

Prospective, Randomized, Multi-Center Trial of
Higher End-expiratory Lung Volume/Lower FiO₂
versus Lower End-expiratory Lung Volume/ Higher
FiO₂ Ventilation in Acute Lung Injury and Acute
Respiratory Distress Syndrome

*Assessment of Low tidal Volume and elevated
End-expiratory volume to Obviate Lung Injury
(ALVEOLI)*

ARDS Clinical Network
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ACTIVE RESEARCH PROTOCOL

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Please note the correction to the following typographical error in the protocol:

Page 34, Section 6: Statistical Considerations

Second paragraph, third sentence currently reads: The trial may be stopped by the DSMB for futility of the Higher ELV/Lower FiO₂ strategy at the first interim analysis if mortality in the Higher ELV/Lower FiO₂ group is **less** than that observed in the Lower ELV/Higher FiO₂ group.

The CORRECT wording should read: The trial may be stopped by the DSMB for futility of the Higher ELV/Lower FiO₂ strategy at the first interim analysis if mortality in the Higher ELV/Lower FiO₂ group is **MORE** than that observed in the Lower ELV/Higher FiO₂ group.

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Part I

Study Summary

- **Title:** Prospective, Randomized, Multi-Center Trial of Higher End-expiratory Lung Volume/Lower FiO₂ versus Lower End-expiratory Lung Volume/Higher FiO₂ Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome.
- **Objectives:** To compare clinical outcomes of patients with acute lung injury and acute respiratory distress syndrome treated with a higher end-expiratory lung volume/lower FiO₂ versus a lower end-expiratory lung volume/higher FiO₂ ventilation strategy.
- **Hypothesis (Ho):** Mortality from ALI/ARDS will be the same in patients treated with a higher end-expiratory lung volume/lower FiO₂ ventilation strategy as in patients treated with a lower end-expiratory lung volume/higher FiO₂ ventilation strategy.
- **Study Design:** Multi-Center, prospective, randomized, controlled clinical trial.
 1. Enrollment: approximately 24 months.
 2. Patients will be treated for 28 days or until they achieve unassisted breathing.
 3. Patients will be followed for 60 days or until discharged home with unassisted breathing.
- **Sample Size/Interim Monitoring:**
 1. The study will accrue a maximum of 750 patients.
 2. Progress of the trial will be reviewed by an independent Data and Safety Monitoring Board to determine if randomization should stop for futility, lack of safety, or proven efficacy. Interim analyses will be conducted after completion of the study procedures in approximately 250 and 500 patients. Stopping for futility or efficacy will be based on formal group sequential stopping boundaries.
- **Inclusion Criteria:** Acute Onset of:

1. $\text{PaO}_2/\text{FiO}_2 \leq 300$ (adjusted for barometric pressure).
2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph.
3. Requirement for positive pressure ventilation through an endotracheal tube.
4. No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure ≤ 18 mmHg.

● **Exclusion Criteria:**

1. Clinicians caring for patient refuse to use Volume Assist/Control ventilation for at least 12 hours.
2. Age < 13 years.
3. Participation in other intervention trials in ALI, ARDS, or sepsis within the previous 30 days.
4. > 36 hours since all inclusion criteria are met.
5. Neuromuscular disease that impairs ability to ventilate without assistance, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis.
6. Pregnancy (negative pregnancy test required for women of child-bearing potential).
7. Increased intracranial pressure, tricyclic antidepressant overdose (if most recent blood level elevated or no blood level available), Hgb SS, Hgb SC, or other conditions where hypercapnia would be contraindicated.
8. Severe chronic respiratory disease.
9. Morbid obesity.
10. Burns $\geq 30\%$ total body surface area.
11. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated $\geq 50\%$.
12. Bone marrow transplant.
13. Lung transplant.
14. Not committed to full support.
15. Severe chronic liver disease (Child-Pugh Score of 10 -15).
16. Vasculitis with diffuse alveolar hemorrhage.

- **Efficacy:** The primary efficacy variable is mortality prior to hospital discharge to 60 days.

Secondary efficacy variables include:

1. Ventilator Free Days, which is the number of days of unassisted breathing after initiating spontaneous breathing to day 28 after randomization (if at least 48 consecutive hours unassisted breathing were achieved). This efficacy measure is related to differences in mortality, morbidity, and cost attributable to differences in time to recovery from respiratory failure or time to death.
2. Percentage of patients who achieve 48 consecutive hours unassisted breathing prior to 28 days.
3. Number of ICU-free days from randomization to day 28.
4. Number of Organ Failure Free Days from randomization to day 28 (renal, hepatic, central nervous system, coagulation, circulation).
5. Number of days meeting commence-weaning criteria from randomization to day 28.
6. Number of days after initially achieving unassisted breathing from randomization to day 28.
7. Incidence of barotrauma (pneumothoraces, pneumatoceles > 2 cm largest diameter, pneumomediastinum).
8. Percentage of patients discharged alive from hospital.
9. Mortality and days of unassisted breathing for patients with pre- randomization $\text{PaO}_2/\text{FiO}_2 \leq 200$.

Part II

Study Description

Large Prospective, Randomized, Multi-Center Trial of Higher End-expiratory Lung Volume/Lower FiO₂ versus Lower End-expiratory Lung Volume/Higher FiO₂ Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome

Protocol for the NIH NHLBI ARDS Network July 20, 1999

1 Background

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) occur when an event such as sepsis or massive aspiration causes inflammation, increased pulmonary vascular permeability, and extravasation of protein-rich fluid into the pulmonary interstitium and alveolar space [1]. The inflammatory process causes inactivation, destruction, and decreased production of surfactant [2],[3]. This leads to increased surface tension at the alveolar air-fluid interface, which causes microatelectasis. Chest radiographs in ALI and ARDS patients are frequently interpreted to demonstrate diffuse disease. However, CT images, histologic sections, and physiologic studies indicate that the disease is patchy [4],[5]. Much of the ALI/ARDS lung is atelectatic or filled with extravascular fluid and is unavailable for ventilation and gas exchange. Other lung regions appear to be normal. Arterio-venous shunt, ventilation-perfusion imbalance, and high dead-space cause severe abnormalities of gas exchange. Management of acute respiratory failure frequently requires positive pressure ventilation to ensure adequate gas exchange. Despite aggressive treatments for the conditions that precipitate ALI/ARDS, many patients die without resolution of the lung injury.

1.1 Use of PEEP and FiO₂ to Support Arterial Oxygenation.

Patients with ALI/ARDS usually receive positive end-expiratory pressure (PEEP) and increased fractions of inspired oxygen (FiO₂) to support arterial oxygenation during mechanical ventilation for acute respiratory failure. However, there are adverse effects of both PEEP and increased FiO₂. Oxygen toxicity from high FiO₂ may cause or worsen acute lung injury [6]-[8]. PEEP allows use of lower FiO₂ and may decrease the risk of oxygen toxicity. However, PEEP may cause circulatory depression from both decreased venous return and increased right ventricular afterload [9]. Moreover, because peak airway pressures and lung volumes increase with increases in PEEP, higher PEEP may increase the risks of barotrauma and stretch-induced lung injury [10]. These risks of PEEP can be modulated by limiting peak inspiratory airway pressures and volumes. However, with both higher PEEP and limited peak airway pressures and volumes, tidal volumes may be very small, leading to severe hypercapnia and acidosis.

1.2 Ventilation-Associated Lung Injury (VALI).

Several studies in animals and humans demonstrated that acute lung injury may be exacerbated or perpetuated by mechanical ventilation [11]-[16]. However, modifications to traditional strategies of mechanical ventilation may attenuate or prevent VALI [11],[16]-[18].

1.2.1 VALI from excessive lung stretch.

When traditional tidal volumes of 10-15 ml/kg are administered to ALI/ARDS patients, the patent air-spaces are distended much more than during normal ventilation. The high airway pressures typically observed in ALI/ARDS patients reflect distention of intrapulmonary air-spaces.

stretching of normal lung tissue causes parenchymal inflammation [13], increased vascular permeability [19], accumulation of lung water [20], alveolar flooding and atelectasis [11],[13], radiographic infiltrates [14], and hypoxemia from right-to-left shunting of blood [14]. These findings are very similar to those observed in ALI and ARDS patients. This suggests

that stretch-induced lung injury may exacerbate or prevent resolution of ALI and ARDS. Many clinicians and investigators have recommended avoiding high peak airway pressures and volumes to reduce stretch-induced lung injury [21]-[23] . This can be achieved by using smaller tidal volumes or lower levels of PEEP. Three recent trials of reduced tidal volume ventilation did not demonstrate improved clinical outcomes [24]-[26] . However, a recently completed larger, multicenter, randomized trial by the NIH NHLBI ARDS Network demonstrated a 20% reduction in mortality with a reduced tidal volume ventilation strategy. This strategy will be used in both arms of the proposed study.

1.2.2 VALI from ventilation with low end-expiratory lung volumes.

Several studies in animals suggest that VALI may occur from injurious mechanical forces in small bronchioles and alveoli that repeatedly snap open and close with each tidal breath or from cyclic application of high stress in the parenchyma at the margins between diseased and normal lung regions [11],[17],[18]. In several animal models of acute lung injury, VALI was attenuated or prevented when PEEP was used during mechanical ventilation. PEEP may protect the lung from VALI by recruiting and maintaining patency of small atelectatic or fluid-filled bronchioles and alveoli [16]-[18], preventing the injurious mechanical forces that occur when these airways repeatedly open during inspiration and collapse during expiration.

It is unclear what level of PEEP is necessary to achieve optimal lung protective effects. Some investigators have recommended construction of static or quasi-static inspiratory pressure-volume curves in ALI/ARDS patients to understand the pressures and volumes at which small bronchioles and alveoli open (Figure 1).

The slope of this curve, dV/dP , is the compliance of the respiratory system (lungs and chest wall). The increasing-slope of the lower portion of the curve represents recruitment (opening) of previously atelectatic or fluid-filled airways. The term “Pflex” is frequently used to indicate the pressure at the mid-point of this portion of the curve. Some investigators have recommended that PEEP should be raised to $P_{flex} + 2 \text{ cmH}_2\text{O}$ in ALI and ARDS patients to achieve and maintain high levels of lung

Figure 1: Respiratory System Pressure-Volume Curve

recruitment, to prevent VALI from ventilation with repeated airway collapse at end-expiration [27]. This recommendation is problematic for several reasons: 1) In many patients, there is no increasing-slope portion of the pressure-volume curve; hence, no P_{flex} can be identified [28]. 2) In many patients, the increasing-slope portion of the curve reflects properties of the chest wall, not the lung [29]. 3) The pressure-volume relationship during tidal ventilation is different from the static or quasi-static inspiratory pressure-volume relationship [28]. 4) Recruitment of small airways continues as airway pressure and volume rise well above P_{flex} + 2 cmH₂O [30]. Higher PEEPs may achieve higher recruitment, but only at the risk of PEEP-induced circulatory depression, increased risk of barotrauma and stretch-induced lung injury, and decreased alveolar ventilation. 5) Refined pressure-volume assessments may eventually identify volumes and pressures with high lung recruitment, but this approach will provide no insight regarding potential adverse effects of PEEP or how to balance the salutary lung protective effects with the adverse effects of PEEP.

The pressure-volume characteristics of the lungs demonstrate hysteresis (at any airway pressure, volume is greater during deflation than during inflation). This is attributed to the differences in opening and closing

pressures of small bronchioles and alveoli: opening pressures are higher than closing pressures [31]-[33]. This behavior is exaggerated in acute lung injury [31]. Thus, many airways in patients with ALI/ARDS may close and remain closed until opened with a relatively high transpulmonary pressure (recruitment maneuver, RM). These airways may then remain open for some time during ventilation at lower transpulmonary pressures. Some workers have recently recommended using RMs in ARDS patients to promote ventilation at higher end-expiratory volumes, to reduce the risk of VALI from ventilating with atelectasis at end-expiration.

A study by Amato et al. [34] showed improved survival in a group of ARDS patients treated with a lung protective strategy that used higher PEEP (Pflex + 2 cmH₂O), recruitment maneuvers, and limited peak inspiratory stretch (tidal volume < 6 ml/kg; peak inspiratory pressure < 40 cmH₂O). In the control group strategy, PEEP was used in a traditional manner to support arterial oxygenation; no recruitment maneuvers were conducted; tidal volumes were 12 ml/kg. This study was small (53 patients), and mortality in the control group (71%) was higher than in recent trials of ALI/ARDS when lung protective ventilation strategies were not used [24]-[26]. Therefore, it is unclear if the lower mortality with the lung protective strategy was due to the method of PEEP adjustment, recruitment maneuvers, limitation of peak inspiratory stretch, or randomization of more high-risk patients to the traditional ventilation strategy.

1.3 Summary: balancing benefits and risks of different strategies

Because of the increasing evidence for lung injury from ventilation with repeated collapse of bronchioles and alveoli at end-expiration, some clinicians and investigators now recommend an approach to mechanical ventilation in which end-expiratory lung volume is maintained at higher levels than have been traditionally targeted. This may be achieved with higher PEEPs than have been commonly used to support arterial oxygenation; and by introducing periodic recruitment maneuvers. With this approach, lower FiO₂s are necessary to support arterial oxygenation but there may be adverse effects on circulation, acid-base balance, and lung stretch. Other clinicians and investigators favor a more traditional

approach that utilizes lower PEEPs and higher FiO_2 s. The two approaches represent different prioritization schemes for several clinical objectives that must be considered in the care of all ALI/ARDS patients:

Higher End-expiratory Lung Volume/Lower FiO_2 (Higher ELV/Lower FiO_2) Prioritization Scheme

- High priority to prevention of VALI from ventilation with repeated airway collapse at end-expiration.
- High priority to prevention of lung injury from oxygen toxicity.
- Lower priority to prevention of VALI from inspiratory stretch.
- Lower priority to maintaining normal arterial PCO_2 and pH.
- Lower priority to prevention of PEEP-induced circulatory depression.

Lower End-expiratory Lung Volume/Higher FiO_2 (Lower ELV/Higher FiO_2) Prioritization Scheme

- High priority to prevention of VALI from inspiratory stretch.
- High priority to maintenance of normal arterial PCO_2 and pH.
- High priority to prevention of PEEP-induced circulatory depression.
- Lower priority to prevention of VALI from ventilation with repeated airway collapse at end-expiration.
- Lower priority to prevention of lung injury from oxygen toxicity.

There is little information from clinical studies to guide clinicians who must balance the risks and benefits of the two approaches to mechanical ventilation. The proposed study will provide useful information to clinicians by comparing important clinical outcomes in ALI/ARDS patients treated with the two different approaches.

Hypothesis (Ho) Mortality from ALI/ARDS will be equivalent with the two ventilation strategies.

2 End-Points

The primary efficacy measure is mortality prior to hospital discharge to day 60 after randomization. Patients alive in hospital at day 60 will be considered to have survived. This efficacy measure has been used to calculate sample size and to develop interim stopping boundaries.

Since survival ALI/ARDS patients may be affected by many other factors that are indirectly or remotely related to mortality, several secondary outcome variables will also be examined. These are chosen to reflect morbidity and cost of medical care:

1) Number of Ventilator Free Days (VFDs): the number of days after initiating unassisted breathing to day 28 after randomization, assuming a patient survives for at least 48 consecutive hours after initiating unassisted breathing. For example, if a patient initiates unassisted breathing on day 16 and survives to day 28, he/she will be assigned a value of 12 VFDs. If a similar patient begins unassisted breathing on day 16 but dies on day 25, he/she will be assigned a value of 9 VFDs. If a patient survives for > 48 consecutive hours of unassisted breathing but requires assisted breathing (for any reason) before day 28, he/she will be assigned only the number of days of unassisted breathing before day 28. Patients who die without initiating unassisted breathing or before 48 consecutive hours of unassisted breathing will be assigned a value of zero VFDs. Patients transferred to another hospital or other health care facility prior to day 28 (intermediate care, nursing home etc.) while still on positive pressure ventilation will be followed to assess this efficacy measure.

VFDs is related to the “days of assisted ventilation”, which would be a simpler measure. However, if there were a trend in one treatment group towards more rapid death on assisted ventilation, the effect of this trend on days of assisted ventilation would be misleading. “Average duration of ventilation in survivors” would avoid this potential problem. However, if there were a trend towards lower mortality in one treatment group with greater days of assisted ventilation in survivors in that group, the measure of days of assisted ventilation in survivors would be misleading. VFDs will be favorably affected by both lower mortality and shorter duration of ventilation in survivors.

- 2 Percentage of patients who achieve 48 consecutive hours of unassisted breathing at 28 days after randomization
- 3 Number of ICU-free days at 28 days after randomization.
- 4 Number of Organ Failure Free days at 28 days after randomization, using previously validated definitions for renal, central nervous, coagulation, circulation, and hepatic organ and system failures [35], [36].
- 5 Number of days between the day of first meeting criteria to commence-weaning and day 28 after randomization.
- 6 Number of days between the day of initially achieving unassisted ventilation and day 28 after enrollment.
- 7 Incidence of barotrauma (pneumothoraces, pneumatoceles > 2 cm largest diameter, pneumomediastinum).
- 8 Percentage of patients discharged alive from hospital. Patients alive in hospital at 60 days will be considered to have been discharged alive.
- 9 Mortality and days of unassisted breathing with pre-randomization $\text{PaO}_2/\text{FiO}_2 \leq 200$.

3 Study Population and Enrollment

3.1 Number/Source/Screening

The trial will accrue a maximum of 750 patients in 2-3 years. Patients with either ALI or ARDS will be recruited from intensive care units in approximately 24 hospitals that comprise the NIH ARDS Network.

Study coordinators at each site will visit each intensive care unit daily to identify potential candidates for enrollment (see inclusion criteria, section 3.2 and exclusion criteria, section 3.3). Permission to approach patients/families will be requested from attending physicians. Demographic and physiologic data from all patients meeting the study inclusion criteria (section 3.2) will be entered on a screening log. The

screening log will include information explaining why patients meeting the inclusion criteria are not enrolled (exclusion criteria, attending physician denial, patient refusal, etc.).

3.2 Inclusion Criteria [37]

Acute Onset of:

1. $\text{PaO}_2/\text{FiO}_2 \leq 300$. If altitude $> 1000\text{m}$, then $(\text{PaO}_2/\text{FiO}_2) (300 \times (\text{B.P.}/760))$.
2. Bilateral infiltrates consistent with pulmonary edema on frontal Chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric.
3. Requirement for positive pressure ventilation through an endotracheal tube.
4. No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure ≤ 18 mmHg.

Criteria 1-3 must all be observed within a 24-hour interval.

“Acute onset” is defined as follows: the duration of the hypoxemia criterion (#1) and the chest radiograph criterion (#2) must be ≤ 28 days at the time of randomization.

3.3 Exclusion Criteria

1. Clinicians caring for patient refuse to use volume Assist/Control ventilation for at least 12 Hours after patient randomization. (This exclusion criterion is intended to avoid randomization of patients who may begin weaning within 12 hours. Other forms of ventilation or gas exchange support, such as pressure control ventilation or ECMO, are not allowed in this study after 12 hours).
2. Age < 13 years.

3. Participation in other intervention trials for ALI, ARDS, or sepsis within the past 30 days.
4. > 36 hours since all inclusion criteria were met (see “Enrollment Time Window”, Section 3.4).
5. Neuromuscular disease that impairs ability to ventilate spontaneously, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and myasthenia gravis.
6. Pregnancy (negative pregnancy test required for women of child-bearing potential required prior to randomization).
7. Elevated intracranial pressure (Appendix A), tricyclic antidepressant overdose (if most recent blood level is elevated or no blood level available), Hgb SS, Hgb SC, or conditions in which hypercapnia would be contraindicated (attending physicians will be advised that hypercapnia may occur).
8. Severe chronic respiratory disease (e.g. COPD, pulmonary fibrosis, morbid obesity, and other chronic diseases of the lung, chest wall or neuromuscular system (Appendix A)).
9. Morbid obesity > 1 kg/cm body weight).
10. . Burns \geq 30% total body surface area.
11. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated \geq 50%.
12. Bone marrow transplant.
13. Lung transplant.
14. Not committed to full support (Exception: A patient will not be excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).
15. Severe chronic liver disease [Child-Pugh Score of 10-15 [38] , Appendix A.
16. Vasculitis with diffuse alveolar hemorrhage.

3.4 Enrollment, Randomization, and Study Initiation Time Window

All patients must be enrolled, randomized, and initial ventilator adjustments made within 36 hours of the time the last inclusion criterion was met. The last inclusion criterion may be met at either the network hospital or a referring hospital. The 36-hour window for randomization will begin at the time of documentation of the last inclusion criterion, regardless of hospital location. Initial ventilator changes must occur within 4 hours of the time of randomization, and must be made within 36 hours of the time that the last inclusion criterion was met.

3.5 Informed Consent

Informed consent will be obtained from each patient or surrogate.

3.6 Randomization

After obtaining a signed and dated informed consent, the data coordinating center will be called and an assignment will be made by computer-generated randomization to either the Higher ELV/Lower FiO₂ or the Lower ELV/Higher FiO₂ study group. Randomization will be in permuted blocks by hospital.

Randomization will be accomplished with Interactive Voice Response technology. Each research coordinator will have a unique Personal Identification Number (PIN). She or he will call the system and provide the PIN. The IVR system will assign either the Higher ELV/Lower FiO₂ or Lower ELV/Higher FiO₂ ventilation strategy and a patient ID number.

3.7 Minorities/Women

Gender and racial patient subsets were considered by the NHLBI in selecting the Network Centers. The demographic profiles of the Centers selected for the Network show that the aggregate ALI/ARDS patient population contains representative proportions of minorities (25%) and

women (39%). (Values from 6702 patients with ALI/ARDS in the ARDSnet 01 Screening Logs from March, 1996 - February, 1999). Recruitment of minorities and women will be monitored by the Network Coordinating Center. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

Randomization will result in approximately equal numbers of patients assigned to the treatment arms within each population subset. It will be possible to make statistical comparisons within these subsets; however, any inferences derived from these analyses will be of low power because of the relatively small number of patients within the subsets. The primary value of such analyses would be for generating additional hypotheses, which is appropriate given the current lack of evidence of gender or race-related interactions with the treatment interventions in the proposed study.

4 Study Procedures

4.1 Ventilator Procedures

4.1.1 Volume Cycled Ventilation

1. Ventilator mode: Volume Cycled Assist Control (all patients)
2. Tidal Volume, Ventilator Rate Setting, and Arterial pH Management.

- (a) Initial Ventilator Tidal Volume and Rate Setting.

Tidal Volume

(In the following procedures, the term “tidal volume” refers to inspired volumes, corrected for volume lost due to gas compression and ventilator conduit expansion.)

Predicted body weights (PBW) will be calculated for all patients([39]):

$$\text{Males: PBW (kg)} = 50 + 2.3 [\text{height (inches)} - 60]$$

$$\text{Females: PBW (kg)} = 45.5 + 2.3 [\text{height (inches)} - 60]$$

Initial tidal volumes in both treatment groups will be 8 ml/kg PBW. This will be reduced by 1ml/kg PBW at intervals of < 2 hours until tidal volume = 6 ml/kg PBW.

Ventilator Rate Setting

Both groups: initial ventilator rate setting will be adjusted to match minute ventilation prior to enrollment, if possible. Maximum rate setting will be 35/min.

(b) **Adjustments to Ventilator Tidal Volume and Rate.**

Goals: Ventilator rate and tidal volume will be adjusted to achieve goals of arterial pH and end-inspiratory plateau pressure, respectively.

Arterial pH Goals

- Goal for all patients: $7.30 \leq \text{pH} \leq 7.45$.
- Arterial pH will be measured when clinically indicated.
- Management of alkalemia and acidemia:
 - i. Alkalemia ($\text{pH} > 7.45$): Decrease ventilator rate, if possible.
 - ii. Mild acidemia ($7.15 \leq \text{pH} < 7.30$):
 - Increase ventilator rate up to maximum of 35 or until $\text{pH} > 7.30$ or $\text{PaCO}_2 < 25$ mm Hg.
 - If ventilator rate = 35 or $\text{PaCO}_2 < 25$, then bicarbonate infusion may be given.
 - iii. Severe acidemia ($\text{pH} < 7.15$):
 - Increase ventilator rate to 35.
 - If ventilator rate = 35 and $\text{pH} < 7.15$ and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until $\text{pH} \geq 7.15$ (under these conditions, the plateau pressure targets described below may be exceeded).

Plateau Pressure Goals

- Goal for all patients: ≤ 30 cmH₂O.

Plateau pressures will be measured at a minimum frequency of q4 hours. Plateau pressures will also be measured and recorded 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients will be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause will be recorded. If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressure will be substituted.

Tidal volumes will be reduced by 1 ml/kg PBW q2-3 hours if necessary to maintain plateau pressures ≤ 30 cm H₂O. (If arterial pH < 7.15 , tidal volume need not be reduced; see section 2(b)iii, management of severe acidemia).

The minimum tidal volume in both groups will be 4 ml/kg PBW.

Changes in the tidal volume, if indicated above, will be made within five minutes.

Tidal volume < 6 ml/kg will be increased if plateau pressure \ll target:

- i. If tidal volume < 6 ml/kg PBW and plateau pressure < 25 cmH₂O, then tidal volume will be increased by 1 ml/kg PBW until plateau pressure > 25 cmH₂O or tidal volume = 6 ml/kg PBW.
- ii. If tidal volume < 8 ml/kg PBW AND P_{plat} < 30 cmH₂O AND airway pressure remains below the PEEP level during inspiration or the ventilator delivers frequent (>3 /minute) double breaths because airway pressure or flow-by falls below trigger threshold at the end of inspiration, then tidal volume will be increased by 1 ml/kg PBW. If these phenomena persist at tidal volume 8 ml/kg PBW or with P_{plat} > 30 cm H₂O, additional sedation or neuromuscular blockade should be considered.

3. Inspiratory flow and I:E ratio.

Inspiratory flow rate will be adjusted to achieve I:E = 1:1 - 1:3. Peak flow and inspiratory waveforms will not be standardized.

4. Oxygenation.

In both treatment groups, target ranges for oxygenation will be:

$$55 \text{ mmHg} \leq \text{PaO}_2 \leq 80 \text{ mmHg}$$

or

$$88\% \leq \text{SpO}_2 \leq 95\%$$

When both PaO₂ and SpO₂ are available simultaneously, the PaO₂ will take precedence.

Oxygenation will be maintained in the target ranges using the following PEEP/FiO₂ combinations:

Lo-PEEP/Hi-FiO₂ Treatment Group FiO₂

FiO ₂	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Hi-PEEP/Lo-FiO₂ Study Group FiO₂

FiO ₂	.30	.30	.30	.30	.30	.40	.40	.50	.50	.50-.80	.80	.90	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

(Levels of PEEP in these FiO₂/PEEP scales represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP.)

- (a) Minimum initial FiO₂/PEEP setting in the Higher ELV/Lower FiO₂ group will be .30/12.
- (b) FiO₂/PEEP setting may not be decreased from its initial level (compatible with the oxygenation goals) in the Higher ELV/Lower FiO₂ group for at least 12 hours after initial protocol ventilator adjustments. Arterial oxygenation may exceed goals during this initial 12hour interval.
- (c) **Recruitment maneuvers (RM)** will be performed in the Higher ELV/Lower FiO₂ group within one hour of the initial FiO₂/PEEP adjustments, once daily (between 0600-1000), after disconnections of the endotracheal tube from the ventilator circuit, and after coughing or agitation that causes (within 5 minutes) a sustained (≥ 10 minutes) decrease in SpO₂ of $\geq 5\%$ or in PaO₂ of ≥ 15 mmHg. No more than 4 recruitment maneuvers will be performed in any 24-hour interval. Each recruitment maneuver will be documented.

RMs will be performed as follows if systolic blood pressure = 100-200 mmHg, heart rate = 70-140, and there were < 4 RMs in the preceding 24 hours:

- (a) If FiO₂ < .90, FiO₂ will be raised to 0.90 for 5 minutes.
- (b) Ventilation mode will be changed to CPAP = most recent PEEP level.

- (c) CPAP will be increased over 10 seconds to 40 cmH₂O (to 45 cmH₂O if measured wt. \geq 150% PBW).
- (d) CPAP will be maintained at 40 (or 45) cmH₂O for 45 seconds.
- (e) The RM will be terminated immediately and CPAP returned to the most recent PEEP level if any of the following signs of distress occur:
 - Systolic blood pressure decreases to 90 mmHg or by > 30 mmHg.
 - Heart rate increases to > 140 /min or by > 20 /min.
 - SpO₂ decreases by 5% and is $< 90\%$
- (f) After 45 Seconds at CPAP = 40 (or 45) cmH₂O, CPAP will be decreased over 5 seconds to the pre-RM level.
- (g) Most recent ventilation settings (Mode, tidal volume, PEEP/FiO₂, etc) will be resumed upon completion or early termination of RM.
- (h) If 2 RMs require early termination within a single 24 hour interval, no additional RMs will be attempted for at least 12 hours.

Arterial oxygenation will be assessed by either SpO₂ or PaO₂ at least every 4 hours. When SpO₂ is used to assess arterial oxygenation, the following measures will be taken if possible to improve accuracy: the SpO₂ sensor will be checked to ensure optimal position, cleanliness, and consistent readings with satisfactory waveforms; no position changes or endobronchial suctioning for at least 10 minutes; no invasive procedures or ventilator changes for at least 30 minutes. SpO₂ will be observed for a minimum of 1 minute, and a representative value will be recorded on the appropriate source-document flowsheet.

If arterial oxygenation is not within the target range, then either FiO₂ or PEEP will be adjusted within 30 minutes. Following these adjustments, oxygenation will be reassessed within 15 minutes and subsequent adjustments made if necessary.

If a patient's PEEP/FiO₂ is not compatible with the PEEP/FiO₂ scale (e.g. immediately after randomization or after urgent changes in FiO₂ or PEEP in response to desaturations, hypotension, etc.), either PEEP or FiO₂ (or both) will be

adjusted at intervals of 5-15 minutes (according to Appendix D) until the PEEP/FiO₂ is compatible with the scale.

In both treatment groups, if PaO₂ < 55 mmHg or SpO₂ < 88% and tidal volume = 4 ml/kg PBW (or the minimum tidal volume necessary for pH control, section 4b above) and plateau pressure ≥ 30 cmH₂O, then FiO₂ will be raised until PaO₂ = 55-80 mmHg or SpO₂ = 88-95% or FiO₂ = 1.0. If PaO₂ < 55 mmHg or SpO₂ < 88% and FiO₂ = 1.0, PEEP will be raised by 2 cmH₂O increments to 24 cmH₂O. In these circumstances, plateau pressure may exceed 30 cmH₂O.

Brief periods (5 minutes) of SpO₂ < 88% or > 95% may be tolerated without making changes in PEEP or FiO₂.

FiO₂ = 1.0 may be used for brief intervals (10 minutes) of transient desaturation or to prevent desaturation during treatments such as tracheo-bronchial suctioning or position changes.

If FiO₂ = 1.0 and PEEP = 24 cmH₂O and PaO₂ < 55 or SpO₂ < 88%, then a PEEP increase trial may be performed as follows:

- (a) Increase PEEP by 2-5 cmH₂O increments to a maximum of 34 cmH₂O or until PaO₂ = 55-80 mmHg or SpO₂ = 88-95%.
- (b) If the PEEP increase trial does not lead to an increase in PaO₂ of ≥ 5 mmHg within 4 hours, PEEP will be set = 24 cmH₂O.

In both study groups, in-line suction catheters will be encouraged to avoid unnecessary disconnections of the ventilator circuit from the endotracheal tube.

In both study groups, endotracheal suctioning will be conducted after changing the ventilator mode to Pressure Support = 15 cmH₂O.

5. Simultaneous changes

Changes in more than one ventilator setting driven by measurements of PO₂, pH, and plateau pressure may be performed simultaneously, if necessary. Arterial blood gases will be obtained after all ventilator changes as clinically indicated.

4.1.2 Weaning

4.1.2.1 Commencement of Weaning

Patients will be assessed for the following criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures may be delayed for up to four hours.

1. 12 hours since initial protocol ventilator changes, if any.
2. $\text{FiO}_2 \leq .40$ in Lower ELV/Higher FiO_2 Group or $\text{PEEP} \leq 10$ cm H_2O in the Higher ELV/Lower FiO_2 Group.
3. Values of both PEEP and $\text{FiO}_2 \leq$ values from previous day (comparing Reference Measurement values, section 5.3).
4. Not receiving neuromuscular blocking agents and without neuromuscular blockade.
5. Patient exhibiting inspiratory efforts. Ventilator rate will be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts if no efforts are evident at baseline ventilator rate.
6. Systolic arterial pressure < 90 mmHg without vasopressor support (≤ 5 $\mu\text{g}/\text{kg}/\text{min}$ dopamine or dobutamine or equivalent low dose of another vasopressor will not be considered a vasopressor).

If criteria 1-5 are met, weaning potential will be assessed during a CPAP trial of ≤ 5 minutes at $\text{CPAP} = 5$ cm H_2O and $\text{FiO}_2 = .50$. If respiratory rate remains $\leq 35/\text{min}$ during the 5-minute CPAP trial, the patient will have met the commencement of weaning criteria and will enter the Pressure Support Wean Procedure (Section 4.1.2.2). If respiratory rate exceeds $35/\text{min}$ during the 5-minute CPAP trial, the patient will resume A/C ventilation at the most recent settings. The patient will be reassessed for weaning the following day at 0600-1000. (If failure to maintain the respiratory rate ≤ 35 during the CPAP trial is attributed primarily to anxiety, then appropriate treatment for anxiety will be given and a second 5-minute CPAP trial initiated within 4 hours).

4.1.2.2 Initial Pressure Support (PS) Setting (for patients with respiratory rate $\leq 35/\text{min}$ during 5-minute CPAP trial).

1. Mode = Pressure Support. Only the following PS levels may be used: 5, 10, 15, and 20 cm H₂O.
2. If respiratory rate ≤ 25 /min during the 5-minute CPAP trial, then PS will be set = 5 cmH₂O.
If respiratory rate = 26-35 during the 5-minute CPAP trial, initial PS will = 20 cmH₂O with adjustments to PS within 5 minutes if necessary to achieve respiratory rate = 26-35.
3. PEEP = 5 cmH₂O.
4. FiO₂ = .50.

4.1.2.3 Assessment for Tolerance

Patients will be assessed for tolerance using the following criteria:

1. Total respiratory rate < 35 (5 min at respiratory rate > 35 may be tolerated).
2. SpO₂ $\geq 88\%$ (< 15 min at $< 88\%$ may be tolerated).
3. No respiratory distress (two or more of the following):
 - (a) Heart rate greater than 120% of the 0600 rate (≤ 5 min at $>120\%$ may be tolerated).
 - (b) Marked use of accessory muscles.
 - (c) Abdominal paradox.
 - (d) Diaphoresis.
 - (e) Marked subjective dyspnea.

If any of goals 1, 2, or 3 are not met on initial set-up to PS, the ventilator mode will be changed back to A/C at most recent A/C settings and the patient will be reassessed the next morning.

4.1.2.4 Subsequent ventilator settings during weaning.

1. Reduce PS level by 5 cm H₂O q1-3 hours. PS will not be decreased below 5 cmH₂O. No decreases in PS will be made after 1900.
2. If PS = 10, 15 or 20 cmH₂O is not tolerated, then return to A/C (patient will remain in previously assigned study group at last A/C settings).
 - (a) At 0600-1000 of the next day, return to last PS level tolerated and continue with step 1.
3. If PS level = 5 cmH₂O is not tolerated, increase PS by 5 cmH₂O to 10 cmH₂O and maintain until the following morning.
 - (a) If a patient on PS=5 or10 must go back to A/C for reasons other than intolerance to weaning (e.g. surgical or other invasive procedures), the weaning sequence will be re-entered with section 4.1.2.1.
4. If PS = 5 cm H₂O is tolerated for two or more hours (using tolerance criteria 1-3 above), assess for ability to sustain unassisted breathing (section 4.1.2.5).

4.1.2.5 Assess for ability to sustain unassisted breathing.

A trial of spontaneous breathing will be initiated on CPAP (5 cm H₂O, T-piece, or tracheostomy mask with FiO₂ ≤ .50. The following criteria will be required to continue with spontaneous breathing:

1. SpO₂ ≥ 90% and/or PaO₂ ≥ 60 mmHg.
2. Spontaneous tidal volume ≥ 4 ml/kg ideal body weight.
3. Respiratory Rate ≤ 35/min.
4. pH ≥ 7.30 if measured.
5. No respiratory distress (2 or more of the following):
 - (a) Heart rate > 120% of the 0600 rate (≤ 5 min at ≥ 120% may be tolerated).
 - (b) Marked use of accessory muscles.

6. Abdominal paradox.
7. Diaphoresis.
8. Marked subjective dyspnea.

If criteria 1-5 are met for > 120 minutes, unassisted breathing will continue (step 4.1.2.6). If any of criteria 1-5 are not met during the 120 minute trial, then PS will resume at 5 cmH₂O and tolerance will be reassessed (step 4.1.2.3).

4.1.2.6 Definition of unassisted breathing.

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP = 5 without PS or IMV assistance.

4.1.3 Completion of ventilator procedures.

Patients will be considered to have completed the study ventilator procedures if any of the following conditions occur:

1. Death.
2. Hospital discharge.
3. Alive 28 days after randomization.

If a patient requires positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures for the group to which the patient was randomized will resume unless the patient was discharged from the hospital or > 28 days elapsed since enrollment.

4.1.4 Premature withdrawal from treatment

Patients will be removed from the protocol if they develop neurologic conditions for which hypercapnia would be contraindicated (Appendix A.#7).

5 Data Collection

5.1 Background Assessments

1. Demographic and Admission Data.
2. Pertinent Medical History and Physical Examination.
3. Height; calculated predicted body weight (PBW).
4. Time on ventilator prior to enrollment.
5. Type of Admission
 - (a) Scheduled surgical
 - (b) Medical
 - (c) Unscheduled surgical
6. Presence of following chronic diseases:
 - (a) Metastatic cancer (proven by surgery, computed tomographic scan, or other documented method).
 - (b) Hematologic malignancy (lymphoma, acute leukemia, or multiple myeloma).
 - (c) AIDS with complications (PCP pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasmosis).

5.2 Baseline Assessments

The following information will be recorded during the four-hour interval that precedes initial protocol ventilator changes (if any). Parameters indicated with "*" will be measured during the four-hour interval. If more

than one value is available during the four-hour interval, the last value will be recorded. For other parameters, most recent values will be recorded. If no values are available during the preceding 24 hours, then values will be measured during the four-hour interval prior to initial ventilator changes (if any).

1. * Vital Signs: heart rate (b/min), systolic and diastolic BP (mmHg), body temperature (°C), total respiratory rate.
2. *Ventilator Parameters: Mode, ventilator rate, tidal volume (inspired), FiO₂, PEEP, plateau pressure (0.5 second pause), ventilator manufacturer and model.
3. Measured body weight (kg).
4. Arterial PO₂, PCO₂, and pH and SpO₂.
5. Urinary output (most recent 24 hour value).
6. Serum electrolytes, BUN, creatinine and glucose.
7. Blood hematocrit, WBC, and platelets.
8. Serum albumin concentration.
9. * Blood for cytokines, mediators, and markers of lung injury. Plasma obtained from two, 10 ml EDTA anticoagulated blood samples will be divided immediately after centrifugation into 12 equal 1 ml aliquots in specified tubes and frozen at -70°C.
10. *Glasgow coma score.
11. Frontal chest radiograph (when available):
 - (a) Radiographic Lung Injury Score ([33], # of quadrants)
 - (b) Presence/absence of barotrauma:
 - i. pneumothoraces (R/L)
 - ii. pneumomediastinum
 - iii. pneumatocèles > 2 cm minimum diameter (R/L)
 - iv. subcutaneous emphysema
12. Administration of the following medications (Y/N):

- (a) Sedatives
- (b) Neuromuscular blocking agents
- (c) Vasopressors (maximum number given simultaneously)
- (d) Corticosteroids (dose ranges)
- (e) Buccal smear for genetic analysis in patients who have consented to genetic testing.

Most recent values for the following additional parameters will be recorded only if they are available from clinically required measurements.

13. Pulmonary artery systolic, diastolic, mean and pulmonary artery occlusion pressures, central venous pressure, and cardiac index.

5.3 Assessments During Enrollment

The following data will provide the basis for assessing protocol compliance and safety as well as between-group differences in several efficacy variables. Data for each of the variables will be recorded on the days shown in the Time-Events schedule (Appendix C) or until death, discharge from intensive care unit, or unassisted ventilation for 48 hours.

Reference Measurements

The following parameters will be measured and recorded between 0600 and 1000 on the days specified in the Time-Events schedule (Appendix C). The following conditions will be ensured prior to measurements: supine position for 15 minutes; no endobronchial suctioning for 10 minutes; no invasive procedures or ventilator changes for 30 minutes. SpO₂ sensors will be checked for optimal position, cleanliness, and consistent readings with satisfactory waveforms, if displayed. SpO₂ values will be observed for 1 minute and a representative value recorded. All vascular pressures will be zero-referenced to the mid-axillary line.

1. If receiving positive pressure ventilation:
 - (a) Ventilator mode
 - (b) Ventilator set inspired tidal volume (if on volume cycled mode)

- (c) Pressure Support level (if on PS for weaning)
 - (d) Total respiratory rate
 - (e) Total minute ventilation
 - (f) PEEP
 - (g) Plateau pressure (if on volume cycled mode)
 - (h) Peak inspiratory pressure (if on volume cycled mode)
2. FiO₂
 3. SpO₂ on current FiO₂
 4. Hemodynamic values
 - (a) Arterial systolic, diastolic and mean pressures
 - (b) Heart Rate (beats/min)

Values for the following variables will be recorded for the dates shown in the Time-Events Schedule. If the measurements are not obtained during the 4-hour reference interval, then the value obtained closest in time to the reference interval on the respective date will be recorded. If more than one value is obtained during the reference interval, then the earliest value during the interval will be recorded.

5. Weight (kg), using same technique for each measurement (bed-scale vs lift vs other)
6. Blood hemoglobin concentration
7. Arterial PO₂, PCO₂, and pH and calculated bicarbonate concentrations
8. Requirements for the following medications (Y/N):
 - (a) Sedatives and tranquilizers
 - (b) Neuromuscular blocking agents
 - (c) Vasopressors (maximum number given simultaneously)
 - (d) Experimental treatments: nitric oxide, fluorocarbons, surfactants, extracorporeal gas exchange (ECMO, ECCO2R, etc.)
9. AP frontal chest radiograph

- (a) Presence/absence of barotrauma (as described for baseline assessments)
 - (b) Radiographic Lung Injury Score ([33], number of quadrants)
10. “Brussels Score” data:
- (a) Worst PaO₂/FiO₂ ratio for the date
 - (b) Worst systolic blood pressure for the date
 - (c) Worst creatinine, bilirubin, and platelet count for the date
 - (d) Use of a vasopressor (Y/N)
 - (e) Glasgow Coma Score
11. Blood for cytokines, mediators, and markers of lung injury.

5.3.1 Ventilator Protocol Monitoring

Ventilator parameters, pH, and SpO₂ will be recorded daily at randomly selected times to assess for accuracy of the ventilator settings relative to the protocol requirements. The following parameters will be recorded:

1. Ventilator mode
2. Tidal volume
3. Respiratory rate (set)
4. Plateau pressure
5. I:E ratio
6. FiO₂
7. PEEP
8. Corresponding pH and SpO₂, when available.

5.4 Endpoint Determinations

1. Vital status at 28 days.
2. Time of initiation of unassisted breathing.
3. Status 48 hours after initiation of unassisted breathing.
4. Date of ICU discharge.
5. Date of hospital discharge.
6. Vital status at 60 days if still in hospital.

6 Statistical Considerations

The primary objective of this trial is to compare mortality prior to hospital discharge in ALI/ARDS patients who receive a Higher ELV/Lower FiO₂ ventilation strategy versus a Lower ELV/Higher FiO₂ strategy. The Lower ELV/Higher FiO₂ strategy is identical to the 6 ml/kg tidal volume strategy used in the recently completed ARDS Network trial. In this previous study, mortality prior to hospital discharge to 60 days after randomization in the 6 ml/kg tidal volume group was 28%. For this study, it is assumed that mortality prior to hospital discharge to day 60 in the Lower ELV/Higher FiO₂ study group will be 28%. This new study will accrue up to 750 subjects and have an 89% chance of finding a significant mortality benefit of the Higher ELV/Lower FiO₂ strategy if the true difference is 10% or greater (from 28% to 18%) using a one-sided 0.025 significance level test (equivalent to a two-sided $p = 0.05$ significance level).

The trial will be monitored by a Data and Safety Monitoring Board (DSMB). Two interim analyses are planned, after 250 and 500 subjects have completed the trial procedures. The trial may be stopped by the DSMB for futility of the Higher ELV/Lower FiO₂ strategy at the first interim analysis if mortality in the Higher ELV/Lower FiO₂ group is less than that observed in the Lower ELV/Higher FiO₂ group. The trial may be stopped at the second interim analysis if mortality in the Higher ELV/Lower FiO₂ group is not at least 2% better. At each interim analysis, overall mortality will be assessed prior to comparison of the group mortality rates. If the overall mortality is such that the futility boundary

would not maintain at least 90% power to detect an absolute 10% difference in mortality, then the futility boundary will be adjusted. If there is no true difference in mortality between study groups, there is a 50% chance that the trial will stop for futility at the first interim analysis and an additional 24% chance of stopping for futility at the second interim analysis.

The DSMB may stop the trial at each of the interim analyses for efficacy of the Higher ELV/Lower FiO₂ strategy. The criteria for stopping the trial for efficacy are based on an O'Brien-Fleming upper boundary with a one-sided $p = 0.025$ level. The boundary will be lowered slightly to counteract the conservatism of the futility boundary. The boundary is $2.0 * \sqrt{3/i}$, where $i = 1, 2, \text{ or } 3$ corresponding to each of the planned analyses.

The sample size consideration is based on the results of the recently completed ARDS Network trial of 6 ml/kg vs 12 ml/kg tidal volume ventilation and also on the study by Amato et al. [31], which this new study attempts to emulate. In our recently completed study, mortality prior to hospital discharge to day 180 after randomization was 31.3% and 39.8% in the 6 ml/kg and 12 ml/kg study groups, respectively. The mortality rates prior to hospital discharge to day 60 were 29% and 38%, respectively. The difference in mortality prior to hospital discharge to day 60 was the same as the difference in mortality prior to hospital discharge to day 180, which suggests that the frequency of late deaths (after day 60) was not affected by ventilation strategy. A reduction in mortality prior to hospital discharge to day 60 from 28% to 18% in this new study represents a 36% reduction. This is similar but slightly less than that found by Amato et al. ([31]), who found a 46% reduction in mortality at 28 days with a Hi-PEEP strategy.

7 Data Collection and Site Monitoring

7.1 Data collection

The research coordinators will enter data on a web-based electronic data capture system. Software is designed with a series of checks to avoid missing or incorrect data.

7.2 Reporting of adverse events

Investigators at each site will determine daily if any clinical adverse experiences occur during the period from when the initial ventilator changes are made to 48 hours after initiating unassisted breathing or day 60, whichever occurs first. The investigator will evaluate any changes in laboratory values and physical signs and will determine if the change is clinically important and different from what is expected in the course of treatment of patients with ALI or ARDS. If clinically important and unexpected adverse experiences occur, they will be recorded on the adverse event case report form.

Investigators will report all serious, unexpected, and study-related adverse events, as defined in Appendix B, to the Clinical Coordinating Center within 24 hours. The local Institutional Review Board will also be informed in a timely manner. The investigator will then submit a detailed written report to the Clinical Coordinating Center no later than 5 days after the investigator discovers the event.

The Clinical Coordinating Center will report all serious, unexpected, and study-related adverse events to the FDA or DSMB within 10 working days and will distribute these reports to investigators for submission to their respective Institutional Review Boards. The DSMB will also review all adverse events during scheduled interval analyses. The Clinical Coordinating Center will distribute the written summary of the DSMB's periodic review of adverse events to investigators for submission to their respective Institutional Review Boards in accordance with NIH Guidelines.

7.3 Site monitoring

Routine site visits will be performed no more than once each year to ensure that all regulatory requirements for the use of investigational agents are being met and to monitor the quality of the data collected. The site visit team will be composed of a research nurse and other members of the Clinical Coordinating Center, a representative of the NHLBI and an investigator from another CCTG. Records of IRB approvals and patient charts will be examined as needed to evaluate the accuracy of the data entered into the database.

8 Risk Assessment

Patients in the Higher ELV/Lower FiO₂ group may experience more hypercapnia. This could cause more dyspnea and agitation, for which they would receive more sedation. Generous sedation (benzodiazepines and narcotics) is given to most critically ill patients because of anxiety and discomfort. There may be additional sedation requirements in the Higher ELV/Lower FiO₂ group. The Higher ELV/Lower FiO₂ study group may also have higher airway pressures, which would indicate higher levels of lung stretch and potential for stretch-induced lung injury. Hypercapnia and respiratory may require more sodium bicarbonate to maintain arterial pH targets. This could cause volume overload or hyponatremia. Fluid balance and serum sodium are assessed frequently in the intensive care units. The potential adverse effects of bicarbonate infusions can be anticipated and avoided, minimized, or counteracted with diuretics and adjustments in fluid management.

Patients in the Lower ELV/Higher FiO₂ group will require higher FiO₂ levels and may be at higher risk of oxygen toxicity. Moreover, they may be at a higher risk of lung injury and inflammatory mediator release from ventilation with atelectasis at end-expiration.

9 Human Subjects

Each study participant or an appropriate surrogate must sign and date an informed consent form. Institutional review board approval will be required before any subject is entered into the study. All study participants or their surrogates will be informed of the objectives of the study and the potential risks. To maintain confidentiality, all laboratory specimens, evaluation forms, and reports will be identified only by a coded number. All records will be kept in a locked, password protected computer. All computer entry and networking programs will require coded numbers. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the FDA, National Heart, Lung, and Blood Institute, and ARDS Clinical Coordinating Center (per 21CFR sec. 50 and 312). Layered informed consent for genetic testing of biological samples will be obtained as outlined in Appendix E.

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10 Appendices

A Exclusion criteria definitions

7. Conditions where hypercapnia-induced elevations in intracranial pressure should be avoided:
 - Intracranial bleeding
 - GCS \leq 8
 - Cerebral contusion
 - Cerebral edema
 - Mass effect (midline shift on CT scan)
 - Papilledema
 - Flat EEG for 48 hours
 - Fixed pupils
 - Absence of responses to deep pain
 - Severe, terminal CNS damage

8. Severe Chronic Respiratory Disease
 - FEV₁ less than 20 ml/kg PBW (e.g. 1.4 L for a 70 kg person), or
 - FEV₁/VC less than 50% predicted, or
 - Chronic hypercarbia (PaCO₂ greater than 45 mmHg) and/or chronic hypoxemia (PaO₂ < 55 mmHg) on FiO₂ = 0.21, or
 - Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration, or
 - Hospitalization within the past six months for respiratory failure (PaCO₂ > 50 mmHg or PaO₂ < 55 mmHg or O₂-Sat < 88% on FiO₂ = .21).
 - Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction, e.g., unable to climb stairs or perform household duties, secondary polycythemia, severe pulmonary hypertension (mean PAP > 40 mmHg), or respirator dependency.

15. Liver Failure: Child-Pugh Class C, which is defined as a total of 10-15 points on the following scoring table [38].

Points	Class
5-6	A
7-9	B
≥ 10	C

Measurement	Numerical score for increasing abnormality		
	1	2	3
Ascites	None	Present	Tense
Encephalopathy	None	Grade I or II	Grade III or IV
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (sec. prolonged)	1-4	4-10	> 10

B Adverse Event Reporting Procedure

1. Procedures for Reporting Adverse Events

Assuring patient safety is an essential component of this protocol.

Each participating investigator has primary responsibility for the safety of the individual participants under his or her care.

All adverse events will be evaluated by the Principal Investigator. The Study Coordinator must view patient records for possible adverse events throughout the study period. All adverse events occurring within the study period must be reported in the participants' case report forms.

The investigator will report all serious, unexpected, and study-related adverse events to the Clinical Coordinating Center within 24 hours. The Institutional Review Board must also be informed in a timely manner. The investigator will then submit a detailed written report to the Clinical Coordinating Center no later than 5 days after the investigator discovers the event.

The Clinical Coordinating Center will report serious, unexpected events to the FDA or DSMB in accordance with FDA guidelines.

2. Definitions of Adverse Events

A serious adverse event is any event that is fatal or immediately life threatening, is permanently disabling, severely incapacitating, or requires or prolongs inpatient hospitalization. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse experiences when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This definition does not include a reaction, which in a more serious form, might have caused death. Assessment of the cause of the event has no bearing on the assessment of the event's severity.

An unexpected adverse event is any experience not identified by type, severity, or frequency in the current study protocol or an

event that is unexpected in the course of treatment for Acute lung Injury or ARDS.

Adverse events will be considered to be study-related if the event follows a reasonable temporal sequence from a study procedure and could readily have been produced by the study procedure.

Organ failures related to ARDS or a patient's underlying condition should not be reported as adverse events since they are systematically captured by the protocol data collection.

C Schedule of Events

D Procedures for PEEP and FiO₂ adjustments when PEEP/FiO₂ is not compatible with protocol.

- If arterial oxygenation is higher than the target range:
Either FiO₂ or PEEP will be decreased (by .10 or 2, respectively), whichever is farther (number of step changes) from the target scale .
If both PEEP and FiO₂ are equidistant from the scale, then:
 - Lower ELV/Higher FiO₂ Study Group: decrease PEEP first
 - Higher ELV/Lower FiO₂ Study Group: decrease FiO₂ first
- If arterial oxygenation is lower than the target range:
Either FiO₂ or PEEP will be increased (by .10 or 2, respectively), whichever is farther (number of step changes) from the target scale.
If both PEEP and FiO₂ are equidistant from the scale, then:
 - Lower ELV/Higher FiO₂ Study Group: increase FiO₂ first
 - Higher ELV/Lower FiO₂ Study Group: increase PEEP first
- If arterial oxygenation is within the target range:
If a single adjustment in either FiO₂ or PEEP would correct the FiO₂/PEEP to the target scale, then a change in either PEEP or FiO₂ will be made, following the study group priority sequence:
 - Lower ELV/Higher FiO₂ Group: decrease PEEP, increase FiO₂, decrease FiO₂, increase PEEP.
 - Higher ELV/Lower FiO₂ Group: increase PEEP, decrease FiO₂, increase FiO₂, decrease PEEP.

If the FiO₂/PEEP cannot be corrected to the target scale with a single adjustment, then FiO₂ will be adjusted by .10 and PEEP will be simultaneously adjusted in the opposite direction by 2 cmH₂O. E.g.: increase FiO₂ by .10 and decrease PEEP by 2 cmH₂O, or decrease FiO₂ by .10 and increase PEEP by 2 cmH₂O.

E Genetic Testing Information

Portions of samples collected, processed, and stored as specified in this protocol may be used for genetic analyses in the future. Genetic analysis will involve, in part, the analysis of genomic DNA and will attempt to link genotypic information to the extensive phenotypic information measured as part of this study. A layered informed consent will be used to obtain the study subjects' consent for genetic testing. Consent for the use of these samples for genetic analysis related to the study of ARDS by the ARDS Network Investigators, consent for future studies not necessarily related to ARDS, or consent for genetic testing in both of these categories will be obtained. The level of an individual's consent for testing (e.g. none, for ARDS studies, for future studies, or all studies) will be recorded in the Case Report Forms and stored in the Clinical Coordinating Center Data Base.

Samples are stored at a central repository per ARDS Network protocol. Samples are identified by their ARDSNet Study Numbers. Approved studies for genetic testing will be sent to the CCC where samples that have the necessary level of informed consent for genetic testing will be identified. The CCC will then instruct the repository to prepare the relevant samples for shipment. The samples will have the ARDSNet Study Numbers removed and will be re-labeled with a new number. The Clinical Coordinating Center will be the only site to keep the database, relating the new sample number to the previous ARDSNet Study number, and this will be kept strictly confidential.

Upon completion of Network activities, the CCC will assign new Study Numbers for all ARDSNet Study subjects. The CCC will then instruct the repository to strip all samples of their ARDSNet identifiers and re-label them with the new study subject numbers. This will prevent investigators from using the ARDS Net Study Numbers to identify individual subjects in the future.

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ALVEOLI

PROTOCOL AMENDMENTS

Changes from the July 20 version of the protocol are in **bold face** type.

Amendment No. 1 Recruitment Maneuver (RM) Procedures

Section 4.1.1.4(c) (page 22 of the July 20, 1999 version of the protocol) is amended as follows:

- (c) **A Recruitment Maneuver (RM) will be performed in the Higher ELV/Lower FiO₂ group between 0600-1000 (reference interval) on days 1 and 3 or on days 2 and 4 after the day of randomization (day 0) if a patient does not meet "Commencement of Weaning" criteria (section 4.1.2). . Odd or even RM days will be assigned by randomization.** Each RM will be documented.

RMs will be performed as follows if systolic pressure = 100-200 mmHg and heart rate = 70-140/min:

- (1) **Initial FiO₂ = pre-RM FiO₂.**
- (2) Ventilation mode will be changed to CPAP = most recent PEEP level.
- (3) CPAP will be increased over ten seconds to **35** cmH₂O (to **40** cmH₂O if measured weight ≥ 150 % PBW).
- (4) CPAP will be maintained at **35** (or **40**) cmH₂O for **30** seconds.
- (5) RM will be terminated immediately and CPAP returned to the most recent PEEP level if any of the following signs of distress occur:
 - Systolic blood pressure decreases to 90 mmHg or by > 30 mmHg.
 - Heart rate increases to > 140/min or by > 20/min.
 - SpO₂ decreases by 5% and is < 88 %.
- (6) After **30** seconds at CPAP = **35** (or **40**) cmH₂O, CPAP will be decreased over five seconds to the pre-RM PEEP level.
- (7) **Most recent ventilator mode and tidal volume will be resumed upon completion or early termination of RM. PEEP and FiO₂ will be adjusted if necessary to maintain arterial oxygenation in the target range.**

- (8) On non-RM days from day 1-4 (e.g. days 2 and 4 in patients assigned to RMs on days 1 and 3), a "Non-RM" time will be assigned between 0600-1000 by the study coordinator. This time will be documented.

Amendment No. 2: Data Collection to assess RM safety and effects on arterial oxygenation and respiratory system compliance.

The following section will be added to the July 20, 1999 version of the protocol:

Section 5.3.2 Recruitment Maneuver Monitoring

The following data will be recorded in all Higher ELV/Lower FiO₂ patients on days 1, 2, 3, and 4 before, during, and after each RM or Sham RM.

1. **PEEP, FiO₂, and SpO₂ at the following times:**
 - a. **Immediately before RM or Sham-RM.**
 - b. **10, 30, and 60 minutes, 2 hours, 4 hours, 6 hours, and 8 hours after each RM or Sham-RM.**
2. **Tidal volume and plateau pressure before and 1, 4, and 8 hours after initiating RM or Sham-RM.**
3. **The highest and lowest SpO₂ in the first ten minutes after initiating RM or Sham-RM.**
4. **Lowest systolic and diastolic blood pressures during the first 10 minutes after initiating RM or Sham-RM.**
5. **Highest and lowest pulse rate during the 10 minutes after initiating RM or Sham-RM.**
6. **Presence of any other dysrhythmia within 10 minutes after initiating RM or Sham-RM.**
7. **Any other adverse event that could be related to a RM during the 24 hours following each RM or Sham-RM.**

After 40 patients have completed the Higher ELV/Lower FiO₂ arm of the trial, RM safety and efficacy data will be reviewed by the ALVEOLI committee, which will offer an opinion regarding continuing or stopping RMs for the remainder of the trial. The DSMB will review the same data and the ALVEOLI committee opinion and will make a recommendation to the ARDS Network regarding continuation of RMs. The decision regarding continuation or stopping will focus primarily on the safety experience. If RMs continue after this review, the frequency of RMs, the RM CPAP level, and the RM duration will be determined by the ALVEOLI committee and DSMB after review of safety and efficacy data.

Amendment No. 3: Endotracheal Suctioning on Pressure Support

The following sentence at the end of section 4.1.1 (page 24 of the July 20, 1999 version of the protocol) will be deleted: “In both study groups, endotracheal suctioning will be conducted after changing the ventilator mode to Pressure Support = 15 cmH₂O.”

Amendment 4: Data Collection - Glasgow Coma Scores

The schedule of events will be modified to require Glasgow Coma Scores on day 0 and the day of hospital discharge. The requirement for GCS on days 4, 7, 14, 21, and 28 will be deleted.

Amendment 5: Exclusion Criteria - Other Trials

The following section will be deleted from the July 20, 1999 version of the protocol:

Section 3.3 Exclusion Criteria, #3

3. Participation in other intervention trials for ALI, ARDS, or sepsis within the past 30 days.

Amendment 6: Exclusion Criteria - Burns

The following section will be deleted from the July 20, 1999 version of the protocol:

Section 3.3 Exclusion Criteria, #10

The following exclusion will be modified:

10. Burns \geq 30% total body surface area

will be changed to:

10. Burns ³ 40% total body surface area.

Amendment 7: Exclusion Criteria Increased ICP

The following section will be modified from the July 20, 1999 version of the protocol.

Section 3.3 Exclusion Criteria, #7 add the word “still”

7. Elevated intracranial pressure (Appendix A), tricyclic antidepressant overdose (if most recent blood level is elevated or no blood level available), Hgb SS, Hgb SC, or conditions in which hypercapnia would **still** be contraindicated (attending physicians will be advised the hypercapnia may occur).

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ALVEOLI

PROTOCOL AMENDMENT
January 25, 2000

Previous 7 amendments were dated October 7, 1999

AMENDMENT 8 (adopted January 13-14, 2000, ARDS Network Steering
Committee Meeting).

Page 25 of the July 20, 1999 (Version 1) Protocol, item #2, is amended to:

2. Lower EELV/Higher FiO₂ Group: FiO₂ ≤ .40.
Higher EELV/Lower FiO₂ Group: If PEEP ≤ 12 cmH₂O, FiO₂/PEEP will
be changed to .40/8 for ≤ 30 minutes. SpO₂ must remain ≥ 88%
during these 30 minutes. If SpO₂ decreases below 88% during these
30 minutes, the previous FiO₂/PEEP setting will be resumed. No
further efforts to wean will occur this day.

Page 25, the paragraph following item 6 is amended to:

"... If respiratory rate exceeds 35/min during the 5-minute CPAP trial, the
patient will resume A/C ventilation. In Higher EELV/Lower FiO₂ patients,
PEEP/FiO₂ will be returned to the Higher EELV/Lower FiO₂ settings that
existed prior to the change to 8/.40. The patient will be reassessed"

Page 27, section 4.1.2.4 (Subsequent ventilator settings during weaning), item 2
is amended to:

"2. If PS = 10, 15, or 20 cmH₂O is not tolerated, then return to A/C at
PEEP/FiO₂ appropriate to Study Group assignment."

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PROTOCOL AMENDMENT (May 15, 2000)

These amendments were adopted by the ARDS Network Steering Committee on May 15, 2000. The first amendment is designed to achieve greater separation between the study groups in mean PEEP levels. The subsequent amendment is designed to allow both study groups to begin to wean at the same level of oxygenation impairment (FiO₂/PEEP requirement).

I. Page 22 of the July 20, 1999 (Version I) Protocol is amended as follows:

1. In the Higher EELV/Lower FiO₂ study group, the following three FiO₂/PEEP combinations are deleted from the low-end of the FiO₂/PEEP scheme: .30/5, .30/8, .30/10.
2. Clause (b), first sentence: "FiO₂/PEEP setting may not be decreased from its initial level ... in the Higher ELV/Lower FiO₂ group for at least 12 hours after initial protocol ventilator adjustments" is amended to read as follows:
 - (b) FiO₂/PEEP setting may not be decreased below .30/14 in the Higher EELV/Lower FiO₂ group (except for possible weaning as described in the subsequent amendment to section 4.1.2.1.2) during the first 48 hours after initial protocol ventilator adjustments. FiO₂/PEEP setting may not be decreased below .30/12 in the Higher EELV/Lower FiO₂ group (except for possible weaning as described in the subsequent amendment to section 4.4.2.1.2) after 48 hours until 28 days elapse from initiation of protocol ventilator procedures.

II. Page 25, Section 4.1.2.1.2 is amended as follows to allow both study groups to begin to wean if arterial oxygenation can be maintained at or above the target range on FiO₂/PEEP of .40/8. This amendment supercedes a previous amendment dated January 14, 2000:

2. Lower EELV/Higher FiO₂ Group: FiO₂/PEEP ≤ .40/8.

Higher EELV/Lower FiO₂ Group:

- From 12-48 hours after initiation of protocol ventilator procedures: If FiO₂ ≤ .30 and PEEP = 14, FiO₂/PEEP will be changed to .40/8. SpO₂ must remain ≥ 88% for 30 minutes at FiO₂/PEEP = .40/8. If SpO₂ falls below 88%, previous FiO₂/PEEP settings will be resumed. (Recruitment Maneuvers will be conducted as defined in Section 4.1.1 after returning to previous FiO₂/PEEP settings if SpO₂ < 88% during the trial at FiO₂/PEEP = .40/8).

- 48 hours-28 days after initiation of protocol ventilator procedures: If FiO₂ ≤ .30 and PEEP = 12, FiO₂/PEEP will be changed to .40/8. SpO₂ must remain ≥ 88% for 30 minutes at FiO₂/PEEP = .40/8. If SpO₂ falls below 88%, previous FiO₂/PEEP settings will be resumed. (Recruitment Maneuvers will be conducted as defined in Section 4.1.1 after returning to previous FiO₂/PEEP settings if SpO₂ < 88% during the trial at FiO₂/PEEP = .40/8).

The following addition in **bold face type** is a clarification of intent of the July 20, 1999 Version I of the protocol

6. ... If respiratory rate exceeds 35/min during the 5-minute CPAP trial, the patient will resume A/C ventilation at the most recent settings. **(In Higher EELV/Lower FiO₂ patients, recruitment maneuvers will be conducted as defined in Section 4.1.1).** The patient will be reassessed

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PROTOCOL AMENDMENT

October 12, 2000

These amendments remove the recruitment maneuvers from the protocol.

I. On pages 22 and 23 of the July 20, 1999 protocol, delete the following sections: 4.1.1.4c on page 22 and sections a-h on pages 22-23

(2) **Recruitment maneuvers** (RM) will be performed in the Higher ELV/Lower FiO₂ group within one hour of the initial FiO₂/PEEP adjustments, once daily (between 0600-1000), after disconnections of the endotracheal tube from the ventilator circuit, and after coughing or agitation that causes (within 5 minutes) a sustained (≥ 10 minutes) decrease in SpO₂ of $\geq 5\%$ or in PaO₂ of ≥ 15 mmHg. No more than 4 recruitment maneuvers will be performed in any 24-hour interval. Each recruitment maneuver will be documented.

RMs will be performed as follows if systolic blood pressure = 100-200 mmHg, heart rate = 70-140, and there were < 4 RMs in the preceding 24 hours:

- (a) If FiO₂ $< .90$, FiO₂ will be raised to 0.90 for 5 minutes.
- (b) Ventilation mode will be changed to CPAP = most recent PEEP level.
- (c) CPAP will be increased over 10 seconds to 40 cmH₂O (to 45 cmH₂O if measured wt. $\geq 150\%$ PBW).
- (d) CPAP will be maintained at 40 (or 45) cmH₂O for 45 seconds.
- (e) The RM will be terminated immediately and CPAP returned to the most recent PEEP level if any of the following signs of distress occur:
 - Systolic blood pressure decreases to 90 mmHg or by > 30 mmHg.
 - Heart rate increases to > 140 /min or by > 20 /min.
 - SpO₂ decreases by 5% and is $< 90\%$
- (f) After 45 Seconds at CPAP = 40 (or 45) cmH₂O, CPAP will be decreased over 5 seconds to the pre-RM level.
- (g) Most recent ventilation settings (Mode, tidal volume, PEEP/FiO₂, etc) will be resumed upon completion or early termination of RM.
- (h) If 2 RMs require early termination within a single 24 hour interval, no additional RMs will be attempted for at least 12 hours.

II. From the May 15, 2000 ALVEOLI Protocol amendments, delete the following sentences.

On the second page, second paragraph with the heading, "Higher EELV/Lower FiO₂ Group";, delete the following sentence which is included in the second and third paragraphs.

(Recruitment Maneuvers will be conducted as defined in Section 4.1.1 after returning to previous FiO₂/PEEP settings if SpO₂ < 88% during the trial at FiO₂/PEEP = .40/8).

In the paragraph which begins with:

6... If respiratory rate exceeds 35/min during the 5-minute CPAP trial...

delete the following phrase:

(In Higher EELV/Lower FiO₂ patients, recruitment maneuvers will be conducted as defined in Section 4.1.1)

III. Delete amendments 1 and 2 from the October 21, 1999 amendments to the July 20, 1999 protocol

.Amendment #1 is Recruitment Maneuver Procedures; Amendment 2 is Data Collection to assess RM safety