Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND
Mechanical-ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes (Vₜ), and higher positive end-expiratory pressures (PEEPs) can improve survival in patients with the acute respiratory distress syndrome (ARDS), but the relative importance of each of these components is uncertain. Because respiratory-system compliance (Cₛ) is strongly related to the volume of aerated remaining functional lung during disease (termed functional lung size), we hypothesized that driving pressure (∆P=Vₜ/Cₛ), in which Vₜ is intrinsically normalized to functional lung size (instead of predicted lung size in healthy persons), would be an index more strongly associated with survival than Vₜ or PEEP in patients who are not actively breathing.

METHODS
Using a statistical tool known as multilevel mediation analysis to analyze individual data from 3562 patients with ARDS enrolled in nine previously reported randomized trials, we examined ∆P as an independent variable associated with survival. In the mediation analysis, we estimated the isolated effects of changes in ∆P resulting from randomized ventilator settings while minimizing confounding due to the baseline severity of lung disease.

RESULTS
Among ventilation variables, ∆P was most strongly associated with survival. A 1-SD increment in ∆P (approximately 7 cm of water) was associated with increased mortality (relative risk, 1.41; 95% confidence interval [CI], 1.31 to 1.51; P<0.001), even in patients receiving “protective” plateau pressures and Vₜ (relative risk, 1.36; 95% CI, 1.17 to 1.58; P<0.001). Individual changes in Vₜ or PEEP after randomization were not independently associated with survival; they were associated only if they were among the changes that led to reductions in ∆P (mediation effects of ∆P, P=0.004 and P=0.001, respectively).

CONCLUSIONS
We found that ∆P was the ventilation variable that best stratified risk. Decreases in ∆P owing to changes in ventilator settings were strongly associated with increased survival. (Funded by Fundação de Amparo e Pesquisa do Estado de São Paulo and others.)
M E C H A N I C A L - V E N T I L A T I O N S T R A T E G I E S that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes (Vₜ), and higher positive end-expiratory pressures (PEEPs) — collectively termed lung-protective strategies — have been associated with survival benefits in randomized clinical trials involving patients with the acute respiratory distress syndrome (ARDS). The different components of lung protection in those strategies, such as lower Vₜ, lower plateau pressure, and higher PEEP, can all reduce mechanical stresses on the lung, which are thought to induce ventilator-induced lung injury. Clinical trials, however, have reported conflicting responses to the manipulation of separate components of lung protection, and clinicians often face a dilemma when the optimization of one component negatively affects another (for instance, increasing PEEP may increase plateau pressure), with unknown net consequences.

To minimize ventilator-induced lung injury, most studies have scaled Vₜ to predicted body weight to normalize Vₜ to lung size. However, in patients with ARDS, the proportion of lung available for ventilation is markedly decreased, which is reflected by lower respiratory-system compliance (C RS). Therefore, we hypothesized that normalizing Vₜ to C RS and using the ratio as an index indicating the “functional” size of the lung would provide a better predictor of outcomes in patients with ARDS than Vₜ alone. This ratio, termed the driving pressure (∆P = P Vₜ/C RS), can be routinely calculated for patients who are not making inspiratory efforts as the plateau pressure minus PEEP.

To determine whether data from previous studies are consistent with this hypothesis, we combined individual data from patients involved in nine randomized trials comparing ventilation strategies in patients with ARDS. We used both a standard risk analysis with multivariate adjustments and a multilevel mediation analysis and examined the extent to which a change in ∆P (or other variables) resulting from a change in ventilator settings could be statistically linked to effects on survival, independent of the underlying severity of the lung injury and of the specific lung-protection protocol.

M E T H O D S

D E R I V A T I O N A N D V A L I D A T I O N C O H O R T S

We derived a survival-prediction model with the use of data from a cohort of 336 patients with ARDS from four early randomized clinical trials testing various strategies of volume-limited ventilation. We next tested and refined this model with data from a validation cohort of 861 patients from a large, randomized trial comparing lower versus higher Vₜ values. Finally, we retested the model with data from a more recent validation cohort of 2365 patients with ARDS enrolled in four randomized trials comparing higher-PEEP versus lower-PEEP strategies (Table 1, and Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

I N D E P E N D E N T V A R I A B L E S A N D O U T C O M E S

The primary outcome (the dependent variable) was survival in the hospital at 60 days (Cox survival model). Data from patients who were discharged home before day 60 were censored at day 60, with the patients considered to be alive at day 60.

The independent variables tested as predictors included treatment group (lung-protective [i.e., varying variables such as Vₜ, PEEP, and plateau pressures with an intention to protect] vs. control assignment), characteristics of patients, baseline severity of illness (e.g., risk according to the Acute Physiology and Chronic Health Evaluation [APACHE] or Simplified Acute Physiology Score [SAPS] and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO₂/FiO₂]), and ventilation variables (e.g., Vₜ and plateau pressure) averaged over the first 24 hours after randomization (Table S3 in the Supplementary Appendix). In a separate analysis, we averaged individual ventilation data over the first 3 days and observed no predictive advantage of this approach (Tables S4, S5, and S6 in the Supplementary Appendix). Patients who received pressure-support ventilation or had respiratory rates that were higher than the ventilator settings (suggesting the presence of ventilatory efforts) were excluded. Both conditions accounted for less than 3% of our sample. Barotrauma was defined as pneumothorax requiring chest-tube drainage during the first 28 days after randomization.

D E R I V A T I O N A N D V A L I D A T I O N O F A S U R V I V A L P R E D I C T I O N M O D E L

Variables that had a significant univariate association with survival were entered into a forward stepwise multivariate analysis and then into a
Table 1. Multivariate Cox Regression Model for 60-Day Hospital Survival.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-V. vs. Low-V. Trials (N = 1020)</th>
<th>High-PEEP vs. Low-PEEP Trials (N = 2060)</th>
<th>Combined Analysis (N = 3080)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>Relative Risk (95% CI)</td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>—</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>1.51 (1.36–1.69)</td>
<td>1.64 (1.50–1.79)</td>
<td>1.59 (1.48–1.70)</td>
</tr>
<tr>
<td>Risk of death†</td>
<td>1.34 (1.20–1.49)</td>
<td>1.41 (1.29–1.54)</td>
<td>1.38 (1.29–1.48)</td>
</tr>
<tr>
<td>Arterial pH at entry</td>
<td>0.69 (0.63–0.77)</td>
<td>0.68 (0.63–0.74)</td>
<td>0.68 (0.64–0.72)</td>
</tr>
<tr>
<td>Pao2:FiO2 at entry</td>
<td>0.85 (0.77–0.95)</td>
<td>0.88 (0.80–0.96)</td>
<td>0.87 (0.81–0.93)</td>
</tr>
<tr>
<td>Day 1 ∆P</td>
<td>1.35 (1.24–1.48)</td>
<td>1.50 (1.35–1.68)</td>
<td>1.41 (1.31–1.51)</td>
</tr>
<tr>
<td>Model 2 (including all the variables in model 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 ∆P</td>
<td>1.32 (1.19–1.47)</td>
<td>1.51 (1.35–1.68)</td>
<td>1.40 (1.30–1.51)</td>
</tr>
<tr>
<td>Day 1 Vr</td>
<td>1.04 (0.95–1.14)</td>
<td>1.05 (0.90–1.23)</td>
<td>1.02 (0.95–1.10)</td>
</tr>
<tr>
<td>Model 3 (including all the variables in model 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 ∆P</td>
<td>1.36 (1.24–1.49)</td>
<td>1.50 (1.34–1.68)</td>
<td>1.41 (1.32–1.52)</td>
</tr>
<tr>
<td>Day 1 PEEP</td>
<td>0.97 (0.80–1.18)</td>
<td>0.78‡</td>
<td>0.99 (0.91–1.09)</td>
</tr>
</tbody>
</table>

* Relative risks are the adjusted relative risks of death associated with a 1-SD increment in the given variable. Values higher than 1 indicate increased mortality. Day 1 values are for the first 24 hours after randomization. The values used for standard deviations were as follows: age, 17 years; risk of death, 26%; arterial pH, 0.09; Pao2:FiO2, 60; driving pressure (∆P), 7; positive end-expiratory pressure (PEEP), 5 cm of water; and tidal volume (Vt), 2 ml per kilogram of predicted body weight. By normalizing relative risk in this way, we were able to compare the strength of the association of different variables with survival as the relative risk per se (using 1/relative risk when the relative risk was <1).

† The risk of death was calculated according to the equations of the Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, or Simplified Acute Physiology Score (SAPS) II, depending on the trial.

‡ The P value is for the test of inclusion of the variable in the model in which the variables in model 1 plus the extra covariate in the line below were previously included.

§ The P value is for the test of inclusion of the variable in the model (the net contribution of the variable to predictive power in a likelihood ratio test) in which the variables in model 1 plus ∆P were previously included.

The derivation model (model 1) was subsequently tested in each of the validation cohorts, as well as in the combined data set. To show that the prognostic information provided by ∆P was independent of PEEP and plateau-pressure values, we resampled the combined data set (see Section III.3 in the Supplementary Appendix), producing subgroups of patients with matched mean levels for one variable (e.g., PEEP) but distinct mean levels for another ranking variable (e.g., driving pressure).

**MEDIATION ANALYSIS**

To investigate whether ∆P was more than a baseline risk predictor, we conducted a mediation analysis, searching for key variables that could be linked to positive outcomes after randomization. When mediation analysis is applied to randomized controlled trials, the goal is to determine whether a specific variable, strongly affected by treatment-group assignment, has an effect on outcomes that explains in whole or in part the effects...
resulting from treatment-group assignment.\textsuperscript{24,25}
For the relevant fraction of the effect in which such a variable (the "mediator" in the model) is implicated, the correlation with outcomes must exceed that of treatment group, typically exhibiting an independent, dose–response relationship (i.e., larger mediator changes are associated with stronger survival effects). For example, in the lower-$V_T$ trials, we tested whether survival was better explained by specific ventilatory variables than by treatment group (the treatment group in these studies incorporated an intention-to-treat bundle including various recommendations, such as $V_T$ reduction, plateau-pressure limitation, and acidosis management). We tested four mediator candidates: $V_T$, plateau pressure, PEEP, and $\Delta P$. The first three variables were explicit targets in the protocols, whereas $\Delta P$, which was a dependent variable in these studies, was the variable we hypothesized a priori to be the key mediator. Following standard procedures for mediation analysis, we examined each mediator candidate through a sequence of four logical tests, ultimately assessing whether variations in the mediator explained the mean benefit of the randomly assigned treatment group, as well as assessing the dose–response effect on outcomes.

We used R software, version 2.10.1, with the R Package for Causal Mediation Analysis (R Project for Statistical Computing),\textsuperscript{23,24} in which a mediation proportion is estimated, indicating how much of the whole risk reduction in the treatment group can be explained by the indirect path in which treatment-group assignment drives a change in the mediator and the change in the mediator then affects the outcome (see the Supplementary Appendix). We calculated an average causal mediation effect,\textsuperscript{24} which expressed the independent hazard (relative risk) associated with this indirect path. Other analyses were conducted with the use of SPSS software, version 20 (SPSS).

To avoid possible biases due to differences in the severity of the underlying respiratory disorder, we preadjusted all mediation models according to the baseline respiratory system tidal elastance (the reciprocal of tidal compliance). For the lower-$V_T$ trials, this calculation was not possible, because baseline data were frequently missing. Thus, we used the elastance ranks within each treatment group (calculated after randomization) for each trial, assuming that the systematic changes in ventilation parameters due to treatment-group assignment might affect absolute values of elastance but would not affect the ranking of individual elastance values within the respective study groups. In the Supplementary Appendix (Section II.4, Fig. S3), we present a sensitivity analysis addressing this assumption.

In addition to the covariates of model 1, we entered baseline respiratory system tidal elastance in all regression models used for the mediation analysis, a procedure that intrinsically filtered out the potential confounding caused by differences in the severity of underlying lung disease. Accordingly, the mediation analysis exclusively addressed the effect of variations in $\Delta P$ related to strategy — that is, variations in $\Delta P$ superimposed by changes in ventilator settings after randomization.

\section*{Results}
\textbf{Building and Testing the Prediction Model}

In univariate analyses in the derivation cohort, several significant associations were detected between independent predictor variables and survival (Table S3 in the Supplementary Appendix). Two baseline variables (risk according to APACHE or SAPS and arterial pH) and two ventilator variables ($F_{O_2}$ and $\Delta P$) were significantly associated with survival after multivariate adjustment.

The test of this preliminary model in our first validation cohort showed that baseline $P_{aO_2}$,$F_{O_2}$ could replace the information associated with the $F_{O_2}$ variable (Table S7 in the Supplementary Appendix), with the advantage of being externally validated.\textsuperscript{26} We also observed that age was a strong, independent predictor of survival even though it is a component of the APACHE score. After conservatively including the trial covariate, our final model included six variables (Table 1, model 1); in this model, $\Delta P$ predicted survival as accurately as did risk according to APACHE or SAPS.

Treatment-group assignment was not independently associated with survival in model 1 and was omitted from Table 1. This variable was considered separately in our mediation analysis. Testing of model 1 in the second validation cohort showed a strong association with survival ($P<0.001$), with all covariates conferring similar relative risks in the two cohorts.
DRIVING PRESSURE AND SURVIVAL IN ARDS

INDEPENDENCE OF INFORMATION
Even though ΔP is mathematically linked to C_{RS} and V_{T}, no other ventilation variable conferred independent predictive information to any survival model when ΔP was already a covariate. In contrast, ΔP always conferred strong, nonredundant predictive information when it was included in models preadjusted for other ventilator variables (Table 1, models 2 and 3; and Table S8 in the Supplementary Appendix, models 2 through 5). This observation was consistent in the derivation, validation, and combined cohorts. Higher ΔP predicted lower survival consistently across trials (P=0.13 for heterogeneity) (Fig. S4 in the Supplementary Appendix).

RISK PRIORITY OF ΔP
Figure 1 shows that in the pooled sample (including 3562 patients), higher plateau pressures were observed in patients with higher ΔP or higher PEEP, but with different consequences (resampling A vs. B): higher mortality was noted only when higher plateau pressures were observed in patients with higher ΔPs. Similarly, the protective effects of higher PEEP were noted only when there were associated decreases in ΔP (resampling B vs. C). In addition, at constant levels of plateau pressure (Fig. S5 in the Supplementary Appendix), we observed that V_{T} was a strong predictor of survival when normalized to C_{RS} (i.e., ΔP) but not when normalized to predicted body weight.

We also found a strong association between ΔP and survival even though all the ventilator settings that were used were lung-protective (relative risk of death, 1.36; 95% confidence interval [CI], 1.17 to 1.58; P<0.001). In contrast, further reductions in plateau pressures or V_{T} below these thresholds (plateau pressures ≤30 cm of water and V_{T} ≤7 ml per kilogram of predicted body weight) had no effect on survival (Fig. S6 in the Supplementary Appendix).

Figure 2 shows the increase in the risk of death as a function of progressive percentiles of ΔP in the combined population. There was also an increase in the odds of pneumothorax requiring drainage as a function of progressive percentiles of ΔP but not of V_{T} (Fig. S7 in the Supplementary Appendix).

TEST OF MEDIATION
After observing that ΔP was associated with outcomes in each study, we performed a multilevel mediation analysis with the use of trial as a random effect, initially pooling the five V_{T} studies and then pooling the four PEEP studies (Fig. S8 through S11 in the Supplementary Appendix). A consistency analysis (Table S9 in the Supplementary Appendix) testing moderated mediation also suggested that there was consistency across trials.

Reductions in ΔP after randomization were significantly associated with better survival in both cohorts (step 2 of mediation analysis) (Fig. S8 and S9 in the Supplementary Appendix), independently of baseline elastance of the respiratory system, and had similar effect sizes in both cohorts (relative risk for V_{T} trials, 0.62; 95% CI, 0.52 to 0.74; relative risk for PEEP trials, 0.57; 95% CI, 0.42 to 0.72).

For the V_{T} and PEEP trials, treatment-group assignment was an independent predictor of survival. Except for ΔP, however, no mediation candidate consistently passed through the stepwise mediation tests (Fig. S10 and S11 in the Supplementary Appendix). V_{T} per se was not a significant mediator in the V_{T} trials (P=0.68 for the average causal mediation effect), and PEEP was not a significant mediator in the PEEP trials (P=0.50). In contrast, ΔP mediated 75% of the benefits due to treatment-group assignment in the V_{T} trials (P=0.004 for the average causal mediation effect) and 45% of these benefits in the PEEP trials (P=0.001). This was enough to suppress the significance of the direct effect of the randomized treatment group, classically characterizing complete mediation.

Thus, although ΔP was not an explicit target, survival benefits in the V_{T} trials were proportional to reductions in ΔP driven by treatment-group assignment rather than to reductions in V_{T} (tested as a continuous variable). Similarly, the survival benefits observed in the PEEP trials occurred in relation to reductions in ΔP rather than in relation to numerical increments in PEEP.

DISCUSSION
In trials of mechanical ventilation involving patients with ARDS, in which V_{T} and PEEP were included as independent variables, the dependent quantity ΔP was the variable that was most strongly associated with survival. Although causality can be inferred only from direct controlled trials, we found, using a statistical approach that
adjusted for the effect of underlying lung disease on the mechanical characteristics of the lung, that \( \Delta P \) was a critical mediator of the benefits of various interventions. Our analyses indicated that reductions in \( V_T \) or increases in PEEP driven by random treatment-group assignment were beneficial only if associated with decreases in \( \Delta P \). No other ventilation variable had such a mediating effect.

We identified the striking correlations between
that the aerated lung available for tidal ventilation. These observations suggest that the aerated lung in a patient with ARDS is not “stiff” but is small, with nearly normal specific compliance (compliance per unit of lung volume) in preserved areas.

The rationale underlying our mediation analysis was that ΔP was the surrogate for cyclic lung strain that was most accessible and easiest to calculate25; ΔP is defined as the amount of cyclic parenchymal deformation imposed on ventilated, preserved lung units. We also postulated that cyclic strain predicts lung injury better than Vt. Implicitly, we hypothesized that the functional lung size during disease is better quantified by Crs than by predicted body weight. Under such conditions, especially when Crs varies considerably among patients, cyclic strain, ventilator-induced lung injury, and survival should all be correlated with ΔP rather than with Vt.

Although this mediation analysis cannot establish causality, experimental studies provide a plausible link between ΔP and ventilator-induced lung injury. Many studies suggest that cell and tissue damage are more closely related to the amplitude of cyclic stretch than to the maximal level of stretch — that is, lung tissue can undergo sustained stretching without damage.5,7,8,27-30

Our study has a number of limitations. First, our conclusions are valid only for ventilation in which the patient is not making respiratory efforts. It is difficult to interpret ΔP in actively breathing patients. Second, we studied a relatively narrow range of variables. Thus, extrapolations to patients with plateau pressures greater than 40 cm of water, PEEPs less than 5 cm of water, or respiratory rates greater than 35 breaths per minute are not warranted. Finally, we did not directly estimate the cyclic gradient of pressures across the lung (transpulmonary ΔP), which is the probable effector of parenchymal injury. Because a large fraction of ΔP is typically applied to inflate the lung in patients with severe ARDS, ΔP was probably a reasonable surrogate for transpulmonary ΔP. However, this approach may not be relevant to patients with extremely low chest-wall compliances.22,31

The Acute Respiratory Distress Syndrome Network (ARDSNet) trial2 is often viewed as showing that low Vt values per se decrease mortality from ARDS. However, our analyses suggest that the efficacy of this strategy is also critically dependent on other components of the lung-protective bundle (e.g., plateau-pressure limitation, respiratory-rate modification, and hypercapnia). For example, when low Vt values were introduced into the lung, improved survival was observed only when large changes in ΔP (the dependent variable during volume control) were avoided.

Our findings might also explain why studies of higher PEEP increments might be protective only when the increased PEEP values result in a change in lung mechanics so that the same Vt can be delivered with a lower ΔP. This hypot-
esis is consistent with recent physiological studies suggesting that the benefits of PEEP are found mainly in patients with greater lung recruitability, with some harm reported when PEEP caused overdistention. Well-known devastating effects of zero-PEEP ventilation have been related to progressive atelectasis, decreased lung compliance, and ultimately higher $\Delta P$. Finally, our work is a post hoc observational analysis. Clinical trials need to be designed in which ventilator changes are linked to achieve changes in $\Delta P$, in order to determine whether our observations can be translated into changes that may be implemented at the bedside.

Supported by Fundação de Amparo e Pesquisa do Estado de São Paulo, Conselho Nacional de Pesquisa e Desenvolvimento, and Financiadora de Estudos e Projetos (FINEP).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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