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Determinants of tidal recruitment/derecruitment assessed by electrical impedance tomography in spontaneously breathing acute respiratory distress syndrome patients

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Abstract

Rationale: **Tidal recruitment/derecruitment (R/D) is a well-known mechanism of lung injury in acute respiratory distress syndrome (ARDS) patients, but its bedside identification is challenging during assisted ventilation.**

Objectives: **To investigate bedside determinants of tidal R/D assessed by electrical impedance tomography (EIT) in spontaneously breathing ARDS patients on pressure support ventilation (PSV).**

Methods: **This is a secondary analysis of a previous study including lightly sedated ARDS patients ventilated on PSV at 2 positive end-expiratory pressure (PEEP) levels selected by EIT ($PEEP_{EIT}$) and low PEEP/FI_{O2} table ($PEEP_{TABLE}$). Detailed physiological assessment was performed, including respiratory mechanics, inspiratory drive and effort, regional mechanics, and tidal R/D measured by EIT.**

Measurements and Main Results: **Of 30 original patients, 1 was excluded due to unstable end-expiratory lung impedance, leaving 29 patients for analysis. Median PEEP was 10.0 (IQR 8.0-12.0) cmH_2O with $PEEP_{EIT}$ and 8.0 (IQR 5.0-10.0) cmH_2O with $PEEP_{TABLE}$. Overall, tidal R/D was 14.3% (IQR 9.0-33.0), but it was lower at $PEEP_{EIT}$ vs $PEEP_{TABLE}$ (11.3% [IQR 4.8-20.5] vs 21.9% [IQR 6.8-31.7]; $P = .008$). Recruitment/derecruitment reduction with $PEEP_{EIT}$ correlated with decreases in collapse (rho = 0.72; $P < .001$) and pendelluft (rho = 0.57; $P = .002$). Analyzing data from both randomized PEEPs together, mixed-effects models showed higher tidal R/D at lower PEEP ($P < .001$), more negative end-expiratory transpulmonary pressure ($PL_{End\text{-}Exp}$) ($P < .001$), larger collapse ($P < .001$), and lower lung compliance ($P = .002$). Higher respiratory drive ($P = .001$), effort ($P = .009$), and dynamic driving transpulmonary pressure ($P = .009$) correlated with higher tidal R/D. Patients with nonfocal infiltrates presented higher tidal R/D ($P = .005$). At multivariable analysis, $PL_{End\text{-}Exp}$, lung collapse, and nonfocal pattern were independently associated tidal R/D.**

Conclusion: **In spontaneously breathing ARDS patients on PSV, the main determinants of tidal R/D are more negative $PL_{End\text{-}Exp}$, higher lung collapse, and nonfocal infiltrates.**

Keywords electrical impedance tomography, physiologic monitoring, assisted ventilation, acute respiratory distress syndrome, ventilator-induced lung injury

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At a Glance Commentary

Tidal recruitment/derecruitment (R/D) was assessed at the bedside by electrical impedance tomography (EIT) in spontaneously breathing patients with ARDS. Tidal R/D was highly prevalent but with large variability. Independent determinants of higher tidal R/D were more negative end-expiratory transpulmonary pressure, lung collapse measured by EIT and non-focal ARDS. Higher drive and effort were also correlated, likely as a consequence of more severe disease.

Introduction

Cyclic alveolar recruitment/derecruitment (R/D) induced by tidal ventilation is a well-known mechanism of lung injury (atelectrauma).[1,2] Multiple studies have shown that repetitive opening and closing of distal airways may intensify the frictional and compressive forces exerted on the lung epithelial surface,[2-6] which disrupts the alveolar-capillary barrier and impairs surfactant function, contributing to pulmonary edema, inflammation, and hyaline membranes formation.[2,4,7-9]

Measuring tidal R/D at the bedside is challenging, particularly in spontaneously breathing patients at risk for patient self-inflicted lung injury (P-SILI). A recent experimental study described a novel method to measure tidal R/D at the bedside by electrical impedance tomography (EIT).[10] Nevertheless, this approach has not yet been applied in patients with the acute respiratory distress syndrome (ARDS) spontaneously breathing at different positive end-expiratory pressure (PEEP) levels. In this context, tidal R/D can be influenced by multiple mechanisms, including respiratory effort, lung stress, and the effect of PEEP on alveolar recruitment. Bedside detection of tidal R/D might add relevant information for a safer transition from controlled to assisted ventilation.[11,12]

In this study, we examined the physiological and clinical determinants of tidal R/D assessed by EIT in intubated patients with ARDS undergoing pressure support ventilation (PSV) at different PEEP levels. Some of these results have been previously reported in the form of an abstract.[13]

Methods

Study design

This study is a secondary analysis of a randomized, crossover trial carried out in 3 Italian ICUs that compared the effects of 2 personalized PEEP levels on lung and diaphragm protection.[14] One method assigned PEEP according to the lower PEEP/FI_{O2} table ($PEEP_{TABLE}$), while the other selected the PEEP associated with lowest absolute difference between alveolar collapse and overdistension measured by EIT and driving transpulmonary pressure ($PEEP_{EIT}$).

Population

The original study enrolled adults with ARDS and Richmond Agitation-Sedation Score between −2 and 0 ventilated on PSV as per clinical decision. Exclusion criteria were clinical $FI_{O2} > 0.8$, age younger than 18 years, hemodynamic instability, pneumothorax, history of severe obstructive pulmonary disease, inability to correctly position the EIT belt, and contraindications to EIT monitoring or to esophageal catheter insertion. For the present study, 1 of the 30 patients originally enrolled was excluded because of unstable end-expiratory lung impedance (EELI) values.

Data collection

At inclusion, we collected demographic data, Simplified Acute Physiology Score II at ICU admission, Sequential Organ Failure Assessment score, days from intubation, days since PSV transition, etiology of ARDS, sedation and analgesia, ventilator settings, and blood gases. Focal and nonfocal lung morphology—assessed through chest computed tomography (CT) ($n = 16$) or chest radiography ($n = 13$)—was classified by 2 independent reviewers (M.L, V.C) with disagreement resolved by consensus. Patient outcomes were collected from electronic clinical records.

Measurements

Esophageal pressure (P_{es}) was monitored by a dedicated catheter (Cooper Surgical, CT, USA, or Nutrivent, Sidam, Italy) inflated according to manufacturer's recommendations. The correct positioning of the balloon was checked.[15] Airway pressure (P_{aw}) and P_{es} were continuously monitored by a dedicated system (PulmoVista 500, Drager, Lu¨beck, Germany), and transpulmonary pressure (PL) was calculated as the difference between P_{aw} and P_{es}. Dynamic driving PL (ΔPL_{dyn}) was computed as the difference between the maximal and minimal PL. The airway occlusion pressure at 100 ms ($P_{0.1}$) and occlusion pressure (ΔP_{occ}) were measured during an occluded airway at the end of expiration.

Electrical impedance tomography monitoring was performed using a dedicated belt with 16 electrodes connected to the EIT monitor (PulmoVista 500, Drager, Lu¨beck, Germany). Electrical impedance tomography data were acquired at a frame rate of 50 Hz and stored for offline analysis.

Study protocol

The original study consisted of 3 phases. First, all patients underwent a decremental PEEP trial from 18 to 4 cmH_2O in supine semirecumbent position, with 2-cmH_2O steps lasting 2 minutes (phase 1). After the decremental trial, 2 PEEP levels were identified ($PEEP_{TABLE}$ and $PEEP_{EIT}$), then patients were ventilated for 20 minutes at each PEEP level in randomized order (phases 2 and 3).

During the decremental PEEP trial and the last minutes of each randomized PEEP, a detailed physiological assessment was performed including respiratory parameters, EIT ventilation data, gas exchange (only for phases 2 and 3), and hemodynamics (see Supplementary material). Throughout the study, analgesia and sedation dose were kept constant.

Quantification of tidal R/D using EIT

Electrical impedance tomography recordings within the same patient were reconstructed against the same baseline

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end-expiratory frames at the lowest PEEP level evaluated during the decremental trial (phase 1, 4 cmH_2O step) (Draeger's proprietary algorithm software version 1.3). Then, the analysis for tidal R/D was performed as follows: toward the end of each 20-minute randomized PEEP level (phases 2 and 3), we visually selected a stable period comprising 13 (IQR 10-18) breaths to reconstruct EIT maps at end-inspiration and end-expiration. By subtraction of the end-inspiratory and end-expiratory maps, tidal breathing images were derived.

We then identified tidal R/D as previously described.[10] At end-expiration, pixels were classified as "aerated" if the increase of EELI from PEEP 4 cmH_2O to the target PEEP level ($PEEP_{EIT}$ and $PEEP_{TABLE}$) was > 10% of the maximal change. Pixels were classified as "ventilated" if their tidal impedance variation exceeded 30% of the maximal value within that tidal image. A detailed explanation for the selected ventilation/aeration thresholds and a sensitivity analysis of the main results are presented in Supplementary material.

A pixel was classified as undergoing tidal R/D if "non-aerated" at end-expiration but "ventilated" in the tidal breathing image (see Figure 1). The percentage of tidal R/D at each PEEP level was computed as

$$\text{Tidal recruitment / derecruitment}_{\%} = \left(\frac{\Sigma \text{Pixels ventilated AND non-aerated}\left(\text{randomized PEEP level}\right)}{\Sigma \text{Pixels aerated OR ventilated}\left(\text{PEEP 18 cmH}_2\text{O}\right)} \right) \text{x100.}$$

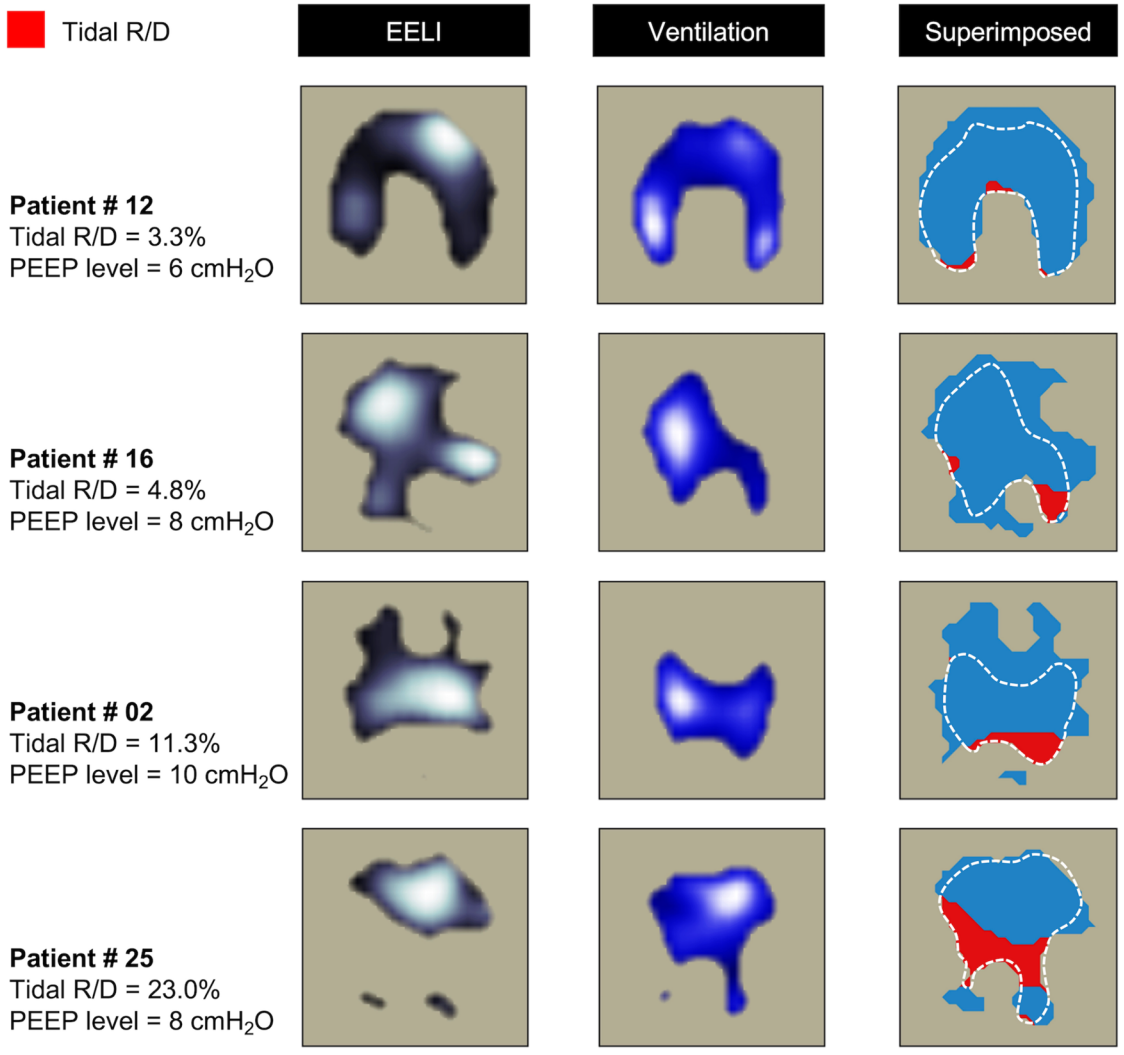


Figure 1 Graphical representation of tidal recruitment/derecruitment (R/D) measure through electrical impedance tomography (EIT) in 4 patients ventilated at the 2 randomized positive end-expiratory pressure (PEEP) levels ($PEEP_{EIT}$ and $PEEP/FI_{O2}$ table [$PEEP_{TABLE}$]). The EIT maps were reconstructed at end-expiration (first row) and end-inspiration during tidal ventilation (second row). In the third row, superimposed images of ventilation (dotted white line) and aeration depict regions of tidal R/D in red, defined as areas that were nonaerated at end-expiration but reopened and ventilated during inspiration. Pixels appearing in the image are those with values higher that the thresholds proposed to define aeration (>10%) and ventilation (>30%).

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Given that tidal R/D is often expressed as a fraction of the total lung volume or lung weight,[16] pixels aerated or ventilated in EIT images obtained at the highest PEEP during the decremental trial (phase 1, PEEP 18 cmH_2O) were used as denominator in the formula, as this PEEP was the closest available proxy to the maximal total lung aeration in our study.

Regional values of tidal R/D were analyzed within 3 horizontal regions of interest from ventral to dorsal: nondependent (11 x 32), middle (10 x 32), and dependent (11 x 32).

Statistical analysis

Data are expressed as mean ± standard deviation or median (first-third quartile), according to Shapiro–Wilk test results. Categorical variables are presented as number (percentage). The comparison between tidal R/D at $PEEP_{EIT}$ and $PEEP_{TABLE}$ was performed with linear mixed-effects models including patient as a random intercept accounting for the hierarchical and dependent structure of data. Correlations between nonrepeated measures were assessed through Spearman coefficient (ρ).

Bivariate associations were explored through mixed-effects models using data from both randomized PEEPs together (2 points per patient). Patients were entered as random intercepts and slopes. Effect estimates are reported as beta coefficients (β) with 95% confidence intervals. When the dependent variable required transformation to satisfy model assumptions, coefficients were reported on the transformed scale. The variance explained by fixed effects alone and by the full model (including random effects) was quantified using marginal and conditional determination coefficient, respectively.[17]

Independent determinants of tidal R/D were evaluated using multivariable linear mixed-effects modeling. A primary multivariable mixed-effects model was constructed with variables selected a priori based on physiological relevance and prior evidence. These included the following parameters treated as numerical continuous predictors: tidal volume adjusted to predicted body weight (Vt/PBW), PEEP, muscular pressure (P_{mus}), ΔPL_{dyn}, pendelluft, and reversible lung collapse.[18-23] To address potential confounding, baseline radiological pattern based on pulmonary infiltrates distribution (treated as categorical variable, focal vs nonfocal) and baseline respiratory system compliance (treated as numerical continuous variable) were also incorporated as fixed effects. A backward stepwise selection was applied to the primary model to reduce complexity and mitigate overfitting, and variables with $P < .15$ were retained (Table E2).[24] The final reduced model was refitted to identify independent determinants of tidal R/D. Additionally, coefficients of continuous numerical variables were standardized to compare the relative magnitude of the effect of each variable on tidal R/D (see Supplementary Material).

We performed additional exploratory analysis. We evaluated the ability of the end-expiratory PL ($PL_{End\text{-}Exp}$), airway occlusion pressure at 100 ms ($P_{0.1}$), P_{mus}, and ΔPL_{dyn} to identify risk of atelectrauma (defined as tidal R/D ≥ 10.0%) through receiver operator curves (ROC) derived from generalized binomial mixed models, incorporating patient-specific random effects.[25,26] The area under the curve (AUC) of each predictor was obtained from the marginal predictions derived from fixed effects. To improve clinical interpretation, we assessed the discriminative power of different clinical cutoffs for each of variable. Sensitivity, specificity, AUC, and Youden index of each cutoff are reported. We also repeated the analysis using alternative tidal R/D percentages (5%, 14.3%, and 20%) to classify patients at risk.

Finally, the predicted probability of hospital discharge and weaning was assessed using Cox regression model, adjusted by age and clinical PEEP level, stratifying patients into high and low tidal R/D groups. For this analysis, tidal R/D values measured at each randomized PEEP were averaged per patient, and the population was dichotomized into high tidal R/D group (≥14.3%) or low tidal R/D group (<14.3%) based on the median value. A 2-tailed *P*-value less than .05 was deemed statistically significant (R software version 4.2.2).

Results

Study population

We included 29 patients (Table 1). The patients were aged 64.0 ± 14.0 years, and most of them had primary ARDS ($n = 22$; 75.8%) and nonfocal distribution of pulmonary infiltrates ($n = 17$; 58.6%). At inclusion, patients had been intubated for 6.0 (IQR 3.5-9.5) days and had spent 3.0 (IQR 1.0-5.0) days on PSV. The mean clinical pressure support (PS) level was 9.0 ± 2.0 cmH_2O, PEEP was 9.2 ± 3.0 cmH_2O, and FI_{O2} was 0.45 (IQR 0.40-0.50). PaO_2/FI_{O2} was 206 ± 54, and $PaCO_2$ was 45 ± 6.3 mmHg.

During the randomized study phases, the median PEEP assigned at $PEEP_{EIT}$ and $PEEP_{TABLE}$ was 10.0 (IQR 8.0-12.0) cmH_2O

Table 1 Characteristics of the patients.

Variable	Value ($n = 29$)
Age, mean ± SD, y	64.0 ± 14.0
Gender, No. (%), M/F	23 (79.3)/6 (20.7)
BMI, mean ± SD, kg/m²	27.8 ± 4.9
SAPS II score at admission, median (Q1-Q3)	41.0 (34.0-46.5)
SOFA points, median (Q1-Q3)	5.0 (3.0-7.0)
Characteristics of ARDS at inclusion	
Days since intubation, median (Q1-Q3)	6.0 (3.5-9.5)
Days since switch to PSV, median (Q1-Q3)	3.0 (1.0-5.0)
Infectious etiology, No. (%)	21 (72.4)
Primary ARDS, No. (%)	22 (75.8)
Focal/nonfocal ARDS, No. (%)	12 (41.4)/17 (58.6)
ARDS category, No. (%), mild/moderate/severe	18 (62)/10 (35)/1 (3.0)
Arterial pH, mean ± SD	7.44 ± 0.05
Pa_{CO2}, mean ± SD, mmHg	45.0 ± 6.3
Pa_{O2}/FI_{O2}, mean ± SD, mmHg	206 ± 54
Outcomes	
Successful weaning by day 60, No. (%)	22 (76)
ICU length of stay, median (Q1-Q3)	16.0 (12.0-28.0)
Hospital length of stay, median (Q1-Q3)	32.0 (24.0-55.0)
Hospital mortality, No. (%)	6 (20.6)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; PSV, pressure support ventilation; Q, quartile; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

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and 8.0 (IQR 5.0-10.0) cmH_2O, respectively. Additional parameters collected during the 2 randomized PEEP levels are detailed in Table S1.

Localization and quantification of tidal R/D

As illustrated in Figure 1, most of tidal R/D occurred in the middle and dorsal parts of the lungs. This regional distribution remained consistent during $PEEP_{EIT}$ and $PEEP_{TABLE}$ phase (Figure E2).

Analyzing data from both randomized PEEP levels together, the median tidal R/D was 14.3% (IQR 5.1-27.7). Tidal R/D magnitude was lower when PEEP was set according to EIT method vs PEEP/FiO_2 table (11.3% [IQR 4.8-20.5] vs 21.9% [IQR 6.8-31.7]; $P = .008$) (Figure 2). The reduction of tidal R/D when the assigned PEEP level was changed from $PEEP_{TABLE}$ to $PEEP_{EIT}$ correlated with decreases in pendelluft and lung collapse (Figure E2).

Variables associated with tidal R/D

Table 2 summarizes the bivariate unadjusted associations between tidal R/D, ventilator settings, monitoring, and patient baseline characteristic, based on mixed-effects models combining data from $PEEP_{EIT}$ and $PEEP_{TABLE}$.

End-expiratory lung inflation and lung compliance

Ventilation at lower PEEP levels and more negative $PL_{End\text{-}Exp}$ led to higher fractions of tidal R/D (Figure 3A). Higher tidal R/D also correlated with larger amounts of reversible lung collapse (Figure 3B) and lower dynamic lung compliance (CL_{dyn}), but it was better associated with collapse localized in the dependent regions (ie, dorsal CL_{dyn}) than with nondependent collapse (Figure E3).

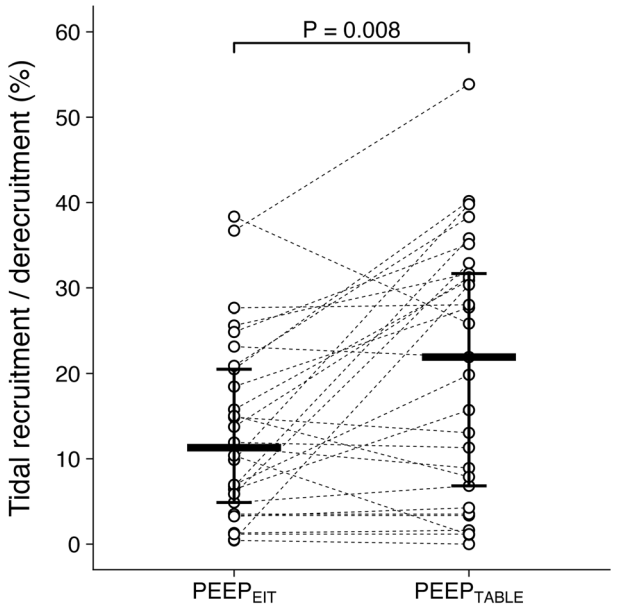


Figure 2 Comparison of tidal recruitment/derecruitment during both randomized positive end-expiratory pressure (PEEP) levels (electrical impedance tomography PEEP [$PEEP_{EIT}$] and PEEP/FI_{O2} table [$PEEP_{TABLE}$]). Points and dotted lines show the individual behavior of each patient. The horizontal and vertical black lines denote the median (25th-75th quantiles) at each randomized PEEP, respectively.

Respiratory drive, effort, and lung stress

Higher respiratory drive ($P_{0.1}$) correlated with more tidal R/D (Figure E4). Similarly, stronger inspiratory effort (P_{mus}, ΔP_{es}, and ΔP_{occ}) and work of breathing (PTP_{mus} per minute) correlated with increased tidal R/D (Figure E5). Higher elastic end-inspiratory pressure was associated with a reduction of tidal R/D, likely because changes in end-inspiratory pressure followed increase of end-expiratory pressure (Figure E6): tidal R/D decreased at increasing plateau pressure, but this association was stronger with higher static $PL_{End\text{-}Insp}$ (Figure E7). Tidal R/D also increased with higher dynamic lung stress (ΔPL_{dyn} and ΔPL_{stat}), but this association was not related to the set PS level. In fact, a greater contribution of respiratory effort to the total dynamic lung stress (ie, $\Delta P_{es}/\Delta PL_{dyn}$ relationship) led to larger tidal R/D. The difference between ΔPL_{dyn} and ΔPL_{stat}—a variable suggested to reflect heterogeneity of lung stress distribution across dependent and nondependent regions[21, 27]—positively correlated with tidal R/D.

Ventilation heterogeneity and breathing pattern

Increased tidal R/D was associated with more heterogeneous intrapulmonary distribution of ventilation (global and local inhomogeneity index). No association was found between pendelluft and tidal R/D. Classical breathing pattern parameters, including Vt/PBW, respiratory rate, and inspiration to expiration ratio, showed no association with tidal R/D (Figure E8).

Baseline patients characteristics

Patients with nonfocal distribution of pulmonary infiltrates ($n = 17$) showed significantly higher values of tidal R/D compared with those with focal lung morphology ($n = 12$) (Figure 3C). The remaining patients' characteristics were not associated with tidal R/D (Table 2).

Independent determinants of tidal R/D

Adjusted multivariable analysis

After applying the stepwise backward regression to the full primary model, the variables retained in the final model as independent determinants of tidal R/D were $PL_{End\text{-}Exp}$, reversible lung collapse, ΔPL_{dyn}, and lung morphology (Table E3).

In the final model, $PL_{End\text{-}Exp}$ (coefficient = −0.12; 95% CI, −0.22 to −0.02), reversible lung collapse (coefficient = 0.07; 95% CI, 0.03-1.10), and morphological distribution of lung infiltrates (coefficient = 1.49; 95% CI, 0.61-2.36) exerted independent effect on tidal R/D, whereas ΔPL_{dyn} did not (coefficient = 0.06; 95% CI, −0.06 to 0.14) (Table 3).

When coefficients of the 3 numerical continuous variables ($PL_{End\text{-}Exp}$, lung collapse, and ΔPL_{dyn}) were standardized to allow comparison, reversible collapse exerted the largest effect on tidal R/D (Figure 4).

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Table 2 Bivariate associations between tidal recruitment/derecruitment, ventilator settings, monitoring, and baseline physiological variables.

Variable	β (95% CI)	R^2m	R^2c	*P*-value
End-expiratory lung inflation and lung compliance				
PEEP level	−2.24 (−3.09 to 1.35)	0.17	0.74	**<.001**
$PL_{End-Exp}$ [a]	−2.46 (−3.46 to 1.46)	0.54	0.73	**<.001**
Reversible lung collapse[a]	0.84 (0.57-1.11)	0.27	0.78	**<.001**
CL_{dyn}	−0.50 (−0.85 to 0.15)	0.20	0.73	**.002**
Dependent CL_{dyn}	−1.18 (−2.08 to 0.35)	0.31	0.63	**<.001**
Nondependent CL_{dyn}	−0.45 (−0.89 to 0.02)	0.09	0.63	**.048**
Respiratory drive, inspiratory effort and lung stress				
Plateau pressure	−1.22 (−2.21 to 0.11)	0.22	0.87	**<.001**
Static $PL_{End-Insp}$	−1.60 (−2.58 to 0.61)	0.29	0.72	**<.001**
ΔPL_{dyn}	0.90 (0.20-1.61)	0.15	0.67	**.009**
ΔPL_{stat}	1.35 (0.02-0.72)	0.11	0.57	**.040**
Pressure support level	0.05 (−1.93 to 2.06)	0.002	0.57	0.797
$P_{0.1}$	6.28 (2.80-9.83)	0.33	0.75	**.001**
P_{mus}	0.95 (0.29-1.63)	0.14	0.66	**.009**
ΔP_{es}	−1.02 (−1.75 to 0.30)	0.16	0.68	**.006**
ΔP_{occ}	−0.56 (−1.15 to 0.05)	0.15	0.62	**.035**
PTP_{mus} per minute	0.08 (0.02-0.14)	0.09	0.66	**.021**
$\Delta P_{es}/\Delta PL_{dyn}$	0.28 (0.03-0.59)	0.14	0.64	**.028**
$\Delta PL_{dyn} - \Delta PL_{stat}$ difference	0.87 (0.01-1.80)	0.10	0.65	**.032**
Ventilation heterogeneity and breathing pattern				
Global inhomogeneity index	0.38 (0.01-0.86)	0.06	0.62	**.050**
Local inhomogeneity index	2.06 (0.63-3.49)	0.15	0.61	**.011**
Pendelluft magnitude	0.02 (−0.05 to 0.10)	0.01	0.61	.462
Vt/PBW	−0.03 (−2.34 to 2.19)	0.001	0.56	.857
Respiratory rate	0.01 (−0.57 to 0.61)	0.001	0.57	.878
I:E ratio	−3.77 (−20.9 to 12.9)	0.001	0.55	.877
Baseline patients characteristics				
Lung morphology, nonfocal	1.61 (0.57-2.65)	0.19	0.57	**.005**
Pa_{O2}/FI_{O2} > 200 mmHg	0.96 (−023 to 2.16)	0.06	0.57	.126
Nonrespiratory SOFA	−0.03 (−0.30 to 0.23)	0.02	0.57	.791
Body mass index	0.003 (−0.11 to 0.12)	0.001	0.57	.957
Static respiratory compliance	−0.03 (−0.01 to 0.04)	0.06	0.63	.089

Abbreviations: β, beta coefficient; CL_{dyn}, dynamic lung compliance; I:E, inspiration: expiration; $P_{0.1}$, airway occlusion pressure during the first 100 ms; ΔPL_{dyn}, dynamic driving transpulmonary pressure; ΔP_{es}, esophageal pressure swing; ΔP_{occ}, airway occlusion pressure; ΔPL_{stat}, static driving transpulmonary pressure; PEEP, positive end-expiratory pressure; $PL_{End-Exp}$, end-expiratory transpulmonary pressure; $PL_{End-Insp}$, end-inspiratory transpulmonary pressure; P_{mus}, muscular pressure; PTP_{mus}, muscular pressure-time product per minute; R^2c, conditional determination coefficient; R^2m, marginal determination coefficient; SOFA, sequential organ failure assessment; Vt/PBW, tidal volume adjusted to predicted body weight.
Bold values indicate statistical significance.
[a]Coefficients are reported with the dependent variable in original scale. In the remaining variables, the dependent variable was transformed to the square root to reach model's assumptions.

Exploratory outcomes

Respiratory monitoring to detect atelectrauma risk

The discriminative performance of different clinical cutoffs of bedside monitoring variables for identifying patients at risk of atelectrauma (defined as a tidal R/D ≥ 10%) is summarized in Table 4. Overall, the ROC curves demonstrated a reasonable predictive capacity, with $PL_{End-Exp}$ and $P_{0.1}$ showing the strongest diagnostic performance. Additional analyses using alternative tidal R/D thresholds (≥5%, ≥14.3%, and ≥20%) to define atelectrauma risk are presented in Table E5.

Tidal R/D and clinical outcomes

Patients in the high tidal R/D group ($n = 14$)—that is, those with a mean tidal R/D ≥ 14.3% calculated as the average of R/D values observed at $PEEP_{EIT}$ and $PEEP_{TABLE}$—had a median magnitude of tidal R/D of 27.7% (IQR 20.8-35.3). The low tidal R/D group ($n = 15$) exhibited a median value of tidal R/D of 5.6% (IQR 2.0-11.3).

After adjusting for age and PEEP level at enrollment, the Cox regression models showed that patients in the high tidal R/D group had lower probabilities of being weaned from mechanical ventilation (hazard ratio [HR] = 0.39; 95% CI, 0.19-0.80; $P = .011$) (Figure E9) and discharged alive from the hospital (HR = 0.37; 95% CI, 0.18-0.76; $P = .006$) (Figure 5) compared with patients in the low tidal R/D group.

Discussion

This study describes key physiological determinants of tidal R/D assessed through EIT in ARDS patients undergoing assisted ventilation. Our main findings are (1) tidal R/D magnitude seems clinically relevant but highly variable among patients; (2) higher respiratory drive, effort, and dynamic lung stress increased tidal R/D, but this association did not remain significant after adjustment by confounders; (3) instead, the main physiological determinants of higher tidal R/D were higher reversible lung collapse, more negative $PL_{End-Exp}$, and nonfocal lung morphology; and (4)

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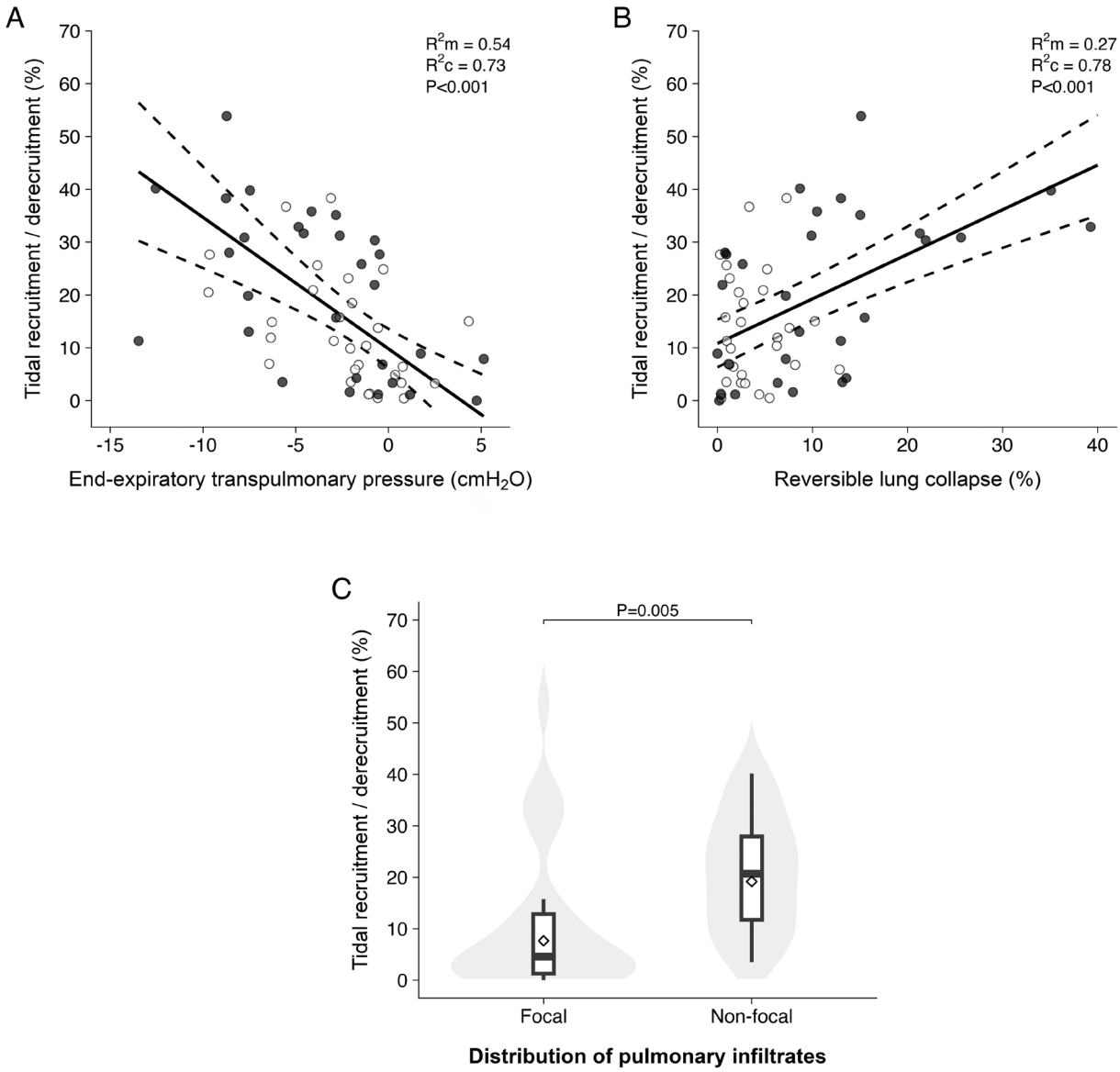


Figure 3 Association between tidal recruitment/derecruitment (R/D) with end-expiratory transpulmonary pressure (A), reversible lung collapse (B), and morphological distribution of pulmonary infiltrates (C). Black and white dots represent data collected at positive end-expiratory pressure/FI_{O2} table ($PEEP_{TABLE}$) and electrical impedance tomography PEEP ($PEEP_{EIT}$), respectively. In panel C, the box plots show the median and quantiles 25th-75th (nonfocal: 20.7% [IQR 11.7-27.9] vs focal: 4.6% [IQR 1.3-12-9]), and white diamonds show the mean value (nonfocal: 20.8% vs focal: 8.3%) of tidal R/D. Violins represent the density of tidal R/D values across patterns of pulmonary infiltrates distribution. Abbreviations: R^2c, conditional determination coefficient; R^2m, marginal determination coefficient.

Table 3 Multivariable mixed-effects regression showing independent determinant of tidal recruitment/derecruitment.

Variable	β coefficient	95% CI	*P*-value[a]
$PL_{End-Exp}$	−0.12	−0.22 to −0.02	**.035**
Reversible lung collapse	0.07	0.03-1.10	**<.001**
Lung morphology (nonfocal)	1.49	0.61-2.36	**.003**
ΔPL_{dyn}	0.06	−0.01 to 0.14	.109

Abbreviations: ΔPL_{dyn}, dynamic driving transpulmonary pressure; $PL_{End-Exp}$, end-expiratory transpulmonary pressure.
Bold values indicate statistical significance.
[a]In the multivariable model, the dependent variable tidal R/D has been transformed to the square-root to achieve model's assumptions. Beta coefficients are expressed in the transformed scale.

patients with higher tidal R/D exhibited lower chances of hospital discharge and weaning.

The pathophysiological implications of tidal R/D have been known for decades,[4,8,9,27-30] yet the physiology of tidal R/D in critically ill patients remains scarcely characterized during assisted ventilation, largely due to the technical challenges in measuring it. The bedside, dynamic, noninvasive, and radiation-free nature of EIT may offer advantages over other less feasible monitoring.[3,30-34]

Of note, the observed values of tidal R/D are higher than those previously reported. Liu et al.[10] reported R/D approximately 10% assessed by EIT in ARDS models during controlled ventilation. Nonetheless, the dynamics of tidal R/D may vary widely with the presence of respiratory effort. According to the solid-like behavior, pressure changes during spontaneous breathing (SB) are

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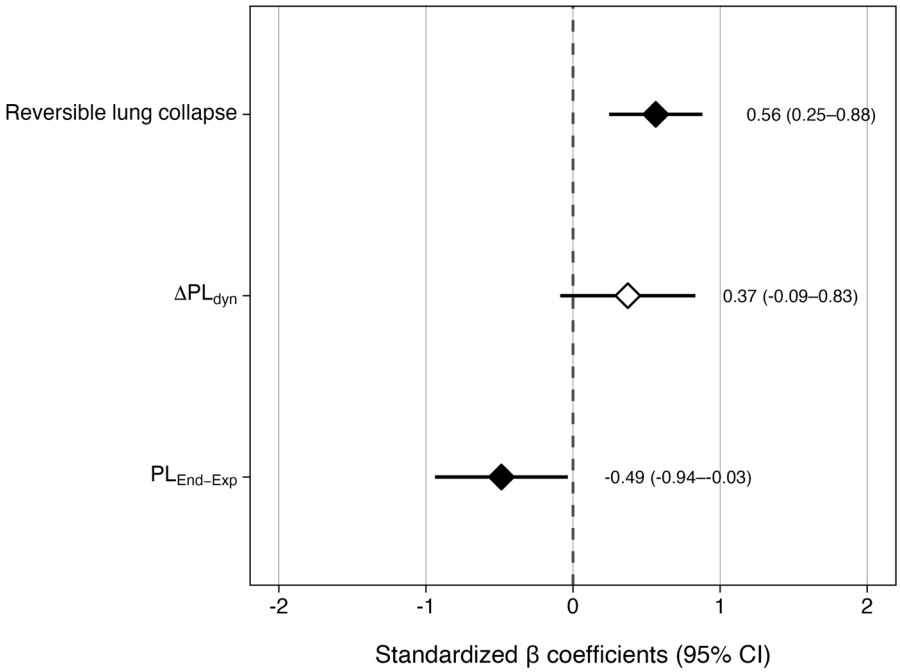


Figure 4 Forest plot of standardized coefficients (extracted from the final multivariable mixed-effects model) showing the association between end-expiratory transpulmonary pressure ($PL_{End-Exp;}$ $P = .035$), reversible lung collapse ($P < .001$), and dynamic driving transpulmonary pressure (ΔPL_{dyn}; $P = .108$) with tidal recruitment/derecruitment. The model is adjusted by lung morphology (focal–nonfocal), but it has been removed from the plot due to the categorical nature of the variable. Values of standardized coefficients are shown at the right of each diamond to allow comparison between the relative effect size of each one. Variables resulting statistically significant in the adjusted model ($P < .05$) are shown with filled black diamond.

Table 4 Discriminative power of different thresholds of bedside monitoring variables to identify tidal recruitment/derecruitment ≥ 10.0%.

	Cutoff value, cmH_2O	Sensitivity	Specificity	Youden index	AUC (95% CI)
$PL_{End-Exp}$	−2	0.74	0.78	0.53	0.84 (0.74-0.95)
	−1	0.83	0.57	0.39	—
	0	0.97	0.43	0.41	—
	1	0.97	0.22	0.19	—
	2	0.97	0.13	0.10	—
$P_{0.1}$	2	0,6	0,65	0,25	0.72 (0.58-0.85)
	3	0,31	0,91	0,23	—
	4	0,17	1.00	0,17	—
	5	0,09	1.00	0,09	—
	6	0,06	1.00	0,06	—
ΔPL_{dyn}	15	0.43	0.83	0.25	0.64 (0.49-0.78)
	20	0.26	0.91	0.17	—
	25	0.17	0.96	0.13	—
	30	0.03	1.00	0.03	—
	35	0.00	1.00	0.00	—
P_{mus}	10	0.51	0.65	0.17	0.67 (0.53-0.82)
	15	0.26	0.87	0.13	—
	20	0.14	1.00	0.14	—
	25	0.06	1.00	0.06	—
	30	0.03	1.00	0.03	—

Abbreviations: $P_{0.1}$, airway occlusion pressure during the first 100 ms; ΔPL_{dyn}, dynamic driving transpulmonary pressure; $PL_{End-Exp}$, end-expiratory transpulmonary pressure; P_{mus}, muscular pressure.
Dashes means that the test was not performed, only the general test is reported in the first line of each item.

concentrated in the dependent-middle lung regions, where more collapse is found and most tidal R/D occurs.[19] Contrarily, during passive ventilation, positive pressure is predominantly applied on the nondependent baby lung, where collapse and tidal R/D are minimal.[34] In fact, tidal R/D was mainly driven by respiratory effort rather than by the pressure support in the bivariate analysis. In another study, tidal R/D ranged from 6% to 16%, as measured by dynamic CT.[18] Importantly, $PL_{End-Exp}$ was highly positive in that study (+4.2 cmH_2O and +4.8 cmH_2O in mild and severe ARDS animal models) compared with values as negative as −10 to −5 cmH_2O in some of our patients. Furthermore, animals had considerably lower effort (ΔP_{es}: 0.4-6 cmH_2O) than the patients enrolled in our study

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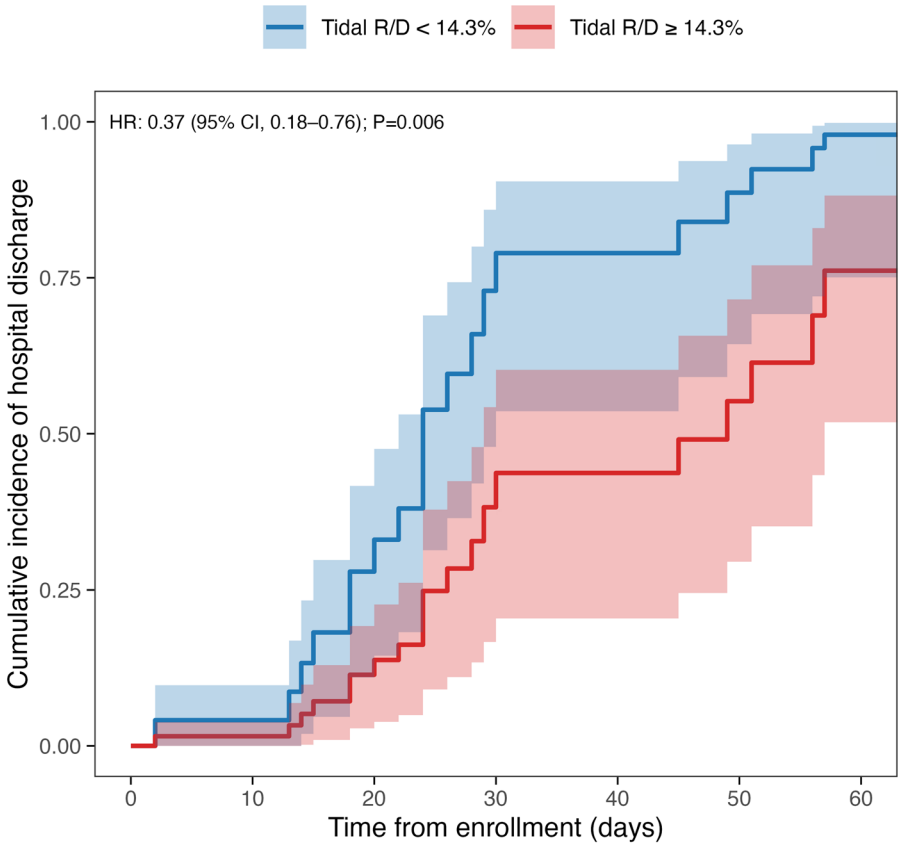


Figure 5 Adjusted cumulative incidence of hospital discharge in patients with low and high average tidal recruitment/derecruitment (R/D). Abbreviation: HR, hazard ratio.

(ΔP_{es}: 3-17 cmH_2O). Interestingly, it has been observed that tidal R/D values may be close to those observed in our cohort (approximately 15%) when $PL_{End\text{-}Exp}$ is clearly negative.[16]

In highly recruitable ARDS models, Yoshida et al.[18] observed that excessive respiratory effort aggravated lung injury partly mediated by tidal R/D. We showed a positive association of respiratory drive, effort, and lung stress with tidal R/D, but this correlation did not remain independent after adjustments. Physiologically, tidal R/D is feasible at increasing lung distending pressures even in mild ARDS.[35] Nonetheless, tidal R/D is expected to occur only when 3 conditions present simultaneously: (1) regional $PL_{End\text{-}Exp}$ lower than alveolar closing pressure, leading to expiratory collapse; (2) potential for lung recruitment during inspiration; and (3) inspiratory transalveolar pressure (alveolar–pleural pressure) higher than alveolar opening pressure.

Contrary to our findings, previous studies have reported that Vt is a central determinant of cyclic R/D.[24,34] This association is reasonable, however, when different Vt are compared under the same PEEP level. Halter et al.[33] observed that increasing Vt from 6 to 12 ml/kg did not increase tidal R/D when PEEP was contemporarily increased from 5 to 10 cmH_2O. In our study, PEEP was actively modified, and changes in Vt were largely secondary to PEEP-induced changes in lung compliance. Under these conditions, lower tidal R/D may occur despite higher Vt, because increased PEEP reduces expiratory derecruitment while simultaneously improving compliance, thereby allowing patients to breathe at higher Vt. Furthermore, Vt was within protective limits in most of the cases, precluding us from exploring the impact of more extreme Vt on tidal R/D.

Although pendelluft magnitude was not independently associated with tidal R/D in our study population, the reduction of pendelluft did correlate with lower tidal R/D when PEEP was adjusted according to the $PEEP_{EIT}$ strategy. This response was mainly observed in patients where $PEEP_{EIT}$ assigned higher PEEP and reduced lung collapse. This is consistent with findings reported by Morais et al.[22] in which higher PEEP appropriately selected in more recruitable patients reduced lung collapse and decreased pendelluft and tidal R/D. Also, these results suggest that changes in pendelluft, rather than its absolute value, when PEEP levels are modified may be more physiologically informative depending on the effects of PEEP on respiratory mechanics. The lack of a baseline association may be explained by the presence of other phenomena beyond reopening collapsed regions contributing to regional gas dyssynchrony and pendelluft especially at low PEEP levels (such as increased distal resistance).[20]

One of our most physiologically sound results is close association between more negative values of $PL_{End\text{-}Exp}$, higher reversible lung collapse, and tidal R/D. Notably, correlations between $PL_{End\text{-}Exp}$, collapse, and tidal R/D were independent from PEEP settings, underscoring the need to appropriately target PEEP during assisted ventilation to counterbalance pleural and superimposed pressures that lead to alveolar collapse.[31,32,36]

Caironi et al.[31] previously reported that tidal R/D was relevant only in patients with diffuse infiltrates distribution. Similarly, we observed that patients with nonfocal ARDS had significantly higher tidal R/D, which may potentially inform in the future about the decision to switch ARDS patients to assisted ventilation. While tidal R/D could be detected by lung hysteresis during controlled

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ventilation,[37,38] EIT may be necessary to identify it during assisted spontaneous breathing.

Tidal R/D seems a potential predictor of outcome, likely because the mean value between the 2 randomized phases conflates a mix of disease severity, treatment response, and risk of additional injury by ventilation. However, these results must be interpreted with great caution because of the physiological nature of our study. Also, the small sample size precluded us from adjusting for other potential confounders. Additionally, other factors such as PEEP settings in the following days could have modified the patient's trajectories and influenced outcome. These findings provide a rationale and conceptual framework for future interventional studies designed to determine whether strategies such as adjusting PEEP to reduce tidal R/D are associated with improved clinical outcomes.

Limitations

First, we did not validate of our EIT-based measure of tidal R/D with a reference technique (eg, CT-scan). This would have been clinically unpracticable considering the associated risks of exposing patients to those interventions. Albeit preliminary and hypothesis-generating, our findings are supported by a strong physiological rational, which encourage further investigation and warrant confirmation in future research. Second, the thresholds selected to define ventilation and aeration were empirical. For this reason, we performed multiple sensitivity analyses combining different thresholds to describe how this selection modified the analysis. Future studies should evaluate how different thresholds correlate with a gold standard technique to define which aeration/ventilation combination must be adopted in future investigation. Third, our cohort included patients in the recovering phase of ARDS. Although tidal R/D could be even more relevant in earlier stages, the results may not be fully applicable to more advanced phases of ARDS in which the magnitude of tidal R/D and association with outcomes could differ. Fourth, although tidal R/D and reversible lung collapse were correlated, their absolute values did not perfectly align in many patients. Because tidal R/D increases compliance even in the absence of stable recruitment,[37-41] estimates of recruitability by EIT based on compliance changes could be poorly correlated, especially in spontaneously breathing patients with higher respiratory drive. Also, lung collapse measured during a decremental PEEP trial could underestimate the loss of lung volume that occurs after 20 minutes with unchanged ventilation settings. Finally, lung morphology was categorized using chest X-rays in nearly half of patients, and only 2 independent reviewers classified the patients; thus the possibility of misclassification cannot be ruled out.

Conclusion

In patients with ARDS undergoing PSV, the magnitude of tidal R/D measured by EIT is highly variable and strongly associated with higher reversible lung collapse, more negative $PL_{End\text{-}Exp}$ values, and diffuse distribution of lung infiltrates. Our results may be a step forward toward a better understanding of P-SILI mechanisms, allowing a more precise titration of protective assisted ventilation.

Author contributions

Substantial contributions to the conception or design of the work: J.P., M.L., and T.M. Acquisition, analysis, or interpretation of data for the work: all authors. Drafting the work or revising it critically for important intellectual content: all authors. Final approval of the version submitted for publication: all authors. Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material.

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