JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Lower vs Higher Positive End-Expiratory Pressure Strategy on Ventilator-Free Days in ICU Patients Without ARDS
A Randomized Clinical Trial

Writing Committee and Steering Committee for the RELAx Collaborative Group

IMPORTANCE It is uncertain whether invasive ventilation can use lower positive end-expiratory pressure (PEEP) in critically ill patients without acute respiratory distress syndrome (ARDS).

OBJECTIVE To determine whether a lower PEEP strategy is noninferior to a higher PEEP strategy regarding duration of mechanical ventilation at 28 days.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority randomized clinical trial conducted from October 26, 2017, through December 17, 2019, in 8 intensive care units (ICUs) in the Netherlands among 980 patients without ARDS expected not to be extubated within 24 hours after start of ventilation. Final follow-up was conducted in March 2020.

INTERVENTIONS Participants were randomized to receive invasive ventilation using either lower PEEP, consisting of the lowest PEEP level between 0 and 5 cm H_2O (n = 476), or higher PEEP, consisting of a PEEP level of 8 cm H_2O (n = 493).

MAIN OUTCOMES AND MEASURES The primary outcome was the number of ventilator-free days at day 28, with a noninferiority margin for the difference in ventilator-free days at day 28 of −10%. Secondary outcomes included ICU and hospital lengths of stay; ICU, hospital, and 28- and 90-day mortality; development of ARDS, pneumonia, pneumothorax, severe atelectasis, severe hypoxemia, or need for rescue therapies for hypoxemia; and days with use of vasopressors or sedation.

RESULTS Among 980 patients who were randomized, 969 (99%) completed the trial (median age, 66 [interquartile range {IQR}, 56-74] years; 246 [36%] women). At day 28, 476 patients in the lower PEEP group had a median of 18 ventilator-free days (IQR, 0-27 days) and 493 patients in the higher PEEP group had a median of 17 ventilator-free days (IQR, 0-27 days) (mean ratio, 1.04; 95% CI, 0.95-∞; *P* = .007 for noninferiority), and the lower boundary of the 95% CI was within the noninferiority margin. Occurrence of severe hypoxemia was 20.6% vs 17.6% (risk ratio, 1.17; 95% CI, 0.90-1.51; *P* = .99) and need for rescue strategy was 19.7% vs 14.6% (risk ratio, 1.35; 95% CI, 1.02-1.79; adjusted *P* = .54) in patients in the lower and higher PEEP groups, respectively. Mortality at 28 days was 38.4% vs 42.0% (hazard ratio, 0.89; 95% CI, 0.73-1.09; *P* = .99) in patients in the lower and higher PEEP groups, respectively. There were no statistically significant differences in other secondary outcomes.

CONCLUSIONS AND RELEVANCE Among patients in the ICU without ARDS who were expected not to be extubated within 24 hours, a lower PEEP strategy was noninferior to a higher PEEP strategy with regard to the number of ventilator-free days at day 28. These findings support the use of lower PEEP in patients without ARDS.

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Visual Abstract
Editorial
Supplemental content

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Invasive ventilation, one of the most frequently applied strategies in the intensive care unit (ICU), is recognized as a potentially harmful intervention.[1] Although the protective role of low tidal volume is well defined, there is much uncertainty regarding the role of higher positive end-expiratory pressure (PEEP). In one meta-analysis, in patients with moderate to severe acute respiratory distress syndrome (ARDS), higher PEEP led to a benefit regarding mortality but prolonged the time to wean from invasive ventilation in patients with mild ARDS.[2] There has been a gradual and noticeable increase in use of higher PEEP in patients without ARDS in ICUs worldwide.[3-6] An increment in PEEP, from a mean of 5 cm H_2O in 1998 to 7 cm H_2O in 2016, was recently demonstrated[6] despite absence of evidence for benefit or harm.[5]

In patients without ARDS, ventilation with higher PEEP could lead to a better distribution of lung aeration, which improves oxygenation.[5] Ventilation with higher PEEP may even prevent ARDS[5] and has been suggested to reduce the development of ventilator-associated pneumonia (VAP).[7] However, in healthy animals, ventilation with higher PEEP may also worsen existing or cause new lung injuries.[8-11] It was shown that ventilation with higher PEEP impaired hemodynamics and increased the need for additional fluid administration or vasopressors during surgery.[12,13] Because it is common practice to extubate at lower PEEP,[14] use of higher PEEP at least in theory could also delay weaning in some settings.

The Restricted vs Liberal Positive End-Expiratory Pressure in Patients Without ARDS (RELAx) study was conducted to test whether a ventilation strategy using lower PEEP is noninferior to a ventilation strategy using higher PEEP with respect to the number of ventilator-free days at day 28 in patients without ARDS.

Key Points

Question In patients in the intensive care unit (ICU) who received invasive ventilation for reasons other than acute respiratory distress syndrome, is a ventilation strategy with lower positive end-expiratory pressure (PEEP) noninferior to a strategy using higher PEEP with respect to the number of ventilator-free days at day 28?

Findings In this randomized clinical trial that included 980 ICU patients receiving invasive ventilation and who were expected not to be extubated within 24 hours of randomization, a ventilation strategy using lower PEEP compared with a strategy using higher PEEP resulted in 18 vs 17 ventilator-free days at day 28, a difference that did not exceed the noninferiority margin of −10%.

Meaning Among patients in the ICU receiving invasive ventilation, a strategy with lower PEEP was noninferior to a strategy using higher PEEP.

Methods

Study Design and Oversight

This was a randomized clinical trial conducted at the ICUs of 8 hospitals in the Netherlands. The protocol has been published,[15] and the final protocol is available in Supplement 1. An updated statistical analysis plan was written before closing the database; the final plan and a table describing the changes to the original study design are available in Supplement 2. The institutional review boards of all participating centers approved the study, and written deferred informed consent was obtained from patient representatives. No interim analyses were performed. An independent committee oversaw conduct of the trial and adverse events while remaining blind to the primary end point at 3 predefined time points, and recommended the trial be continued.

Patients

The trial enrolled patients who received invasive ventilation shortly before or after admission to the ICU and who were expected not to be extubated within 24 hours of randomization. Patients were to be randomized within 1 hour of initiation of ventilation in the ICU. One main exclusion criterion was presence of ARDS, according to the current definition.[16] Another key exclusion criterion was invasive ventilation that had lasted longer than 12 hours before ICU admission. Other exclusion criteria are presented in eAppendix 2 in Supplement 3.

Randomization and Masking

Patients were randomized in a 1:1 ratio to a lower or higher PEEP strategy group. The local investigators performed randomization using a central, dedicated, password-protected, encrypted, web-based automated randomization system (SSL-encrypted website with ALEA software, TenALEA Consortium). Randomization was conducted using random block sizes with a maximum of 8 patients.

Interventions

The PEEP ventilation strategies are shown in eFigure 1 in Supplement 3. Briefly, patients randomized to the lower PEEP strategy started with PEEP at 5 cm H_2O and an inspired oxygen fraction (F_{IO_2}) between 0.21 and 0.6. After intubation and start of ventilation, every 15 minutes PEEP was downtitrated by 1 cm H_2O to a minimum of 0 cm H_2O, as long as pulse oximetry–measured oxygen saturation (S_{PO_2}) was greater than 92% or P_{AO_2} was greater than 60 mm Hg. Thereafter, ventilation continued with the lowest PEEP according to this target, while using an F_{IO_2} of between 0.21 and 0.6. S_{PO_2} was allowed to decrease to less than 92% or P_{AO_2} to less than 60 mm Hg for brief periods (up to 5 minutes) without the need for any intervention. Then, F_{IO_2} was increased to a maximal 0.6 before PEEP was increased in steps of 1 cm H_2O up to 5 cm H_2O. In the case of severe hypoxemia, defined as a decrease in S_{PO_2} to less than 88% or P_{AO_2} to less than 55 mm Hg, common causes such as a mucus plug requiring pulmonary toilet were considered and treated. As a rescue, F_{IO_2} could be increased to a maximal 1.0 and PEEP to 5 cm H_2O or more, according to the attending physician. Development of atelectasis diagnosed by chest imaging was to be accepted unless S_{PO_2} decreased to less than 92% or P_{AO_2} to less than 60 mm Hg and did not respond to an increase of F_{IO_2} to

a maximal 0.6. In the case of hemodynamic instability, evidenced by increased need for vasopressors, PEEP could be set at 5 cm H_2O for 1 to 2 hours. Down-titration of PEEP was resumed after stabilization or after the decrease in Spo_2 or Pao_2 was resolved.

Patients randomized to the higher PEEP strategy started with PEEP at 8 cm H_2O and Fio_2 between 0.21 and 0.6. The goal was to maintain PEEP at 8 cm H_2O. Brief periods (up to 5 minutes) could be tolerated of an Spo_2 decrease to less than 92% or a Pao_2 decrease to less than 60 mm Hg. Then, Fio_2 was increased to a maximal 0.6 before PEEP was increased. If Spo_2 decreased to less than 88% or Pao_2 to less than 55 mm Hg, similar steps were taken as in the low PEEP group. In the case of hemodynamic instability, PEEP was set at 5 cm H_2O for 1 to 2 hours. After stabilization, PEEP was set back to 8 cm H_2O.

Oxygenation Targets

In both groups, oxygenation targets for Spo_2 were 92% to 96% and for Pao_2 were 60 to 85 mm Hg.[17-19] The oxygenation target was primarily assessed by pulse oximetry and, in the case of unreliable readings, by arterial blood gas analysis. For patients in whom the risk of potentially dangerous hypoxemia could become unacceptable (eFigure 1 in Supplement 3), oxygenation targets could be increased to Spo_2 of 94% to 96% and Pao_2 of 68 to 85 mm Hg.

Standard Care and Weaning From the Ventilator

Standard care and weaning from the ventilator followed strict protocol,[20] as described in eAppendix 2 in Supplement 3.

Outcomes

The primary outcome was the number of ventilator-free days at day 28, defined as the number of days that a patient was alive and free of invasive ventilation, calculated from the moment of randomization, if the period of unassisted breathing lasted at least 24 consecutive hours.[21] Patients who died or received invasive ventilation for more than 28 days were considered to have 0 ventilator-free days.

Secondary outcomes included ICU and hospital lengths of stay; ICU, hospital, and 28- and 90-day mortality; duration of ventilation among survivors; and pulmonary complications, including development of ARDS,[16] VAP, severe atelectasis, severe hypoxemia, and pneumothorax. Mortality at day 28 and duration of ventilation among survivors were not included as secondary outcomes in the original protocol but were added in the updated statistical analysis plan.[21] Other secondary outcomes were need for rescue therapies for severe hypoxemia or severe atelectasis, including recruitment maneuvers, prone positioning, and bronchoscopy for opening atelectasis; days with use of vasopressors; and days with use of sedation (see full definitions in eTable 1 in Supplement 3).

Other Study Parameters

It was difficult to collect complete and reliable data for 2 secondary outcomes, the Therapeutic Intervention Scoring System score and the Nursing Activities Score; therefore, these findings are not reported. An analysis of health care–related costs is planned. Substudies investigating cardiac performance, lung aeration, and systemic inflammation, as assessed by ultrasound and plasma biomarkers, respectively, were performed in a subset of patients enrolled in the Amsterdam University Medical Center. The results of these 4 substudies will be reported elsewhere.

Statistical Analysis

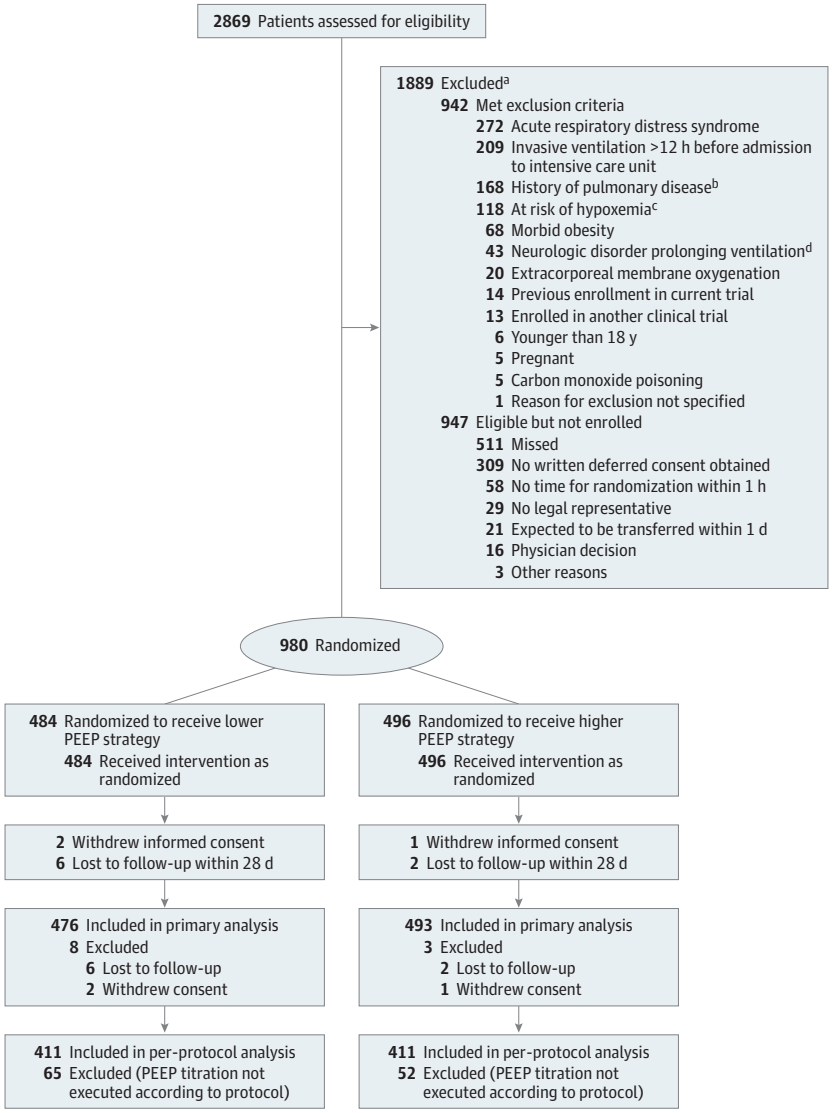
The trial was designed to last until 980 patients were enrolled. This number of patients was expected to be sufficient to show noninferiority of the lower PEEP strategy compared with the higher PEEP strategy with a noninferiority margin of −10%, assuming no difference in the number of ventilator-free days in both groups, with a mean of 16 (SD, 10) days.[20,22] A 1-sided $\alpha = .05$, a power of 80%, a 1:1 ratio of patient randomization, and correction for 10% of dropouts was considered. The choice of a noninferiority margin of −10%, representing 0.5 days of ventilation or 1.6 ventilator-free days, was motivated by what could be considered acceptable from a clinical point of view. Practically, this margin meant that a difference of less than 12 hours in duration of ventilation or 1.6 ventilator-free days with lower PEEP was considered noninferior to higher PEEP.

Categorical variables are reported as numbers and percentages and continuous variables as medians and interquartile ranges (IQRs). In all analyses, patients were analyzed according to their randomization group, with the exception of those who withdrew informed consent or were lost to follow-up in the first 28 days. No imputation was used for any missing value, since there was less than 1% missing values for the primary outcome. In addition, a per-protocol analysis was conducted that included only patients who completed PEEP titrations according to the study protocol. Patients in the lower PEEP strategy were excluded if, during the first 2 days of ventilation, they received in at least 2 of the 4 measurements per day a PEEP greater than 5 cm H_2O and an Fio_2 of 0.6 or less or an Spo_2 greater than 92%. Patients randomized to the higher PEEP strategy were excluded if, during the first 2 days of ventilation, they received in at least 2 of the 4 measurements per day a PEEP less than 8 cm H_2O without any documented hemodynamic instability.

The effect of a lower PEEP strategy compared with a higher PEEP strategy on the primary outcome was calculated as a mean ratio, tested for noninferiority considering a margin of 10% with a 1-sided 95% CI. Thus, noninferiority would be established if the lower boundary of the 1-sided 95% CI was higher than 0.90. The mean ratio was estimated using a generalized additive model for location scale and shape, considering a zero-inflated β distribution and using the delta method to estimate the 95% CI. A 1-sided *P* value for noninferiority was calculated. If noninferiority was confirmed, superiority of lower PEEP was tested considering a 95% CI following a hierarchical closed testing procedure.

All analyses of the secondary outcomes were 2-sided and assessed superiority. The effect of the intervention on binary outcomes was assessed with risk ratios and 95% CIs calculated with a Wald likelihood ratio approximation test and with χ^2 hypothesis testing. The duration of ventilation among survivors, ICU and hospital lengths of stay, and 28- and

Figure 1. Flow of Participants in the Restricted vs Liberal Positive End-Expiratory Pressure in Patients Without ARDS Trial



In all analyses, patients were analyzed according to their randomization group, with the exception of those who withdrew informed consent or were lost to follow-up in the first 28 days. PEEP indicates positive end-expiratory pressure.

[a] Patients could have more than 1 reason for exclusion; the main reason for exclusion is presented.

[b] Includes chronic obstructive pulmonary disease (COPD) stages III and IV in the Global Initiative for COPD (GOLD) classification and restrictive pulmonary disease. GOLD stage III COPD is defined as severe obstruction of the airways, with the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) less than 70% and FEV_1 between 30% and 50% of predicted values. GOLD stage IV COPD is defined as very severe obstruction of the airways, with FEV_1/FVC less than 70% and FEV_1 less than 30% of predicted values.

[c] Includes ongoing cardiac ischemia due to cardiac infarction and failed revascularization, uncontrollable intracranial pressure, delayed cerebral ischemia after subarachnoid hemorrhage, necrotizing fasciitis, and severe untreated anemia.

[d] Includes Guillain-Barré syndrome, high spinal cord lesion, amyotrophic lateral sclerosis, multiple sclerosis, or myasthenia gravis.

90-day mortality were compared using Kaplan-Meier curves and hazard ratios with 95% CIs calculated with Cox proportional hazard models. The proportional hazard assumption was assessed through inspection of Schoenfeld residuals. Days with use of vasopressors and sedation were compared as mean differences between the groups from an independent *t* test.

The homogeneity of treatment effects on the primary outcome across prespecified subgroups was examined via a test for treatment × subgroup interaction in the generalized additive model for location scale and shape considering a zero-inflated β distribution. In addition to the unadjusted *P* values for secondary outcomes, a Holm-Bonferroni procedure was applied to control for multiple testing. As a sensitivity analysis, primary and secondary outcomes were reassessed in mixed-effects models considering further adjustments by age, sex, and Acute Physiology and Chronic Health Evaluation (APACHE) IV score and including centers as random effects. In addition, the duration of ventilation among survivors and the times to ICU and hospital discharge were reassessed in a competing risk model with death before extubation, ICU discharge, or hospital discharge, respectively, treated as a competing risk and reported as subdistribution hazard ratios with 95% CIs estimated from a Fine-Gray model.

All analyses were performed with R software, version 3.6.3 (R Core Team). Additional details regarding the statistical analysis are provided in the statistical analysis plan in Supplement 2.

Results

Patients

From October 26, 2017, to December 17, 2019, 2869 patients were screened. Final follow-up was completed on

Table 1. Baseline Participant Characteristics

Characteristics	Lower PEEP (n = 476)[a]	Higher PEEP (n = 493)[a]
Age, median (IQR), y	65.5 (56.0-74.0)	66.0 (57.0-74.0)
Sex, No. (%)		
Female	164 (34.5)	182 (36.9)
Male	312 (65.5)	311 (63.1)
BMI, median (IQR)	25.8 (23.1-28.4)	26.1 (23.5-29.8)
APACHE score, median (IQR)		
APACHE IV[b]	83.5 (59.8-103.2) [n = 376]	90.0 (67.0-111.2) [n = 388]
APACHE II[c]	23.0 (18.0-29.0) [n = 321]	24.0 (19.0-30.0) [n = 322]
SAPS II, median (IQR)[d]	56.0 (43.2-67.0) [n = 254]	58.0 (43.0-68.0) [n = 270]
LIPS, median (IQR)[e]	3.0 (1.5-5.1)	3.0 (1.5-5.0)
Patients at risk of ARDS, No. (%)	206 (43.3)	197 (40.0)
SOFA score, median (IQR)[f]	9.0 (7.0-12.0) [n = 290]	10.0 (8.0-12.0) [n = 283]
Septic shock, No./total (%)	42/448 (9.4)	48/465 (10.3)
Smoking, No./total (%)		
Never	107/295 (36.3)	128/305 (42.0)
Current	104/295 (35.3)	104/305 (34.1)
Former	84/295 (28.5)	73/305 (23.9)
Reason for ICU admission, No. (%)		
Medical	371 (77.9)	398 (80.7)
Urgent surgery	88 (18.5)	76 (15.4)
Elective surgery	17 (3.6)	19 (3.9)
Reason for intubation, No. (%)		
Respiratory failure	146 (30.7)	147 (29.8)
Cardiac arrest[g]	123 (25.8)	142 (28.8)
Depressed level of consciousness	74 (15.5)	81 (16.4)
Planned postoperative ventilation	78 (16.4)	59 (12.0)
Airway protection	38 (8.0)	52 (10.5)
Other	17 (3.6)	12 (2.4)
Time with ventilation before randomization, median (IQR), h	0.6 (0.2-1.1)	0.6 (0.2-1.1)
Physiological features and support		
Ventilatory mode, No./total (%)		
Pressure controlled	312/429 (72.7)	310/429 (72.3)
Volume controlled	73/429 (17.0)	71/429 (16.6)
Pressure support	35/429 (8.2)	35/429 (8.2)
Other	9/429 (2.1)	13/429 (3.1)
Respiratory and physiological measures, median (IQR)		
Tidal volume, mL/kg PBW	7.0 (6.1-8.0)	6.9 (6.1-8.0)
Plateau pressure, cm H_2O	19.9 (16.0-24.0)	20.0 (17.0-24.0)
Total respiratory rate, /min	19.0 (16.0-22.0)	19.0 (15.0-22.0)
PEEP, cm H_2O	5.0 (5.0-8.0)	7.0 (5.0-8.0)
Driving pressure, cm H_2O	14.0 (11.0-17.0)	13.0 (11.0-16.0)
F_{IO_2}	0.50 (0.40-0.65)	0.50 (0.40-0.70)
P_{aO_2}/F_{IO_2}, mm Hg	210.0 (128.5-342.8)	209.5 (132.1-334.4)
P_{aCO_2}, mm Hg	42.8 (37.5-51.8)	44.3 (37.5-51.0)
Arterial pH	7.29 (7.20-7.38)	7.30 (7.21-7.36)
S_{pO_2}, %	98.0 (95.0-100.0)	98.0 (95.0-100.0)
S_{pO_2}/F_{IO_2}, mm Hg	192.0 (150.0-242.5)	192.0 (138.6-245.0)
Heart rate, /min	94.0 (77.0-111.0)	93.0 (75.0-114.0)
Mean arterial pressure, mm Hg	80.0 (68.0-93.0)	81.0 (69.0-95.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; F_{IO_2}, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; LIPS, Lung Injury Prediction Score; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment; S_{pO_2}, oxygen saturation as measured by pulse oximetry.

SI conversion factor: to convert P_{aCO_2} and S_{pO_2}/F_{IO_2} to kilopascals, divide by 7.5.

[a] Percentages may not total 100% because of rounding.

[b] The APACHE IV score ranges from 0 to 286, with higher scores indicating more severe disease and a higher risk of death; eg, an APACHE IV score of 90 indicates a 34% probability of mortality in a medical patient admitted for a respiratory condition.

[c] The APACHE II score ranges from 0 to 71, with higher scores indicating more severe disease and a higher risk of death; eg, an APACHE II score of 24 indicates a 40% probability of mortality in a medical patient admitted for a respiratory condition.

[d] The SAPS II score ranges from 0 to 163, with higher scores indicating a more severe condition; eg, a SAPS II score of 55 indicates a 55% probability of mortality.

[e] The LIPS score ranges from 0 to 32.5, with higher scores indicating a more severe condition and a higher risk of ARDS; eg, scores ≥4 are considered high risk for ARDS.

[f] The SOFA score ranges from 0 to 24, with higher scores indicating a more severe condition; eg, a SOFA score of 10 indicates a 40% probability of mortality.

[g] Patients who had cardiac arrest were treated with targeted normothermia management.

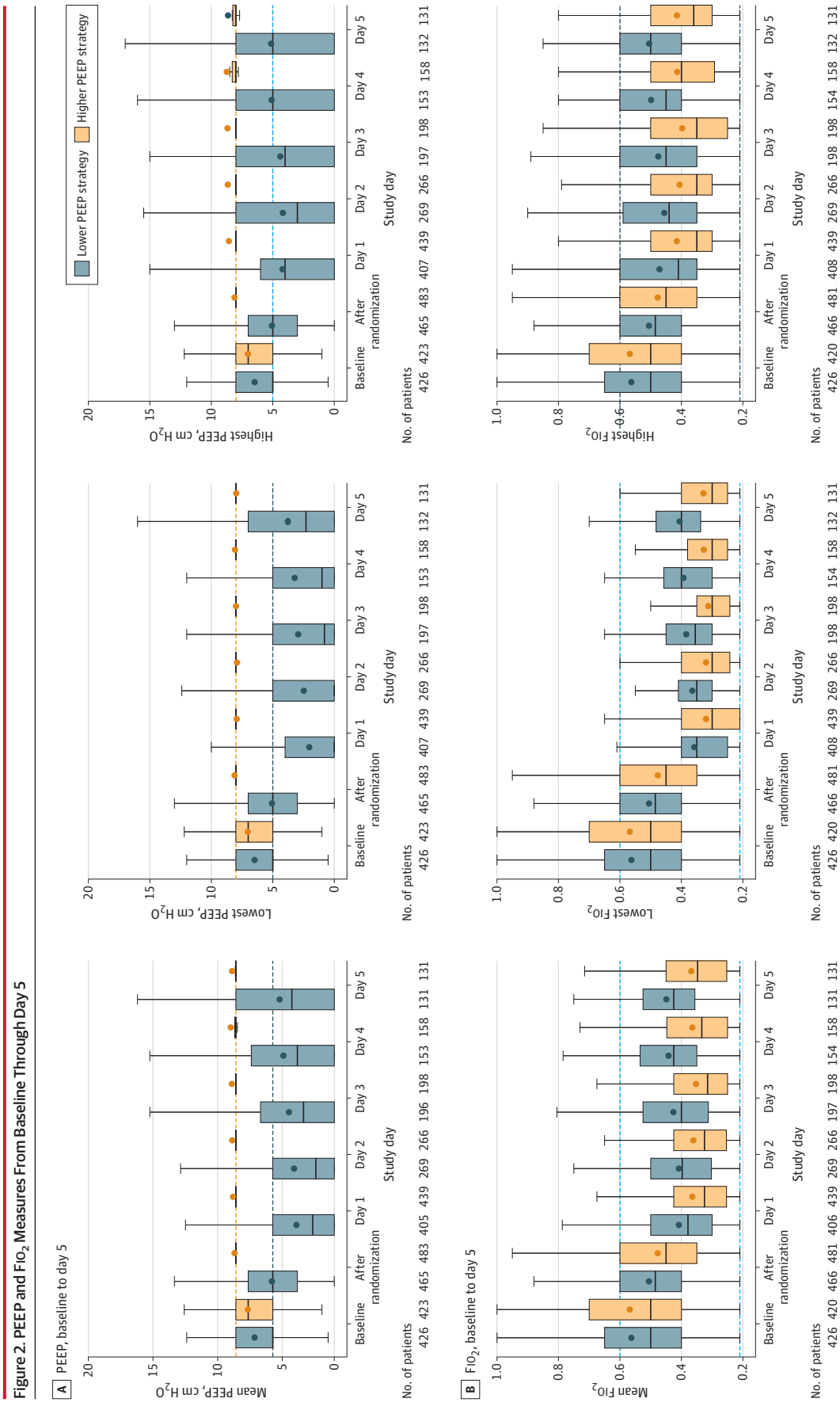
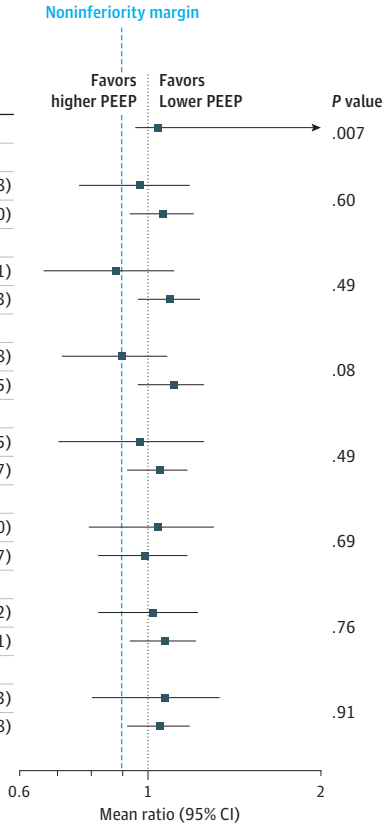


Figure 2. PEEP and FIO_2 Measures From Baseline Through Day 5

FIO_2, indicates fraction of inspired oxygen; PEEP, positive end-expiratory pressure. The figure shows the mean, lowest, and highest PEEP and FIO_2 values recorded from measurements taken every 6 hours while patients were undergoing invasive mechanical ventilation. Horizontal bars inside boxes represent medians; box tops and bottoms, interquartile ranges. Whiskers extend to 1.5 times the interquartile range beyond the first and third quartiles per the conventional Tukey method. Circles represent means. Dashed lines represent the limits imposed by the protocol in each group. Data labeled "after randomization" were recorded 1 hour after randomization (on day 0). The number of participants with available data decreases over successive study days because of deaths and discontinuation of invasive mechanical ventilation.

Figure 3. Noninferiority Analysis of the Primary Outcome in the Overall Cohort and in Subgroup Analyses

Source	No. of patients	Ventilator-free days at day 28, median (IQR)		Absolute difference (95% CI)	Mean ratio (95% CI)
		Lower PEEP strategy (n = 476)	Higher PEEP strategy (n = 493)		
All patients		17.7 (0.0-26.6)	16.7 (0.0-26.5)	0.41 (-1.16 to 1.98)	1.04 (0.95-∞)
Type of admission					
Surgical	200	21.3 (0.0-27.0)	22.9 (0.0-27.0)	-0.81 (-4.26 to 2.63)	0.97 (0.76-1.18)
Medical	769	16.1 (0.0-26.5)	12.7 (0.0-26.3)	0.65 (-1.10 to 2.42)	1.06 (0.93-1.20)
Cardiac arrest					
Yes	265	0.0 (0.0-26.6)	12.2 (0.0-26.7)	-1.86 (-4.97 to 1.25)	0.88 (0.66-1.11)
No	704	20.7 (0.0-26.6)	18.0 (0.0-26.3)	1.17 (-0.63 to 2.98)	1.09 (0.96-1.23)
Reason for intubation					
Respiratory failure	293	11.1 (0.0-24.9)	17.7 (0.0-25.9)	-1.63 (-4.36 to 1.10)	0.90 (0.71-1.08)
Other	676	21.2 (0.0-27.0)	16.3 (0.0-26.6)	1.31 (-0.60 to 3.22)	1.11 (0.96-1.25)
Body mass index					
>30	197	5.0 (0.0-25.9)	5.8 (0.0-26.1)	-0.49 (-4.07 to 3.08)	0.97 (0.70-1.25)
≤30	758	19.9 (0.0-26.4)	19.3 (0.0-26.6)	0.42 (-1.33 to 2.19)	1.05 (0.92-1.17)
Admission Pao_2/Fio_2, mm Hg					
≤200	265	5.7 (0.0-25.2)	0.6 (0.0-25.6)	0.11 (-2.82 to 3.04)	1.04 (0.79-1.30)
>200	323	20.5 (0.0-26.9)	22.7 (0.0-26.9)	-0.28 (-3.02 to 2.45)	0.99 (0.82-1.17)
LIPS					
≥4	403	5.5 (0.0-25.0)	5.3 (0.0-25.1)	0.11 (-2.23 to 2.46)	1.02 (0.82-1.22)
<4	566	23.4 (0.0-7.0)	22.8 (0.0-26.8)	0.85 (-1.21 to 2.92)	1.07 (0.93-1.21)
APACHE IV score					
≥86	382	0.0 (0.0-25.3)	0.0 (0.0-24.3)	0.42 (-1.99 to 2.84)	1.07 (0.80-1.33)
<86	370	25.0 (7.1-27.1)	24.8 (0.0-27.1)	0.80 (-1.54 to 3.15)	1.05 (0.92-1.18)



APACHE indicates Acute Physiology and Chronic Health Evaluation (range, 0-286; higher scores indicate more severe disease and higher risk of death); Fio_2, fraction of inspired oxygen; IQR, interquartile range; LIPS, Lung Injury Protection Score (range, 0-32.5; higher scores indicate more severe condition and higher risk of acute respiratory distress syndrome); PEEP, positive end-expiratory pressure. Body mass index is calculated as weight in kilograms divided by height in meters squared. The primary outcome is the mean ratio (with 1-sided 95% CI) for the comparison of ventilator-free days at day 28 between the lower and higher PEEP groups, with the noninferiority margin set at 0.90. Absolute differences are mean differences. *P* values shown are from the β-binomial part of the model. *P* values for interaction for the binary logistic regression for 0 ventilator-free days at 28 days are *P* = .62 for type of admission, *P* = .14 for cardiac arrest, *P* = .22 for reason for intubation, *P* = .74 for body mass index, *P* = .66 for Pao_2/Fio_2, *P* = .65 for LIPS, and *P* = .74 for APACHE IV score.

March 16, 2020. A total of 1889 patients were not enrolled, of whom 942 (49.8%) met exclusion criteria and 947 (50.2%) were eligible but not enrolled for other reasons (**Figure 1**). Of the 980 randomized patients enrolled in the study, 484 were randomized to the lower PEEP strategy and 496 to the higher PEEP strategy. Representatives of 3 patients withdrew consent to use study data. Follow-up to day 28 was incomplete for 8 patients. Thus, data for 969 patients (476 randomized to the lower PEEP strategy and 493 to the higher PEEP strategy) were used in the final analysis (Figure 1).

Baseline characteristics are presented in **Table 1**. Among the enrolled patients, 79.4% were admitted to the ICU for a nonsurgical reason. The most frequent reason for invasive ventilation was respiratory failure (30.2%).

Intervention

The median time between start of ventilation in the ICU and randomization was 0.6 hours (IQR, 0.2-1.1 hours). Mean PEEP values from postrandomization through day 5 were significantly lower in the lower PEEP group than in the higher PEEP group (**Figure 2**). Driving pressure was significantly higher and plateau pressure was significantly lower in the lower PEEP group than in the higher PEEP group. During the first 5 days of ventilation, Fio_2, Spo_2, and Pao_2/Fio_2 differed significantly between groups (Figure 2; eTables 2-4 and eFigures 2-14 in Supplement 3). There was no statistically significant difference in sedation level, heart rate, mean arterial pressure, administered fluids, transfusions, vasopressor support, and sequential organ failure assessment score between the groups (eTables 2 and 3 and eFigure 7 in Supplement 3). There was a statistically significant interaction for time and PEEP group regarding the cumulative fluid balance within the first 5 days (eFigure 15 in Supplement 3).

Outcomes

Twenty-eight days after randomization, patients randomized to the lower PEEP strategy had a median of 18 ventilator-free days (IQR, 0-27 days) and patients randomized to the

Table 2. Secondary Outcomes

Outcomes	Lower PEEP (n = 476)[a]	Higher PEEP (n = 493)[a]	Absolute difference (95% CI)	Effect estimate (95% CI)	*P* value[b]
Duration of ventilation among survivors, d			0.67 (−0.47 to 1.81)[c]	0.93 (0.79 to 1.09)[d]	.99
Mean (SD)	5.5 (7.4)	4.8 (6.6)			
Median (IQR)	2.0 (0.8-6.8)	2.0 (1.0-5.7)			
ARDS, No. (%)	13 (2.7)	5 (1.0)	1.72 (0.04 to 3.60)[e]	2.70 (0.97 to 7.49)[f]	.86
Ventilator-associated pneumonia, No. (%)					
Suspected	10 (2.1)	10 (2.0)	0.07 (−1.78 to 1.95)[e]	1.03 (0.43 to 2.46)[f]	.99
Confirmed	6 (1.3)	7 (1.4)	−0.16 (−1.70 to 1.38)[e]	0.89 (0.30 to 2.62)[f]	.99
Severe atelectasis, No. (%)	20 (4.2)	15 (3.0)	1.16 (−1.21 to 3.61)[e]	1.38 (0.71 to 2.66)[f]	.99
Severe hypoxemia, No. (%)	98 (20.6)	87 (17.6)	2.94 (−2.01 to 7.91)[e]	1.17 (0.90 to 1.51)[f]	.99
Pneumothorax, No. (%)	19 (4.0)	12 (2.4)	1.56 (−0.66 to 3.89)[e]	1.64 (0.81 to 3.34)[f]	.99
Need for rescue therapy, No. (%)	94 (19.7)	72 (14.6)	5.14 (0.40 to 9.91)[e]	1.35 (1.02 to 1.79)[f]	.54
Recruitment maneuvers	62 (13.0)	39 (7.9)	5.11 (1.28 to 9.02)[e]	1.64 (1.12 to 2.41)[f]	NR[g]
Prone positioning	25 (5.3)	29 (5.9)	−0.63 (−3.56 to 2.29)[e]	0.89 (0.53 to 1.50)[f]	NR[g]
Bronchoscopy for atelectasis	30 (6.3)	26 (5.3)	1.03 (−1.93 to 4.03)[e]	1.19 (0.72 to 1.99)[f]	NR[g]
Days with continuous use of vasopressors			0.05 (−0.41 to 0.51)[c]	0.05 (−0.41 to 0.51)[h]	.99
Mean (SD)	3.1 (3.7)	3.1 (3.5)			
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-3.0)			
Days with continuous use of sedation			0.22 (−0.27 to 0.71)[c]	0.22 (−0.27 to 0.71)[h]	.99
Mean (SD)	3.5 (3.9)	3.3 (3.8)			
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-4.0)			
Length of stay					
Intensive care unit			0.81 (−0.57 to 2.18)[c]	0.97 (0.83 to 1.13)[d]	.99
Mean (SD)	8.1 (11.5)	7.2 (10.3)			
Median (IQR)	4.0 (2.0-10.0)	4.0 (2.0-8.0)			
Hospital			0.94 (−1.81 to 3.70)[c]	1.01 (0.86 to 1.20)[d]	.99
Mean (SD)	19.9 (22.1)	19.0 (21.4)			
Median (IQR)	12.0 (5.0-26.2)	12.0 (4.0-24.0)			
Mortality, No./total (%)					
Intensive care unit	163/476 (34.2)	185/492 (37.6)	−3.36 (−9.38 to 2.69)[e]	0.91 (0.77 to 1.08)[f]	.99
Hospital	185/472 (39.2)	208/489 (42.5)	−3.34 (−9.54 to 2.88)[e]	0.92 (0.79 to 1.07)[f]	.99
28 d	183 (38.4)	207 (42.0)	−3.54 (−9.70 to 2.63)[e]	0.89 (0.73 to 1.09)[d]	.99
90 d	196/471 (41.6)	218/492 (44.3)	−2.70 (−8.93 to 3.56)[e]	0.92 (0.76 to 1.11)[d]	.99

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; PEEP, positive end-expiratory pressure.

[a] Percentages may not total 100% because of rounding.

[b] Adjusted *P* values using Holm-Bonferroni procedure for multiple statistical tests controlling for the 16 comparisons. Unadjusted *P* values are shown in eTable 7 in Supplement 3.

[c] Absolute difference is mean difference.

[d] Effect estimate is hazard ratio (2-sided 95% CI) from a Cox proportional hazard model. *P* values for Schoenfeld residuals are *P* = .14 for duration of ventilation among survivors, *P* = .85 for intensive care unit length of stay, *P* = .91 for hospital length of stay, *P* = .90 for 28-day mortality, and *P* = .89 for 90-day mortality.

[e] Absolute difference is risk difference.

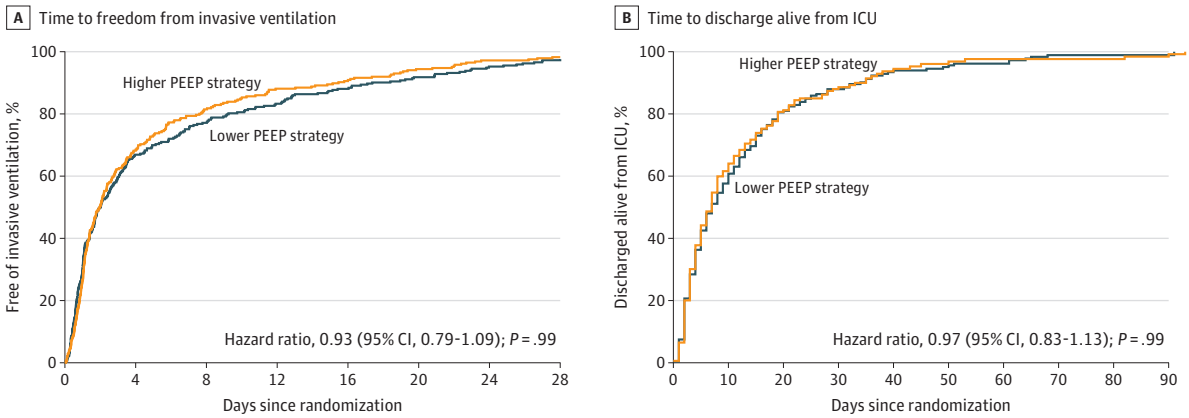
[f] Effect estimate is risk ratio (2-sided 95% CI) by Wald likelihood ratio approximation test and with χ^2 hypothesis tests.

[g] Not reported (NR) because it is not a secondary outcome but is a component of the need for rescue therapy.

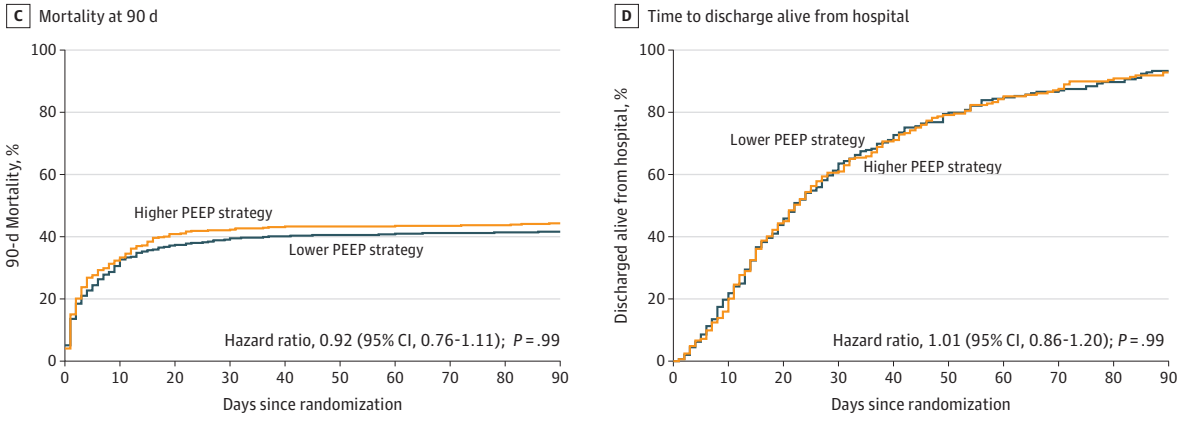
[h] Effect estimate is mean difference (2-sided 95% CI) from a generalized linear model with Gaussian distribution.

higher PEEP strategy had a median of 17 ventilator-free days (IQR, 0-27 days) (mean ratio, 1.04; 1-sided 95% CI, 0.95-∞; *P* = .007 for noninferiority); the lower boundary of the 95% CI was within the noninferiority margin of −10% (**Figure 3**). The superiority analysis showed no statistically significant difference between the randomization groups (*P* = .22). The results of the per-protocol analysis and the sensitivity analysis adjusted by baseline factors and including centers as random effects confirmed the results of the primary analysis (eTables 5 and 6 in Supplement 3). There was no statistically significant difference in the duration of ventilation or ICU or hospital lengths of stay in the competing risk analysis (eFigures 16 and 17 in Supplement 3). Median ICU and hospital lengths of stay and ICU-, hospital-, and 28- and 90-day mortality were not significantly different between the groups (**Table 2** and **Figure 4**; eFigure 18 in Supplement 3).

Figure 4. Kaplan-Meier Estimates for Patients in the Lower PEEP and Higher PEEP Groups



Lower PEEP strategy											
No. of patients											
At risk	293	97	67	49	35	24	14	0	451	105	40	22	11	8	7	2	2	2
Censored	0	0	0	0	0	0	0	7	23	143	159	163	163	163	163	163	163	163
No. of events	0	196	226	244	258	269	279	286	2	228	277	291	302	305	306	311	311	311
Higher PEEP strategy																		
No. of patients																		
At risk	286	91	53	34	26	16	8	0	473	102	35	18	7	4	3	3	3	1
Censored	0	0	0	0	0	0	0	5	16	151	178	182	185	185	185	185	185	185
No. of events	0	195	233	252	260	270	278	281	3	239	279	292	300	303	304	304	304	306



Lower PEEP strategy											
No. of patients											
At risk	447	317	295	285	282	280	278	277	276	0	458	253	152	94	68	46	34	29	23	0
Censored	0	0	0	0	0	0	0	0	0	275	14	137	165	175	178	183	184	184	184	199
No. of events	24	154	176	186	189	191	193	194	195	196	0	82	155	203	226	243	254	259	265	273
Higher PEEP strategy																				
No. of patients																				
At risk	472	328	291	284	279	279	278	278	277	0	478	266	157	97	65	46	31	26	19	0
Censored	0	0	0	0	0	0	0	0	0	274	10	147	179	196	204	205	207	207	207	222
No. of events	20	164	201	208	213	213	214	214	215	218	0	75	152	195	219	237	250	255	262	266

ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure. For each panel, an unadjusted hazard ratio and 95% CI calculated from a Cox proportional hazard model is presented. A, The median observation period for time to freedom from invasive ventilation was 2.0 (IQR, 1.7-2.6) days for the lower PEEP group and 2.0 (IQR, 1.6-2.4) days for the higher PEEP group; $P = .14$ for Schoenfeld residuals. B, The median observation period for time to discharge alive from the ICU was 7.0 (IQR, 6.0-9.0) days for the lower PEEP group and 7.0 (IQR, 6.0-8.0) days for the higher PEEP group; $P = .85$ for Schoenfeld residuals. C, The median observation time for 90-day mortality was not computed because the minimum observed value was 0.44 days; $P = .89$ for Schoenfeld residuals. D, The median observation period for time to discharge alive from the hospital was 22.0 (IQR, 20.0-27.0) days for the lower PEEP group and 22.0 (IQR, 20.0-25.0) for the higher PEEP group; $P = .91$ for Schoenfeld residuals.

There was no statistically significant difference in the occurrence of ARDS, VAP, pneumothorax, or severe atelectasis or in days with use of vasopressors or sedatives between groups (Table 2; eTable 7 in Supplement 3). Occurrence of severe hypoxemia was 20.6% vs 17.6% (risk ratio, 1.17; 95% CI, 0.90-1.51; $P = .99$) and need for rescue strategy was 19.7% vs 14.6% (risk ratio, 1.35; 95% CI, 1.02-1.79; adjusted $P = .54$) among patients in the lower and higher PEEP groups, respectively (Table 2).

There was no significant interaction in the effect of PEEP on the primary outcome according to prespecified subgroups (Figure 3).

Discussion

In this trial of adult patients in the ICU without ARDS who received invasive ventilation and were expected not to be extubated within 24 hours, a ventilation strategy using lower PEEP was noninferior to a strategy using higher PEEP with respect to the number of ventilator-free days at day 28. In addition, there was no statistically significant difference in ICU and hospital lengths of stay, mortality rate, or occurrence of pulmonary complications between the groups. There was also no statistically significant difference in use of vasopressors or sedatives.

To our knowledge, this is the largest randomized clinical trial addressing whether a ventilation strategy using lower PEEP is noninferior to a ventilation strategy using higher PEEP in patients without ARDS using a relevant patient-centered outcome. The composite end point was chosen because it reflects duration of ventilation among surviving patients as well as 28-day mortality.[21,23] A noninferiority design was chosen because higher levels of PEEP have been increasingly used in ICUs in recent years[3-6,24] despite lack of evidence for benefit or harm.[5] It may not be better to use a lower PEEP strategy, but it could be as good as higher PEEP. Thus, in this study we did not test the superiority of lower PEEP but, rather, whether lower PEEP is noninferior to higher PEEP.

This study has several strengths. It was designed to minimize bias by using concealed allocation and by analyzing patients according to their randomized group following a clear protocol that was strictly adhered to. Furthermore, loss to follow-up was minimal and both academic and nonacademic centers participated, contributing to its generalizability. To minimize a possible carryover effect, randomization was performed within 1 hour after start of ventilation in the ICU. Patients were enrolled over a period of 2 years, during which standardized care did not change.

This study adds information to previous studies. With the use of higher PEEP, oxygenation improved and driving pressure decreased in the first days, as found in meta-analyses of patients with and without ARDS.[2,5,25] In patients with moderate to severe ARDS, 1 meta-analysis suggested mortality benefit with higher PEEP, but a recent randomized clinical trial showed harm.[26]

In a meta-analysis of patients with mild ARDS, higher PEEP did not improve survival and even prolonged the duration of weaning.[2] In a meta-analysis of patients without ARDS, higher PEEP resulted in decreased incidence of ARDS and hypoxemia.[5] However, the overall quality of evidence in that meta-analysis was low. In the present study, which enrolled patients who did not have ARDS but who potentially had lung injury, a strategy using lower PEEP was noninferior to a strategy using higher PEEP with regard to 1 important patient-centered outcome.

In contrast to results from a Spanish randomized clinical trial,[7] the present study did not find a reduction in VAP during ventilation with higher PEEP compared with lower PEEP. The incidence of VAP reported in this study was 1.3%, much lower than previously reported. Factors that could explain this finding include that nurses in the participating centers performed standard airway care and that all centers used infection prevention strategies against VAP, including selective digestive decontamination.[27]

The finding of a lower F_{IO_2} and higher oxygenation in patients with higher PEEP could be explained by better aeration.[28] However, incidence of severe atelectasis was similar between the groups. It is possible that in some patients, a benefit of higher PEEP with respect to less atelectasis was nullified by coinciding overdistension. This was also suggested in studies comparing lower PEEP with higher PEEP during intraoperative ventilation.[12,13] There were no statistically significant differences in development of ARDS, and after adjustment for multiple comparisons, there was no statistically significant difference in the need for rescue strategies between the groups. However, the point estimate for the percentage requiring rescue strategies was greater in the lower PEEP group, and the study may have been underpowered to detect a statistically significant difference.

Limitations

This study has several limitations. First, blinding was not possible because of the nature of the intervention. However, there were no differences in local guidelines for respiratory care, rescue therapies, or sedation practices, and local health care workers did not show specific interest in the trial or its primary outcome. Second, some patients were missed because of screening failures, possibly because of the very short time between start of invasive ventilation and randomization. Third, although the protocol foresaw randomization within 1 hour after start of ventilation in the ICU, this was not always possible. However, the majority of patients were randomized within 1 hour, which is a relatively short period compared with the duration of ventilation after randomization. Fourth, a heterogeneous group of patients without ARDS was included, but subgroup analyses did not reveal any interaction. Fifth, although the other disease severity scores were comparable between the 2 groups, APACHE IV scores were higher in the higher PEEP group. However, an analysis adjusted for APACHE IV scores showed results similar to the primary analysis. Sixth, this study compared a ventilation strategy using lower PEEP with one using a PEEP of 8 cm H_2O. Although a PEEP of 8 cm H_2O may not be standard care, it is increasingly used in ICU patients without ARDS, as shown in several observational studies[3-6,24] and recent clinical trials.[20,22]

Conclusions

Among patients in the ICU without ARDS who were expected not to be extubated within 24 hours, a lower PEEP strategy was noninferior to a higher PEEP strategy with regard to the number of ventilator-free days at day 28. These findings support the use of lower PEEP in patients without ARDS.

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Data Sharing Statement: See Supplement 4.

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REFERENCES

1. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2014;370(10):980-980. doi:10.1056/NEJMc1400293

2. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873. doi:10.1001/jama.2010.218

3. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188(2):220-230. doi:10.1164/rccm.201212-2169OC

4. Neto AS, Barbas CSV, Simonis FD, et al; PRoVENT and PROVE Network Investigators. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): an international, multicentre, prospective study. *Lancet Respir Med*. 2016;4(11):882-893. doi:10.1016/S2213-2600(16)30305-8

5. Serpa Neto A, Filho RR, Cherpanath T, et al; PROVE Network Investigators. Associations between positive end-expiratory pressure and outcome of patients without ARDS at onset of ventilation: a systematic review and meta-analysis of randomized controlled trials. *Ann Intensive Care*. 2016;6(1):109. doi:10.1186/s13613-016-0208-7

6. Peñuelas O, Muriel A, Abraira V, et al. Inter-country variability over time in the mortality of mechanically ventilated patients. *Intensive Care Med*. 2020;46(3):444-453. doi:10.1007/s00134-019-05867-9

7. Manzano F, Fernández-Mondéjar E, Colmenero M, et al. Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. *Crit Care Med*. 2008;36(8):2225-2231. doi:10.1097/CCM.0b013e31817b8a92

8. Vreugdenhil HA, Heijnen CJ, Plötz FB, et al. Mechanical ventilation of healthy rats suppresses peripheral immune function. *Eur Respir J*. 2004;23(1):122-128. doi:10.1183/09031936.03.00035003

9. Carvalho ARS, Jandre FC, Pino AV, et al. Effects of descending positive end-expiratory pressure on lung mechanics and aeration in healthy anaesthetized piglets. *Crit Care*. 2006;10(4):R122-R128. doi:10.1186/cc5030

10. Villar J, Herrera-Abreu MT, Valladares F, et al. Experimental ventilator-induced lung injury: exacerbation by positive end-expiratory pressure. *Anesthesiology*. 2009;110(6):1341-1347. doi:10.1097/ALN.0b013e31819fcba9

11. Collino F, Rapetti F, Vasques F, et al. Positive end-expiratory pressure and mechanical power. *Anesthesiology*. 2019;130(1):119-130. doi:10.1097/ALN.0000000000002458

12. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet*. 2014;384(9942):495-503. doi:10.1016/S0140-6736(14)60416-5

13. Gama de Abreu M, Schultz M, Pelosi P; Writing Committee for the PROBESE Collaborative Group. Intraoperative ventilation strategies to reduce pulmonary complications in obese patients [letter reply]. *JAMA*. 2019;322(18):1829. doi:10.1001/jama.2019.14400

14. Blackwood B, Alderdice F, Burns K, Cardwell C, Lavery G, O'Halloran P. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. *BMJ*. 2011;342:c7237-c7237. doi:10.1136/bmj.c7237

15. Algera AG, Pisani L, Bergmans DCJ, et al; RELAx Investigators and PROVE Network Investigators. RELAx—Restricted Versus Liberal Positive End-Expiratory Pressure in Patients Without ARDS: protocol for a randomized controlled trial. *Trials*. 2018;19(1):272. doi:10.1186/s13063-018-2640-5

16. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

17. Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative oxygen therapy in mechanically ventilated patients: a pilot before-and-after trial. *Crit Care Med*. 2014;42(6):1414-1422. doi:10.1097/CCM.0000000000000219

18. Panwar R, Hardie M, Bellomo R, et al; CLOSE Study Investigators; ANZICS Clinical Trials Group. Conservative versus liberal oxygenation targets for mechanically ventilated patients. a pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med*. 2016;193(1):43-51. doi:10.1164/rccm.201505-1019OC

19. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. *JAMA*. 2016;316(15):1583-1589. doi:10.1001/jama.2016.11993

20. Simonis FD, Serpa Neto A, Binnekade JM, et al; Writing Group for the PReVENT Investigators. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial. *JAMA*. 2018;320(18):1872-1880. doi:10.1001/jama.2018.14280

21. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of ventilator-free days in critical care research. *Am J Respir Crit Care Med*. 2019;200(7):828-836. doi:10.1164/rccm.201810-2050CP

22. van Meenen DMP, van der Hoeven SM, Binnekade JM, et al. Effect of on-demand vs routine nebulization of acetylcysteine with salbutamol on ventilator-free days in intensive care unit patients receiving invasive ventilation: a randomized clinical trial. *JAMA*. 2018;319(10):993-1001. doi:10.1001/jama.2018.0949

23. Schoenfeld DA, Bernard GR; ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med*. 2002;30(8):1772-1777. doi:10.1097/00003246-200208000-00016

24. Schaefer MS, Serpa Neto A, Pelosi P, et al. Temporal changes in ventilator settings in patients with uninjured lungs: a systematic review. *Anesth Analg*. 2019;129(1):129-140. doi:10.1213/ANE.0000000000003758

25. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-755. doi:10.1056/NEJMsa1410639

26. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al; Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low peep on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2017;318(14):1335-1345. doi:10.1001/jama.2017.14171

27. Bos LD, Stips C, Schouten LR, et al. Selective decontamination of the digestive tract halves the prevalence of ventilator-associated pneumonia compared to selective oral decontamination. *Intensive Care Med*. 2017;43(10):1535-1537. doi:10.1007/s00134-017-4838-5

28. Carvalho AR, Spieth PM, Pelosi P, et al. Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. *Intensive Care Med*. 2008;34(12):2291-2299. doi:10.1007/s00134-008-1301-7