Prospective, Randomized, Multi-Center Trial of 12 ml/kg vs. 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARMA)

ARDS Network
ARDSNet Study 01, Version III

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Contents

1 Data Collection

1.1 Background Assessments

1. Demographic and Admission Data.
2. Pertinent Medical History and Physical Examination.
3. Height; calculated ideal body weight (IBW).
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).

1.2 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 (^{o}C) , total respiratory rate.
2. * Ventilator Parameters: Mode, ventilator rate, tidal volume (inspired), FiO_2, PEEP, plateau pressure (0.5 second pause), ventilator manufacturer and model.
3. Body weight (kg).
4. Arterial PO_2, PCO_2, and pH and SpO_2.
5. Urinary output (most recent 24 hour value).
6. Serum electrolytes, BUN, creatinine and glucose.
7. Blood hematocrit/hemoglobin, WBC , and platelets.
8. Serum albumin concentration.
9. * Blood for drug levels, cytokines and mediators. Blood will be drawn sufficient to yield 6 ml of EDTA anticoagulated plasma and divided immediately after centrifugation into 3 equal 2 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. pneumatoceles > 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)

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 capillary wedge pressures, central venous pressure, and cardiac index.

1.3 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 $\geq$ 15 minutes; no endobronchial suctioning for $\geq$ 10 minutes; no invasive procedures or ventilator changes for $\geq$ 30 minutes. SpO_2 sensors will be checked for optimal position, cleanliness, and consistent readings with satisfactory waveforms, if displayed. SpO_2 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. FiO_2

3. SpO_2 on current FiO_2

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 single 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 PO_2, PCO_2, 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, $ECCO_2R$, etc.)

9. AP frontal chest radiograph
   Presence/absence of barotrauma (as described for baseline assessments)
   Radiographic Lung Injury Score ([33], number of quadrants)

10. Brussels Score

    (a) Worst PaO_2/FiO_2 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

1.3.1 Ventilator protocol monitoring

Ventilator parameters, pH, and SpO_2 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. FiO_2
7. PEEP
8. Corresponding pH and SpO_2, when available.

1.4 Endpoint determinations

1. Patient vital status at discharge or 180 days after enrollment.
2. Time of initiation of unassisted breathing.
3. Patient status 48 hours after initiation of unassisted breathing.
4. Date of ICU discharge.
5. Date of hospital discharge.

2 Statistical Considerations

This study is a 2×2 factorial design comparing 6 ml/kg tidal volume to 12 ml/kg tidal volume Volume Assist/Control ventilation and comparing lisofylline injection to placebo. The ventilator and the lisofylline trials will be analyzed separately and one may stop before the other.

There are two primary efficacy measures. The first is *Percentage of patients alive with unassisted breathing at hospital discharge*. Patients still alive in hospital at 180 days will be defined as survivors. For the analysis, survival of the two groups will be compared using a test based on the 180-day Kaplan-Meier estimate. This efficacy measure is used to calculate sample size and to develop interim stopping boundaries. The second efficacy measure, *Number of Days of Unassisted Breathing*, is designed to examine differences in time to recovery from acute respiratory failure, which will reflect morbidity and cost (see Section 3, Study Design). *Number of Days of Unassisted Breathing* will be compared between treatments using a Wilcoxon test.

2.1 Treatment of multiple endpoints

We do not plan to use a bonferroni correction to correct for the fact that there are two efficacy measures because these measures are affected by different effects of treatment. If a treatment does not reduce mortality it may still reduce the duration of mechanical ventilation which would benefit patients financially and decrease their morbidity. This effect is measured

by *Number of Days of Unassisted Breathing*. This is a better efficacy measure than the duration of ventilation for all patients or the duration of ventilation for survivors because, in either case, the duration of ventilation is potentially biased against a treatment that saves the lives of a portion of the patients by increasing the time that they must be ventilated.

2.2 Sample size and early stopping for the ventilator protocol

2.2.1 Sample size

The sample size depends on the magnitude of the difference in mortality that is considered important. The study is designed to detect a difference between 6 ml/kg tidal volume and 12 ml/kg tidal volume of 10%, from 40% to 50%.

2.2.2 Early stopping

There will be four interim analyses and one final analysis at 200, 400, 600, 800, and 1000 patients. The interim analyses will use the sequential design described in DeMets and Ware ([8] pp 661-3.Table 1,
$N = 5, 1 - \beta = .9, \alpha = .025$). With this design we achieve an 87% power to show a 10% difference in mortality rate (From 40% to 50%) at a two-sided significance level. The cumulative probabilities of rejecting a true null hypothesis for this design are
$\alpha_i, i = 1, \ldots, 5 = 3.1 \times 10^{-6}, 7 \times 10^{-4}, .0048, .01335, .025$ at the 5 interim analyses and the z-scores to stop and declare superiority at 200, 400, 600, 800, and 1000 patients are 4.5213296, 3.1970628, 2.6103909, 2.2606648, 2.0220001. The z-scores to stop for futility are -0.7740587, -0.0184263, 0.4168130, 0.7349707, 0.9918935. .1 100 2.277 1.496 2.022".

The analysis plan for mortality is based on the last value of the Kaplan-Meier curve which will always occur on or before 180 days. Patients who leave the hospital alive, off the ventilator are assumed to be alive at 180 days.

The z-score used for each analysis will be calculated using a stratified

analysis where differences between ventilator strategies calculated within each strata are weighted by the inverse of their variance and summed. The strata are defined by concurrent randomized drug treatment.

At each analysis the information available may differ from the amount of information provided by 200, 400, 600, or 800 patients. The *effective sample size* at the ith analysis will be calculated as the sample size that would give the observed variance if all information were available. The stopping z-score will be adjusted if the effective sample size is not equal to 200, 400, 600, or 800 by first finding the cumulative probability of stopping that corresponds to the *effective sample size*. This will be accomplished using linear interpolation (or extrapolation for the first analysis.)

Then the stopping z-value for efficacy at the ith analysis will be found so that the cumulative spending function will equal the cumulative probability of stopping under the null hypothesis. The stopping z-value for futility will be found so that the cumulative probability of stopping under the alternative hypothesis will be preserved in the same manner as for the efficacy stopping rule.

3 Data Collection and Site Monitoring

3.1 Data Collection

Each site will have a lap-top computer. The research coordinator will be responsible for maintaining a data base using a custom designed data base application. Once a week the research coordinator will connect his/her computer to a modem. The coordinating center computer will call the site computers during the evening and download the active database from each site. The software is designed with a series of checks to avoid missing or incorrect data.

3.2 Reporting of Adverse Events

Adverse events shall be reported as described in Appendix B.

3.3 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.

4 Risk Assessment

1. Patients in the 6 ml/kg treatment group will probably experience more hypercapnia and may experience worse shunt ([14]). Therefore, they may require higher FiO_2's to achieve the target PaO_2 or SpO_2, which could lead to some increased risk of oxygen toxicity. Patients in the 12 ml/kg treatment group will have higher airway pressures, consistent with the higher levels of lung stretch and potential for barotrauma.

2. Hypercapnia and respiratory acidosis in the 6 ml/kg tidal volume group may require more sodium bicarbonate to maintain arterial pH targets. This could cause volume overload or hypernatremia. However, 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.

3. 6 ml/kg tidal volume patients may experience more dyspnea, for which they would receive more sedation. Generous sedation (benzodiazepines and narcotics) is given to most critically ill patients because of anxiety and discomfort. Additional sedation requirements in the 6 ml/kg tidal volume group will likely be small.

5 Human Subjects

All protocols will require that all study participants or a member of a patient's family sign and date an informed consent. All protocols will require prior IRB approval before any subject is entered into the study. All study participants or their families will be informed about the objectives of the study and the potential risks. All laboratory specimens, evaluation forms and reports will be identified by a coded number only to maintain patient confidentiality. All records will 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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6 Appendices

A Exclusion criteria definitions

7. Conditions where hypercapnia-induced elevations in intracranial pressure should be avoided:
   - Intracranial bleeding
   - GCS ≤ 8
   - Cerebral contusion
   - Cerebral edema
   - Mass effect (midline shift on CT scan)
   - Papilledema
   - Intracranial pressure monitoring
   - Flat EEG for 48 hours
   - Fixed pupils
   - Absence of responses to deep pain
   - "Severe, terminal CNS damage"
8. Severe Chronic Respiratory Disease
   - FEV_1 less than 20 ml/kg IBW (e.g. 1.4 L for a 70 kg person), or
   - FEV_1/VC less than 50% predicted, or
   - Chronic hypercarbia ($PaCO_2$ greater than 45 mmHg) and/or chronic hypoxemia ($PaO_2 < 55$ mmHg) on $FiO_2 = 0.21$ or
   - Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration, or
   - Hospitalization within the past six months for respiratory failure ($PaCO_2 > 50$ mmHg or $PaO_2 < 55$ mmHg or O_2-Sat $< 88\%$ on $FiO_2 = .21$).
   - 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.

16. Liver Failure: Child-Pugh Class C, which is defined as a total of $\geq$ 10 points on the following scoring table ([37]).

    Use the table to assess severity of abnormalities in each of the five clinical variables. Add the numerical scores.

Points	Class
5-6	A
7-9	B
≥ 10	C

	Numerical score for increasing abnormality		
Measurement	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, unexpected, adverse events throughout the study period. All serious adverse events occurring within the study hospitalization 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 and the Institutional Review Board no later than 5 days after the investigator discovers the event.

2. Definition of Adverse Events

   A **serious** adverse event is any event that is fatal or immediately life-threatening, is permanently disabling, or severely incapacitating or requires or prolongs inpatient hospitalization.

   Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include the reaction that, had it occurred in 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, investigators brochure, or clinical safety updates or an event unexpected in ARDS or more severe or frequent than expected in ARDS.

   Please note that organ failures related to ARDS or the patient's underlying condition should not be reported as adverse events since they are systematically captured by the protocol.

C Schedule of Events

D Oxygenation Goals

- **Arterial oxygenation higher than the target range:**

  FiO_2 or PEEP will be decreased (by .10 or 2.0, respectively), whichever is farther (number of step changes) from the target scale shown in the accompanying table. If both PEEP and FiO_2 are equally distanced from the scale, then PEEP will be decreased.

- **Arterial oxygenation lower than the target range:**

  FiO_2 or PEEP will be increased (by .10 or 2.0, respectively), whichever is farther from the target scale shown in the table. If both PEEP and FiO_2 are equidistant from the scale, then PEEP will be increased first.

- **Arterial oxygenation within the target range:**

  If a single adjustment in either FiO_2 or PEEP would correct the FiO_2/PEEP to the target scale, then FiO_2 will be adjusted.

  If the FiO_2/PEEP cannot be corrected to the target scale with a single adjustment, then FiO_2 will be adjusted by .10 and PEEP will be simultaneously adjusted in the opposite direction by 2.0. E.g.: increase FiO_2 by .10 and decrease PEEP by 2.0, or decrease FiO_2 by .10 and increase PEEP by 2.0.

Oxygenation Goals

E Genetic Testing Information

Portions of the blood or BAL 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.