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Driving pressure of respiratory system and lung stress in mechanically ventilated patients with active breathing

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Abstract

Background During control mechanical ventilation (CMV), the driving pressure of the respiratory system (ΔP_{rs}) serves as a surrogate of transpulmonary driving pressure (ΔP_{lung}). Expiratory muscle activity that decreases end-expiratory lung volume may impair the validity of ΔP_{rs} to reflect ΔP_{lung}. This prospective observational study in patients with acute respiratory distress syndrome (ARDS) ventilated with proportional assist ventilation (PAV+), aimed to investigate: (1) the prevalence of elevated ΔP_{lung}, (2) the ΔP_{rs}-ΔP_{lung} relationship, and (3) whether dynamic transpulmonary pressure ($Plung_{sw}$) and effort indices (transdiaphragmatic and respiratory muscle pressure swings) remain within safe limits.

Methods Thirty-one patients instrumented with esophageal and gastric catheters ($n = 22$) were switched from CMV to PAV+ and respiratory variables were recorded, over a maximum of 24 h. To decrease the contribution of random breaths with irregular characteristics, a 7-breath moving average technique was applied. In each patient, measurements were also analyzed per deciles of increasing lung elastance (E_{lung}). Patients were divided into Group A, if end-inspiratory transpulmonary pressure (P_{LEI}) increased as E_{lung} increased, and Group B, which showed a decrease or no change in P_{LEI} with E_{lung} increase.

Results In 44,836 occluded breaths, $\Delta P_{lung} \geq 12$ cmH_2O was infrequently observed [0.0% (0.0–16.9%) of measurements]. End-expiratory lung volume decrease, due to active expiration, was associated with underestimation of ΔP_{lung} by ΔP_{rs}, as suggested by a negative linear relationship between transpulmonary pressure at end-expiration (P_{LEE}) and $\Delta P_{lung}/\Delta P_{rs}$. Group A included 17 and Group B 14 patients. As E_{lung} increased, ΔP_{lung} increased mainly due to P_{LEI} increase in Group A, and P_{LEE} decrease in Group B. Although ΔP_{rs} had an area receiver operating characteristic curve (AUC) of 0.87 (95% confidence intervals 0.82–0.92, $P < 0.001$) for $\Delta P_{lung} \geq 12$ cmH_2O, this was due exclusively to Group A [0.91 (0.86–0.95), $P < 0.001$]. In Group B, ΔP_{rs} showed no predictive capacity for detecting $\Delta P_{lung} \geq 12$ cmH_2O [0.65 (0.52–0.78), $P > 0.05$]. Most of the time $Plung_{sw}$ and effort indices remained within safe range.

Conclusion In patients with ARDS ventilated with PAV+, injurious tidal lung stress and effort were infrequent. In the presence of expiratory muscle activity, ΔP_{rs} underestimated ΔP_{lung}. This phenomenon limits the usefulness of ΔP_{rs} as a surrogate of tidal lung stress, regardless of the mode of support.

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Introduction

Transpulmonary driving pressure (ΔP_{lung}) represents a direct measurement of static tidal lung stress and is proportional to lung strain, key mediators of ventilator-induced lung injury [1–4]. Despite its importance during mechanical ventilation, its clinical use remains limited due to the need for esophageal catheter insertion [5]. For this reason, during passive mechanical ventilation, the driving pressure of the respiratory system (ΔP_{rs}), which is calculated as the difference between end-inspiratory plateau pressure (P_{plat}) and total positive end-expiratory pressure (PEEP), is used as a surrogate for ΔP_{lung}. Indeed, ΔP_{rs} can reliably predict increased ΔP_{lung}, with high ΔP_{rs} ($\geq$15 cmH_2O) being associated with elevated morbidity and mortality [2, 6–8].

In mechanically ventilated patients with active breathing, measurement of ΔP_{rs} is challenging for two reasons. Firstly, P_{plat} calculation requires end-inspiratory occlusions during which respiratory muscle activity should be absent, which is often not the case during conventional assisted ventilation [9]. Proportional assist ventilation with load adjustable gain factors (PAV+), automatically performs end-inspiratory occlusions to measure P_{plat}. The interference of respiratory muscle activity with P_{plat} calculation is largely minimized with this mode, because the end of mechanical inflation follows the end of neural inspiration [10]. Secondly, expiratory muscle activity is often observed in critically ill patients, potentially lowering end-expiratory lung volume below the level corresponding to PEEP [11–13]. As a result, the relaxation of expiratory muscles contributes to tidal volume (V_T) [14–16]. This is a reflex protective mechanism, which at increased demands, increases V_T at the same end-inspiratory lung stress [14, 16]. Under these conditions ΔP_{rs}, which assumes that the starting point of inflation is PEEP, does not account for the decrease in end-expiratory lung volume below the level corresponding to PEEP, leading to an underestimation of ΔP_{lung} (Fig. 1 and Additional file 1: Fig. S1). Unfortunately, this later issue is largely ignored in the literature.

Studies have shown that, in critically ill patients ventilated with PAV+, which via the control of breathing mechanisms permits the patients to determine V_T [10], ΔP_{rs} can be effectively maintained low [15, 17]. However, these studies did not measure ΔP_{lung}. It is unknown whether ΔP_{rs} reliably predicts tidal static lung stress in patients with active expiration that lowers end-expiratory lung volume below that corresponding to PEEP. The primary aim of this study was to determine the occurrence of injurious tidal lung stress, as expressed by a high ΔP_{lung} ($\geq$12 cmH_2O) [18] in patients with acute respiratory distress syndrome (ARDS) ventilated with PAV+, and to elucidate the relationship between ΔP_{rs} and ΔP_{lung}. We hypothesize that in a given patient, the decrease in end-expiratory lung volume, secondary to expiratory muscle contraction because of increased demands, can lead to underestimation of ΔP_{lung} by ΔP_{rs} to an unknown extent. A secondary objective was to explore if dynamic transpulmonary pressure swings ($Plung_{sw}$) and indices of respiratory effort, reflected by transdiaphragmatic (ΔPdi) and respiratory muscles pressure ($Pmus_{sw}$) swings, remain within a safe range. It was deemed safe to have values for $Plung_{sw}$, ΔPdi, and $Pmus_{sw}$ of less than 20, 3–12, and 3–15 cmH_2O, respectively [19–22].

(See figure on next page.)

Fig. 1 Effect of decreasing end-expiratory lung volume below ($V_{EE<FRC}$) that corresponding to PEEP ($V_{EE,PEEP}$) on calculation of driving pressure of respiratory system (ΔP_{rs}) and lung (ΔP_{lung}). Lung (E_{lung}) and chest wall (E_{cw}) elastance were kept constant at all lung volumes. Blue and white circles denote lung and chest wall, respectively. Set values are shown using italics. The numbers between the circles represent pleural pressure (P_{pl}). Arrows show the magnitude of PEEP, end-inspiratory plateau pressure (P_{plat}), elastic recoil pressure of chest wall (P_{cw}) and lung (P_{lung}), and expiratory muscle pressure ($Pmus_{exp}$). Panel **A** shows applied pressures (cmH_2O) when expiration is passive. Tidal volume (V_T) is set to 500ml, P_{pl} at end-expiration to 4 cmH_2O and P_{plat} to 22 cmH_2O. $\Delta P_{rs} = P_{plat}$-PEEP = 12 cmH_2O and respiratory system elastance (E_{rs}) = $\Delta P_{rs}/V_T$ = 12/0.5 = 24 cmH_2O/l. E_{cw} is set to 20% of E_{rs} (4.8 cmH_2O/l). At end-expiration, alveolar pressure (P_{alv}) = PEEP, $P_{cw} = P_{pl} = 4$ cmH_2O and $P_{lung} = P_{alv}$-P_{pl} = 6 cmH_2O. Notice that $P_{alv} = P_{lung} + P_{cw}$. At end-inspiration P_{pl} increases to 6.4 cmH_2O ($4 + E_{cw} \times V_T = 4 + 2.4 = 6.4$), P_{cw} = 6.4 cmH_2O and $P_{lung} = P_{alv}$-P_{pl} = 22–6.4 = 15.6 cmH_2O. ΔP_{lung} = 15.6–6 = 9.6 cmH_2O and $E_{lung} = \Delta P_{lung}/V_T$ = 9.6/0.5 = 19.2 cmH_2O/l. Panel **B** shows pressures when expiration is active. Because of expiratory muscle activity, $V_{EE<FRC}$ is set to 260 ml and therefore, compared to passive expiration, P_{cw} decreases by 1.2 cmH_2O ($E_{cw} \times 0.26$). At end-expiration, $Pmus_{exp}$ is set to 6.2 cmH_2O and P_{pl} is 9 cmH_2O ($P_{pl} = P_{cw} + Pmus_{exp}$). $P_{lung} = P_{alv}$-P_{pl} = 10–9 = 1 cmH_2O. Transdiaphragmatic pressure (Pdi) is deemed similar to A and begins to rise when flow is expiratory, before the full relaxation of expiratory muscles. Assuming that Pdi increases volume above $V_{EE,PEEP}$ by 300ml (only a portion of Pdi increases volume above $V_{EE,PEEP}$), V_T is 560 ml. At end-inspiration, P_{plat} = PEEP plus the increase in elastic recoil pressure of respiratory system due to 300 ml increase in volume above $V_{EE,PEEP}$ (P_{plat} = PEEP + 0.3 × 24 = 17.2 cmH_2O). $\Delta P_{rs} = P_{plat}$-PEEP = 7.2 cmH_2O and calculated E_{rs} = 7.2/0.56 = 12.9 cmH_2O/l, underestimated by 46%, because ΔP_{rs} should be divided by 0.3 (the volume inflated above PEEP). P_{cw} is 5.44 cmH_2O, 1.44 cmH_2O higher than that at $V_{EE,PEEP}$ (0.3 × 4.8 = 1.44). $P_{lung} = P_{alv}$-P_{pl} = 17.2–5.44 = 11.76 cmH_2O, ΔP_{lung} = 11.76–1 = 10.76 cmH_2O and $E_{lung} = \Delta P_{lung}/V_T$ = 19.2 cmH_2O/l, similar to that in A. See Fig. S1 in the Additional file 1 for detailed further explanation

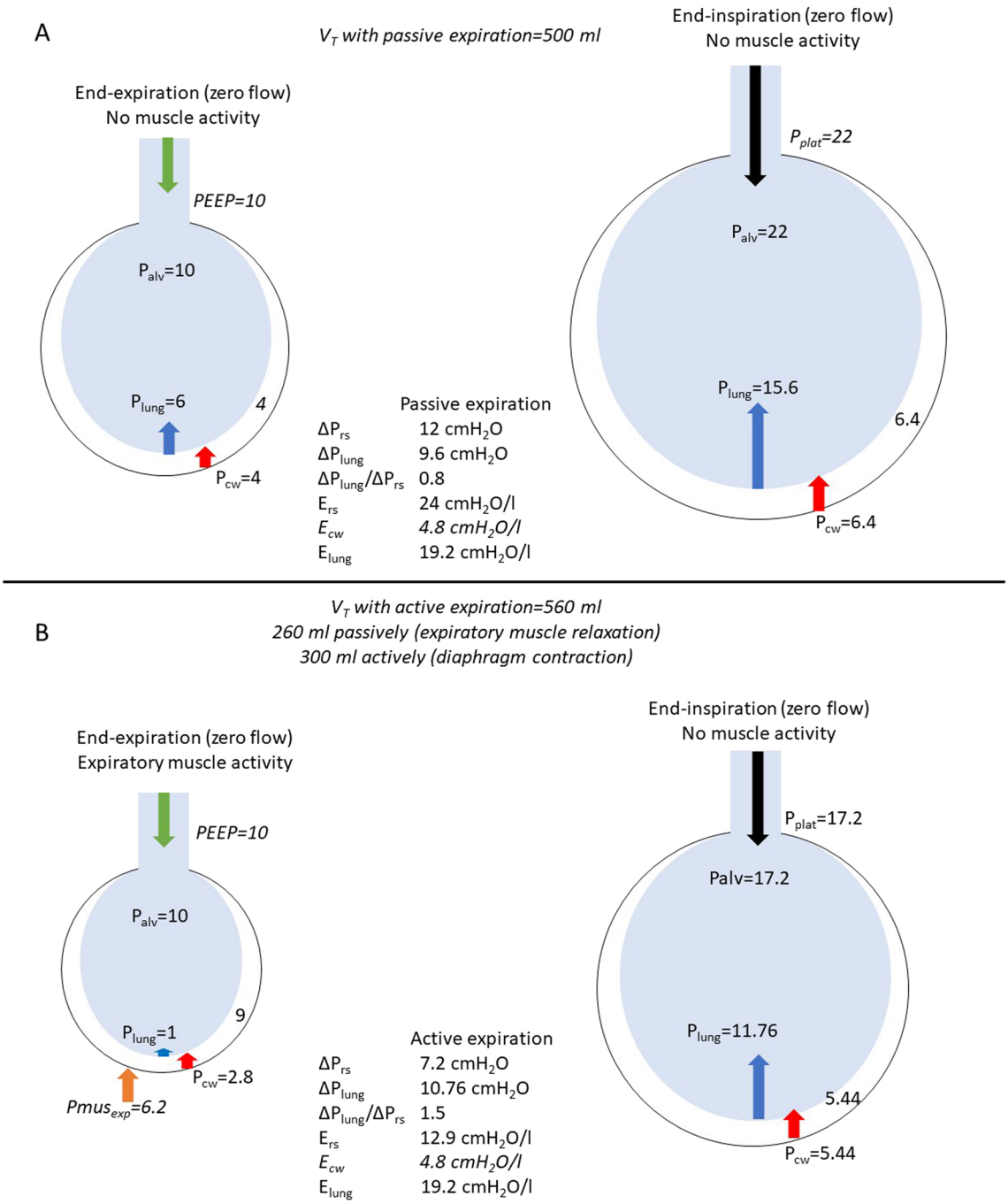

Fig. 1 (See legend on previous page.)

Methods

This prospective observational study was conducted in the medical–surgical intensive care unit (ICU) of the University Hospital of Heraklion. The study was approved by the Hospital Ethics Committee (339/09/20-03-2019), and since there was no interference with patients' management, signed informed consent was waived.

Patients

Eligible for inclusion were intubated patients, admitted to the ICU for management of ARDS, and instrumented with esophageal and gastric catheters (NutriVent™) or only an esophageal catheter (Cooper-Surgical esophageal balloon kit) for clinical purposes. The patients were included at any time the treating physician switched them from control modes to PAV+ (Puritan-Bennett 840

ventilator, Medtronic, Boulder, CO) and estimated that they would remain on assisted mechanical ventilation for at least 24 h. The recording period was approximately 24 h, unless the patient was switched to other modes, placed on a T-piece earlier, or the recording was interrupted for procedural reasons. Patients who remained on PAV+ for less than 1 h were excluded from the analysis.

Measurements: analysis

Airflow (V′), volume and airway (Paw), esophageal (Pes), gastric (Pgas), dynamic transpulmonary (P_{lung} = Paw-Pes), and transdiaphragmatic (Pdi = Pgas-Pes) pressures were monitored continuously. Using a customized computer program, all breaths with 300-ms end-inspiratory occlusions were identified and the beginning (zero flow) and end of inspiration (end of 300-ms occlusion) were marked. At these two points, Paw and Pes were measured and various respiratory variables, including static transpulmonary pressures and $Pmus_{sw}$, were calculated using standard formulas [18, 23, 24]. $Plung_{sw}$ and $Pmus_{sw}$ during the breath were measured as the difference between the peak and nadir values. Expiratory muscle activity was estimated in the preceding breath by measuring the rise in Pgas (ΔPgas) during the expiratory phase [25, 26]. Each recording underwent a thorough examination to identify artifacts mainly due to esophageal peristalsis and issues related to improper balloon filling and position.

Significant expiratory muscle activity during expiration was determined by either an average ΔPgas > 1 cmH_2O over the recording time or, in patients without gastric catheters, by a thorough examination of expiratory flow and Pes waveforms, which unequivocally demonstrated signs of active expiration [27]. Dynamic intrinsic PEEP (PEEPi) was calculated only in patients in whom both Pes and Pgas were available, as described previously [28].

In order to decrease the contribution of random breaths with irregular characteristics on the measured values, a seven-breath moving average (7-brMA) technique was performed and the results of this analysis are reported. Furthermore, in each patient all the artifact-free 7-brMA measurements were divided into deciles based on progressive increase in lung elastance (E_{lung}) (Decile 1: the lowest range of E_{lung}, Decile 10; the highest range of E_{lung}, see Additional file 2 for reasoning of choosing E_{lung} to characterize deciles of 7-brMA measurements). Patients were divided into two groups (A and B), depending on how their end-inspiratory transpulmonary pressure (P_{LEI}) responded to an increase in E_{lung}, with the assumption that expiratory muscle contraction could, as a reflex protective mechanism, prevent increases in P_{LEI}. Group A was characterized by an increase in end-inspiratory lung stress, as measured by the P_{LEI}, with increasing E_{lung}, whereas patients in Group B showed a decrease or no change in P_{LEI}.

Statistical analysis

Values are presented as median (interquartile range) or counts (percentage) unless otherwise stated. Normal distribution was checked by the Shapiro–Wilk test and comparisons within and between patients were performed by nonparametric or parametric tests, as appropriate. The diagnostic accuracy of ΔP_{rs} in detecting $\Delta P_{lung} \geq 12$ cmH_2O was evaluated using the receiver operating characteristic (ROC) method [29, 30]. The effect of E_{lung} deciles on end-expiratory transpulmonary pressure (P_{LEE}) and ΔPgas was analyzed using a linear mixed-effect model. A similar analysis was performed to examine the effect of ΔPgas on P_{LEE}, as well as that of P_{LEE} on $\Delta P_{lung}/\Delta P_{rs}$. Regression analysis with curve estimation was performed on average values per decile between E_{lung} and P_{LEE}, E_{lung} and ΔPgas, P_{LEE} and $\Delta P_{lung}/\Delta P_{rs}$, and ΔPgas and P_{LEE} and the coefficient of determination (r^2) was calculated. Patients were classified into Group A if, within each patient, there was a significant linear increase in P_{LEI} with increasing E_{lung}. Binary logistic analysis was performed to examine if patients' characteristics and outcomes can predict the pattern of response to changes in E_{lung}. $P < 0.05$ was the statistically significant threshold. Statistical analysis was performed by using SPSS 26 software.

Results

We obtained demographic, clinical, and ventilation data from 31 patients (22 instrumented with both esophageal and gastric balloons) during a 30-month period (Table 1). Data collected during 468 h of ventilation with PAV+ were examined and a total of 44,836 artifact-free occluded breaths were analyzed.

The results of 7-brMA analysis and analysis of all occluded breaths were similar, except at high values of ΔP_{lung} where 7-brMA analysis eliminated the sporadic high values (Additional file 2: Figs. S2, S3). Details of recorded parameters on the day of the study and the variation of ΔP_{lung} and other respiratory variables during the recording period are shown in Additional file 2: Tables S1 and S2.

Primary outcomes

Occurrence of injurious lung stress

The median number of 7-brMA measurements and the percentage of these measurements where ΔP_{lung} aligns within the range of each cmH_2O, from ≤ 5 cmH_2O to the maximum value is illustrated in Fig. 2. ΔP_{lung} values ≥ 12 cmH_2O were observed in 15 out of 31 patients (Additional file 3: Individual data). One patient had constantly

Table 1 Patients' characteristics

Age (years)	68 (63–73)
Sex (M/F)	14/17
PBW, kg	61.4 (52.4–69.6)
BMI, kg/m^2	31.6 (27.5–35.6)
COVID-19 status (Yes/No)	13/18
APACHE-II*	17.0 (14.0–19.5)
SOFA score*	8.0 (6.0–9.0)
PaO_2/FIO_2*	180 (153–210)
PaO_2, mmHg*	85.0 (77.5–94.5)
$PaCO_2$, mmHg*	38.0 (36.0–44.5)
pH	7.35 (7.29–7.40)
PEEP, cmH_2O*	12 (9–15)
V_T, ml/kg*	6.5 (5.9–7.3)
E_{rs}, cmH_2O/l*	25.0 (20.0–30.8)
E_{lung}, cmH_2O/l‡	20.1 (12.9–24.1)
E_{cw}, cmH_2O/l‡	7.8 (5.0–9.6)
ΔP_{rs}, cmH_2O*	10.0 (8.5–12.0)
ΔP_{lung}, cmH_2O‡	7.5 (4.5–10.0)
$\Delta P_{lung}/\Delta P_{rs}$ ‡	0.74 (0.62–0.79)
Days on MV at inclusion	7.0 (4.5–9.5)
Days on MV after inclusion	6.0 (3.5–14.5)
Total days on MV	14.0 (8.5–24.5)
ICU LOS (days)	20.0 (13.5–29.0)
ICU mortality, %	19.4

Values are median (1st to 3rd quartiles) or counts (percentage). PBW; Predicted body. BMI; Body mass index. APACHE-II; Acute Physiology and Chronic Health Evaluation II. SOFA; Sequential organ failure assessment. PaO_2, $PaCO_2$; Partial pressure of arterial O_2 and CO_2, respectively. PEEP; Positive end-expiratory pressure. V_T; Tidal volume. E_{rs}, E_{lung}, E_{cw}; Elastance of respiratory system, lung and chest wall, respectively. ΔP_{rs}; driving pressure of respiratory system. ΔP_{lung}; driving transpulmonary pressure. MV; Mechanical ventilation. ICU; Intensive care unit. LOS; Length of stay

*Data on Day 1 of control mechanical ventilation (passive, $n=31$)

‡ Data during control mechanical ventilation (passive) before switching to BiPAP or PAV+ ($n=15$)

$\Delta P_{lung} \geq 12$ cmH_2O, while in the remaining 14 patients, ΔP_{lung} above and below this threshold were noted. The median (IQR) percentage of measurements with $\Delta P_{rs} < 15$ cmH_2O and $\Delta P_{lung} < 12$ cmH_2O is presented in Table 2.

The number and percentage of 7-brMA measurements where ΔP_{rs} aligns within the range of each cmH_2O, from ≤ 5 cmH_2O to the maximum value is illustrated in Additional file 2: Figure S4.

Relationship between ΔP_{rs} and ΔP_{lung}

Twenty-one patients exhibited significant expiratory muscle activity (16 had average $\Delta Pgas > 1$ cmH_2O and 5 exhibited signs of active expiration in V′ and Pes waveforms). In several of them, expiratory muscle relaxation contributed to a portion of the V_T measured (Fig. 3). This led to an underestimation of ΔP_{lung} by ΔP_{rs}. Most patients (24/31, 77.4%) had readings of ΔP_{lung} that exceeded ΔP_{rs} due to this underestimation. The median number of such measurements was 332 (13–490), accounting for 31.7% (2.2–94.5%) of the total measurements. In two patients, ΔP_{lung} always exceeded ΔP_{rs}.

A total of 310 deciles with progressive increases in E_{lung} were analyzed (10 deciles per patient). When E_{lung} increased, ΔP_{lung} increased in all patients (Additional file 2: Table S3). There was a highly significant relationship of quadratic function ($y = a + b1x + b2x^2$) between per decile average values of E_{lung} and P_{LEE} and a negative linear relationship of P_{LEE} and $\Delta P_{lung}/\Delta P_{rs}$ (Fig. 4). The decrease in P_{LEE} with increasing E_{lung} was due to expiratory muscle contraction, as reflected by a quadratic function relationship between E_{lung} and ΔP_{gas} (Additional File 2: Fig. S5).

Response to increasing Elung by patient Group

Seventeen out of thirty-one patients were included in Group A and the remaining 14 were in Group B. Although with increasing E_{lung}, ΔP_{lung} increased similarly between groups, in Group A this increase was mainly due to a P_{LEI} increase, while in Group B to a P_{LEE} decrease. With increasing E_{lung}, contrary to Group A, Group B was characterized by constant ΔP_{rs} and P_{plat}, a significant decrease in P_{LEE}, and an increase in ΔP_{gas} (Fig. 5). The response of other variables is shown in Additional file 2: Table S4. Similar results were observed when only patients with gastric pressure measurements ($n=22$) were analyzed (Additional file 2: Fig. S6). The linear mixed-effects model analysis, with P_{LEE} as the dependent variable, E_{lung} deciles and group category as fixed effects, and each subject as a random effect, demonstrated a significant effect ($P < 0.001$) of E_{lung} on P_{LEE}. There was no effect of group category on P_{LEE}. Similarly, a significant effect of ΔP_{gas} on P_{LEE} was also observed. When $\Delta P_{lung}/\Delta P_{rs}$ was used as the dependent variable, there was a significant effect ($P < 0.001$) of P_{LEE}, as a fixed variable, but there was no significant effect of group category. Binary logistic regression showed that none of the patients' characteristics, including age and body mass index, length of ICU stay, days on mechanical ventilation, and ICU outcome, predicted the Group classification.

Accuracy of ΔP_{rs} to predict injurious ΔP_{lung}

ROC curve analysis revealed that, although ΔP_{rs} had high accuracy for detecting $\Delta P_{lung} \geq 12$ cmH_2O in the overall population, this effect was due to patients of Group A. In Group B, ΔP_{rs} showed no predictive capacity for detecting injurious ΔP_{lung} (Fig. 6).

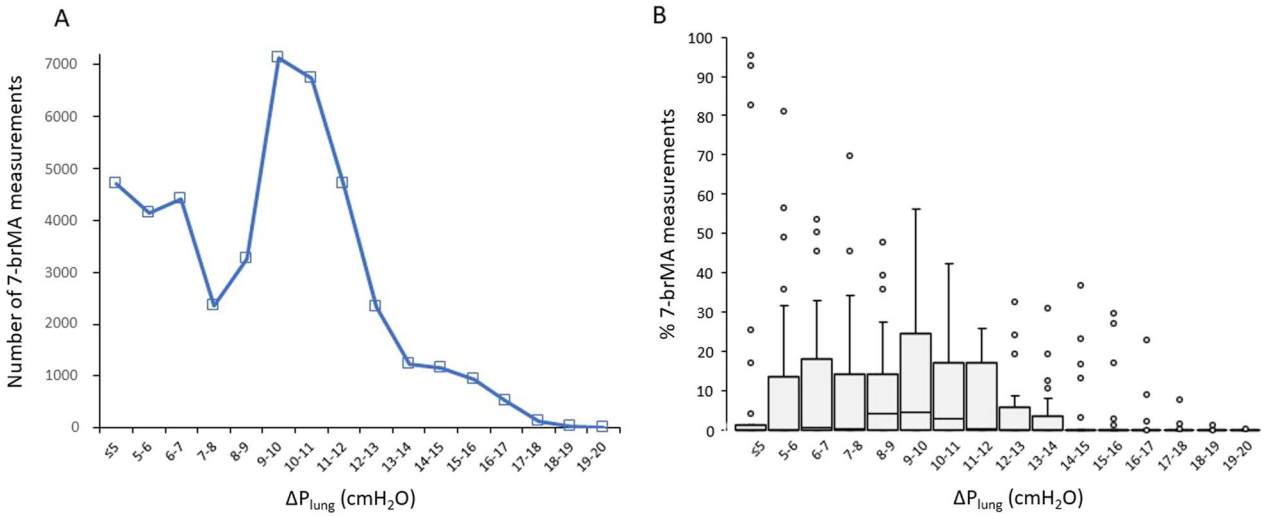

Fig. 2 Number of 7-breath moving average measurements (**A**) and % of total measurements (**B**) with ΔP_{lung} within the range of each cmH_2O from ≤ 5 cmH_2O to maximum values. Outliers are shown by circles

Table 2 Percentage of 7-brMA measurements with quasi-static and dynamic lung stress and respiratory effort indices within optimum range

Optimum range	(% of total 7-brMA measurements)
$\Delta P_{rs} < 15$ cmH_2O	100 (99.1–100)
$\Delta P_{lung} < 12$ cmH_2O	100 (88.0–100)
$Plung_{sw} < 15$ cmH_2O	85.0 (33.1–100)
$Plung_{sw} < 20$ cmH_2O	100 (97.1–100)
$3 \le \Delta Pdi < 12$ cmH_2O*	98.0 (83.3–100)
$3 \le Pmus_{sw} < 15$ cmH_2O‡	89.2 (49.3–100)

Values are median and interquartile range (IQR). ΔP_{rs}; driving pressure of respiratory system. ΔP_{lung}; driving transpulmonary pressure. ΔPdi; transdiaphragmatic pressure swings. $Plung_{sw}$; dynamic transpulmonary pressure swings. $Pmus_{sw}$; Respiratory muscles (inspiratory and expiratory) pressure swings

*In 3 patients ΔPdi < 3 cmH_2O was observed for 11.9%, 35.4%, and 21.2% of total measurements

‡ $Pmus_{sw} < 3$ cmH_2O was not observed

Secondary outcomes

Dynamic transpulmonary pressure swings and effort

The median (IQR) percentage of measurements with $Plung_{sw}$, inspiratory Pdi swings (ΔPdi), and $Pmus_{sw}$ falling within a range considered optimum [19, 21, 22, 31] is presented in Table 2.

$\Delta P_{lung} \ge 12$ cmH_2O was associated with higher values of effort indices, V_T, and $Plung_{sw}$ (Additional file 2: Table S5). As E_{lung} increased, $Plung_{sw}$ and efforts indices significantly increased, despite significant decreases in V_T (Additional file 2: Table S3).

Discussion

In this study, tidal lung stress was documented in ARDS patients during their early transmission from controlled mechanical ventilation to assisted breathing with PAV+. The main findings are as follows: (1) Half of the patients (51.6%) did not exhibit ΔP_{lung} exceeding 12 cmH_2O and in cases where it was observed, such instances were of limited duration. (2) Most of the time, $Plung_{sw}$ and inspiratory effort indices were within a range considered optimum. (3) A significant proportion of patients exhibited expiratory muscle recruitment and a reduction in end-expiratory lung volume, as evidenced by decreased P_{LEE}. (4) In these patients, the relaxation of expiratory muscles contributed to V_T and as a result, ΔP_{rs} underestimated ΔP_{lung}, making it non-suitable as an alternative for tidal static lung stress.

Certain methodological issues of the study should be discussed first. The calculation of ΔP_{rs} during PAV+ ventilation, relies on the measurement of P_{plat}, by random application of short end-inspiratory occlusions. Younes et al. have shown that since with PAV+ there is a link between the end of neural and mechanical inflation, this method provides a reliable estimate of passive elastic recoil pressure of the respiratory system at the corresponding V_T [10]. Indeed, we observed that Pdi at the end of occlusion had returned to baseline and in the vast majority of the patients, Pgas remained constant during the pause time, assuring passive condition (Fig. 3). In a few patients, a small increase in Pgas (0.5–< 1.5 cmH_2O) was occasionally observed, leading to an overestimation of the measured P_{plat} and ΔP_{rs} by this amount. This, however, did not affect the computation of the P_{LEI}, since expiratory muscle contraction during

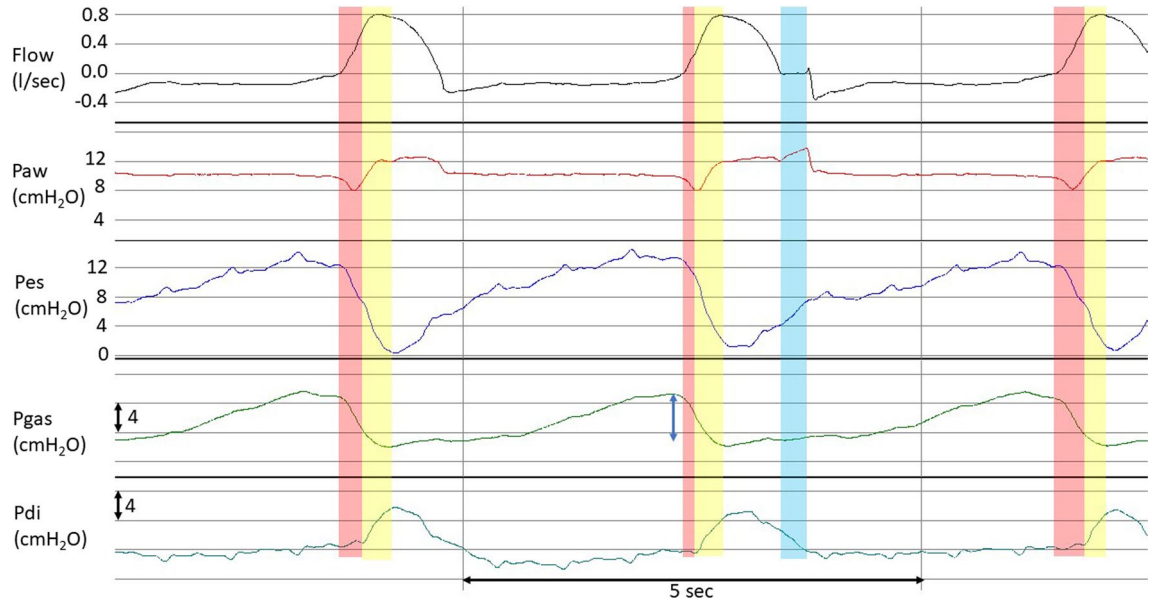

Fig. 3 Flow and airway, esophageal, gastric, and transdiaphragmatic pressures in a patient with ARDS ventilated on PAV+. An occluded and two, preceding and following, un-occluded breaths are shown. Notice that in all breaths inspiratory flow initially is generated only be relaxation of expiratory muscles (red areas). Thereafter, the diaphragm contracts, while expiratory muscles continue to relax (yellow areas). At the beginning of inflation of the occluded breath (zero flow) P_{LEE} is −3.44 cmH_2O and at the end of occlusion (end of blue area) P_{LEI} is 6.48 cmH_2O. The calculated ΔP_{lung} is 9.92 cmH_2O. The corresponding values of Paw are 9.62 and 13.64 cmH_2O and ΔP_{rs} is 4.02 cmH_2O. Totally passive inspired volumes (integrated flow-time red area) in these three breaths are 76, 28 and 85 ml, respectively. The end of relaxation of expiratory muscles occurred when inspired volumes (sum of red and yellow areas) were 265 ml (1st breath), 247 ml (2nd breath), and 268 ml (3rd breath). Notice that before the occluded breath gastric pressure increased by 6.4 cmH_2O (blue double edge arrow), indicating significant expiratory muscle activity that is able to decrease expiratory volume below that determined by PEEP. Notice also that the drop in Pgas due to expiratory muscle relaxation was 7.0 cmH_2O. Observe also that at the end of occlusion Pdi returned to baseline and during occlusion the change in Pgas was negligible (0.3 cmH_2O), indicating passive condition during measurements of P_{plat}. Tidal volume of occluded breath was 562 ml and calculated elastance of respiratory system was 7.2 cmH_2O/l, while that of the lung 17.8 cmH_2O. $\Delta P_{lung}/\Delta P_{rs}$ (and E_{lung}/E_{rs}) was 2.5

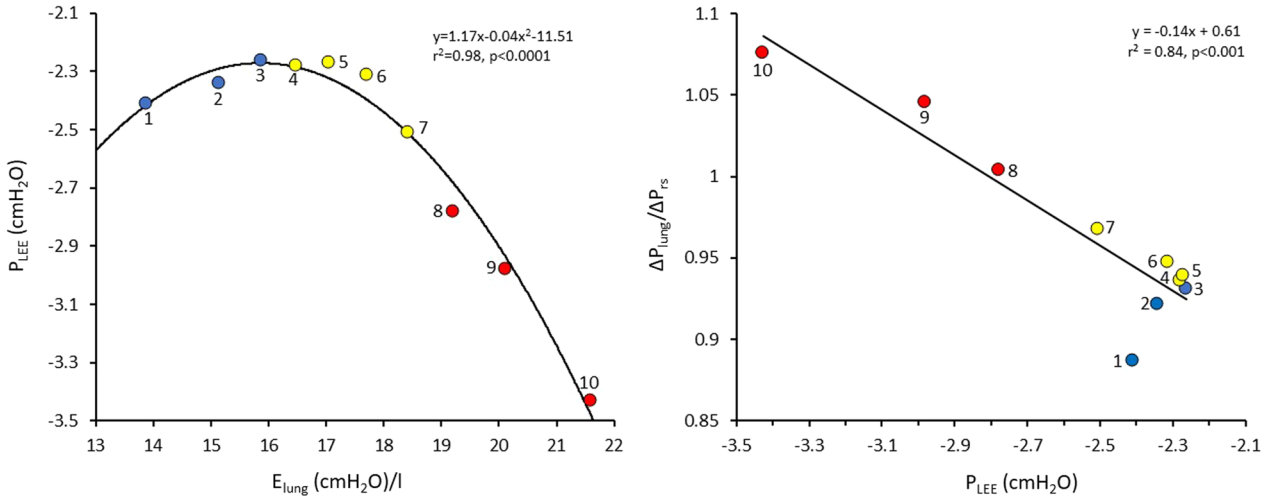

Fig. 4 Relationship between lung elastance (E_{lung}) and transpulmonary pressure at the end of expiration (P_{LEE}) (Left) and P_{LEE} and ratio of driving transpulmonary pressure to that of respiratory system ($\Delta P_{lung}/\Delta P_{rs}$) (Right). Each circle represents the average values of these variables in each of the 10 segments characterized by increasing E_{lung}. Blue circles: Deciles 1–3 (low E_{lung}). Yellow circles: Deciles 4–7 (moderate E_{lung}). Red circles: Deciles 8–10 (high E_{lung}). Notice that the highest E_{lung} (Decile 10) is associated with the lowest P_{LEE} and the highest $\Delta P_{lung}/\Delta P_{rs}$. Observe also that at highest E_{lung} (Decile 10) average ΔP_{lung} is greater than ΔP_{rs}. The number in each circle indicates the corresponding decile. Notice that P_{LEE} begins to decrease after decile 6. This is reflected in almost constant $\Delta P_{lung}/\Delta P_{rs}$ from decile 1 to 6

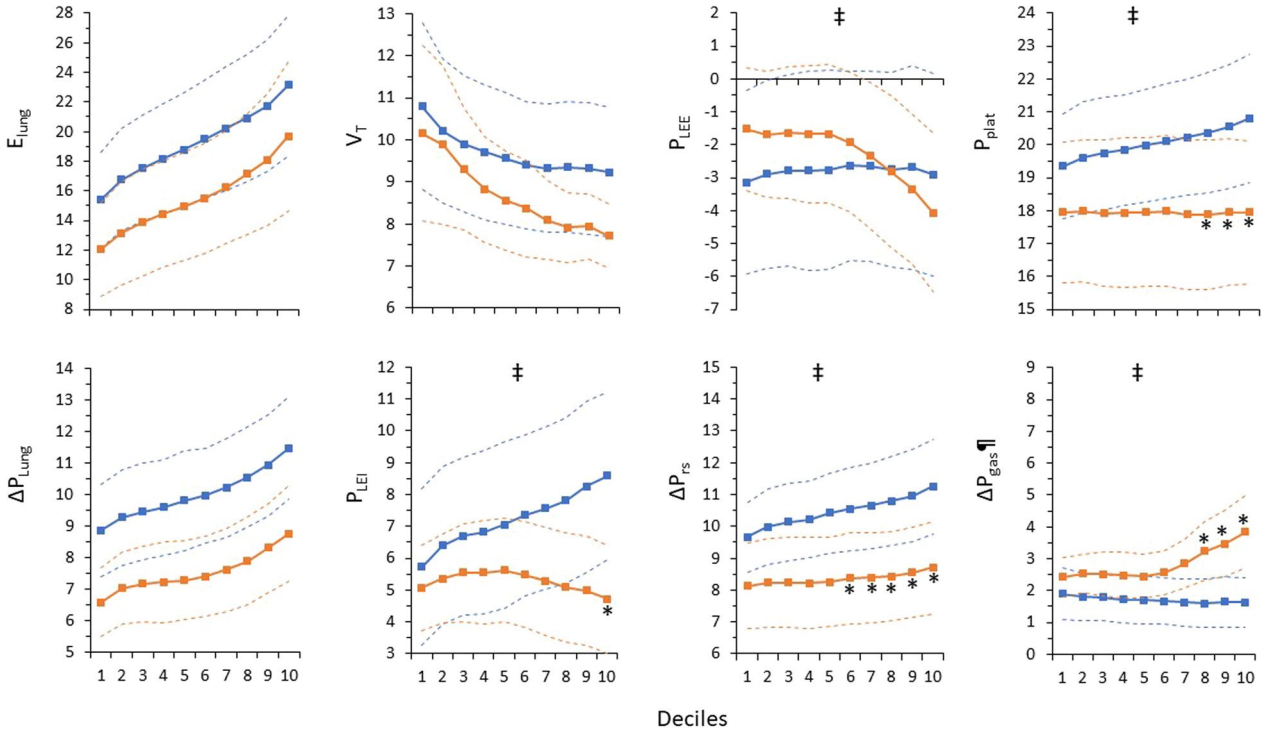

Fig. 5 Effects of a progressive increase in E_{lung} (Decile 1: the lowest E_{lung}; Decile 10 the highest E_{lung}) on average respiratory variables in Group A (blue squares connected by blue lines, characterized by a linear increase in P_{LEI} with increasing E_{lung}) and Group B (orange squares connected by orange lines, characterized by no increase in P_{LEI} with increasing E_{lung}). Blue and orange dashed lines indicate standard deviation range in Groups A and B, respectively. Notice the significant interaction between groups in transpulmonary pressure at end-inspiration (P_{LEI}) and end-expiration (P_{LEE}), driving pressure (ΔP_{rs}), end-inspiratory plateau pressure (P_{plat}), and gastric pressure increase during expiration (ΔP_{gas}). ‡Significant interaction between Groups (Split-plot ANOVA). *Significant difference from the corresponding value of Group A. ¶Pertains to 22 patients (11 in each group)

occlusion equally elevates Paw and Pes. Secondly, consistent with earlier investigations [32–34], P_{LEE} remained predominantly negative throughout the recording period in 20 out of 31 patients. While this observation might raise concerns about the precision of Pes measurements [35, 36], a recent study involving lung-injured pigs and human cadavers assessed directly pleural pressure and demonstrated that Pes accurately mirrors pleural pressure in lung regions proximal to the esophageal balloon [37]. In this study, consistently negative P_{LEE} values were observed, whether based on pleural or esophageal pressure measurements.

Transpulmonary driving pressure, dynamic transpulmonary pressure swings, and effort indices

It has been demonstrated that keeping $\Delta P_{lung} < 12$ cmH_2O and $Plung_{sw} < 20$ cmH_2O in patients with ARDS without spontaneous breathing activity is linked to improved survival [18, 38]. These thresholds have been also suggested as targets during assisted breathing [22]. We demonstrated that $\Delta P_{lung} \geq 12$ cmH_2O occurred rarely and for a short period of time, while in half of the patients (51.6%) such values were never observed (Table 2). Similarly, $Plung_{sw}$ remained within the safe range for most of the time, even when the more conservative threshold of 15 cmH_2O was examined. However, it is unknown if these results, documented during PAV+ventilation, are also applicable in conventional assisted modes. Proportional ventilation, including PAV+and neurally adjusted ventilator assist (NAVA), allows control of breathing system to regulate V_T using chemical and reflex feedback mechanisms [39, 40], that tend to naturally protect the lung from over-distension [41, 42].

While direct studies in humans are lacking, it is generally considered safe to maintain ΔPdi within the range of 3 to 12 cmH_2O and $Pmus_{sw}$ within the range of 3 to 15 cmH_2O to prevent both over-assistance and under-assistance, thereby ensuring the protection of the lungs and diaphragm [21]. In our study, primary physicians, who did not have access to study data, selected a level of assistance that averaged 50%. At this average assist, which amplifies inspiratory muscle pressure by a factor of 2 [43], both ΔPdi and, to a lesser extent, $Pmus_{sw}$ fell within the optimal ranges.

These results are in contrast to those obtained by Di Mussi et al. [44]. In their study, 16 patients transitioned

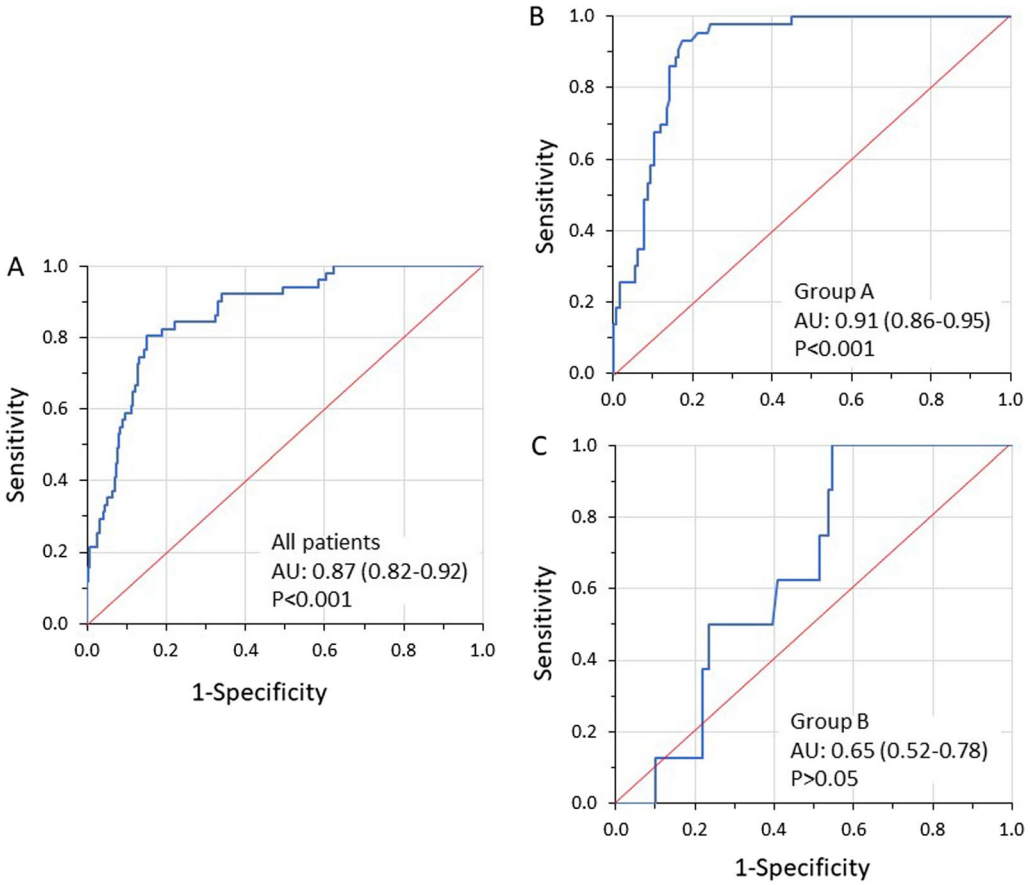

Fig. 6 Receiver operating characteristics curves (blue lines). Area under the curve (AUC) of driving pressure of respiratory system (ΔP_{rs}) to predict transpulmonary driving pressure (ΔP_{lung}) ≥ 12 cmH_2O in all patients (**A**, 310 segments) and patients of Group A (**B**, 170 segments) and Group B (**C**, 140 segments). Notice that contrary to patients of Group A, in patients of Group B ΔP_{rs} does not have a significant predictive value for $\Delta P_{lung} \geq 12$ cmH_2O. Values of AUC are with 95% confidence intervals, and *P* values pertain to the test of AUC to the guess. Best cutoff measurements based on Youden index was 11.5 cmH_2O in all patients (**A**) and 11.8 cmH_2O in patients of Group A (**B**)

from control to pressure support ventilation, with continuous monitoring of electrical activity of the diaphragm (EAdi) over a 12-h period. They observed that 50% of breaths were either over-assisted (28%) or under-assisted (22%). Notwithstanding that in the study of Di Mussi et al. [44] EAdi was used as an index of under- or over-assistance, this disparity can be attributed to the functional principles of pressure support, which, unlike PAV+, hinders the control of breathing system in regulating V_T [45, 46]. The observed greater variation in $Pmus_{sw}$ in our study (Table 2) is likely influenced by expiratory and accessory inspiratory muscle pressures, which contribute to the calculation of Pmus, as well as uncertainties related to passive chest wall properties.

Driving pressure of respiratory system and relationship to driving transpulmonary pressure

Consistent with our previous studies involving a general population of critically ill patients [15, 17], the current study showed that in ARDS patients ventilated with PAV+, ΔP_{rs} rarely exceeded 15 cmH_2O. Although in our previous studies, we postulated that $\Delta P_{rs} < 15$ cmH_2O was associated with acceptable tidal lung stress, the current investigation challenges this assumption. We found a considerably low (11.5 cmH_2O) threshold of ΔP_{rs} for detecting $\Delta P_{lung} \geq 12$ cmH_2O (Fig. 6), suggesting that the calculated ΔP_{rs} underestimated ΔP_{lung}. These results conflict those reported recently by Perez et al. in a small ARDS patients' cohort during pressure support ventilation [47]. In that study, ΔP_{rs} had an excellent precision to predict ΔP_{lung}, with a value of 15 cmH_2O being identified as the best threshold for detecting $\Delta P_{lung} \geq 12$ cmH_2O. However, Perez et al. selectively analyzed only a few occluded breaths while patients with expiratory muscles activity were excluded. The vast majority of our patients exhibited expiratory muscle activity during expiration, limiting the applicability of the findings of Perez et al. in routine clinical practice.

The explanation why ΔP_{rs} underestimated ΔP_{lung}, as well as why in several measurements ΔP_{lung} was found higher than ΔP_{rs} lies in the effect of end-expiratory lung volume on ΔP_{rs} calculation (Fig. 1). When analyzing all breaths, a negative linear relationship between P_{LEE} and $\Delta P_{lung}/\Delta P_{rs}$ was observed in 81% of patients. Additionally, by analyzing the response to E_{lung} changes, the linear mixed-effect model analysis found a significant effect of ΔPgas on P_{LEE}, as well as of P_{LEE} on $\Delta P_{lung}/\Delta P_{rs}$. These findings indicate that in several patients, expiratory muscle contraction reduced end-expiratory lung volume, as reflected by a lower P_{LEE}. In these patients, ΔP_{rs} underestimated the true driving pressure of the respiratory system because it assumed that the elastic recoil pressure when volume started to enter the lungs was equal to PEEP. However, expiratory muscle activation had decreased lung volume to a lower value than that corresponding to PEEP, and the very first moment that expiratory muscles relaxed, volume started to enter the lungs as a result of an alveolar pressure lower than PEEP (Fig. 1 and 3). Obviously, underestimation of the actual respiratory system driving pressure means underestimation of the calculated respiratory system elastance. Additionally, at lung volumes well below the level determined by PEEP, not only is the actual change in ΔP_{rs} higher than the calculated value, but the elastance of the respiratory system may also increase. In this situation, the actual ΔP_{rs} is even higher than what is calculated assuming a linear relationship between pressure and volume during lung inflation.

Response of respiratory variables to Elung changes

As anticipated, E_{lung} changed considerably in all patients over the observation period and ΔP_{lung} unanimously increased at higher E_{lung}. However, we found two distinct responses to E_{lung} increases. One group of patients (Group A), responded with increased P_{LEI}, which drove the increase in ΔP_{lung}. The second group (Group B), maintained constant or even decreased the end-inspiratory lung stress (P_{LEI}) at higher E_{lung}, and the higher ΔP_{lung} resulted from P_{LEE} decrease. Gastric pressure measurements showed that the observed decrease in P_{LEE} was accomplished by a considerable increase in expiratory muscle activity. It is of interest to note that the further decrease in P_{LEE} and increase in ΔP_{gas} occurred when E_{lung} increased by 27% (Fig. 4 and Additional file 2: Fig. S5), signifying a considerable increase in ventilatory demands. This response played a pivotal role in effectively mitigating the extent of end-inspiratory lung stress associated with a specific magnitude of ΔP_{lung} elevation. It is not clear why this different response was observed. However, in Group A, the consistently higher E_{lung} at all deciles and the already low P_{LEE} values at low E_{lung} (Fig. 5) suggest that some patients could not further decrease their already low-end-expiratory lung volume. Nevertheless, the response pattern was not dependent on patients' characteristics, total duration of mechanical ventilation, length of ICU stay, and ICU outcome.

Interestingly, in Group B patients, ΔP_{rs} remained constant and, consequently, lacked predictive value for high ΔP_{lung}. This underscores the importance of end-expiratory lung volume reduction below that corresponding to PEEP, as the primary determinant of $\Delta P_{lung}/\Delta P_{rs}$. Therefore, interpreting ΔP_{rs} as an index of tidal lung stress should be approached with great caution. Although the ΔP_{rs}-ΔP_{lung} relationship was examined during PAV+, similar results should be expected during all modes of assisted mechanical ventilation, since the underestimation of ΔP_{lung} by ΔP_{rs} does not depend on the mode but on the ability of expiratory muscles to decrease end-expiratory lung volume below that determined by PEEP.

We cannot determine whether the distinct response to deteriorating lung elastance conferred a lung-protected benefit in one group compared to the other. Lower P_{LEE} was associated with minimal or no increase in end-inspiratory lung stress despite ΔP_{lung} increase (Fig. 5). However, it remains uncertain to what extent this provides protection, as decreases in end-expiratory lung volume may potentially be associated with lung injury (atelectrauma), derecruitment, and gas exchange abnormalities [48].

Limitations

This study has certain limitations that should be considered. Firstly, end-expiratory lung volume changes were not directly monitored; instead, P_{LEE} was utilized for this purpose. However, we believe that P_{LEE} can provide valuable insights into the direction of change. When E_{lung} remains constant or increases, a decrease in P_{LEE} is indicative of a reduction in end-expiratory lung volume [11]. Therefore, we feel confident that in our study, a decrease in P_{LEE} resulted from lower end-expiratory lung volume. Secondly, this single-center study included a group of patients with ARDS, who were enrolled when the primary physician opted for PAV+ as the initial assisted mode, following judgment of safety for allowing spontaneous breathing activity. Thus, the time lag between intubation and assisted ventilation differed. However, based on clinical judgment, the patients were included at relatively early stages of recovery from ARDS, when the respiratory drive was relatively high, as evidenced by the significant proportion displaying expiratory muscle activity [45]. Nevertheless, these findings may not be generalizable to all critically ill patients, although this patient group is particularly relevant when assessing ΔP_{rs} as a

surrogate for tidal lung stress. Thirdly, this prospective observational study is subject to the inherent biases associated with patient selection and the lack of strict adherence to specific algorithms when titrating PEEP and the level of assist with PAV+ [49]. Nevertheless, this can also be considered a strength, since it allows us to capture the impact of every day clinical practice on ΔP_{lung} and effort indices. Fourthly, since this was beyond the scope of the study, the impact of factors that influence the recruitment of expiratory muscles, such as respiratory acidosis, sedation, and diaphragmatic weakness on group response could not be assessed. Finally, the pendelluft phenomenon, which may occur in patients with high respiratory drive and unpredictably change tidal volume, was not considered.

Conclusions

Transpulmonary driving pressures and inspiratory efforts were largely maintained within a safe range during proportional assist ventilation. Contrary to existing assumptions, the respiratory system driving pressure underestimated the transpulmonary driving pressure due to expiratory muscle activity which lowers end-expiratory lung volume below that determined by PEEP. This phenomenon, which should occur regardless of the mode of support, limits the usefulness of respiratory system driving pressure as a substitute for transpulmonary driving pressure in patients with active breathing.

Abbreviations

ΔP_{lung}	Transpulmonary driving pressure
ΔP_{rs}	Driving pressure of the respiratory system
P_{plat}	End-inspiratory plateau pressure
PEEP	Positive end-expiratory pressure
V_T	Tidal volume
$Plung_{sw}$	Transpulmonary pressure swings
ARDS	Acute respiratory distress syndrome
V'	Airflow
Paw	Airway pressure
Pes	Esophageal pressure
Pgas	Gastric pressure
P_{lung} (Paw-Pes)	Transpulmonary pressure
Pdi (Pgas-Pes)	Transdiaphragmatic pressure
$Pmus_{sw}$	Respiratory muscles (inspiratory and expiratory) pressure swings
ΔP_{gas}	Rise in gastric pressure during the expiratory phase
PEEPi	Dynamic intrinsic PEEP
7-brMA	Seven-breath moving average
E_{lung}	Lung elastance
ROC	Receiver operating characteristic
AUC	Area under the receiver operating characteristic curve
ΔPdi	Inspiratory Pdi swings
P_{LEI}	End-inspiratory transpulmonary pressure
P_{LEE}	End-expiratory transpulmonary pressure
CMV	Control mechanical ventilation
PAV+	Proportional assist ventilation with load adjustable gain factors
ICU	Intensive care unit

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-04797-3.

Additional file 1. Figure S1.

Additional file 2. Supplementary Methods, Results, Figures, Tables and References.

Additional file 3. Individual data of Transpulmonary driving pressure over time.

Author contributions

DG conceived the study. VS and EA conducted data collection. VS, EA, DG, KV, and EK conducted data analysis. DG drafted the manuscript first version. ES developed and validated the computer program for identifications of occluded breaths. All authors critically revised and approved the final version to be published.

Declarations

Competing interests

DG, EA, and KV received lecture fee from Medtronic. The other authors declare no competing interests. Medtronic was not involved in any aspect of the design or conduct of the study, the data analysis, or the manuscript preparation and presentation.

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