Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED): A Quasi-Experimental, Before-After Trial

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Study objective: We evaluated the efficacy of an emergency department (ED)–based lung-protective mechanical ventilation protocol for the prevention of pulmonary complications.

Methods: This was a quasi-experimental, before-after study that consisted of a preintervention period, a run-in period of approximately 6 months, and a prospective intervention period. The intervention was a multifaceted ED-based mechanical ventilator protocol targeting lung-protective tidal volume, appropriate setting of positive end-expiratory pressure, rapid oxygen weaning, and head-of-bed elevation. A propensity score–matched analysis was used to evaluate the primary outcome, which was the composite incidence of acute respiratory distress syndrome and ventilator-associated conditions.

Results: A total of 1,192 patients in the preintervention group and 513 patients in the intervention group were included. Lung-protective ventilation increased by 48.4% in the intervention group. In the propensity score–matched analysis (n=490 in each group), the primary outcome occurred in 71 patients (14.5%) in the preintervention group compared with 36 patients (7.4%) in the intervention group (adjusted odds ratio 0.47; 95% confidence interval [CI] 0.31 to 0.71). There was an increase in ventilator-free days (mean difference 3.7; 95% CI 2.3 to 5.1), ICU-free days (mean difference 2.4; 95% CI 1.0 to 3.7), and hospital-free days (mean difference 2.4; 95% CI 1.2 to 3.6) associated with the intervention. The mortality rate was 34.1% in the preintervention group and 19.6% in the intervention group (adjusted odds ratio 0.47; 95% CI 0.35 to 0.63).

Conclusion: Implementing a mechanical ventilator protocol in the ED is feasible and is associated with significant improvements in the delivery of safe mechanical ventilation and clinical outcome. [Ann Emerg Med. 2017;■:1-13.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Annually, approximately 250,000 patients receive mechanical ventilation in US emergency departments (ED), many of whom have protracted lengths of stay while awaiting ICU admission.[1,2] Pulmonary complications, such as acute respiratory distress syndrome and ventilator-associated conditions, develop in more than 20% of ED patients receiving ventilation and adversely affect outcome and resource use.[3-9] Because there is increased focus on reducing complications in this high-risk cohort, the time spent in the ED represents a vulnerable period in which preventive therapies could have a significant effect. However, the ED has not been targeted as an arena for prevention.[10]

Importance

Lung-protective ventilation, by reducing ventilator-associated lung injury, is one important strategy to aid in prevention of pulmonary complications. Although lung-protective ventilation is associated with a lower incidence of acute respiratory distress syndrome, evidence demonstrates that potentially injurious ventilator practices are common in the ED.[4,5,8,9,11] Lung-protective ventilation in the ED may be effective at reducing pulmonary complications for several reasons. Experimental data have established that ventilator-associated lung injury can occur shortly after the initiation of mechanical ventilation.[12,13] This is supported by evidence showing that initial ventilator settings influence outcome in patients with, and at risk for, acute respiratory distress syndrome.[3,8,9,14] Even if

Editor's Capsule Summary

What is already known on this topic

Patients intubated in the emergency department (ED) are at risk for subsequent acute respiratory distress syndrome and other ventilator-associated complications.

What question this study addressed

Can a 4-part "lung-protective" mechanical ventilation protocol decrease the frequency of such complications?

What this study adds to our knowledge

In this before-and-after analysis of 980 intubated ED adults, the frequency of acute respiratory distress syndrome and other ventilator-associated complications decreased after protocol implementation (14.5% to 7.4%), as did mortality (34.1% to 19.6%).

How this is relevant to clinical practice

Although outcome improvement caused by factors other than the intervention cannot be excluded, these data support the efficacy of a 4-part lung-protective protocol.

delivered for comparatively brief periods, early lung-protective ventilation during vulnerable periods seems to carry subsequent benefit, as demonstrated by data from the operating room and in lung donation.[15,16] Finally, initial ventilator settings influence the future delivery of lung-protective ventilation; it is therefore possible that establishing a lung-protective strategy during the earliest phases of respiratory failure can improve downstream adherence to lung-protective ventilation.[14]

Goals of This Investigation

The objective of this study was to evaluate the effectiveness of an ED-based lung-protective mechanical ventilation protocol on reducing the incidence of pulmonary complications. Given the high risk of pulmonary complications in mechanically ventilated ED patients, low adherence to lung-protective ventilation, and the association between initial ventilator settings and outcome, we hypothesized that a multifaceted strategy aimed at improving ED mechanical ventilation practices would reduce the incidence of pulmonary complications after ICU admission from the ED.

MATERIALS AND METHODS

Study Design and Setting

The Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED) trial was a quasi-experimental, before-after study. It consisted of a preintervention period (September 2009 to January 2014), a run-in period of approximately 6 months, during which lung-protective ventilation was implemented as the standard approach in the ED, and an intervention period (October 2014 to March 2016). The study was approved with waiver of informed consent because lung-protective ventilation in the ED was adopted as the default approach to mechanical ventilation locally. A detailed description of the methods has been published.[17]

The study was conducted in the ED (intervention) and ICUs (pertinent data and outcomes assessment) of an academic, tertiary medical center.

Selection of Participants

For the preintervention group, a validated electronic query method was used to identify all consecutive mechanically ventilated patients in the ED.[17] Briefly, this method used a Boolean key word search of ED documents. As an assurance against systematic sampling bias between the 2 groups, it was validated with a previously published prospective observational study as a test cohort for the search strategy.[5] The search yielded perfect recall (no false-negative cases) and perfect precision (no false-positive cases). We then applied this search to a random subset of ED documents for each cohort year. This validation set yielded perfect precision each time to identify all consecutive mechanically ventilated patients. The intervention group was followed prospectively and enrolled consecutively, 24 hours per day.

Mechanically ventilated patients in the ED were assessed for inclusion. Inclusion criteria for both groups were adult patients aged 18 years or older and mechanical ventilation through an endotracheal tube. Exclusion criteria for both groups were death or discontinuation of mechanical ventilation within 24 hours of presentation, long-term mechanical ventilation, presence of a tracheostomy, transfer to another hospital, and fulfillment of acute respiratory distress syndrome criteria during ED presentation.[18]

Interventions

After a run-in period that included education and collaboration initiatives between respiratory care services and the ED, the intervention period commenced. The ventilator intervention implemented in the ED addressed

the parameters in need of quality improvement, as demonstrated by our previous research: lung-protective tidal volume for prevention of volutrauma, appropriate setting of positive end-expiratory pressure to limit atelectrauma, rapid oxygen weaning to limit hyperoxia, and head-of-bed elevation.[3-5] After intubation, the ED respiratory therapist obtained an accurate height with a tape measure, and tidal volume was indexed to predicted body weight. Ventilator settings were then established per protocol (Figure 1), and head-of-bed elevation was performed for all patients unless specifically contraindicated. The study was designed to be pragmatic and to record data as part of usual care after implementation of the intervention. Therefore, all interventions, including ventilator settings, were performed by the ED clinical staff. If the treating team believed that more appropriate ventilator settings could be established off protocol (eg, higher tidal volume and lower respiratory rate for status asthmaticus), this was allowed and at the discretion of the clinical team.

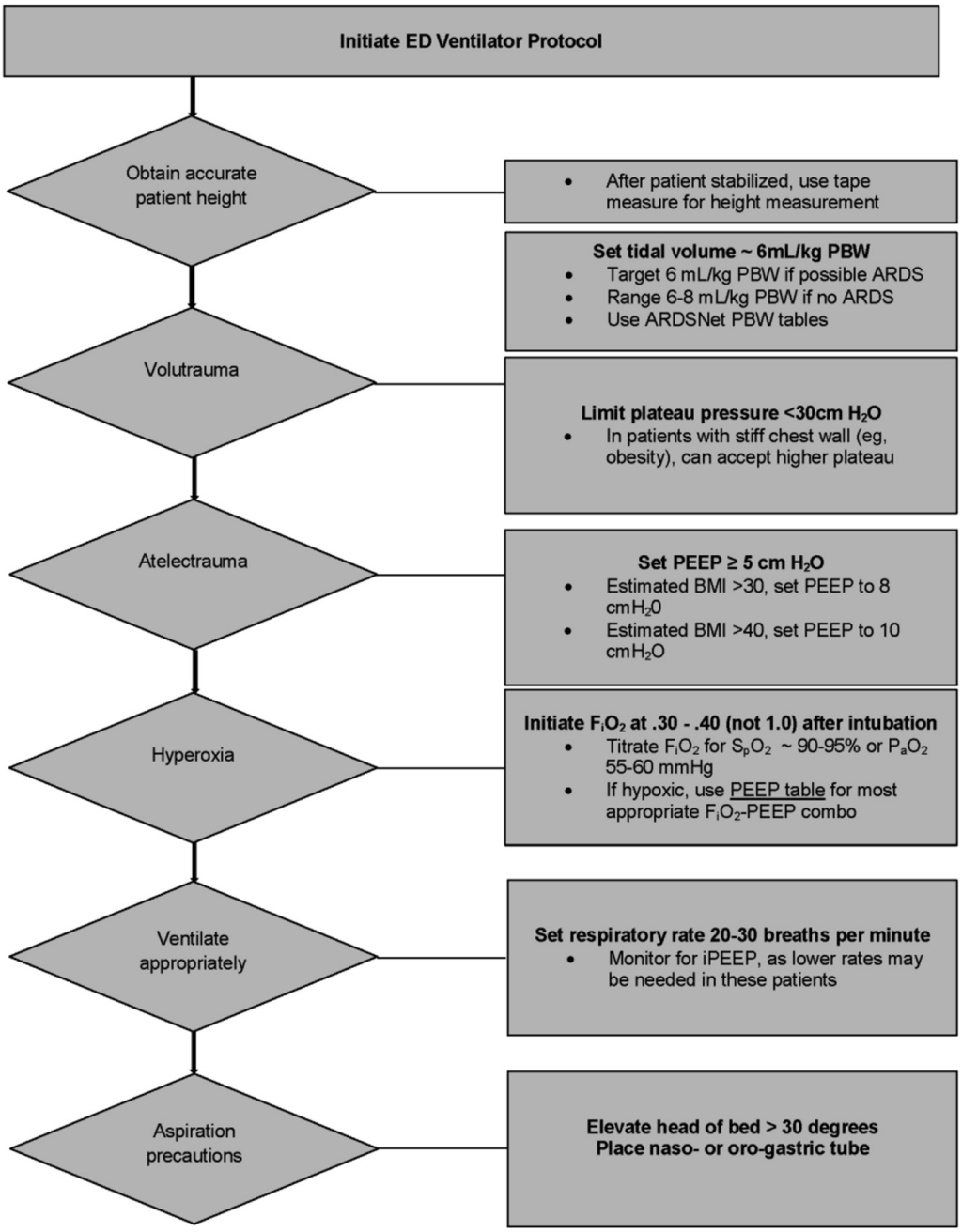


Figure 1. ED ventilator protocol. *PBW*, Predicted body weight; *ARDS*, acute respiratory distress syndrome; *PEEP*, positive end-expiratory pressure.

Methods of Measurement

Data on baseline demographics, comorbid conditions, vital signs at presentation, laboratory variables, illness severity (Acute Physiology and Chronic Health Evaluation II score), ED length of stay, and indication for intubation were collected.[19-21] Treatment variables in the ED included intravenous fluid, administration of blood products, central venous catheter placement, antibiotics, and vasopressor use.

All ED mechanical ventilator settings, airway pressures, pulmonary mechanics, and gas exchange variables were collected. ICU ventilator settings were followed for up to 2 weeks and collected twice daily. For pressure-targeted modes of ventilation, in which plateau pressure is not usually measured, peak pressure was used. Fluid balance was recorded daily after ICU admission. Patients were followed until hospital discharge or death.

To ensure that data from both groups were accurate and comparable, after identification and retrieval of the preintervention cohort, they were organized into an electronic database to exactly mirror the prospective data collection. Electronic data were then imported into the database. As further assurance of data accuracy, a research assistant, trained and blinded to study objectives and hypotheses, verified data accuracy. Routine meetings between the principal investigator and the research assistant occurred to monitor data collection.

Comorbid conditions are provided in Appendix E1, available online at http://www.annemergmed.com. Severe sepsis and septic shock were defined as previously described.[22] Lung-protective tidal volume was defined as the use of tidal volume of less than or equal to 8 mL/kg, predicted body weight, because this was the upper limit of tidal volume allowed by previous investigations of low-tidal-volume ventilation in acute respiratory distress syndrome.[23]

Outcome Measures

The a priori primary outcome was a composite of pulmonary complications after admission: acute respiratory distress syndrome and ventilator-associated conditions. Acute respiratory distress syndrome was defined according to the Berlin definition and adjudicated as previously described.[5,18] Adjudicators of acute respiratory distress syndrome status were blinded to all clinical variables, including ventilator settings and treatment period. See Appendix E2 (available online at http://www.annemergmed.com) for our standard operating procedure in adjudicating acute respiratory distress syndrome status. Ventilator-associated conditions were defined according to the Centers for Disease Control and Prevention criteria.[7,17] In accordance with these criteria, to qualify for a ventilator-associated condition, a patient must have 2 days of stable or improving ventilator settings, followed by 2 days of worsening oxygenation (increase in FiO_2 or positive end-expiratory pressure). Secondary outcomes included ventilator-, hospital-, and ICU-free days, as well as hospital mortality. The effect of the intervention on the odds of receiving lung-protective ventilation in the ICU was also explored. To screen for heterogeneous treatment effects, a priori subgroups were analyzed according to sepsis, trauma, lactate levels, ED length of stay, patients who received blood products in the ED, and those treated with vasopressors in the ED. After propensity score matching, for patients with baseline end-stage renal disease and those intubated for congestive heart failure or pulmonary edema, there was an imbalance between the preintervention group and the intervention group. Therefore, 2 post hoc subgroup analyses, which excluded these patients, were performed.

Primary Data Analysis

Participants were divided into 2 cohorts: a preintervention group (before implementation of ED lung-protective ventilation) and an intervention group (after implementation of ED lung-protective ventilation).

Descriptive statistics, including mean (SD), median (interquartile range), and frequency distributions, were used to assess patient characteristics. The Spearman's correlation coefficient (r_s) was used to assess the relationship between ED and ICU tidal volume. The primary analysis compared the proportion of patients in each cohort who met the composite primary outcome. Categorical characteristics were compared with the χ^2 test. Continuous characteristics were compared with the independent-samples t test or Wilcoxon's rank-sum test.

Given the nonrandomized treatment assignment and to balance the covariate distribution between the cohorts, a propensity score was derived with multivariable logistic regression, with cohort as the dependent variable.[24,25] Several variables were identified a priori to be important confounding factors to use for the derivation of the propensity score (illness severity, body mass index, vasopressor use, and sepsis). Additional patient characteristics at ED admittance that were unbalanced with clinically important differences were also considered for inclusion in the propensity score. Lack of collinearity among propensity score variables was confirmed with Spearman's correlations. Matching with optimal and greedy methods with various absolute difference thresholds and

with different propensity scores was performed, with the goal of achieving balance between clinically important covariates while retaining as many patients as possible in the intervention group. Ultimately, a propensity score was derived that, after 1:1 greedy matching (with 0.3 set as the largest absolute difference compatible with a valid match), achieved balance between the 2 cohorts in the matched sample for the most important covariates. The final propensity score was derived with the following independent variables: illness severity (ie, Acute Physiology and Chronic Health Evaluation II score), body mass index, vasopressor use in the ED, sepsis, trauma, and age. Outcome analysis was performed with the final matched sample, with 490 patients in each cohort. Categorical outcomes were compared with logistic regression modeling the odds of the outcome event, in which the preintervention group was the reference for the odds ratio. Count variables (ie, ventilator-, hospital-, and ICU-free days) were compared with generalized estimating equations negative binomial regression.

The study duration for the prospective intervention period was 72.9 weeks. Given the before-after study design, to account for potential secular trends (ie, temporal drift) in mechanical ventilation and clinical outcomes occurring over time, the preintervention cohort was divided into thirds, based on roughly equivalent epochs (73.7 weeks), for comparison to the intervention cohort.

We calculated a priori that with a sample of 513 patients in the intervention group, the study would have at least 80% power to detect a reduction in the primary outcome of 5 to 6 percentage points, α=.05, assuming an event rate of approximately 20% to 25% in the preintervention group.[3-7] After propensity score matching, the sample of 490 patients per cohort provided 80% statistical power to detect a difference between cohorts of at least 6.7% in the event rate. All tests were 2-tailed, and P<.05 was considered statistically significant.

RESULTS

Characteristics of Study Subjects

Figure 2 presents the study flow diagram and the final study population.

Baseline characteristics of the study population are shown in Table 1. Matching on the propensity score allowed the selection of 490 pairs of patients with greater similarity in illness severity and clinically relevant predictors of the primary outcome. After the propensity match, there was a significance difference between the 2 groups in patients with dialysis dependence and those intubated as a result of congestive heart failure or pulmonary edema.

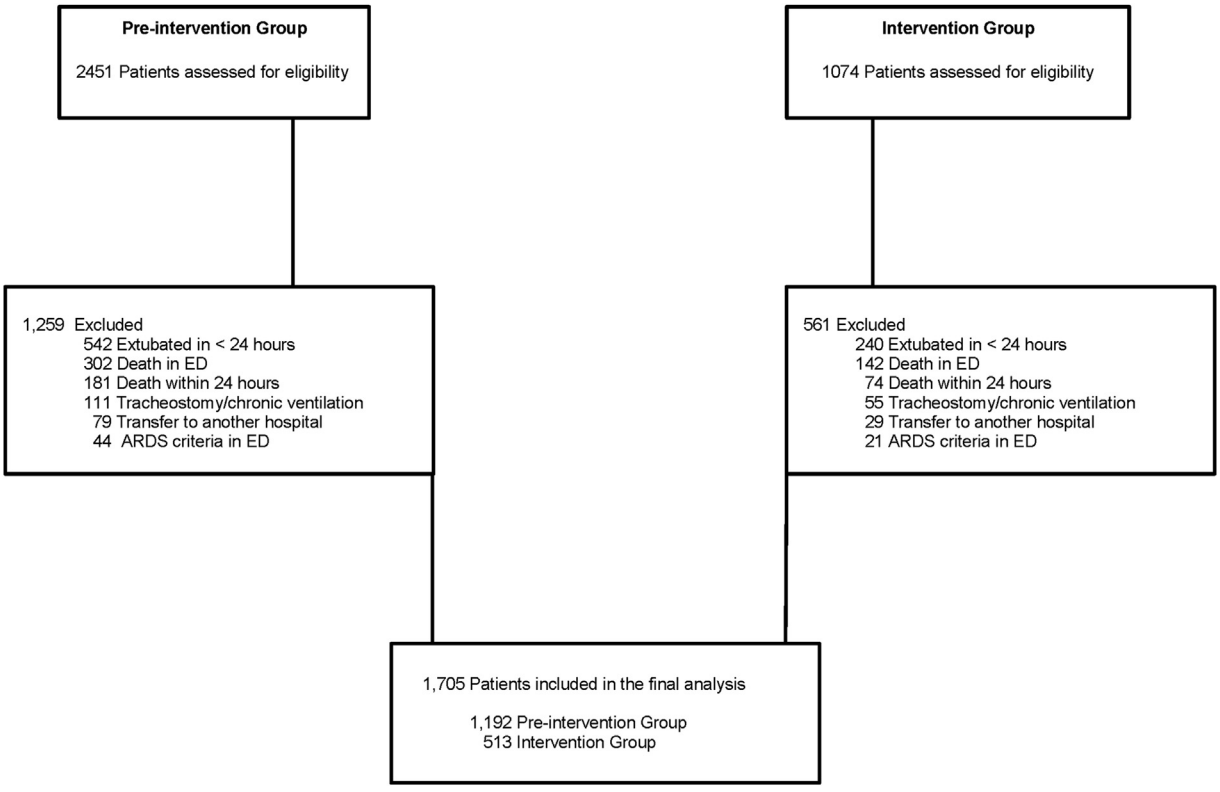


Figure 2. Study flow diagram.

Table 1. Characteristics of mechanically ventilated ED patients.

	Before Matching		After Matching	
Baseline Characteristics	**Preintervention Group (n=1,192)**	**Intervention Group (n=513)**	**Preintervention Group (n=490)**	**Intervention Group (n=490)**
Age, y	60.4 (21.1)	58.0 (24.0)	58.2 (18.3)	58.0 (24.0)
Male patient, No. (%)	628 (52.7)	303 (59.0)	271 (55.3)	288 (58.8)
Height, in	67.1 (4.1)	67.9 (3.9)	67.4 (4.0)	67.9 (3.9)
Weight, kg	84.7 (30.6)	83.9 (26.5)	82.0 (27.5)	83.9 (26.5)
BMI, lb/in^2	29.3 (10.7)	28.2 (8.8)	28.1 (9.5)	28.2 (8.8)
APACHE II score*	14.0 (8.0)	17.0 (13.0)	17.0 (8.0)	16.0 (11.0)
Sepsis, No. (%)	421 (35.3)	183 (35.7)	165 (33.7)	170 (34.7)
ED LOS, h	6.6 (3.8)	5.1 (3.0)	6.6 (3.8)	5.1 (3.0)
Race, No. (%)				
White	478 (40.1)	232 (45.2)	194 (39.6)	228 (46.5)
Black	698 (58.6)	280 (54.6)	287 (58.6)	261 (53.3)
Other	16 (1.3)	1 (0.2)	9 (1.8)	1 (0.20)
Comorbidities, No. (%)				
Diabetes	427 (35.8)	166 (32.4)	172 (35.1)	153 (31.2)
Cirrhosis	84 (7.0)	41 (8.0)	41 (8.4)	37 (7.6)
CHF	289 (24.2)	115 (22.4)	121 (24.7)	101 (20.6)
Dialysis	95 (8.0)	43 (8.4)	65 (13.3)	30 (6.1)
COPD	304 (25.5)	122 (23.8)	119 (24.3)	113 (23.1)
Immunosuppression	95 (8.0)	66 (12.9)	70 (14.3)	59 (12.0)
Alcohol abuse	177 (14.8)	76 (14.8)	72 (14.7)	76 (15.5)
HIV/AIDS	29 (2.4)	6 (1.2)	16 (3.3)	6 (1.2)
Vital signs and lab studies				
Temperature, °C	36.9 (1.1)	36.5 (1.2)	36.9 (1.2)	36.5 (1.2)
Mean arterial pressure, mmHg	87.3 (22.5)	84.0 (41.6)	86.0 (38.0)	85.3 (54.0)
Lactate, mmol/L	2.2 (1.4–3.9)	3.0 (1.6–5.2)	2.5 (1.4–4.7)	2.9 (1.6–5.2)
Creatinine, mg/dl	1.2 (0.8–2.0)	1.1 (0.8–1.8)	1.3 (0.8–2.7)	1.1 (0.8–1.7)
Hemoglobin, g/dl	11.6 (2.5)	12.2 (2.6)	11.2 (2.7)	12.3 (2.5)
WBC count, 10^9/L	12.9 (7.7)	13.7 (7.5)	13.9 (9.9)	13.8 (7.4)
Platelet, 10^9/L	221.7 (112.1)	233.3 (105.1)	219.0 (120.6)	235.2 (105.4)
INR	1.4 (0.9)	1.4 (0.9)	1.2 (1.1–1.5)	1.1 (1.0–1.3)
Total bilirubin, mg/dl	0.5 (0.3–0.9)	0.4 (0.3–0.7)	0.5 (0.3–0.9)	0.4 (0.3–0.7)
Albumin, g/dl	3.3 (0.7)	3.4 (0.7)	3.2 (0.8)	3.4 (0.6)
Sodium, mmol/L	140 (6.3)	139 (6.2)	140 (7.0)	139 (6.0)
Potassium, mmol/L	4.5 (1.0)	4.4 (1.1)	4.5 (1.1)	4.4 (1.0)
Reason for mechanical ventilation, No. (%)				
Asthma	30 (2.5)	9 (1.8)	4 (0.8)	9 (1.8)
COPD	95 (8.0)	29 (5.7)	23 (4.7)	29 (5.9)
CHF/pulmonary edema	85 (7.1)	15 (2.9)	37 (7.6)	11 (2.2)
Sepsis	322 (27.0)	152 (29.6)	130 (26.5)	141 (28.8)
Trauma	245 (20.6)	147 (28.7)	132 (26.9)	143 (29.2)
Cardiac arrest	81 (6.8)	37 (7.2)	41 (8.4)	35 (7.1)
Drug overdose	53 (4.4)	22 (4.3)	15 (3.1)	21 (4.3)
Other	281 (23.6)	101 (19.7)	108 (22.0)	101 (20.6)
Process-of-care variables				
Intravenous fluids in ED, L	1.8 (1.9)	1.5 (1.4)	1.9 (2.0)	1.6 (1.5)
Fluid balance first 24 h	2.9 (3.9)	3.0 (3.8)	3.4 (3.2)	3.0 (2.9)
Blood product administration, No. (%)	126 (10.6)	88 (17.2)	76 (15.5)	80 (16.3)
Central venous catheter, No. (%)	357 (29.9)	163 (31.8)	181 (36.9)	149 (30.4)
Antibiotics, No. (%)	517 (43.4)	230 (44.8)	220 (44.9)	215 (43.9)
Vasopressor infusion, No. (%)	233 (19.6)	148 (28.9)	132 (26.9)	133 (27.1)

CHF, Congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *BMI*, body mass index; *INR*, international normalized ratio; *APACHE II*, Acute Physiology and Chronic Health Evaluation II; *LOS*, length of stay.
Continuous variables are reported as mean (SD) and median (interquartile range).
*Modified score, which excludes Glasgow Coma Scale.

Main Results

A total of 3,273 ED ventilator settings were analyzed. Table 2 shows the effect of the intervention on mechanical ventilation practices in the ED. The intervention period was associated with significant changes in tidal volume, positive end-expiratory pressure, respiratory rate, FiO_2, and

Table 2. Ventilator variables in the ED.

	Preintervention Group (n=1,192)	Intervention Group (n=513)	Odds Ratio or Between–Group Difference (95% CI)*
Tidal volume, mL			
Median (IQR)	500 (500 to 550)	420 (370 to 470)	
Mean (SD)	515.7 (71.6)	422.0 (71.5)	−93.7 (−99.5 to −87.8)
Tidal volume, mL/kg PBW			
Median (IQR)	8.1 (7.3 to 9.1)	6.3 (6.0 to 6.7)	
Mean (SD)	8.3 (1.5)	6.4 (0.8)	−1.8 (−1.9 to −1.7)
PEEP, cmH_2O			
Median (IQR)	5 (5 to 5)	5 (5 to 8)	
Mean (SD)	5.4 (1.5)	6.5 (2.5)	1.1 (0.9 to 1.3)
Respiratory rate			
Median (IQR)	14 (12 to 16)	20 (20 to 24)	
Mean (SD)	15.3 (3.5)	20.9 (3.8)	5.6 (5.3 to 5.9)
FiO_2, %			
Median (IQR)	80 (50 to 100)	40 (40 to 60)	
Mean (SD)	75.0 (25.9)	53.4 (21.7)	−21.6 (−23.5 to −19.8)
Head-of-bed elevation, No. (%)	989 (39.4)	704 (92.6)	19.4 (14.6 to 25.7)
Lung-protective ventilation, No. (%)	1,202 (47.8)	731 (96.2)	37.6 (21.8 to 64.7)
Ventilator mode, No. (%)			
VC-AC	2,274 (90.5)	687 (90.4)	0.9 (0.8 to 1.3)
PC-AC	92 (3.7)	12 (1.6)	0.4 (0.2 to 0.8)
VC-SIMV	32 (1.3)	2 (0.3)	0.2 (0.05 to 0.9)
PRVC-AC	92 (3.7)	57 (7.5)	2.1 (1.5 to 3.0)
Other	23 (0.9)	2 (0.3)	0.3 (0.07 to 1.2)
Peak pressure, cm H_2O			
Median (IQR)	29 (24 to 36)	26 (21 to 31)	
Mean (SD)	30.2 (8.8)	26.7 (7.3)	−3.4 (−4.1 to −2.8)
Plateau pressure, cm H_2O			
Median (IQR)	19 (15 to 23)	18 (15 to 23)	
Mean (SD)	19.5 (6.2)	19.5 (5.7)	−0.04 (−0.7 to 0.7)
Mean airway pressure, cm H_2O			
Median (IQR)	10 (8 to 12)	11 (9 to 14)	
Mean (SD)	10.4 (3.0)	11.8 (3.5)	1.5 (1.2 to 1.7)
Compliance respiratory system, mL/cm H_2O			
Median (IQR)	38.2 (29.4 to 50.0)	34.6 (26.3 to 45.0)	
Mean (SD)	41.6 (18.0)	36.7 (14.9)	−4.9 (−7.0 to −2.9)
Driving pressure, cm H_2O			
Median (IQR)	13 (10 to 17)	12 (10 to 16)	
Mean (SD)	14.3 (6.2)	13.1 (5.1)	−1.2 (−1.9 to −0.5)
Oxygenation index			
Median (IQR)	3.7 (2.4 to 6.5)	4.1 (2.7 to 7.8)	
Mean (SD)	5.2 (4.2)	6.3 (5.8)	1.2 (0.6 to 1.7)
pH			
Median (IQR)	7.34 (7.24 to 7.41)	7.29 (7.19 to 7.38)	
Mean (SD)	7.30 (0.14)	7.27 (0.15)	−0.05 (−0.06 to −0.03)
PaO_2, mmHg			
Median (IQR)	156 (102 to 239)	118 (80 to 172)	
Mean (SD)	186.7 (108.5)	137.8 (80.6)	−48.9 (−58.4 to −39.5)
$PaCO_2$, mmHg			
Median (IQR)	41 (34 to 52)	43 (37 to 54)	
Mean (SD)	46.4 (19.7)	48.5 (19.9)	2.1 (0.05 to 4.2)
PaO_2:FiO_2			
Median (IQR)	227 (135 to 334)	263 (158 to 371)	
Mean (SD)	241.3 (122.5)	273.1 (136.0)	31.8 (17.9 to 45.6)

IQR, Interquartile range; *VC*, volume control; *AC*, assist control; *PC*, pressure control; *SIMV*, synchronized intermittent mandatory ventilation; *PRVC*, pressure-regulated volume control.

A total of 3,273 ED ventilator settings were analyzed (2,513 preintervention group; 760 intervention group). In the preintervention group, peak pressure was monitored for 1,865 settings (74.2%), plateau pressure for 422 settings (16.8%), and mean pressure for 1,804 settings (71.8%). In the intervention group, all pressures were monitored for each recorded ventilator setting (100%).

*Odds ratio is presented for binary data and between-group difference is presented as the difference in means for the continuous data.

adherence to head-of-bed elevation. Tidal volume was reduced by a median of 1.8 mL/kg predicted body weight. Figure 3 shows the distribution of ED tidal volume in the 2 cohorts. Lung-protective ventilation increased by 48.4%.

A total of 22,960 ICU ventilator settings were analyzed. Table 3 shows the comparison of ICU ventilator settings between the 2 groups. After the intervention, ICU tidal volume decreased by a median of 1.1 mL/kg predicted body weight. Lung-protective ventilation increased by 30.7%. Multivariable logistic regression analysis demonstrated that the intervention was associated with an increased probability of receiving lung-protective ventilation in the ICU (adjusted odds ratio 5.1; 95% confidence interval [CI] 3.76 to 6.98). The correlation between ED tidal volume and ICU tidal volume was 0.71 (95% CI 0.67 to 0.73).

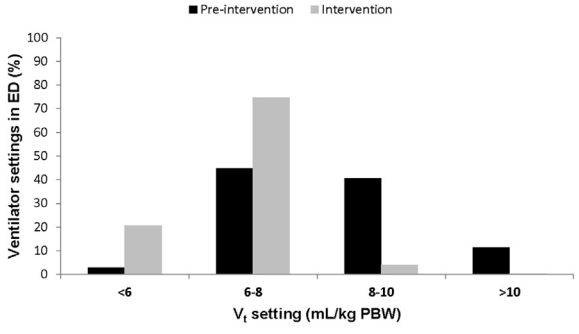
The 2 groups were well balanced with respect to fluid administration in the ED, at 24 hours, and during the first week of admission (Table 1, Figure E1 [available online at http://www.annemergmed.com]).

In the propensity score–matched analysis, there was an absolute risk reduction for the primary outcome of 7.1% (adjusted odds ratio 0.47; 0.31 to 0.71) (Table 4).

Secondary outcomes are also presented in Table 4. There was an increase in ventilator-free days (mean difference 3.7; 95% CI 2.3 to 5.1), ICU-free days (mean difference 2.4; 95% CI 1.0 to 3.7), and hospital-free days (mean difference 2.4; 95% CI 1.2 to 3.6) associated with the intervention. There was an absolute risk reduction for mortality of 14.5% (adjusted odds ratio 0.47; 0.35 to 0.63).

Subgroup analyses are shown in Table E1 (available online at http://www.annemergmed.com). There was a significant reduction in the primary outcome across all subgroups, excluding trauma patients.

During the intervention period, the practice changes in mechanical ventilation in the ED and ICU were a deviation from the temporal trends of the preintervention period (Table E2, Figures E2 and E3, available online at http://www.annemergmed.com). The change in primary outcome, ventilator-free days, and mortality was also a deviation from the secular trends of the preintervention period and consistent with implementation of the intervention (Table E2, available online at http://www.annemergmed.com).



There was an increase in lung-protective ventilation in the ED associated with the intervention (47.8% to 96.2%).
ED: emergency department; PBW: predicted body weight

Figure 3. Distribution of ED tidal volume.

LIMITATIONS

There are several limitations to the present study. A before-after study design is prone to temporal trends that may lead to independent changes in care. Analysis of secular changes did not demonstrate this; the greatest change in clinical practice and outcomes was isolated to the intervention period. However, unmeasured confounders that improved overall care during the intervention may have accounted for some of the improved outcomes. The study design can raise concern over proof of causation. These results may be better viewed as an association, yet our results are consistent with some of the randomized controlled trials that have shown benefit in critical care. Consistent findings across trial design suggest cause and effect.[26] Dose-response also suggests causality, and greater benefit was derived for the subgroup of patients with longer ED lengths of stay. Because this was a single-center study, results could be prone to an overestimation of effect. A randomized, multicenter trial would be the most robust way to test the hypothesis and reduce bias. However, many randomized trials in critical care exclude up to 90% of screened patients, limiting external validity and implementation into practice.[27] We aimed to be pragmatic for the current investigation and believe it applies well to actual clinical care because all consecutive patients, satisfying inclusion and exclusion criteria, were enrolled (enhancing external validity).

Some imbalance in baseline characteristics between the 2 study groups did exist. However, propensity score adjustment reduced imbalance in the most important clinical covariates; most of the statistical imbalances before propensity score adjustment reflected little clinical significance. Furthermore, subgroup analyses across potentially clinically important imbalances demonstrated a similar significant effect of the intervention (ie, high internal consistency). After the propensity score match, there was imbalance between the groups in dialysis dependence and heart failure or pulmonary edema as the cause of respiratory failure. We know of no data to suggest that the event rate for our primary outcome is higher in these cohorts. The ultimate goal of the

Table 3. Ventilator variables in the ICU.

	Preintervention Group (n=1,192)	Intervention Group (n=513)	Odds Ratio or Between–Group Difference (95% CI)*
Tidal volume, mL/kg PBW			
Median (IQR)	8.1 (7.3 to 9.1)	7.0 (6.4 to 8.0)	
Mean (SD)	8.3 (1.5)	7.3 (1.4)	−0.9 (−1.0 to −0.9)
PEEP, cmH_2O			
Median (IQR)	5 (5 to 5)	5 (5 to 5)	
Mean (SD)	5.6 (1.9)	5.8 (1.9)	0.3 (0.2 to 0.3)
FiO_2, %			
Median (IQR)	40 (40 to 50)	40 (40 to 40)	
Mean (SD)	48.3 (17.2)	41.4 (11.5)	−6.8 (−7.3 to −6.4)
Lung-protective ventilation, No. (%)	8,404 (46.0)	3,700 (76.7)	3.9 (3.6 to 4.2)
Ventilator mode, No. (%)			
VC-AC	13,052 (72.0)	2,925 (60.6)	0.6 (0.56 to 0.64)
PC-AC	749 (4.1)	342 (7.1)	1.8 (1.6 to 2.0)
VC-SIMV	1,456 (8.0)	145 (3.0)	0.4 (0.3 to 0.4)
PRVC-AC	2,783 (15.3)	977 (20.2)	1.4 (1.3 to 1.5)
Other	94 (0.5)	437 (9.1)	19.1 (15.3 to 23.9)
Peak pressure, cm H_2O			
Median (IQR)	27 (23 to 33)	24 (20 to 29)	
Mean (SD)	28.3 (7.7)	24.1 (7.6)	−4.2 (−4.4 to −3.9)
Plateau pressure, cm H_2O			
Median (IQR)	21 (17 to 25)	20 (16 to 23)	
Mean (SD)	21.9 (6.4)	20.3 (5.6)	−1.7 (−1.8 to −1.5)
Mean airway pressure, cm H_2O			
Median (IQR)	11 (10 to 13)	11 (9 to 13)	
Mean (SD)	11.8 (3.4)	11.6 (3.3)	−0.2 (−0.3 to −0.1)
Compliance respiratory system, mL/cm H_2O			
Median (IQR)	33.3 (26.2 to 42.9)	34.5 (26.7 to 44)	
Mean (SD)	36.1 (14.6)	37.3 (15.8)	1.2 (0.7 to 1.7)
Driving pressure, cm H_2O			
Median (IQR)	15 (12 to 20)	14 (11 to 17)	
Mean (SD)	16.4 (6.1)	14.4 (5.2)	−2.0 (−2.1 to −1.8)
Oxygenation index			
Median (IQR)	4.2 (2.9 to 6.9)	3.8 (2.6 to 5.9)	
Mean (SD)	5.8 (4.7)	5.0 (4.0)	−0.8 (−1.0 to −0.7)
pH			
Median (IQR)	7.41 (7.35 to 7.45)	7.4 (7.36 to 7.44)	
Mean (SD)	7.39 (0.09)	7.39 (0.08)	0.0 (0.0 to 0.0)
PaO_2, mmHg			
Median (IQR)	118 (86 to 154)	120 (89 to 154)	
Mean (SD)	129.1 (63.4)	124.9 (46.5)	−4.2 (−6.0 to −2.3)
PaO_2:FiO_2			
Median (IQR)	265 (182 to 360)	300 (213 to 398)	
Mean (SD)	281.8 (135.5)	311.0 (126.2)	29.1 (24.3 to 34.0)

A total of 22,960 ventilator settings were analyzed (18,134 preintervention group; 4,826 intervention group). In the preintervention group, all airway pressures were recorded (100%). In the intervention group, peak pressure was monitored for 4,826 settings (100%); plateau pressure and mean airway pressure, for 4,428 settings (91.8%). After adjustment for covariates (age, sex, body mass index, lactate, and APACHE II score), the intervention group was associated with an increased probability of receiving lung-protective ventilation in the ICU (aOR 5.1; 95% CI 3.76 to 6.98).

*Odds ratio is presented for binary data and between-group difference is presented as the difference in means for the continuous data.

propensity match was to achieve balance between the most clinically important variables and retain as many patients as possible because the large sample size is a strength of the study. We believe the propensity match was a success in that regard because there was balance in the most important predisposing conditions (illness severity, shock, sepsis, and trauma) and risk modifiers (male sex, alcohol abuse, obesity, immunosuppression, diabetes, and blood product administration). Also, in the post hoc subgroup analyses that focused on these imbalances, the intervention remained associated with a reduction in the primary outcome, with a near-identical effect size. We did not formally study potential complications, such as patient-ventilator dyssynchrony. The majority of data show that lung-protective ventilation is well tolerated.[28] Given the known

Table 4. Results of outcome analyses.

	Before Matching			After Matching		
	Preintervention Group (n=1,192)	Intervention Group (n=513)	OR or Between-Group Difference (95% CI)	Preintervention Group (n=490)	Intervention Group (n=490)	aOR or Between-Group Difference (95% CI)*
Primary composite outcome, No. (%)	171 (14.3)	38 (7.4)	0.48 (0.33 to 0.69)	71 (14.5)	36 (7.4)	0.47 (0.31 to 0.71)
ARDS	130 (10.9)	22 (4.3)	0.37 (0.23 to 0.58)	53 (10.8)	20 (4.1)	0.35 (0.21 to 0.60)
VACs	86 (7.2)	23 (4.5)	0.60 (0.38 to 0.97)	37 (7.6)	23 (4.7)	0.60 (0.35 to 1.03)
Secondary outcomes						
Ventilator-free days	16.0 (11.4)	18.2 (10.5)	2.17 (1.06 to 3.29)	14.7 (11.7)	18.4 (10.4)	3.69 (2.30 to 5.07)
Hospital-free days	10.8 (9.6)	11.6 (9.2)	0.87 (−0.09 to 1.84)	9.4 (9.5)	11.7 (9.2)	2.38 (1.21 to 3.55)
ICU-free days	15.0 (10.8)	15.8 (10.0)	0.77 (−0.30 to 1.83)	13.6 (11.1)	16.0 (9.9)	2.36 (1.04 to 3.68)
Mortality, No. (%)	338 (28.4)	105 (20.5)	0.65 (0.51 to 0.83)	167 (34.1)	96 (19.6)	0.47 (0.35 to 0.63)

OR, Odds ratio; *aOR*, adjusted OR; *VAC*, ventilator-associated condition.
The primary outcome was a composite pulmonary outcome that combines the event rate for ARDS and VACs.
*From logistic regression modeling (categorical data) and generalized estimating equations negative binomial regression (continuous data).

deleterious effects of dyssynchrony, if this were present to a significant degree across the study cohort, results would have also been biased toward the null hypothesis.[29] It is impossible to prescribe a standard ventilator approach to all patients, and some may tolerate a low tidal volume approach poorly (eg, status asthmaticus, chronic obstructive pulmonary disease, severe metabolic acidosis). These are a minority of patients mechanically ventilated in the ED, suggesting that lung-protective protocols could decrease the unnecessary heterogeneity in management and improve outcome. Finally, the intervention was multifaceted and addressed several ventilator parameters (ie, a bundle). Given the abundance of preclinical and clinical data in regard to ventilator-associated lung injury, we hypothesize that mitigation of early ventilator-associated lung injury is responsible for these findings. The tidal volume difference between the 2 groups was approximately 2 mL/kg predicted body weight. This is an interesting finding but a smaller tidal volume difference than that observed in previous work on lung-protective ventilation in at-risk patients.[9,11,15] Although it may be difficult to ascribe the observed clinical effects to this tidal volume difference, improved outcomes have been observed with tidal volume differences approximately 1 mL/kg predicted body weight in patients with acute respiratory distress syndrome and at risk.[3,14] Our intervention also achieved a significant decrease in the FiO_2 and resultant PaO_2, which has been shown to improve mortality and decrease ventilator duration in mechanically ventilated ICU patients.[30] So it is possible that both of these interventions were influential on outcome. However, without a different trial design or any mechanistic outcomes, we are unable to fully dissect from where the exact benefit is derived.

DISCUSSION

The rationale for implementing lung-protective ventilation in the ED hinges on the premise that there is a temporal link between ventilator management during the earliest period of respiratory failure and the development of subsequent complications; early adherence to lung-protective ventilation could therefore improve outcome. Multiple studies show a link between nonprotective ventilation in the ICU and acute respiratory distress syndrome incidence, with syndrome onset typically 2 days after admission.[8,9,11,31-36] In a randomized controlled trial of abdominal surgery patients ventilated for 5.5 hours in the operating room (the approximate ED length of stay in the current study), lung-protective ventilation decreased major pulmonary complications and hospital length of stay.[15] The results of this large before-after study extend mechanical ventilation interventions to the ED and have several implications.

First, lung-protective ventilation strategies can be implemented effectively in the ED. Critical care interventions considered overly complex are unlikely to be implemented effectively in the ED.[37] Because mechanically ventilated patients have higher mortality and longer ED lengths of stay compared with nonventilated ED patients, implementing effective and feasible therapies is paramount.[1] The current study provides data to suggest that an ED-based lung-protective ventilation protocol, which is simple and relatively easy to implement, could be adopted widely and affect outcome.

Second, the implementation of an ED-based lung-protective ventilator protocol not only changed ED mechanical ventilation practices but also exerted similar influence on ventilator practices in the ICU. This is demonstrated by correlation statistics, a multivariable analysis of predictors of ICU lung-protective ventilation,

and analysis of secular trends in ICU mechanical ventilation. Initial ventilator settings in the ICU influence subsequent adherence to lung-protective ventilation in acute respiratory distress syndrome patients.[14] Similarly, in a preplanned secondary analysis of the patients with acute respiratory distress syndrome in this LOV-ED trial, the intervention was associated with increased adherence to lung-protective ventilation and a reduction in mortality.[38] Given the known poor adherence to lung-protective ventilation that exists in the ICU, combined with our current results, timely attention to mechanical ventilation immediately after intubation could be a high-fidelity intervention to improve clinical practice and outcome.

Third, the intervention was associated with a significant reduction in pulmonary complications, hospital mortality, and health care resource use. These findings were significant after propensity score adjustment and were stable in subgroup and secular analyses. Therefore, within the context of otherwise routine care in the ED and ICU, these data suggest that lung-protective ventilation initiated in the ED could improve clinical outcome.

In conclusion, this before-after study of mechanically ventilated patients demonstrates that implementing a mechanical ventilator protocol in the ED is feasible and associated with improvements in the delivery of safe mechanical ventilation and clinical outcome. Innovation can improve societal health only if it reaches the patient and is externally valid. Previous critical care medicine research demonstrates that lung-protective ventilation remains implemented poorly, even for patients with a clear indication for it.[14,39] By attempting to standardize care delivery and reduce unnecessary practice variability, the present study demonstrated clinical benefit when targeting a site typically not considered for mechanical ventilation research (ie, the ED).[40] In this regard, a new approach of setting the ventilator appropriately immediately after intubation could help overcome existing shortfalls in the implementation of lung-protective ventilation.[41]

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APPENDIX E1

Definitions of comorbid conditions

Diabetes mellitus: Documentation of clinical history in patient's medical record; current presentation congruent with diabetes mellitus (eg, diabetic ketoacidosis).

Cirrhosis: Biopsy-proven cirrhosis or medical record history suggestive of cirrhosis (ascites, coagulopathy, nodular liver on computed tomography or ultrasonography).

Heart failure: Clinical diagnosis on current presentation or history of heart failure in the medical record; includes systolic and diastolic heart failure.

Dialysis/end-stage renal disease: Current use of peritoneal dialysis or hemodialysis as an outpatient.

COPD: Not fully reversible airflow limitation; FEV1 $<80\%$+FEV1/FVC $<70\%$; history of COPD in patient's medical record.

Immunosuppression: Therapy with immunosuppressants, chemotherapy, radiation, long-term/recent high-dose steroids, active leukemia, lymphoma, or AIDS.

Alcohol abuse: Known diagnosis of chronic alcoholism; previous admission for alcohol detoxification or withdrawal; daily consumption of >14 drinks/wk or >5 binges.

AIDS: CD4 count<200 mm^3 or AIDS-indicator condition

FEV1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *COPD*, Chronic obstructive pulmonary disease.

APPENDIX E2

Protocol for adjudication of acute respiratory distress syndrome diagnosis

Study: Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED): a quasi-experimental, before-after trial.

Objectives: To evaluate the effectiveness of an ED-based lung-protective mechanical ventilation protocol on reducing the incidence of pulmonary complications after admission to the ICU.

The term "acute lung injury" is no longer used.

Acute respiratory distress syndrome (ARDS) is now divided into subgroups:

Mild ARDS: 200 mm Hg$<PaO_2$:$FiO_2\leq300$ mm Hg

Moderate ARDS: 100 mm Hg$<PaO_2$:$FiO_2\leq200$ mm Hg

Severe ARDS: PaO_2:$FiO_2\leq100$ mm Hg

Oxygenation criterion for potential ARDS (PaO_2:$FiO_2\leq300$ mm Hg) is screened daily.

Chest Radiograph Interpretation for the Diagnosis of ARDS

Defining ARDS status is challenging, despite a consensus definition of the syndrome. There is high interobserver variability in chest radiograph interpretation, which can confound and bias study results when diagnosing study subjects as "ARDS vs no ARDS."[42] The Berlin definition of ARDS attempts to address this by stating that chest radiograph abnormalities consist of "bilateral opacities consistent with pulmonary edema that are not fully explained by effusions, lobar/lung collapse, or nodules/masses on chest radiograph."[18]

The purpose of this section is to decrease heterogeneity among reviewers in how the chest radiograph is interpreted during the adjudication process for ARDS.

The Process

Focusing on the "Chest Radiograph Interpretation" section, read "Supplementary Material" from Ferguson et al[43] for a set of illustrative chest radiographs. These represent a spectrum of findings and clinical scenarios that are consistent, inconsistent, or equivocal for the diagnosis of ARDS. These should serve as training radiographs.

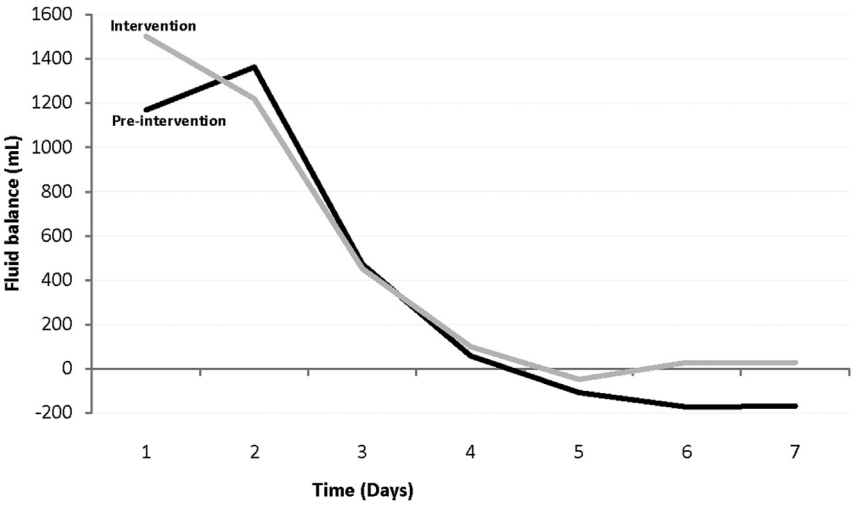
Evaluate each chest radiograph during the first 7 days of hospital admission because data suggest that ARDS develops early in the course of ICU admission. It is also less likely that ARDS developing later after admission from the ED could reliably be attributed to factors present in the ED.[4,5,11,31,32]

Categorize each radiograph as consistent (C), inconsistent (I), or equivocal (E) for the diagnosis of ARDS.

To limit ascertainment bias, most radiographs will be reviewed by more than one reviewer at some point, and certainly all equivocal radiographs. When agreement exists between reviewers, then the patient will be deemed acceptable for ARDS adjudication status.

When disagreement exists, the images will be further reviewed independently by another reviewer, and consensus will be reached by e-mailed data set or conference call if further discussion is necessary.

Patients fulfilling ARDS oxygenation criteria within a 24-h window of having bilateral infiltrates not fully explained by myocardial dysfunction or fluid overload will be deemed to have ARDS.



There was no significant difference in net fluid balance during the first week of admission, pre-intervention group 2.6 liters (7.5) vs. 3.3 liters (6.2) in the intervention group, mean difference 0.67 liters (95% CI -0.019 to 1.36).

Figure E1. Fluid balance (milliliters) during the first week of admission.

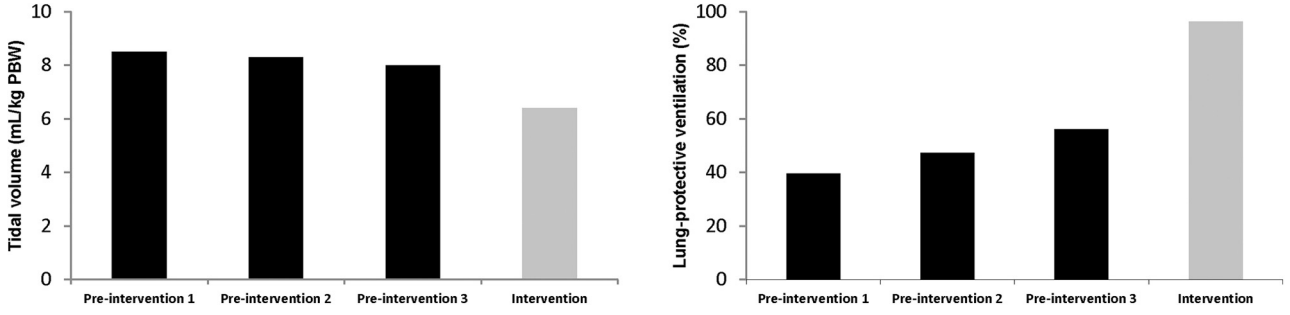


Figure E2. Secular trends in ED tidal volume (left panel) and lung-protective ventilation (right panel).

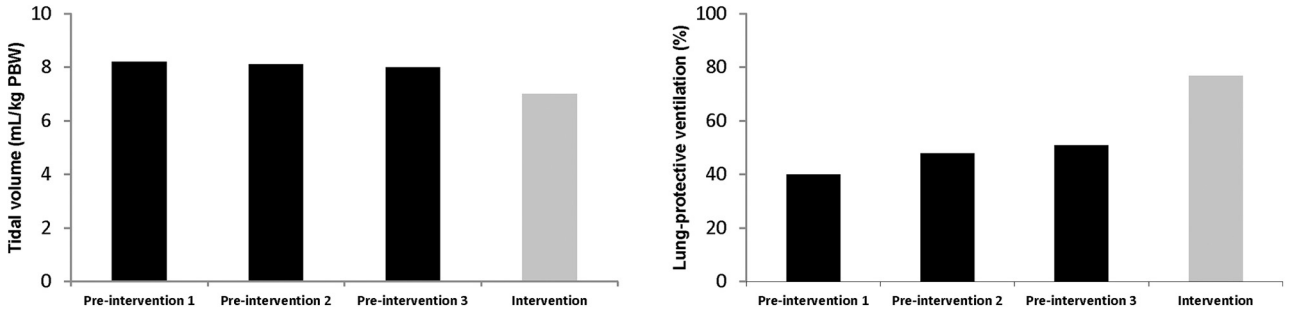


Figure E3. Secular trends in ICU tidal volume (left panel) and lung-protective ventilation (right panel).

Table E1. Subgroup analyses for primary composite outcome.

Subgroup	Preintervention Group	Intervention Group	aOR	95% CI
Blood product transfusion	34/126 (27.0)	9/88 (10.2)	0.23	0.10–0.57
Vasopressor infusion	53/233 (22.7)	17/148 (11.5)	0.42	0.23–0.76
Sepsis	88/421 (20.9)	14/183 (7.7)	0.22	0.11–0.45
Trauma	25/245 (10.2)	14/147 (9.5)	0.71	0.32–1.56
Lactate				
≤4	106/604 (17.5)	23/290 (7.9)	0.42	0.25–0.70
>4	36/185 (19.5)	14/155 (9.0)	0.23	0.11–0.45
ED LOS, h				
≤6	86/614 (14.0)	30/360 (8.3)	0.44	0.28–0.71
>6	85/578 (14.7)	8/153 (5.2)	0.18	0.08–0.41
Excluding dialysis patients*	161/1,097 (14.7)	36/470 (7.7)	0.36	0.24–0.54
Excluding patients intubated with CHF/pulmonary edema*	166/1,107 (15.0)	38/498 (7.6)	0.35	0.23–0.53

Data presented as number of composite pulmonary outcome events/number of patients (%). aOR adjusted for the covariates of age, lactate, APACHE II score, intravenous fluids, blood product transfusion, and vasopressor infusion.

*Post hoc subgroup analyses were conducted after baseline imbalance was detected after propensity score matching.

Table E2. Secular trends for tidal volume and lung-protective ventilation in the ED and ICU, as well as clinical outcomes.

	Period			
Variable	**Preintervention 1 (n=391)**	**Preintervention 2 (n=394)**	**Preintervention 3 (n=407)**	**Intervention (n=513)**
ED				
Ventilator settings, n	800	876	837	760
Tidal volume, mL/kg PBW	8.4 (7.5–9.1)	8.2 (7.3–9.2)	7.8 (7.0–8.8)	6.3 (6.0–6.7)
Lung protective ventilation, No. (%)	317 (39.6)	415 (47.3)	470 (56.1)	731 (96.2)
ICU				
Ventilator settings, n	6,369	6,296	5,469	4,826
Tidal volume, mL/kg PBW	8.2 (7.5–9.1)	8.1 (7.3–9.1)	8.0 (7.1–8.9)	7.0 (6.4–8.0)
Lung protective ventilation, No. (%)	2,551 (40.0)	3,047 (47.8)	2,806 (50.8)	3,700 (76.7)
Outcomes				
Primary outcome, No. (%)	60 (15.3)	60 (15.2)	51 (12.5)	38 (7.4)
Ventilator-free days	15.5 (11.5)	16.2 (11.2)	16.4 (11.5)	18.2 (10.5)
Hospital-free days	10.4 (9.7)	10.7 (9.6)	11.2 (9.5)	11.6 (9.2)
ICU-free days	14.6 (10.9)	15.3 (10.7)	15.2 (10.9)	15.8 (10.0)
Mortality, No. (%)	110 (28.1)	108 (27.4)	120 (29.5)	105 (20.5)

Continuous variables are reported as mean (SD) and median (IQR).