Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

LIST OF SITE INVESTIGATORS BY ENROLLMENT CONTRIBUTION

Site	Location	Principal Investigator	Study Coordinator & Respiratory Therapist
Beth Israel Deaconess Medical Center, Harvard Medical School	Boston, MA, USA	Daniel Talmor, MD, MPH Todd Sarge, MD	Valerie Banner-Goodspeed, MPH Emily Fish, MD, MPH Sayuri Jinadasa, MD, MPH Ray Ritz, RRT, FAARC Joseph Previtera, RRT
Montefiore Medical Center, Albert Einstein College of Medicine	Bronx, NY, USA	Michelle N. Gong, MD, MSc	Lawrence Lee, PhD, PA-C
University of California San Diego	San Diego, CA, USA	Jeremy R. Beitler, MD, MPH	
St. Joseph's Healthcare, McMaster University	Hamilton, ON, Canada	Deborah Cook, MD, MS	France Clarke, RRT Tom Piraino, RRT
Stanford University	Palo Alto, CA, USA	Joseph Levitt, MD, MS	Rosemary Vojnik, BS
University of Michigan	Ann Arbor, MI, USA	Pauline Park, MD, FACS, FCCM	Kristin Brierley, CCRP Carl Haas MLS, RRT-ACCS, FAARC Andrew Weirauch BS, RRT-ACCS
Toronto General Hospital, University of Toronto	Toronto, ON, Canada	Eddy Fan, MD, FRCPC, PhD	Andrea Matte, RRT
Massachusetts General Hospital, Harvard Medical School	Boston, MA, USA	R. Scott Harris, MD	Mamary Kone, MD, MPH
University of Massachusetts	Worcester, MA, USA	Stephen Heard, MD	Karen Longtine, BS, RN, CCRC
Université Laval	Quebec City, QC, Canada	François Lellouche, MD, PhD	Pierre-Alexandre Bouchard, RRT
R. Adams Cowley Shock Trauma Center, University of Maryland	Baltimore, MD, USA	Lewis Rubinson, MD, PhD, FCCP	Jennifer (Titus) McGrain, RRT
Vancouver General Hospital	Vancouver, BC, Canada	Donald E G Griesdale, MD, MPH, FRCPC	Denise Foster, RN, CCRP
Mayo Clinic	Rochester, MN, USA	Richard Oeckler, MD, PhD	Amy Amsbaugh RRT, RCP
Orlando Health, Inc.	Orlando, FL, USA	Edgar Jimenez, MD, FCCM	Valerie Danesh, RN, BSN, MHSA, CCRP

CORE STUDY TEAM FOR TRIAL ADMINISTRATION

All core trial activities were coordinated through Beth Israel Deaconess Medical Center, Harvard Medical School in Boston, MA, USA.

Role	**Name**
Overall Trial PIs	Daniel Talmor, MD, MPH & Stephen Loring, MD
Director, Medical Coordinating Center	Daniel Talmor, MD, MPH
Director, Physiology Core Lab	Stephen Loring, MD
Director, Trial Operations	Valerie Banner-Goodspeed, MPH

eAppendix 1. Methods

Eligibility Criteria

Eligible for enrollment were adults aged 16 years or older with moderate or severe ARDS (PaO_2:$FiO_2 \leq 200$) onset within the last 36 hours. ARDS onset was defined from the moment the last of the four Berlin definition criteria[1] for moderate ARDS was met.

Patients were excluded for any of the following: mechanical ventilation for more than 96 hours; contraindication to esophageal catheter insertion including severe coagulopathy (platelet < 5000/microliter or international normalized ratio > 4); lung transplant recipient; high risk of elevated intracranial pressure (including intracranial hemorrhage, cerebral contusion, edema, or mass effect, or flat electroencephalogram); active air leak from the lung (pneumothorax, pneumomediastinum, bronchopleural fistula, or air leak from an existing chest tube); neuromuscular disease that impairs spontaneous ventilation; use of protocol-defined rescue therapies prior to enrollment (nitric oxide, extracorporeal gas exchange, prone positioning, high frequency oscillation); severe chronic liver disease (Child-Pugh score of 12 or higher); lack of commitment to full medical support; inability to obtain informed consent; treating clinician refusal; or participation in another intervention trial for ARDS or sepsis within the prior 30 days.

The initial protocol also excluded enrollment of liver transplant recipients. This exclusion was removed in a protocol amendment during the trial.

Physiologic Measurements in Both Arms

Upon enrollment in either study arm, an airway flow/pressure transducer was inserted in-line with the ventilator circuit between the endotracheal tube and ventilator Y-tubing. An esophageal balloon catheter was inserted to a depth of 35-40 cm from the incisors, inflated with 1 mL of air, and transduced to record esophageal pressure during ventilation.

Correct balloon position in the retrocardiac mid-thoracic esophagus was confirmed via four steps: (1) waveform appearance inconsistent with airway pressure waveform; (2) pressure increase during inspiration and decrease during expiration in the passive patient; (3) presence of cardiac artifact; and (4) constant P_L with airway occlusion during either gentle manual compression of the chest wall or patient respiratory effort. Catheter position was adjusted as needed prior to study measurements.

P_{ES} measured in the relaxed esophagus is widely believed to reflect pleural pressure in the area immediately surrounding the balloon.[2,3] Placing the balloon in the retrocardiac mid-thoracic esophagus approximates the center of the chest cavity and affords a reasonable estimate of average pleural pressure in the chest,[4-7] although spatial pleural pressure gradients exist.[8,9]

P_L was measured during end-inspiratory and end-expiratory breath holds at baseline and at least once daily thereafter on study protocol. Airway and esophageal waveforms were recorded during these measurements and uploaded to a central repository for independent quality control by the physiology core lab.

Protocol Elements Common to Both Arms

In both arms, P_L measurements were obtained on baseline ventilator settings. Then, after assessment of hemodynamic stability, intravascular volume, and continued passive ventilation, a single recruitment maneuver was performed that consisted of an apneic high-pressure breath hold at 35 cmH_2O for 30 seconds duration. The maneuver was terminated early if systolic blood pressure decreased to below 90 mmHg.

Following the recruitment maneuver, patients were placed on ventilator settings per protocol (Table 1). In both groups, a tidal volume of 6 mL/kg predicted body weight was targeted using either the pressure or volume assist-control mode. Respiratory rate, pH, partial pressure of arterial CO_2 ($PaCO_2$) and oxygen (PaO_2), and oxygen pulse-oximetry values were targeted according to ranges adopted by the NIH ARDS Network protocol.[10] PEEP was adjusted according to treatment assignment as described below.

P_L was measured during end-inspiratory and end-expiratory breath holds at baseline and at least once daily thereafter on study protocol. Airway and esophageal waveforms were recorded during these measurements and uploaded to a central repository for independent quality control by the physiology core lab.

Sedation, neuromuscular blockade, and resuscitation were administered at discretion of the treating physician. Additional sedative and paralytic doses could be given if needed to facilitate passive ventilation during P_L measurements. Ventilator weaning was directed by protocol (see Protocol Supplement). Protocol-directed ventilator

management was continued for a maximum of 28 days or until the patient could breathe unassisted for 48 hours, experienced protocol failure, was withdrawn for safety reasons or rescinded consent, discharged, or died. In the event of protocol failure (refractory hypoxemia or acidemia), rescue measures could be employed according to local site practice.

P_{ES}-guided PEEP Arm

The overall philosophy of this arm was to individualize PEEP to minimize risk of mechanical lung injury, relying primarily on FiO_2 titration to achieve adequate oxygenation. The goal was to select PEEP high enough to keep open lung units at greatest risk of cyclic opening/closure (atelectrauma) while also sufficiently low to minimize overdistension. PEEP was adjusted to maintain end-expiratory P_L between 0 to 6 cmH_2O, to ensure airway pressure at end-expiration was never less than nor substantially more than pleural pressure estimated by P_{ES}. An empiric P_L-FiO_2 table was used (Table 1), permitting more positive end-expiratory P_L when higher FiO_2 was required to meet oxygenation goals. End-expiratory P_L was measured at least once daily and PEEP and FiO_2 adjusted accordingly to maintain the lowest P_L-FiO_2 combination possible on the table while maintaining oxygenation goals. Once the patient tolerated end-expiratory P_L 0 with $FiO_2 \leq 0.5$ for at least 24 hours, the patient was transitioned to a weaning protocol and PEEP and FiO_2 were incrementally decreased further without regard for P_L (see Protocol Supplement).

The protocol also sought to minimize tidal overdistension. End-inspiratory P_L was measured daily with an end-inspiratory plateau hold. If end-inspiratory P_L exceeded 20 cmH_2O, tidal volume was decreased to as low as 4 mL/kg PBW as necessary. For severe dyspnea or acidemia, tidal volume could be increased to as high as 8 mL/kg PBW as long as end-inspiratory P_L remained $\leq$ 20 cmH_2O.

Empiric PEEP-FiO_2 Arm

The high PEEP-FiO_2 table employed in this arm was adapted from a recent multicenter clinical trial and presented in Table 1 of the main manuscript.[11] P_L measurements were made daily but were not disclosed to the treating team and were not considered in selecting PEEP. Rather, PEEP was adjusted to maintain the lowest PEEP-FiO_2 combination possible on the table while maintaining oxygenation goals. Cross-over to the P_{ES}-guided arm was prohibited. In effort to minimize tidal overdistension, tidal volume could be decreased to as low as 4 mL/kg PBW as necessary if airway plateau pressure exceeded 35 cmH_2O. For severe dyspnea or acidemia, tidal volume could be increased to as high as 8 mL/kg PBW as long as airway plateau pressure remained $\leq$ 35 cmH_2O.

Study Endpoints

The primary endpoint was a ranked composite score that incorporated death and days free from mechanical ventilation through day 28, calculated in such a manner that death constitutes a worse outcome than fewer days off the ventilator.[12] Days free from mechanical ventilation was calculated as the time between successful liberation from the ventilator and study day 28. Each patient was compared to every other patient in the study and assigned a score (tie: 0, win: +1, lose: -1) for each pairwise comparison based on whom fared better. If one patient survived and the other did not, scores of +1 and -1 were assigned, respectively, for that pairwise comparison. If both patients in the pairwise comparison survived, the assigned score depended on which patient had more days free from mechanical ventilation: the patient with more days off the ventilator received a score of +1, while the patient with fewer days received a score of -1. If both patients survived and had the same number of days off the ventilator, or if both patients died, they both were assigned a score of 0 for that pairwise comparison. For each patient, scores for all pairwise comparisons were summated, resulting in a cumulative score for each patient. These cumulative scores were ranked and compared between study arms via the Mann-Whitney U technique. Effect size is reported as the probability of more favorable outcome, also known as the probabilistic index, which describes the estimated probability that an individual randomly selected from one treatment group will have a higher score (more favorable outcome) than an individual randomly selected from the other treatment group.[13-16]

Pre-specified secondary endpoints included all-cause mortality at 28 days, 60 days, and one year, ventilator-free days[13] and shock-free days through day 28, acute kidney injury requiring renal replacement therapy in the first 28 days, ICU and hospital lengths of stay, and protocol failure requiring rescue therapy. Ventilator- and shock-free days were calculated as previously described,[17] assigning a value of zero failure-free days for patients who died before day 28. Patients on chronic dialysis at baseline were excluded from determination of acute kidney injury. Shock was defined by any vasopressor or inotropic infusion, and patients transferred out of ICU were assumed to be shock-free. Protocol failure was defined as refractory hypoxemia ($PaO_2 < 55$ mmHg or $SpO_2 < 88\%$) despite maximum PEEP and

FiO_2 settings or refractory acidemia (pH < 7.15) despite maximum tidal volume and respiratory rate settings permitted on protocol. Although mentioned in the original protocol, data on fluid balance were not collected. Plasma biomarkers of lung injury, a pre-specified secondary endpoint, are not reported here as results are not yet available.

Long-term functional outcomes assessed at 1-year follow-up included Barthel index, Medical Outcome Study Short Form-12 (SF-12), and the Vulnerable Elderly Survey. Data are reported only for survivors who completed the surveys. The Barthel index measures functional independence in activities of daily living.[18] It ranges from 0 to 100, with 0 indicating complete dependence and 100 indicating complete independence with no deficit.[19] The Barthel index was analyzed as a dichotomized variable as ≥ 95 or < 95.[19,20] The Medical Outcomes Study Short Form-12 (SF-12) is a widely utilized health-related quality of life measure, typically analyzed as physical and mental component scores (SF-12 PCS and SF-12 MCS), and with lower scores indicating worse quality of life.[21] The Vulnerable Elderly Survey was used to assess frailty at one-year follow-up among patients aged ≥ 65 years.[22]

Secondary mechanistic endpoints included PaO_2:FiO_2, P_L during end-inspiratory and end-expiratory holds, and lung compliance. Safety endpoints included incidence of barotrauma, change in vasopressor requirements, and serious adverse events.

External Validation of P_{ES} and P_L Readings

Agreement between site and physiology core laboratory readings of end-expiratory P_{ES} and P_L values were assessed for bias by comparing mean difference and for accuracy by quantifying the proportion of readings that fell within a specified range (± 2 or 3 cmH_2O).[23]

eAppendix 2. Results

Study Population: Additional Details

The protocol initially planned enrollment of 200 patients. During the trial, consent was withdrawn for two patients after randomization but prior to esophageal balloon catheter insertion or protocol-directed ventilator adjustments. In response, the data safety monitoring board approved an increase in enrollment by two patients. Thus, the trial enrolled and randomized 202 patients, with 102 patients assigned to the P_{ES}-guided arm and 100 to the empiric PEEP-FiO_2 arm. Consent was withdrawn for two patients assigned to the PEEP-FiO_2 arm, leaving 102 and 98 patients in the P_{ES}-guided and PEEP-FiO_2 arms, respectively, for inclusion in the primary analysis (Fig. 1). An esophageal balloon catheter could not be inserted successfully in one patient randomized to P_{ES}-guided PEEP; that patient did not undergo subsequent study procedures but regardless did complete 28-day follow-up and was included in corresponding analyses.

Enrollment occurred between October 2012 and September 2017. Enrollment was slower than expected due to three main factors. (1) Not all ICUs at each site participated in the trial. (2) Another trial targeting a similar patient population began at most sites while this study was ongoing, competing for patients since co-enrollment was prohibited. (3) Standardized recording of ventilator and esophageal pressure waveforms daily for independent quality control required use of specialized bioengineering software. Use of this dedicated software, which was not designed explicitly for this purpose and thus lacked a user-friendly interface customary for clinical devices, precluded protocol execution beyond the dedicated study staff trained in the software. Some sites owned commercial ventilators with P_{ES}-monitoring capabilities that may have overcome this issue. However, standardization of equipment, prioritization of recording waveforms for external validation, and external monitoring of protocol adherence all necessitated use of the stand-alone manometer, recording equipment, and bioengineering software.

Agreement of Site with Core Lab P_{ES} and P_L Measurements

Esophageal pressure (P_{ES}) readings differed by mean 0.0 (SD 1.3) cmH_2O between site investigator versus core laboratory. Forty-six of 1,022 end-expiratory P_{ES} readings (4.5%) differed by more than 2 cmH_2O between site versus core lab, and 1.8% of P_{ES} readings differed by more than 3 cmH_2O.

Transpulmonary pressure (P_L) readings differed by mean 0.0 (SD 1.2) cmH_2O between site investigator versus core laboratory. Only 3.4% of end-expiratory P_L readings differed by more than 2 cmH_2O and 1.4% by more than 3 cmH_2O. Instances of disagreement were evenly distributed across sites.

Protocol Adherence

Protocol adherence was high and did not meaningfully differ between study groups (eTable 1). Overall, 94.0% (948/1009) of all PEEP values for which data were available during the first seven study days were within ± 2 cmH_2O of the protocol-specified value. Most PEEP deviations (43/61, 70.5%) more than 2 cmH_2O beyond the protocol-specified value occurred during the ventilator weaning phase when FiO_2 was between 0.3 and 0.4.

Rescue Therapy

Sixteen patients received protocol-defined rescue therapy during the trial, initiated a median of 4 [interquartile range 2-6] days after enrollment. Rescue was initiated for refractory hypoxemia in 10 cases (62.5%), refractory acidemia in 2 cases (12.5%), and reasons not reported in 4 cases (25.0%).

Eight of the 14 sites (57.1%) had at least one study patient require rescue therapy. Rescue therapy was required in median 8% (IQR 0% to 12%) of enrollments per site.

Patients assigned to P_{ES}-guided PEEP were significantly less likely to receive rescue therapy than patients assigned to empiric PEEP-FiO_2 (3.9% vs. 12.2%; $p = 0.04$). Significantly fewer patients assigned to P_{ES}-guided PEEP received inhaled pulmonary vasodilators (2.9% vs. 10.2%; $p = 0.046$). Differences in use of rescue prone positioning (1.0% vs. 3.1%; $p = 0.36$) and extracorporeal membrane oxygenation (1.0% vs. 3.1%; $p = 0.36$) did not achieve statistical significance.

In exploratory post-hoc analysis, patients receiving rescue therapy experienced significantly higher mortality at 28 days (56.3% vs. 29.3%; $p = 0.046$) and 60 days (68.8% vs. 35.0%; $p = 0.01$), and significantly fewer ventilator-free days, shock-free days, ICU-free days, and hospital-free days compared to patients not receiving rescue (eTable 5). Patients receiving rescue therapy had at baseline significantly lower pH and higher mean airway pressure, FiO_2, and end-inspiratory P_L (eTable 3). Respiratory measurements from the last study evaluation prior to initiating rescue are presented in eTable 4.

Functional Outcomes at One Year

Overall survey completion rates among one-year survivors were 69% for the Barthel index and 67% for the SF-12. Only 7 of 23 survivors (30%) aged ≥ 65 years completed the Vulnerable Elderly Survey (VES). Results for the Barthel index and SF-12 are reported in eTable 6. Given the low number of total respondents and low response rate for the VES, data were thought unrepresentative of the study population and underpowered for statistical inference; therefore, we elected not to report those data.

eTable 1. Protocol Adherence During the First 7 Days			
Protocol Adherence Assessment	**P_{ES}-guided PEEP**	**Empiric PEEP-FiO_2**	***P* Value**
Difference in protocol-specified versus observed PEEP, cm H_2O [a]			
Day 1	0 (1)	0 (1)	0.96
Day 2	0 (1)	0 (0)	0.08
Day 3	0 (1)	0 (1)	0.03
Day 4	0 (2)	0 (1)	0.12
Day 5	0 (2)	0 (1)	0.90
Day 6	0 (2)	1 (2)	0.15
Day 7	1 (2)	1 (2)	0.59
Observed PEEP within ± 2 cmH_2O of protocol-specified PEEP, no./total no. (%)[a]			
Day 1	91/95 (95.8)	96/97 (99.0)	0.21
Day 2	89/92 (96.7)	92/93 (98.9)	0.37
Day 3	85/87 (97.7)	81/85 (95.3)	0.44
Day 4	68/74 (91.9)	65/70 (92.9)	>.99
Day 5	53/57 (93.0)	59/63 (93.7)	>.99
Day 6	39/49 (79.6)	50/56 (89.3)	0.19
Day 7	36/40 (90.0)	44/51 (86.3)	0.75
All measures Days 1-7	461/494 (93.3)	487/515 (94.6)	0.43

Data presented as mean (SD) or number/total number (%).

[a] Protocol-specified PEEP refers to the PEEP value permissible per protocol for the observed FiO_2.

eTable 2. Regression Coefficients for Linear Mixed Effects Models of Physiologic Measures[a]				
Physiological measures	Group Effect	P Value for Group Effect	Group × Time Interaction	P Value for Interaction
P_L at end-expiration	0.53 (0.55)	0.33	0.24 (0.11)	0.03
P_L at end-inspiration	0.30 (0.70)	0.66	0.19 (0.14)	0.18
PEEP	1.26 (0.73)	0.08	0.06 (0.10)	0.58
Plateau pressure	1.88 (1.05)	0.07	0.01 (0.17)	0.93
P_{ES} at End-expiration	0.93 (0.77)	0.23	-0.12 (0.13)	0.36
PaO_2:FiO_2	8.96 (11.08)	0.42	-1.47 (2.11)	0.49
Airway driving pressure	0.87 (0.58)	0.13	-0.24 (0.11)	0.03
Transpulmonary driving pressure	-0.28 (0.51)	0.59	-0.04 (0.10)	0.71

Regression coefficients are presented as fixed effect ß (standard error).

[a] Linear mixed models with random intercept modeled physiological parameters (outcome) from day 1 through day 7 with treatment group, time, and the interaction of group × time entered as fixed effects. Baseline values were not significantly different between treatment groups and excluded from models. Positive values for group effect indicate higher values in the P_{ES}-guided PEEP arm compared to empiric PEEP-FiO_2 arm, and corresponding p-values reflect the overall test for difference between groups across the 7 days during which P_{ES} and P_L were measured in both groups. P-values for group × time interaction evaluate if change over time from day 1 to day 7 differed by treatment group. There is multiple testing without adjustment. Transpulmonary pressure (P_L) equals airway pressure minus pleural pressure. Airway driving pressure equals plateau pressure minus PEEP. Transpulmonary driving pressure equals end-inspiratory P_L minus end-expiratory P_L.

eTable 3. Baseline Characteristics of Patients Later Receiving Rescue Therapy vs. No Rescue Therapy			
Variable	**Rescue (n = 16)**	**No Rescue (n = 184)**	**P Value**
Randomization to P_{ES}-guided PEEP, no. (%)	4 (25.0)	98 (53.3)	0.04
Age, mean (SD), yr	56 (13)	56 (16)	0.97
Female, no. (%)	7 (43.8)	85 (46.2)	>.99
Predicted body weight, mean (SD), kg	61.1 (14.0)	62.1 (12.0)	0.74
Actual body weight, mean (SD), kg	105.7 (49.3)	93.3 (37.6)	0.22
Body mass index, mean (SD), kg/m^2	37.1 (14.1)	32.6 (11.6)	0.15
APACHE-II score, mean (SD)	27 (6)	27 (8)	0.90
SOFA, mean (SD)	10 (3)	11 (4)	0.42
Hours intubated prior to enrollment, mean (SD)	27 (17)	24 (15)	0.47
ARDS risk factors			
Pneumonia, no. (%)	14 (87.5)	135 (73.4)	0.37
Aspiration, no. (%)	0 (0)	42 (22.8)	0.03
Multiple transfusions, no. (%)	0 (0)	19 (10.3)	0.37
Prolonged shock, no. (%)	0 (0)	26 (14.1)	0.23
Sepsis, no. (%)	16 (100)	155 (84.2)	0.14
Acute pancreatitis, no. (%)	0 (0)	7 (3.8)	>.99
Trauma, no. (%)	0 (0)	6 (3.3)	>.99
Any pulmonary risk factor, no. (%)	14 (87.5)	156 (84.8)	>.99
Respiratory Characteristics			
pH, mean (SD)	7.28 (0.10)	7.33 (0.09)	0.04
$PaCO_2$, mean (SD), mm Hg	49 (13)	45 (11)	0.13
PaO_2, mean (SD), mm Hg	73 (17)	75 (22)	0.75
PaO_2:FiO_2, mean (SD), mm Hg	95 (36)	100 (37)	0.55
Tidal volume, mean (SD), mL/kg PBW	6.3 (1.1)	6.4 (1.1)	0.66
Plateau airway pressure, mean (SD), cm H_2O	29 (4)	28 (5)	0.24
Mean airway pressure, mean (SD), cm H_2O	22 (5)	19 (5)	0.03
Set PEEP, mean (SD), cm H_2O	15 (3)	14 (4)	0.17
FiO_2, mean (SD)	0.74 (0.20)	0.62 (0.18)	0.02
Respiratory rate, mean (SD), breaths/min	28 (4)	26 (6)	0.24
Minute-ventilation, mean (SD), L/min	10.1 (2.5)	10.3 (2.8)	0.87
P_{ES} at end-inspiration, mean (SD), cm H_2O	20 (8)	19 (5)	0.52
P_{ES} at end-expiration, mean (SD), cm H_2O	17 (5)	16 (5)	0.60
P_L at end-inspiration, mean (SD), cm H_2O	11 (6)	8 (5)	0.03
P_L at end-expiration, mean (SD), cm H_2O	1 (4)	–1 (4)	0.14
Airway driving pressure, median (IQR), cm H_2O	13 (10-14.5)	12 (10-15)	0.76
Transpulmonary driving pressure, median (IQR), cm H_2O	8 (8-11)	9 (7-11)	0.88
Lung compliance, mean (SD), mL/cm H_2O	44 (15)	49 (23)	0.40
Respiratory system compliance, mean (SD), mL/cm H_2O	34 (20)	33 (15)	0.70
Cointerventions at baseline			
Neuromuscular blockade, no. (%)	7 (43.8)	59 (32.1)	0.41
Vasopressors or inotropes, no. (%)	8 (50.0)	106 (57.6)	0.60
Systemic corticosteroids, no. (%)	7 (43.8)	62 (33.7)	0.42

eTable 4. Respiratory Characteristics of Patients Receiving Rescue Therapy on Last Study Evaluation Before Rescue was Initiated[a]	
Variable (*n*)	**Value**
pH (*n* = 12)	7.31 (7.21-7.39)
$PaCO_2$, mm Hg (*n* = 12)	48 (41-63)
PaO_2, mm Hg (*n* = 12)	76 (65-119)
PaO_2:FiO_2, mm Hg (*n* = 12)	95 (82-136)
Tidal volume, mL/kg PBW (*n* = 15)	5.8 (4.9-6.6)
Plateau airway pressure, cm H_2O (*n* = 11)	30 (27-34)
Mean airway pressure, cm H_2O (*n* = 15)	24 (17-26)
Set PEEP, cm H_2O (*n* = 15)	18 (8-20)
FiO_2 (*n* = 15)	0.80 (0.70-1.0)
Respiratory rate, breaths/min (*n* = 15)	30 (24-35)
P_L at end-inspiration, cm H_2O (*n* = 9)	14 (10-17)
P_L at end-expiration, cm H_2O (*n* = 9)	3 (0-5)
Lung compliance, mL/cm H_2O (*n* = 9)	38 (32-50)
Respiratory system compliance, mL/cm H_2O (*n* = 11)	27 (17-36)
Airway driving pressure, cm H_2O (*n* = 11)	14 (12-19)
Transpulmonary driving pressure, cm H_2O (*n* = 9)	9 (8-10)

Data presented as median (interquartile range).

[a] Bedside measurements were performed once daily between 0800 and 1400. Values reported in this table represent the last daily measurements documented within 24 hours prior to rescue therapy, except for one instance of pH and three instances of PaO_2 documented at the time of rescue initiation. Because values were not necessarily obtained at the moment rescue criteria were met, they may not be reflective of rescue trigger. If no value was within the preceding 24 hours before rescue, the data were considered missing and not reported.

eTable 5. Patient Outcomes by Whether Rescue Therapy Was Administered			
Variable	**Rescue (n = 16)**	**No Rescue (n = 184)**	**P Value**
Mortality through day 28, no. (%)	9 (56.3)	54 (29.3)	0.046
Mortality through day 60, no./total no. (%)[a]	11/16 (68.8)	64/183 (35.0)	0.01
Ventilator-free days through day 28, median (IQR)	0 (0-4.5)	18 (0-23)	< 0.01
Shock-free days, median (IQR)	0 (0-13.5)	16 (0-22)	0.01
ICU length of stay through day 28, median (IQR)	13.5 (7-18.5)	9.5 (5-15)	0.32
Hospital length of stay through day 28, median (IQR)	18 (7-26)	16 (9-24)	0.92
ICU-free days through day 28, median (IQR)	0 (0-11.5)	15 (0-21)	0.02
Hospital-free days through day 28, median (IQR)	0 (0-0)	0.5 (0-14)	0.02
Pneumothorax, no. (%)	0 (0)	5 (2.7)	>.99
Barotrauma, no. (%)[b]	2 (12.5)	9 (4.9)	0.22

[a] Complete outcome data were available for all study participants except for 60-day mortality, for which one patient assigned to P_{ES}-guided PEEP was lost to follow-up as noted.

[b] Barotrauma includes pneumothorax, pneumomediastinum, or subcutaneous emphysema.

eTable 6. Long-term Functional Outcomes Among Survivors at One Year[a]			
	P_{ES}-guided PEEP	**Empiric PEEP-FiO_2**	***P* Value**
Barthel index			
No. of respondents	41	34	
Score ≥ 95, no. (%)	26 (63.4)	28 (82.4)	0.08
Short Form-12			
No. of respondents	40	32	
Physical Component Score, median (IQR)	38 (30-56)	42 (30-52)	0.64
Mental Component Score, median (IQR)	54 (41-58)	55 (40-58)	0.96

[a] Analysis reports unadjusted results among survivors who completed follow-up surveys only and does not count for differences in survival or survey completion rates.

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