Open Lung Approach for the Acute Respiratory Distress Syndrome: A Pilot, Randomized Controlled Trial*

Robert M. Kacmarek, PhD, RRT, FCCM[1,2]; Jesús Villar, MD, PhD, FCCM[3,4]; Demet Sulemanji, MD[1,2]; Raquel Montiel, MD[5]; Carlos Ferrando, MD, PhD[6]; Jesús Blanco, MD, PhD[3,7]; Younsuck Koh, MD, PhD, FCCM[8]; Juan Alfonso Soler, MD, PhD[9]; Domingo Martínez, MD[10]; Marianela Hernández, MD[11]; Mauro Tucci, MD, PhD[12]; Joao Batista Borges, MD, PhD[12]; Santiago Lubillo, MD, PhD[5]; Arnoldo Santos, MD, PhD[13]; Juan B. Araujo, MD[14]; Marcelo B. P. Amato, MD, PhD[12]; Fernando Suárez-Sipmann, MD, PhD[3,13]; the Open Lung Approach Network

*See also p. 237.

[1]Department of Respiratory Care, Massachusetts General Hospital, Boston, MA.

[2]Department of Anesthesia, Critical Care and Pain Medicine, Harvard Medical School, Boston, MA.

[3]CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

[4]Multidisciplinary Organ Dysfunction Evaluation Research Network, Research Unit, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canaria, Spain.

[5]Intensive Care Unit, Hospital Universitario NS de Candelaria, Santa Cruz de Tenerife, Spain.

[6]Department of Anesthesiology, Hospital Clinico de Valencia, Valencia, Spain.

[7]Intensive Care Unit, Hospital Universitario Río Hortega, Valladolid, Spain.

[8]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.

[9]Intensive Care Unit, Hospital Universitario Morales Meseguer, Murcia, Spain.

[10]Intensive Care Unit, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain.

[11]Intensive Care Unit, Hospital Universitario de Txagorritxu, Vitoria, Spain.

[12]Respiratory ICU, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil.

[13]Intensive Care Unit, Hospital Universitario Fundacion Jiménez Díaz, Madrid, Spain.

[14]Intensive Care Unit, Hospital Virgen de La Luz, Cuenca, Spain.

Drs. Amato and Suárez-Sipmann contributed equally as senior authors.

The complete list of investigators of the Open Lung Approach Network is provided in Appendix 1.

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For information regarding this article, E-mail: rkacmarek@partners.org

Objective: The open lung approach is a mechanical ventilation strategy involving lung recruitment and a decremental positive end-expiratory pressure trial. We compared the Acute Respiratory Distress Syndrome network protocol using low levels of positive end-expiratory pressure with open lung approach resulting in moderate to high levels of positive end-expiratory pressure for the management of established moderate/severe acute respiratory distress syndrome.

Design: A prospective, multicenter, pilot, randomized controlled trial.

Setting: A network of 20 multidisciplinary ICUs.

Patients: Patients meeting the American-European Consensus Conference definition for acute respiratory distress syndrome were considered for the study.

Interventions: At 12-36 hours after acute respiratory distress syndrome onset, patients were assessed under standardized ventilator settings ($F_{IO_2} \geq 0.5$, positive end-expiratory pressure ≥10 cm H_2O). If Pao_2/F_{IO_2} ratio remained less than or equal to 200 mm Hg, patients were randomized to open lung approach or Acute Respiratory Distress Syndrome network protocol. All

patients were ventilated with a tidal volume of 4 to 8 ml/kg predicted body weight.

Measurements and Main Results: From 1,874 screened patients with acute respiratory distress syndrome, 200 were randomized: 99 to open lung approach and 101 to Acute Respiratory Distress Syndrome network protocol. Main outcome measures were 60-day and ICU mortalities, and ventilator-free days. Mortality at day-60 (29% open lung approach vs. 33% Acute Respiratory Distress Syndrome Network protocol, $p = 0.18$, log rank test), ICU mortality (25% open lung approach vs. 30% Acute Respiratory Distress Syndrome network protocol, $p = 0.53$ Fisher's exact test), and ventilator-free days (8 [0-20] open lung approach vs. 7 [0-20] d Acute Respiratory Distress Syndrome network protocol, $p = 0.53$ Wilcoxon rank test) were not significantly different. Airway driving pressure (plateau pressure - positive end-expiratory pressure) and Pao_2/Fio_2 improved significantly at 24, 48 and 72 hours in patients in open lung approach compared with patients in Acute Respiratory Distress Syndrome network protocol. Barotrauma rate was similar in both groups.

Conclusions: In patients with established acute respiratory distress syndrome, open lung approach improved oxygenation and driving pressure, without detrimental effects on mortality, ventilator-free days, or barotrauma. This pilot study supports the need for a large, multicenter trial using recruitment maneuvers and a decremental positive end-expiratory pressure trial in persistent acute respiratory distress syndrome. (*Crit Care Med* 2016; 44:32–42)

Key Words: acute respiratory distress syndrome; barotrauma; decremental positive end-expiratory pressure trial; mechanical ventilation; positive end-expiratory pressure; recruitment maneuver; ventilator-free days

The approach to ventilatory support affects outcome in the acute respiratory distress syndrome (ARDS) (1–5). The ARDS network (ARDSnet) (1) established the benefit on mortality of using small tidal volume (V_T) in patients with ARDS. However, substantial controversy still exists over the application of positive end-expiratory pressure (PEEP) (3–9) and the use of lung recruitment (10, 11).

There are 6 randomized controlled trials examining the effects of PEEP in patients with ARDS (3–8). However, the results of these trials vary greatly. In the majority of these studies, patients did not have established ARDS, defined as patients who on standard ventilator settings 24 hours after ARDS diagnosis still had a Pao_2/Fio_2 less than or equal to 200 mm Hg. Patients meeting the American-European Consensus Conference (AECC) criteria for ARDS whose Pao_2/Fio_2 is more than 200 mm Hg on standardized ventilator settings have an ICU mortality of about 12–23%, whereas those with a Pao_2/Fio_2 up to 200 mm Hg on standardized ventilator settings have a mortality of about 45–55% (12–14). These figures are consistent with recent epidemiologic data (15–17).

All of the studies with a positive effect on outcome also established a V_T and plateau and driving pressure difference between groups (3, 5, 9), applied PEEP based on the patient's lung mechanics, and enrolled patients meeting the AECC criteria for ARDS (18). Speculation regarding the lack of benefit from higher PEEP in the Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury (4), Lung Open Ventilation (6), and Express (7) trials is that it is not known how many of these patients had established ARDS and if those without established ARDS were harmed by inadvertently high PEEP levels. Appropriate patient selection is a critical aspect of enrollment criteria since it has been demonstrated that response to standardized ventilator settings identifies patients with established ARDS and predicts mortality (12–15).

Several authors (19–24) have argued that the most appropriate method for setting PEEP is to recruit the lung and then to determine the least PEEP necessary to maintain the lung open by a decremental PEEP trial (open lung approach, OLA). Theoretically, this temporal sequence insures ventilation on the deflation curve of the respiratory system's pressure-volume curve, improves lung mechanics, and decreases cyclic lung stress by avoiding derecruitment (20–24). Since hypoxemia in ARDS is primarily a result of intrapulmonary shunt, failure to recruit lung not only allows shunting to persist but may also result in overdistension of open alveoli (20). Recent data indicate that lung recruitment maneuvers are capable of safely recruiting lung volume and improving gas exchange and lung mechanics (11, 20–24). Based on these data, we hypothesized that the use of lung recruitment maneuvers and a decremental PEEP trial (individualized moderate to high PEEP) would result in a lower mortality than the original ARDSnet protocol (lower levels of PEEP) (1). Our goal was to compare 60-day all-cause mortality (patients were followed for 60 d following randomization) in patients with established ARDS managed with the OLA lung protective ventilation strategy compared with the ARDSnet protocol.

METHODS

This multicenter, pilot, randomized, controlled trial was performed in 20 ICUs (**Appendix 1**). The study was approved by the institutional review boards of all participating hospitals. All patients and/or family members provided written informed consent.

Patients

All adult patients (> 18 yr) admitted to participating ICUs and meeting AECC criteria for ARDS (12) who were on mechanical ventilation for less than 96 hours were considered for enrollment. Inclusion criteria were Pao_2/Fio_2 up to 200 mm Hg, acute onset, bilateral infiltrates on anterior-posterior chest radiograph, no (clinical, echocardiographic, or hemodynamic) evidence of left heart failure, recruited into the trial within 48 hours of meeting above criteria. Exclusion criteria were age less than 18 years; weight less than 35 kg predicted body weight (PBW); body mass index greater than 50; intubation as a result of an acute exacerbation of chronic pulmonary disease: chronic obstructive pulmonary disease, asthma, cystic fibrosis, etc; acute brain injury or elevated intracranial pressure (> 18 mm Hg); immunosuppressed patients receiving chemotherapy or radiation therapy (< 2 mo after chemotherapy or

radiation therapy); and severe cardiac disease: New York Heart Association class 3 or 4 or acute coronary syndrome or persistent ventricular tachyarrhythmias. See **online data supplement** (Supplemental Digital Content 1, http://links.lww.com/CCM/B466) for additional details. During the subsequent 12–36 hours after enrollment, patients were ventilated according to the ARDSnet protocol (**Table 1**) (1) and then reassessed (qualifying blood gas) on specific ventilator settings for established moderate/severe ARDS (25). Baseline arterial blood gases were then obtained on 100% oxygen. Subsequently, patients' were randomized to ARDSnet or OLA.

Protocol

ARDSnet. ARDSnet patients were managed throughout the entire study by the original ARDSnet protocol (1) (Table 1) (online data supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B466). In both groups, permissive hypercapnia was allowed and target V_T referred to a volume calculated based on the patients' PBW (26). All patients were managed in the supine position, although head of bed elevation was not specified.

OLA. A lung recruitment maneuver followed by a decremental PEEP trial was performed before establishing initial

TABLE 1. Mechanical Ventilation Protocol

Standard ventilation settings	All enrolled patients	
Ventilator mode	VC	
V_T range	4–8 mL/kg PBW	
Respiratory rate	Adjusted to maintain $Paco_2$ between 35 and 60 mm Hg	
PEEP	Set using Fio_2-PEEP table	
Fio_2	Set using Fio_2-PEEP table	
Recruitment maneuvers	No	
Inspiratory time	≤ 1 s	
Plateau pressure goal	≤ 30 cm H_2O	
Specific ventilation settings	All enrolled patients	
Ventilator mode	VC	
V_T	≤ 6 mL/kg PBW	
Respiratory rate	Adjusted to maintain $Paco_2$ between 35 and 60 mm Hg	
PEEP	≥ 10 cm H_2O	
Fio_2	≥ 0.5	
Recruitment maneuvers	No	
Inspiratory time	≤ 1 s	
Plateau pressure goal	≤ 30 cm H_2O	
After randomization settings	Open lung approach	Acute Respiratory Distress Syndrome network protocol
Ventilator mode	PC	VC
V_T target	6 mL/kg PBW	6 mL/kg PBW
V_T range	4–8 mL/kg PBW	4–8 mL/kg PBW
Respiratory rate	≤ 35 breaths/min	≤ 35 breaths/min
PEEP	Set using decremental PEEP trial	Set using Fio_2-PEEP table
Recruitment maneuvers	Yes	No
Inspiration: expiration ratio	1:1–1:3	1:1–1:3
Arterial pH goal	≥ 7.30 and ≤ 7.45	≥ 7.30 and ≤ 7.45
Plateau pressure goal	≤ 30 cm H_2O	≤ 30 cm H_2O
Partial pressure of arterial oxygen goal	55–80 mm Hg	55–80 mm Hg
Oxygen saturation by pulse oximetry	88–95%	88–95%

VC = volume control, V_T = tidal volume, PBW = predicted body weight, PEEP = positive end-expiratory pressure, PC = pressure control.

ventilator settings (19–24). After ensuring hemodynamic stability, a lung recruitment maneuver was performed using pressure control ventilation to a peak pressure between 50 and 60 cm H_2O and PEEP 35–45 cm H_2O depending on patient's response (22). Patients were sedated to apnea before the recruitment maneuver and neuromuscular-blocking agents were used if necessary to insure patient safety during the maneuver by avoiding large increases in transpulmonary pressure. For details, see online data supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B466).

For the decremental PEEP trial, mechanical ventilation mode was volume assist/control, V_T 4–6 mL/kg, PEEP 25 cm H_2O, and ventilatory rate set at the level prior to the recruitment maneuver. After a 3-minute stabilization period, dynamic compliance (V_T divided by peak pressure – PEEP) was recorded. PEEP was then decreased in 2 cm H_2O steps and compliance recorded after stabilization. Dynamic compliance was automatically calculated and displayed on the Servo-i ventilator with each breath (on a daily basis, static compliance was determined: V_T divided by plateau pressure – PEEP). This process was continued until the PEEP level corresponding to the maximum compliance was identified. Once the maximum compliance PEEP was identified, the lung was again recruited and PEEP set at the maximum compliance PEEP + 3 cm H_2O. Following the second recruitment maneuver, the mode was changed to pressure assist/control, maximum compliance PEEP + 3 cm H_2O, pressure assist/control level set to establish a peak inspiratory pressure less than 30 cm H_2O, V_T 4–8 mL/kg. If V_T was set less than 5 mL/kg PBW, plateau pressure was allowed to exceed 30 cm H_2O. Finally, the F_{IO_2} was reduced to the lowest level maintaining the target Pa_{O_2}. For details, see online data supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B466). In addition, after PEEP was set, PEEP was not to be modified for 24 hours and then only when the F_{IO_2} decreased to 0.40. When PEEP was decreased, it was decreased at a rate not to exceed 2 cm H_2O every 8 hours; if the decrease in PEEP resulted in a loss of oxygenation or lung mechanics, PEEP was to be reestablished. Management of ventilation for OLA throughout the study followed the ARDSnet protocol.

In both groups, patients were assessed daily for readiness for a spontaneous breathing trial based on the ARDSnet criteria (1) (for details, see online data supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B466). Those meeting criteria received a 30- to 60-minute spontaneous breathing trial. If the patients passed the trial, they were extubated, unless there was a specific reason not to extubate. Patients older than 65 years, hypercapnic (> 45 mm Hg after extubation), with an ineffective cough and excessive secretions, with more than one weaning failure, with more than one comorbid condition (any chronic organ failure), upper airway obstruction, or Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 12 on the day of extubation received noninvasive ventilation (bilevel positive airway pressure) for 24–48 hours until stable or requiring reintubation (for details, see online data supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B466).

Data Gathering

Data were collected on day 0 (enrollment), day 1 (randomization), and days 2, 3, 4, 5, 6, 7, 10, 14, 21, 28, and every 7 days after randomization until extubation, including APACHE II (27), lung injury score, Simplified Acute Physiology Score (28), and Sequential Organ Failure Assessment (29) scores, and organ failures (30, 31). Data gathering after randomization included the highest and lowest value for each parameter within the specific 24-hour period. For details, see online data supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B466). The primary outcome was all-cause death at 60 days after randomization (patients were followed for 60 d). Secondary outcomes included ventilator-free days at day 28 (32), incidence of barotrauma, development of extrapulmonary organ failures, length of ICU and hospital stay, and ICU and hospital mortality. In addition, we compared PEEP, F_{IO_2}, driving pressure (plateau pressure minus PEEP), V_T, respiratory rate, plateau pressure, gas exchange, number of organs failures, and APACHE II score between groups.

Power Analysis/Study Design

The power analysis was based on an expected 45% mortality in the ARDSnet group. This mortality was determined from the recent data on effect of standard ventilator setting trial conducted by the Spanish Hospitales Españoles para el estudio de la Lesión Pulmonar aguda network (5). In that study, patients with severe and persistent ARDS managed with a V_T of 6–8 mL/kg PBW had a mortality of 45.5%. In the OLA group, a mortality of 33% was expected. This was based on the findings of the Spanish Acute Respiratory Insufficiency: España Study (14) P_{flex} trial in which the mortality in the P_{flex} group was 33%. Based on these data, it was expected that approximately 600 patients would need to be randomized into the 2 groups, ARDSnet protocol and OLA, with an α of less than 0.05 and a β of greater than 80%.

Statistical Analysis

Descriptive statistics are expressed as mean ± SD or median and interquartile range depending on the nature and distribution of the variables. Inferential statistics used estimates of the mean of the differences and their 95% CI. Variables normally distributed were compared with the Student *t* test. For variables without a normal distribution, the Mann-Whitney *U* rank test was used for comparison. Categorical variables were compared using Fisher exact test. The difference in 60-day mortality between the ARDSnet and OLA groups was compared by the Kaplan-Meier survival analysis with the log-rank test, and the Fisher exact test was used to compare actual categorical differences at 60 days. The relative risks and their 95% CIs were estimated. A two-sided *p* value of less than 0.05 was considered significant.

RESULTS

Patients

Enrolment of patients began on September 1, 2007, and the patient follow-up was completed on August 9, 2013. The trial

was terminated at the time of the first planned interim analysis because of the low rate of enrollment, precluding timely completion of the original study size ($n = 600$). From a total of 1,874 screened patients with ARDS, 297 met initial inclusion criteria and 200 were randomized: 99 OLA; 101 ARDSnet (**Fig. 1**). There were no differences between the two groups at baseline, at randomization, and while receiving 100% oxygen (**Table 2**).

Primary and Secondary Outcome Data

No statistically significant differences in 60-day all-cause mortality were found ($n = 28$, 29% OLA vs $n = 33$, 33% ARDSNet) ($p = 0.18$, log-rank test) (**Table 3** and **Fig. 2**). Multiple system organ failure and septic shock were the most frequent causes of death in OLA, whereas refractory hypoxemia and multiple system organ failure were the most frequent causes of death in ARDSnet protocol. ICU mortality did not differ between groups (25% vs 30%; $p = 0.53$) (Table 3).

There were no significant differences in ventilator-free days at day 28 (Table 3). OLA was associated with a trend to lower rate of progressive respiratory failure than ARDSnet protocol (12% vs 33%; $p = 0.11$) (Table 3).

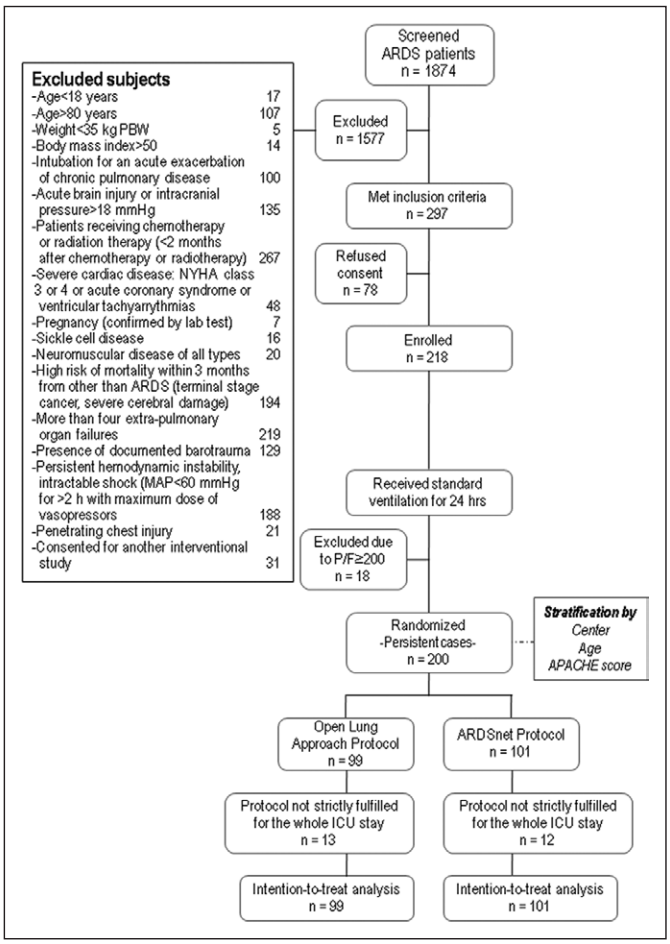

Figure 1. Flow chart of the study. After appropriate enrollment, patients were randomized to having positive end-expiratory pressure (PEEP) set by the Acute Respiratory Distress Syndrome network (ARDSnet) protocol or by a decremental PEEP trial following a recruitment maneuver. PBW = predicted body weight, NYHA = New York Heart Association, MAP = mean airway pressure, P/F = Pao_2/Fio_2, APACHE = Acute Physiology and Chronic Health Evaluation.

Respiratory and Ventilatory Variables

Oxygenation improved after recruitment maneuvers irrespective of baseline Pao_2/Fio_2. At 24 hours after randomization, Pao_2/Fio_2 increased significantly in OLA (199 ± 79 mm Hg, 133+38 mm Hg on day before randomization) but remained unchanged in ARDSnet (136 ± 44 mm Hg, 128+31 mm Hg on day before randomization) ($p < 0.0001$). In general, during the first week after randomization, patients in ARDSnet protocol were ventilated with the same Pplat and a lower PEEP, a higher driving pressure and Fio_2 with a lower Pao_2/Fio_2 than patients in OLA protocol ($p < 0.05$) (**Table 4**). In a total of six patients in the ARDSnet group and 18 patients in OLA when the V_T was set less than 5 mL/kg PBW, the plateau pressure exceeded 30 cm H_2O.

Lung Recruitment and Decremental PEEP

Prior to the lung recruitment maneuver, OLA patients were managed with a PEEP of 11.8 ± 2.4 cm H_2O. After lung recruitment, PEEP increased to 15.8 ± 3.8 cm H_2O and Fio_2 decreased from 0.70 (0.51–0.70) to 0.40 (0.40–0.60) (Table 4). A total of 231 recruitment maneuvers were performed, 23% of these required that 0.5 L (0.2–0.5 L) of fluid be administered prior to the recruitment maneuver. In seven patients, the lung recruitment maneuver was stopped because of hypotension (none of these patients received fluid before the recruitment maneuver). In three of these patients, an additional 0.5–1.5 L of fluid was administered allowing the recruitment maneuver to continue. However, four patients did not receive any fluid, and the recruitment maneuver was stopped. Recruitment maneuvers were not applied to 10 patients because the medical staff considered them too unstable to tolerate the recruitment maneuver or for other unspecified reasons. All patients received sedatives prior to the recruitment maneuvers and 60 patients received neuromuscular-blocking agents on day 1 compared with 42 patients in the ARDSnet protocol group ($p < 0.05$). At baseline and on all subsequent days, there were no differences in the number of OLA and ARDS patients who received neuromuscular-blocking agents.

Adverse Events

There were no significant differences in major adverse events reported: pneumothorax (6% vs 8%; $p = 0.78$) and cardiac arrests (8% vs 6%; $p = 0.58$) or mild transient events; hypotension (35% vs 29%; $p = 0.45$), desaturation (34% vs 22%; $p = 0.06$), and arrhythmias (15% vs 10%; $p = 0.29$) in percent of patients in OLA versus ARDSnet protocol, respectively.

Protocol Violations

The study protocol was discontinued after the second day post-randomization due to consent withdrawal by the treating physician or by patient's family in three OLA patients and nine ARDSnet patients. Since the application of PEEP and the use of a specific mode of ventilation were the primary differences in the two protocols, we report adherence to these aspects of the protocols as the primary area of protocol violation. In the

TABLE 2. Baseline Characteristics of Study Subjects

Characteristics	Open Lung Approach ($n = 99$)	Acute Respiratory Distress Syndrome Network Protocol ($n = 101$)
At the time of screening for ARDS		
Age (yr)	52.2 ± 15.1	53.4 ± 14.5
Gender (male/female, *n*)	57/42	67/34
Acute Physiology and Chronic Health Evaluation II score	18 ± 10	17 ± 6
PBW (kg)	61 ± 11	62 ± 11
Risk factors for ARDS, no. of patients (%)		
Sepsis	45 (45)	44 (44)
Pneumonia	53 (54)	54 (53)
Aspiration of gastric content	14 (14)	13 (13)
Other	16 (16)	23 (23)
V_T (mL/kg PBW)	7.4 ± 1.8	7.1 ± 1.5
Plateau pressure (cm H_2O)	27 ± 5	27 ± 5
Set PEEP (cm H_2O)	11.9 ± 3.3	11.9 ± 3.8
P/F ratio (mm Hg)	121 ± 37	114 ± 33
Pa_{O_2} (mm Hg)	85 ± 26	81 ± 19
F_{IO_2} (%)	70 (50–100)	70 (60–90)
Arterial pH	7.32 ± 0.09	7.32 ± 0.09
Pa_{CO_2} (mm Hg)	48 ± 12	47 ± 12
Respiratory rate (breaths/min)	22 ± 6	22 ± 6
Minute ventilation (L/min)	9.2 ± 2.3	9.3 ± 2.3
Organ/system dysfunctions, no. of patients (%)	62 (63)	67 (66)
Coma	6 (6)	3 (3)
Renal	17 (17)	16 (16)
Hepatic	1 (1)	5 (5)
Cardiovascular	50 (51)	59 (58)
Disseminated intravascular coagulation	4 (4)	6 (6)
At the time of "qualifying arterial blood gas" (after 12- to 36-hr standard ventilation and 30-min specific settings)		
V_T (mL/kg PBW)	6.3 ± 0.9	6.2 ± 0.8
Plateau pressure (cm H_2O)	25.9 ± 5.5	25.9 ± 4.4
Set PEEP (cm H_2O)	12 ± 2.7	12 ± 2.3
Respiratory rate (breaths/min)	25.8 ± 6	25.2 ± 4.7
Minute ventilation (L/min)	9.6 ± 2.3	9.6 ± 2.3
P/F ratio (mm Hg)	133 ± 38	128 ± 31
Pa_{O_2} (mm Hg)	86 ± 22	82 ± 15
F_{IO_2} (%)	70 (50–70)	70 (51–70)
Arterial pH	7.32 ± 0.08	7.34 ± 0.08
Pa_{CO_2} (mm Hg)	49.7 ± 11	47.9 ± 9

(*Continued*)

TABLE 2. (*Continued*). Baseline Characteristics of Study Subjects

Characteristics	Open Lung Approach ($n = 99$)	Acute Respiratory Distress Syndrome Network Protocol ($n = 101$)
At the time of "baseline arterial blood gas" ($F_{IO_2} = 100\%$)		
Pa_{O_2} (mm Hg)	179 ± 88	174 ± 74
Arterial pH[a]	7.33 ± 0.08[a]	7.35 ± 0.09[a]
Pa_{CO_2} (mm Hg)	47 (41–55.5)	46.4 (40.5–54)
At the time of randomization		
Duration of mechanical ventilation (d)	1.9 ± 1.3	2.0 ± 1.2

ARDS = acute respiratory distress syndrome, PBW = predicted body weight, V_T = tidal volume, PEEP = positive end-expiratory pressure, $P/F = Pa_{O_2}/F_{IO_2}$.
[a]$p = 0.0367$.

ARDSnet group, the PEEP/F_{IO_2} table was not followed on 5% of days (violation 79 d/total ventilation days 1,528 times 100). In OLA, PEEP was inappropriately adjusted on 3% of days (violation 42 d/total ventilation days 1,344 times 100). Pressure assist/control was used in 3% of days on ARDSnet patients (violation 40 d/total ventilation days 1,528 times 100), and volume assist/control was used on 8% of days in OLA (violation 110 d/total ventilation days 1,344 times 100).

DISCUSSION

Our study demonstrates that OLA can be safely applied to patients with established ARDS. This is the first randomized controlled trial to compare an OLA strategy based on a PEEP titration using maximal compliance to select optimal PEEP to the ARDSnet protocol. The major difference between the OLA and ARDSnet protocol was the use of lung recruitment maneuvers and a decremental PEEP trial versus the ARDSnet table to manage F_{IO_2} and PEEP.

It has been well established that in some patients, lung recruitment maneuvers improve lung mechanics and oxygenation similar to the response we noted in the OLA group (21–23). Titrating PEEP to the maximum compliance on the deflation limb of the respiratory system pressure-volume curve was intended to sustain the benefits of the recruitment maneuver, as evidenced by the oxygenation and driving pressure throughout the first week of the protocol. Setting PEEP at this level ensured that PEEP was set just higher than the pressure associated with the beginning of dependent lung collapse (21–23). It should be emphasized that this approach is very different from that proposed by Suter et al (33) who set PEEP according to the best incremental PEEP

TABLE 3. Study Outcomes

Outcomes	Open Lung Approach	Acute Respiratory Distress Syndrome Network Protocol	*p*
28-d mortality, *n* (%)	22 (22)	27 (27)	0.51 F
60-d mortality, *n* (%)	28 (29)	33 (33)	0.54 F
ICU mortality, *n* (%)	25 (25)	30 (30)	0.53 F
Hospital mortality, *n* (%)	29 (30)	35 (35)	0.45 F
Length of ICU stay, d, median (IQR)	18 (10–28)	16 (11–28)	0.79 W
Length of hospital stay, d, median (IQR)	27 (16–46)	23 (14–41)	0.49 W
Ventilator-free days, d, median (IQR)	8 (0–20)	7 (0–20)	0.53 W
Primary cause of death in ICU—univariate analysis			
Progressive respiratory failure, *n* (% nonsurvivors)	3 (12)	10 (33)	0.11 F
Septic shock, *n* (% of nonsurvivors)	10 (40)	3 (10)	0.01 F
Multiple organ failure, *n* (% of nonsurvivors)	4 (16)	10 (33)	0.22 F
Cardiac failure, *n* (% of nonsurvivors)	1 (4)	1 (3)	0.99 F
Other, *n* (% of nonsurvivors)	6 (24)	4 (13)	0.48 F
Unknown cause of death, *n* (% of nonsurvivors)	1 (4)	2 (7)	

IQR = interquartile range, *p* values: F = Fisher exact test, W = Wilcoxon rank test.

TABLE 4. Change of Ventilatory Parameters and Arterial Blood Gas Variables Over Time

Variables	Groups	Day 0	Randomization			
			Day 1	Day 3	Day 5	Day 7
No. of patients (*n*)	ARDSnet	101	101	98	86	78
	OLA	99	94	90	83	73
Ventilation						
Peak inspiratory pressure (cm H_2O)	ARDSnet	31.9 ± 5.5	32.2 ± 6.1	30.7 ± 8.0[a]	30.0 ± 8.8[a]	30.0 ± 10.1[a]
	OLA	32.8 ± 5.2	30.1 ± 3.7[b,c]	28.2 ± 5.2[a,b]	26.9 ± 5.4[a,b]	25.9 ± 5.8[a,b]
Plateau pressure (cm H_2O)	ARDSnet	26.2 ± 4.3	25.2 ± 4.6	24.5 ± 5.1	24.4 ± 4.8	24.8 ± 5.9
	OLA	25.1 ± 4.7	27.9 ± 3.8[c,d]	26.2 ± 3.9[b]	24.8 ± 3.9	23.7 ± 6.0
Mean airway pressure (cm H_2O)	ARDSnet	17.9 ± 3.7	17.3 ± 3.2	16.5 ± 4.6	16.5 ± 4.8	16.8 ± 5.8
	OLA	18.4 ± 3.7	20.6 ± 3.6[c,d]	19.7 ± 4.7[d]	16.5 ± 4.3[c]	16.7 ± 4.7
PEEP (cm H_2O)	ARDSnet	12.0 ± 2.4	11.6 ± 2.5	10.7 ± 3.3[c]	10.4 ± 3.7[c]	10.5 ± 3.9[c]
	OLA	11.8 ± 2.4	15.8 ± 3.8[a,d]	14.3 ± 3.9[a,d]	12.5 ± 3.9[d]	11.2 ± 4.4
Driving pressure (cm H_2O)	ARDSnet	14.2 ± 3.9	13.8 ± 3.7	13.6 ± 3.8	13.3 ± 3.4	13.9 ± 4.1
	OLA	14.0 ± 4.3	11.8 ± 3.5[c,d]	11.4 ± 3.1[c,d]	12.4 ± 3.2	12.9 ± 3.8
Auto-PEEP (cm H_2O)	ARDSnet	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1.1)
	OLA	0 (0–1)	0.5 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Tidal volume (mL/kg predicted body weight)	ARDSnet	6.5 ± 1.0	6.2 ± 0.7	6.4 ± 1.1	6.4 ± 1.2	6.7 ± 1.6
	OLA	6.6 ± 1.3	5.6 ± 1.1[a,d]	5.8 ± 1.2[a,d]	6.4 ± 1.4	6.8 ± 1.5
Compliance of the respiratory system (mL/cm H_2O)	ARDSnet	28.0 (22.5–36.7)	28.8 (22.0–36.9)	27.5 (22.0–34.6)	28.2 (22.0–38.1)	27.1 (21.1–37.1)
	OLA	29.0 (21.8–38.9)	29.6 (20.6–38.1)	30.4 (23.4–39.5)	29.8 (25.3–34.0)	30.8 (23.0–35.8)
Respiratory rate (breaths/min)	ARDSnet	24.8 ± 5.0	26.0 ± 4.8	26.4 ± 4.9	25.4 ± 5.5	25.8 ± 5.4
	OLA	25.1 ± 6.0	28.9 ± 5.6[a,d]	28.4 ± 5.5[a,b]	27.2 ± 6.7[b,c]	25.3 ± 6.7
Inspiratory time (s)	ARDSnet	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.6–1.0)	0.8 (0.6–1.0)
	OLA	0.9 (0.7–1.0)	0.8 (0.8–0.9)	0.8 (0.7–1)	0.8 (0.7–0.9)	0.8 (0.7–1.0)
Blood gas						
Pao_2 (mm Hg)	ARDSnet	82.2 ± 14.9	81.7 ± 21.3	83.8 ± 24.5	81.9 ± 21.7	85.1 ± 26.4
	OLA	85.5 ± 22	100.6 ± 58.4[a,d]	90.3 ± 25.6[d]	87 ± 25.4	81.8 ± 24.3
F_{IO_2} (%)	ARDSnet	70 (50–70)	60 (50–70)	60 (50–70)[c]	60 (45–70)[a]	50 (40–70)[a]
	OLA	70 (51–70)	40 (40–60)[a,d]	40 (40–50)[a,d]	40 (40–50)[a,d]	40 (40–50)[a,d]
Pao_2/F_{IO_2} ratio	ARDSnet	128.3 ± 30.5	135.6 ± 43.5	148.3 ± 54.9	154.0 ± 70.1[c]	168.3 ± 82.9[a]
	OLA	133.4 ± 37.8	198.5 ± 78.6[a,d]	212.5 ± 84.4[a,d]	197.3 ± 73.8[a,d]	193.0 ± 75.7[a,b]
$Paco_2$ (mm Hg)	ARDSnet	47.9 ± 8.8	48.2 ± 9.4	51.1 ± 12.4	50.1 ± 11.9	49.5 ± 13.1
	OLA	49.7 ± 11.1	57.2 ± 16.6[c,d]	50.4 ± 13.9	49.3 ± 12.7	49.5 ± 13.3
pH	ARDSnet	7.34 ± 0.08	7.36 ± 0.08	7.38 ± 0.09[c]	7.41 ± 0.08[a]	7.41 ± 0.08[a]
	OLA	7.32 ± 0.08	7.30 ± 0.1[d]	7.37 ± 0.1	7.39 ± 0.09	7.30 ± 0.89
Spo_2 (%)	ARDSnet	94.5 ± 3.0	93.9 ± 4.9	94.8 ± 2.9	95.1 ± 3.2	94.1 ± 4.6
	OLA	94.2 ± 4.1	95.1 ± 3.7[b]	95.5 ± 3.3[b]	95.2 ± 3.1	95.0 ± 2.9

ARDSnet = Acute Respiratory Distress Syndrome network, OLA = open lung approach, PEEP = positive end-expiratory pressure.
[a]$p < 0.001$ vs day 0 (baseline) value.
[b]$p < 0.05$ vs ARDSnet.
[c]$p < 0.05$ vs day 0 (baseline) value.
[d]$p < 0.01$ vs ARDSnet.

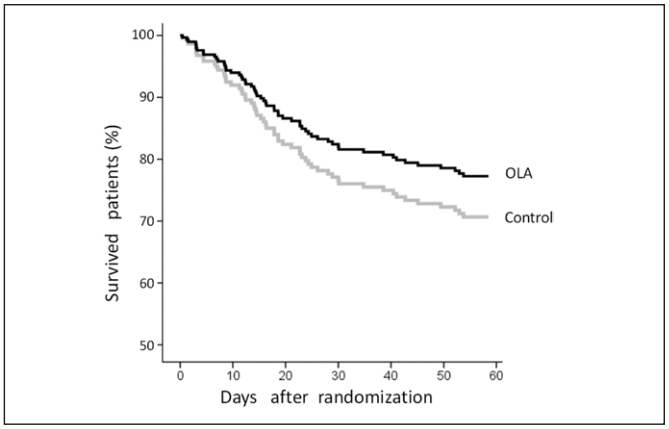

Figure 2. Study outcomes for the Open Lung Approach (OLA) and Acute Respiratory Distress Syndrome Network protocol groups. Survival curves adjusted for prespecified baseline covariates (Acute Physiology and Chronic Health Evaluation, age, Pa_{O_2}/F_{IO_2} ratio, arterial pH) using Kaplan-Meier survival analysis. Please note that the vertical axis has been truncated at 0.5 for better visualization. However, this should not be perceived as a larger difference than actually indicated.

titration without lung recruitment. Suter et al's (33) approach results in a much lower end-expiratory lung volume. This is because ventilation occurs on the inflation limb of the respiratory system's pressure-volume curve (21–23). It is the decremental PEEP trial postrecruitment that ensures that the resulting PEEP may sustain the benefits of the lung recruitment maneuver.

The application of PEEP using OLA resulted in PEEP set after the lung recruitment maneuver (Table 4) similar to the PEEP level in other trials comparing high and low PEEP (3–8). At day 1, mean PEEP was only 4 cm H_2O higher than in the ARDSnet protocol group but the daily PEEP level in OLA decreased, being essentially equal to the ARDSnet protocol by day 7. As expected, the higher PEEP was accomplished by a higher mean airway pressure but it nevertheless resulted in a lower driving pressure. As noted in Table 4, driving pressure was significantly lower in the OLA group throughout day 3 and trended lower throughout the first week while mean airway pressure was significantly higher throughout day 3. In addition, F_{IO_2} was markedly lower and Pa_{O_2}/F_{IO_2} higher in OLA patients than in the ARDSnet protocol group for the first week of the trial.

Contrary to the reports by others (34, 35), the benefits of the lung recruitment maneuver were sustained in most patients as a result of the best decremental PEEP being identified in each patient. On average, only 2.57 recruitment maneuvers were needed per patient. However, care was exercised to avoid inadvertent derecruitment. All patients had inline suction catheters, ventilator circuits were not disconnected for routine care, and the OLA protocol required a specific process to adjust PEEP level. Specifically, after PEEP was set, PEEP was not to be modified for 24 hours and then only when the F_{IO_2} decreased to 0.40. As a result, it was rare that PEEP needed to be reestablished after a decrease and the number of recruitment maneuvers per patients is so few. Essentially PEEP was sustained until there was little likelihood of derecruitment with PEEP decrease.

There are major differences between our study and other randomized controlled trials (3–8) evaluating the impact of high PEEP during lung protective mechanical ventilation. First, none of those trials reevaluated patients at 24 hours after ARDS to ensure only patients with established ARDS were randomized. As a result, those previous studies enrolled patients with less severe lung injury (3–8) than in our trial. We ensured that all studied patients had established moderate/severe ARDS 24 hours after meeting the AECC definition while on standardized ventilator settings. Therefore, the cohort of patients we studied was different from those studied by the ARDSnet (6) and others (3–5, 8, 36, 37). Second, with the exception of the liquid ventilation (38) and PROne positioning in SEVere Ards prone positioning trials (39), 60-day mortality and ICU mortality of our OLA group were one of the lowest reported for patients with established ARDS. Third, PEEP was set in the OLA group by a recruitment maneuver and a decremental PEEP trial according to maximal compliance. It is the combination of these two sequential interventions that defines an OLA strategy. Forth, a positive physiologic consequence of the OLA strategy was the significant reduction in driving pressure.

Finally, the application of OLA changed patients' oxygenation from a persistent Pa_{O_2}/F_{IO_2} less than 200 mm Hg to a mean sustained Pa_{O_2}/F_{IO_2} near 200 mm Hg within the first 24 hours after randomization. We speculate that this oxygenation benefit was a direct result of recruitment of lung units and the sustaining of recruited lung units open by patient-specific selection of PEEP. This oxygenation benefit also resulted in sustained lower F_{IO_2}.

We speculate that the application of OLA may have changed the course of ARDS by avoiding atelectrauma together with a reduction in driving pressure (40). That is contrary to patients who were managed with the ARDSnet approach, where the majority of patients continued to have a mean Pa_{O_2}/F_{IO_2} less than 150 mm Hg despite being ventilated with mean PEEP greater than 10 cm H_2O and F_{IO_2} more than > 0.5. This benefit from OLA remained on day 7 despite PEEP differences between OLA and the ARDSnet groups being eliminated.

A recent experimental study by Hussein's group (41) provides insights into why the OLA approach may sustain oxygenation better than approaches that do not open the lung and keep it open. They reported in rats that cell injury was minimal in dry lungs compared with wet lungs regardless of V_T. They also demonstrated that the application of high PEEP to partially fluid (edema)-filled lungs prevented epithelial injury even when lungs were inflated to very large end-expiratory volumes (PEEP levels) and very high end-expiratory pressures provided V_Ts were small. They indicate that these findings may provide the rationale of the OLA.

As indicated, patients were managed in the supine position. Prone positioning was only allowed in patients failing to respond to either protocol. In the ARDSnet protocol group, 10 patients were proned and in OLA four patients. We did not include prone positioning as part of the protocol but do consider it an alternative in those situations where OLA fails to improve oxygenation.

As indicated, this trial was stopped early because of inability to enroll sufficient number of patients after 5 years. There are a number of reasons for this. First, the incidence of patients with

ARDS in Europe, specifically in Spain, is markedly lower than in North America (42). Recent North American data indicate 35–70 patients per 100,000 population, whereas in Spain, the incidence of ARDS is only seven patients per 100,000 population (41). Second, there was no funding to support research individuals in any of the participating institution; thus, there were long periods where specific institutions were unable to screen patients. Third, and most importantly, the investigators lost their equipoise regarding the study. Over time they began to use the OLA to manage patients from the onset of ARDS and as a result chose not to consider recruiting these patients into the study.

The adverse event rate for both groups was very low. This is especially true for pneumothorax rate. None of the previous ARDS randomized controlled trials published to date demonstrated as low a pneumothorax rate (1, 3–10, 37). Of note, none of the pneumothoraces reported were directly associated with the performance of a recruitment maneuver. The biggest concern was the hemodynamic adverse events and the transient hypoxemia. However, these issues were managed with fluid administration as per protocol, but in a few cases, they did require cessation of the lung recruitment maneuver until hemodynamic stability could be reestablished. As a result, careful monitoring of patients during lung recruitment and decremental PEEP trial is essential. It is impossible to determine which patients may initially poorly tolerate the recruitment maneuver. Of note, patients in the ARDSnet protocol group also experienced transient hypoxemic and hemodynamic events as observed in all patients with ARDS.

Our study is limited by the fact that it was powered for 600 patients but stopped because of inability to recruit patients. Thus, it is impossible to know if any of the trends in outcome would hold up in a larger study. However, this study did demonstrate the safety of applying the OLA to managing patients with ARDS. In addition, we did not track fluid management except during the recruitment procedures; thus, we cannot determine if OLA required more aggressive ongoing fluid management than the ARDSnet.

In summary, OLA significantly improved oxygenation, lung mechanics, and driving pressure and did not adversely affect duration of ventilatory support and ICU and 60-day mortality in patients with established ARDS. In addition, there were no significant differences in major adverse events between OLA and the ARDSnet approach. This pilot study should be considered the foundation for a large, multicenter trial on the use of lung recruitment maneuvers and a decremental PEEP trial in patients with established ARDS.

REFERENCES

1. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
2. Tremblay L, Valenza F, Ribeiro SP, et al: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997; 99:944–952
3. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
4. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336
5. Villar J, Kacmarek RM, Pérez-Méndez L, et al: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. *Crit Care Med* 2006; 34:1311–1318
6. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637–645
7. Mercat A, Richard JC, Vielle B, et al; Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655
8. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359:2095–2104
9. Ranieri VM, Suter PM, Tortorella C, et al: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1999; 282:54–61
10. The ARDS Clinical Trials Network, National Heart, Lung, and Blood Institute, National Institutes of Health: Effects of recruitment maneuvers in patients with ALI and ARDS ventilated with high positive end-expiratory pressure. *Crit Care Med* 2003; 31:2592–2597
11. Huh JW, Jung H, Choi HS, et al: Efficacy of positive end-expiratory pressure titration after the alveolar recruitment manoeuvre in patients with acute respiratory distress syndrome. *Crit Care* 2009; 13:R22
12. Villar J, Pérez-Méndez L, Kacmarek RM: Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999; 25:930–935
13. Ferguson ND, Kacmarek RM, Chiche JD, et al: Screening of ARDS patients using standardized ventilator settings: Influence on enrollment in a clinical trial. *Intensive Care Med* 2004; 30:1111–1116
14. Villar J, Pérez-Méndez L, Blanco J, et al; Spanish Initiative for Epidemiology, Stratification, and Therapies for ARDS (SIESTA) Network: A universal definition of ARDS: The PaO_2/FiO_2 ratio under a standard ventilatory setting–A prospective, multicenter validation study. *Intensive Care Med* 2013; 39:583–592
15. Villar J, Blanco J, Añón JM, et al; ALIEN Network: The ALIEN study: Incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med* 2011; 37:1932–1941
16. Esteban A, Anzueto A, Frutos F, et al; Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. *JAMA* 2002; 287:345–355
17. Brun-Buisson C, Minelli C, Bertolini G, et al; ALIVE Study Group: Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004; 30:51–61
18. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
19. Hickling KG: The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med* 1998; 158:194–202
20. Lachmann B: Open up the lung and keep the lung open. *Intensive Care Med* 1992; 18:319–321
21. Cereda M, Emami K, Kadlecek S, et al: Quantitative imaging of alveolar recruitment with hyperpolarized gas MRI during mechanical ventilation. *J Appl Physiol (1985)* 2011; 110:499–511
22. Borges JB, Okamoto VN, Matos GF, et al: Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 174:268–278

23. Albaiceta GM, Luyando LH, Parra D, et al: Inspiratory vs. expiratory pressure-volume curves to set end-expiratory pressure in acute lung injury. *Intensive Care Med* 2005; 31:1370–1378
24. Medoff BD, Harris RS, Kesselman H, et al: Use of recruitment maneuvers and high-positive end-expiratory pressure in a patient with acute respiratory distress syndrome. *Crit Care Med* 2000; 28:1210–1216
25. Villar J, Pérez-Méndez L, López J, et al; HELP Network: An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 176:795–804
26. Devine BJ: Gentamicin therapy. *Drug Intell Clin Pharm* 1974; 8:655–670
27. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
28. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
29. Ferreira FL, Bota DP, Bross A, et al: Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; 286:1754–1758
30. Bell RC, Coalson JJ, Smith JD, et al: Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med* 1983; 99:293–298
31. Villar J, Manzano JJ, Blazquez MA, et al: Multiple system organ failure in acute respiratory failure. *J Crit Care* 1991; 6:75–80
32. 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; 30:1772–1777
33. Suter PM, Fairley B, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975; 292:284–289
34. Fan E, Wilcox ME, Brower RG, et al: Recruitment maneuvers for acute lung injury: A systematic review. *Am J Respir Crit Care Med* 2008; 178:1156–1163
35. Hodgson C, Keating JL, Holland AE, et al: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation. *Cochrane Database Syst Rev* 2009; 2:CD006667
36. Phua J, Badia JR, Adhikari NK, et al: Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009; 179:220–227
37. Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693
38. Kacmarek RM, Wiedemann HP, Lavin PT, et al: Partial liquid ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173:882–889
39. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
40. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755
41. Hussein O, Walters B, Stroetz R, et al: Biophysical determinants of alveolar epithelial plasma membrane wounding associated with mechanical ventilation. *Am J Physiol Lung Cell Mol Physiol* 2013; 305:L478–L484
42. Villar J, Sulemanji D, Kacmarek RM: The acute respiratory distress syndrome: Incidence and mortality, has it changed? *Curr Opin Crit Care* 2014; 20:3–9

APPENDIX 1. COMPLETE LIST OF INVESTIGATORS OF THE OPEN LUNG APPROACH NETWORK

Santiago Lubillo, Raquel Montiel, Dácil Parrilla, Sergio T. Rodriquez-Ramos (Intensive Care Unit, Hospital Universitario NS de Candelaria, Santa Cruz de Tenerife, Spain); Marcelo Amato, Joao Batista Borges, Mauro Tucci, Adriana Hirota, Carlos Toufen, Roberta Ribeiro Santis, Carlos Roberto Ribeiro de Carvalho (Respiratory Intensive Care Unit, Hospital das Clinicas, Sao Paolo, Brazil); Fernando Suárez-Sipmann, Arnoldo Santos (Intensive Care Unit, Hospital Fundación Jiménez Díaz, Madrid, Spain); Younsuck Koh (Intensive Care Unit, Asan Medical Center, Ulsan College, South Korea); Javier Belda, Carlos Ferrando (Department of Anesthesia and Intensive Care, Hospital Clínico Universitario, Valencia, Spain); Jesús Blanco, Virginia Fraile, Jesus Sanchez-Ballesteros (Intensive Care Unit, Hospital Universitario Río Hortega, Valladolid, Spain); Gumersindo González, Juan Alfonso Soler (Intensive Care Unit, Hospital Universitario Morales Meseguer, Murcia, Spain); Domingo Martínez (Hospital Universitario Virgen de la Arrixaca, Murcia, Spain); Marianela Hernández (Intensive Care Unit, Hospital Universitario de Txagorritxu, Vitoria, Spain); José M. Añón, Juan B. Araujo, Elena González (Intensive Care Unit, Hospital Virgen de La Luz, Cuenca, Spain); Higinio Martín, Virginia Arnáiz (Intensive Care Unit, Hospital Universitario de Galdakano, Vizcaya, Spain); Juan Pedro Tirapu (Intensive Care Unit, Hospital Clínico de Pamplona, Navarra, Spain); Rollin Roldán (Intensive Care Unit, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru); Julia López (Intensive Care Unit, Hospital Universitario La Paz, Madrid, Spain); Elizabeth Zavala, María José Arguis, Ramón Adalia (Intensive Care Unit, Hospital Clinic, Barcelona, Spain); Vinko Tomicic (Intensive Care Unit, Clínica Alemana de Santiago, Santiago de Chile, Chile); Pilar Marco (Intensive Care Unit, Hospital Universitario Donostia, San Sebastián, Spain); Jesús Villar, Rosa L. Fernández (Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain); Robert M. Kacmarek, Demet Sulemanji (Departments of Respiratory Care and Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA).