Critical Care

BRIEF REPORT

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Physiological effects of lung-protective ventilation in patients with lung fibrosis and usual interstitial pneumonia pattern versus primary ARDS: a matched-control study

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Abstract

Background Although patients with interstitial pneumonia pattern (ILD-UIP) and acute exacerbation (AE) leading to severe acute respiratory failure may require invasive mechanical ventilation (MV), physiological data on lung mechanics during MV are lacking. We aimed at describing the physiological effect of lung-protective ventilation in patients with AE-ILD-UIP compared with primary ARDS.

Methods Partitioned lung and chest wall mechanics were assessed in a series of AE-ILD-UIP patients matched 1:1 with primary ARDS as controls (based on BMI and PaO_2/FiO_2 ratio). Three PEEP levels (zero = *ZEEP*, 4–8 cmH_2O = *PEEP*$_{LOW}$, and titrated to achieve positive end-expiratory transpulmonary pressure $P_{L,EE}$ = *PEEP*$_{TITRATED}$) were used for measurements.

Results Ten AE-ILD-UIP patients and 10 matched ARDS were included. In AE-ILD-UIP median $P_{L,EE}$ at ZEEP was −4.3 [−7.6–−2.3] cmH_2O and lung elastance (E_L) 44 [40–51] cmH_2O/L. At PEEP$_{LOW}$, $P_{L,EE}$ remained negative and E_L did not change ($p = 0.995$) versus ZEEP. At PEEP$_{TITRATED}$, $P_{L,EE}$ increased to 0.8 [0.3–1.5] cmH_2O and E_L to 49 [43–59] ($p = 0.004$ and $p < 0.001$ compared to ZEEP and PEEP$_{LOW}$, respectively). ΔP_L decreased at PEEP$_{LOW}$ ($p = 0.018$) and increased at PEEP$_{TITRATED}$ ($p = 0.003$). In matched ARDS control PEEP titration to obtain a positive $P_{L,EE}$ did not result in significant changes in E_L and ΔP_L.

Conclusions In mechanically ventilated AE-ILD-UIP patients, differently than in patients with primary ARDS, PEEP titrated to obtain a positive $P_{L,EE}$ significantly worsened lung mechanics.

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Keywords Interstitial lung disease, Pulmonary fibrosis, Usual interstitial pneumonia, Acute respiratory failure, ARDS, Lung elastance, Lung elastance, Respiratory mechanics, End-inspiratory transpulmonary pressure, End-expiratory transpulmonary pressure, Invasive mechanical ventilation, VILI, Transpulmonary pressure

Background

Patients with interstitial lung disease and usual interstitial pneumonia pattern (ILD-UIP) may experience severe acute hypoxic respiratory failure (AHRF) during acute exacerbations (AE-ILD-UIP) [1], requiring invasive respiratory support (MV) [2]; nevertheless, the mortality following MV exceeds 80% [3]. Patho-physiologically, AE-ILD resembles acute respiratory distress syndrome (ARDS) with diffuse alveolar damage (DAD), superimposed on a background of lung fibrosis [4].

In ARDS, lung-protective MV strategies contributed to mitigate ventilatory induced lung injury (VILI), thus decreasing mortality [5, 6]. Talmor and coworkers showed that an esophageal pressure (P_{es})-guided positive end-expiratory pressure (PEEP) titration to obtain a positive end-expiratory transpulmonary pressure ($P_{L,EE}$) is useful to recruit dependent lung regions, improve lung mechanics and minimize atelectrauma in these patients [7].

Retrospective data suggest that patients with AE-ILD are particularly susceptible to stress and strain, and hence at higher risk of VILI [8]. Thus, it seems straightforward to use lung-protective ventilatory strategies in these patients. However, little is known on $P_{L,EE}$ in patients with AE-ILD-UIP and even less on the potential impact of lung-protective strategies aimed at maintaining positive $P_{L,EE}$.

We studied the impact of different PEEP settings (zero PEEP [ZEEP], $PEEP_{LOW}$ and $PEEP_{TITRATED}$ to obtain positive $P_{L,EE}$) in patients with AE-ILD-UIP, compared it with matched primary ARDS controls. We hypothesized that the impact of PEEP titration on partitioned respiratory mechanics could be different between the groups.

Methods

Study setting and population

The study (ClinicalTrial.gov ID NCT05098717) was carried out at the Respiratory Intensive Care Unit (RICU) of the University Hospital of Modena (Italy) in accordance with the Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 327/2022). Informed consent to divulgate data was obtained from participants or their relatives, as appropriate.

Patients with AE-ILD-UIP developing AHRF and consecutively admitted to the RICU (August 1st, 2016, to July 1st, 2022) were eligible for enrollment. Inclusion criteria were age > 18 years; established diagnosis of ILD with a UIP pattern on a high-resolution computed tomography scan; invasive MV in volume-controlled mode. Patients suffering from chronic obstructive pulmonary disease, neuromuscular disease and chest wall deformities were excluded. AE-ILD-UIP were then matched 1:1 by body mass index, PaO_2/FIO_2 and acute physiology and chronic health evaluation (APACHE) II score at admission, to a group of patients with primary ARDS under MV extracted from our dataset over the same period.

Study procedures and aim

According to our institutional protocol, patients with AE-ILD-UIP or ARDS requiring MV were submitted to a partitioned respiratory mechanics measurements within 24 h from admission during three different lung-protective strategies including low V_T (6 ml/Kg/PBW) and three consecutive PEEP levels, i.e., 0 cmH_2O (ZEEP), 4–8 cmH_2O ($PEEP_{LOW}$), and P_{es}-guided titration to obtain positive $P_{L,EE}$ ($PEEP_{TITRATED}$). At each phase, PEEP level was maintained for 30 min before recording all respiratory parameters and arterial blood sampling (see details in Additional file 1: Supplement [9, 10]).

The aim was to report measures of partitioned respiratory mechanics under lung-protective MV at different PEEP levels in patients with AE-ILD-UIP compared with ARDS.

Data collection and analysis plan

Demographics, clinical characteristics, available pulmonary functions tests within 12 months before AE-ILD and partitioned respiratory mechanics were collected.

Data were displayed as median and interquartile range for continuous variables and numbers and percentages for dichotomous variables. Group comparison was built using a one-to-one propensity score matching procedure with the nearest-neighbor method without replacement (caliper = 0.2). Comparison between continuous variables was performed with Wilcoxon

and Wilcoxon signed-rank tests. Dichotomous variables were compared using the χ^2 test. Kruskal–Wallis was used to test as an interaction for whether the change in respiratory mechanics and physiological variables according to PEEP settings was different between groups. Statistics was performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

Results

Respiratory mechanics of AE-ILD-UIP

Over the study period a total of 21 patients with AE-ILD-UIP underwent MV. Of these, 10 patients were analyzed according to inclusion criteria (see Additional file 1: Supplement). All of them died while on MV.

Respiratory mechanics of AE-ILD-UIP at different PEEP levels are reported in Table 1, while changes in respiratory mechanics at different levels are shown in Fig. 1 (and Additional file 1: eFigure 2, Supplement). At ZEEP the median lung elastance (E_L) was 44.4 cmH_2O/L, transpulmonary driving pressure (ΔP_L) was 21.1 cmH_2O, $P_{L,EE}$ was −4.3 cmH_2O and end-inspiratory transpulmonary pressure ($P_{L,EI}$) was 16.7 cmH_2O (Table 1). During the $PEEP_{LOW}$ phase $P_{L,EE}$ remained below 0 cmH_2O (Table 1), median E_L and $P_{L,EI}$ did not change (Fig. 1, panel A and E) while ΔP_L significantly decreased from baseline ($p=0.018$,). During the $PEEP_{TITRATED}$ phase $P_{L,EE}$ was 0.8 cmH_2O (Table 1) and E_L significantly increased as compared to both ZEEP and $PEEP_{LOW}$ ($p=0.04$ and $p<0.0001$, respectively, Fig. 1, panel A), while $P_{L,EI}$ and ΔP_L were higher as compared to $PEEP_{LOW}$ ($p<0.001$ and $p=0.003$, respectively, Fig. 1, panel E and G).

AE-ILD-UIP as compared with historical, matched, ARDS controls

AE-ILD-UIP and matched ARDS groups were similar for SAPS II score (Additional file 1: eTable 1, Supplement). Lung infection was the cause for developing ARDS in all patients.

$PEEP_{TITRATED}$, but not $PEEP_{LOW}$ setting, resulted in higher PEEP in ARDS () compared with AE-ILD-UIP (14

Table 1 Blood gas analyses and partitioned respiratory mechanics of the AE-ILD-UIP and the ARDS population at different PEEP levels. Data are presented as median value and IQR

Variable	AE-ILD-UIP	ARDS	*p*-value
ZEEP phase			
E_L, cmH_2O/L	44.4 (39.7–50.7)	17.9 (9.9–23.3)	< 0.0001
E_{cw}, cmH_2O/L	3.2 (2.5–5.7)	5.4 (4–7.4)	0.12
E_{tot}, cmH_2O/L	49 (43.9–54.7)	22 (16.8–28)	< 0.0001
$P_{L,EI}$, cmH_2O	16.7 (14.8–19)	4.4 (2.9–6.3)	< 0.0001
$P_{L,EE}$, cmH_2O	−4.3 (−7.6–−2.3)	−4.1 (−7.6–−2.9)	0.66
ΔP_{aw}, cmH_2O	16.8 (13.8–19.3)	14.4 (11.5–21.2)	0.56
ΔP_L, cmH_2O	21.1 (17.8–23.6)	9.3 (7–11.5)	< 0.0001
pH, value	7.42 (7.41–7.42)	7.4 (7.37–7.41)	0.07
pO2, cmH_2O	74 (66.5–80)	83 (75–89)	0.3
pCO2, cmH_2O	39.5 (38–45)	39 (36.8–40)	0.06
$PEEP_{LOW}$ phase			
E_L, cmH_2O/L	43.3 (36.8–53)	14.6 (12.2–19.1)	< 0.0001
E_{cw}, cmH_2O/L	3.4 (2.3–5.6)	5.7 (4.3–8.3)	0.09
E_{tot}, cmH_2O/L	48.5 (40–56.8)	22.1 (19.1–25.2)	< 0.0001
$P_{L,EI}$, cmH_2O	15.3 (11.3–18.7)	10.5 (5–14)	0.01
$P_{L,EE}$, cmH_2O	−2.6 (−4.3–−1.2)	−2.5 (−4.6–−0.5)	0.75
ΔP_{aw}, cmH_2O	16.8 (14.3–18.6)	15.1 (11.9–21.4)	0.9
ΔP_L, cmH_2O	18.4 (15.6–21.8)	12.3 (8.5–16.6)	0.02
PEEP, cmH_2O	4 (4–4)	4 (4–5)	0.2
pH, value	7.41 (7.38–7.42)	7.4 (7.36–7.42)	0.3
pO_2, cmH_2O	93.5 (73.3–107)	74.5 (68.3–80.5)	0.1
pCO_2, cmH_2O	41 (38.5–42)	42 (39.8–47)	0.18
$PEEP_{TITRATED}$ phase			
E_L, cmH_2O/L	48.8 (59–42.8)	15.2 (12.4–19.7)	< 0.0001
E_{cw}, cmH_2O/L	3.7 (3.2–5.9)	5.7 (4.7–7.2)	0.1
E_{tot}, cmH_2O/L	55.3 (45.9–62.5)	20.6 (19–24.5)	< 0.0001
$P_{L,EI}$, cmH_2O	23.3 (21.3–26.7)	16.9 (13.5–19.2)	0.001
$P_{L,EE}$, cmH_2O	0.8 (0.3–1.5)	2.4 (0.6–4.9)	0.04
ΔP_{aw}, cmH_2O	19.1 (16.1–21.6)	15.3 (9.4–17)	0.01
ΔP_L, cmH_2O	22.6 (20.8–25.8)	13.9 (6.6–16.5)	0.0001
PEEP, cmH_2O	12 (10–14)	14 (12–−17.5)	0.03
pH, value	7.38 (7.35–7.4)	7.37 (7.34–7.4)	0.34
pO2, cmH_2O	80 (58–93)	105 (80–134)	0.01
pCO2, cmH_2O	42 (39.5–43.3)	45 (40–48)	0.08

AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome; IQR, interquartile range; ΔP_L, transpulmonary driving pressure; $P_{L,EI}$, end-inspiratory transpulmonary pressure; $P_{L,EE}$, end-expiratory transpulmonary pressure; ΔP_{aw}, driving pressure; E_{tot}, respiratory system elastance; E_{cw}, chest wall elastance; E_L, lung elastance; *PEEP, positive end-expiratory pressure*

VS 12 cmH_2O, $p<0.001$). At ZEEP, ARDS patients had lower E_L (17.9 cmH_2O/L, $p \leq 0.0001$), $P_{L,EI}$ (4.4 cmH_2O, $p<0.0001$), and ΔP_L (9.3 cmH_2O, $p<0.0001$) compared with AE-ILD-UIP. During the $PEEP_{LOW}$ and the $PEEP_{TITRATED}$ phases, ARDS patients still had lower E_L (14.6 cmH_2O/L, $p<0.0001$ and 15.2 cmH_2O/L, $p<0.0001$ respectively), $P_{L,EI}$ (10.5 cmH_2O, $p<0.0001$ and 16.9 cmH_2O, $p=0.001$ respectively), and ΔP_L (12.3 cmH_2O, $p=0.02$ and 13.9 cmH_2O, $p=0.0001$ respectively) as compared to AE-ILD-UIP.

Figure 1 shows that during the PEEP trial E_L, $P_{L,EI}$ and ΔP_L were different in AE-ILD-UIP and ARDS patients. E_L remained unchanged at $PEEP_{LOW}$ and worsened at $PEEP_{TITRATED}$ in AE-ILD-UIP, whereas it did not change in patients with ARDS (Fig. 1, panel A and B).

Discussion

With this study, we report for the first time that AE-ILD-UIP patients under lung-protective MV strategy respond favorably in terms of respiratory mechanics to low PEEP levels, whereas respond unfavorably (and rather uniformly) to a P_{es}-guided PEEP strategy to obtain positive $P_{L,EE}$. The mechanical behavior of AE-ILD-UIP was different from that of matched "pulmonary" ARDS controls.

In our AE-ILD-UIP patients a low PEEP strategy resulted in reduction of ΔP_L indirectly suggesting alveolar recruitment, probably occurring in the areas of DAD superimposed to UIP. Indeed, despite we did not measure alveolar recruitment, we assume that in AE-ILD-UIP patients the lung regions spared by fibrosis but affected by DAD were likely de-recruited at ZEEP. Thus, it seems that the low PEEP strategy could be wise in patients with AE-UIP-ILD at least in terms of lung mechanics. These results are novel and referred to a cohort of patients rarely studied in the intensive care context. A previous study by Nava et al. assessed the respiratory mechanics during MV in seven patients with end-stage idiopathic pulmonary fibrosis [11] and reported values of lung elastance (46.1 cmH_2O/L) similar to those found in our work. However, in that study lung mechanics were only measured at ZEEP.

Tailored PEEP titration in the context of lung-protective ventilation is still under debate [12]. During controlled MV, $P_{L,EE}$ may be negative at ZEEP, indicating that the dependent lung regions are compressed [13]. This condition predisposes to tidal alveolar collapse and re-opening, resulting in high local shear forces that enhance VILI (atelectrauma) [14]. Negative $P_{L,EE}$ is common in ARDS patients ventilated with lower PEEP levels in supine position and this largely explains the beneficial physiological effects of PEEP titration to achieve a positive $P_{L,EE}$ reported in preclinical and clinical studies [15, 16]. Notwithstanding, the EPVent-2 trial showed that these positive physiological effects have to deal with the potential PEEP-induced lung injury caused by overdistension in the non-dependent lung regions [17]. We hypothesized the "Talmor" PEEP titration protocol in AE-ILD-UIP could lead to beneficial physiological effects also in patients with AE-ILD-UIP; however we found a rather sharp increase in E_L and ΔP_L in all of them (Fig. 1). It is tempting to speculate that P_{es}-guided PEEP titration resulted in squishing among the patchy fibrotic tissue of the non-fibrotic lung regions (so called "*squishy ball lung*" phenomenon*)* [18] and that this effect invalidated the potential benefits of alveolar recruitment in the dependent lung regions.

Our study suffers from limitations: the small sample, the lack of quantitative analysis of hyper-inflated lung tissue [19] during PEEP titration and no end-expiratory lung volume assessment [20] allow only preliminary pathophysiological insights. Moreover, we did not assess the role of fluid balance as confounding factor. Finally, a selection bias should be acknowledged, as patients with AE-ILD are not usually placed on MV given the poor prognosis.

Conclusions

In AE-ILD-UIP mechanically ventilated patients, low PEEP strategy may improve respiratory mechanics and, at difference with primary ARDS, PEEP titrated to obtain a positive $P_{L,EE}$ significantly worsened lung mechanics. This paves the way to larger studies to clarify the best physiological response to PEEP in these patients. However, we feel that our findings could have practical implications when managing patients with AE-ILD-UIP under MV, suggesting that low PEEP strategy may be preferable to prevent lung injury.

(See figure on next page.)

Fig. 1 Measured individual values of E_L, $P_{L,EE}$, $P_{L,EI}$ and ΔP_L the matched study groups at ZEEP, $PEEP_{LOW}$ and $PEEP_{TITRATED}$ phase. When testing as an interaction for whether the change in physiological variables at different PEEP levels was different between AE-ILD-UIP and ARDS (dotted *p*-values line), statistical difference was found for E_L ($p<0.001$, panel **A** and **B**), $P_{L,EI}$ ($p<0.001$, panel **E** and **F**, $p<0.00$) and ΔP_L (<0.001, panel **G** and **H**). E_L, lung elastance; $P_{L,EI}$, end-inspiratory transpulmonary pressure; $P_{L,EE}$, end-expiratory transpulmonary pressure; P_L, transpulmonary driving pressure; ZEEP, zero positive end-expiratory pressure; PEEP, positive end-expiratory pressure; AE-ILD-UIP, acute exacerbation of interstitial lung disease with usual interstitial pneumonia pattern; ARDS, acute respiratory distress syndrome

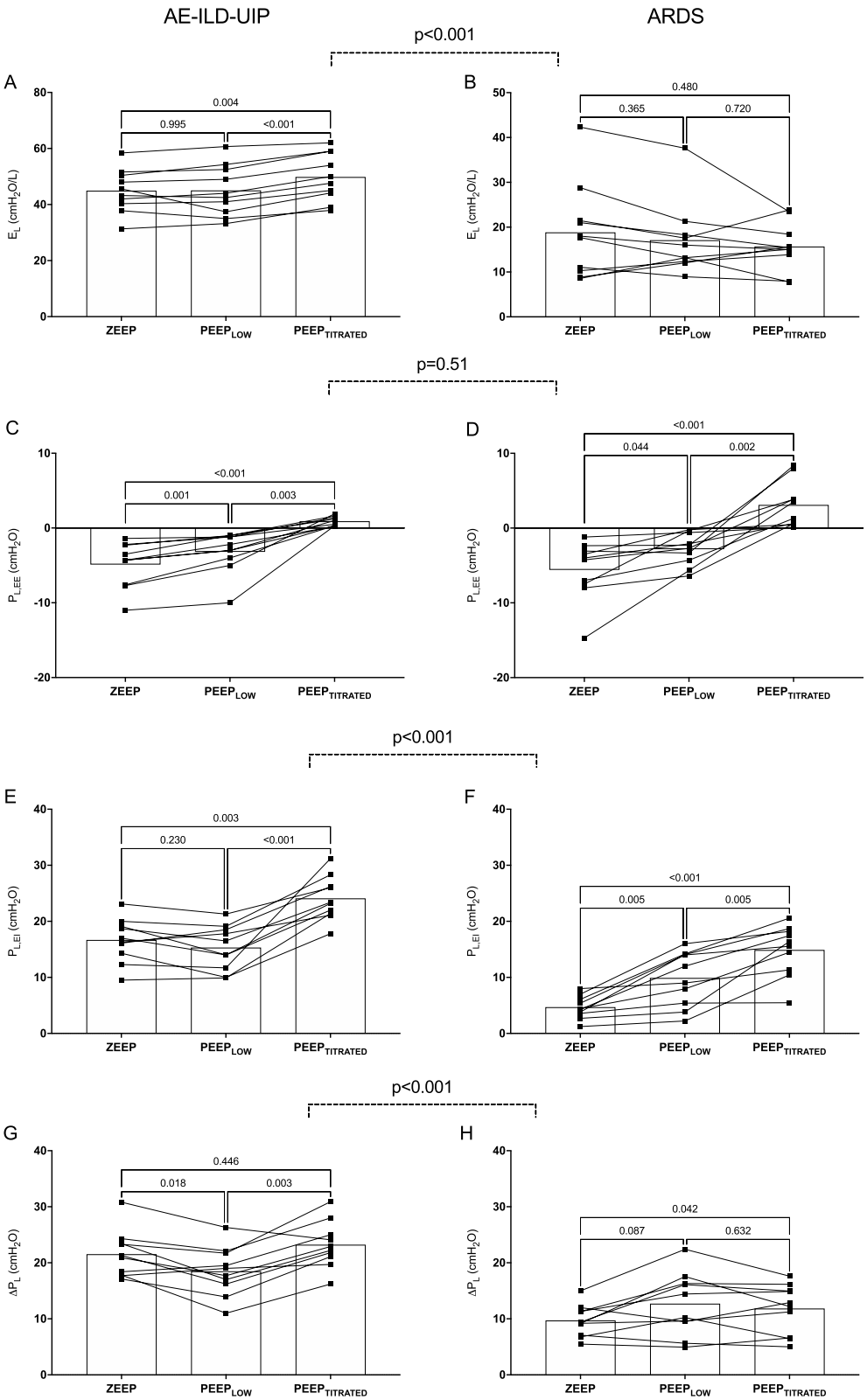

Fig. 1 (See legend on previous page.)

Abbreviations

ILD	Interstitial lung disease
AE-ILD	Acute exacerbation of ILD
UIP	Usual interstitial pneumonia
ARDS	Acute respiratory distress syndrome
AHRF	Acute hypoxic respiratory failure
bpm	Breaths per minute
MV	Invasive mechanical ventilation
ETI	Endotracheal intubation
NIV	Noninvasive mechanical ventilation
PEEP	Positive end-expiratory pressure
PBW	Predicted body weight
PSV	Pressure support
APACHE II	Acute physiology and chronic health evaluation II
SAPS II	Simplified Acute Physiology Score
IPF	Idiopathic pulmonary fibrosis
RICU	Respiratory intensive care unit
ICU	Intensive care unit
P_{es}	Esophageal pressure
$P_{es,EI}$	End-inspiratory esophageal pressure
$P_{es,EE}$	End-expiratory esophageal pressure
P_L	Transpulmonary pressure
ΔP_L	Transpulmonary driving pressure
$P_{L,EI}$	End-inspiratory transpulmonary pressure
$P_{L,EE}$	End-expiratory transpulmonary pressure
P_{plat}	End-inspiratory plateau pressure
ΔP_{aw}	Driving pressure
E_{tot}	Respiratory system elastance
E_{cw}	Chest wall elastance
E_L	Lung elastance
Vt	Tidal volume
IQR	Interquartile range

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-023-04682-5.

Additional file 1. Respiratory mechanics assessment protocol. Study algorithm and clinical and additional mechanical characteristics of the study population.

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None.

Author contributions
RT and SG designed the study, enrolled the patients, analyzed the data, and wrote the paper and should be considered as first authors. IC, LT, RF, DA, FG, GB, LM, A Moretti and A Carzoli made substantial contributions to the literature review, data collection, and paper writing. AVS, GR, and SB reviewed the literature, wrote the manuscript, and produced the figures. A Cortegiani and LB, analyzed data and produced figures. GG designed the study. RR elaborated the analysis and wrote the paper. A Marchioni and EC designed the study, wrote, reviewed, and edited the manuscript, and share senior authorship. All authors have read and approved the final version of the manuscript. RT and SG share first authorship. AM and EC share senior authorship.

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Availability of data and materials
Data are available at the Respiratory Disease Unit of the University Hospital of Modena, Italy, upon request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 327/2022). Informed consent to participate in the study and to allow their clinical data to be analyzed and published were obtained from participants, as appropriate.

Consent for publication
Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Competing interests
Authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

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