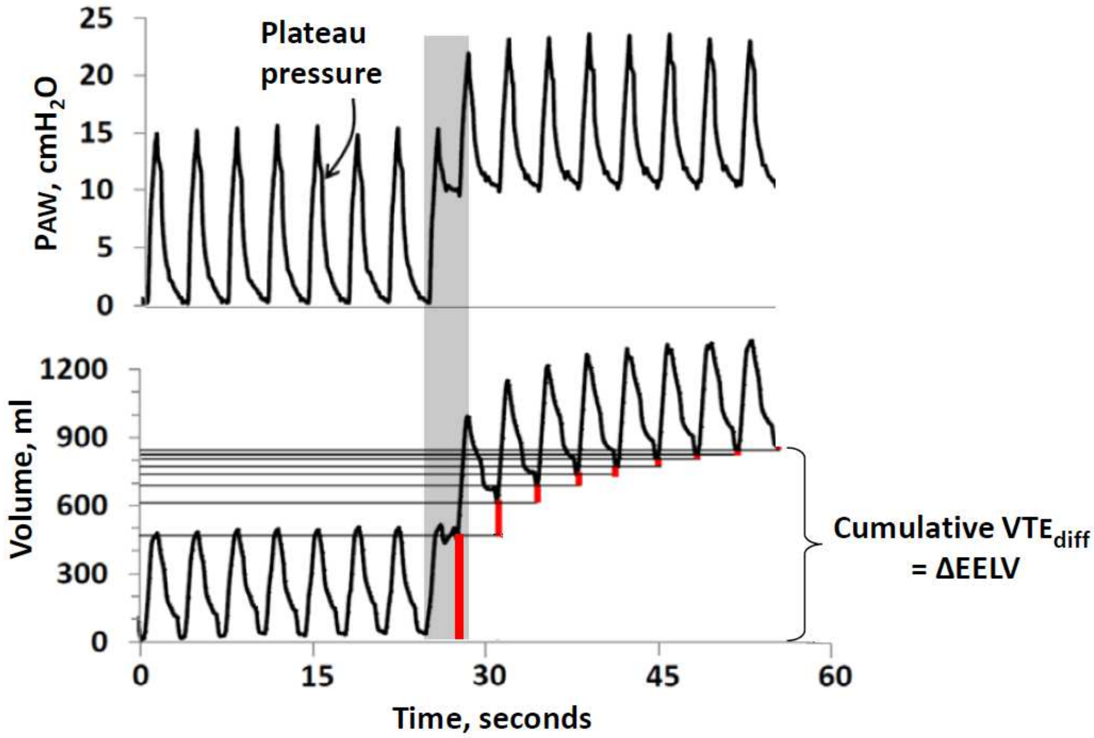

Fig. 2. Recording from an ARDS patient [33]. Upper panel: airway pressure. Lower panel: volume by electric impedance tomography (EIT). The registration is done during volume control ventilation with a tidal volume of 500 ml with an airway driving pressure (ΔP_{AW}) of 10 cmH_2O at baseline PEEP followed by an equal PEEP increase of 10 cmH_2O. The red bars indicate the breath-by-breath difference in expiratory tidal volume (V_{TE}) from baseline VTE, until VTE is again equal to baseline.

Note that an airway driving pressure of 10 cmH_2O is needed to inflate a tidal volume of 500 ml, while an increase in PEEP of 10 cmH_2O causes an increase in EELV of 900 ml. Respiratory system compliance ($V_T/\Delta P_{AW}$) is 500/10 = 50 ml/cmH_2O. The end-expiratory respiratory system compliance, which is equal to lung compliance ($\Delta EELV/\Delta P_{AWEE} = \Delta EELV/\Delta P_{TPEE}$) is 900/10 = 90 ml/$cmH_2O$ (see further below).

Calculation of the lung P/V curve

The term *compliance* (C) is normally used in the clinic, but for calculations, inverted compliance, 1/C = elastance (E), is more suitable, as respiratory system elastance is the sum of lung and chest wall elastance and consequently airway driving pressure the sum of transpulmonary and chest wall (pleural) driving pressure, ΔPAW = ΔPTP + ΔPPL. The relationship between compliance and elastance is shown in table 2.

Compliance, ml/cmH_2O	Elastance, cmH_2O/L
10	100
20	50
30	33
40	25
50	20
60	17
70	14
80	13
90	11
100	10
110	9
120	8

Table 2. The relationship between "clinical" compliance and "mathematical" elastance. Normal lung compliance is around 100 ml/cmH_2O, moderate ARDS 60 – 70 ml/cmH_2O and severe ARDS below 40 ml/cmH_2O. Elastance is 1/C (1000/C to make it cmH_2O/L). Compliance is additive in parallel lungs, i.e. global lung compliance is the sum of compliance of the left and right lung. Elastance is additive in serial structures, i.e. respiratory system elastance is the sum of lung and chest wall elastance.

As the change in end-expiratory lung volume, ΔEELV = ΔPEEP/EL, lung elastance can be determined as

EL = ΔPEEP/ΔEELV

Lung elastance can also be determined as

EL = ΔPTP/VT

and when tidal volume and ΔEELV are equal

$\Delta PTP/VT = \Delta PEEP/\Delta EELV$

and consequently, the transpulmonary driving pressure of a tidal volume equal to ΔEELV is equal to the change in PEEP

$\Delta PTP = \Delta PEEP$.

Tidal pleural pressure variation of a tidal volume equal to ΔEELV (VT=ΔEELV) is the difference between airway and transpumonary driving pressure, ΔPAW – ΔPTP, and as transpulmonary driving pressure is equal to ΔPEEP, tidal pleural pressure variation is

$\Delta PPL = \Delta PAW - \Delta PEEP$.

On the basis of this derivation, the lung P/V curve was obtained by plotting the end-expiratory transpulmonary pressure (PEEP) versus the end-expiratory lung volume at each PEEP level. Lung compliance is determined as the difference in end-expiratory lung volume between two PEEP levels divided by the change in PEEP.

The transpulmonary pressure at each PEEP level is equal to the end-expiratory airway pressure (PEEP), and, the lung P/V curve between ZEEP and PEEP 16 cmH_2O can be obtained by plotting the end-expiratory transpulmonary pressure (PEEP) versus the end-expiratory lung volume at each PEEP level. By solving the equation of the best-fit lung P/V curve for the end-inspiratory lung volume level at each PEEP level, end-inspiratory transpulmonary pressures are obtained. It is an inherent feature of the PEEP step method that end-inspiratory transpulmonary pressure at the highest PEEP level (16 cmH_2O) cannot be determined, but has to be estimated by calculating end-inspiratory transpulmonary pressure as end-inspiratory airway pressure minus tidal pleural pressure variation (ΔPPL) extrapolated from the lower PEEP levels. Chest wall compliance (CCW) and ΔPPL are mainly constant when PEEP is increased [21, 23, 24, 37]. However, analysis of individual patient´s behavior of the present study and in Stahl and coworkers studies [38, 39], shows that CCW increases slightly when PEEP is increased in extrapulmonary ARDS patients, but remains mainly unchanged in pulmonary ARDS patients, which makes it necessary to perform the extrapolation procedure (Fig. 3). 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 for the clinically used tidal volume.

Total lung compliance (CL_{TOT}) was calculated as the lung volume at end-inspiration (ΔEELV 0-16 + VT) divided by the end-inspiratory transpulmonary pressure at PEEP 16 cmH_2O.

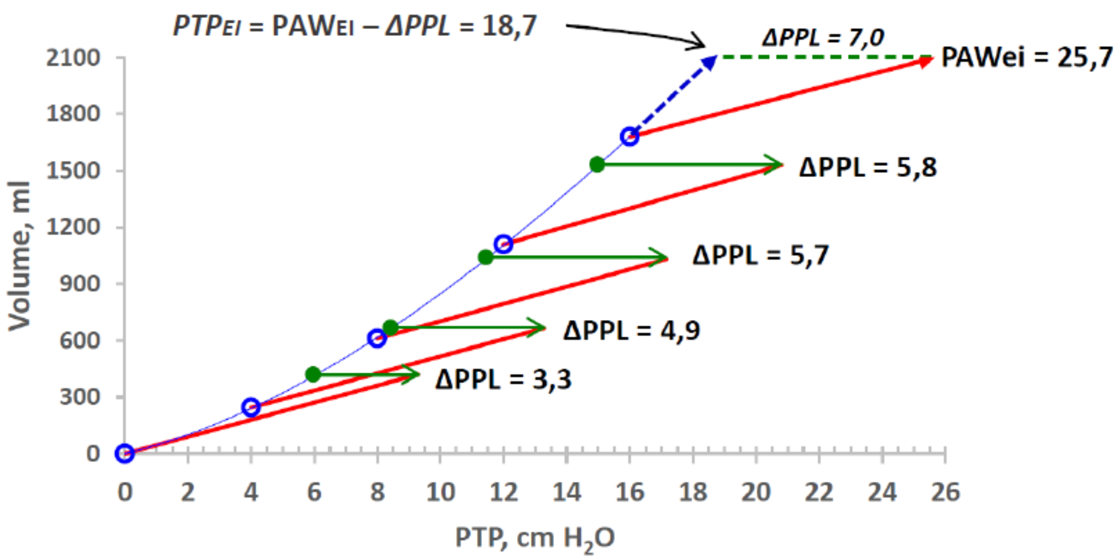

Fig. 3. As the end-expiratory transpulmonary pressure increases as much as PEEP is increased and the increase in end-expiratory lung volume following a PEEP increase is equal to ΔPEEP/EL, a lung P/V curve can be obtained by plotting the end-expiratory airway pressure vs cumulative end-expiratory lung volume. Red arrows: tidal airway P/V curves, Blue line: lung P/V curve. Note that the end-expiratory and inspiratory lung P/V curves and end-expiratory airway (respiratory system) P/V curve coincide. The green arrows mark the tidal pleural pressure variation, ΔPPL. The end-inspiratory transpulmonary pressure at the highest PEEP level is estimated by extrapolation of ΔPPL at PEEP 16 cmH_2O from the ΔPPL at the four lower PEEP levels and estimate the end-inspiratory transpulmonary

pressure at PEEP 16 cmH$_2$O as end-inspiratory airway pressure minus extrapolated ΔPPL_{PEEP16}. The dashed blue line indicates the estimated tidal lung P/V curve at the highest PEEP level.

Results

The static steady state end-expiratory and end-inspiratory transpulmonary pressure and volume points were obtained for the whole PEEP trial from end-expiration at the lowest PEEP level to end-inspiration of the highest, and used to compose lung P/V curve. The lung P/V curves of the ten patients are ranked according to total lung compliance calculated as end-inspiratory lung volume divided by end-inspiratory transpulmonary pressure at the highest PEEP level (fig. 4). There are significant differences in the shape of the P/V curve of individuals with almost the same total lung compliance, but in spite of this, in all cases, the end-expiratory and end-inspiratory transpulmonary P/V points are aligned on a common single lung P/V curve. In all patients, the lung P/V curves show a lower inflection point (LIP), or rather a lower inflection *zone*, when lung compliance is increasing with PEEP increase from 0 to 8 – 12 cmH$_2$O (Fig. 4).

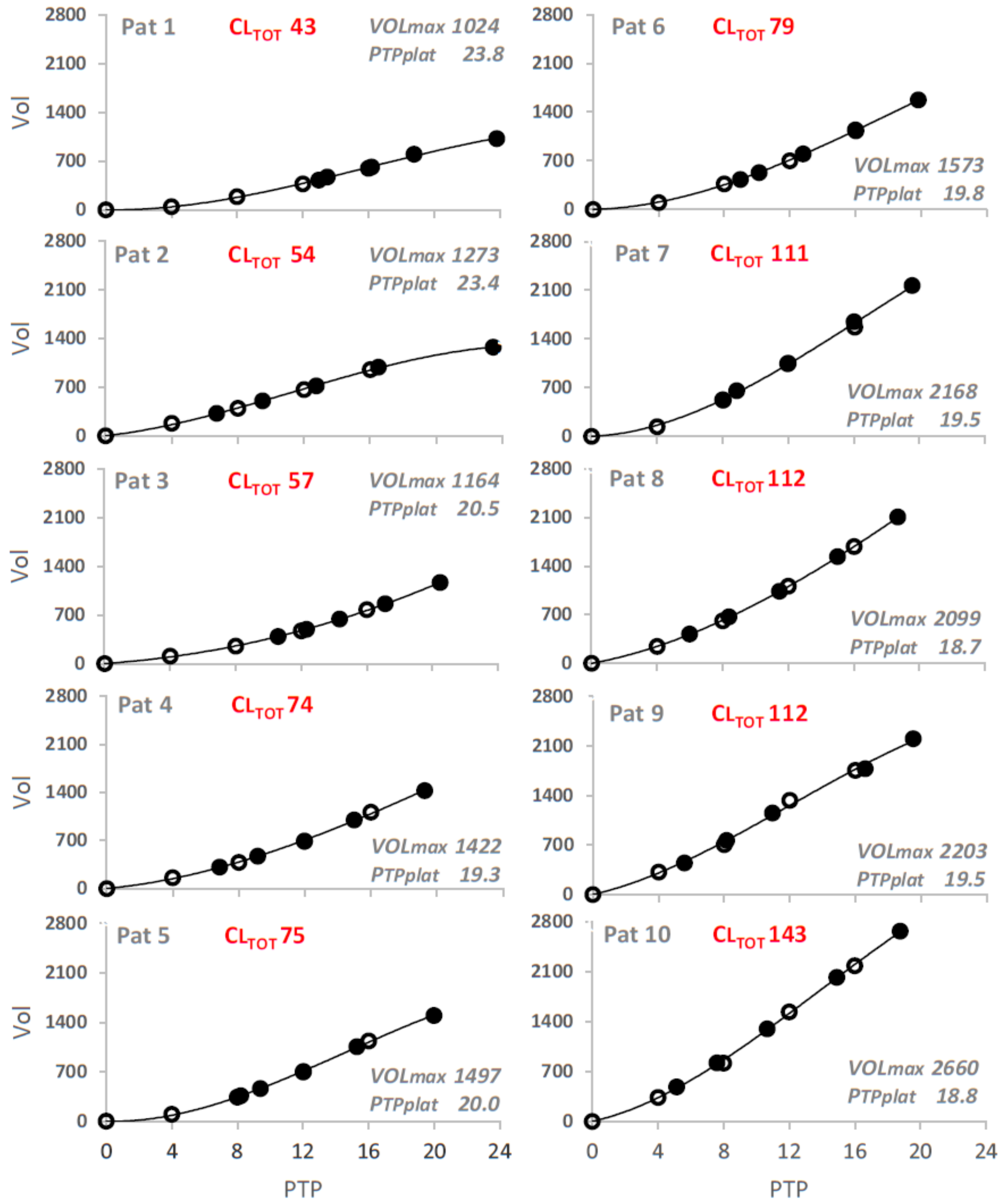

Fig. 4. Lung P/V measured data points and best fit curves (according to a third degree equation) in ten patients with lung compliance ranging from 43 to 143 ml/cmH_2O. The correlation coefficient (r^2) of the end-expiratory and end-inspiratory transpulmonary P/V points to the best-fit curve is above 0.99. 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.

As the calculation of the lung P/V curve requires measurement of ΔEELV, total lung compliance (CLTOT) can be regarded as an indicator of Inspiratory Capacity. In figure 5, the lung P/V curves of the ten patients are plotted to illustrate that patients treated for acute respiratory failure has very diverse lung mechanical properties, ranging from signs of emphysema with supernormal total lung compliance to a patient showing lung elastic properties comparable of a baby lung situation.

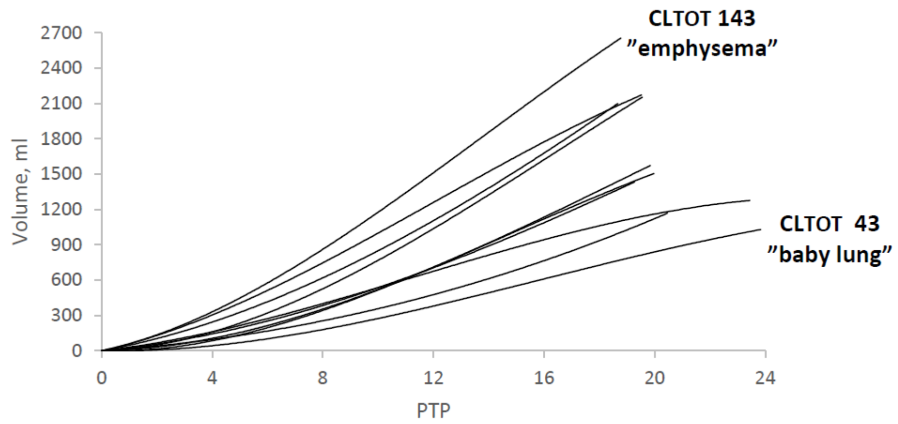

Fig. 5. Lung P/V curves from end-expiration at ZEEP to end-inspiration at PEEP 16 cmH$_2$O showing the diverse lung mechanics of patients with acute respiratory failure.

The ratio of transpulmonary to airway driving press, ΔPTP/ΔPAW changes with changes in PEEP. When changing from PEEP 12 cmH$_2$O to 16 cmH$_2$O, ΔPTP and ΔPAW may even change in opposite direction (Fig. 6).

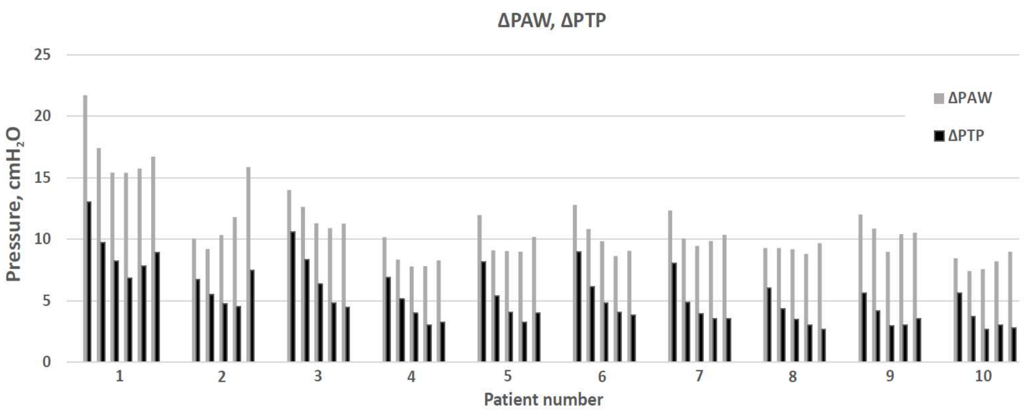

Fig. 6. Airway and transpulmonary driving pressure during PEEP steps 0-4-8-12-16 cmH_2O (also 20 cmH_2O in patient 1). Note that the relation between ΔPTP and ΔPAW changes with changing PEEP and in the individual patient, airway driving pressure does not track transpulmonary pressure during PEEP titration

Minimizing the number of PEEP steps of the measurement procedure

To reduce the time required for the measurement procedure, the lung P/V curve was calculated from PEEP 8 cmH_2O (regarded as a possible clinical PEEP level) with two steps up to 12 and 16 cmH_2O of PEEP. The transpulmonary plateau pressure at PEEP 16 cmH_2O was extrapolated by principally the same method as described for the original four-PEEP-step procedure, but that reduces the number of PEEP levels, which can be used as basis for extrapolation procedure from four to two. Estimated end-inspiratory transpulmonary plateau pressure with the two-step procedure was 20.3 ± 1.2 cmH_2O and the corresponding pressure after the original four-step procedure was 20.3 ± 1.8 cmH_2O. (Fig. 7). Lung compliance calculated as ΔEELV from 8 to 16 cmH_2O PEEP divided by a ΔPEEP of 8 cmH_2O correlated closely to lung compliance calculated as ΔEELV from 0 to 16 cmH_2O PEEP divided by a ΔPEEP of 16 cmH_2O, Y = 1.28X, r^2 = 0.97.

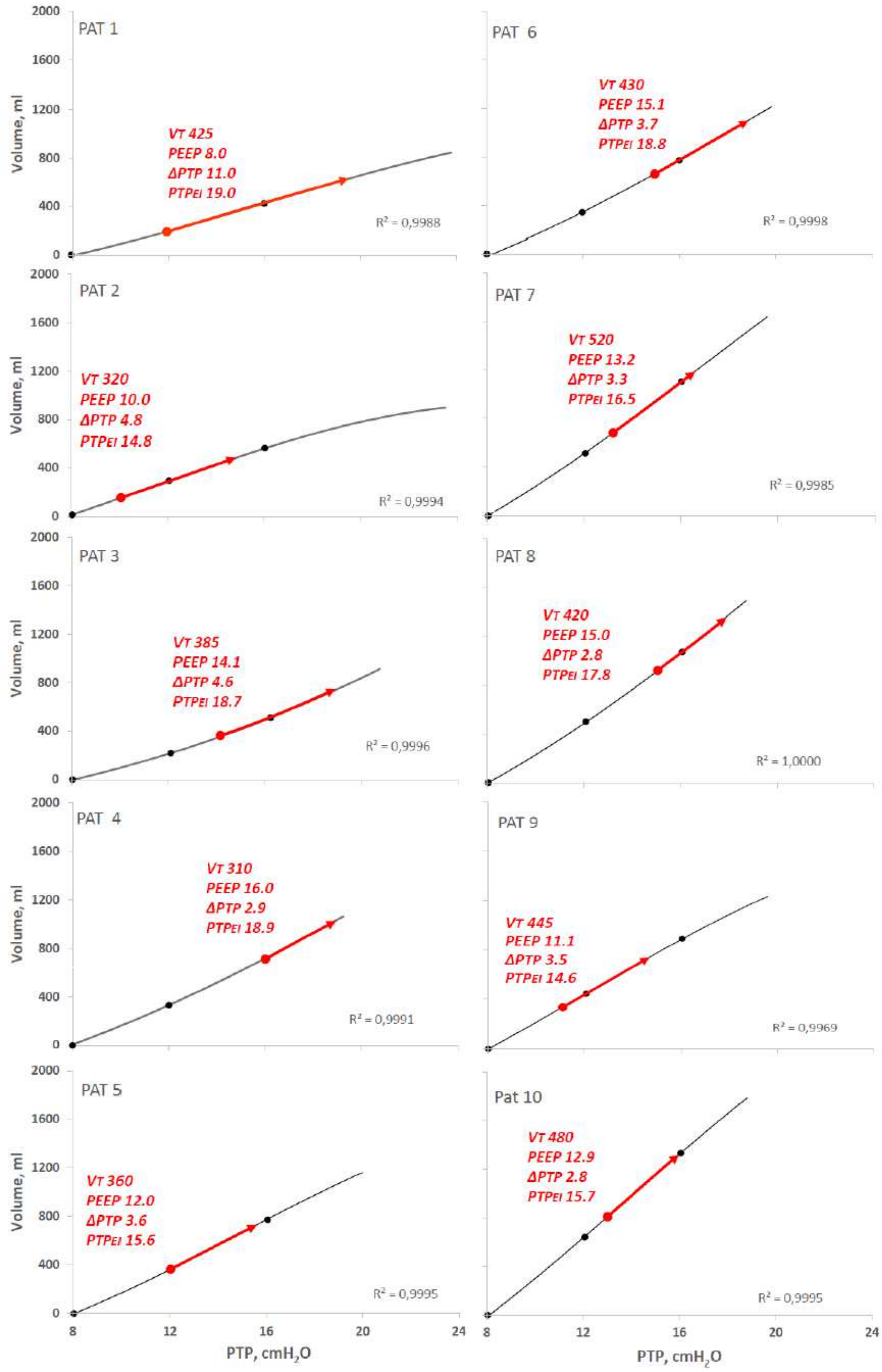

Fig. 7. Lung P/V curves by a two PEEP step up-down procedure (black line). The black filled circles indicate that PEEP levels of 8, 12 and 16 cmH_2O were used together with the estimated end-inspiratory transpulmonary P/V point at the highest PEEP level for determining the best-fit lung P/V curve. The end-inspiratory transpulmonary pressure is, except for patient 1 and 2, who are PEEP non-responders, 18-20 cmH_2O. As the corresponding lung volume also is determined by the PEEP-step

measurement procedure, it is possible to calculate the over-all lung compliance, which normally should be around 100 ml/cmH_2O and where a low compliance indicates a low inspiratory capacity and possibly the existence of a baby lung, which is highly likely in patient 1 and 2.

The red arrow shows the tidal lung P/V curve with the lowest transpulmonary driving pressure for the tidal volume used clinically in the patients (6-7 ml/kg ideal body weight).

PEEP response

Lung compliance increases with increasing PEEP in PEEP responders and is associated with higher over-all lung compliance, 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 lung compliance around 50 ml/cmH_2O, which is half the lung compliance seen in lung healthy [23, 37]. The PEEP non-responder is characterized by decreasing lung compliance with an upper deflection point on the lung P/V curve at higher PEEP levels (Fig. 8).

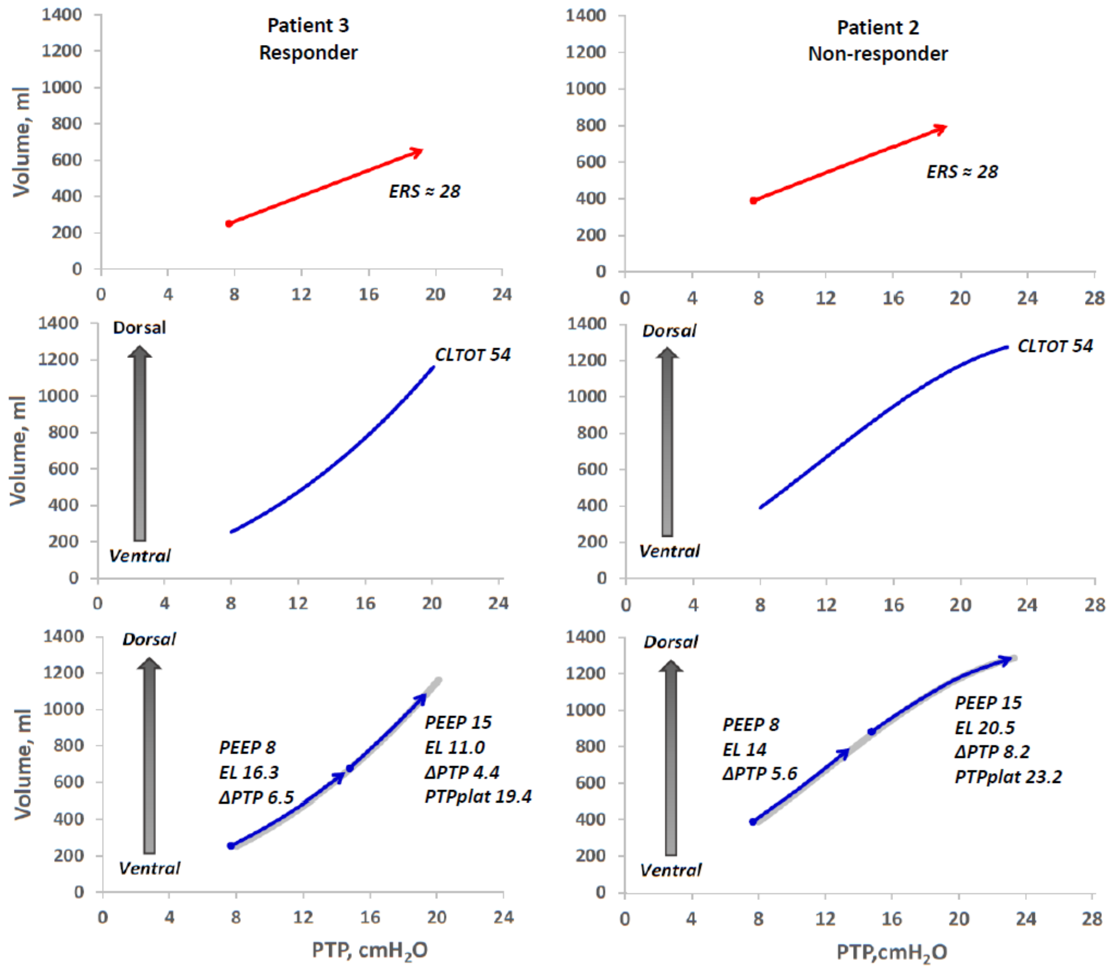

Fig. 8. Implementation of a short two-PEEP step procedure in two patients with the same respiratory system compliance at a baseline clinical PEEP of 8 cmH_2O (upper panels). PEEP is increased stepwise from 8 to 12 and 16 cmH_2O and the lung P/V curve (blue line) is determined from end-expiration of PEEP 8 to end-inspiration at PEEP 16 cmH_2O (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 cmH_2O, 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 cmH_2O results in a decrease in ΔPTP from 6.5 to 4.4 cmH_2O and a transpulmonary plateau pressure, which is well below VILI levels. Note, that inflation by PEEP occurs from ventral to dorsal region (grey-black, thick arrow), which causes tidal ventilation to be moved in dependent direction when PEEP is increased.

Discussion

In this observational study, we could show that it was possible to obtain precise lung P/V curves without esophageal pressure measurements during a PEEP trial. Lung mechanics showed marked individual variation with over-all lung compliance between 143 and 43 ml/cmH_2O. Eight of the ten patients showed varying degree of positive PEEP response lung compliance increasing with PEEP, while the two patients with the lowest lung compliance were PEEP non-responders lung compliance decreasing with increasing PEEP. In the individual patient, there was no correlation between transpulmonary- and airway driving pressure. We also showed that a lung P/V curve covering the transpulmonary pressure/volume range within minimal risk of VILI could be obtained with only two PEEP steps, making the measurement procedure fast and easy in a clinical situation. This best-fit lung P/V curve could be used to determine the PEEP level where transpulmonary driving pressure was lowest for any given tidal volume.

Methodological considerations

At FRC/ZEEP there is a balance between the recoil of the lung and the expanding thoracic wall, which has caused inflation of the lung from residual volume to FRC with a positive transpulmonary pressure, and an equally negative pleural pressure as result. The thoracic cage strives outwards until 70 – 80 % of TLC, but cannot reach higher end-expiratory volume than FRC unless the lung is inflated by PEEP. As the chest wall complex does not lean on the lung at end-expiration, even when PEEP is increased, until lung volume reaches 70-80 % of TLC, transpulmonary pressure increases as much as PEEP is increased. Consequently, lung and chest wall mechanics can be separated by a PEEP trial as lung compliance is equal to ΔEELV divided by ΔPEEP. A lung P/V curve derived from a PEEP trial is a true static lung P/V curve, where end-expiratory and end-inspiratory transpulmonary P/V points are aligned on a single common curve, as transpulmonary pressure at a certain lung volume is independent of whether this volume is reached by tidal or PEEP inflation (Fig. 1, 3, 4). An additional section shows the complete mathematical derivation of PEEP inflation [see Additional file 1].

Our aim was to develop a method for separation of lung and chest wall mechanics that was fast and easy that it could be used under any circumstances, at any time of ventilator treatment from start until extubation. We investigated whether a two-PEEP-step, three PEEP level procedure was as precise as the four-step five PEEP level procedure and delivered similar information on lung elastic properties, which it did. The two PEEP-step-up procedure takes around three minutes. It is probable that the lung P/V curve would be more precise if yet another PEEP step was used, for example 8 – 12-16 – 20 cmH_2O, for improved estimation (extrapolation) of end-inspiratory transpulmonary pressure. but this will lead to a prolongation of the measurement procedure from 3 to ≈ 4,5 minutes. If the PEEP step method is implemented in a ventilator, it can be programmed to make a PEEP-down procedure from a high initial PEEP level as prolonged expirations step-wise down to lower PEEP levels, which will make the procedure very rapid. However, such a procedure needs to be evaluated as hysteresis phenomenon during fast procedures may cause less adequate results [40-42].

It is an inherent feature of the PEEP step method that the end-inspiratory transpulmonary pressure (PTPplat) at the highest PEEP level used during the measurement procedure has to be estimated instead of measured (Fig. 3). In the present analysis, 8 out of ten patients had a PTPplat below 20 cmH_2O and the estimation procedure could have been avoided by adding a PEEP step up to 20 cmH_2O. In cases with severely compromised oxygenation, ECMO treatment may be avoided if PEEP can be increased safely, i.e. without risk of exceeding the upper transpulmonary pressure limit (≈ 24 cmH_2O) [43-46]. In such cases, it seems reasonable to extend the measurement procedure to a PEEP of 24 cmH_2O to obtain a correct measured lung P/V curve for the whole PEEP/EELV range within the safety limit.

In the present study ΔEELV was determined as the cumulative difference in expiratory tidal volume between PEEP levels, but as a long duration, 5 PEEP-level trial was performed, the changes in end-expiratory lung volume was enhanced by EIT tracking (Fig.2). An additional paragraph provides detailed information on the tidal volume calibration by EIT process [see Additional file 1]. During a two or three PEEP-step procedure, ΔEELV can be determined by cumulative expiratory tidal volume difference determined by the ventilator spirometry alone with high precision (± 3.5 %)[37].

To assess cumulative DEELV from ZEEP to the highest PEEP level, the two-step procedure should be preceded by a PEEP decrease down to ZEEP and back again to baseline PEEP. This also makes the correct calculation of total lung compliance (CLTOT) as (DEELV0-16 + VT)/$PTPplat_{PEEP16}$ possible. This is an advantage as total lung compliance reflects the size of the lung at ZEEP, low CLTOT – baby lung, high CLTOT – normal FRC.

The two-step procedure can be regarded as a diagnostic procedure, but to allow for continual monitoring of transpulmonary pressure only a simple PEEP step up and down procedure where PEEP is changed as much as the existing transpulmonary driving pressure, is required. Such a PEEP up-down procedure should be performed on a regular basis and when patient position is changed or after interventions, such as suctioning has been performed.

Transpulmonary plateau and driving pressure and lung capacity

The most striking feature of the PEEP-step method is that not only transpulmonary pressure is determined, but also the increase in end-expiratory lung volume caused by increasing PEEP. The cumulative increase in EELV, the PEEP volume [28, 47], is an indicator of the volume capacity of the lung and directly related to **lung** compliance. In a lung healthy individual, the over-all lung compliance is 80 – 125 ml/cmH_2O and a PEEP increase of 10 cmH_2O should accordingly result in a ΔEELV of 800 – 1250 ml. In table 3, we have identified some key data for different lung conditions and calculated the transpulmonary driving pressure of a tidal volume of ≈ 7 ml/kg IBW in a person with an ideal body weight (IBW) of 70 kg, 500 ml. This shows that such a “protective” tidal volume causes almost twice the ΔPTP in a pulmonary ARDS patient, as in a lung healthy.

	EL, cmH_2O/L	CL, ml/cmH_2O	VT 6 - 7 ml/kg ibw for 70 kg ibw	ΔPTP, cmH_2O for VT 500 ml (70 kg IBW)
Emphysema	< 8	> 125	500	< 4
Normal	8 - 12.5	125 - 80	500	4 - 6.5
Moderate ARDS, PEEP responder	12.5 - 17	80 - 60	500	6.5 - 8.5
Severe ARDS, PEEP non-responder	> 17	< 60	500	> 8.5

Table 3. Overall lung compliance for different lung conditions compiled from [23, 24, 33, 37, 48]. A protective tidal volume of 6 – 7 ml/kg ideal body weight (IBW) for a person with an IBW of 70 kg, corresponds to a tidal volume around 500 ml. Dependent on the lung condition, the transpulmonary driving pressure (ΔPTP) ranges from below 4 cmH_2O in an emphysematic patient, to above 8.5 cmH_2O in severe ARDS. In extreme cases, with pulmonary ARDS with lung compliance around 30 ml/cmH_2O, ΔPTP would reach ≈ 17 cmH_2O. This is above even the ***airway*** *driving pressure upper limit of 15 cmH_2O, proposed by Amato and colleagues [16].*

In the ARDSnet study in 2000, a tidal volume of 12 and 6 ml IBW was compared in ARDS patients and mortality was highly significantly lower when using the lower tidal volume. Since then, a tidal volume of 6 ml/kg IBW is regarded as "protective" and commonly used. In our study, all patients were ventilated with a tidal volume of 6 – 7 ml, but as lung mechanics were highly varying, with lung compliance from above normal to levels corresponding to pulmonary ARDS, such a protective tidal volume is not protective in all individual patients. In fact, these tidal volumes did not correlate with respective individual total lung compliance, which reflects the size of the lung at FRC [48, 49]. Thus, from a lung mechanical point of view, it would be an advantage to adapt the tidal volume to lung capacity as a surrogate for functional residual capacity when calculating the stress/strain ratio [48].

VILI assessment

A low PEEP volume, ΔEELV between ZEEP and the highest PEEP level of the measurement procedure, is a result of a small lung at FRC, in the worst cases a “baby lung” [49]. PEEP inflation, like slow and tidal inflation [50-52], occurs successively from non-dependent to dependent lung regions [53]. When the PEEP volume is low, it indicates that more dependent lung regions are consolidated and cannot be PEEP recruited and inflated unless very high pressures are used. In these patients, PEEP will mainly cause further inflation of the small ventral lung, like the ensuing tidal volume, with risk of overdistension and VILI (Fig. 9). This risk can be minimized by adapting ventilator settings to the mechanical condition of the **lung**, and this is best done by identifying when the mechanical condition diverge from “normality” or where the mechanical insult is lowest. PEEP titration is commonly used to find the PEEP level where **respiratory system** compliance is highest [15, 54-57] and consequently airway driving pressure lowest [16], which supposedly is the PEEP level where the risk of VILI is lowest. However, the transpulmonary driving pressure to airway driving pressure ratio, ΔPTP/ΔPAW changes significantly when changing PEEP (fig. 6) making the airway driving pressure less suitable as surrogate for transpulmonary driving pressure [18, 48, 49] . Thus, instead of seeking the PEEP level with the lowest airway driving, the PEEP level with the lowest transpulmonary driving pressure ($PEEP_{min}$) is preferable. As the **tidal** transpulmonary P/V curve is positioned along the lung P/V curve between end-expiration at baseline PEEP and end-inspiration at the highest PEEP level (Fig. 1, 3, 4), the transpulmonary plateau and driving pressure and can be determined for any PEEP – VT combination [58, 59]. The two PEEP-step lung P/V curve starts at PEEP 8 cmH_2O, which is above the lower inflection zone, seen in the 0 – 16 cmH_2O P/V curve and $PEEP_{mIn}$ is in all patients positioned at the steepest part of the curve. In the PEEP responders, $PEEP_{mIn}$ may be quite high and obviously, also the end-inspiratory transpulmonary plateau pressure level must be considered when finally selecting best (mechanical) PEEP. When assessing the risk of VILI (by for example the power concept), transpulmonary driving pressure and plateau pressure are preferable to airway (respiratory system) driving and plateau pressure [19, 28, 29, 31].

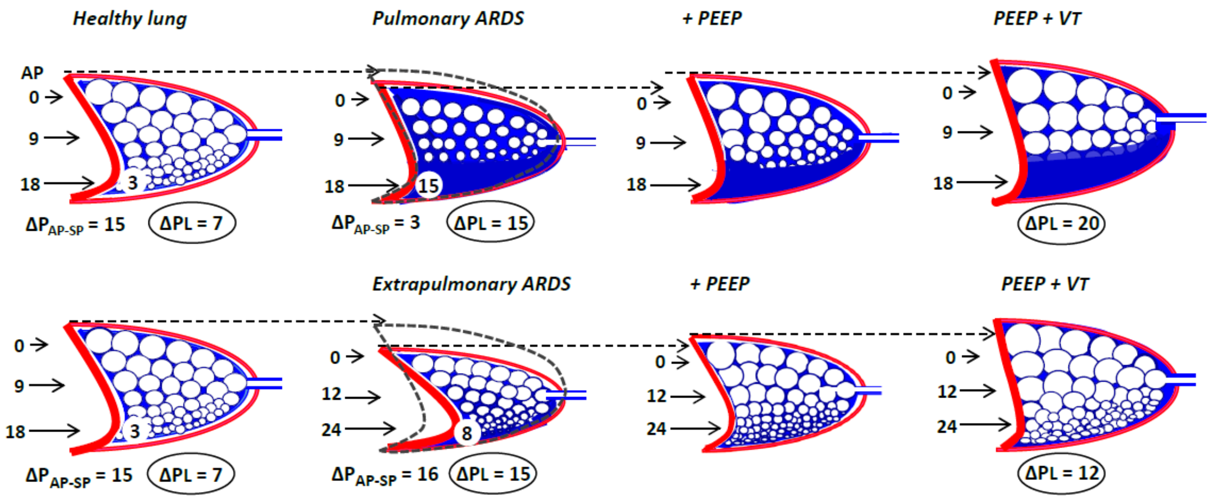

Fig. 9. Schematic graph showing the development from healthy lung (left upper and lower panels) to pulmonary ARDS, PEEP non-responder (upper panels) and extra-pulmonary ARDS, PEEP responder (lower panels). In pulmonary ARDS, the gradient between abdominal pressure (AP) and superimposed pressure (SP) is small. Exterior lung volume and diaphragm position are almost normal. PEEP causes inflation of the non-dependent baby lung, but not of consolidated dependent lung. In extra-pulmonary ARDS, the increased edema of the abdomen pushes the diaphragm in cranial direction and decreases FRC. Dependent lung is compressed and poorly aerated. When PEEP is applied, already open lung will be further inflated and the diaphragm pushed in caudal direction, increasing space for the lung to expand.

Identifying "under-treatment"

As important it is to minimize VILI, it is to identify, where it is possible to increase PEEP to improve oxygenation without risk of VILI. Grasso and coworkers managed to avoid ECMO treatment in half of the patients with influenza A (H1N1)[43], when they determined transpulmonary pressure using esophageal pressure and found that in half the patients, PEEP could be further increased without reaching the upper limit for transpulmonary plateau pressure, 25 cmH_2O [44-46]. In the present study, two patients had the same respiratory system compliance and airway driving pressure at 8 cmH_2O of PEEP. After a two-step PEEP procedure, we could show that increasing PEEP to 15 cmH_2O in one of the patients, resulted in around 30 % decrease in transpulmonary driving pressure, while in the other, transpulmonary driving pressure increased with 30 % and plateau pressure reached a dangerous level, 23.2 cmH_2O (Fig. 8).

Very early diagnostics

Preventive measures to avoid worsening of lung condition with consolidation of atelectasis should be taken early in the course of ventilator treatment [60-62], but little is known about very early lung mechanics conditions, as esophageal pressure measurements seldom are instigated directly after start of ventilator treatment. Most studies of PEEP strategies even include patients up to 72 hours after start of ventilator treatment. In contrast to esophageal pressure measurements, 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.

Study limitations

In this analysis, we have only access to PEEP trials up to 16 cmH_2O. As it is an inherent feature of the PEEP step method, that the transpulmonary inspiration pressure at the highest PEEP level always has to be estimated by extrapolation, it has not been possible to determine how precise estimated transpulmonry plateau pressure at 16 cmH_2O of PEEP is. Ideally, from a measurement precision point of view, PEEP steps up to 25 cmH_2O should be used, as this is the upper limit for safe transpulmonary plateau pressure [44-46]. In most cases however, it is probably sufficient if the highest PEEP level of the measurement procedure is 16-18 cmH_2O, because the plateau pressure at such PEEP levels will reach levels close to the upper safety limit.

Conclusions

There is no correlation between airway driving pressure and transpulmonary driving pressure in individual patients, indicating that airway driving pressure is less suitable for individualization of protective ventilation. However, applying PEEP causes separation of lung and chest wall mechanics, which makes it possible to identify the lung P/V curve from end-expiration at a low clinical PEEP, to end-inspiration at the highest PEEP level of a rapid PEEP-step procedure. The best-fit equation for the lung P/V curve can be used to determine the PEEP level where transpulmonary driving pressure is lowest and possibly least injurious for any given tidal volume. The measurement procedure is non-invasive and can easily be implemented from immediately after start of ventilator treatment until extubation.

Acknowledgement

We thank Anders Larsson, Hedenstierna laboratory, Uppsala University for invaluable discussions on lung mechanics.

We thank Daniel Dencker for refining the mathematics of this analysis.

Declarations:

Ethics approval and consent to participate: **T**he study is 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.

Consent for publication: N/A

Availability of data and material: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: OS holds share in the Lung Barometry Sweden AB. GS has no competing interest.

Funding: This study was supported by grants from the Swedish Heart and Lung Foundation, Sahlgrenska Academy at the University of Gothenburg and the Medical Society of Gothenburg, Sweden.

Authors' contributions: CG has done all data acquisition and detailed analysis and interpretation of data as a background for the present analysis. She has also revised and approved the final manuscript.

OS has developed the current concept of the PEEP-step method and performed the protective PEEP level analysis. OS has drafted and revised the manuscript.

Acknowledgements: Anders Larsson, Hedenstierna laboratory, Uppsala University has given invaluable advice during the analysis and drafting of the manuscript.

Daniel Dencker has refined the mathematical derivation of the mechanics of PEEP

References

1. Kumar A, Pontoppidan H, Falke KJ, Wilson RS, Laver MB: **Pulmonary barotrauma during mechanical ventilation**. *Critical care medicine* 1973, **1**(4):181-186.
2. Dreyfuss D, Saumon G: **From ventilator-induced lung injury to multiple organ dysfunction?** *Intensive care medicine* 1998, **24**(2):102-104.
3. Dreyfuss D, Saumon G: **Ventilator-induced lung injury: lessons from experimental studies**. *American journal of respiratory and critical care medicine* 1998, **157**(1):294-323.
4. Dreyfuss D, Saumon G: **Barotrauma is volutrauma, but which volume is the one responsible?** *Intensive care medicine* 1992, **18**(3):139-141.
5. Plotz FB, Slutsky AS, van Vught AJ, Heijnen CJ: **Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses**. *Intensive care medicine* 2004, **30**(10):1865-1872.
6. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome**. *The New England journal of medicine* 2000, **342**(18):1301-1308.
7. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R *et al*: **Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome**. *The New England journal of medicine* 1998, **338**(6):347-354.
8. Tobin MJ: **Culmination of an era in research on the acute respiratory distress syndrome**. *The New England journal of medicine* 2000, **342**(18):1360-1361.
9. Webb HH, Tierney DF: **Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure**. *The American review of respiratory disease* 1974, **110**(5):556-565.

10. Dreyfuss D, Soler P, Basset G, Saumon G: **High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure**. *The American review of respiratory disease* 1988, **137**(5):1159-1164.

11. Muscedere JG, Mullen JB, Gan K, Slutsky AS: **Tidal ventilation at low airway pressures can augment lung injury**. *American journal of respiratory and critical care medicine* 1994, **149**(5):1327-1334.

12. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L *et al*: **Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial**. *JAMA : the journal of the American Medical Association* 2008, **299**(6):637-645.

13. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A *et al*: **Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial**. *JAMA : the journal of the American Medical Association* 2008, **299**(6):646-655.

14. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D *et al*: **Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis**. *JAMA : the journal of the American Medical Association* 2010, **303**(9):865-873.

15. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial I, Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, Romano ER, Regenga MM, Taniguchi LNT *et al*: **Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial**. *JAMA : the journal of the American Medical Association* 2017, **318**(14):1335-1345.

16. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A *et al*: **Driving pressure and survival in the acute respiratory distress syndrome**. *The New England journal of medicine* 2015, **372**(8):747-755.

17. Guerin C, Papazian L, Reignier J, Ayzac L, Loundou A, Forel JM, investigators of the A, Proseva t: **Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials**. *Critical care* 2016, **20**(1):384.

18. Gattinoni L, Chiumello D, Carlesso E, Valenza F: **Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients**. *Critical care* 2004, **8**(5):350-355.

19. Loring SH, Malhotra A: **Driving pressure and respiratory mechanics in ARDS**. *The New England journal of medicine* 2015, **372**(8):776-777.

20. Stenqvist O: **Transpulmonary driving pressure, without esophageal pressure measurements, instead of airway driving pressure**. *Intensive care medicine* 2020.

21. Stenqvist O, Grivans C, Andersson B, Lundin S: **Lung elastance and transpulmonary pressure can be determined without using oesophageal pressure measurements**. *Acta anaesthesiologica Scandinavica* 2012, **56**(6):738-747.

22. Stenqvist O, Kjelltoft B, Lundin S: **Evaluation of a new system for ventilatory administration of nitric oxide**. *Acta anaesthesiologica Scandinavica* 1993, **37**(7):687-691.

23. Pelosi P, Cereda M, Foti G, Giacomini M, Pesenti A: **Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure**. *American journal of respiratory and critical care medicine* 1995, **152**(2):531-537.

24. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A: **Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes?** *American journal of respiratory and critical care medicine* 1998, **158**(1):3-11.

25. Garnero A, Tuxen D, Ducros L, Demory D, Donati SY, Durand-Gasselin J, Cooper J, Hodgson C, Arnal JM: **Non-invasive assessment of lung elastance in patients with acute respiratory distress syndrome**. *Minerva anestesiologica* 2015, **81**(10):1096-1104.

26. Gudmundsson M, Persson P, Perchiazzi G, Lundin S, Rylander C: **Transpulmonary driving pressure during mechanical ventilation-validation of a non-invasive measurement method**. *Acta anaesthesiologica Scandinavica* 2020, **64**(2):211-215.

27. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, Morais CCA, Gomes S, Costa ELV, Cardoso PFG *et al*: **Esophageal Manometry and Regional Transpulmonary Pressure in Lung Injury**. *American journal of respiratory and critical care medicine* 2018, **197**(8):1018-1026.

28. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E *et al*: **Ventilator-related causes of lung injury: the mechanical power**. *Intensive care medicine* 2016, **42**(10):1567-1575.

29. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, Cammaroto A, Brioni M, Montaruli C, Nikolla K *et al*: **Mechanical Power and Development of Ventilator-induced Lung Injury**. *Anesthesiology* 2016, **124**(5):1100-1108.

30. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, Niewenhuys J, Behnemann T, Camporota L, Hahn G *et al*: **Positive End-expiratory Pressure and Mechanical Power**. *Anesthesiology* 2019, **130**(1):119-130.

31. Giosa L, Busana M, Pasticci I, Bonifazi M, Macri MM, Romitti F, Vassalli F, Chiumello D, Quintel M, Marini JJ *et al*: **Mechanical power at a glance: a simple surrogate for volume-controlled ventilation**. *Intensive care medicine experimental* 2019, **7**(1):61.

32. Marini JJ: **How I optimize power to avoid VILI**. *Critical care* 2019, **23**(1):326.

33. Lundin S, Grivans C, Stenqvist O: **Transpulmonary pressure and lung elastance can be estimated by a PEEP-step manoeuvre**. *Acta anaesthesiologica Scandinavica* 2015, **59**(2):185-196.

34. Frerichs I: **Electrical impedance tomography (EIT) in applications related to lung and ventilation: a review of experimental and clinical activities**. *Physiological measurement* 2000, **21**(2):R1-21.

35. Grivans C, Lundin S, Stenqvist O, Lindgren S: **Positive end-expiratory pressure-induced changes in end-expiratory lung volume measured by spirometry and electric impedance tomography**. *Acta anaesthesiologica Scandinavica* 2011, **55**(9):1068-1077.

36. Hinz J, Hahn G, Neumann P, Sydow M, Mohrenweiser P, Hellige G, Burchardi H: **End-expiratory lung impedance change enables bedside monitoring of end-expiratory lung volume change**. *Intensive care medicine* 2003, **29**(1):37-43.

37. Persson P, Stenqvist O, Lundin S: **Evaluation of lung and chest wall mechanics during anaesthesia using the PEEP-step method**. *British journal of anaesthesia* 2018, **120**(4):860-867.

38. Stahl CA, Moller K, Schumann S, Kuhlen R, Sydow M, Putensen C, Guttmann J: **Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome**. *Critical care medicine* 2006, **34**(8):2090-2098.

39. Stahl CA, Moller K, Steinmann D, Henzler D, Lundin S, Stenqvist O: **Determination of 'recruited volume' following a PEEP step is not a measure of lung recruitability**. *Acta anaesthesiologica Scandinavica* 2015, **59**(1):35-46.

40. Chiumello D, Arnal JM, Umbrello M, Cammaroto A, Formenti P, Mistraletti G, Bolgiaghi L, Gotti M, Novotni D, Reidt S *et al*: **Hysteresis and Lung Recruitment in Acute Respiratory Distress Syndrome Patients: A CT Scan Study**. *Critical care medicine* 2020, **48**(10):1494-1502.

41. Marini JJ: **Hysteresis As an Indicator of Recruitment and Ventilator-Induced Lung Injury Risk**. *Critical care medicine* 2020, **48**(10):1542-1543.

42. Koefoed-Nielsen J, Andersen G, Barklin A, Bach A, Lunde S, Tonnesen E, Larsson A: **Maximal hysteresis: a new method to set positive end-expiratory pressure in acute lung injury?** *Acta anaesthesiologica Scandinavica* 2008, **52**(5):641-649.

43. Grasso S, Terragni P, Birocco A, Urbino R, Del Sorbo L, Filippini C, Mascia L, Pesenti A, Zangrillo A, Gattinoni L *et al*: **ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure**. *Intensive care medicine* 2012, **38**(3):395-403.

44. Colebatch HJ, Greaves IA, Ng CK: **Exponential analysis of elastic recoil and aging in healthy males and females**. *Journal of applied physiology: respiratory, environmental and exercise physiology* 1979, **47**(4):683-691.

45. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V: **Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy**. *Anesthesiology* 2002, **96**(4):795-802.

46. Ranieri VM, Brienza N, Santostasi S, Puntillo F, Mascia L, Vitale N, Giuliani R, Memeo V, Bruno F, Fiore T *et al*: **Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension**. *American journal of respiratory and critical care medicine* 1997, **156**(4 Pt 1):1082-1091.

47. Gattinoni L, Giosa L, Bonifazi M, Pasticci I, Busana M, Macri M, Romitti F, Vassalli F, Quintel M: **Targeting transpulmonary pressure to prevent ventilator-induced lung injury**. *Expert review of respiratory medicine* 2019, **13**(8):737-746.

48. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A *et al*: **Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome**. *American journal of respiratory and critical care medicine* 2008, **178**(4):346-355.

49. Gattinoni L, Pesenti A: **The concept of "baby lung"**. *Intensive care medicine* 2005, **31**(6):776-784.

50. Muders T, Luepschen H, Zinserling J, Greschus S, Fimmers R, Guenther U, Buchwald M, Grigutsch D, Leonhardt S, Putensen C *et al*: **Tidal recruitment assessed by electrical impedance tomography and computed tomography in a porcine model of lung injury***. *Critical care medicine* 2012, **40**(3):903-911.

51. Victorino JA, Borges JB, Okamoto VN, Matos GF, Tucci MR, Caramez MP, Tanaka H, Sipmann FS, Santos DC, Barbas CS *et al*: **Imbalances in regional lung ventilation: a validation study on electrical impedance tomography**. *American journal of respiratory and critical care medicine* 2004, **169**(7):791-800.

52. Lowhagen K, Lundin S, Stenqvist O: **Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome assessed by electric impedance tomography**. *Minerva anestesiologica* 2010, **76**(12):1024-1035.

53. Gattinoni L, Pelosi P, Crotti S, Valenza F: **Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome**. *American journal of respiratory and critical care medicine* 1995, **151**(6):1807-1814.

54. Suarez-Sipmann F, Bohm SH, Tusman G, Pesch T, Thamm O, Reissmann H, Reske A, Magnusson A, Hedenstierna G: **Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study**. *Critical care medicine* 2007, **35**(1):214-221.

55. Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS *et al*: **Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome**. *American journal of respiratory and critical care medicine* 2006, **174**(3):268-278.

56. de Matos GF, Stanzani F, Passos RH, Fontana MF, Albaladejo R, Caserta RE, Santos DC, Borges JB, Amato MB, Barbas CS: **How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography**. *Critical care* 2012, **16**(1):R4.

57. Hodgson CL, Tuxen DV, Davies AR, Bailey MJ, Higgins AM, Holland AE, Keating JL, Pilcher DV, Westbrook AJ, Cooper DJ *et al*: **A randomised controlled trial of an open lung strategy with**

staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. *Critical care* 2011, **15**(3):R133.

58. Stenqvist O, Persson P, Lundin S: **Can we estimate transpulmonary pressure without an esophageal balloon?-yes**. *Ann Transl Med* 2018, **6**(19):392.

59. McKown AC, Semler MW, Rice TW: **Lung Recruitment and Positive End-Expiratory Pressure Titration in Patients With Acute Respiratory Distress Syndrome**. *JAMA : the journal of the American Medical Association* 2018, **319**(9):932-933.

60. Moran JL, Solomon PJ, Fox V, Salagaras M, Williams PJ, Quinlan K, Bersten AD: **Modelling thirty-day mortality in the Acute Respiratory Distress Syndrome (ARDS) in an adult ICU**. *Anaesthesia and intensive care* 2004, **32**(3):317-329.

61. Shari G, Kojicic M, Li G, Cartin-Ceba R, Alvarez CT, Kashyap R, Dong Y, Poulose JT, Herasevich V, Garza JA *et al*: **Timing of the onset of acute respiratory distress syndrome: a population-based study**. *Respiratory care* 2011, **56**(5):576-582.

62. Litell JM, Gong MN, Talmor D, Gajic O: **Acute lung injury: prevention may be the best medicine**. *Respiratory care* 2011, **56**(10):1546-1554.

Additional files:

Additional file 1.

Grivans Stenqvist PEEP step method for Crit Care E-supplement 27 April 2021.pdf

Figures

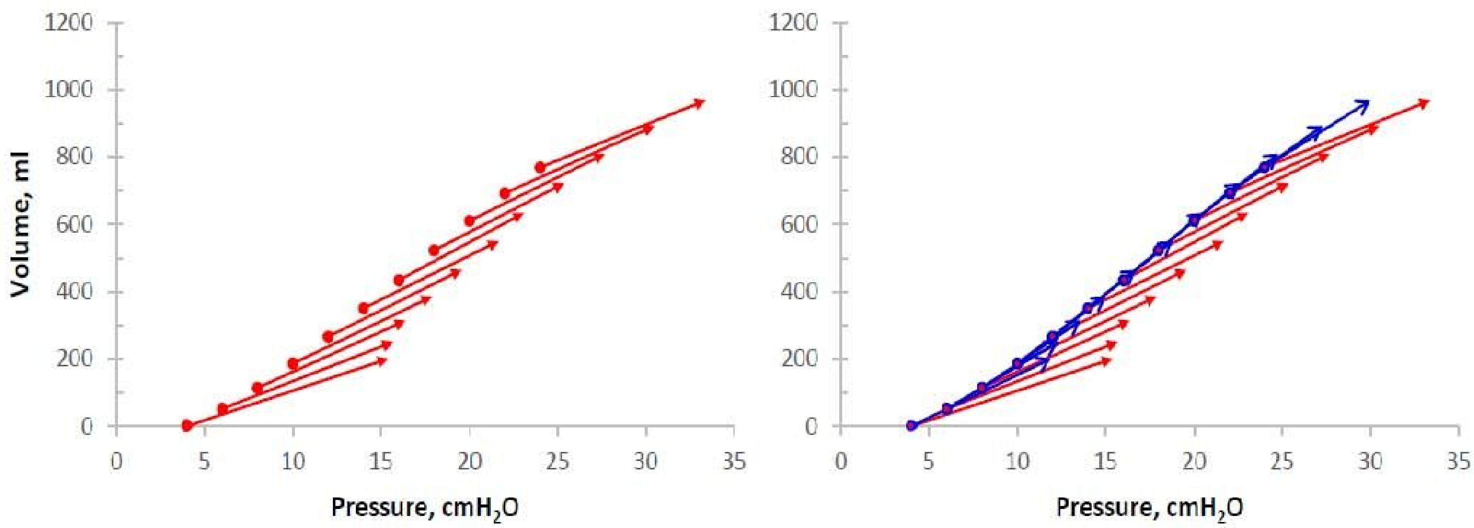

Figure 1

Tidal airway (red arrows) and lung P/V curves (blue arrows) calculated from end-expiratory and end-inspiratory esophageal and transpulmonary pressure data at each PEEP (ΔPAW/VT, (ΔPAW - ΔPES)/VT) level of the Yoshida et al study 2018 [27]. This makes it possible to determine transpulmonary and chest wall driving pressure and lung and chest wall elastance (EL, ECW) and respiratory system elastance (ERS) as the sum of tidal lung and chest wall elastance at each PEEP level. Also, ΔEELV between PEEP levels can be calculated as ΔPEEP/EL (ΔPEEP x CL). Left panel: Tidal airway P/V curves at PEEP 4 to 24 cmH2O with tidal volume of 200 ml from Yoshida et al [27] where ΔEELV was determined for each 2 cmH2O PEEP step as ΔPEEP/EL, and EL calculated as ΔPTP/VT. Right panel: Tidal airway and lung P/V curves are plotted in the same diagram, showing that the lung P/V curve coincides with the end-expiratory airway P/V curve, which confirms that lung elastance can be determined as ΔPEEP/ΔEELV (lung compliance, CL = ΔEELV/ΔPEEP).

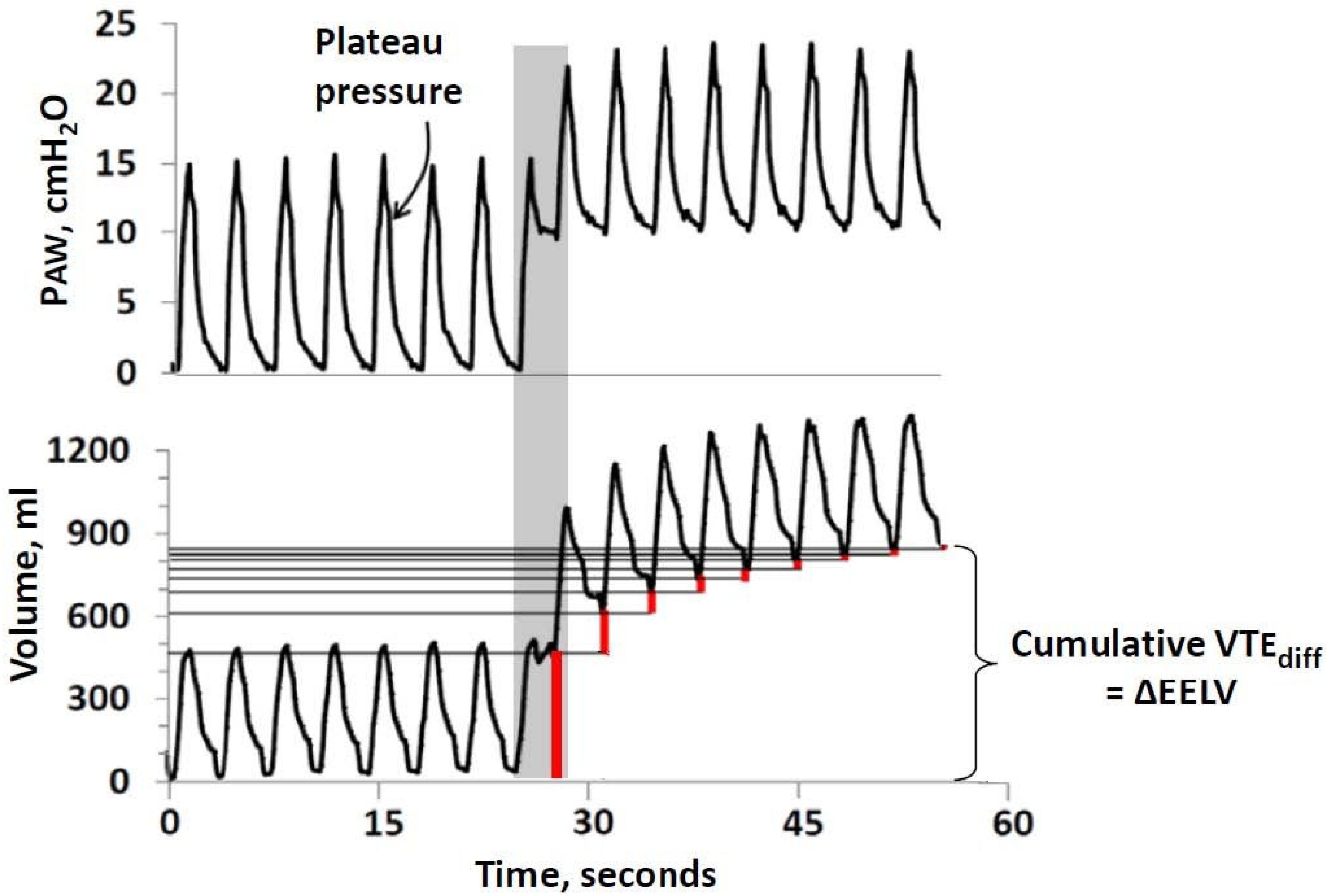

Figure 2

Recording from an ARDS patient [33]. Upper panel: airway pressure. Lower panel: volume by electric impedance tomography (EIT). The registration is done during volume control ventilation with a tidal volume of 500 ml with an airway driving pressure (ΔPAW) of 10 cmH2O at baseline PEEP followed by an equal PEEP increase of 10 cmH2O. The red bars indicate the breath-by-breath difference in expiratory tidal volume (VTE) from baseline VTE, until VTE is again equal to baseline. Note that an airway driving pressure of 10 cmH2O is needed to inflate a tidal volume of 500 ml, while an increase in PEEP of 10 cmH2O causes an increase in EELV of 900 ml. Respiratory system compliance (VT/ΔPAW) is 500/10 = 50 ml/cmH2O. The end-expiratory respiratory system compliance, which is equal to lung compliance (ΔEELV/ΔPAWEE = ΔEELV/ΔPTPEE) is 900/10 = 90 ml/cmH2O (see further below).

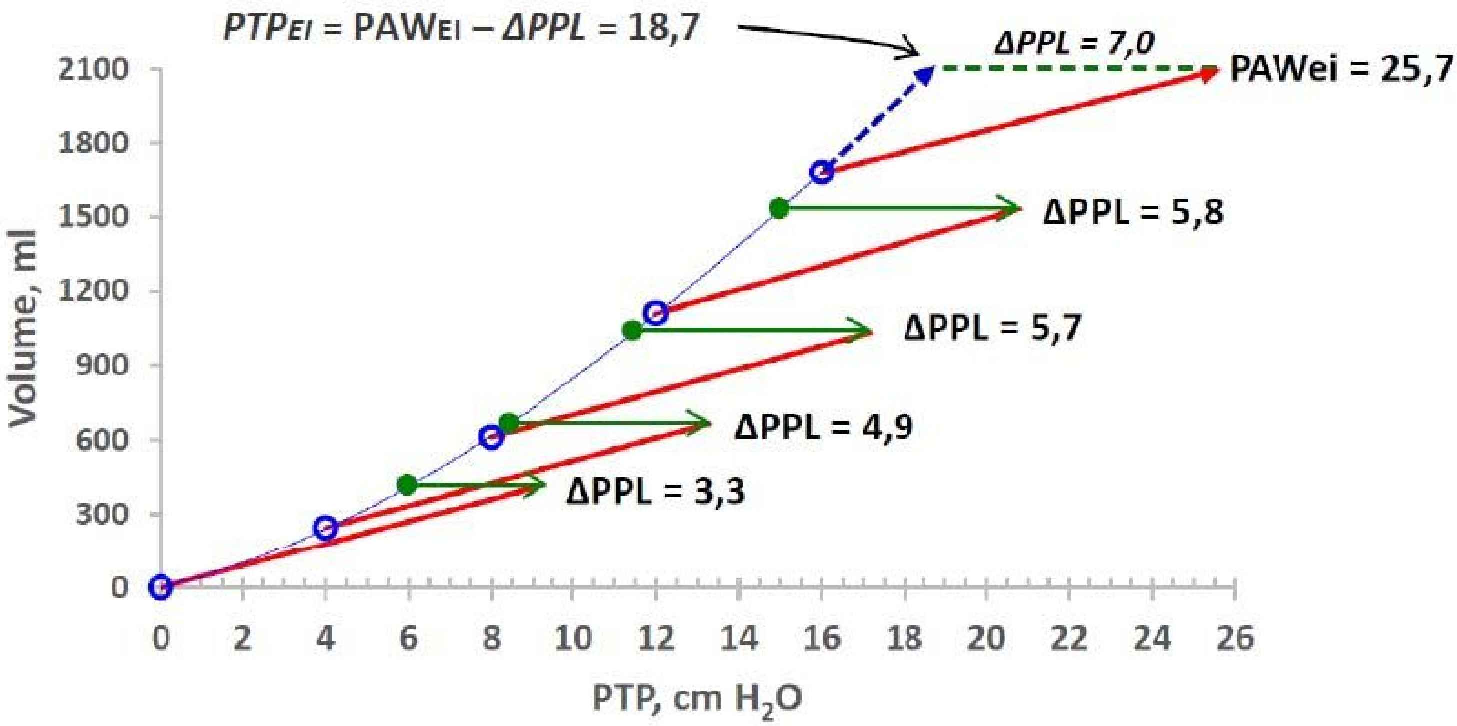

Figure 3

As the end-expiratory transpulmonary pressure increases as much as PEEP is increased and the increase in end-expiratory lung volume following a PEEP increase is equal to ΔPEEP/EL, a lung P/V curve can be obtained by plotting the end-expiratory airway pressure vs cumulative end-expiratory lung volume. Red arrows: tidal airway P/V curves, Blue line: lung P/V curve. Note that the end-expiratory and inspiratory lung P/V curves and end-expiratory airway (respiratory system) P/V curve coincide. The green arrows mark the tidal pleural pressure variation, ΔPPL. The end-inspiratory transpulmonary pressure at the highest PEEP level is estimated by extrapolation of ΔPPL at PEEP 16 cmH2O from the ΔPPL at the four lower PEEP levels and estimate the end-inspiratory transpulmonary pressure at PEEP 16 cmH2O as end-inspiratory airway pressure minus extrapolated ΔPPLPEEP16. The dashed blue line indicates the estimated tidal lung P/V curve at the highest PEEP level.

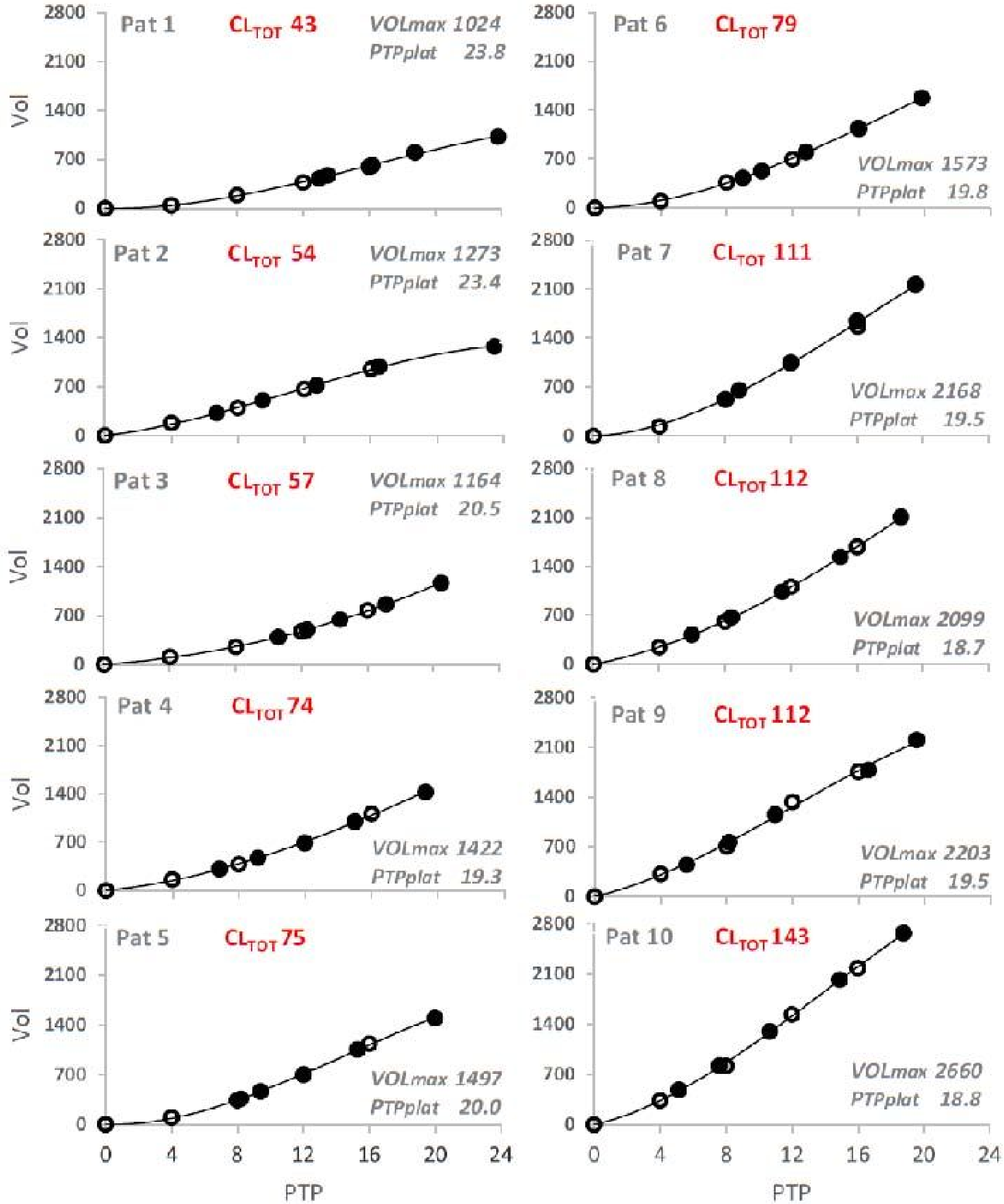

Figure 4

Lung P/V measured data points and best fit curves (according to a third degree equation) in ten patients with lung compliance ranging from 43 to 143 ml/cmH2O. The correlation coefficient (r2) of the end-expiratory and end-inspiratory transpulmonary P/V points to the best-fit curve is above 0.99. 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.

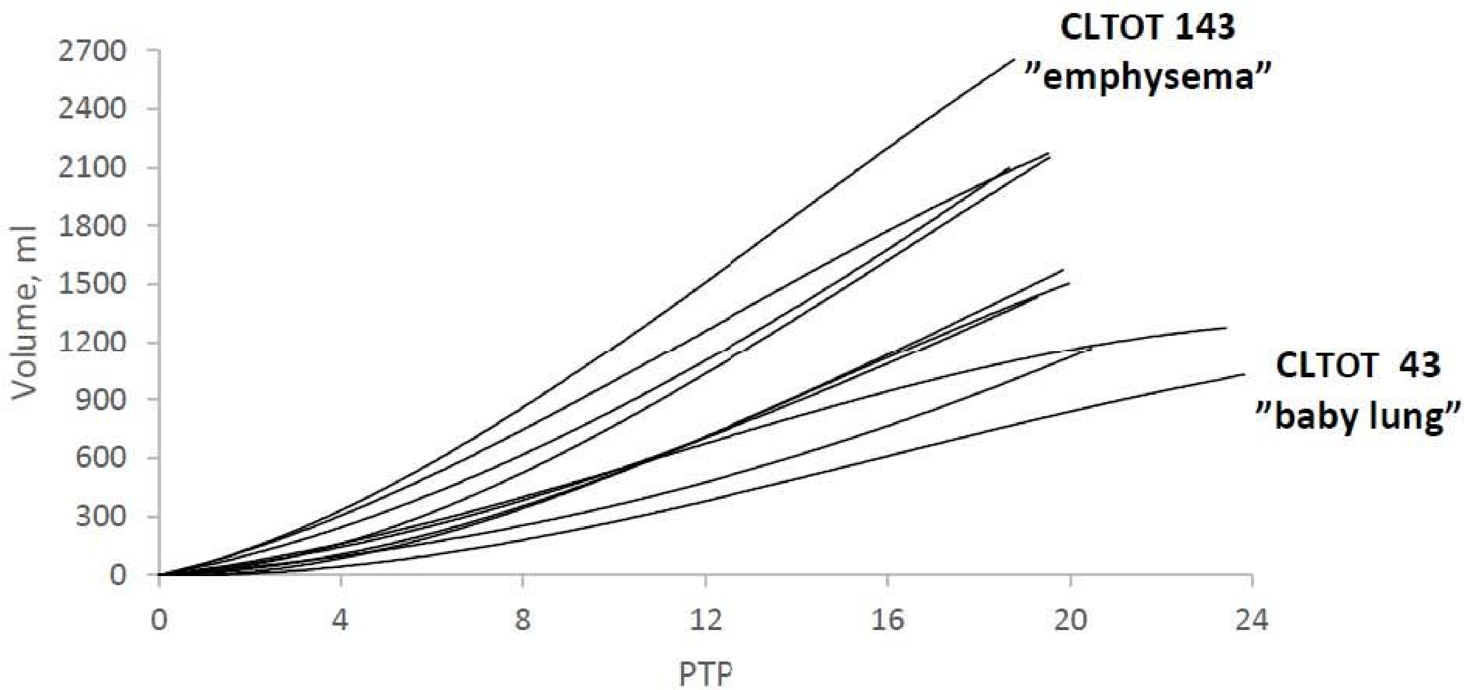

Figure 5

Lung P/V curves from end-expiration at ZEEP to end-inspiration at PEEP 16 cmH2O showing the diverse lung mechanics of patients with acute respiratory failure.

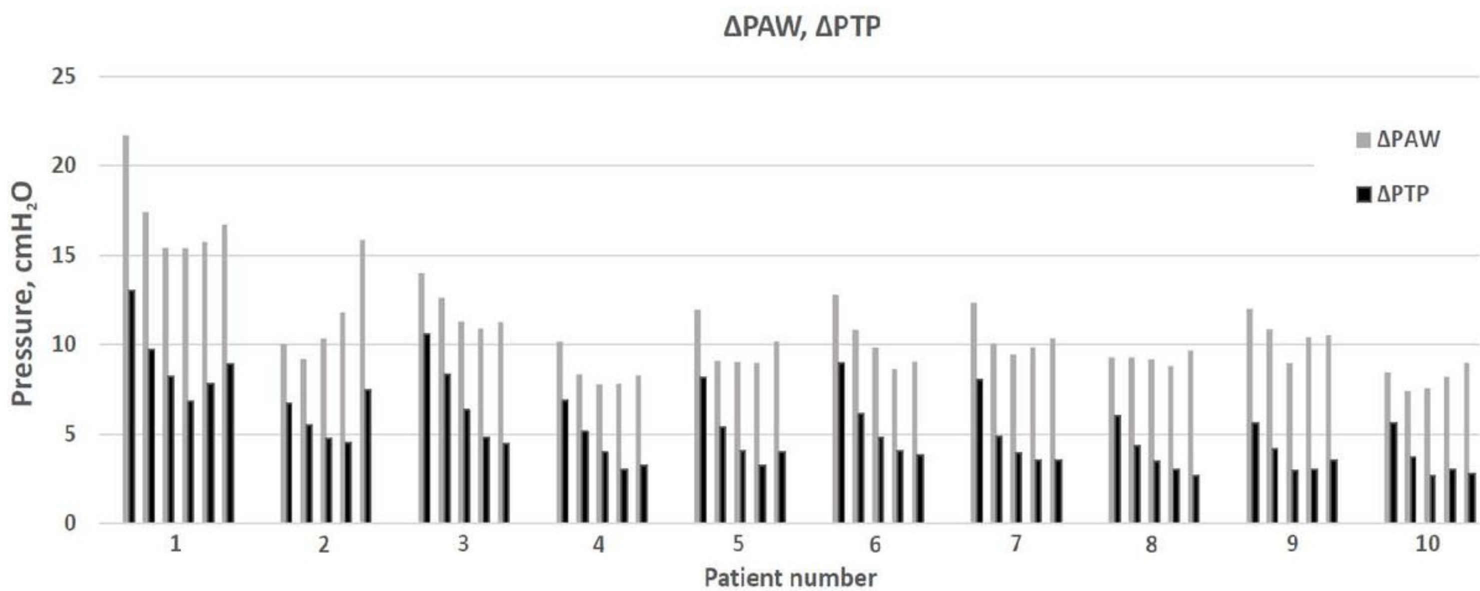

Figure 6

Airway and transpulmonary driving pressure during PEEP steps 0-4-8-12-16 cmH2O (also 20 cmH2O in patient 1). Note that the relation between ΔPTP and ΔPAW changes with changing PEEP and in the individual patient, airway driving pressure does not track transpulmonary pressure during PEEP titration

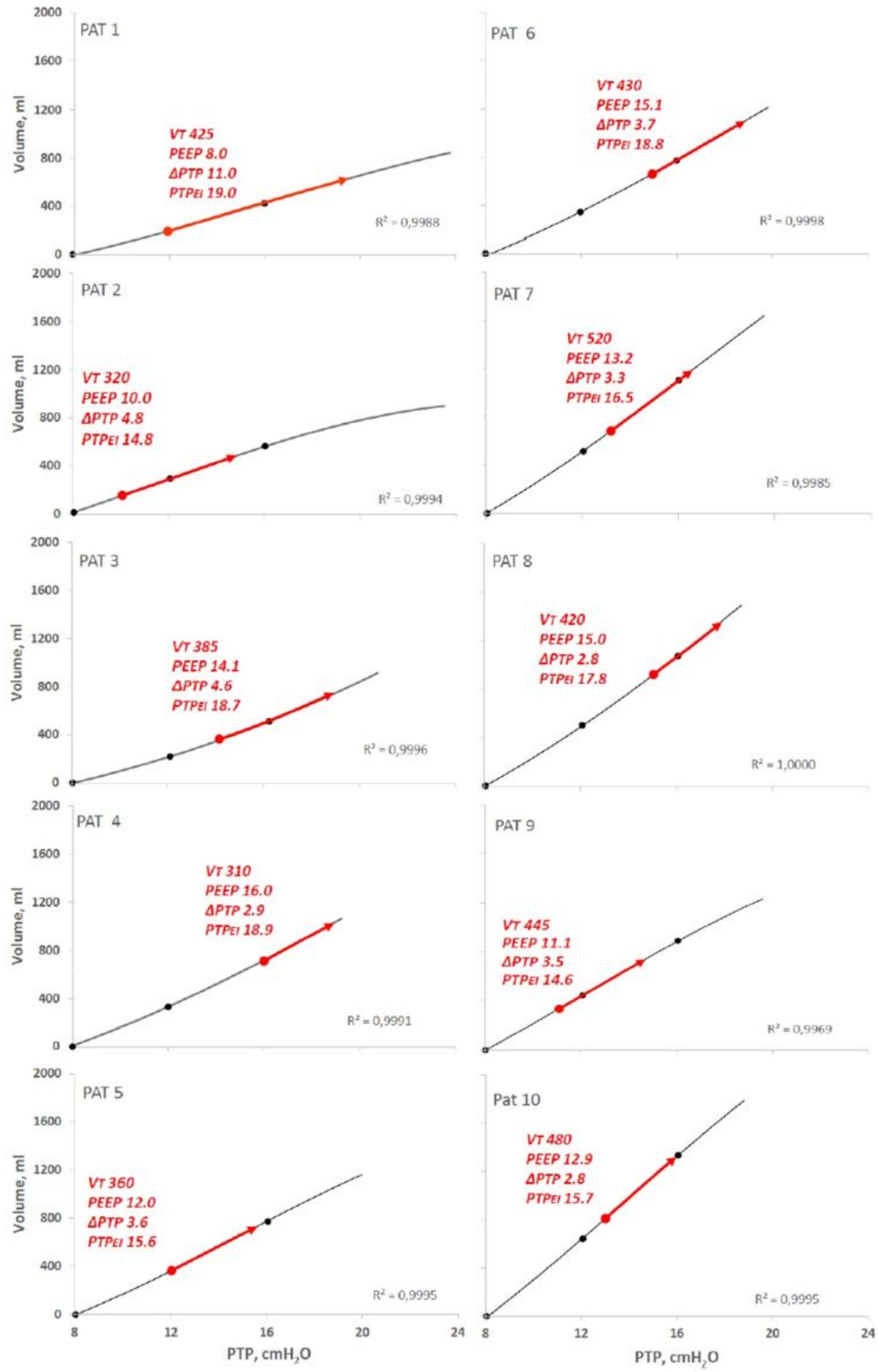

Figure 7

Lung P/V curves by a two PEEP step up-down procedure (black line). The black filled circles indicate that PEEP levels of 8, 12 and 16 cmH2O were used together with the estimated end-inspiratory transpulmonary P/V point at the highest PEEP level for determining the best-fit lung P/V curve. The end-inspiratory transpulmonary pressure is, except for patient 1 and 2, who are PEEP non-responders, 18-20 cmH2O. As the corresponding lung volume also is determined by the PEEP-step measurement procedure, it is possible to calculate the over-all lung compliance, which normally should be around 100 ml/cmH2O and where a low compliance indicates a low inspiratory capacity and possibly the existence of a baby lung, which is highly likely in patient 1 and 2. The red arrow shows the tidal lung P/V curve with the lowest transpulmonary driving pressure for the tidal volume used clinically in the patients (6-7 ml/kg ideal body weight).

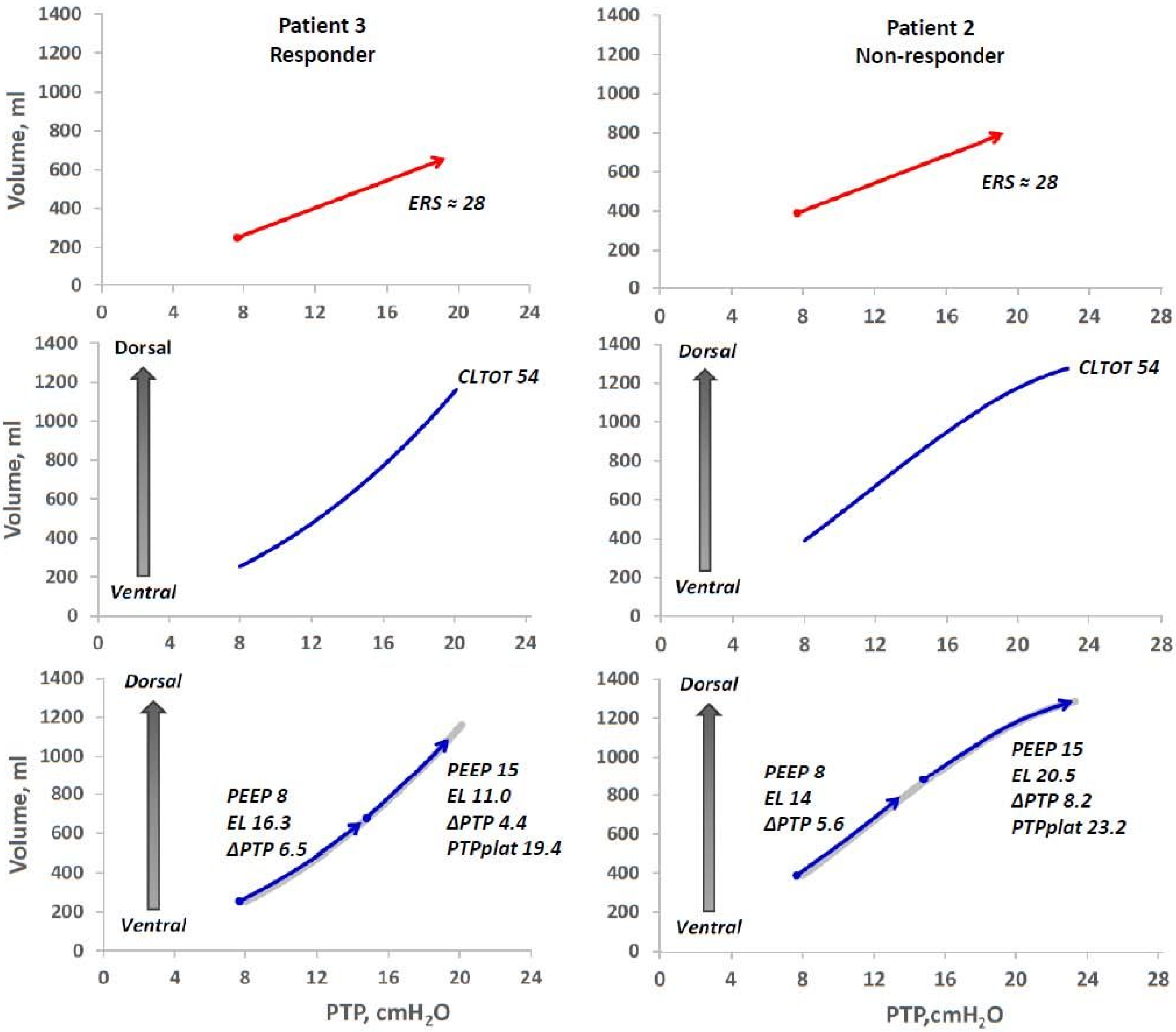

Figure 8

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. Note, that inflation by PEEP occurs from ventral to dorsal region (grey-black, thick arrow), which causes tidal ventilation to be moved in dependent direction when PEEP is increased.

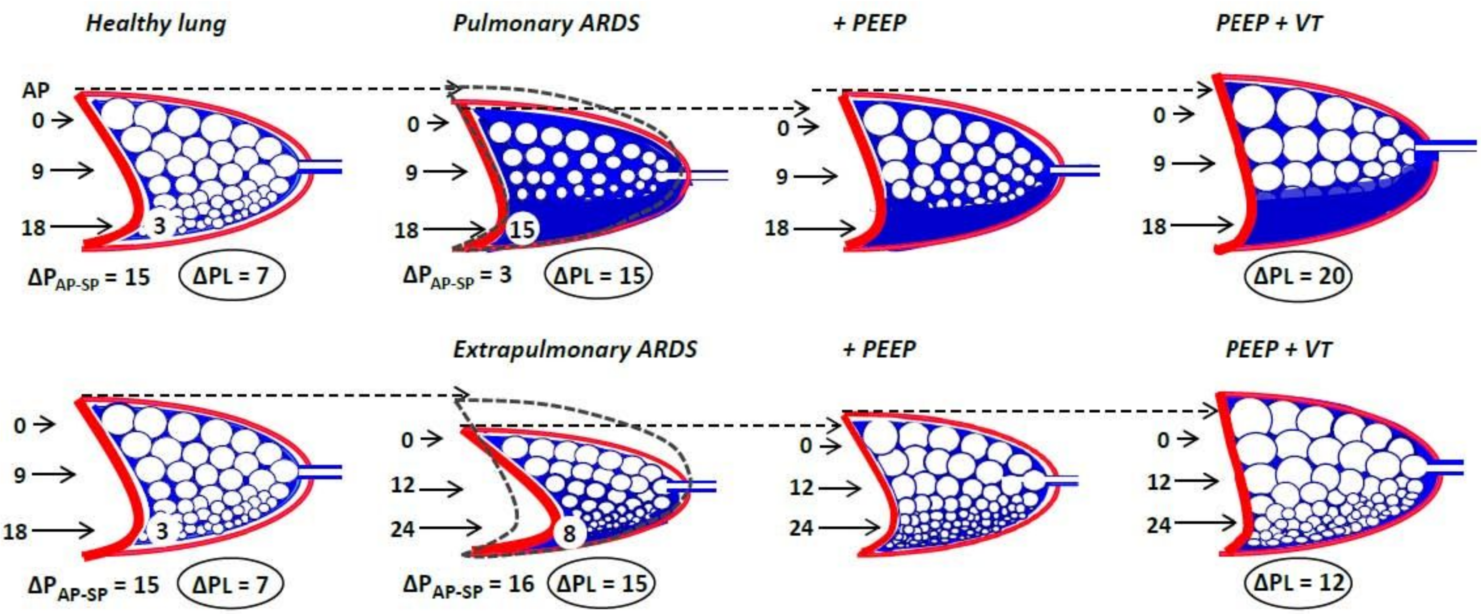

Figure 9

Schematic graph showing the development from healthy lung (left upper and lower panels) to pulmonary ARDS, PEEP non-responder (upper panels) and extra-pulmonary ARDS, PEEP responder (lower panels). In pulmonary ARDS, the gradient between abdominal pressure (AP) and superimposed pressure (SP) is small. Exterior lung volume and diaphragm position are almost normal. PEEP causes inflation of the non-dependent baby lung, but not of consolidated dependent lung. In extra-pulmonary ARDS, the increased edema of the abdomen pushes the diaphragm in cranial direction and decreases FRC. Dependent lung is compressed and poorly aerated. When PEEP is applied, already open lung will be further inflated and the diaphragm pushed in caudal direction, increasing space for the lung to expand.

Supplementary Files

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

- GrivansStenqvistProtectivePEEPforCCESUPPL26042021.pdf