It is possible that a three-dose series is daunting to parents of teens and their clinicians, whether because of the cost (even if borne by private insurance or the VFC program) or the difficulty of making three office visits during a stage when school and extracurricular activities can be all-consuming. Expanding in-network insurance coverage to pharmacies could present a convenient option for the completion of multidose series during the teenage years, but immunization data for these encounters should be made accessible to primary care physicians through immunization information systems. Regulatory authorities in several countries have approved two-dose series for young adolescents for both the quadrivalent and bivalent HPV vaccine based on the noninferior immunogenicity of two doses administered 6 months apart.[8] The ACIP has reviewed available data for two-dose schedules and will review forthcoming data on the immunogenicity of alternative schedules for the 9-valent vaccine.

Even with the availability of another HPV vaccine targeting additional cancer-causing virus types, vaccination of a much higher proportion of preteens is needed. Otherwise, decades from now oncologists will still be talking about HPV-associated cancers with thousands of new patients every year. Instead, I hope that in a few decades we will be able to tell a generation of adults who never had HPV-associated cancers or precancers that when they were teenagers, we had them covered.

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

From the Centers for Disease Control and Prevention, Atlanta.

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DOI: 10.1056/NEJMe1415742

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Driving Pressure and Respiratory Mechanics in ARDS

Stephen H. Loring, M.D., and Atul Malhotra, M.D.

In this issue of the *Journal*, Amato et al.[1] use data from previously published trials to determine whether it is possible to predict outcomes in patients with the acute respiratory distress syndrome (ARDS) on the basis of the settings of their mechanical ventilators or parameters derived from monitoring the mechanics of the ventilation achieved. Previous articles published in the *Journal* had shown that a lung-protective strategy — that is, limiting the tidal volume (V_T) and plateau pressure while providing relatively high positive end-expiratory pressure (PEEP), can improve survival in ARDS,[2,3] thus demonstrating the importance of respiratory mechanics in determining outcomes in patients.[4] Lung-protective ventilation strategies maintain alveolar aeration, prevent overexpansion of the lung, and limit driving pressure (ΔP, which can be calculated as ventilator-measured plateau pressure minus applied PEEP) and thereby are thought to reduce ventilator-induced lung injury.

Amato et al. focus on ΔP as a predictor of outcome in ARDS. Because ΔP is the tidal increase in static transrespiratory pressure, it is proportional to V_T, with respiratory-system elastance (the inverse of compliance) being the constant of proportionality; elastance reflects the severity and extent of lung injury. Thus, ΔP is determined by variables known to predict or affect mortality in ARDS. The authors conducted a statistical mediation analysis of the aforementioned data, in which variations of V_T, PEEP, ΔP, and respiratory-system compliance were assessed to determine which of the operator-set or measured variables was most

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closely linked to outcomes. They concluded that ΔP was the variable most closely related to survival.

Several concepts are important in the consideration of these findings. First, transpulmonary pressure (the pressure difference from airway opening to pleural space) is the relevant distending pressure for the lung.[5] This concept is often overlooked when practitioners focus on the plateau pressure without considering the effect of the chest wall in determining lung expansion and stress.[6,7] High transpulmonary pressures can cause lung injury resembling ARDS or gross barotrauma in the form of pneumothorax. Indeed, abundant data have shown that low V_T, and consequently lower plateau and transpulmonary pressures, improve survival.[3] Importantly, ΔP limitation may not be helpful for patients who are actively breathing and who have pleural-pressure decreases during inspiration as a result of their own efforts to breathe in that result in high transpulmonary pressures. Second, atelectrauma,[8] caused by the repetitive collapse and reexpansion of lung units, has been shown to be damaging. Lung collapse can result from surfactant dysfunction, in which case surfactant fails to have its physiologic effect and the surface tension of alveolar-lining fluid becomes high, promoting alveolar collapse. Collapse can also occur when elevated pleural pressures — for example, caused by pleural effusions, obesity, or ascites — effectively compress the lung externally.[6] Applying adequate PEEP can help to prevent collapse of the lung at end exhalation and thus prevent atelectrauma.[4,8,9]

The ability of ΔP to predict outcome is attributable to the fact that the variables that define it are themselves highly predictive of survival. As the authors emphasize, previous studies were not designed to assess ΔP as an independent variable, and thus the findings reported by Amato et al. should be considered hypothesis-generating rather than definitive. The authors argue for the "baby lung" concept, in which some portion of the lung in patients with ARDS is collapsed or flooded and thus does not participate in gas exchange, leaving the rest of the lung (i.e., the "baby lung") to effect gas exchange.[10] If this is the case, limiting ΔP may be a way to scale the delivered breath to the size of the lung that is available to participate in gas exchange, rather than scaling to body size, which may be less biologically relevant. Although the concept of limiting ΔP is appealing, the question of whether the manipulation of ΔP rather than V_T is beneficial remains. Designing prospective, randomized trials to assess the independent role of high versus low ΔP in clinical outcomes will be complicated and will require consideration of the effect that limiting ΔP has on V_T and subsequent minute ventilation, as indicated by levels of carbon dioxide in arterial blood, as well as the fact that a given ΔP would have very different effects depending on the PEEP level chosen (e.g., a PEEP of 5 cm of water vs. 15 cm of water).

Is a strategy in which ventilators are set to limit ΔP superior to our current approach? We strongly urge caution in accepting the idea that limiting ΔP is what we should do at the bedside now. Instead, the meta-analytic findings reported by Amato et al. form the basis for a robust debate regarding how to design a controlled trial to be sure the idea of limiting ΔP is correct. Although the design of such a trial will not be easy, the problem is important. In the words of Piet Hein, "Problems worthy of attack prove their worth by hitting back."

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

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DOI: 10.1056/NEJMe1414218
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SPECIAL ARTICLE

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 (V_T), 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 (C_{RS}) is strongly related to the volume of aerated remaining functional lung during disease (termed functional lung size), we hypothesized that driving pressure ($\Delta P = V_T/C_{RS}$), in which V_T 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 V_T 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 ΔP as an independent variable associated with survival. In the mediation analysis, we estimated the isolated effects of changes in ΔP resulting from randomized ventilator settings while minimizing confounding due to the baseline severity of lung disease.

RESULTS

Among ventilation variables, ΔP was most strongly associated with survival. A 1-SD increment in ΔP (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 V_T (relative risk, 1.36; 95% CI, 1.17 to 1.58; P<0.001). Individual changes in V_T 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 ΔP (mediation effects of ΔP, P=0.004 and P=0.001, respectively).

CONCLUSIONS

We found that ΔP was the ventilation variable that best stratified risk. Decreases in ΔP 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.)

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N Engl J Med 2015;372:747-55.
DOI: 10.1056/NEJMsa1410639
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Mechanical-ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes (V_T), 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).[1-4] The different components of lung protection in those strategies, such as lower V_T, lower plateau pressure, and higher PEEP, can all reduce mechanical stresses on the lung, which are thought to induce ventilator-induced lung injury.[5-9] Clinical trials, however, have reported conflicting responses to the manipulation of separate components of lung protection,[10-14] 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.[15]

To minimize ventilator-induced lung injury, most studies have scaled V_T to predicted body weight to normalize V_T 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}).[13,16-18] Therefore, we hypothesized that normalizing V_T 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 V_T alone. This ratio, termed the driving pressure ($\Delta P = V_T/C_{RS}$), 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.[1,2,10-12,19-22] We used both a standard risk analysis with multivariate adjustments and a multilevel mediation analysis[23,24] and examined the extent to which a change in ΔP (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.

Methods

Derivation and Validation Cohorts

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.[1,19-21] We next tested and refined this model with data from a validation cohort of 861 patients from a large, randomized trial[2] comparing lower versus higher V_T 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[4,10-12,22] (Table 1, and Tables S1 and S2 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Independent Variables and Outcomes

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 V_T, 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 [Pao_2:FIo_2]), and ventilation variables (e.g., V_T 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.

Derivation and Validation of a Survival Prediction Model

Variables that had a significant univariate association with survival were entered into a forward stepwise multivariate analysis and then into a

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Table 1. Multivariate Cox Regression Model for 60-Day Hospital Survival.*

Variable	High-V_T vs. Low-V_T Trials (N=1020)		High-PEEP vs. Low-PEEP Trials (N=2060)		Combined Analysis (N=3080)	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Model 1						
Trial	—	<0.001	—	0.83	—	<0.001
Age	1.51 (1.36–1.69)	<0.001	1.64 (1.50–1.79)	<0.001	1.59 (1.48–1.70)	<0.001
Risk of death†	1.34 (1.20–1.49)	<0.001	1.41 (1.29–1.54)	<0.001	1.38 (1.29–1.48)	<0.001
Arterial pH at entry	0.69 (0.63–0.77)	<0.001	0.68 (0.63–0.74)	<0.001	0.68 (0.64–0.72)	<0.001
Pao_2:FIO_2 at entry	0.85 (0.77–0.95)	0.004	0.88 (0.80–0.96)	0.005	0.87 (0.81–0.93)	<0.001
Day 1 ΔP	1.35 (1.24–1.48)	<0.001	1.50 (1.35–1.68)	<0.001	1.41 (1.31–1.51)	<0.001
Model 2 (including all the variables in model 1)						
Day 1 ΔP	1.32 (1.19–1.47)	<0.001‡	1.51 (1.35–1.68)	<0.001‡	1.40 (1.30–1.51)	<0.001‡
Day 1 V_T	1.04 (0.95–1.14)	0.42§	1.05 (0.90–1.23)	0.52§	1.02 (0.95–1.10)	0.58§
Model 3 (including all the variables in model 1)						
Day 1 ΔP	1.36 (1.24–1.49)	<0.001‡	1.50 (1.34–1.68)	<0.001‡	1.41 (1.32–1.52)	<0.001‡
Day 1 PEEP	0.97 (0.80–1.18)	0.78§	0.99 (0.91–1.09)	0.90§	1.03 (0.95–1.11)	0.51§

* 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; Pao_2:FIO_2, 60; driving pressure (ΔP), 7; positive end-expiratory pressure (PEEP), 5 cm of water; and tidal volume (V_T), 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). For instance, in the combined analysis, ΔP had a stronger association with survival (relative risk, 1.4) than did Pao_2:FIO_2 (1/relative risk=1/0.87=1.15). Although it is not shown in the table, the variables day 1 plateau pressure, day 1 respiratory-system compliance, and day 1 mean airway pressure were tested before and after inclusion of ΔP in model 1 and showed no significant association with survival (see Section II.6, Table S8, in the Supplementary Appendix). CI denotes confidence interval.

† 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 ΔP were previously included.

backward stepwise multivariate analysis. Variables that were consistently found to be associated with survival with the use of both modeling procedures were included in the final derivation model. We adjusted all analyses for the trial variable (Fig. S2 in the Supplementary Appendix). 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 ΔP 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 ΔP was more than a baseline risk predictor, we conducted a mediation analysis,[24,25] 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

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resulting from treatment-group assignment.[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 studies, 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 ΔP. The first three variables were explicit targets in the protocols, whereas ΔP, 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),[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,[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 ΔP related to strategy — that is, variations in ΔP superimposed by changes in ventilator settings after randomization.

RESULTS

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_{IO_2} and ΔP) were significantly associated with survival after multivariate adjustment.

The test of this preliminary model in our first validation cohort showed that baseline Pa_{O_2}:F_{IO_2} could replace the information associated with the F_{IO_2} variable (Table S7 in the Supplementary Appendix), with the advantage of being externally validated.[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, ΔP 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.

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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).[2,11] 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[23] 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

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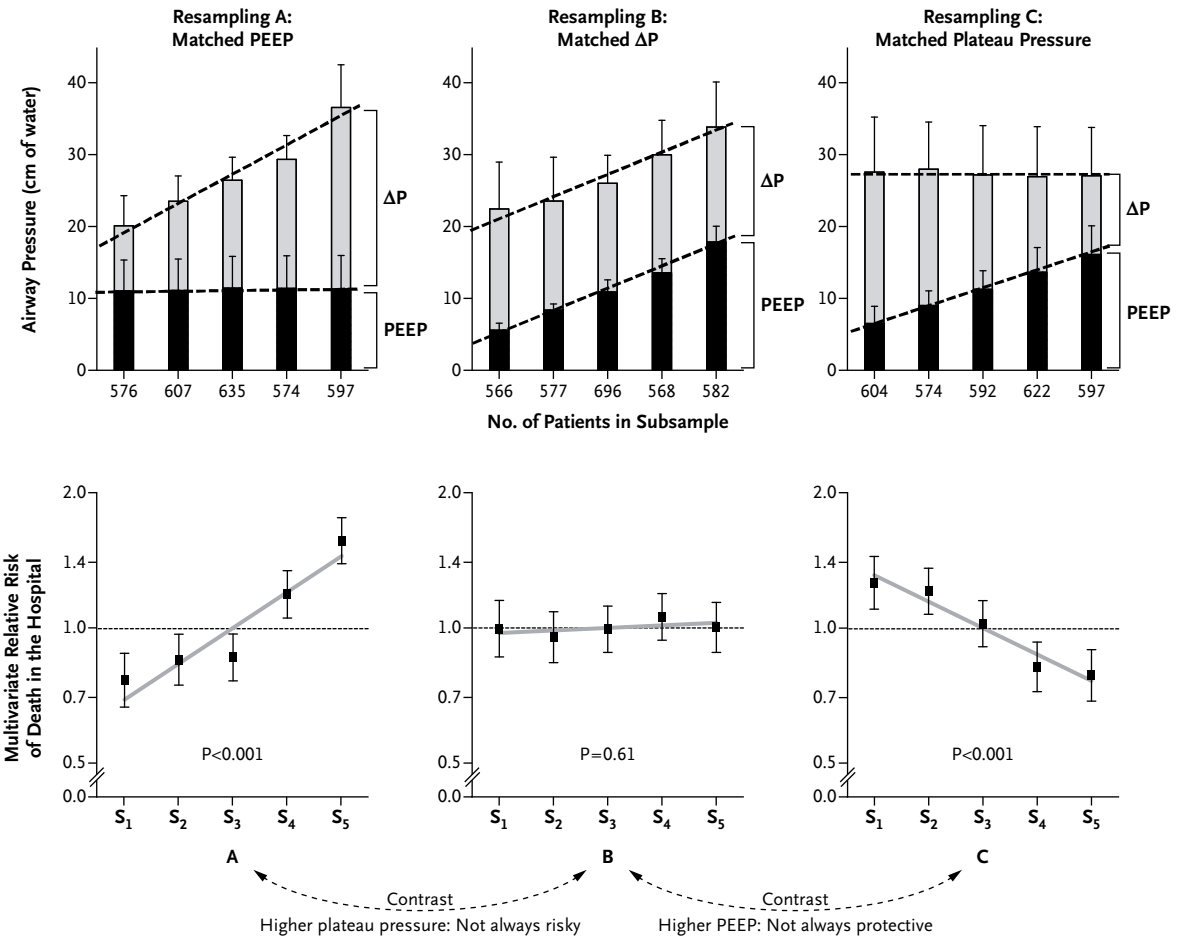

Figure 1. Relative Risk of Death in the Hospital across Relevant Subsamples after Multivariate Adjustment — Survival Effect of Ventilation Pressures.

Using double stratification procedures (obtaining subgroups of patients with matched mean levels for one variable but very different mean levels for another ranking variable; see Section III.3 in the Supplementary Appendix for details), we partitioned our data set into five distinct subsamples (each including approximately 600 patients with the acute respiratory distress syndrome [ARDS]) and calculated the relative risk (adjusted mortality) for each subsample in comparison with the mean risk in the combined population. The upper stacked-bar diagrams illustrate the mean values for positive end-expiratory pressure (PEEP), plateau pressure, and driving pressure (ΔP) observed in each subsample. The error bars represent 1 standard deviation. Each resampling (A, B, and C) produced subsamples with similar mean values for one ventilator variable but very distinct values for the two other variables. At the bottom, the respective relative risks for death in the hospital are shown, calculated for each subsample after multivariate adjustment (at the patient level) for the five covariates (trial, age, risk of death according to the Acute Physiology and Chronic Health Evaluation [APACHE] or Simplified Acute Physiology Score [SAPS], arterial pH at entry, and Pao_2:FIo_2 at entry) specified in model 1. Error bars represent 95% confidence intervals. A relative risk of 1 represents the mean risk of the pooled population, which had an adjusted survival rate of 68% at 60 days. Note that a lower survival rate was observed among patients with higher ΔP and higher survival was observed among patients with lower ΔP, independent of concomitant variations in PEEP and plateau pressure.

adjusted for the effect of underlying lung disease on the mechanical characteristics of the lung, that ΔP 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 ΔP. No other ventilation variable had such a mediating effect.

We identified the striking correlations between

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V_T and survival or between V_T and barotrauma only when we scaled V_T to individual C_{RS} values ($\Delta P = V_T/C_{RS}$) (Fig. S5 in the Supplementary Appendix). This scaling has a strong physiological basis. In patients with ARDS, C_{RS} is directly related to functional lung size (the volume of aerated lung available for tidal ventilation).[17,18] 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 calculate[27]; 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 V_T. Implicitly, we hypothesized that the functional lung size during disease is better quantified by C_{RS} than by predicted body weight. Under such conditions, especially when C_{RS} varies considerably among patients, cyclic strain, ventilator-induced lung injury, and survival should all be correlated with ΔP rather than with V_T.

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]

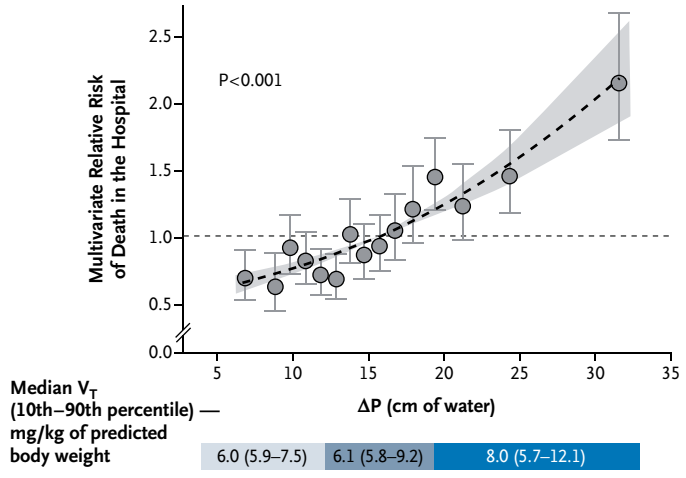

Figure 2. Relative Risk of Death in the Hospital versus ΔP in the Combined Cohort after Multivariate Adjustment.

The combined cohort (with 1249 death events) was partitioned into 15 quantiles of ΔP, and the relative risk for each quantile was calculated in relation to the mean risk of the combined population (assumed to be 1). The mean risk and 95% confidence intervals (error bars) for each percentile were calculated after multivariate adjustment at the patient level (Cox proportional-hazards model) for the five covariates (trial, age, risk of death according to APACHE or SAPS, arterial pH at entry, and Pao_2:Fio_2 at entry) specified in model 1. The gray zone represents the 95% confidence interval for the Cox regression (dashed line) across the whole population when ΔP is considered as a continuous variable.

The Acute Respiratory Distress Syndrome Network (ARDSNet) trial[2] is often viewed as showing that low V_T 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 V_T 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 PEEPs did not show consistent survival benefits[4,10-12]; PEEP increments might be protective only when the increased PEEP values result in a change in lung mechanics so that the same V_T can be delivered with a lower ΔP. This hypoth-

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esis is consistent with recent physiological studies suggesting that the benefits of PEEP are found mainly in patients with greater lung recruitability,[15] with some harm reported when PEEP caused overdistention.[15,32,33] Well-known devastating effects of zero-PEEP ventilation[7,8] have been related to progressive atelectasis, decreased lung compliance, and ultimately higher ΔP.[34]

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 ΔP, 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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