EDITORIAL

Lung Recruitment and Titrated PEEP in Moderate to Severe ARDS
Is the Door Closing on the Open Lung?

Sarina K. Sahetya, MD; Roy G. Brower, MD

Mechanical ventilation is critical for the survival of many patients with the acute respiratory distress syndrome (ARDS) but can also cause ventilator-induced lung injury (VILI). One form of VILI occurs when the lungs exhale to relatively low volumes and airway pressures. This may cause injurious tidal closing and reopening of small bronchioles and alveoli or excessive stress at the margins between aerated and atelectatic airspaces.[1,2] In animal studies, positive end-expiratory pressure (PEEP) reduced or prevented VILI from exhalation to low volumes and pressures.[1,3-5] PEEP can also recruit some previously atelectatic or fluid-filled lung regions, allowing more of the lung to be available for inflation during inspiration. This could reduce VILI from overdistention of an otherwise reduced amount of aerated lung.

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In some early studies, the levels of PEEP that were applied for lung-protection exceeded the levels that most clinicians use when managing patients with ARDS. This led to recommendations to use higher PEEP in patients with ARDS to minimize low volume and low pressure VILI and hopefully to improve clinical outcomes. The "open lung approach" (OLA) aims to achieve high levels of lung aeration in patients with ARDS by first conducting recruitment maneuvers (RMs) to reverse atelectasis and then applying high levels of PEEP to keep recruited alveoli open.[6] Recruitment maneuvers typically involve a ventilatory approach that transiently increases pulmonary airway pressure to reopen recruitable lung areas. For example, an RM can be conducted by raising inspiratory airway pressures to 50 cm of water for 1 or 2 minutes.

However, 3 large randomized clinical trials of higher PEEP and RMs in patients with ARDS and a PaO_2/FIO_2 ratio of 300 or less did not demonstrate significant reductions in mortality.[7-9] An individual patient data meta-analysis of these 3 clinical trials suggested that higher PEEP reduced mortality in patients with more severe hypoxemia (PaO_2/FIO_2 ≤200), but this finding has not been tested in clinical trials.[10] A recent pilot trial of the OLA involved 200 patients and used more aggressive RMs and higher levels of PEEP than in the 3 earlier trials.[11] Arterial oxygenation improved and driving pressures decreased in the OLA group compared with the control group in which RMs were not conducted and PEEP was set according to the ARDS Network lower $PEEP/FIO_2$ table. There were small but nonsignificant differences in mortality and ventilator-free days that favored the OLA group, but the trial was not large enough to analyze these outcomes.[11]

In this issue of *JAMA*, the Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators[12] report the results of a large randomized clinical trial that was conducted in 120 intensive care units in 9 countries and compared patients treated with the OLA (n = 501) with those managed with conventional PEEP (n = 509). As in the recent pilot OLA trial, patients in this trial had moderate to severe ARDS (PaO_2/FIO_2 ≤200). To reduce VILI from overdistention in both study groups, the target tidal volume was 6 mL/kg of predicted body weight with inspiratory plateau pressures of 30 cm H_2O or less, consistent with the National Institutes of Health (NIH) ARDS Network protocol.[13] Patients in the OLA study group received RMs with PEEP as high as 45 cm H_2O and peak airway pressures as high as 60 cm H_2O.[14] These were followed immediately by a decremental PEEP titration to identify the PEEP at which lung compliance was maximal, presumably representing the best balance between recruitment and overdistention. The control group used the NIH ARDS Network lower $PEEP/FIO_2$ table without RMs.[7]

As the authors report, the OLA was associated with a significantly higher 28-day mortality and 6-month mortality (55.3% vs 49.3% and 65.3% vs 59.9%, respectively). A small but statistically significant difference in ventilator-free days favored the control group (5.3 days in the OLA group vs 6.4 days in the control group), and there was a higher rate of barotrauma among patients in the OLA group (5.6%) than among those in the control group (1.6%).

The difference in mean levels of PEEP between the OLA and the control group in the study by the ART investigators was only 3 to 4 cm H_2O over the first 7 days. The lung-protection that results from these differences in PEEP is probably small. Also, the difference between study groups in driving pressure over the first 3 days was less than 2 cm H_2O. Because tidal volumes were similar in the 2 study groups, the differences in driving pressure reflect primarily the differences in volumes of aerated lung. The small differences in driving pressures suggest that the OLA protocol did not result in much recruitment. Additionally, higher PEEP in the OLA group may have caused more overdistention, which would tend to increase driving pressures, offsetting the decreases that might have resulted from additional recruitment of aerated lung.

The mean PEEP in the control group of the ART investigators' trial was approximately 3 cm H_2O higher than the mean PEEP levels in the control groups of the other 3 large clinical trials. The authors suggest that the reason for higher PEEP levels in their control group was stricter adherence to the lower tidal volume protocol resulting in tidal volumes that were lower in their control group compared with the other control groups. The authors suggest that these lower tidal volumes could have caused hypoxemia from atelectasis, which could have triggered the use of higher PEEP to maintain the arterial oxygenation goal. It is possible that the lower tidal volumes, rather than the higher PEEP, contributed to the lower mortality in their control group.

Therapies are intended to improve patient outcomes, but all therapies have the potential to cause harm. PEEP can reduce VILI from injurious tidal opening and closing. However, PEEP also raises intracardiac pressures, including right atrial pressure, which impedes venous return and cardiac output. Moreover, especially in the absence of significant lung recruitment, PEEP increases right ventricular afterload by compressing alveolar septal capillaries, increasing pulmonary vascular resistance. Many critically ill patients experience shock from acute right ventricular failure, and high levels of PEEP may contribute to this.[15] In the study by the ART investigators, patients in the OLA group required more vasopressors within 1 hour of beginning the protocol, and 3 patients experienced cardiac arrests. PEEP also causes higher inspiratory pressures and volumes, increasing the risk of barotrauma and VILI from overdistention. The only way to know with confidence that beneficial effects of a therapy outweigh the detrimental effects is to conduct a randomized clinical trial and monitor important clinical outcomes. In the trial by the ART investigators, the detrimental effects of the OLA exceeded the beneficial effects. A mechanical ventilation strategy that is designed to be lung-protective may not be "patient-protective."

Despite abundant evidence in experimental models that the OLA can reduce VILI, 4 large randomized clinical trials of higher PEEP and RMs have now failed to demonstrate improved clinical outcomes, and the trial by the ART investigators suggested actual harm. In other studies, only approximately 50% of all patients with ARDS responded to higher airway pressures by recruiting previously atelectatic or flooded alveoli.[16,17] It follows from this observation that the OLA is more likely to have overall beneficial effects among patients whose affected lung segments can be recruited. As in the previous large randomized clinical trials of higher PEEP, the ART investigators did not attempt to identify PEEP responders and exclude the nonresponders. It is possible that there were different effects of the OLA in this trial among the subsets of patients whose involved lung areas were more or less recruitable.

The ART investigators have conducted a rigorous, large, multicenter, international trial that demonstrated that an OLA improves arterial oxygenation and driving pressure compared with the control group, similar to findings from the recent pilot trial,[11] but appears to worsen patient outcomes including mortality. The results are not only disappointing but will be unexpected for many intensive care physicians and researchers working on VILI and lung-protective ventilation. However, such results frequently lead to greater insights and more productive directions for the future. The results of the trial by the ART investigators were different than what would have been predicted from the individual patient data meta-analysis.[10] The harmful effects of the OLA observed in the trial by the ART Investigators may have been due to the aggressive RMs and decremental PEEP titration.

PEEP has been used during mechanical ventilation since the landmark description of ARDS 50 years ago.[18] However, the best method for setting PEEP levels has still not been established. Perhaps further refinements in the OLA strategy with less aggressive attempts at lung recruitment and a focus on identifying patients who recruit in response to PEEP will lead to more favorable results and leave the door to the OLA cracked open.[19,20] On the other hand, now that 4 large, randomized clinical trials of strategies designed to promote lung recruitment have failed to demonstrate improved mortality, perhaps the door on the OLA should be allowed to close so that the clinical and research community can move on to other, potentially more effective strategies. Because tidal volume reduction is a powerful tool to prevent VILI[13] and because lower tidal volumes reduce VILI from both overdistention and from opening-closing injury, perhaps future studies should push the limits of lowering tidal volume below 6 mL/kg of predicted body weight. Ultimately, allowing part of the lung to stay closed with permissive atelectasis may be more patient-protective than aggressive efforts to keep the lung open.

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LIVES 2017: Lung recruitment and PEEP trial reports results

Results from the Alveolar Recruitment for Acute Respiratory Distress Trial (ART) randomised trial ("ART"), which compared a strategy using a lung recruitment manoeuvre and titrated positive end-expiratory pressure (PEEP) with low PEEP, increased 28-day all-cause mortality of patients with moderate to severe acute respiratory distress syndrome (ARDS). The findings, published in JAMA and presented at the 30th European Society of Intensive Care Medicine in Vienna, do not support the routine use of lung recruitment manoeuvre and PEEP titration in these patients.

Mechanical ventilation is critical for the survival of many patients with ARDS but can also cause ventilator-induced lung injury (VILI). One form of VILI occurs when the lungs exhale to relatively low volumes and airway pressures. This may cause injurious tidal closing and reopening of small bronchioles and alveoli or excessive stress at the margins between aerated and atelectatic airspaces. In animal studies, PEEP reduced or prevented VILI from exhalation to low volumes and pressures.

In some early studies, the levels of PEEP that were applied for lung-protection exceeded the levels that most clinicians use when managing patients with ARDS. This led to recommendations to use higher PEEP in patients with ARDS to minimise low volume and low pressure VILI and hopefully to improve clinical outcomes. The "open lung approach" (OLA) aims to achieve high levels of lung aeration in patients with ARDS by first conducting recruitment manoeuvres (RMs) to reverse atelectasis and then applying high levels of PEEP to keep recruited alveoli open.

The ART study was conducted at 120 intensive care units (ICUs) from nine countries enrolling adults (mean [SD] age, 50.9 [17.4] years) with moderate to severe ARDS. The study compared patients treated with the OLA (n = 501) with those managed with conventional PEEP (n = 509). Patients in the OLA study group received RMs with PEEP as high as 45 cm H2O and peak airway pressures as high as 60 cm H2O.

The results showed that the OLA was associated with a significantly higher 28-day mortality and 6-month mortality (55.3% vs. 49.3% and 65.3% vs. 59.9%, respectively). A small but statistically significant difference in ventilator-free days favoured the control group (5.3 days in the OLA group vs. 6.4 days in the control group), and there was a higher rate of barotrauma among patients in the OLA group (5.6%) than among those in the control group (1.6%).

The study's corresponding author Alexandre Biasi Cavalcanti, MD, PhD, HCor Research Institute-Hospital do Coração, São Paulo, Brazil, explained the findings in an email to ICU Management & Practice.

"We have found that the strategy with lung recruitment manoeuvre (with stepwise increases in PEEP, achieving a PEEP of 35 cm H2O and peak pressure of 50 cm H2O), followed by PEEP titrated according to the best static compliance increases the 28-day mortality of moderate-to-severe ARDS patients. It may also increase the risk of barotrauma within 7 days and hypotension or need to start or increase vasopressors within 1 hour. Thus, we believe this strategy should not be used for patients with moderate-to-severe ARDS," Dr. Cavalcanti said.

However, the author doesn't think that this is the end of the Open Lung Approach for ARDS. As the results of ART show us that this strategy may be deleterious when applied to general patients with moderate-to-severe ARDS, the doctor said "we should refrain from doing so in routine practice."

An accompanying editorial in JAMA says the results of the ART trial are not only disappointing but will be unexpected for many intensive care physicians and researchers working on VILI and lung-protective ventilation.

"PEEP has been used during mechanical ventilation since the landmark description of ARDS 50 years ago. However, the best method for setting PEEP levels has still not been established. Perhaps further refinements in the OLA strategy with less aggressive attempts at lung recruitment and a focus on identifying patients who recruit in response to PEEP will lead to more favourable results and leave the door to the OLA cracked open," write Sarina K. Sahetya, MD, and Roy G. Brower, MD, both from the Pulmonary and Critical Care Medicine at Johns Hopkins University School of Medicine (Baltimore, Maryland) in the editorial.

Dr. Cavalcanti agrees with the authors of the editorial that one way forward is to identify patients who respond to PEEP. "I do agree with the position that a way forward is to find in advance patients that respond to increases in PEEP, for example by administering a 'test dose' of PEEP – increasing PEEP from 5 to 15 cm H2O, and seeing the response in terms of markers of lung recruitment (imaging or perhaps, improvement in static compliance) (Goligher et al. 2015). Then, enrolling those patients in a randomised controlled trial to test if this subset of PEEP responders actually has benefits on relevant clinical outcomes compared to the conventional low-PEEP strategy," the doctor said.

The ART investigator also cited the need to develop models to predict responsiveness so that we can use several characteristics at baseline to identify patients which are more likely to benefit. "We have begun to work on such predictive models using our database. An excellent example of this strategy is the subgrouping of ARDS into subphenotypes as done by Calfee et al. using statistical techniques (latent class analysis) (Calfee et al. 2014). Subphenotypes are classified using several biomarkers and clinical variables and seem to be useful to predict clinical responsiveness to PEEP," Dr. Cavalcanti explained.

Moreover, the doctor agrees with the editorial authors' suggestion that “allowing part of the lung to stay closed with permissive atelectasis may be more patient-protective than aggressive efforts to keep the lung open.

As Dr. Cavalcanti stated: "I definitely agree with the editorialists that a strategy allowing atelectasis, with low to intermediate PEEP levels, may be more lung-protective than a strategy of aggressive lung recruitment manoeuvres combined with high PEEP. I have specified low to intermediate PEEP because the control group in the ART study actually received PEEP levels that were slightly higher than the PEEP levels applied in the control group of previous PEEP trials."

ESICM LIVES 2017
Alexandre B. Cavalcanti, will present the results of the trial in the hot topics session, Room Berlin, on Wednesday 27th September, 14.10-17.30.

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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

Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators

Editorial

Supplemental content

IMPORTANCE The effects of recruitment maneuvers and positive end-expiratory pressure (PEEP) titration on clinical outcomes in patients with acute respiratory distress syndrome (ARDS) remain uncertain.

OBJECTIVE To determine if lung recruitment associated with PEEP titration according to the best respiratory-system compliance decreases 28-day mortality of patients with moderate to severe ARDS compared with a conventional low-PEEP strategy.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized trial conducted at 120 intensive care units (ICUs) from 9 countries from November 17, 2011, through April 25, 2017, enrolling adults with moderate to severe ARDS.

INTERVENTIONS An experimental strategy with a lung recruitment maneuver and PEEP titration according to the best respiratory-system compliance (n = 501; experimental group) or a control strategy of low PEEP (n = 509). All patients received volume-assist control mode until weaning.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality until 28 days. Secondary outcomes were length of ICU and hospital stay; ventilator-free days through day 28; pneumothorax requiring drainage within 7 days; barotrauma within 7 days; and ICU, in-hospital, and 6-month mortality.

RESULTS A total of 1010 patients (37.5% female; mean [SD] age, 50.9 [17.4] years) were enrolled and followed up. At 28 days, 277 of 501 patients (55.3%) in the experimental group and 251 of 509 patients (49.3%) in the control group had died (hazard ratio [HR], 1.20; 95% CI, 1.01 to 1.42; P = .041). Compared with the control group, the experimental group strategy increased 6-month mortality (65.3% vs 59.9%; HR, 1.18; 95% CI, 1.01 to 1.38; P = .04), decreased the number of mean ventilator-free days (5.3 vs 6.4; difference, −1.1; 95% CI, −2.1 to −0.1; P = .03), increased the risk of pneumothorax requiring drainage (3.2% vs 1.2%; difference, 2.0%; 95% CI, 0.0% to 4.0%; P = .03), and the risk of barotrauma (5.6% vs 1.6%; difference, 4.0%; 95% CI, 1.5% to 6.5%; P = .001). There were no significant differences in the length of ICU stay, length of hospital stay, ICU mortality, and in-hospital mortality.

CONCLUSIONS AND RELEVANCE In patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality. These findings do not support the routine use of lung recruitment maneuver and PEEP titration in these patients.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01374022

Group Information: The authors/writing group and a complete list of investigators for The Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) are listed at the end of this article.

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Acute respiratory distress syndrome (ARDS) is a common clinical problem among critically ill patients and is associated with high mortality and limited long-term quality of life.[1,2] The functional lung size is decreased in ARDS, since many lung units become poorly or nonaerated due to collapse, flooding, or consolidation.[3] This places patients at increased risk of ventilator-induced lung injury due both to overdistention of aerated lung units and cyclic opening and closing of small airways and alveoli (atelectrauma).[4-6]

The aim of recruitment maneuvers and positive end-expiratory pressure (PEEP) titration is to open collapsed lung units and keep them opened, potentially decreasing the risk of atelectrauma. Prospective noncontrolled trials have shown that a lung recruitment maneuver with stepwise increases in PEEP, achieving inspiratory pressures up to 60 cm H_2O, is able to open most of the collapsed lung tissue in patients with ARDS.[7,8] Two randomized trials[9,10] comparing similar recruitment maneuvers followed by decremental PEEP titration vs a well-established low-PEEP strategy[6] suggested beneficial effects on oxygenation, respiratory-system compliance, and biomarkers of systemic inflammation, without increasing barotrauma or other adverse events. Additionally, systematic reviews evaluating recruitment maneuvers suggested a reduction in mortality, also without increase in barotrauma.[11,12] However, quality of evidence is limited by high risk of bias in most trials and variable use of cointerventions. Thus, the Alveolar Recruitment for ARDS Trial (ART) was conducted to assess whether a strategy of lung recruitment maneuver associated with PEEP titrated according to the best respiratory-system compliance vs a well-established low-PEEP strategy[6] improves clinical outcomes of patients with moderate to severe ARDS.

Key Points

Question Does use of a lung recruitment maneuver associated with positive end-expiratory pressure (PEEP) titration according to the best respiratory-system compliance reduce 28-day mortality of patients with moderate to severe acute respiratory distress syndrome (ARDS) compared with a conventional low-PEEP strategy?

Findings In this randomized trial of 1010 patients, 28-day mortality was significantly higher among patients treated with a strategy of lung recruitment and PEEP titration (55.3%) than those treated with a conventional low-PEEP strategy (49.3%).

Meaning A strategy using a lung recruitment maneuver and titrated PEEP, in association with volume-assist control ventilation, increased mortality of patients with moderate to severe ARDS.

Methods

Study Design and Oversight

We conducted a randomized clinical trial in 120 intensive care units (ICUs) from 9 countries (Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain, and Uruguay). The protocol and statistical analysis plan (in Supplement 1) were published previously.[13,14] Data analysis started after the statistical analysis plan was accepted for publication (see eAppendix in Supplement 2 for details). Ethics committees of all institutions approved the study. Informed consent was obtained from all patients' representatives. An independent data monitoring committee oversaw efficacy and safety data.

Patients

We enrolled patients receiving invasive mechanical ventilation with moderate to severe ARDS of less than 72 hours of duration. Eligibility was evaluated in 2 phases, a screening and a confirmatory phase. In the screening phase, patients were considered for inclusion in the study if they met the American-European Consensus Conference criteria[15] for ARDS. The exclusion criteria were age younger than 18 years; use of vasoconstrictor drugs in increasing doses over the past 2 hours or mean arterial pressure (MAP) less than 65 mm Hg; contraindications to hypercapnia, such as intracranial hypertension or acute coronary syndrome; pneumothorax, subcutaneous emphysema, pneumomediastinum or pneumatocele; patients in palliative care only; or previously enrolled patients.

Before confirming eligibility, patients received at least 3 hours of mechanical ventilation using a low-PEEP and low-tidal volume strategy proposed by the Acute Respiratory Distress Syndrome Network (ARDSNet).[6] After that, the fraction of inspired oxygen (FIO_2) was set at 100% and the PEEP at 10 cm H_2O or more for 30 minutes and arterial blood gases were collected. Eligibility was confirmed if the ratio of the partial pressure (PaO_2) of oxygen to the FIO_2 (PaO_2:FIO_2) was 200 or lower and less than 72 hours had passed since the first time a PaO_2:FIO_2 ratio of 200 or less was determined.

Randomization and Masking

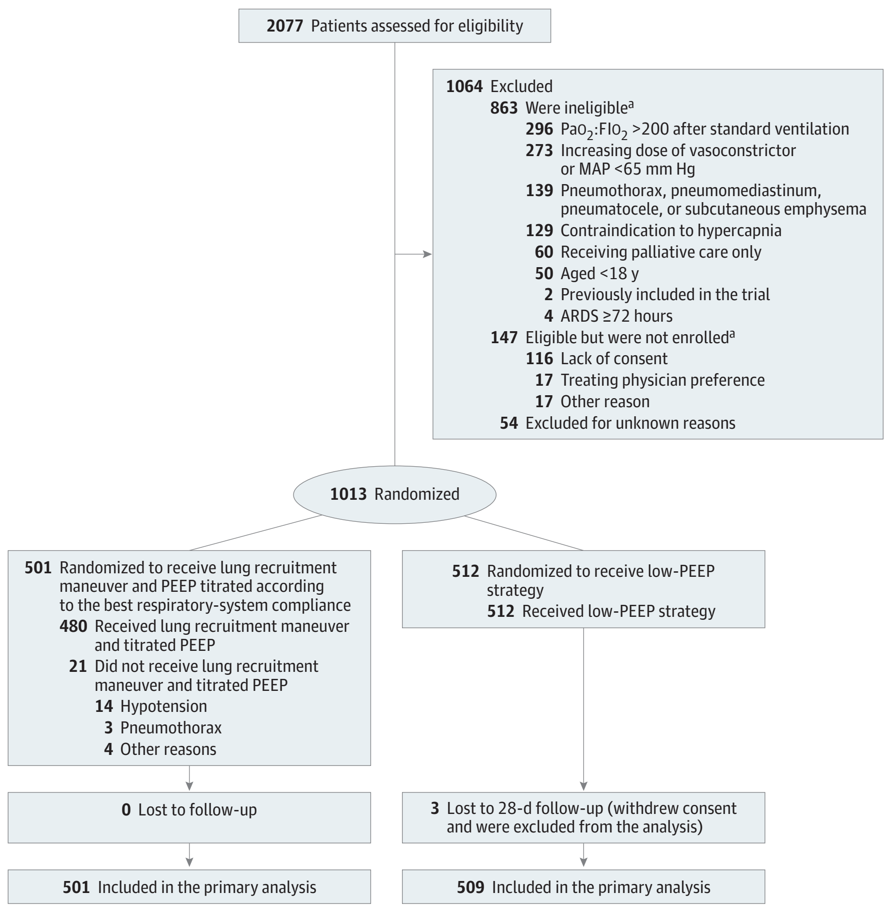
Patients were randomized in a 1:1 ratio to a strategy of lung recruitment associated with PEEP adjusted according to the respiratory-system compliance or to a low-PEEP strategy. The random allocation list was generated by a statistician with no clinical involvement in the trial using a computer-generated random number list. Randomization was conducted with blocks of 4 and stratification by site, age (≤55 years or >55 years) and PaO_2:FIO_2 ratio (≤100 or >100). Allocation concealment was ensured via a central web-based system. The treatment to which a patient was allocated was disclosed only after the patient was enrolled in the study.

Participant, clinicians, and outcome assessors were aware of the assigned treatment.

Interventions

Patients assigned to the control group continued to receive the low-PEEP strategy.[6] Immediately after randomization, patients assigned to the experimental strategy received a bolus of neuromuscular blocker and hemodynamic status was maintained by administering intravenous fluids when there were signs of fluid responsiveness. Then, we conducted a lung recruitment maneuver with incremental PEEP levels, followed by a decremental PEEP titration according to the best respiratory-system static compliance and by a second recruitment maneuver. The lung recruitment maneuver and PEEP

Figure 1. Flow of Patients in the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial



ARDS indicates acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Patients could have more than 1 reason for exclusion.

titration technique were based on those used in previous noncontrolled studies.[7,8] After recruitment and PEEP titration, patients were ventilated under volume-assist control mode with PEEP set at the titrated value (the PEEP associated with highest respiratory-system compliance plus 2 cm H_2O). If PaO_2:FIO_2 levels were stable or increasing for 24 hours or more after recruitment, weaning of PEEP was started with decreases of 2 cm H_2O every 8 hours. Apart from the lung recruitment maneuver and PEEP titration scheme, other aspects of care were similar for both groups. The experimental and control group procedures are detailed in the protocol and the manual of operations (Supplements 1 and 3).

Initially, we applied a recruitment maneuver using pressure-controlled ventilation and driving pressure of 15 cm H_2O. We started with a PEEP of 25 cm H_2O for 1 minute, then a PEEP of 35 cm H_2O for 1 minute, and then 45 cm H_2O for 2 minutes. After recruitment, decremental PEEP titration was started with a PEEP of 23 cm H_2O in volume-controlled mode. PEEP levels were decreased in steps of 3 cm H_2O down to a minimum of 11 cm H_2O. After 4 minutes in each step, we measured respiratory-system static compliance. The PEEP associated with the best compliance plus 2 cm H_2O was considered the optimal PEEP. After PEEP titration, a new recruitment in pressure-controlled ventilation was conducted in 1 step using PEEP of 45 cm H_2O for 2 minutes.

In June 2015, starting with the 556th patient, the steering committee, in consultation with the data monitoring committee, decided to modify the recruitment maneuver and PEEP titration strategy after 3 cases of resuscitated cardiac arrest possibly associated with the experimental group treatment were observed. During the recruitment maneuver, PEEP was increased to 25 cm H_2O, 30 cm H_2O, and then 35 cm H_2O, in steps of 1 minute. Maximum plateau pressure was 50 cm H_2O. Decremental PEEP trial was shorter, with each PEEP step lasting 3 minutes, followed by a new recruitment maneuver with PEEP of 35 cm H_2O.

Outcomes

Our primary outcome was mortality until 28 days. Secondary outcomes were length of ICU and hospital stay; ventilator-free days from day 1 until day 28; pneumothorax requiring drainage within 7 days; barotrauma within 7 days; and ICU, in-hospital, and 6-month mortality. We defined as pneumothorax requiring drainage for any case that was possibly due to barotrauma; that is, we did not consider cases judged to be clearly caused by invasive procedures such as central venous punction or thoracocentesis. We defined as barotrauma within 7 days any pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele of more than 2 cm detected on image examinations between

Table 1. Baseline Characteristics of the Patients

Characteristic	Lung Recruitment Maneuver With PEEP Titration Group (n = 501)	Low-PEEP Group (n = 509)
Age, mean (SD), y	51.3 (17.4)	50.6 (17.4)
Women, No. (%)	188 (37.5)	191 (37.5)
SAPS 3 score, mean (SD)[a]	63.5 (18.1)	62.7 (18.1)
No. of nonpulmonary organ failures, median (IQR)	2 (2-3)	2 (2-3)
Septic shock, No. (%)	336 (67.1)	331 (65.0)
Cause of ARDS, No. (%)		
Pulmonary ARDS	313 (62.5)	313 (61.5)
Pneumonia	280 (55.9)	276 (54.2)
Gastric aspiration	26 (5.2)	32 (6.3)
Lung contusion	7 (1.4)	4 (0.8)
Near drowning	0	1 (0.2)
Extrapulmonary ARDS	188 (37.5)	196 (38.5)
Nonseptic shock	9 (1.8)	12 (2.4)
Sepsis or septic shock	99 (19.8)	97 (19.1)
Trauma without lung contusion	5 (1.0)	5 (1.0)
Cardiac surgery	3 (0.6)	0
Other major surgery	20 (4.0)	23 (4.5)
Head trauma	4 (0.8)	6 (1.2)
Smoke inhalation	4 (0.8)	6 (1.2)
Multiple transfusions	8 (1.6)	3 (0.6)
Drug or alcohol abuse	1 (0.2)	2 (0.4)
Other	35 (7.0)	42 (8.3)
Prone position, No./total No. (%)[b]	31/304 (10.2)	30/303 (9.9)
Time since onset of ARDS, median (IQR), h	15 (7-34)	16 (7-30)
Days intubated prior to randomization, median (IQR)	2 (1-4)	2 (1-4)
Respiratory measures, mean (SD)		
Pao_2:Fio_2[c]	119.5 (43.5)	117.2 (41.9)
Tidal volume, mL/kg predicted body weight	5.8 (1.1)	5.8 (1.0)
Plateau airway pressure, cm H_2O	25.8 (4.7)	26.2 (5.2)
Minute ventilation, L/min	8.9 (2.5)	8.9 (2.4)
Respiratory rate, breaths/min	25.3 (6.4)	25.3 (6.4)
Driving pressure, cm H_2O[d]	13.5 (4.2)	13.5 (4.6)
Positive end-expiratory pressure, cm H_2O	12.2 (3.0)	12.7 (3.3)
Respiratory system static compliance, mL/cm H_2O[e]	29.2 (12.4)	30.3 (14.4)

Abbreviations: ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; SAPS, Simplified Acute Physiology Score.

[a] The SAPS 3 score can range from 0 to 217, with higher values indicating higher severity of illness.

[b] We started collecting baseline data on prone position from the 407th patient onward.

[c] Pao_2:Fio_2 at baseline was measured with Fio_2 at 100%.

[d] Driving pressure is the difference between plateau pressure and positive end-expiratory pressure.

[e] Respiratory system static compliance is the ratio of tidal volume to driving pressure.

randomization and 7 days, except those judged to be clearly caused by invasive procedures.

Other exploratory outcomes were death with refractory hypoxemia within 7 days; death with refractory acidosis within 7 days; death with barotrauma within 7 days; cardiorespiratory arrest on day 1; need of commencement or increase of vasopressors or hypotension (MAP<65 mm Hg) within 1 hour after randomization; refractory hypoxemia (Pao_2<55 mm Hg) within 1 hour after randomization; and severe acidosis (pH<7.10) within 1 hour after randomization.

Length of ICU stay (secondary outcome) and all other exploratory outcomes were included in our statistical analysis plan[14] and ClinicalTrials.gov, although they were not originally in our study protocol (see eAppendix in Supplement 2 for details).

Statistical Analysis

ART was an event-driven study designed to continue until 520 events (28-day deaths) had accrued. This number of events was estimated to provide 90% power, assuming a hazard ratio of 0.75 and type I error of 5%. This hazard ratio is similar to the size of effect used to estimate sample size in other trials in the field.[16,17]

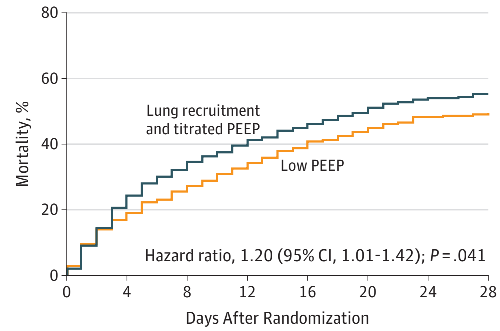
All analyses followed the intention-to-treat principle, considering all patients in the treatment groups to which they were randomly assigned, except for cases lost to follow-up. We carried out complete-case analysis for all outcomes. We planned to conduct sensitivity analysis for the primary outcome using multiple imputation techniques only if follow-up data of 1% or more of the patients was lost. Baseline characteristics were reported as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate. Hypothesis tests were 2-sided. Two interim analyses were performed after recruitment of one-third and two-thirds of the planned sample size to assess effects on clinical outcomes. The data monitoring committee would consider stopping the trial early if there was evidence of harm with 1-sided *P* value <.01. The significance level for the primary outcome final analysis was .042, to maintain overall α at .05. For all other outcomes, the significance level was .05, without adjustment for multiple comparisons. Because of this, all secondary outcomes and analyses should be interpreted as exploratory.

We assessed the effect of the trial treatments on the primary outcome using Kaplan-Meier curves and calculated the hazard ratio with 95% CI using the Cox proportional hazard model. We conducted 2 sensitivity analyses. The first was a prespecified Cox proportional hazards model adjusted for age, Simplified Acute Physiology Score 3 (SAPS 3) score, and Pao_2:Fio_2 ratio. The second was a post hoc frailty Cox model with stratification variables (site, age, and Pao_2:Fio_2) as random effects.

We used Kaplan-Meier curves and the Cox proportional hazard model to assess the effect of treatment on 6-month survival. We assessed the effects of the intervention on categorical variables with risk ratios and 95% CIs, and we used the χ^2 test to compare between-group differences. For continuous outcomes, we estimated the effects of the intervention with generalized linear models using gamma distributions (for lengths of ICU and hospital stay) or a truncated Poisson distribution (for ventilator-free days).

We used Cox proportional hazards to assess interactions between treatment effect and the following prespecified subgroups: $Pa{O_2}$:$F{IO_2}$ (≤100 vs >100 mm Hg); SAPS 3 score (<50 vs ≥50); pulmonary vs extrapulmonary ARDS; duration of ARDS (≤36 hours vs >36 to <72 hours); mechanical ventilation (≤2 days, 3-4 days, ≥5 days); and prone position. As an exploratory analysis, we tested whether treatment effects were similar before and after the protocol amendment of June 2015. We also tested in a post hoc analysis whether treatment effects per quartiles according to order of enrollment in the trial (earlier vs later) were homogeneous. All analyses were performed using the R (R Core Team, 2016) software.

Figure 2. 28-Day Mortality in the Lung Recruitment Maneuver With Titrated PEEP Group vs the Low-PEEP Group



No. at risk								
Lung recruitment and titrated PEEP	501	397	340	303	276	254	233	225
Low PEEP	509	423	378	343	312	286	264	260

PEEP indicates positive end-expiratory pressure.

Results

Patients

From November 17, 2011, through April 25, 2017, we screened 2077 patients with moderate to severe ARDS. A total of 1064 were not enrolled, of whom 863 (81.1%) met exclusion criteria and 201 (18.9%) were eligible but were not enrolled for other reasons. We randomized 1013 patients, 501 to the lung recruitment strategy and 512 to the low-PEEP strategy. Representatives of 3 patients assigned to the control group withdrew consent to use study data. We obtained 28-day and 6-month follow-up data of all remaining patients, except for 23 who were followed up and censored between 2 and 6 months. Thus, data of 1010 patients (501 in the experimental group and 509 in the control groups) were considered for the final analysis. The data monitoring committee evaluated 2 interim analyses and recommended the trial to be continued. (**Figure 1**)

Baseline characteristics were well balanced between the study groups (**Table 1**). Two-thirds of the patients had septic shock. The mean number of nonpulmonary organ failures was more than 2. Most ARDS cases were of pulmonary (62.0%) rather than extrapulmonary origin (38.0%). In the experimental and control groups, baseline mean (SD) tidal volume and plateau pressures were 5.8 (1.1) and 5.8 (1.0) mL/Kg of predicted body weight, and 25.8 (4.7) and 26.2 (5.2) cm H_2O, respectively.

Lung Recruitment

A total of 480 patients (95.8%) in the experimental group received a lung recruitment maneuver after randomization (eTable 1 in Supplement 2). In 78 cases (15.6%) the maneuver had to be interrupted, most often due to hypotension or a decrease in oxygen saturation. In 21 cases, a recruitment maneuver was not attempted due to uncontrolled hypotension (14 cases), detection of pneumothorax (3 cases) after randomization, or other reasons (4 cases). The mean (SD) titrated PEEP was 16.8 (3.8) cm H_2O. Lung recruitment was repeated after PEEP titration in 393 patients (78.4%). After the initial recruitment and PEEP titration, alveolar recruitment was not repeated from day 1 to 7 in most patients (62.7%). Conversely, 28 patients in the control group also received a recruitment maneuver within the first 7 days.

Ventilator Settings and Respiratory Variables

Mean PEEP values from hour 1 through day 7 were higher in the experimental than in the control group (eTable 2 in Supplement 2). Mean values of plateau pressure were also higher in the experimental group, although always below 30 cm H_2O in both groups. Mean tidal volumes were below 6 mL/kg of predicted body weight in both groups from hour 1 through day 3. The mean $Pa{O_2}$:$F{IO_2}$ ratios were higher in the experimental group. Yet decreases in driving pressure from control to experimental group were limited to less than 2 cm H_2O from day 1 through day 7. Partial pressure of carbon dioxide was higher and arterial pH was lower in experimental group only at the first hour, with values that were not significantly different after day 1.

Cointerventions

Use of neuromuscular blockers was higher in the experimental than the control group (96.8% vs 73.3%; difference, 23.5%; 95% CI, 19.2%-27.9%; $P < .001$), reflecting the protocol requirement for their use before the recruitment maneuver (eTable 3 in Supplement 2). The proportion of patients who received sedatives on any day was higher in the experimental group (99.0% vs 97.1%; difference, 1.9%; 95% CI, 0.0%-3.9%; $P = .05$), although there was no difference between groups in the median number of days receiving sedatives. There were no differences among groups in other cointerventions or on the need of rescue therapies for hypoxemia.

Outcomes

At 28 days, there were 277 deaths (55.3%) among 501 patients in the experimental group and 251 deaths (49.3%) among 509 patients in the control group, with a hazard ratio of 1.20 (95% CI, 1.01-1.42; $P = .041$) (**Figure 2**). After adjustment for baseline covariates, age, SAPS 3, and $Pa{O_2}$:$F{IO_2}$, the hazard ratio for

Table 2. Outcomes Among Patients Treated With Lung Recruitment Maneuver With Positive End-Expiratory Pressure (PEEP) vs Low-PEEP Strategy

Outcome	Lung Recruitment Maneuver With PEEP Titration Group (n = 501)	Low-PEEP Group (n = 509)	Type of Effect Estimate	Effect Estimate (95% CI)	*P* Value
Primary Outcome					
Death ≤28 d, No. of events/total No. (%)	277/501 (55.3)	251/509 (49.3)	HR	1.20 (1.01 to 1.42)	.041
Secondary Outcomes					
Death, No. of events/total No. (%)					
In intensive care unit	303/500 (60.6)	284/509 (55.8)	RD	4.8 (−1.5 to 11.1)	.13
In hospital	319/500 (63.8)	301/508 (59.3)	RD	4.5 (−1.7 to 10.7)	.15
Within 6 mo[a]	327/501 (65.3)	305/509 (59.9)	HR	1.18 (1.01 to 1.38)	.04
Length of stay, d					
Intensive care unit, mean (SD)	18.2 (22.4)	19.2 (25.9)	MD	−1.0 (−4.0 to 2.0)	.51
Median (IQR)	12.0 (5.0 to 23.0)	14.0 (7.0 to 23.0)			
Hospital, mean (SD)	25.5 (32.3)	26.2 (31.7)	MD	−0.7 (−4.6 to 3.3)	.74
Median (IQR)	15.0 (5.0 to 32.0)	18.0 (7.0 to 35.0)			
No. of ventilator-free d from d 1 to d 28, mean (SD), d	5.3 (8.0)	6.4 (8.6)	MD	−1.1 (−2.1 to −0.1)	.03
Median (IQR)	0.0 (0.0 to 11.0)	0.0 (0.0 to 14.0)			
Pneumothorax requiring drainage ≤7 d, No./total No. (%)	16/501 (3.2)	6/509 (1.2)	RD	2.0 (0.2 to 3.8)	.03
Barotrauma ≤7 d, No./total No. (%)	28/501 (5.6)	8/509 (1.6)	RD	4.0 (1.5 to 6.5)	.001
Exploratory Outcomes, No./Total No. (%)					
Death					
Within 7 d	160/501 (31.9)	130/509 (25.5)	RD	6.4 (0.6 to 12.2)	.03
With refractory hypoxemia ≤7 d[b]	45/501 (9.0)	51/509 (10.0)	RD	−1.0 (−4.9 to 2.8)	.59
With refractory acidosis ≤7 d[c]	68/501 (13.6)	56/509 (11.0)	RD	2.6 (−1.7 to 6.8)	.25
With barotrauma ≤7 d[d]	7/501 (1.4)	0/509 (0.0)	RD	1.4 (0.2 to 2.6)	.007
Cardiorespiratory arrest on day 1[e]	5/501 (1.0)	2/509 (0.4)	RD	0.6 (−0.6 to 1.8)	.28
Need of commencement or increase of vasopressors or hypotension (MAP <65 mm Hg) within 1 h	174/500 (34.8)	144/508 (28.3)	RD	6.5 (0.5 to 12.4)	.03
Refractory hypoxemia ($Pa{O_2}$<55 mm Hg) ≤1 h	8/496 (1.6)	10/506 (2.0)	RD	−0.4 (−2.2 to 1.5)	.81
Severe acidosis (pH<7.10) ≤1 h	65/496 (13.1)	55/506 (10.9)	RD	2.2 (−2.0 to 6.5)	.29

Abbreviations: HR, hazard ratio; IQR; interquartile range; MAP; mean arterial pressure; MD, mean difference; RD, risk difference.

[a] Six-month follow-up data was obtained from all patients, except for 23 cases who were followed up and censored between 2 and 6 mo.

[b] Death with refractory hypoxemia defined as death with last arterial blood gas analysis before dying collected with $F{IO_2}$ = 100% showing $Pa{O_2}$<55 mm Hg.

[c] Death with refractory acidosis defined as death with last arterial blood gas analysis before dying with pH<7.10.

[d] Death with barotrauma defined as persistent pneumothorax or expanding subcutaneous emphysema or persistent pneumomediastinum with chest tube at the involved site.

[e] Cardiorespiratory arrest defined as unexpected cardiac arrest, not due to progressive refractory shock.

28-day mortality was 1.22 (95% CI, 1.03-1.45; *P* = .02). In the post hoc frailty Cox model, the hazard ratio was 1.21 (95% CI, 1.02-1.44; *P* = .03).

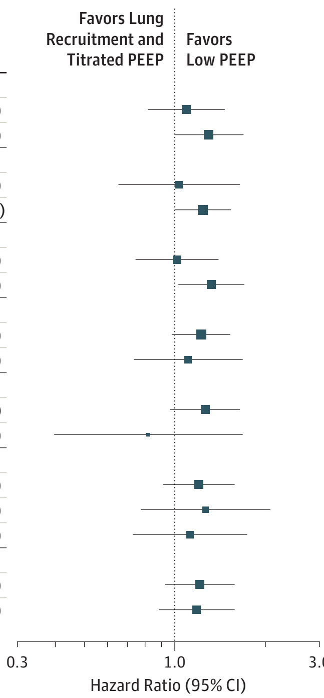
All-cause mortality was also higher within 6 months in the experimental than in the control group (65.3% vs 59.9%; hazard ratio, 1.18; 95% CI, 1.01-1.38; *P* = .04) (**Table 2**). Differences in the ICU or in-hospital mortality between groups were not statistically significant. Compared with the control group, mortality in the experimental group was higher during the first 7 days, with increased rates of death with barotrauma (Table 2). There were no significant differences in the rates of death with refractory hypoxemia, death with acidosis, and cardiorespiratory arrest between groups. Lengths of stay in the ICU or hospital were also not significantly different. The experimental group had fewer ventilator-free days during the first 28 days. The rates of pneumothorax requiring drainage and rates of any barotrauma increased in the experimental group. Within 1 hour, commencement or increase in vasopressors or hypotension were more common in the experimental group, but there were no differences in refractory hypoxemia or severe acidosis.

Subgroup and Exploratory Analyses

Effects of experimental vs control strategy on 28-day mortality were not significantly different across subgroups (**Figure 3**). Treatment effects were also not significantly different in the periods of study before and after the protocol was modified with reduction in the length and in the maximum PEEP and pressure levels of the recruitment maneuver (*P* = .89). Treatment effects were also not significantly different per quartiles according to order of enrollment in the trial (*P* = .76).

Figure 3. Effects of the Lung Recruitment Maneuver With Titrated PEEP vs the Low-PEEP Group on Mortality According to Subgroups

Subgroup	No. of Deaths/Total No. (%) Lung Recruitment and Titrated PEEP (n = 501)	Low PEEP (n = 509)	Hazard Ratio (95% CI)	*P* Value for Interaction
PaO_2: FIO_2				
≤100 mm Hg	117/197 (59.4)	120/214 (56.1)	1.09 (0.82-1.46)	.33
>100 mm Hg	160/304 (52.6)	131/295 (44.4)	1.30 (1.00-1.69)	
Simplified Acute Physiology Score 3				
<50	47/117 (40.2)	48/119 (40.3)	1.03 (0.65-1.64)	.42
≥50	230/384 (59.9)	203/390 (52.1)	1.24 (1.00 -1.54)	
Type of ARDS				
Extrapulmonary	98/188 (52.1)	102/196 (52)	1.02 (0.74-1.40)	.15
Pulmonary	179/313 (57.2)	149/313 (47.6)	1.32 (1.03-1.69)	
Duration of ARDS at randomization, h				
≤36	214/388 (55.2)	196/405 (48.4)	1.22 (0.98-1.52)	.63
>36 to <72	63/113 (55.8)	55/104 (52.9)	1.11 (0.73-1.67)	
Position 1 h after randomization				
Supine (dorsal decubitus) or lateral decubitus	153/274 (55.8)	132/273 (48.4)	1.26 (0.96-1.64)	.21
Prone	19/31 (61.3)	20/30 (66.7)	0.82 (0.40-1.67)	
Duration of mechanical ventilation before randomization, d				
0-2	160/297 (53.9)	152/320 (47.5)	1.20 (0.92-1.56)	.91
3-4	54/88 (61.4)	41/77 (53.2)	1.26 (0.77-2.07)	
≥5	63/116 (54.3)	58/112 (51.8)	1.12 (0.73-1.71)	
Protocol modification				
Before	151/273 (55.3)	138/280 (49.3)	1.21 (0.93-1.57)	.89
After	126/228 (55.3)	113/229 (49.3)	1.18 (0.88-1.58)	



The size of data markers is proportional to the inverse of variance. Protocol modification indicates the modification in the experimental group strategy after the 556th patient, with decreases in the pressures and duration of the recruitment maneuver.

ARDS indicates acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Discussion

In this trial enrolling adults with moderate to severe ARDS, a strategy of lung recruitment and PEEP titration according to the respiratory-system compliance increased 28-day mortality compared with an established low-PEEP strategy. In addition, the lung recruitment strategy increased 6-month mortality, the risk of any barotrauma and death with barotrauma, and the need for vasopressors or hypotension in the first hour. Conversely, the lung recruitment strategy decreased the number of days free of mechanical ventilation during 28 days.

One potential explanation for the findings of this trial relates to an unfavorable balance between potential positive (reduction in driving pressure)[10] and negative (increase in overdistention, hemodynamic impairment)[18,19] physiological consequences of lung recruitment and PEEP. Although some studies showed almost full opening of collapsed alveoli after recruitment maneuvers achieving high inspiratory pressures,[7,8] only mild responses were observed in this trial as suggested by the small increments in the respiratory-system compliance and reductions in driving pressure. Furthermore, the driving pressure, a strong predictor of survival in ARDS,[20,21] decreased by a mean of only less than 2 cm of water. On the contrary, the risk of barotrauma within 7 days and signs of hemodynamic impairment within 1 hour increased in the experimental group, suggesting lung injury and hemodynamic impairment as mechanisms that may have driven increased mortality. Nevertheless, the incidence of barotrauma, even in the experimental group, was lower than in any previous studies using high PEEP levels.[22]

Another potential explanation for the results observed in this trial lies in the lung protective characteristics of the control group, which may have offset any potential physiological advantages of the lung recruitment and PEEP titration strategy. The control group strategy called for a tidal volume of 6 mL/kg (or less if plateau pressure was >30 cm H_2O) and use of lower PEEP levels.[6] Adherence to low tidal volume was very strict, with lower mean tidal volumes than the ARDSNet trials.[6,23] Conversely, PEEP values were approximately 3 cm H_2O higher than that observed in control groups from previous studies.[22] The use of strictly low tidal volumes and resulting low driving pressures may have reduced lung injury due to tidal overdistention. Furthermore, intermediate levels of PEEP may have contributed to maximizing homogeneity and preventing atelectrauma.

A third possible explanation for the findings of this trial is the breath stacking phenomenon, which may occur inadvertently in patients receiving protective ventilation, especially in the volume-assist control mode and with low tidal volumes.[24,25] It was documented in 1 patient enrolled in the experimental group and routinely monitored with electrical impedance tomography (eFigure 1 in Supplement 2).

The patient received 12 mL/kg of effective tidal volume in more than 40% of the breaths, whereas the ventilator displayed 6 mL/kg. Although the incidence of this phenomenon was likely similar in both groups, it may have caused more lung overstretch with disproportionally higher driving pressures in patients submitted to higher PEEP levels.

The choice of the ARDSNet table of lower instead of higher PEEP values for the control group in this trial might be questioned, since an individual patient data meta-analysis suggested a survival benefit for higher PEEP levels in the subgroup of patients with moderate to severe ARDS.[22] Three main reasons supported the option for lower PEEP values. First, the meta-analysis did not show benefit of high PEEP for the overall group of patients with ARDS.[22] Second, none of the individual trials showed a significant effect on mortality.[17,23,26] Third, the trials included in the meta-analysis used substantially different strategies both in the experimental and control groups, with variable use of recruitment maneuvers. Therefore, it is uncertain whether the potential benefit was due to higher PEEP or to the lung recruitment maneuver itself.

This trial has strengths. Bias was controlled by using concealed allocation, intention-to-treat analysis, and by avoiding losses to follow-up. Analyses were based on a large number of events, which allowed for adequate random error control. Patient eligibility was confirmed only after ventilation with a lung protective low-tidal volume strategy and standardized FIO_2 and PEEP settings before collecting arterial blood gases. Except for the lung recruitment maneuvers and PEEP titration scheme, identical mechanical ventilation protocol with low-tidal volume was applied for both groups. In addition, the study involved centers from 9 countries, which contributes to generalizability of its results.

Limitations

This study has several limitations. First, it was not feasible to blind participants, clinicians, and outcome assessors. It is possible that processes of care might have been affected by knowledge of treatment allocation. Conversely, blinding would not affect classification of the primary outcome. Second, it was not possible to classify enrolled patients into ARDS subphenotypes, which may respond differently to therapies such as PEEP.[27,28] Determination of subphenotype requires collecting plasma samples to perform analysis of biomarkers; however, this was not conducted due to funding restrictions. Third, it has been suggested that baseline responsiveness to a test of PEEP elevation predicts percentage of potentially recruitable lung and the clinical response to a strategy of lung recruitment associated with high PEEP.[29,30] However, since responsiveness to PEEP at baseline was not assessed, it is not possible to analyze whether this characteristic modifies treatment effect. Nevertheless, there was no evidence of heterogeneity of treatment effect in any of the subgroups examined. Fourth, patients were enrolled in the trial over 6 years. The care of patients with ARDS may have changed during this period, which might have affected results. However, an analysis of treatment effects on mortality according to order of enrollment provides no evidence that effects changed over time. Fifth, a strategy involving lung recruitment and PEEP titration (primary interventions) is complex in the sense that not only the primary interventions are part of it, but also cointerventions that need to be aggregated. For example, administering neuromuscular blockers and fluids in preparation for the recruitment maneuver. As a consequence, it is not possible to ascribe observed clinical effects exclusively to the direct effects of lung recruitment maneuver and PEEP.

Conclusions

In patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality. These findings do not support the routine use of lung recruitment maneuver and PEEP titration in these patients.

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