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Volume Delivered During Recruitment Maneuver Predicts Lung Stress in Acute Respiratory Distress Syndrome*

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Objective: Global lung stress varies considerably with low tidal volume ventilation for acute respiratory distress syndrome. High stress despite low tidal volumes may worsen lung injury and increase risk of death. No widely available parameter exists to assess global lung stress. We aimed to determine whether the volume delivered during a recruitment maneuver \( V_{RM} \) is inversely associated with lung stress and mortality in acute respiratory distress syndrome.

Design: Substudy of an acute respiratory distress syndrome clinical trial on esophageal pressure-guided positive end-expiratory pressure titration.

Setting: U.S. academic medical center.

Patients: Forty-two patients with acute respiratory distress syndrome in whom airflow, airway pressure, and esophageal pressure were recorded during the recruitment maneuver.

Interventions: A single recruitment maneuver was performed before initiating protocol-directed ventilator management. Recruitment maneuvers consisted of a 30-second breath hold at 40 cm H\(_2\)O airway pressure under heavy sedation or paralysis. \( V_{RM} \) was calculated by integrating the flow-time waveform during the maneuver. End-inspiratory stress was defined as the transpulmonary (airway minus esophageal) pressure during end-inspiratory pause of a tidal breath and tidal stress as the transpulmonary pressure difference between end-inspiratory and end-expiratory pauses.

Measurements and Main Results: \( V_{RM} \) ranged between 7.4 and 34.7 mL/kg predicted body weight. Lower \( V_{RM} \) predicted high end-inspiratory and tidal lung stress (end-inspiratory: \( \beta = -0.449; 95\%\ CI, -0.664 \) to \(-0.234; p < 0.001\); tidal: \( \beta = -0.267; 95\%\ CI, -0.423 \) to \(-0.111; p = 0.001\)). After adjusting for \( Pao_2/Fio_2 \) and other driving pressure, tidal volume, or plateau pressure and positive end-expiratory pressure, \( V_{RM} \) remained independently associated with both end-inspiratory and tidal stress. In unadjusted analysis, low \( V_{RM} \) predicted increased risk of death (odds ratio, 0.85; 95\% CI, 0.72–1.00; \( p = 0.026\)). \( V_{RM} \) remained significantly associated with mortality after adjusting for study arm (odds ratio, 0.84; 95\% CI, 0.71–1.00; \( p = 0.022\)).

Conclusions: Low \( V_{RM} \) independently predicts high lung stress and may predict risk of death in patients with acute respiratory distress syndrome. (Crit Care Med 2016; 44:91–99)
In patients with acute respiratory distress syndrome (ARDS), the volume of aerated lung is substantially reduced due to alveolar edema and atelectasis (1). Heterogeneous involvement is a key pathologic feature, in which areas of well-aerated lung are adjacent to atelectatic but potentially recruitable lung as well as collapsed, nonrecruitable lung (2–4). Aerated lung regions maintain normal specific compliance (compliance per volume of tissue), whereas in nonaerated regions, specific compliance is considerably lower (5). Thus, regional distension may vary considerably with tidal ventilation (6, 7).

High tidal volumes contribute to lung injury in part through cyclic overdistension of well-aerated lung regions, which may constitute a relatively small fraction of the lung in patients with ARDS. This smaller “baby lung,” so-called for its reduced aerated volume available for ventilation, requires smaller tidal volumes than would be needed in healthy lungs to prevent regional overdistension (8, 9). Indeed, the discovery of this baby lung phenomenon in the 1980s (2–4) inspired the landmark clinical trials testing low tidal volume ventilation for ARDS that inform current standard of care (9–12).

Regional overdistension from high tidal volumes relative to baby lung size leads directly to alveolar epithelial and capillary endothelial cell junction breaks, basement membrane detachment, edema formation, and systemic inflammation (13). Due to individual differences in baby lung size, lung stress and strain, and thus risk of ventilator-induced lung injury (VILI), may vary considerably between patients with ARDS receiving the same low tidal volume strategy (8, 9, 14).

To date, no routinely available clinical parameter exists to assess reliably global lung stress or baby lung size. Measurement of global lung stress requires esophageal manometry to estimate pleural pressure and calculate transpulmonary pressure (airway minus pleural pressure) (15). Global strain measurements have been performed experimentally with quantitative chest CT or helium dilution to measure lung volumes (1, 14, 16).

Recruitment maneuvers (RMs), typically performed as a continuous positive airway pressure of 30–50 cm H₂O sustained over 30–40 seconds, attempt to open atelectatic but recruitable lung units. Although RMs transiently may increase aerated lung volume, improve gas exchange, and minimize lung stress during tidal ventilation, the therapeutic role for RMs is unclear (17). We instead considered RMs for their potential to measure the maximum insufflation volume achievable with clinically prudent continuous airway pressures. We reasoned that this volume increase during a recruitment maneuver ($V_{RM}$), when measured beginning from the resting lung volume at positive end-expiratory pressure (PEEP), is analogous to the inspiratory capacity of the baby lung. We hypothesized that $V_{RM}$ is inversely associated with global lung stress in patients with ARDS, thus identifying patients at heightened risk of VILI and death.

### METHODS

#### Population

A substudy of the EPVent1 ARDS clinical trial (18) was performed. EPVent1 was a single-center randomized trial of PEEP titration guided by esophageal pressures versus the ARDS Network PEEP-Fio₂ titration table. The trial's primary analysis demonstrated significantly lower mortality with esophageal pressure-guided PEEP titration after adjusting for baseline illness severity (Acute Physiology and Chronic Health Evaluation [APACHE] II score). Eligibility criteria and results of the primary trial are published elsewhere (18).

All trial participants with airflow, airway pressure, and esophageal pressure recorded during the protocol-directed RM were eligible for the present study. Patients were excluded if a large air leak occurred during the RM. The hospital institutional review board approved the study under the original trial protocol, for which informed consent was obtained for all participants.

#### Study Procedures and Measurements

A single RM was performed on all trial participants before initiating protocol-directed ventilator management. RMs consisted of a 30-second breath hold at 40 cm H₂O airway pressure under heavy sedation or paralysis. Airflow was measured via a Fleisch pneumotachograph placed in-line between the endotracheal tube and ventilator circuit. Airway pressure was measured via a separate pressure transducer. Pleural pressure was estimated by measuring esophageal pressure via a thin-walled balloon catheter as previously described (18).

Airflow, airway pressure, and esophageal pressure were recorded continuously during the maneuver. The flow-time waveform was integrated to calculate volume (Fig. 1). When the RM was initiated end-expiration (zero flow), flow was integrated for the duration of the RM to calculate $V_{RM}$. When the RM was initiated during tidal insufflation or exhalation (non-zero flow), $V_{RM}$ was calculated by integrating flow beginning from end-expiration of the preceding breath. In both cases, the preset PEEP level represents the starting airway pressure immediately prior to the RM, which had been set at the clinician’s discretion. To account for between-patient differences in healthy lung size, $V_{RM}$ was scaled to predicted body weight (PBW) (9). For comparison, predicted inspiratory capacity was calculated using reference equations recommended by the American Thoracic and European Respiratory Societies (19, 20).

#### Determination of Global Lung Stress and Tidal Volume-to-$V_{RM}$ Ratio

Stress refers to the internal forces per unit area that balance an external load. Transpulmonary pressure is the pertinent distending pressure of the lung (21). It represents global lung stress when considering the load placed on the lung by insufflation. Global lung stress was quantified in two ways, as end-inspiratory stress and tidal stress. End-inspiratory stress was defined as the transpulmonary pressure during end-inspiratory pause of a tidal breath (end-inspiratory stress = end-inspiratory transpulmonary pressure). Tidal stress was defined as the transpulmonary...
pressure difference between end-inspiratory and end-expiratory pauses during a tidal breath (tidal stress = change in transpulmonary pressure) \( (14, 15) \). Unlike tidal stress, end-inspiratory stress additionally accounts for the stress already present before tidal inflation—the stress on the lung from its end-expiratory volume at PEEP—which may differ substantially depending on the preset PEEP, chest wall characteristics, and ARDS severity \( (15) \).

Strain refers to the deformation of an object relative to its resting size or shape. The ideal resting conformation of the ARDS lung is unknown. Therefore, to assess relative lung deformation, we instead considered the tidal volume-to-V_\text{RM} ratio \( \frac{V_T}{V_\text{RM}} \). \( V_\text{RM} \) was chosen as the reference volume because it represents the maximum insufflation volume achievable under clinically prudent conditions (maintaining a continuous airway pressure of 40 cm H_2O during the RM) beginning from the resting lung volume at PEEP. Therefore, \( \frac{V_T}{V_\text{RM}} \) as defined here represents the proportion of maximum insufflation volume delivered during tidal breaths.

### Statistical Analysis

To compare baseline characteristics, patients were grouped as having \( V_\text{RM} \) above or below the median \( V_\text{RM} \) and compared using \( t \) test, Fisher exact test, or analysis of variance (ANOVA) as appropriate. \( P_{A0}/F_{I02} \) was handled as a categorical variable following the Berlin criteria for ARDS severity (mild, \( 200 < P_{A0}/F_{I02} \leq 300 \); moderate, \( 100 < P_{A0}/F_{I02} \leq 200 \); severe, \( P_{A0}/F_{I02} \leq 100 \) \( (22) \). The association between \( V_\text{RM} \) and predicted inspiratory capacity was evaluated using a paired \( t \) test. Pearson correlation was used to inspect the association between compliance and each of \( V_\text{RM} \), plateau pressure, and driving pressure (airway plateau pressure minus PEEP) \( (23) \). Linear regression models were developed to test the association between lung stress and each of the following: \( V_\text{RM} \), plateau pressure, driving pressure, and tidal volume per PBW. Simple linear regression was performed first without adjustment for covariates. Multiple linear regression then was used to determine whether \( V_\text{RM} \) added predictive value over currently used surrogates for lung stress. \( V_\text{RM} \) was entered into multivariable models with \( P_{A0}/F_{I02} \) and either driving pressure, tidal volume per PBW, or plateau pressure and PEEP. Simple linear regression also was used to evaluate the association between \( \frac{V_T}{V_\text{RM}} \) and lung stress.

Logistic regression models were used to compare the association between \( V_\text{RM} \) and 28-day mortality. First, univariate logistic regression was performed. Study arm treatment assignment was then forced into the model for face validity.

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**Figure 1.** Depiction of the calculation of \( V_\text{RM} \). The recruitment maneuver (RM) entailed a 30-s breath hold at 40 cm H_2O airway pressure under heavy sedation or paralysis. The preset positive end-expiratory pressure level represents the starting airway pressure, with associated resting end-expiratory lung volume, immediately prior to the RM. Airflow was recorded continuously during the RM via an inline Fleisch pneumotachograph. The flow-time waveform was integrated over the duration of the RM (shaded area under the curve) to calculate the insufflation volume, \( V_\text{RM} \). \( V_\text{RM} \) = volume delivered during a recruitment maneuver.
Additional multivariable logistic regression analyses were not performed to avoid overfitting data given the limited sample size and observed event rate. The likelihood ratio test was used for maximum statistical power to compare regression coefficients of nested models. For all analyses, statistical significance was determined using a two-sided p value threshold of 0.05.

RESULTS
Sixty-one participants were enrolled in the clinical trial, of which 49 had airflow, airway pressure, and esophageal pressure waveforms recorded during the RM. Seven recordings exhibited evidence of air leak and were excluded. Thus, 42 participants were included in this study, of which 32 (76.2%) survived to day 28. Excluded patients had higher end-inspiratory and end-expiratory transpulmonary pressures (end-inspiratory: 11 ± 6 vs 7 ± 5 cm H2O, p = 0.027; end-expiratory: 0 ± 5 vs –3 ± 5 cm H2O, p = 0.046), but did not differ significantly by other baseline characteristics nor 28-day mortality (Table E1, Supplemental Digital Content 1, http://links.lww.com/CCM/B440).

RM Characteristics
Mean $V_{RM}$ was 16.6 ± 6.2 mL/kg PBW (1,097 ± 435 mL) and ranged from a minimum of 7.4 mL/kg PBW (369 mL) to maximum of 34.7 mL/kg PBW (2,160 mL). $V_{RM}$ was significantly lower than predicted inspiratory capacity (mean difference, 29.5 ± 8.6 mL/kg PBW; p < 0.001) (Fig. 2) and did not correlate with predicted inspiratory capacity (r = –0.075; p = 0.638). Peak transpulmonary pressure during the RM was 21 ± 7 cm H2O.

![Figure 2. $V_{RM}$ and predicted inspiratory capacity. Box plots illustrate the median and interquartile range (boxes), mean (diamond), and maximum and minimum values (whiskers). $V_{RM}$ was significantly lower than predicted inspiratory capacity (mean difference, 29.5 ± 8.6 mL/kg predicted body weight [PBW]; p < 0.001). When measured beginning from resting lung volume at positive end-expiratory pressure, $V_{RM}$ is analogous to the inspiratory capacity of the acute respiratory distress syndrome baby lung. $V_{RM}$ = volume delivered during a recruitment maneuver.](image)

$V_{RM}$ and Compliance
$V_{RM}$ correlated strongly with lung compliance (r = 0.572; p < 0.001) and moderately with respiratory system compliance (r = 0.469; p = 0.002). $V_{RM}$ was not significantly correlated with chest wall compliance (r = –0.190; p = 0.233).

Plateau pressure correlated weakly with lung compliance (r = –0.359; p = 0.020) and moderately with respiratory system compliance (r = –0.469; p = 0.002) but was not associated with chest wall compliance (r = 0.047; p = 0.772). In contrast, driving pressure correlated neither with lung (r = –0.182; p = 0.247) nor chest wall compliance (r = 0.035; p = 0.827), although it was significantly correlated with respiratory system compliance (r = –0.393; p = 0.010).

$V_{RM}$ and Global Lung Stress
In univariate analysis, lower $V_{RM}$ per PBW was associated with higher end-inspiratory lung stress ($\beta$ = –0.449; 95% CI, –0.664 to –0.234; p < 0.001) (Fig. 3). Higher plateau pressure also was associated with higher end-inspiratory stress in univariate analysis ($\beta$ = 0.565; 95% CI, 0.325–0.805; p < 0.001). Neither tidal volume per PBW, driving pressure, nor Pao2/Fio2 was significantly associated with end-inspiratory stress (tidal volume $\beta$ = 0.253; 95% CI, –0.880 to 1.387; p = 0.654; driving pressure $\beta$ = 0.394; 95% CI, –0.019 to 0.807; p = 0.061; Pao2/Fio2 ANOVA $p = 0.444$)

In a multivariable model including $V_{RM}$, driving pressure, and Pao2/Fio2, $V_{RM}$ remained significantly associated with end-inspiratory stress ($\beta$ = –0.428; 95% CI, –0.657 to –0.199; p < 0.001), while driving pressure was not significantly associated with end-inspiratory stress. In a similar model replacing driving pressure with plateau airway pressure and PEEP as separate terms, both $V_{RM}$ and plateau pressure were significantly associated with end-inspiratory stress. In the model, the association between $V_{RM}$ and end-inspiratory stress remained significant ($\beta$ = –0.481; 95% CI, –0.708 to –0.254; p < 0.001), while tidal volume per PBW was not significantly associated with end-inspiratory stress.

Similar findings were observed with tidal lung stress (Fig. 3). In univariate analysis, lower $V_{RM}$ per PBW was associated with higher tidal stress ($\beta$ = –0.267; 95% CI, –0.423 to 0.013; p = 0.109) and moderately with respiratory system compliance (r = –0.359; p = 0.020). In a multivariable model, $V_{RM}$ remained significantly associated with tidal stress ($\beta$ = –0.294; 95% CI, –0.525 to –0.063; p = 0.014) and driving pressure ($\beta$ = 0.385; 95% CI, 0.032–0.738; p = 0.033), while PEEp was not significantly associated with tidal stress.

Patient Characteristics According to $V_{RM}$ Quantile
Patients with higher $V_{RM}$ (> median) had significantly lower pre-RM PEEP (12 ± 4 vs 15 ± 5 cm H2O; p = 0.034), plateau pressure (28 ± 6 vs 31 ± 5; p = 0.049), and end-inspiratory transpulmonary pressure (5 ± 5 vs 9 ± 4 cm H2O; p = 0.002) and higher respiratory system (41 ± 13 vs 32 ± 7 mL/cm H2O; p = 0.009) and lung compliance (65 ± 32 vs 44 ± 12 mL/cm H2O; p = 0.008). Patients with higher versus lower $V_{RM}$ did not differ significantly by body mass index, APACHE II, Pao2/Fio2, tidal volume, driving pressure, or treatment assignment (Table 1).

Table 1
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Overall (n = 42)</th>
<th>Lower $V_{\text{RM}}$ (n = 21)$^a$</th>
<th>Higher $V_{\text{RM}}$ (n = 21)$^a$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53 ± 20</td>
<td>53 ± 22</td>
<td>54 ± 18</td>
<td>0.880</td>
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<tr>
<td>Female (%)</td>
<td>15 (35.7)</td>
<td>8 (38.1)</td>
<td>7 (33.3)</td>
<td>1.000</td>
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<tr>
<td>Nonwhite race (%)</td>
<td>5 (11.9)</td>
<td>1 (4.8)</td>
<td>4 (19.0)</td>
<td>0.343</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 11</td>
<td>172 ± 12</td>
<td>174 ± 11</td>
<td>0.478</td>
</tr>
<tr>
<td>Actual body weight (kg)</td>
<td>92.0 ± 29.7</td>
<td>91.2 ± 33.8</td>
<td>92.7 ± 25.7</td>
<td>0.869</td>
</tr>
<tr>
<td>Predicted body weight (kg)</td>
<td>66.4 ± 10.8</td>
<td>65.2 ± 10.8</td>
<td>67.7 ± 10.9</td>
<td>0.466</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.8 ± 9.8</td>
<td>30.8 ± 10.6</td>
<td>30.7 ± 9.1</td>
<td>0.965</td>
</tr>
</tbody>
</table>

Clinical characteristics

Acute Physiology and Chronic Health Evaluation II 27 ± 6 27 ± 6 27 ± 6 0.853

Primary cause of lung injury (%)

- Pulmonary 7 (16.7) 4 (19.0) 3 (14.3)
- Abdominal 17 (40.5) 8 (38.1) 9 (42.9)
- Trauma 11 (26.2) 6 (28.6) 5 (23.8) 1.000
- Sepsis 5 (11.9) 2 (9.5) 3 (14.3)
- Other 2 (4.8) 1 (4.8) 1 (4.8)

Organ failure at baseline (%)

- Cardiac 15 (35.7) 7 (33.3) 8 (38.1) 1.000
- Renal 22 (52.4) 11 (52.4) 11 (52.4) 1.000
- Hepatic 15 (35.7) 8 (38.1) 7 (33.3) 1.000
- Hematologic 8 (19.0) 3 (14.3) 5 (23.8) 0.697

Respiratory characteristics

Randomized to Esophageal Pressure-Guided Study Arm (%) 20 (47.6) 10 (47.6) 10 (47.6) 1.000

Tidal volume (mL) 497 ± 107 469 ± 83 525 ± 122 0.087

Tidal volume (mL/kg predicted body weight) 7.6 ± 1.4 7.3 ± 1.3 7.8 ± 1.5 0.274

Positive end-expiratory pressure 13 ± 5 15 ± 5 12 ± 4 0.034

$F_{\text{iO}_2}$ 70 ± 18 68 ± 17 73 ± 19 0.400

$P_{\text{A}_{\text{O}}2}/F_{\text{iO}_2}$ 146 ± 54 147 ± 57 145 ± 52 0.891

Berlin acute respiratory distress syndrome severity

- Mild ($200 < P_{\text{A}_{\text{O}}2}/F_{\text{iO}_2} \leq 300$) (%) 8 (19.0) 5 (23.8) 3 (14.3)
- Moderate ($100 < P_{\text{A}_{\text{O}}2}/F_{\text{iO}_2} \leq 200$) (%) 25 (59.5) 11 (52.4) 14 (66.7) 0.693
- Severe ($P_{\text{A}_{\text{O}}2}/F_{\text{iO}_2} \leq 100$) (%) 9 (21.4) 5 (23.8) 4 (19.0)

Plateau pressure (cm H$_2$O) 29 ± 5 31 ± 5 28 ± 6 0.049

Driving pressure (cm H$_2$O) 16 ± 4 16 ± 4 16 ± 4 0.842

End-inspiratory transpulmonary pressure (cm H$_2$O) 7 ± 5 9 ± 4 5 ± 5 0.002

End-expiratory transpulmonary pressure (cm H$_2$O) −3 ± 5 −2 ± 4 −4 ± 6 0.095

Respiratory system compliance (mL/cm H$_2$O) 37 ± 11 32 ± 7 41 ± 13 0.009

Lung compliance (mL/cm H$_2$O) 54 ± 26 44 ± 12 65 ± 32 0.008

Chest wall compliance (mL/cm H$_2$O) 190 ± 144 205 ± 151 174 ± 139 0.493

Dead-space fraction 0.66 ± 0.10 0.66 ± 0.12 0.66 ± 0.06 0.896

$V_{\text{RM}}$ = volume delivered during a recruitment maneuver.

$^a$Patients grouped as having $V_{\text{RM}}$ either higher or lower than the median $V_{\text{RM}}$ (15.7 mL/kg predicted body weight).
In a multivariable model including $V_{RM}$, driving pressure, and $\text{PaO}_2/\text{FiO}_2$, $V_{RM}$ again remained significantly associated with tidal stress ($\beta = -0.202; 95\% \text{ CI}, -0.340$ to $-0.064; p = 0.005$). Driving pressure also was significantly associated with tidal stress in the multivariable model ($\beta = 0.495; 95\% \text{ CI}, 0.273–0.717; p < 0.001$), while $\text{PaO}_2/\text{FiO}_2$ did not reach statistical significance. In a similar model replacing driving pressure with plateau airway pressure and PEEP as separate terms, $V_{RM}$ remained significantly associated with tidal stress ($\beta = -0.180; 95\% \text{ CI}, -0.332$ to $-0.027; p = 0.023$), while plateau pressure and PEEP also achieved statistical significance (plateau pressure $\beta = 0.518; 95\% \text{ CI}, 0.285–0.752; p < 0.001$; PEEP $\beta = -0.447; 95\% \text{ CI}, -0.707$ to $-0.186; p = 0.001$). In a similar model replacing driving pressure with tidal volume per PBW, $V_{RM}$ again was significantly associated with tidal stress ($\beta = -0.260; 95\% \text{ CI}, -0.431$ to $-0.089; p = 0.004$), while tidal volume per PBW was not significantly associated with tidal stress.

**$V_{TM}/V_{RM}$ and Global Lung Stress**

$V_{TM}/V_{RM}$, which represents the degree of tidal distension relative to maximum insufflation volume achievable under clinically prudent conditions, was on average 51.5% ± 19.5%. End-inspiratory lung stress increased linearly with increasing $V_{TM}/V_{RM}$ as expected ($\beta = 1.170; 95\% \text{ CI}, 0.437–1.903$ per 10% increase in $V_{TM}/V_{RM}$; $p = 0.003$) (Fig. 4). To determine whether this relationship was explained by driving pressure, a second model was developed including both $V_{TM}/V_{RM}$ and driving pressure as covariates. In this multivariable model, $V_{TM}/V_{RM}$ remained significantly predictive of end-inspiratory lung stress ($\beta = 1.048; 95\% \text{ CI}, 0.299–1.798$ per 10% increase in $V_{TM}/V_{RM}$; $p = 0.007$), while driving pressure was

-10.111; $p = 0.001$). Plateau pressure and driving pressure also were associated with tidal stress (plateau pressure $\beta = 0.337; 95\% \text{ CI}, 0.161–0.513$; driving pressure $\beta = 0.542; 95\% \text{ CI}, 0.301–0.783; p < 0.001$ for both). Neither tidal volume per PBW nor $\text{PaO}_2/\text{FiO}_2$ was significantly associated with tidal stress (tidal volume $\beta = -0.119; 95\% \text{ CI}, -0.900$ to $0.661; p = 0.759$; $\text{PaO}_2/\text{FiO}_2$ $\alpha = 0.409$).

**Figure 3.** Prediction of global lung stress. *Left,* End-inspiratory lung stress, calculated as the transpulmonary pressure during end-inspiratory pause of a tidal breath. *Right,* Tidal lung stress, calculated as the transpulmonary pressure difference between end-inspiratory and end-expiratory pauses during a tidal breath. Unlike tidal stress, end-inspiratory stress additionally accounts for the stress already present before tidal inflation—the stress on the lung from its end-expiratory volume at positive end-expiratory pressure (PEEP)—which may differ substantially depending on the preset PEEP, chest wall characteristics, and $\text{PaO}_2/\text{FiO}_2$. Regression coefficients represent unadjusted association between each predictor and lung stress. $V_{TM} =$ volume delivered during a recruitment maneuver.
Tidal lung stress, calculated as the transpulmonary pressure during end-inspiratory pause of a tidal breath. End-inspiratory lung stress, calculated as the transpulmonary pressure difference between end-inspiratory and end-expiratory pauses of a tidal breath. $V_{\text{RM}}$ = volume delivered during a recruitment maneuver.

Figure 4. Global lung stress and $V_{\text{T}}/V_{\text{RM}}$. The ratio of the tidal volume ($V_{\text{T}}$) to $V_{\text{RM}}$ defines the degree of tidal distention relative to maximum insufflation volume. $V_{\text{RM}}$ was measured beginning from the resting lung volume at end-expiration. Left, End-inspiratory lung stress, calculated as the transpulmonary pressure during end-inspiratory pause of a tidal breath. Right, Tidal lung stress, calculated as the transpulmonary pressure difference between end-inspiratory and end-expiratory pauses of a tidal breath. $V_{\text{RM}}$ was unique in our cohort, compared with alternative clinical measures, in its ability to predict independently the latter. End-inspiratory stress predicted 28-day mortality in our cohort. Similarly, $V_{\text{RM}}$ predicted 28-day mortality even after accounting for treatment effect of the clinical trial’s randomly assigned study intervention. Our findings suggest that the association of $V_{\text{RM}}$ with mortality is explained by its prediction of end-inspiratory lung stress.

Traditionally, RMs have been performed to open atelectatic but recruitable lung units, aiming to improve oxygenation and perhaps decrease VILI (17). Human studies of RMs have found improvements in oxygenation and mechanics are variable and transient (24, 25). Adverse events, namely hypotension and desaturation, occur infrequently, but these effects too are transient (17). While animal models have suggested RMs may elicit a proinflammatory response in the lung (26), similar findings have not been replicated in humans (27). Taken together, RMs appear to be well tolerated without contributing to serious adverse events, although their therapeutic utility is questionable.

A key rationale that spurred use of low tidal volumes for ARDS was the discovery using CT that only part of the ARDS lung is well aerated and available for ventilation (2–4). However, use of the baby lung concept to individualize therapy in research and clinical practice has been limited by lack of a simple bedside measure that can be performed without specialized equipment and expertise. $V_{\text{RM}}$ represents a fast and direct measurement of the maximum insufflation volume achievable under clinically prudent conditions (maintaining a continuous airway pressure of 40 cm H$_2$O during the RM). When measured beginning from resting lung volume at PEEP, $V_{\text{RM}}$ quantifies the maximum baby lung volume available for tidal ventilation, analogous to the baby lung inspiratory capacity.

Some important study limitations are worth noting. Use of end-inspiratory transpulmonary pressure ($\beta$) as a surrogate for lung injury risk is controversial because it requires esophageal manometry to estimate pleural pressure (14, 15). Transpulmonary pressure is the pertinent distending pressure of the lung (21). Esophageal manometry, as an estimate of pleural pressure, has been shown previously to yield findings consistent with known respiratory physiology in healthy individuals and patients with ARDS (15, 28). Furthermore, the present study found that higher end-inspiratory stress was associated with increased risk of death, further suggesting our measure of transpulmonary pressure has clinical relevance. $V_{\text{RM}}$ may include some degree of hyperinflation depending on respiratory system compliance and the transpulmonary pressure achieved during the RM. However, the contribution of markers of lung injury risk. $V_{\text{RM}}$ was unique in our cohort, compared with alternative clinical measures, in its ability to predict independently the latter. End-inspiratory stress predicted 28-day mortality in our cohort. Similarly, $V_{\text{RM}}$ predicted 28-day mortality even after accounting for treatment effect of the clinical trial’s randomly assigned study intervention. Our findings suggest that the association of $V_{\text{RM}}$ with mortality is explained by its prediction of end-inspiratory lung stress. Traditionally, RMs have been performed to open atelectatic but recruitable lung units, aiming to improve oxygenation and perhaps decrease VILI (17). Human studies of RMs have found improvements in oxygenation and mechanics are variable and transient (24, 25). Adverse events, namely hypotension and desaturation, occur infrequently, but these effects too are transient (17). While animal models have suggested RMs may elicit a proinflammatory response in the lung (26), similar findings have not been replicated in humans (27). Taken together, RMs appear to be well tolerated without contributing to serious adverse events, although their therapeutic utility is questionable.

A key rationale that spurred use of low tidal volumes for ARDS was the discovery using CT that only part of the ARDS lung is well aerated and available for ventilation (2–4). However, use of the baby lung concept to individualize therapy in research and clinical practice has been limited by lack of a simple bedside measure that can be performed without specialized equipment and expertise. $V_{\text{RM}}$ represents a fast and direct measurement of the maximum insufflation volume achievable under clinically prudent conditions (maintaining a continuous airway pressure of 40 cm H$_2$O during the RM). When measured beginning from resting lung volume at PEEP, $V_{\text{RM}}$ quantifies the maximum baby lung volume available for tidal ventilation, analogous to the baby lung inspiratory capacity.

Some important study limitations are worth noting. Use of end-inspiratory transpulmonary pressure ($\beta$) as a surrogate for lung injury risk is controversial because it requires esophageal manometry to estimate pleural pressure (14, 15). Transpulmonary pressure is the pertinent distending pressure of the lung (21). Esophageal manometry, as an estimate of pleural pressure, has been shown previously to yield findings consistent with known respiratory physiology in healthy individuals and patients with ARDS (15, 28). Furthermore, the present study found that higher end-inspiratory stress was associated with increased risk of death, further suggesting our measure of transpulmonary pressure has clinical relevance. $V_{\text{RM}}$ may include some degree of hyperinflation depending on respiratory system compliance and the transpulmonary pressure achieved during the RM. However, the contribution of markers of lung injury risk.
hyperinflation to $V_{RM}$ appears to be negligible. A prior human ARDS study using CT performed during RMs at 30–50 cm H$_2$O airway pressure found hyperinflation accounted for only 2.9% ± 4.0% of total lung volume (29). Furthermore, the transpulmonary pressures achieved during RMs in our study were comparable to those observed at total lung capacity using the same measurement techniques in healthy individuals (30), further supporting use of $V_{RM}$ as a measure of inspiratory capacity.

$V_{RM}$ also may include potentially recruitable lung, that is, lung units that are collapsed at the current set PEEP but could be recruited with higher airway pressures. If the RM transiently recruits lung that otherwise remains collapsed during tidal ventilation, $V_{T}/V_{RM}$ may underestimate relative lung deformation, limiting use of $V_{T}/V_{RM}$ as a surrogate for lung strain. In the present study, average PEEP was 13 ± 5 cm H$_2$O, which is considerably higher than in most other clinical trials of ARDS and likely reduced the proportion of potentially recruitable lung. Furthermore, $V_{RM}$ correlated strongly with lung compliance, and prior CT studies have shown compliance to predict baby lung size (5, 31). This association between $V_{RM}$ and lung compliance would be weakened had a large volume of collapsed lung been recruited variably during the RM. In future studies, PEEP could be set using a mechanics-based approach (11, 18, 32) prior to measuring $V_{RM}$ in effort to standardize lung volumes between patients and minimize contribution of transient lung recruitment to $V_{RM}$.

In the present study, PEEP immediately before the RM had been set at the clinician’s discretion, and participants with lower $V_{RM}$ had slightly higher PEEP. Higher PEEP may increase end-expiratory lung volume and bias toward smaller $V_{RM}$. However, patients with lower $V_{RM}$ also had worse lung and respiratory system compliance such that higher PEEP likely was required to maintain comparable transpulmonary pressure and lung recruitment at end-expiration. Indeed, end-expiratory transpulmonary pressure did not differ according to higher versus lower $V_{RM}$. Furthermore, statistical adjustment for PEEP did not affect the association between $V_{RM}$ and either end-inspiratory or tidal stress. Future studies might consider standardizing PEEP according to respiratory mechanics as above before the RM is performed.

Additionally, while low $V_{RM}$ appears to predict increased risk of death, results are not definitive. $V_{RM}$ was inversely associated with 28-day mortality in unadjusted analysis. $V_{RM}$ remained significantly predictive of 28-day mortality after adjusting for study arm in the primary clinical trial. Additional multivariable regression models were not performed to minimize risk of overfitting data due to our limited sample size. A larger validation cohort is required to confirm an independent association between $V_{RM}$ and mortality and to provide reliable effect estimates.

Finally, the implications of $V_{RM}$ as a bedside measure of baby lung relative inspiratory capacity require further investigation. Based on current understanding of biomechanical mechanisms, lower $V_{RM}$ should predict higher risk of VILI when ventilator settings are standardized to healthy lung size (e.g., 6 mL/kg PBW). However, the association between $V_{RM}$ and VILI was not tested directly. We speculate that scaling tidal volume to each patient’s baby lung size (e.g., targeting a specified percentage of $V_{RM}$) rather than healthy lung size (mL/kg PBW) might confer additional lung protection. The observed association between $V_{RM}$ and mortality supports this possibility, but validation of our findings and ultimately prospective interventional trials will be needed.

**CONCLUSIONS**

$V_{RM}$ represents a novel, widely available measure to determine maximum insufflation volume of the ARDS baby lung, analogous to the inspiratory capacity relative to resting volume at PEEP. $V_{RM}$ independently predicts end-inspiratory and tidal lung stress, can be used to quantify the degree of tidal dis-tension relative to maximum insufflation volume, and may be associated inversely with increased risk of death.

**REFERENCES**


