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Risk Factors for Underuse of Lung Protective Ventilation in Acute Lung Injury

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Abstract

Purpose—We assessed factors associated with underutilization of lung protective ventilation (LPV) in patients with acute lung injury (ALI).

Methods—Secondary analysis of ARDSNet trial data, 1999-2005. Tidal volumes recorded prior to trial randomization were analyzed to determine receipt of LPV [tidal volume ≤ 6.5 cc/kg of predicted body weight (PBW)].

Results—430/1385 (31.2%) participants received LPV. Average tidal volume was 7.65±1.82 cc/kg PBW; measured tidal volumes were greater than "lung protective" tidal volumes predicted by 6.5cc/kg PBW (mean difference 67±108cc, p<0.0001). Multivariate predictors of LPV underutilization were older age [odds ratio (OR) per standard deviation (std) year 1.18 (95% confidence interval: 1.02-1.38)], white race [OR, 1.40 (1.05-1.88)], shorter stature [OR per std centimeter 0.55 (0.48-0.63)], lower Simplified Acute Physiology Score (SAPS)II [OR per std, 0.78 (0.67-0.92)], lower lung injury score [OR per std 0.83 (0.70-0.95)], decreased serum bicarbonate [OR per std mmol/l 0.83 (0.71-0.97)], shorter pre-enrollment ICU stay [OR per std day 0.84 (0.73-0.98)], and use of non-volume-controlled ventilation [OR 3.07 (1.78, 5.27)]. Setting tidal volumes to 450ml (men) or 350ml (women) would provide LPV to 80% of patients with ALI.

Conclusions—Simple interventions could substantially improve adherence with LPV among patients with ALI and warrant prospective study.

Keywords

acute lung injury; risk factors; quality improvement

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INTRODUCTION

Although a decade has elapsed since publication of the landmark Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) "ARMA" trial in support of a lung protective ventilation (LPV) approach, LPV has been poorly adopted.[1] Previous studies have found that less than 50% of patients with acute lung injury (ALI) are ventilated with evidence-based 6cc/kg predicted body weight tidal volumes.[2-6] Two small studies have investigated specific factors associated with use of LPV. These showed that metabolic acidosis, lack of a formal ARDS protocol[5] higher lung compliance, and higher PaO_2/FiO_2[4] were associated with underuse of LPV. Others have hypothesized that under-recognition of ALI[7] and difficulties with calculating predicted body weight (PBW),[8-10] may be factors contributing to underuse of ALI.

Identification of barriers to implementation of evidence-based practice is a critical step towards improving patient outcomes. However, no adequately powered studies have investigated patient-level clinical and demographic factors associated with underuse of LPV. Baseline data from ARDSNet trial participants present a unique opportunity to study practice patterns across multiple centers. We sought to determine the factors associated with underuse of LPV prior to randomization of these trial participants with recognized ALI. We hypothesized that demographic (e.g., age, sex, and race), anthropometric, and severity of illness-associated factors would be predictive of LPV underutilization.

MATERIALS AND METHODS

Patients

We assembled the study cohort using open access de-identified data from participants previously enrolled in the two National Heart Lung and Blood Institute (NHLBI) ARDS Network trials conducted following release of ARMA trial[11] results that demonstrated improved outcomes with LPV. These included the Assessment of Low tidal Volume and End expiratory volume to Obviate Lung Injury (ALVEOLI) trial,[12] and the factorial Fluid and Catheter Treatment Trials (FACCT).[13,14] Data from the Late Steroid Rescue Study (LaSRS),[15] which began enrollment prior to release of ARMA findings,[15] were not used for the present study.

The ARDSNet is comprised of 42 hospitals across the United States; details regarding protocols of ARDSNet studies can be found at the ARDSNet.org website. All study procedures were approved by the Boston University School of Medicine Institutional Review Board as well as the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

Baseline demographics and clinical information were obtained prior to randomization of ARDSNet trial participants. This data was collected ideally from within 4 hours of study initiation, with allowance for up to 24 hours prior to randomization. This "baseline" data was used as the source data for the current research because it represents the care of patients after they have met American European Consensus ALI criteria,[16] but prior to initiation of mechanical ventilation per study protocols (which mandated use of LPV for all enrolled patients).

Outcome

Lung protective ventilation (LPV) was defined in the primary analysis as tidal volume of less than 6.5 cc/kg PBW. ARDSNet calculated PBW for each patient based on height and sex. The choice of the threshold of 6.5cc/kg to represent LPV is supported by literature precedent,[2,5] proximity to the mean tidal volumes (6.2-6.5 cc/kg PBW) actually delivered

to the ARMA low tidal volume intervention group, and the fact that 6.5cc/kg PBW was selected by the ARDSNet investigators as the threshold for defining "on target" 6cc/kg ventilation for internal monitoring of the ARMA trial (B. Taylor Thompson, personal communication, 5/31/2011). Two sensitivity analyses to evaluate stability of predictors of LPV were performed: 1) using a tidal volume cutoff of less than or equal to 8cc/kg, which was recommended as the initial tidal volume in the ARDSNet ARMA Mechanical Ventilation Protocol and was allowed if a patient developed breath stacking or ventilator dys-synchrony to 6cc/kg PBW and plateau pressures remained less than 30 cm H2O (ARDSNet.org ventilator protocol), and 2) using cc/kg PBW as a continuous dependent variable.

Covariates

We compared pre-randomization characteristics of those participants who received LPV with those that did not. These characteristics included demographics and body morphology: [age, sex, race, body mass index (BMI), height, and weight], comorbidities [diabetes, acquired immune deficiency syndrome, end stage renal disease (dialysis requirement), and end stage liver disease], primary acute lung injury risk factor [characterized as direct lung injury (pneumonia, aspiration) or indirect lung injury (sepsis, trauma, transfusions)], number of quadrants affected by infiltrate on frontal chest radiograph (i.e., radiographic lung injury score), the duration of mechanical ventilation, and duration of intensive care unit stay prior to study enrollment. Baseline Simplified Acute Physiology II Scores (SAPS II)[17] and Brussels multiple organ dysfunction scores[18] were calculated for all participants. Because tidal volume setting may affect PaO_2/FiO_2,[11] airway pressures, lung compliance[19], $PaCO_2$, and minute ventilation, as well as influence choice of positive end expiratory pressure (PEEP), these mechanical ventilation variables were not included as potential predictors of LPV.

Statistical Methods

In order to achieve 80% power to identify risk factors for use of LPV with an odds ratio of at least 1.50 at an alpha of 0.05, 1120 subjects were required.

Wilcoxon rank sum tests, t-tests and Fisher exact tests were used to determine differences in continuous and categorical variables, as applicable. In order to visually demonstrate differences in the distribution of actual and 6.5 cc/kg-predicted tidal volumes (calculated from PBW), we generated histograms of delivered tidal volumes and tidal volumes calculated from PBW, stratified by sex. Associations between LPV and clinical covariates were determined through multivariable logistic regression models. Associations between tidal volume as a continuous variable of cc/kg PBW and clinical covariates were determined through Analysis of Covariance. For all multivariable models, covariates with unadjusted *p* values less than 0.2 were entered into the model and remained in the model via backward selection if *p* was less than 0.05, the alpha threshold for statistical significance. SAS version 9.1 statistical software (Cary, NC) was used for all analyses.

RESULTS

A baseline tidal volume and PBW was recorded for 1385/1550 (89%) of trial participants. The study cohort had an average age of 50 ± 16 years and was 54% male. 430/1385 (31.2%) participants received lung protective ventilation, defined as less than or equal to 6.5cc/kg PBW. **Figure 1** demonstrates the distribution of tidal volumes in all participants; the average tidal volume was 7.65±1.82 cc/kg PBW. **Figure 2** demonstrates the distribution of observed (**Figure 2A, Figure 2B**) and 6.5 cc/kg PBW-calculated "lung protective" tidal volumes (cc) (**Figure 2C, Figure 2D**) for males and females, respectively. Delivered tidal volumes were

significantly greater than “lung protective” tidal volumes predicted by 6.5 cc/kg PBW (mean difference 67 ± 108cc, p<0.0001). Histograms in **Figure 2** show that the range of delivered tidal volumes is approximately two times the range of predicted “lung protective” tidal volumes.

Baseline subject characteristics stratified by LPV status are shown in **Table 1**.

Table 2 demonstrates the significant unadjusted and multivariable-adjusted predictors of LPV. Multivariable predictors of LPV underutilization were older age, white race, shorter height, less severe illness (as indicated by lower SAPSII and lower radiographic lung injury scores), lower serum bicarbonate levels, shorter duration of pre-enrollment ICU stay, and use of non-volume-targeted ventilation.

In our sensitivity analysis, we found that 909/1385 (66%) of participants received less than or equal to 8cc/kg PBW. Using the cutoff of 8cc/kg PBW, the predictors of receiving LPV were similar to the 6.5cc/kg threshold model, except that age and duration of ICU stay were no longer significant, and lack of dialysis requirement [OR 4.57 (1.35, 15.4), p=0.014] and lower weight [OR per 10kg 0.91 (0.85, 0.97), p=0.003] were associated with LPV. In sensitivity analysis using cc/kg PBW as a continuous variable, significant predictors of tidal volume were identical to the 6.5cc/kg analysis, with the exception that increasing weight was an additional predictor of increasing tidal volumes (beta 0.01 per kg, p<0.0001).

DISCUSSION

Similar to previous studies, we found substantial underutilization of evidence-based LPV among patients with ALI - only 1 of 3 participants with ALI received LPV with tidal volumes less than or equal to 6.5cc/kg PBW prior to randomization in the ARDSNet trials.[2,5,10] Our study has identified novel patient characteristics associated with underuse of LPV that may be amenable to simple quality improvement interventions. Participants most at risk for LPV underutilization were older, of shorter stature and Caucasian race. Additional clinical risk factors for underuse of LPV included metabolic acidosis, lower illness severity, and use of non-volume targeted ventilator modes. Our findings were robust across a range of definitions of LPV. Results from this study suggest that suboptimal assessment of PBW and poor response to less severe lung injury are major factors affecting implementation of LPV.

Our study expands upon results of three prior studies that investigated reasons for underutilization of LPV. A survey of ARDSNet center nurses and respiratory therapists identified multiple factors felt to be contributing to underuse of LPV; these included under-recognition of ALI, difficulties in calculating PBW, and discomfort with the hypoxemia, hypercapnea and acidosis often associated with LPV.[9] The opinions documented by Rubenfeld et al. are in accordance with our data. Similar to our findings, an observational study by Umoh et al. (n=250) identified metabolic acidosis as an independent association with LPV.[5] A smaller study by Kalhan et al. (n=88) found an unadjusted association between poor lung compliance and oxygenation with use of LPV.[4] Although we found similar univariate relationships to Kalhan et al., we chose not to include respiratory variables in our models because low tidal volume ventilation can affect compliance and oxygenation.[11,19]

We identified multiple novel factors associated with underuse of LPV. Patients of shorter height were least likely to receive LPV. Thus, women were disproportionately affected by underuse of LPV. Past studies have identified that height is inaccurately estimated and recorded in the critically ill.[20,21] Therefore, increased attention to accurate height measurement as a “vital sign” in all mechanically ventilated patients, accompanied by

accessible methods of translating height into PBW and tidal volumes, is essential for improving care of patients with ALI. In our institution, charts attached to ventilators translate height into 6cc/kg PBW tidal volumes. Others have shown such simple interventions, coupled with educational initiatives, to be effective for tidal volume reduction.[22]

Patients with longer ICU stay prior to study enrollment, less severe illness (as measured by SAPS II) and less obvious lung injury (lower radiographic lung injury score) were also at increased risk for not receiving LPV. The observation that larger tidal volumes were associated with longer ICU stay prior to enrollment is supported by data presented by Kallet showing that increased duration of mechanical ventilation in the absence of a protocol was associated with large variation in tidal volumes, with a trend towards increasing tidal volumes over time.[23] The association of LPV underutilization with less severe lung injury suggests under-recognition of ALI. Because outcomes are improved with LPV regardless of lung injury severity,[11] further development of innovative decision support interventions that facilitate ALI recognition[24,25] is especially important.

However, ALI recognition is only a part of the reason for LPV underutilization. In patients with recognized ALI, interventions to facilitate use of LPV are also warranted. For example, we identified that non-volume-targeted mechanical ventilation strategies were associated with increased tidal volumes. Because tidal volume during pressure-controlled modes is determined by respiratory system compliance and work of breathing, increases in compliance or work of breathing may result in high tidal volumes during pressure-controlled modes.[26] Thus, increased vigilance in monitoring tidal volumes during pressure targeted ventilation is warranted - lower tidal volumes are associated with improved outcomes regardless of plateau pressure.[27]

The association between older age and decreased use of LPV is consistent with the slower adoption of evidence-based treatment in elderly patients that has been demonstrated in other areas, such as beta-blockade after myocardial infarction.[28] In addition, underutilization of LPV in the elderly might be due to diagnostic uncertainty between cardiogenic and noncardiogenic pulmonary edema in older patients with greater cardiac comorbidity, or due to demographic variations by study site. Variations in study center demographics and practice patterns may also explain the association between white race and LPV underutilization; study center-level information was not available in our dataset. Further investigation of the demographic factors associated with LPV underutilization is warranted.

As shown in one prior study,[5] metabolic acidosis was associated with decreased use of LPV. Because of the respiratory acidosis that often accompanies LPV through “permissive hypercapnea”, a concomitant metabolic acidosis may induce significant acidemia and high respiratory drive potentially increasing ventilator dys-synchrony and difficulty implementing LPV. However, on average, metabolic acidosis was mild (mean bicarbonate: 21.1 mmol/L) and not associated with significant acidemia (mean pH 7.37). Greater adherence to the ARDSNet protocol (ardsnet.org) or other proposed strategies[29] for management of acidosis in ALI may decrease the proportion of patients who inappropriately receive potentially injurious tidal volumes to compensate for metabolic acidosis. While compensatory metabolic alkalosis due to permissive hypercapnea may develop in patients ventilated with LPV, it is unlikely to develop within the median 24 hours of mechanical ventilation prior to study enrollment and this “reverse causation” is unlikely to explain the decreased use of LPV in the presence of metabolic acidosis.

The systematic discrepancy between predicted and actual tidal volumes we observed suggests that patients are generally placed on a ‘default’ tidal volume at the time of

intubation that is independent of measured height. The distribution of delivered tidal volumes in this study shows that male and female participants with ALI were most often placed on 500ml and 400ml tidal volumes, respectively (**Figure 2A, Figure 2B**). While accurate height measurement in all patients requiring mechanical ventilation is ideal practice, assessment of height may not occur until well after initial tidal volumes have been selected in a newly intubated patient, particularly if the patient is not clinically stable. These initial, non-lung-protective tidal volumes may then be propagated through inaction. Simple interventions that decrease the initial 'default' tidal volumes selected for patients with ALI risk factors would greatly increase both the proportion of ALI patients treated with LPV and the duration of time receiving LPV. For example, the histograms of tidal volumes predicted from calculation of PBW in this sample suggest that more than 80% of men and women with ALI would receive LPV if initial 'default' tidal volumes were lowered to 450ml and 350ml, respectively (**Figure 2C, Figure 2D**). Lowering the 'default' tidal volume may be advantageous for patients with ALI risk factors in light of recent studies demonstrating that use of LPV in patients without ALI may decrease incident ALI.[22,30] Future studies investigating strategies that combine early calculation of a Lung Injury Prediction Score, [31] (for example, in the emergency department) with lower default tidal volumes for patients with high ALI risk are warranted.

Our study has limitations. First it is unclear if risk factors for underuse of LPV identified in the ARDSNet centers are generalizable to other settings. However, ARDSNet centers do represent a range of hospital settings across the US and rates of LPV underutilization in the ARDSNet centers were not substantially different from rates reported in other centers. Second, it is unclear if identification of individual study centers may have changed our results. It is possible that practice variation by study center might account for many observed differences in LPV utilization; however this data was unavailable in the BioLincc data set. Third, tidal volumes were recorded at single time points prior to trial enrollment; identifying temporal patterns of tidal volume change was not possible with this trial data. It is possible that with longer duration of mechanical ventilation, tidal volumes may be lowered; however, this is not supported by other studies[23] and we did not observe an association between duration of mechanical ventilation and use of LPV to support this assertion. Finally, it is possible that we may have misclassified some patients as not having received LPV who were appropriately given tidal volumes between 6.5 and 8cc/kg PBW for severe dyspnea, breath stacking and plateau pressures less than 30 cm H2O. Unfortunately, an indicator of breath stacking or severe dyspnea was not available in the BioLincc dataset. However, predictors of LPV were robust across various definitions of LPV, including a sensitivity analysis defining LPV as less than or equal to 8cc/kg PBW.

In conclusion, we have identified multiple novel factors amenable to quality improvement interventions that may promote use of LPV. Patients of shorter stature, the elderly, and those with less severe lung injury, acidosis, or pressure-targeted ventilation modes are particularly at risk for not receiving LPV. A systematic reduction of the default tidal volumes in patients with ALI risk factors to 450ml in men and 350ml in women would likely provide LPV to 80% of patients at risk for ALI. Studies of initiatives aimed at decreasing default tidal volumes and increasing recognition of patients with the risk factors for LPV underutilization identified in this study are warranted.

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Abbreviation List

ARDS	Acute respiratory distress syndrome
ALI	Acute lung injury
ALVEOLI	Assessment of Low tidal Volume and End expiratory volume to Obviate Lung Injury Trial
BioLINCC	Biologic Specimen and Data Repository Information Coordinating Center
BMI	Body mass index
FACCT	Fluid and Catheter Treatment Trials
LaSRS	Late Steroid Rescue Study
LPV	lung protective ventilation strategy
PBW	predicted body weight
PEEP	positive end expiratory pressure
SAPS II	Simplified Acute Physiology II Scores

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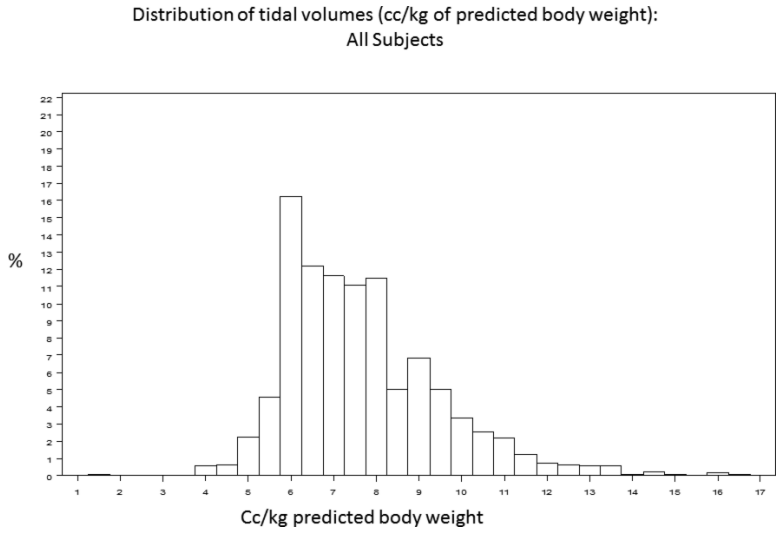
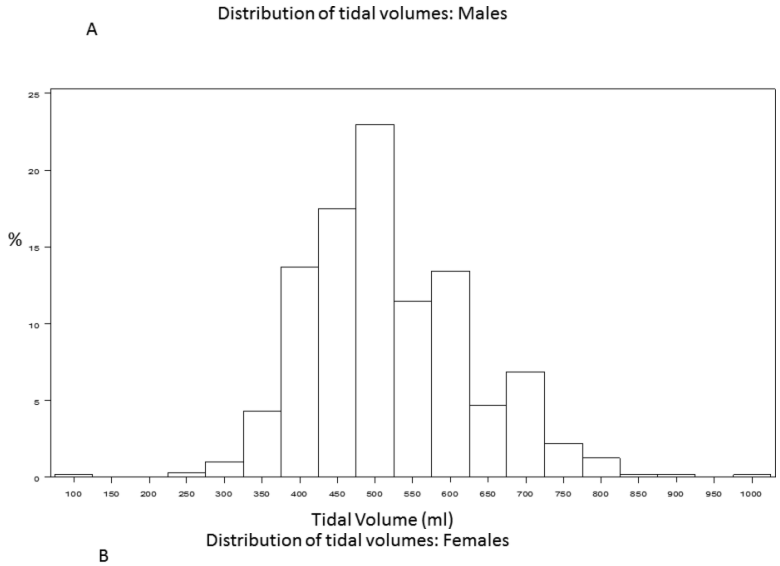


Figure 1.
Distribution of tidal volumes (cc/kg predicted body weight) in all participants.

A



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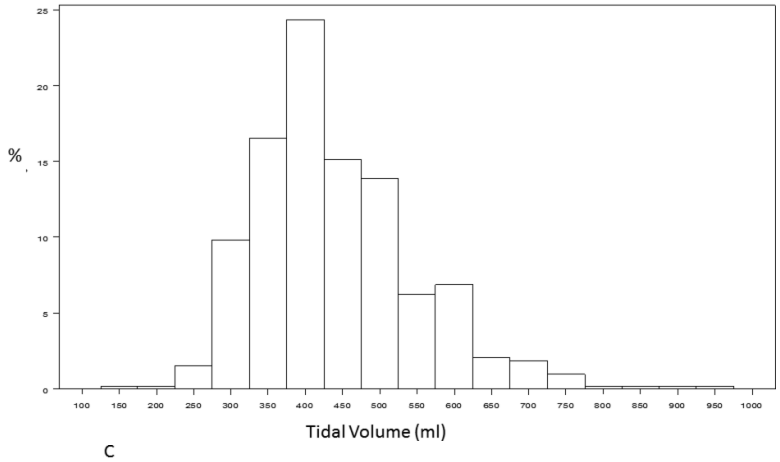

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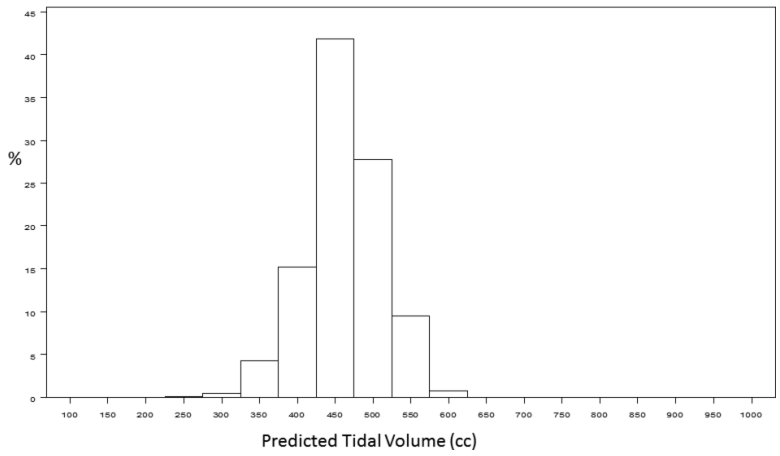

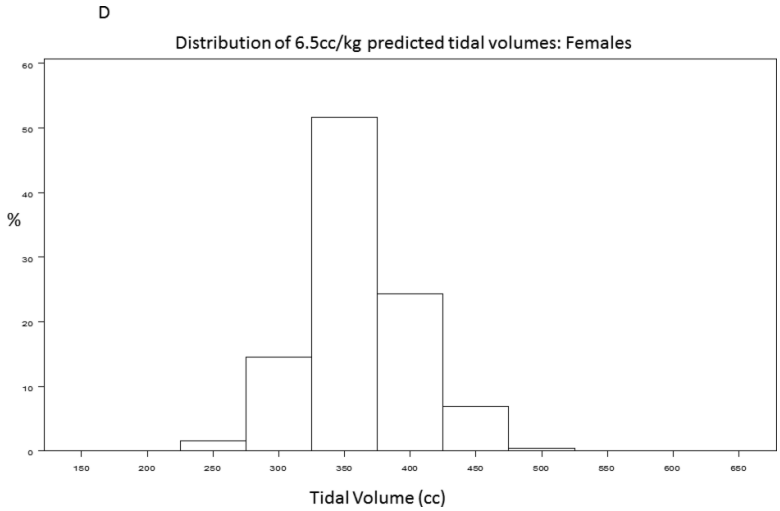

Figure 2.
Distribution of observed (2A, 2B) and 6.5 cc/kg PBW-calculated “lung protective” (2C, 2D) tidal volumes (cc) for males and females, respectively.

Table 1

Baseline variables

	Lung Protective Ventilation N=430	No Lung protective Ventilation N=955	p
Age, years	48.5 ± 16.5	50.7 ± 16.4	0.024
Sex, male	282 (65.6)	462 (48.4)	0.001
Race			0.011
White	276 (64.2)	662 (69.3)	
Black	103 (24.0)	163 (17.1)	
Other	51 (11.9)	130 (13.6)	
Body Mass Index, (kg/m^2)	27.6 ± 7.2	28.4 ± 7.3	0.04
Height (cm)	173.7 ± 10.3	168.0 ± 10.1	0.001
Weight (kg)	83.5 ± 22.8	80.1 ± 22.0	0.015
SAPS II	50.0 ± 13.9	47.9 ± 14.2	0.03
Brussels organ failures	1.93 ± 0.98	1.99 ± 0.97	0.21
Brussels non-pulmonary organ failures	0.99 ± 0.91	1.0 ± 0.92	0.34
ARDS (PaO_2/FiO_2 <200)	383 (89)	821 (86)	0.067
ALI Risk Factor			
Direct lung injury	272 (69.7)	566 (63.7)	0.04
Pneumonia	197 (45.8)	432 (45.2)	0.86
Sepsis	85 (19.8)	233 (24.4)	0.062
Aspiration	75 (17.4)	134 (14.0)	0.10
Trauma	22 (5.1)	71 (7.4)	0.13
Transfusion	11 (2.6)	19 (2.0)	0.55
Other	40 (9.3)	66 (6.9)	0.13
Co-Morbidities			
Malignancy	19 (4.4)	42 (4.4)	1.0
AIDS	40 (9.7)	60 (6.4)	0.04
Dialysis	2 (0.48)	17 (1.8)	0.076
Diabetes	71 (17.2)	157 (16.7)	0.87
Mechanical ventilation parameters			
Volume assist control mode	406 (94.4)	804 (84.2)	0.001
PaO_2/FiO_2	122 ± 55	131 ± 60	0.017
Pplat (cm H_2O)	25.7 ± 7.2	26.8 ± 6.8	0.01
$PaCO_2$ (mm Hg)	43.2 ± 11.1	38.3 ± 8.9	0.001
PEEP (cm H_2O)	10.2 ± 4.3	9.2 ± 3.9	0.001
Static compliance (cc/cmH_2O)	29.8 ± 34	31.0 ± 33.8	0.001
Minute ventilation (L/minute)	12.3 ± 3.7	12.3 ± 4.0	0.51
Arterial pH	7.34 ± 0.096	7.37 ± 0.092	0.001
Radiographic Lung Injury Score	3.8 ± 0.50	3.70 ± 0.58	0.002
Serum Bicarbonate (mmol/L)	21.6 ± 5.3	21.1 ± 5.6	0.11
Duration Intubation prior to enrollment (days)	1.1 ± 1.0	1.1 ± 1.2	0.48
Duration ICU stay prior to enrollment (days)	1.8 ± 1.9	1.6 ± 2.1	0.03

Abbreviations: kg: kilogram, m: meter, cm: centimeter, SAPS: Simplified Acute Physiology Score, mmol: millimoles, L: liter, NS: not-significant and not included in final adjusted model, PaO2/FiO2: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, Pplat: static (plateau) airway pressure, PaCO2: partial pressure of arterial carbon dioxide, PEEP: positive end expiratory pressure, ICU: intensive care unit

Table 2

Unadjusted and multivariable-adjusted predictors of not receiving lung protective ventilation

Variable	Unadjusted Odds Ratio (95% Confidence Interval), p	Adjusted Odds Ratio (95% Confidence Interval), p
Age, per std (16 years)	1.14 (1.02-1.28), 0.024	1.18 (1.02-1.38), 0.028
Sex, female	2.03 (1.61-2.58), 0.0001	NS
Race, white vs. non-white	1.26 (0.99-1.60), 0.059	1.40 (1.05-1.88), 0.023
Body Mass Index per std (7.3 kg/m^2)	1.12 (0.99-1.26), 0.076	NS
Height, per std (10cm)	0.56 (0.50-0.64), 0.0001	0.55 (0.48-0.63), 0.0001
Weight, per std (22 kg)	0.86 (0.77-0.97), 0.01	NS
SAPS II, per std (14)	0.86 (0.77-0.97), 0.01	0.78 (0.67-0.92), 0.003
Direct lung injury	0.76 (0.59-0.98), 0.035	NS
Dialysis	3.80 (0.87-16.5), 0.075	NS
Acquired Immunodeficiency Syndrome	0.64 (0.42-0.97), 0.036	NS
Radiographic lung injury score per std (0.57)	0.84 (0.74-0.95), 0.005	0.83 (0.70-0.95), 0.009
Non-volume control ventilator mode	3.18 (2.03-3.97), 0.0001	3.07 (1.78, 5.27), 0.0001
Serum bicarbonate per std (5.5 mmol/L)	0.92 (0.82-1.03), 0.14	0.83 (0.71-0.97), 0.017
Duration of ICU stay prior to study enrollment per std (2 days)	0.90 (0.80-1.01), 0.078	0.84 (0.73-0.98), 0.02

Hosmer-Lemeshow Goodness of fit for adjusted model p=0.33, c-statistic 0.712

Abbreviations: std: standard deviation, kg: kilogram, m: meter, cm: centimeter, SAPS: Simplified Acute Physiology Score, mmol: millimoles, L: liter, NS: not-significant and not included in final adjusted model.