Lung-Protective Ventilation in Acute Respiratory Distress Syndrome

How Soon Is Now?

Fifteen years after the landmark trial from the Acute Respiratory Distress Syndrome (ARDS) Network showed improved survival with lung-protective ventilation, using tidal volumes of 6 ml/kg predicted body weight (PBW) and plateau pressures below 30 cm H_2O (1), controversies remain on the specific application of the intervention (2, 3). In this issue of the *Journal*, Needham and colleagues (pp. 177–185) add to this discussion by examining the timing and duration of low tidal volume ventilation in ARDS (4). They screened all ventilated patients in 13 intensive care units (ICUs) at four hospitals for what we would now term mild, moderate, or severe ARDS (5). Data on the tidal volume were collected on the first available reading after ARDS onset and then twice daily while the patient remained ventilated, resulting in 11,558 assessments for 482 patients with ARDS. This remarkable level of time-dependent data allows for a detailed examination of the day-to-day changes in tidal volume during ARDS.

Many randomized trials in ARDS exclude 80 to 90% of patients screened. In contrast, this observational cohort captured 70% of patients with ARDS and better reflects real-world practice. Patients were enrolled 4 to 7 years after publication of the landmark trial, yet only 32% of the patients with ARDS had an initial tidal volume of 6.5 ml/kg PBW or lower, which was similar to other cohorts from those years (6). More recent data still show high rates of noncompliance with low tidal volume ventilation in ARDS (7, 8). Tidal volumes did not decrease much over the subsequent ICU days. Forty-four percent of the patients with initial tidal volumes 6.5 ml/kg PBW or higher never had any recorded tidal volumes of 6.5 ml/kg PBW or lower. The initial tidal volume after the onset of ARDS set the course for the entire duration of mechanical ventilation. At any time, more than 70% of the patients ventilated at each point either stayed in lung-protective ventilation if they started with volumes of 6.5 ml/kg PBW or lower, or remained with elevated tidal volumes, if their initial volumes were set higher than 6.5 ml/kg PBW.

This analysis emphasizes the association between low tidal volume ventilation and mortality in ARDS with a 23% relative increase in ICU mortality for every 1 ml/kg PBW increase in initial tidal volume. Additional research on long-term mortality will be needed, but a prior report from this group did show that the low tidal volume ventilation was associated with better survival at 2 years (9). Among those patients with initial tidal volumes of 6.5 ml/kg PBW or higher, any subsequent decrease in tidal volume was associated with improved mortality compared with those patients with ARDS whose tidal volume was increased or unchanged. No significant difference in mortality was seen with changes in tidal volume if the patient had an initial tidal volume of 6.5 ml/kg PBW or less, although this is likely because both the number of these patients and the magnitude of their tidal volume change were small. A previous study from the ARDS Network found no association between hospital mortality and tidal volume in the 48 hours before enrollment into trials (10). However, this was in a highly selected population that was exposed to 48 hours or less of preenrollment tidal volume after ARDS onset, and then, as part of the trial, all participants were all placed on low tidal volume ventilation for the rest of their time in the ICU. Thus, the total time of exposure to higher tidal volume was very limited.

What about tidal volumes during weaning? In this study, tidal volume was measured throughout the course of mechanical ventilation, so some increases in tidal volume may reflect the spontaneous tidal volumes during breathing trials or on pressure support ventilation. This would not explain the findings here, as it would bias the results toward the null. The results from this study suggest that the greatest effect of low tidal volume ventilation occurs initially at the onset of ARDS. Thus, patients with ARDS who are weaning successfully from the ventilator should not be sedated and placed back on low tidal volume ventilation if they are able to spontaneously breathe in larger volumes. This is also consistent with practices used in most trials of lung-protective ventilation, in which tidal volume limits did not apply to those on low levels of positive end-expiratory pressure, $F_{I_{O_2}}$, and pressure support (1, 11). The question of what to do about patients early in the course of ARDS who still have significant lung injury and who are generating large spontaneous breaths remains open.

What are the implications of these findings for clinical practice? Lack of equipoise preclude any randomized control trial on timing of low tidal volume ventilation in ARDS, but the results from this cohort are robust under various sensitivity analyses and consistent with prior clinical and preclinical studies (12, 13). Clinicians should move to initiate low tidal volume ventilation as soon as possible in ARDS. To do so, several challenges must be addressed. First, there must be more timely detection of ARDS. Conceivably, respiratory therapists in the ICU can routinely screen all ventilated patients for ARDS by the oxygen saturation, as measured by pulse oximetry/$F_{I_{O_2}}$ or $Pa_{O_2}/F_{I_{O_2}}$ ratios. Although electronic ARDS sniffers have been reported to be sensitive and specific (14), screening for the radiologic component of ARDS can be difficult to operationalized electronically. Nevertheless, it is entirely possible for most hospital electronic medical systems to electronically detect and alert clinicians to ventilated patients with severe hypoxemia for the evaluation of ARDS and lowering of tidal volume.

With detection of ARDS, there is still the challenge of ensuring that patients are actually placed on low tidal volumes. As this study shows, female and obese patients are more likely to be placed on high tidal volume ventilation. This pattern is often reported in other studies and likely reflects the calculation of tidal volume based on actual body weight, rather than PBW (15, 16). In this article, the authors suggest a default setting of 6 ml/kg PBW for all ventilated patients, as lung-protective ventilation may decrease pulmonary complications and development of ARDS in patients without ARDS. Although challenges

remain with patients who spontaneously generate large tidal volumes, we agree with this recommendation that ICU clinicians should rarely set or target a tidal volume much above 6 ml/kg PBW.

The issue of timing of treatment is familiar to critical care physicians in sepsis, trauma, acute myocardial infarction, and acute cerebrovascular accidents. It should not be surprising that timely recognition and treatment of ARDS should also be important. With this study, Needham and colleagues have brought the issue to forefront and started the clock. ■

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Toward Improved Diagnosis of Early Asthma

A well-known adage among clinicians is that "all that wheezes is not asthma," which invites the question, Which wheezing is asthma? This is an especially difficult question to answer in the preschooler, but it is an important one. Wheezing is very common in children younger than 6 years, with almost half of children having at least one episode early in life (1). However, wheezing resolves by age 6 years in the majority of these children, so they are diagnosed in retrospect as having "transient wheeze of childhood" (2). However, most of the children who are eventually diagnosed with asthma report wheezing early in life (3), so the challenge is to identify the subset of children who will eventually go on to develop persistent wheezing.

The tools currently available to clinicians and researchers to predict asthma in young children are generally easy to use, but they have relatively poor positive predictive value. The Asthma Predictive Index (API) developed from the Tucson Children's Respiratory Study is a well-studied and simple tool for use in children who wheeze, incorporating information on child eczema, parental asthma, child rhinitis, and blood eosinophilia (4). In multiple studies, the API performs best as a negative predictive tool (i.e., a negative API indicates very low asthma risk), but the

ORIGINAL ARTICLE

Timing of Low Tidal Volume Ventilation and Intensive Care Unit Mortality in Acute Respiratory Distress Syndrome

A Prospective Cohort Study

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Abstract

Rationale: Reducing tidal volume decreases mortality in acute respiratory distress syndrome (ARDS). However, the effect of the timing of low tidal volume ventilation is not well understood.

Objectives: To evaluate the association of intensive care unit (ICU) mortality with initial tidal volume and with tidal volume change over time.

Methods: Multivariable, time-varying Cox regression analysis of a multisite, prospective study of 482 patients with ARDS with 11,558 twice-daily tidal volume assessments (evaluated in milliliter per kilogram of predicted body weight [PBW]) and daily assessment of other mortality predictors.

Measurements and Main Results: An increase of 1 ml/kg PBW in initial tidal volume was associated with a 23% increase in ICU mortality risk (adjusted hazard ratio, 1.23; 95% confidence interval [CI], 1.06–1.44; $P = 0.008$). Moreover, a 1 ml/kg PBW increase in subsequent tidal volumes compared with the initial tidal volume was associated with a 15% increase in mortality risk (adjusted hazard ratio, 1.15; 95% CI, 1.02–1.29; $P = 0.019$). Compared with a prototypical patient receiving 8 days with a tidal volume of 6 ml/kg PBW, the absolute increase in ICU mortality (95% CI) of receiving 10 and 8 ml/kg PBW, respectively, across all 8 days was 7.2% (3.0–13.0%) and 2.7% (1.2–4.6%). In scenarios with variation in tidal volume over the 8-day period, mortality was higher when a larger volume was used earlier.

Conclusions: Higher tidal volumes shortly after ARDS onset were associated with a greater risk of ICU mortality compared with subsequent tidal volumes. Timely recognition of ARDS and adherence to low tidal volume ventilation is important for reducing mortality.
Clinical trial registered with www.clinicaltrials.gov (NCT 00300248).

Keywords: acute lung injury; tidal volume; artificial respiration; prospective studies

Randomized trials and metaanalyses have shown that use of low tidal volumes reduces mortality in patients with acute respiratory distress syndrome (ARDS) (1–4). However, as part of routine clinical care, patients may not consistently receive this evidence-based therapy in part because of barriers in the timely recognition of ARDS and in initiating and sustaining low tidal volume ventilator settings thereafter (5–11). The potential harm of delayed initiation of low tidal volume ventilation

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At a Glance Commentary

Scientific Knowledge on the Subject: Reducing tidal volume decreases mortality in mechanically ventilated patients with acute respiratory distress syndrome (ARDS); however, the effect of the timing of low tidal volume ventilation is not well understood.

What This Study Adds to the Field: In this multisite, prospective cohort study of patients with ARDS, higher tidal volumes shortly after ARDS onset were associated with an even greater risk of intensive care unit mortality compared with subsequent tidal volumes. Timely recognition of ARDS and prompt adherence to low tidal volume ventilation thereafter may be important for maximally reducing intensive care unit mortality in patients with ARDS.

is not fully understood. Preclinical studies and randomized trials support that higher tidal volumes, for periods as short as minutes to hours, may be harmful (12–17). Despite this evidence, one prior study, using data from ARDS Network clinical trials, could not detect an association between hospital mortality and tidal volumes received in the initial 36- to 48-hour period after ARDS onset and before study enrollment (18). This prior study's finding may have been influenced by evaluating a select patient population who (*1*) were eligible and consenting for a clinical trial, (*2*) survived for 36–48 hours after ARDS onset before trial enrollment, and (*3*) were strictly managed with a low tidal volume ventilation protocol after enrollment. Hence, using a multisite prospective cohort study of patients with ARDS receiving routine medical care, our objective was to evaluate the association of initial tidal volume and change in tidal volume over time, with mortality in the intensive care unit (ICU).

Methods

On a daily basis, we prospectively screened patients for eligibility in this study, including detailed review of data in medical records and review of chest radiograph to enroll 520 patients with ARDS from 13 medical, surgical, and trauma ICUs at four teaching hospitals in Baltimore, Maryland. The ARDS inclusion criteria for enrollment were mechanical ventilation, $Pa_{O_2}/F_{I_{O_2}}$ ratio less than 300, and meeting the American-European Consensus Conference criteria (1) that were in effect at the time of screening for this study (2004–2007). ARDS onset was defined as the time at which a patient met all inclusion criteria. Consistent with the more recent Berlin consensus meeting (19), we use the term ARDS, rather than acute lung injury, throughout this report. Neurologic specialty ICUs and patients with ARDS with primary neurologic disease or head trauma were not eligible for this study. Because the study was designed to evaluate the association of critical illness and ICU care, in particular lung protective mechanical ventilation, on patient's long-term mortality and functional outcomes (5, 20), the study had the following relevant exclusion criteria (Figure 1) at the onset of ARDS: (*1*) prior lung resection, (*2*) transfer from another hospital with preexisting ARDS of greater than 24 hours duration, (*3*) mechanically ventilated for more than 5 days before ARDS onset, (*4*) a physician order limiting the use of life-support therapies or preexisting comorbid illness with a life expectancy less than 6 months (e.g., metastatic cancer), (*5*) preexisting cognitive impairment or communication/language barriers, and (*6*) no fixed address.

Institutional review board approval was obtained from all participating sites with a waiver of informed consent granted for abstraction of preexisting data from the medical record. Written informed consent was obtained from survivors after they regained decision-making capacity (or from a proxy if a patient remained incapable of decision-making).

Assessment of Primary Outcome: ICU Survival

At the study site hospitals, patients receiving mechanical ventilation were rarely transferred elsewhere within the hospital (e.g., a stepdown unit) or to another healthcare facility (e.g., a long-term acute care hospital). Hence, because of its temporal proximity to the primary exposure in this analysis, the primary outcome, selected *a priori*, was time to death in the ICU (in days) during patients' ICU admission for ARDS.

Assessment of Primary Exposure: Tidal Volume

The primary exposure was tidal volume received while mechanically ventilated, modeled as milliliter per kilogram of predicted body weight (PBW; calculated based on patient sex and height [2]). This time-varying exposure was recorded at 12-hour increments over the entire duration of mechanical ventilation and partitioned into two parts: the first available tidal volume after ARDS onset, and the time-varying change in current tidal volume relative to this initial tidal volume.

Baseline and Time-Varying Covariates

Our analysis adjusted for 29 baseline and time-varying covariates previously identified as potential confounders (5) and obtained from patients' medical records. Baseline variables included age, sex, body mass index, Charlson comorbidity index (21), severity of illness within 24 hours of ICU admission (Acute Physiology And Chronic Health Evaluation II score [22]), ARDS risk factor (sepsis vs. other), ICU type (medical vs. surgical), patient location before ICU admission (e.g., emergency department), year of study enrolment, and study site identifier. Time-varying covariates were obtained either daily or twice-daily. Daily covariates included organ dysfunction (Sequential Organ Failure Assessment score [23]), sedation and delirium status (Richmond Agitation and Sedation Scale [24] and Confusion Assessment Method for the ICU [25], respectively), dose of systemic corticosteroids and neuromuscular blocking agents, and net fluid balance (total fluid input minus total fluid output). Twice-daily covariates represented mechanical ventilation parameters, including positive end-expiratory pressure, Pa_{O_2}, $F_{I_{O_2}}$, arterial pH, actual respiratory rate, use of high-frequency oscillatory and airway pressure release ventilation modes, and static compliance of the respiratory system (3).

Statistical Analysis

Descriptive statistics summarized the baseline and time-varying covariates for all subjects, with comparison between patient groups conducted using the Wilcoxon rank-sum and Fisher exact tests, as appropriate. As per the original clinical trial (1), a tidal volume of less than or equal to 6.5 ml/kg PBW was used to define

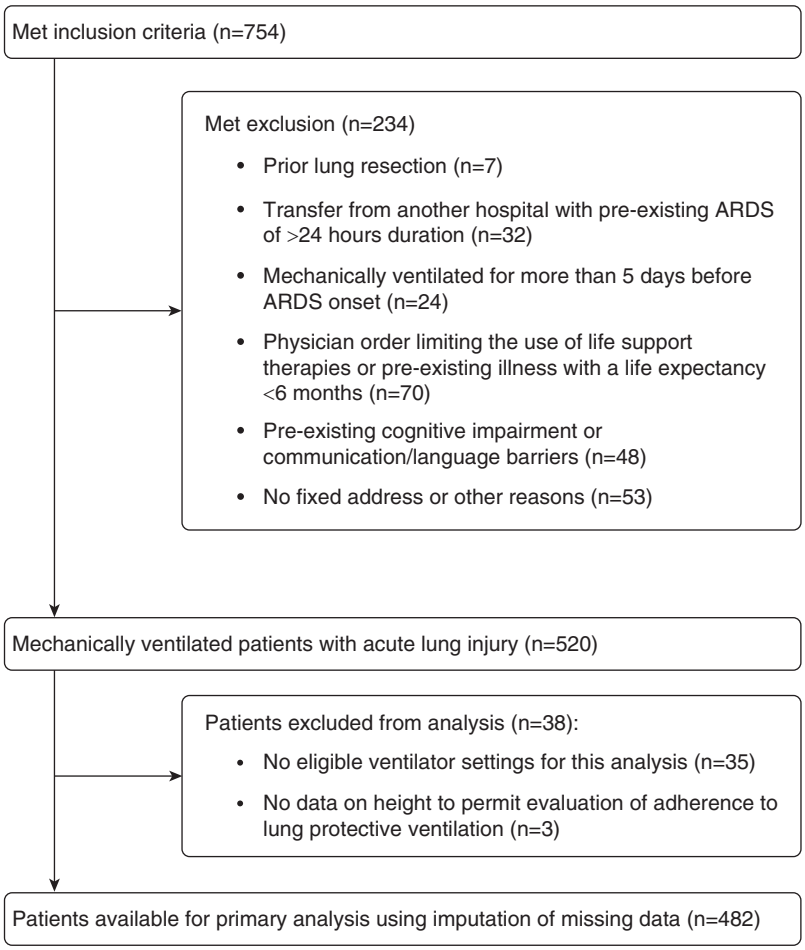

Figure 1. Flow of patients through study. ARDS = acute respiratory distress syndrome.

adherence to the low tidal volume goal of 6.0 ml/kg PBW. Kaplan-Meier plots with log-rank tests were used for unadjusted analyses of patient survival. A multivariable Cox regression model was used to evaluate death as a function of the time-varying tidal volume (primary exposure), after accounting for the duration of mechanical ventilation and the other 28 baseline and time-varying covariates as previously described, with the time-varying covariates modeled as cumulative averages. A potential time-varying effect of tidal volume on ICU mortality over the duration of a patient's ICU stay was evaluated by including statistical interaction of the primary exposure (as previously described) with time (measured in 12-h intervals). Statistical interaction between the two parts of the primary exposure (i.e., initial tidal volume and change in current tidal volume relative to initial tidal volume) was also evaluated. As a sensitivity analysis, a Fine and Gray proportional subhazards regression model was fit, treating ICU discharge as a competing risk. This sensitivity analysis was conducted to confirm appropriateness of the Cox regression analysis assumption of noninformative censoring of ICU discharge in evaluating the outcome of ICU mortality.

We used standard statistical diagnostic procedures to evaluate the model. To assess the linearity assumption for continuous covariates, we plotted Martingale residuals against covariate values using a nonparametric LOESS-smoother. For each covariate, we also assessed the proportional hazards assumption via graphical displays of scaled Schoenfeld residuals and via performing individual tests of proportional hazards. We assessed the influence of individual observations by comparing the relative change in the estimated regression coefficients by deleting each observation, in turn, from the model, with no observation demonstrating high influence.

To illustrate the effects of the exposure-outcome relationship, the previously described Cox regression model was used to estimate the absolute difference in the cumulative risk of mortality at 8 days after ARDS onset, for a prototypical patient having median values for all continuous covariates and mode values for all binary covariates, with various profiles of tidal volume settings assumed during the ICU stay.

There were no missing data for patient-level characteristics. For the ventilator setting data (i.e., positive end-expiratory pressure, Pa_{O_2}/FI_{O_2}, and respiratory rate), there were less than 0.2% missing for the cumulative averages used in the regression model. To impute the 10% missing data for plateau pressure (used to calculate static compliance of the respiratory system [26]), we used multiple imputation (with five imputed datasets), as previously described (5). As an *a priori* sensitivity analysis for this imputation, we repeated all analyses using a subset of the entire dataset that excluded ventilator settings with missing plateau pressure (analysis of "complete data"). Statistical significance was defined as a two-sided P less than 0.05. All statistical analyses were completed using R statistical software (version 3.0.3) (Foundation for Statistical Computing, Vienna, Austria) and STATA 12.1 (StataCorp, College Station, TX).

Results

Overall, prospective screening identified 754 patients meeting inclusion criteria, of whom 234 met exclusion criteria (Figure 1). Consequently, 520 patients were enrolled in the study, of whom 38 were excluded from the analysis, 35 (7%) had no eligible ventilator settings for this analysis (e.g., exclusive use of high-frequency oscillation or airway pressure release ventilation), and 3 (<1%) had missing data on height (required for calculating PBW for the primary exposure). Thus, 482 patients, with 11,558 total ventilator settings, were available for analysis. For the sensitivity analysis of complete data (see METHODS), 482 patients with 10,397 ventilator settings were available.

Tables 1 and 2 present patient characteristics and mechanical ventilation data by initial tidal volume of less than or equal to 6.5 versus greater than 6.5 ml/kg PBW (n = 154 [32%] vs. 328 [68%]) and by ICU mortality status. During their ICU

Table 1. Patient Characteristics by First Tidal Volume after ARDS and ICU Mortality Status

		First Tidal Volume			At ICU Discharge		
	All Patients (*n* = 482)	⩽6.5 ml/kg PBW (*n* = 154)	>6.5 ml/kg PBW (*n* = 328)	*P* Value	Alive (*n* = 313)	Dead (*n* = 169)	*P* Value
Median (IQR) age	53 (42–63)	51 (41–60)	53 (43–65)	0.015	51 (41–61)	55 (45–66)	0.033
Male sex	271 (56%)	119 (77%)	152 (46%)	<0.001	181 (58%)	90 (53%)	0.338
Underweight (body mass index < 18.5)	27 (6%)	10 (6%)	17 (5%)	0.533	15 (5%)	12 (7%)	0.305
Overweight or obese (body mass index ⩾ 25)	306 (63%)	84 (55%)	222 (68%)	0.006	202 (65%)	104 (62%)	0.552
Median (IQR) Charlson comorbidity index	2 (1–4)	3 (1–5)	2 (1–4)	0.224	2 (1–4)	3 (2–5)	<0.001
Median (IQR) APACHE II score	27 (20–33)	27 (21–36)	26 (20–33)	0.115	24 (19–30)	31 (25–37)	<0.001
Sepsis as acute lung injury risk factor	358 (74%)	121 (79%)	237 (72%)	0.148	220 (70%)	138 (82%)	0.006
Admission to medical ICU	410 (85%)	144 (94%)	266 (81%)	<0.001	256 (82%)	154 (91%)	0.007
Admission to ICU from emergency department	201 (42%)	60 (39%)	141 (43%)	0.429	138 (44%)	63 (37%)	0.175
Median (IQR) mean daily SOFA score	8 (5–12)	9 (6–12)	8 (5–13)	0.151	6 (4–9)	13 (9–15)	<0.001
Median (IQR) number of days of delirium in ICU	1 (0–5)	1 (0–4)	1 (0–6)	0.072	2 (0–6)	0 (0–2)	<0.001
Median (IQR) number of days of deep sedation in ICU	3 (1–7)	4 (1–9)	3 (1–7)	0.022	3 (1–7)	3 (1–7)	0.568
Ever received corticosteroid	324 (67%)	109 (71%)	215 (66%)	0.298	190 (61%)	134 (79%)	<0.001
Median (IQR) number of days of steroid use, if any	5 (3–9)	5 (2–9)	5 (3–10)	0.502	6 (3–10)	5 (2–9)	0.045
Median (IQR) cumulative dose of prednisone, if any, mg	322 (150–726)	300 (107–648)	339 (153–759)	0.202	355 (156–893)	291 (126–534)	<0.001
Ever received neuromuscular blockade	117 (24%)	45 (29%)	72 (22%)	0.088	68 (22%)	49 (29%)	0.095
Median (IQR) number of days of neuromuscular blockade, if any	2 (1–3)	2 (1–4)	1 (1–2)	0.127	1 (1–2)	2 (1–4)	0.073
Median (IQR) cumulative dose of vecuronium, if any, mg	2 (1–23)	3 (1–51)	1 (1–12)	0.089	1 (1–8)	3 (1–72)	0.036
Median (IQR) cumulative ICU fluid balance, L	9 (2–20)	8 (1–20)	10 (3–21)	0.182	6 (0–18)	14 (6–23)	<0.001
HFOV (ever)	57 (12%)	20 (13%)	37 (11%)	0.650	27 (9%)	30 (18%)	0.005
APRV (ever)	62 (13%)	10 (6%)	52 (16%)	0.003	51 (16%)	11 (7%)	0.002
Median number of settings with HFOV, if any	5 (2–11)	4 (2–8)	7 (3–13)	0.382	8 (4–13)	4 (2–8)	0.082
Median number of settings with APRV, if any	10 (5–18)	9 (5–19)	10 (5–17)	0.800	10 (6–17)	14 (2–32)	0.830
Median days of ventilation (all settings) (IQR)	9 (5–17)	9 (5–17)	9 (5–17)	0.746	11 (7–19)	7 (3–13)	<0.001
ICU length of stay	13 (8–22)	13 (7–20)	14 (8–23)	0.474	16 (10–25)	8 (5–16)	<0.001

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; APRV = airway pressure release ventilation; ARDS = acute respiratory distress syndrome; HFOV = high-frequency oscillatory ventilation; ICU = intensive care unit; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

stay, 169 (35%) of the 482 patients died. The entire 482 patient cohort had a median (interquartile range) age of 53 (42–63) years and Acute Physiology and Chronic Health Evaluation II score of 27 (20–33), with 56% male, 74% with sepsis as the primary ARDS risk factor, and 85% in a medical ICU (Table 1). Across all 11,558 twice-daily mechanical ventilator settings observed throughout the ICU stay for the 482 patients, the median (interquartile range) positive end-expiratory pressure was 5 (5–10) and tidal volume was 6.6 (5.9–8.0) ml/kg PBW (Table 2). More specifically, 328 (68%) of the 482 patient cohort had an initial tidal volume greater than 6.5 ml/kg PBW, with 183 (56%) of these 328 patients ever having a tidal volume of less than or equal to 6.5 ml/kg PBW thereafter and 23 (7%) of them having all subsequent tidal volumes less than or equal to 6.5 ml/kg. Additional details describing changes in tidal volume over time are provided in Figure 2.

Unadjusted survival analysis of patients with their first tidal volume after ARDS onset of greater than 6.5 ml/kg PBW demonstrated that a subsequent decrease (vs. increase) in tidal volume was associated with significantly improved survival ($P = 0.008$) that was not observed for patients with a first tidal volume of less than or equal to 6.5 ml/kg PBW ($P = 0.446$) (Figure 3). After adjusting for all covariates, an increase of 1 ml/kg PBW in initial tidal volume was associated with a 23% increase in the risk of ICU mortality (hazard ratio, 1.23; 95% confidence interval, 1.06–1.44; $P = 0.008$). Moreover, during

Table 2. Mechanical Ventilation Variables by First Tidal Volume after ARDS and ICU Mortality Status*

	All Ventilator Settings† (*n* = 11,558)	First Tidal Volume			At ICU Discharge		
		≤6.5 ml/kg PBW (*n* = 3,366)	>6.5 ml/kg PBW (*n* = 8,192)	*P* Value	Alive (*n* = 8,335)	Dead (*n* = 3,223)	*P* Value
Median (IQR) positive end-expiratory pressure, per 1 cm H_2O	5 (5–10)	5 (5–10)	5 (5–10)	<0.001	5 (5–8)	5 (5–10)	<0.001
Median (IQR) Pa_{O_2}/FI_{O_2}	199 (142–299)	188 (118–253)	199 (154–299)	<0.001	199 (160–299)	176 (104–242)	<0.001
Number of pH < 7.25	887 (11%)	337 (13%)	550 (10%)	<0.001	426 (7%)	461 (20%)	<0.001
Median (IQR) static compliance of respiratory system, per 10 ml/cm H_2O	31 (22–40)	31 (24–40)	30 (21–40)	<0.001	32 (23–41)	29 (21–37)	<0.001
Median (IQR) respiratory rate, per 1 breath/min	25 (20–33)	30 (22–35)	24 (19–31)	<0.001	24 (19–32)	29 (22–35)	<0.001
Median (IQR) tidal volume (ml/kg predicted body weight)	6.6 (5.9–8.0)	6.0 (5.7–6.6)	7.0 (6.2–8.2)	<0.001	6.7 (6.0–8.0)	6.6 (5.9–7.8)	0.140

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; PBW = predicted body weight.

*Proportions were calculated based on ventilator settings without missing or unknown data and may not add to 100% because of rounding. Missing or unknown data are as follows: positive end-expiratory pressure, 473 (4%); Pa_{O_2}/FI_{O_2}, 81 (1%); pH, 3,527 (31%); static compliance of respiratory system, 1,161 (10%); respiratory rate, 480 (4%); and tidal volume, 1,441 (12%).

†Includes ventilator settings during mechanical ventilator weaning, which represented a mean of 31% (SD, 30%) of patients' entire mechanical ventilation duration. Weaning was generally conducted using daily spontaneous breathing trials with 16% of all mechanical ventilator settings being pressure support mode.

the time after the initial tidal volume setting, a 1 ml/kg PBW increase in tidal volume from the initial setting was associated with a 15% increase in risk of ICU mortality (hazard ratio, 1.15; 95% confidence interval, 1.02–1.29; $P = 0.019$) (*see* Table E1 in the online supplement for full model results). There were no significant statistical interactions of the

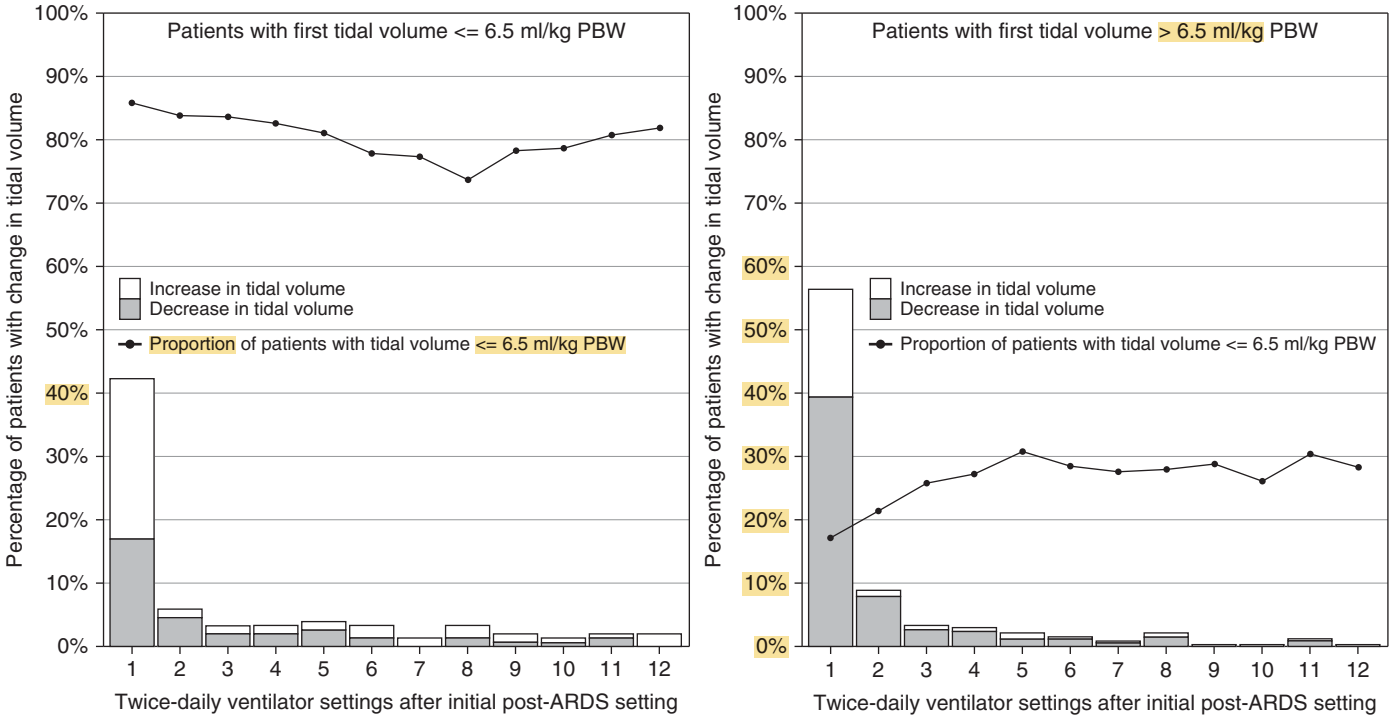

Figure 2. Timing and direction of first change in tidal volume from initial ventilator setting after ARDS onset. The numbers of patients with their first tidal volume after ARDS onset of ≤6.5 and >6.5 ml/kg PBW, respectively, were 154 and 328. The data represented by the *dots* and *connecting line* represent the proportion of patients with tidal volume ≤6.5 ml/kg PBW, calculated based on the number of patients at that point in time that were alive and receiving mechanical ventilation with a measurable tidal volume. In patients with their first tidal volume >6.5 ml/kg, 17% had no change in tidal volume or an increase in tidal volume over all subsequent mechanical ventilator settings, whereas 39% had a decrease in the next ventilator setting with 78% ever having a decrease in tidal volume over all subsequent mechanical ventilator settings. ARDS = acute respiratory distress syndrome; PBW = predicted body weight.

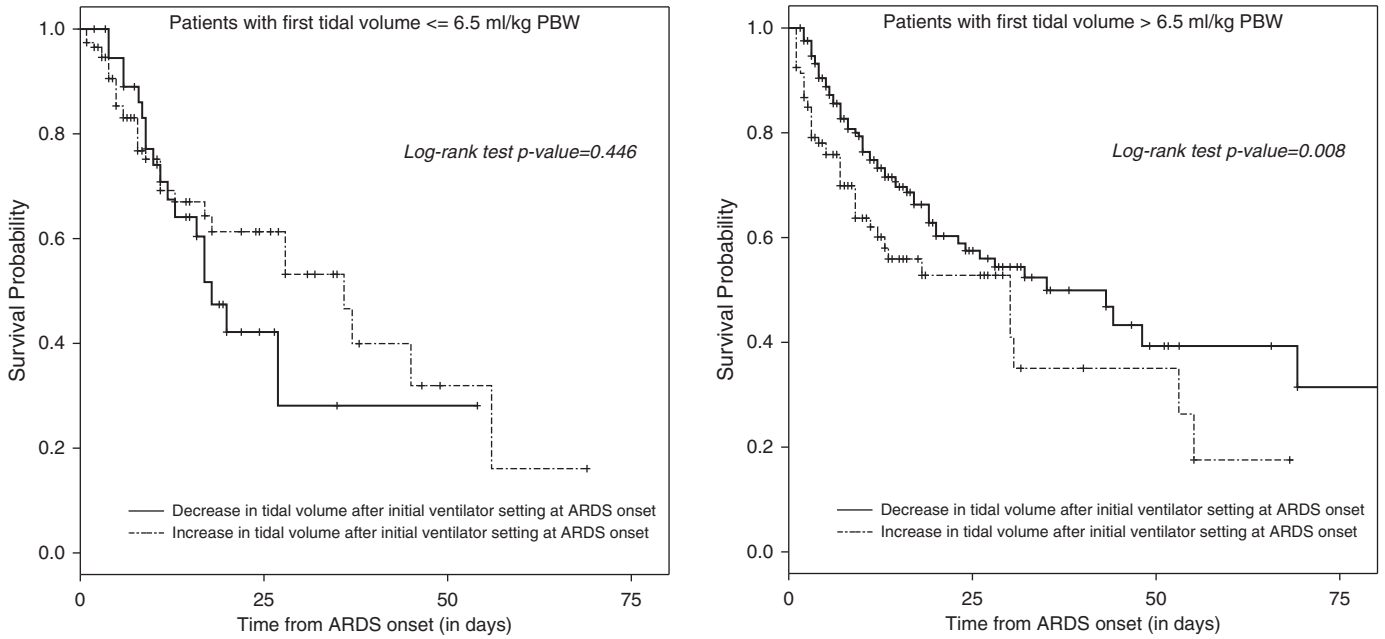

Figure 3. Kaplan-Meier survival curves for increase versus decrease in tidal volume from initial ventilator setting after ARDS onset. The numbers of patients with their first tidal volume after ARDS onset ≤6.5 and >6.5 ml/kg PBW, respectively, were 154 and 328. For patients with first tidal volume >6.5 ml/kg PBW, a subsequent decrease (vs. increase) in tidal volume was associated with significant improvement in survival as illustrated by the Kaplan-Meier survival curves and the log-rank test ($P = 0.008$). For patients with first tidal volume ≤6.5 ml/kg PBW, a subsequent decrease (vs. increase) in tidal volume was not associated with a significant difference in survival ($P = 0.446$). ARDS = acute respiratory distress syndrome; PBW = predicted body weight.

initial tidal volume with the change in current tidal volume relative to initial tidal volume (*see* Table E2), or of these two primary exposures variables with time (*see* Table E3). Sensitivity analyses evaluating ICU discharge as a competing risk (*see* Table E4) and evaluating missing data imputation, as previously described (*see* Table E1), demonstrated results consistent with the primary analysis.

The absolute risk difference in ICU mortality comparing various example profiles of initial and subsequent tidal volume settings for a prototypical patient are summarized in Table 3. Compared with a reference case of the prototypical patient receiving 8 days of mechanical ventilation with a tidal volume of 6 ml/kg PBW, there was an estimated absolute increase in mortality (95% confidence interval) of 7.2% (3.0–13.0%) and 2.7% (1.2–4.6%) for receiving 10 and 8 ml/kg PBW tidal volume across all 8 days. In tidal volume profiles with 4 days of 6 ml/kg PBW and 4 days of 10 ml/kg PBW, the estimated absolute increase in mortality was substantially greater when the 10 ml/kg PBW tidal volume was received in the first 4 days versus in the last 4 days of the 8-day mechanical ventilation period at 4.8% (1.9–8.5%) versus 2.0% (0.6–3.9%) (Table 3).

Discussion

In this multisite, prospective cohort study of patients with ARDS, higher tidal volumes shortly after ARDS onset were associated with an even greater risk of ICU mortality, compared with subsequent tidal volumes. Specifically, after adjusting for other covariates potentially associated with ICU mortality, a 1 ml/kg PBW increase in initial tidal volume or in a subsequent tidal volume setting was associated with a 23% and 15%, respectively, increase in the risk of ICU mortality. Thus, within the setting of routine clinical practice, timely adherence to the use of low tidal volumes for patients with ARDS is associated with improved survival.

In other aspects of care for critically ill patients, such as receipt of antibiotics in septic shock, timely and appropriate initial therapy reduces hospital mortality (27, 28). With respect to ARDS, randomized trials and metaanalyses have shown that use of low tidal volumes reduces mortality (1–4). Moreover, in a randomized trial of abdominal surgery patients mechanically ventilated in the operating room for an average of 5.5 hours, reduced tidal volumes (along with positive end-expiratory pressure and recruitment maneuvers) significantly decreased major postoperative complications (including acute respiratory failure requiring mechanical ventilation) and hospital length of stay (29). Similarly, our analysis demonstrated that earlier use of low tidal volumes was associated with improved ICU survival. Such findings may be explained by higher tidal volumes, even when used for only minutes to hours, overstretching alveoli, releasing inflammatory mediators systematically, and resulting in pulmonary and extrapulmonary organ dysfunction (12–17).

A single prior study, using data from ARDS Network clinical trials, did not find an association of hospital mortality with higher tidal volumes in the 36 to 48 hours preceding strict protocolized implementation of low tidal volume ventilation (18). Differences in study design may explain the discrepancy between our findings and the prior study. For instance, by evaluating patients enrolled in the ARDS Network trials, any patients dying after

Table 3. Estimated Absolute Increase in Risk of ICU Mortality for Prototypical Patient Requiring 8 Days of Mechanical Ventilation*

Case Scenario	Estimated Absolute Increase in ICU Mortality (95% CI)
Reference case with 6 ml/kg PBW tidal volume throughout mechanical ventilation	
Case 0: 8 d of tidal volume = 6 ml/kg PBW*	Reference
Cases with 10 ml/kg PBW tidal volume during mechanical ventilation	
Case 1: 8 d of tidal volume = 10 ml/kg PBW*	7.2% (3.0–13.0%)
Case 2: 4 d of 10 ml/kg PBW, then 4 d of 6 ml/kg PBW	4.8% (1.9–8.5%)
Case 3: 2 d of 10 ml/kg PBW, then 6 d of 6 ml/kg PBW	3.1% (0.8–6.0%)
Case 4: 4 d of 6 ml/kg PBW, then 4 d of 10 ml/kg PBW	2.0% (0.6–3.9%)
Cases with 8 ml/kg PBW tidal volume during mechanical ventilation	
Case 5: 8 d of tidal volume = 8 ml/kg PBW*	2.7% (1.2–4.6%)
Case 6: 4 d of 8 ml/kg PBW, then 4 d of 6 ml/kg PBW	1.8% (0.7–3.1%)
Case 7: 2 d of 8 ml/kg PBW, then 6 d of 6 ml/kg PBW	1.2% (0.3–2.3%)
Case 8: 4 d of 6 ml/kg PBW, then 4 d of 8 ml/kg PBW	0.8% (0.3–1.5%)

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; PBW = predicted body weight.
*To illustrate the effects of the tidal volume (in milliliters per kilogram PBW) over time on ICU mortality, the time-varying multivariable Cox regression model (as described in the METHODS) was used to estimate the absolute difference in the cumulative risk of mortality at 8 d after the onset of acute respiratory distress syndrome, for a prototypical patient who had median values for all continuous covariates and mode values for all binary covariates, across various profiles of tidal volume settings during the ICU stay. Of patients with at least 8 d of mechanical ventilation within the study, 17%, 16%, and 2%, respectively, had tidal volumes of ≤6.5, ≥7.5, and ≥9.5 ml/kg PBW for the first 8 d.

ARDS onset, before enrollment, were excluded. Also, in the ARDS Network trials, all patients after enrollment were strictly managed with a low tidal volume protocol; however, in the usual care setting of our study, among those who did not have an initial tidal volume less than or equal to 6.5 ml/kg PBW, 44% never received tidal volumes less than or equal to 6.5 ml/kg PBW thereafter and only 7% always received tidal volumes less than or equal to 6.5 ml/kg PBW thereafter. Finally, there were differences in patient populations, with more stringent enrollment criteria excluding sicker patients in the ARDS Network trials versus our prospective cohort study.

The findings of this research draw attention to the need for early use of low tidal volume ventilation. In our study, approximately two-thirds of patients with ARDS had their initial tidal volume above 6.5 ml/kg PBW. To facilitate early use of low tidal volumes, timely recognition of ARDS is required along with communication of patient tidal volumes in terms of milliliter per kilogram PBW (7, 30). Moreover, given a high frequency of obesity, the calculation of tidal volume in milliliter per kilogram should be based on PBW, calculated using accurate height measurements rather an actual body weight. For mechanically ventilated patients, daily reevaluation for the onset of ARDS and the appropriateness of tidal volumes is important. Given the mortality benefit of low tidal volume ventilation and challenges in timely recognition of ARDS, there may be benefit for all mechanically ventilated patients of ICU-wide protocols that default to 6 ml/kg PBW, with a specific physician order required for use of higher tidal volumes (6, 12, 31, 32). Such an approach may play a role in preventing the development of ARDS in mechanically ventilated patients in addition to reducing mortality in those with ARDS (12). Moreover, having better integration between electronic medical records and mechanical ventilators may allow for improved setting of tidal volumes or creating alerts to notify clinicians of potentially harmful ventilator settings (33).

This study has potential limitations. First, this study was observational in design; hence, we cannot prove causation between the magnitude and timing of tidal volumes and ICU survival because there are both measured and unmeasured differences in patient groups with higher versus lower tidal volumes. However, a randomized trial evaluating delayed delivery of low tidal volume ventilation to patients with ARDS would not be ethical to conduct. Moreover, causality is plausible given the dose-response effect observed in this study, along with the consistency of our findings with both preclinical studies and randomized trials (12–17). Second, missing data on plateau pressure (used to calculate static compliance of the respiratory system [26]) have potential to bias study results; however, the primary analysis with multiple imputation of missing data and a secondary analysis of complete data showed similar results, which is reassuring. Third, only teaching hospitals from a single city were included in this research and there were exclusion criteria for patient enrollment which may limit the generalizability of these findings. However, four hospitals with 13 ICUs were included in the study, with substantial variability in routine medical care delivered, and the eligibility criteria were relatively limited compared with prior randomization controlled trials of low tidal volume ventilation, which aid in generalizability of our findings. Fourth, the data for this study are from 2004–2007. Since this study period, clinical practices with respect to adherence to low tidal volume ventilation and other aspects of ICU care may have changed and potentially modified these findings. However, the consistency of these results to both older and more recent preclinical and clinical data (12–17, 29) may support their continued importance to clinical care for patients with ARDS. Fifth, this study only collected ventilation data twice per day and did not capture instances in which there were more frequent adjustments to tidal volume settings, which may have understated our characterization of adherence to low tidal volume ventilation. Lastly, although *a priori* research has demonstrated the long-term survival benefit of lung protective ventilation (5), our current analysis evaluating the timing of low tidal volume ventilation only focused on ICU mortality. Hence, future research should evaluate long-term effects.

In conclusion, in this multisite, prospective cohort study of patients with ARDS, higher tidal volumes shortly after ARDS onset were associated with an even greater risk of ICU mortality compared with subsequent tidal volumes. Hence, timely recognition of ARDS and timely adherence to low tidal volume ventilation are important considerations for maximally improving survival for patients with ARDS. ■

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