SPECIAL ARTICLE

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D., Laurent Brochard, M.D., Eduardo L.V. Costa, M.D., David A. Schoenfeld, Ph.D., Thomas E. Stewart, M.D., Matthias Briel, M.D., Daniel Talmor, M.D., M.P.H., Alain Mercat, M.D., Jean-Christophe M. Richard, M.D., Carlos R.R. Carvalho, M.D., and Roy G. Brower, M.D.

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.)

From the Cardio-Pulmonary Department, Pulmonary Division, Heart Institute (Incor), University of São Paulo (M.B.P.A., E.L.V.C., C.R.R.C.), and the Research and Education Institute, Hospital Sirio-Libanês (E.L.V.C.) — both in São Paulo; the Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, ON (M.O.M., T.E.S., M.B.), and the Keenan Research Centre for Biomedical Science, St. Michael's Hospital (A.S.S., L.B.), and the Interdepartmental Division of Critical Care Medicine and Department of Medicine, University of Toronto (A.S.S., L.B.), Toronto — all in Canada; the Massachusetts General Hospital Biostatistics Center, Harvard Medical School (D.A.S.), and Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School (D.T.) — both in Boston; the Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland (M.B.); the Department of Intensive Care and Hyperbaric Medicine, Angers University Hospital, Angers (A.M.), the Emergency Department, General Hospital of Annecy, Annecy (J.-C.M.R.), and INSERM UMR 955, Creteil (J.-C.M.R.) — all in France; and the Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore (R.G.B.). Address reprint requests to Dr. Amato at Faculdade de Medicina, Universidade de São Paulo., Av. Dr. Arnaldo 455, sala 2144 (2nd Fl.), 01246-903, São Paulo, Brazil, or at amato.marcelo.bp@gmail.com.

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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

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

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.

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

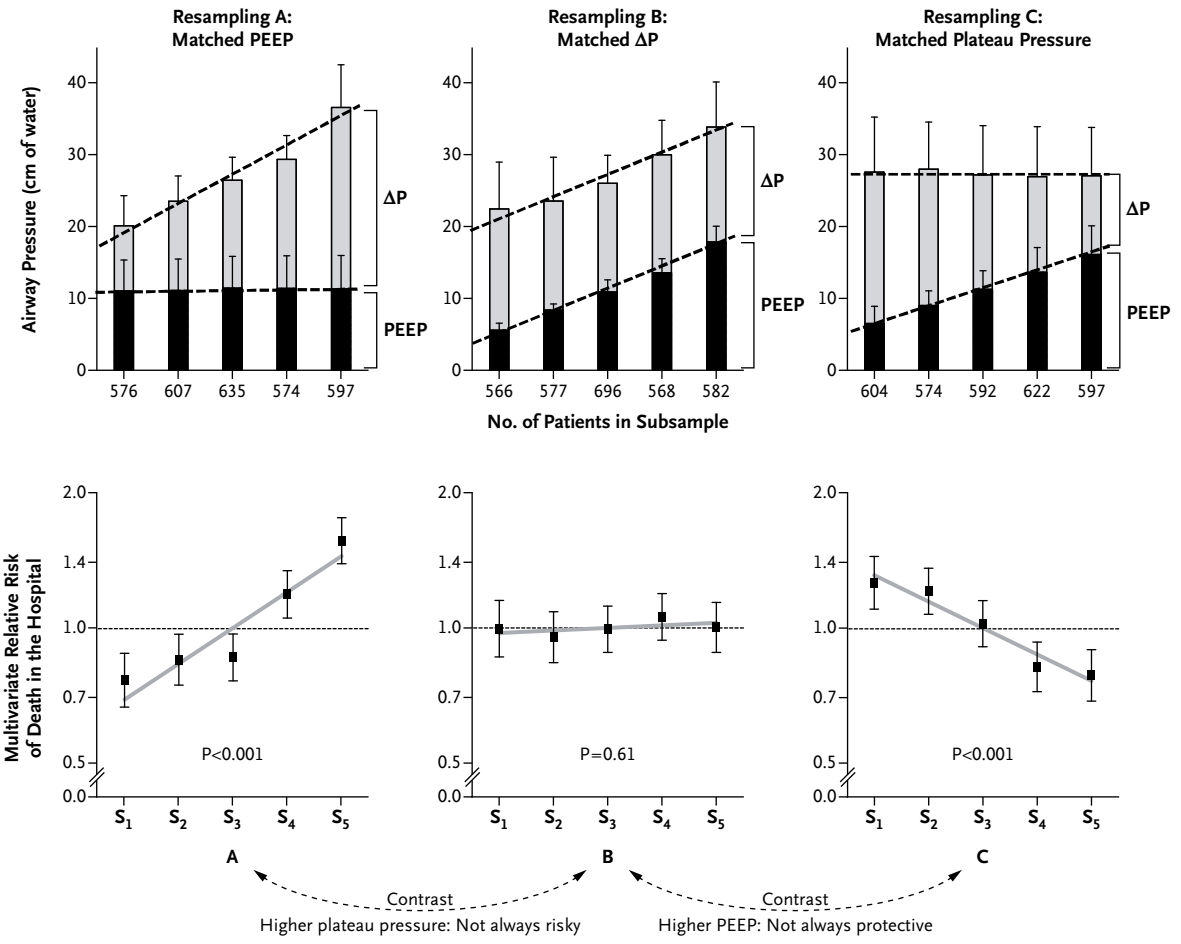

Figure 1. Relative Risk of Death in the Hospital across Relevant Subsamples after Multivariate Adjustment — Survival Effect of Ventilation Pressures.

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

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]

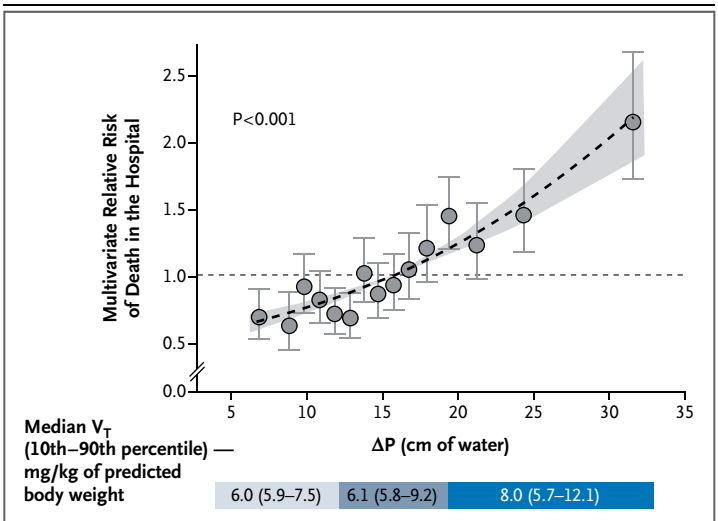

Figure 2. Relative Risk of Death in the Hospital versus ΔP in the Combined Cohort after Multivariate Adjustment.

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-

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.

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

REFERENCES

1. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347-54.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
3. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med 2006;34:1311-8.
4. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303:865-73.
5. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: protection by positive end-expiratory pressure. Am Rev Respir Dis 1974;110:556-65.
6. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137:1159-64.
7. Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 1994;149:1327-34.
8. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 1997;99:944-52.
9. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369:2126-36.
10. Brower RG, Lanken PN, MacIntyre N, et al.Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327-36.
11. Mercat A, Richard J-CM, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:646-55.
12. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:637-45.
13. Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;175:160-6.
14. Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. Am J Respir Crit Care Med 2007;176:761-7.
15. Grasso S, Fanelli V, Cafarelli A, et al. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 2005;171:1002-8.
16. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. Am Rev Respir Dis 1987;136:730-6.
17. Gattinoni L, Pesenti A, Baglioni S, Vitale G, Rivolta M, Pelosi P. Inflammatory pulmonary edema and positive end-expiratory pressure: correlations between imaging and physiologic studies. J Thorac Imaging 1988;3:59-64.
18. Gattinoni L, Pesenti A. The concept of "baby lung." Intensive Care Med 2005;31:776-84.
19. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. Am J Respir Crit Care Med 1998;158:1831-8.
20. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med 1998;338:355-61.
21. Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 1999;27:1492-8.
22. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;359:2095-104.
23. Imai K, Keele L, Tingley D, Yamamoto T. Causal mediation analysis using R. In: Vinod HD, ed. Advances in social science research using R. New York: Springer, 2010:129-54.
24. Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the black box of causality: learning about causal mechanisms from experimental and observational studies. Am Polit Sci Rev 2011;105:765-89.
25. Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. Psychol Methods 2002;7:422-45.
26. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
27. Protti A, Andreis DT, Monti M, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? Crit Care Med 2013;41:1046-55.
28. Verbrugge SJ, Sorm V, van 't Veen A, Mouton JW, Gommers D, Lachmann B. Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental Klebsiella pneumoniae inoculation. Intensive Care Med 1998;24:172-7.
29. Tschumperlin DJ, Oswari J, Margulies AS. Deformation-induced injury of alveolar epithelial cells: effect of frequency, duration, and amplitude. Am J Respir Crit Care Med 2000;162:357-62.
30. Garcia CS, Rocco PR, Facchinetti LD, et al. What increases type III procollagen mRNA levels in lung tissue: stress in-

duced by changes in force or amplitude? Respir Physiol Neurobiol 2004;144:59-70.
31. Ranieri VM, Brienza N, Santostasi S, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med 1997;156:1082-91.
32. Vieira SR, Puybasset L, Lu Q, et al. A scanographic assessment of pulmonary morphology in acute lung injury: significance of the lower inflection point detected on the lung pressure-volume curve. Am J Respir Crit Care Med 1999;159:1612-23.
33. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-86.
34. Seah AS, Grant KA, Aliyeva M, Allen GB, Bates JH. Quantifying the roles of tidal volume and PEEP in the pathogenesis of ventilator-induced lung injury. Ann Biomed Eng 2011;39:1505-16.