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Implementation of an ED-based bundled mechanical ventilation protocol improves adherence to lung-protective ventilation

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Introduction

Mechanical ventilation is a common life-saving protocol, but it has also been linked to ventilator-associated lung injury (VALI), a progressive injury caused by positive pressure ventilation.[1] Despite decades of research, lung-protective ventilation (LPV) with low tidal volume (V_T) remains one of the few effective protocols for patients with acute respiratory distress syndrome (ARDS).[2–5] Growing evidence suggests that low V_T may also benefit critically ill patients without pre-existing lung injury.[6–11] In addition to low V_T, adequate positive-end expiratory pressure (PEEP) and early titration of oxygen concentration (FiO_2) are important components of LPV that minimize atelectasis[12, 13] and oxygen toxicity,[14–16] respectively.

The emergency department (ED) is a crucial setting for the prevention and treatment of VALI. ED overcrowding, boarding, and increased ICU admissions have tripled the amount of critical care and prolonged mechanical ventilation delivered in US EDs.[17, 18] Of the estimated 240,000 patients mechanically ventilated in US EDs each year, one-quarter are ventilated for more than five hours.[19, 20] These initial hours of care are influential in the outcome of critically ill patients, as VALI has been shown to occur within minutes to hours of initiating mechanical ventilation[21–23] and progression to ARDS occurs early during ventilation of at-risk patients.[7] For these reasons, initial ventilator settings provided in the immediate post-intubation period can be critically important in determining patient outcomes. Observational data show large V_T is commonly used in the ED, ED V_T influences

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ventilation strategy in the ICU, and injurious early ventilation strategies are associated with worse clinical outcomes, implicating the ED as a vital link in the provision of LPV.[24, 25]

Standardization of mechanical ventilation through order sets and protocols provides an evidence-based and cost-effective opportunity to reduce variability in the care of ventilated ED patients.[26] Respiratory care protocols administered by non-physician staff has been shown to improve arterial blood gas sampling,[27, 28] early ventilator weaning, [29, 30] and adoption of PEEP-FiO_2 combination guidelines.[31] Successful adherence to a V_T-focused ventilator order set further supports the feasibility of protocol-driven ventilation in the ED.[32] Implementation of a similar mechanical ventilation protocol in an academic ED increased ventilator-free days and hospital-free days while being associated with significantly decreased hospital mortality.[33] Based on the association between lung protective ventilation and improved clinical outcomes demonstrated in the LOV-ED study and the previously demonstrated prevalence of non-protective ventilation in multiple EDs, an RT-driven LPV protocol was implemented in the ED of a large, academic medical center to standardize care of mechanically ventilated ED patients. We hypothesized that implementation of this protocol would improve adherence to LPV ventilation parameters and improve clinical outcomes of patients intubated and mechanically ventilated in the ED.

Methods

Study Design

This retrospective before-after observational cohort study was conducted at an academic 60,000-visit ED between March 2016 and July 2018, 15 months before through 13 months after the implementation of a lung-protective mechanical ventilation protocol. Inclusion criteria were adult patients (age ≥ 18 years) receiving mechanical ventilation following intubation while in the ED. Exclusion criteria included death or extubation while in the ED, missing height or ED V_T in the electronic medical record (EMR), non-invasive ventilation only, and transfer from the ED to another facility. This study is reported in accordance with the Standards for Quality Improvement Reporting Excellence (SQUIRE) Statement: Guidelines for Reporting Observational Studies[34] and was approved by the local Institutional Review Board under a waiver of informed consent.

Protocol

In June 2017, a new mechanical ventilation protocol was implemented in the ED to mimic the Lung Protective Ventilation Initiated in the Emergency Department (LOV-ED) study protocol.[33] The protocol was divided into five components, each intended to prevent a potential mechanism of VALI (Figure 1). Mode selection of choice for this protocol was assist control-volume control (AC-VC).

Education for respiratory therapists included hands-on sessions with the mechanical ventilator, a computer-based tutorial, and a quiz. Tools were provided to respiratory therapists including laminated protocol sheets detailing ideal predicted body weight (PBW)-V_T charts and tape measures to measure patient height. These tools were attached to the ED ventilators as part of standard protocol procedures. After implementation, weekly audits of

all ventilated ED patients were performed to review adherence to the protocol, immediate feedback was provided, and adherence was reported at regular staff meetings.

Procedures

Baseline patient characteristics were abstracted from the EMR. Sequential organ failure assessment (SOFA) scores were calculated at the time of ED admission and 24 hours after admission.[35] The first ventilator settings recorded in the ED and ICU were abstracted from the medical record. Names of the treating respiratory therapist, intubating physician (typically a resident), and attending physician were also recorded. Data were abstracted by trained data abstractors with regular meetings and monitoring of data collection. All variables were collected in a standardized format using a standard case report form.

Outcomes

The primary outcome of this study was mean difference in V_T (mL/kg) administered in the ED between groups. Difference in V_T was selected as the primary outcome because it is the most widely studied and supported mediator of VALI and would reflect a change in clinical practice induced by the protocol. Secondary outcomes included 24-hour change in SOFA score, ventilator-free days, ICU V_T, protocol adherence, mortality, ARDS, hospital-free days, and ventilator-associated pneumonia (VAP). We also tested adherence with individual protocol elements.

Definitions

Patient height and weight from the hospital encounter were used to calculate BMI and PBW as shown previously.[36] LPV was defined as the use of $V_T \leq 8$ mL/kg PBW.

SOFA scores were calculated as described previously.[35] Saturation by pulse oximetry (SpO_2)/FiO_2 ratios were used to calculate the SOFA score because of ED arterial blood gas infrequency. SpO_2/FiO_2 ratios approximated partial pressure of oxygen (PaO_2)/FiO_2 ratios using methods validated in a prior report.[37] Due to the shape of the oxyhemoglobin dissociation curve, any SpO_2 values above 97% was assigned a zero for the respiratory component of the SOFA score because large PaO_2 changes can occur with small changes in the SpO_2 near 100%.[38]

Adherence to each facet of the ventilator protocol was determined according to Figure 1. If the patient received a tidal volume ≤ 8 mL/kg, they were considered adherent to the “Volutrauma Prevention” facet of the protocol. PEEP was to be ≥ 5 cm H20 to satisfy “Atelectrauma Prevention.” For “Hyperoxia Prevention,” FiO2 must have been set to between 0.3–0.4 immediately within 15 minutes of intubation. If a higher FiO2 was initially selected, the corresponding PEEP value must have been in accordance with the provided PEEP-FiO2 table (Figure 1) to be considered adherent. Respiratory rate was to be set between 16–30 breaths per minute. Head-of-bed elevation was not included in adherence determinations due to lack of notation in the medical record (98.2% missing). For a patient to be considered adherent to the full protocol, each facet must have been satisfied. If any data value was not adherent, that patient was considered not adherent to the protocol.

ARDS was defined according to the Berlin definition through hospital day five. [10, 24, 39, 40] A panel of three research team clinicians reviewed blinded chest radiographs independently and classified them as “consistent”, “inconsistent”, or “equivocal” for ARDS, and the diagnosis was made by consensus. Each member of the panel reviewed a set of training radiographs[41] prior to study participation and was blinded to protocol group and all other clinical data during the chest radiograph review. Patients were assumed to have clinical evidence of left atrial hypertension if respiratory failure was attributed to congestive heart failure or dialysis-dependent end-stage renal disease in the EMR, and thus were categorized as “not ARDS.”

VAP was defined as clinical suspicion for pneumonia by a board-certified intensivist with initiation of antibiotic treatment for a lower respiratory tract infection more than 48 hours after initiation of mechanical ventilation, among patients not already being treated for pneumonia.[42]

Sample Size

A mean detectable difference for ED V_T of 0.33 mL/kg (SD 1.28) for pre- versus post-protocol (power 0.8, alpha 0.05) required 476 patients (238 pre-protocol patients and 238 post-protocol patients). A mean difference of 0.33 mL/kg was chosen due to the low mean V_T observed in a sample of pre-protocol patients performed prior to final data analysis. Given the already low pre-protocol tidal volume, the likelihood of demonstrating a smaller difference in tidal volume after protocol would require a greater number of patients than would be feasible for the study, but one could not expect a different that would bring the mean tidal volume to less than 6 mL/kg. We determined that a 0.33 mL/kg change was a compromise vale that would detect a meaningful change in clinical practice.

Analysis

Chi-square tests, Wilcoxon Mann-Whitney tests, and Fisher’s exact tests compared distributions of baseline characteristics between the two groups. A scatterplot was used to visualize associations between ED and ICU V_T.

Univariable and multivariable regression assessed the impact of the protocol on clinical and ventilator outcomes. For the primary outcome, a log-transformation of outcome was used, since the error terms on the continuous outcomes followed a right-skewed distribution. Linear, logistic, and negative binomial regression were used to estimate secondary outcomes as appropriate.

Covariate selection was guided by clinical knowledge and previous literature,[33] and, stepwise backwards selection guided by Akaike Information Criterion (AIC) was used to select the final model. Respiratory therapist and intubator were also included as fixed effects to account for variance, observed and unobserved, associated with each fixed effect. A *post hoc* test for effect modification of protocol effect by subject height was conducted by testing an interaction term and then stratifying the analysis by protocol time (pre- vs. post-protocol).

Differences in the time to ARDS and VAP (in days) between the protocol groups were assessed using log-rank tests and univariable Cox proportional hazards regression models.

Finally, variation in ED LPV rates ($V_T \leq 8$ mL/kg) by intubator and respiratory therapist were estimated with risk-adjustment (adjusting for: sex, BMI, and initial SOFA score) and reliability-adjustment.[43] Predictive capability of attending physician, intubating physician, and respiratory therapist for ED LPV were separately estimated using univariable logistic regression models to estimate the area under the curve (AUC), using bootstrapping of 1,000 independent data samples to estimate precision of the AUC confidence interval. Data analysis was completed in R (version 3.6; RStudio Inc., Vienna, Austria) and SAS (version 9.4; SAS Institute, Inc., Cary, NC), and figures were created in Prism (version 8.2, GraphPad, Inc., San Diego, CA).

Sensitivity Analysis

A *post hoc* sensitivity analysis was conducted restricting the study population to resemble the eligibility criteria of a previous before-after study of LPV protocols in the ED[33]: excluding subjects that had ARDS at hospital admission or were extubated or died within 24 hours.

Results

Characteristics of Study Subjects

A total of 500 patients were enrolled in this study. Baseline characteristics of the study population are shown in Table 1. All measured baseline characteristics, including initial SOFA scores and ED length of ventilation, were similar between the two groups.

Main Results

Of the study cohort, 272 subjects (54.4%) were in the pre-protocol group and 228 (45.6%) were in the post-protocol group (Table 1). Without adjustment, ED V_Ts were smaller in the post-protocol group (6.2 vs. 6.5 mL/kg IBW, $p<0.001$), and more patients received LPV in the post-protocol group (94.3% vs. 87.7%, $p=0.012$) (Table 1) than the pre-protocol group. Time to ARDS and time to VAP did not differ between the pre- and post-protocol groups (ARDS: HR 0.64 [0.34 – 1.20] and VAP: HR 1.12 [0.58 – 2.18]). Overall, ICU and ED V_Ts were moderately correlated ($r^2=0.484$, $p<0.001$) (Figure 2).

After adjustment for sex, BMI, and initial SOFA score, ED V_T remained lower in the post-protocol group when compared to the pre-protocol group (−0.76 mL/kg [95%CI −1.03 to −0.48]) (Table 2). There was no difference in proportion of patients who developed ARDS, VAP, or died between the protocol groups. There were differences in the change in SOFA scores after adjustment with the post-protocol group having greater increases in SOFA score from the ED to 24-hour score (1.40 [95%CI: 0.64 to 2.17]) (Table 2). When GCS was removed from the SOFA calculation, there was no longer a significant difference in the change in SOFA scores.

Subject height modified the relationship between the protocol and use of ED LPV ($p = 0.044$). Before the protocol, a 10% increase in subject height was associated with a 3.39 (95% CI 2.14 – 4.64) times higher odds of ED LPV. Whereas, after the protocol, the association between height and the protocol was no longer significant (95%CI 0.24 – 2.46).

Protocol Adherence

Protocol adherence in the ED was greater in the post-protocol group (27.6% vs. 13.6%, p<0.001) (Table 1) than the pre-protocol group. Adherence to all components in the protocol was modest in both the pre- and post- group (Table 3). Using the same methods, ICU protocol adherence increased from 20.2% before protocol to 33.8% after protocol (p = 0.001). When missing protocol components were assumed adherent for sensitivity analysis, neither relationship changed significantly.

Variation by Intubator and Respiratory Therapist

Adherence to use of LPV ($V_T \leq 8$ mL/kg IBW) varied by intubating physician and respiratory therapist (Figure 3). More variation was observed by respiratory therapists than by intubator in adjusted proportion of ED LPV. Across intubators, the median adjusted rate of ED LPV was 90.7% (IQR 84.3 – 90.9). Whereas among respiratory therapists, the median adjusted proportion was similar, but more variation was observed (median 90.9% [IQR 77.8 – 91.7]). The impact of the care team in predicting adherence with the protocol was estimated with univariable models with respiratory therapist or intubator as the predictor and ED LPV as the outcome. Overall, the individual respiratory therapist affected ED LPV more than the intubating physician (Figure 4), and respiratory therapists become even stronger predictors after the intervention (AUC 0.919 [95% CI 0.917 – 0.920]). There was no association between attending physician and use of ED LPV.

Sensitivity Analysis

Of this study cohort, 5.2% had ARDS on arrival to the ED and 41.2% were extubated on the date of admission; no subjects died on the date of admission. In the sensitivity analysis including only patients who remained ventilated beyond 24 hours, the adjusted associations between the protocol and ED V_T (adj. β−0.16 [95% CI −0.21 to −0.12]) and between the protocol and mortality (aOR 0.28[95%CI 0.02 – 3.41]) were similar to the primary analysis.

DISCUSSION

This before-after observational cohort study was conducted to determine the impact of a bundled mechanical ventilator protocol on use of LPV in an academic ED. We found that such a protocol can be implemented and influence ventilation practices in the ED. After adjusting for multiple confounders, protocol administration was associated with a 0.76 mL/kg reduction in ED V_T. Though LPV was widely used in the ED pre-protocol group, use of V_T less than 8 mL/kg was significantly increased after implementation of the protocol. Adherence to PEEP, FiO_2, and respiratory rate protocol parameters were improved in the ED post-protocol group, though full ED protocol adherence increased from 13.6% to only 27.6%. Despite the observed changes in ventilation practices, protocol implementation did not influence any of the measured clinical outcomes, including ARDS, VAP, hospital-free days, or mortality.

Our study is the third to analyze the effect of a bundled, lung-protective mechanical ventilation protocol administered in the ED. A previous before-after study, the LOV-ED trial, demonstrated a reduction in pulmonary complications and mortality following protocol

implementation.[33] Our study did not find a significant difference in clinical outcomes between groups despite improvement in overall protocol adherence and reduction in ED V_T. There are multiple potential explanations for a finding of a statistically significant decrease in ED V_T without a change in clinical outcomes. First, our study was primarily quality improvement (QI) in nature, and thus was not adequately powered to detect a change in clinical outcomes. Second, our study included patients who underwent extubation or death at less than 24 hours following ED admission and those meeting ARDS criteria while in the ED. This creates a broader range of illness severity across our patient population and makes direct comparison in clinical outcomes between the studies difficult. However, a sensitivity analysis using the same exclusion criteria as the LOV-ED study did not significantly change our primary outcome (change in V_T) or mortality. Third, we detected a 0.76 mL/kg adjusted difference in V_T between the pre and post protocol groups, which differs significantly from the 2 mL/kg difference detected in the LOV-ED trial.[33] Though reductions of 1 mL/kg have been shown to decrease mortality in patients with ARDS,[44] 0.76 mL/kg may not be sufficient to elicit a change in secondary outcomes in a population that was receiving high rates of LPV even before protocol. The injurious effects of very high tidal volumes may be much more than modest tidal volumes, so the relatively protective settings in the pre-intervention group may not have led to high rates of clinical deterioration. Alternatively, the lack of clinical change could support the results of multiple studies challenging the clinical benefit of low V_T ventilation in populations including patients without ARDS.[20, 45]

Consistent adherence to all parameters of a complex, bundled protocol can be difficult to attain. Despite improvement in adherence to each facet of the ventilation protocol between the pre- and post-protocol groups, full adherence was seen in only 27.6% of ED patients in the post-protocol group. This finding can be at least partially attributed to protocol dissemination and implementation. Similar before-after respiratory protocol studies were prospective in nature and involved run-in periods of up to 6 months.[31–33] Our study, on the other hand, was retrospective and did not utilize a run-in period. While compliance to the protocol was monitored in the post-protocol group, these differences may have contributed to the observed sub-optimal adherence. The protocol parameter with the lowest adherence involved the setting of FiO_2 between 0.30–0.40 or in accordance with ARDSNet PEEP-FiO2 table for hyperoxia prevention (37.7% in the post-protocol group). This finding is consistent with previous studies demonstrating frequent use of FiO_2 levels greater than 90% with little oxygen titration in mechanically ventilated ED patients.[24, 25] While use of low V_Ts had become standard practice in the ED, our results suggest that immediate titration of FiO2 (Figure 1) remains poor. Future studies of bundled care protocols should involve active identification of barriers to implementation to ensure successful translation into clinical practice.

ED and ICU patients in both protocol groups received LPV at a much higher proportion than previous reports. We found that 87.7% of ED patients (median V_T of 6.5 mL/kg) and 82.0% of ICU patients (median V_T of 6.6 mL/kg) intubated at our site were ventilated with LPV in the ED *prior* to protocol implementation. This differs significantly from previous studies demonstrating use of LPV in 23–55.7% of ED patients and 20–46% of ICU patients.[24, 32, 33] Our data more closely resembles the recent Low Tidal Volume Universal Support (LOTUS) trial feasibility study, which showed an average V_T of 7.1 mL/kg and LPV

percentage of 78.2% in the ICUs of 49 hospitals.[46] In this context, our findings could reflect a shift in general practice to low V_T ventilation in all patients undergoing respiratory failure, regardless of ARDS status.

Our study found that variation in V_T administration was greater among RTs than intubating physicians, suggesting that the RTs were most directly influencing ventilator settings. Previous survey studies have identified discomfort of emergency medicine residents and physicians in the care of mechanically ventilated patients, causing them to frequently defer care to respiratory therapists.[47, 48] Our findings indicate that respiratory therapists are influential in determining ventilator settings, which highlights the importance of tailoring protocols for mechanically ventilated patients to respiratory therapy staff.

This study has several important limitations. As a before-after study, the results may be reflective of temporal changes in care. Since there were no other institutional efforts aimed at prophylactic LPV during the period of this study, however, we think that it remains likely that the ED protocol influenced care. The retrospective design of this study limits data available, but the research team took steps to validate data when possible and selected measures are likely to be recorded accurately. This study was conducted at a single academic teaching facility, which limits generalizability, but since prior reports were also single-center studies, we feel that local factors may lead to heterogeneity in treatment effects. ED providers' and respiratory therapists' awareness of this study may have introduced a Hawthorne effect, in which providers performed differently knowing they were being monitored. However, as data was collected through chart review, providers were never directly observed. Finally, we did not include plateau pressure in our definition of LPV[49–51], because it could not be measured with our standard ED transport ventilators.

CONCLUSION

Implementation of a bundled, ED-based mechanical ventilation protocol is associated with a significant decrease in ED V_T and increase in use of LPV. The protocol was not associated with change in any measured clinical outcomes, including ventilator-free days, ARDS, VAP, or mortality. The results of our study support the use of protocols to standardize care of ventilated ED patients and emphasize the importance of tailoring these protocols to respiratory therapists, who were shown to have a more significant impact on LPV use than intubating physician. Further study to maximize adherence to protocol parameters, particularly the immediate titration of FiO2, and clarify the influence of ED V_T on patient-centered outcomes is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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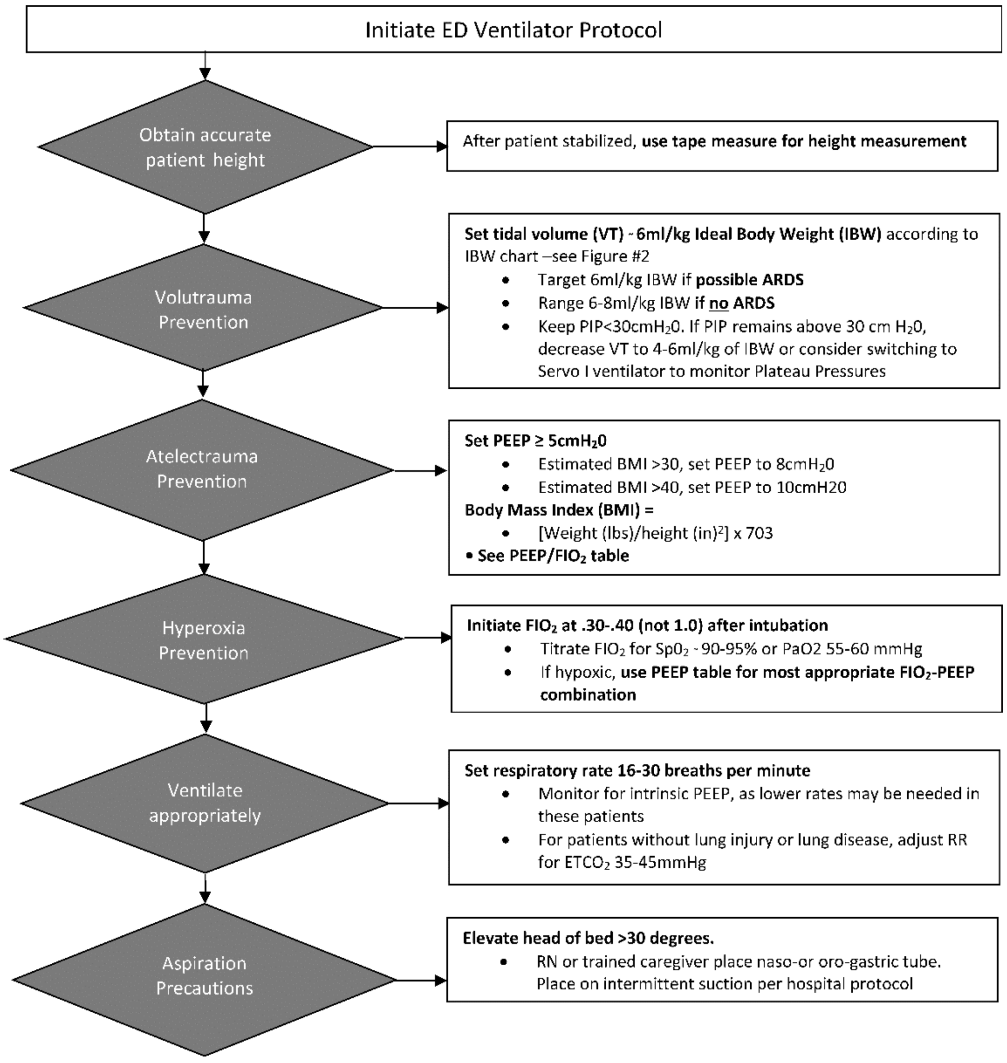

PEEP-FiO2 Table

FIO2	30	40	40	50	50	60	70	70	70	80	90	90	90	100
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20-24

Figure 1.
Study Protocol Diagram

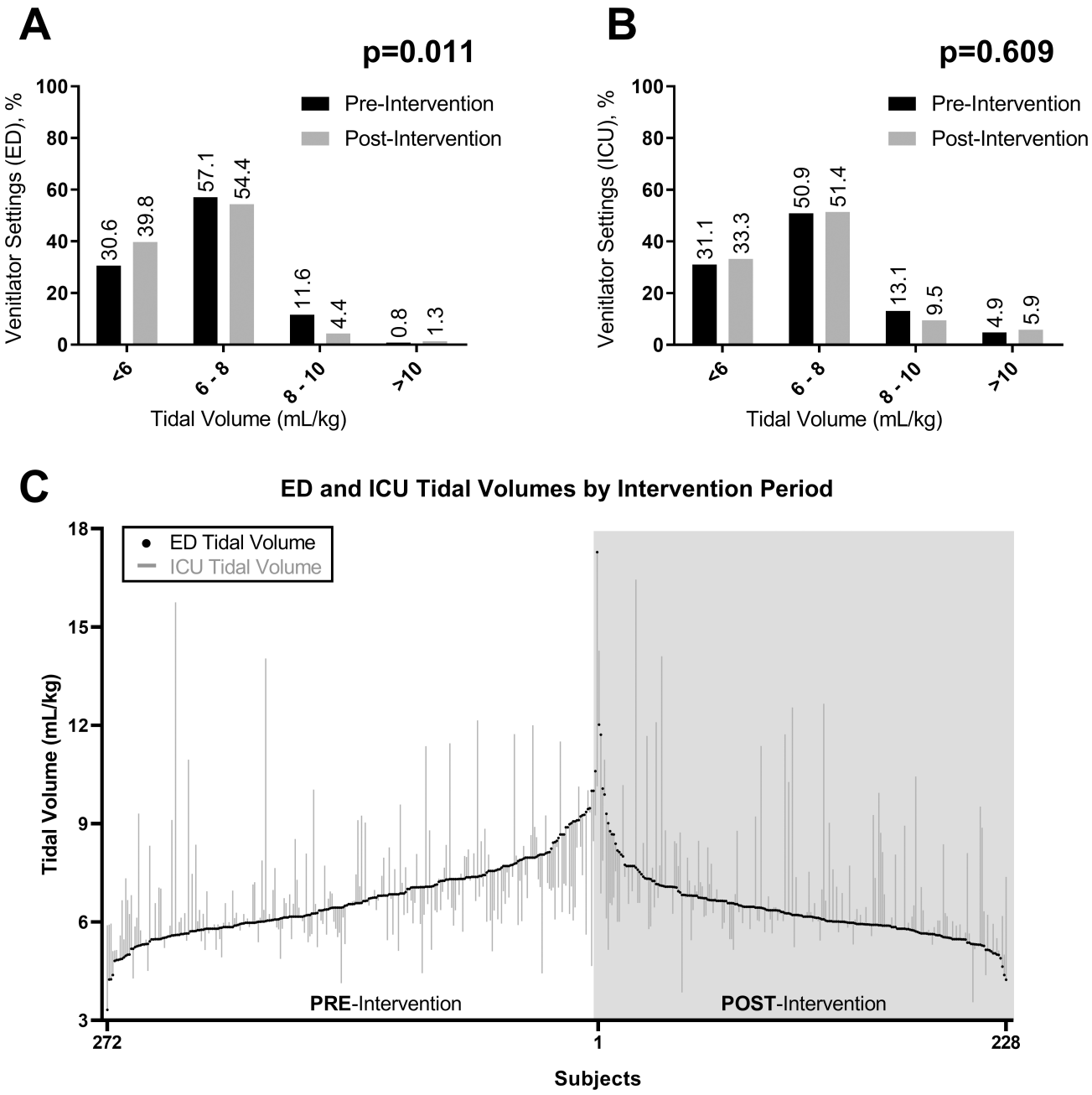

Figure 2.

(A) Upper left: differences in ED tidal volume by pre- and post-intervention; (B) Upper right: differences in ICU tidal volume by pre- and post-intervention; (C) Lower: plot of differences in individual subjects' ED (black dot) to ICU tidal volume in pre- and post-intervention groups. Differences between ED and ICU tidal volume are represented by the grey line. Subjects are rank-ordered by ED tidal volume.

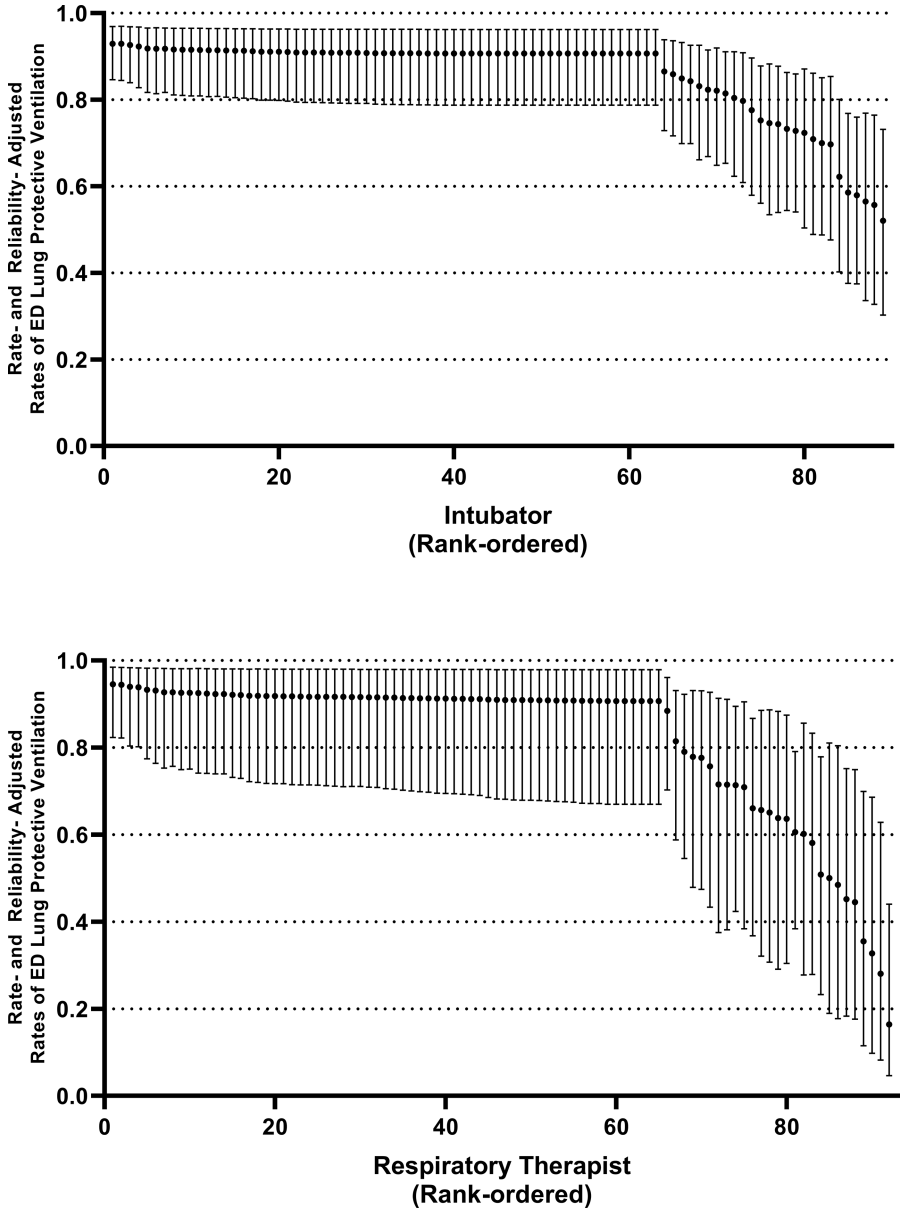

Figure 3.
Variation in ED Lung Protective Ventilation Rates by Intubator and Respiratory Therapist.

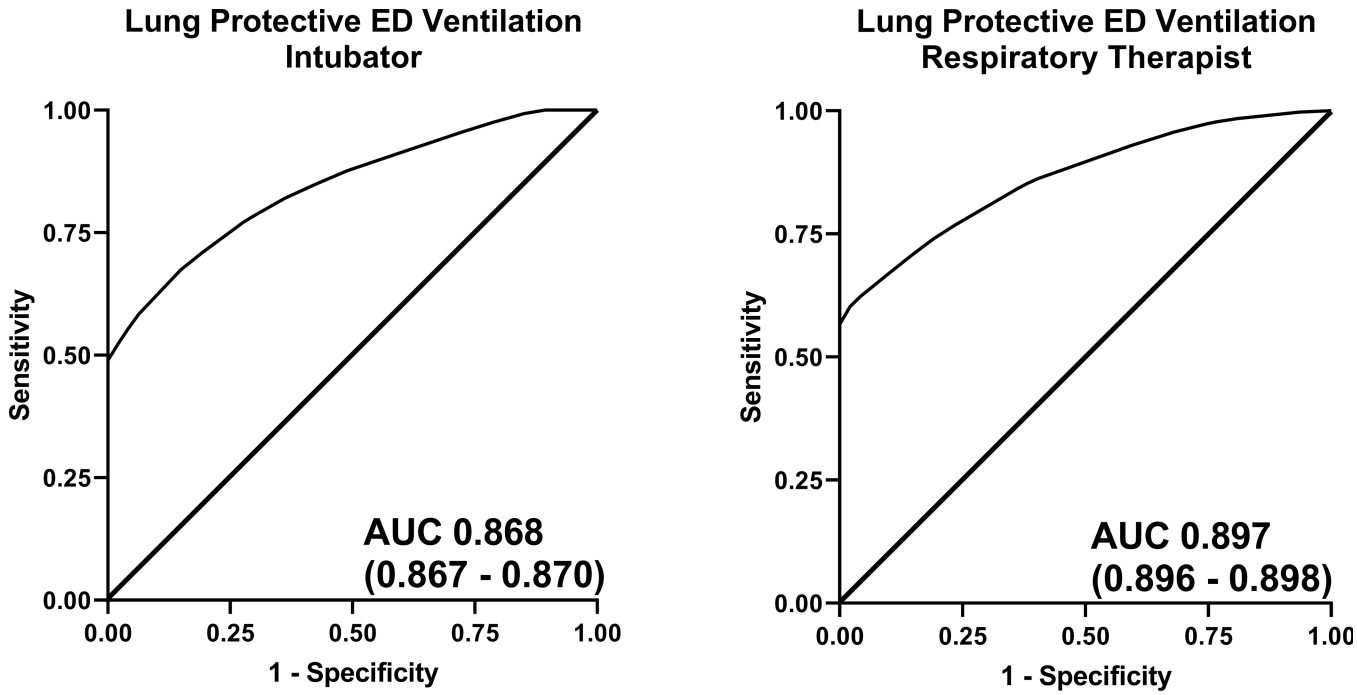

Figure 4.
Variation in ED Lung Protective Ventilation Rates by Intubator and Respiratory Therapist.

Table 1.

Subject Demographics and Ventilator Settings Pre/Post

	Total		Pre-Intervention		Post-Intervention		
	N		n		n		p-value
Total	**500**		**272**	**54.4%**	**228**	**45.6%**	
Age (yrs.)							
Median (IQR)	58.0	(43.0 – 71.0)	57.5	(41.5 – 70.0)	45.0	(45.0 – 71.0)	0.378
Sex							0.769
Male	293	58.6%	161	59.2%	132	57.9%	
Female	207	41.4%	111	40.8%	96	42.1%	
Height (cm)	172.7	(165.1 – 180.3)	172.7	(165.1 – 180.3)	172.7	(165.1 – 180.2)	0.664
Weight (kg)	82.3	(68.0 – 97.1)	84.9	(69.9 – 97.9)	80.6	(66.4 – 95.2)	0.271
BMI	27.4	(23.7 – 32.6)	28.0	(23.7 – 33.1)	27.1	(23.7 – 32.2)	0.242
Reason for Intubation							0.295
Asthma	4	0.8%	3	1.1%	1	0.4%	
Chronic Obstructive Pulmonary Disease	5	1.0%	5	1.8%	0	0.0%	
Chronic Heart Failure/Pulmonary Edema	20	4.0%	9	3.3%	11	4.8%	
Sepsis	71	14.2%	42	15.4%	29	12.7%	
Trauma	86	17.2%	51	18.8%	35	15.4%	
Cardiac Arrest	15	3.0%	9	3.3%	6	2.6%	
Alcohol/Drug Overdose	76	15.2%	41	15.1%	35	15.4%	
Neurological	119	23.8%	49	18.0%	55	24.1%	
Other	104	20.8%	63	23.2%	56	24.6%	
SOFA Score, median (IQR)							
Initial SOFA	2	(0–4)	0	(0–4)	2	(0–4)	0.419
24-hr SOFA	4	(2–7)	4	(2–6)	4	(2–7)	0.185
ED Length of Ventilation (minutes), median (IQR)	106.0	66.0 – 161.5	101.5	66.5 – 159.5	107.5	65.5 – 163.0	0.317
ED Ventilator Variables							
Tidal Volume (mL) median (IQR)	425	(380 – 450)	440	(400 – 462.5)	405	(370 – 450)	<0.001
Tidal Volume (ml/kg IBW), median (IQR)	6.4	(5.8 – 7.1)	6.5	(5.8 – 7.4)	6.2	(5.8 – 6.7)	<0.001
PEEP, cmH_2O, median (IQR)	5	(5 – 5)	5	(5 – 5)	5	(5 – 5)	0.068
Respiratory Rate, median (IQR)	18	(16 – 20)	18	(15.5 – 20)	18	(16 – 20)	0.006
FiO_2, Median (IQR)	50	(40 – 75)	60	(40 – 80)	50	(40 – 70)	0.029
Lung-protective Ventilation** (%)	448	90.7	235	87.7	213	94.3	0.012
Ventilator Mode							0.068
VC-AC	454	90.8	238	87.5	216	94.7	
PC-AC	19	3.8	13	4.8	6	2.6	
VC-SIMV	14	2.8	10	3.7	4	1.8	
PC-SIMV	12	2.4	10	3.7	2	0.9	
PS	1	0.3	1	0.4	0	0.0	

	Total		Pre-Intervention		Post-Intervention		
	N		n		n		p-value
Total	**500**		**272**	**54.4%**	**228**	**45.6%**	
ED Protocol Adherence	100	20.0	37	13.6	63	27.6	<0.001
ICU Ventilator Variables							
Tidal Volume (mL)	430	380 – 475	439.5	381 – 480	420	380 – 460	0.161
Tidal Volume (ml/kg IBW)	6.4	5.9 – 7.3	6.6	5.9 – 7.4	6.3	5.9 – 7.2	0.254
PEEP, cmH_2O	5	(5 – 5)	5	(5 – 5)	5	(5 – 5)	0.322
Respiratory Rate	18	15 – 22	18	15 – 22	18	16 – 21	0.340
FiO_2 (%)	40	40 – 60	40	40 – 60	40	40 – 55	0.128
Lung-protective Ventilation** (%)	407	82.2	219	82.0	188	84.7	0.433
Ventilator Mode							0.002
VC-AC	238	48.2	135	50.0	103	46.0	
PC-AC	37	7.5	23	8.5	14	6.3	
VC-SIMV	4	0.8	2	0.7	2	0.9	
PRVC-AC	97	19.6	38	14.1	59	26.3	
PS	76	15.4	40	14.8	36	16.1	
ICU Protocol Adherence	132	33.8	55	20.2	77	33.8	0.001

** Lung protective ventilation defined as tidal volume ≤ 8 mL/kg.

Table 2.

Regression Models

	n/Mean	%/SE	Unadjusted OR/Between Group Difference (95% CI)	Adjusted OR/ Between Group Difference (95% CI)
Primary Outcome				
ED Tidal Volume (mL/kg)	6.6	0.1	**−0.37 (−0.58 to −0.15) *p=0.001***	**−0.71 (−0.94 to −0.48) *p<0.001***
Log-transformed ED TV	-	-	**−0.05 (−0.08 to −0.02) *p=0.001***	**−0.10 (−0.13 to −0.06) *p<0.001***
Secondary Outcomes				
ARDS, n (%)	42	8.4%	0.64 (0.33 – 1.23) *p=0.179*	0.57 (0.08 – 4.11) *p=0.577*
VAP, n (%)	35	7.0%	1.14 (0.58 – 2.27) *p=0.703*	0.76 (0.12 – 4.61) *p=0.762*
28-Day Hospital Free Days, mean (SE)	14.7	0.5	−0.03 (−0.26 to 0.20) *p=0.798*	−0.30 (−0.65 to 0.04) *p=0.085*
Change in SOFA, mean (SE)	−1.0	0.2	0.26 (−0.34 to 0.86) *p=0.392*	**1.42 (0.67 to 2.18) *p<0.001***
Change in SOFA (excluding GCS), mean (SE)	−0.79	0.1	−0.01 (−0.47 to 0.46) p=0.983	0.50 (−0.02 to 1.02) p=0.061
Change in SOFA Components				
PaO_2/FiO_2 Ratio	−1.0	0.1	−0.19 (−0.51 to 0.14) P=0.260	**0.39 (0.12 to 0.67) p=0.006**
Platelets	0.2	0.0	0.06 (−0.05 to 0.16) p=0.279	0.08 (−0.07 to 0.23) p=0.304
Glasgow Coma Score	−0.1	0.1	0.27 (−0.06 to 0.59) p=0.107	**0.90 (0.46 to 1.35) p<0.001**
Creatinine	−0.1	0.0	−0.04 (−0.16 to 0.07) p=0.460	−0.14 (−0.30 to 0.01) p=0.075
Bilirubin	0.0	0.1	0.17 (−0.09 to 0.43) p=0.208	0.28 (−7.06 to 7.63) p=0.940
Mean Arterial Pressure	0.2	0.1	0.24 (−0.00 to 0.49) p=0.055	0.30 (−0.03 to 0.63) p=0.073
Mortality, n(%)	120	24.0%	1.03 (0.68 – 1.57) *p=0.873*	1.22 (0.50 – 3.00) *p=0.666*
Total Length of Ventilation, (minutes)	3,831	272	0.06 (−0.13 to 0.25) *p=0.527*	−0.12 (−0.40 to 0.17) *p=0.424*
ED Volume Settings				
TV cut-point of 8, n(%)	448	90.6%	**2.29 (1.17 – 4.48) *p=0.015***	3.92 (0.35 – 43.99) *p=0.268*

	n/Mean	%/SE	Unadjusted OR/Between Group Difference (95% CI)	Adjusted OR/ Between Group Difference (95% CI)
ICU Volume Settings				
Continuous TV, mean(SE)	6.8	0.1	−0.05 (−0.34 to 0.24) *p=0.739*	−0.15 (−0.52 to 0.22) *p=0.416*
Log-transformed ICU TV	-	-	−0.01 (−0.05 to 0.03) *p=0.566*	−0.03 (−0.08 to 0.01) *p=0.180*
TV cut-point of 8, n(%)	407	83.2%	1.29 (0.75 – 1.95) *p=0.435*	1.97 (0.59 – 6.50) *p=0.268*

*Adjusted for: sex, BMI (logarithmic transform), height (logarithmic transform), initial SOFA score, respiratory therapist, and intubator.

Table 3.

Protocol Adherence

	Total		Pre		Post	
	Adherent n(%)	**Missing n(%)**	**Adherent n(%)**	**Missing n(%)**	**Adherent n(%)**	**Missing n(%)**
ED Protocol Components						
PEEP FiO2 or FiO2 (Hyperoxia)	174 (32.8)	1 (0.2)	75 (27.6)	1 (0.4)	99 (43.4)	0 (0.0)
PEEP (Atelectrauma)	351 (70.2)	15 (3.0)	181 (66.5)	7 (2.6)	170 (74.6)	8 (3.5)
Respiratory Rate (Ventilate)	397 (79.4)	2 (0.4)	203 (74.6)	0 (0.0)	194 (85.1)	2 (0.9)
Tidal Volume (Volutrauma)	448 (89.6)	6 (1.2)	235 (86.4)	4 (1.5)	213 (93.4)	2 (0.9)
ICU Protocol Components						
PEEP FiO2 or FiO2 (Hyperoxia)	307 (61.4)	6 (1.2)	151 (55.5)	2 (0.7)	156 (68.4)	4 (0.8)
PEEP (Atelectrauma)	368 (73.6)	7 (1.4)	195 (71.7)	2 (0.7)	173 (75.9)	5 (2.2)
Respiratory Rate (Ventilate)	342 (68.4)	6 (1.2)	182 (66.9)	2 (0.7)	160 (70.2)	4 (1.8)
Tidal Volume (Volutrauma)	407 (81.4)	11 (2.2)	219 (80.5)	5 (1.8)	188 (82.5)	6 (2.6)