Use of Electrical Impedance Tomography for Optimization of Positive End-Expiratory Pressure in Acute Respiratory Distress Syndrome

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ABBREVIATIONS

ALI = Acute Lung Injury
ARDS = Acute Respiratory Distress Syndrome
BAL = Bronchoalveloar lavage
BMI = Body Mass Index
BUN = Blood Urea Nitrogen
CHF = Congestive Heart Failure
CPAP = Continuous Positive Airway Pressure
Cst = Static compliance
Cdyn = Dynamic compliance
C20 = change in compliance over the last 20% of inspiration
CT = Computed Tomography
DBP = Diastolic Blood Pressure
DSMB = Data Safety Monitoring Board
ECMO = Extracorporeal Membrane Oxygenation
EIT = Electronic Impedance Tomography
FiO_2 = Fraction of Inspired Oxygen
GCS = Glasgow Coma Scale
IBW = Ideal body weight
ICU = Intensive Care Unit
IL-6 = Interleukin 6
IL-8 = Interleukin 8
INR = International Normalized Ratio
LAR=legally authorized relative
LTAC = Long Term Acute Care facility
mBW = measured body weight
OR = Odds Ratio
P/F = PaO2/FiO2 ratio
$PaCO_2$ = Partial pressure of arterial carbon dioxide
PaO_2 = Partial pressure of arterial oxygen
PAP = Pulmonary Artery Pressure
PB = Barometric Pressure
PBW = Predicted Body Weight
PEEP = Positive End-Expiratory Pressure
PI = Principal investigator
PIN = Personal Identification Number
Pmean = Mean airway pressure
Ppeak= Peak airway pressure
Pplat = Plateau pressure
PS = Pressure Support Ventilation
RASS = Richmond Agitation Severity Score
SBP = Systolic Blood Pressure
S/F = SpO2/FiO2 ratio
SP-D = Surfactant protein D
SpO_2 = Oxygen Saturation
sRAGE = Soluble Form of Receptor for Advanced Glycation End Products
TNFR1 = Tumor necrosis factor receptor 1
VAP = Ventilator-associated Pneumonia
VFD = Ventilator-free Days
VWF = Von Willebrand Factor
WBC = White Blood Cell

DEFINITIONS

Controlled Ventilation: Any mode with a backup rate and which allows clinicians to either set tidal volume to a target or adjust pressures to target a tidal volume. Examples include volume assist control, pressure assist control, pressure regulated volume control.

Study withdrawal: Defined as permanent withdrawal from study before completion of study activities. This does not include those subjects who have completed the protocol procedures or stopped procedures because they have reached unassisted breathing. If a patient or surrogate requests withdrawal from the study the clinician should seek explicit permission to continue data collection.

Invasive Mechanical Ventilation: Assisted ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube

Legal Representative: An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

Study Day: The day of randomization is study day zero. The next day is study day one.

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1 Background

Acute respiratory distress syndrome (ARDS) is a common condition in the intensive care unit [1] which requires invasive mechanical ventilation. Because the administration of mechanical breaths from the ventilator can exacerbate lung injury, patients with ARDS are treated with lung protective ventilation (LPV), which entails providing a low tidal volume in order to maintain a plateau pressure under 30 cm H2O [2]. LPV decreases lung inflammation as a means of improving outcomes [2,3]. In ARDS, the distribution of delivered gas via mechanical ventilation is heterogeneous: there are areas of atelectatic lung which are not ventilated and this accounts for the refractory hypoxemia seen in ARDS.

Efforts to recruit areas of atelectatic lung via the administration of a high positive end-expiratory pressure (PEEP) have been employed in an attempt to further improve the outcome of patients with ARDS; but this has met with mixed results [4,5]. On a breath by breath basis, during mechanical ventilation with ARDS and PEEP some areas of the lung may become over-distended, ostensibly worsening lung injury, a phenomenon called tidal hyperinflation [6]. In addition, patients with ARDS receiving LPV can develop ventilator asynchrony which results in the intermittent development of potentially injurious large tidal volumes [7,8].

In ARDS, there is also heterogeneity between patients: some patients respond to PEEP with recruitment of atelectatic lung regions and improvement in gas exchange while others do not [9]. Ideally, mechanical ventilation in ARDS patients would be individualized such that the right amount of airway pressure is applied to each patient, maximizing recruitment while avoiding potentially harmful over-distension and tidal hyperinflation.

At present, it is unknown how to make the best tradeoff between lung recruitment and over-distension. The best work in this area has been performed utilizing CT scanning, a tool not routinely available to clinicians [9,10]. The work of Chiumello, using CT scanning, has suggested the best tradeoff among four different approaches to mechanical ventilation in ARDS is the PEEP table utilized in the Canadian LOVS trial [10,11].

Electrical impedance tomography (EIT) offers an opportunity to evaluate regional lung ventilation at the patient's bedside [12-14]. Although EIT has been utilized to assess the distribution of lung ventilation in ARDS patients, large clinical trials are lacking. Single-center pilot studies are insufficient to make a determination regarding whether ventilator optimization via EIT improves clinical outcomes. Lung protective ventilation

results in some mitigation of lung inflammation and can be a useful surrogate endpoint in smaller trials [3,15]. Bronchoalveolar lavage specimens obtained from intubated patients with ARDS are studied for biomarkers of lung inflammation which reflect the relative success or failure of different forms of mechanical ventilation to protect the lung from additional injury.

1.1 STUDY RATIONALE

To date, studies of EIT in ARDS patients have only assessed the distribution of ventilation and not whether lung inflammation is decreased. Our research goals are to assess markers of lung inflammation: IL-6, IL-8, TNFR1, sRAGE, SP-D, Angiopoentin-2, and VWF in conjunction with ventilator changes made in ARDS patients correlated with EIT in order to determine whether the optimization of mechanical ventilation may be achieved by this means.

One arm of the protocol will have best PEEP determined by oxygenation response using a PEEP/FiO2 combination table, similar to the one used in the LOVS protocol [11]. A modified version of the LOVS's table (High-PEEP) has been incorporated into the University of Michigan ARDS protocol. EIT findings will be determined but the bedside respiratory therapist will be blinded to the EIT findings during this arm of the protocol. Alternatively, in the second arm of the protocol, EIT will be used to determine the best PEEP – i.e. the PEEP level at which recruitment is maximized and over-distension minimized. Lung inflammatory markers obtained at 6 hours post recruitment via EIT will be compared with markers obtained 6 hours after the time when PEEP had been guided by the High-PEEP table. In addition, following crossover to the opposite group, biomarkers will be obtained after an additional 14 to 18 hours.

2 Objectives

2.1 Primary Objective

- To compare the effect of EIT in patients with moderate to severe and severe ARDS for the optimization of PEEP titration with standard PEEP titration using the High-PEEP table on changes in relevant physiological and biomarker outcomes.

2.2 Secondary Objective

- The BAL fluid will be examined for the presence of monocytes to determine whether mini-BAL is an effective method for collecting this type of specimen for future research.

2.3 Primary Hypothesis

- The use of electrical impedance tomography (EIT) to titrate positive end-expiratory pressure (PEEP) will result in less lung inflammation and better physiologic parameters than use of the High-PEEP table in patients with moderate to severe acute respiratory distress syndrome (ARDS).

3 End Points

- The protocol duration is 24 hours.

3.1 Physiologic Endpoints

- PaO2
- P/F ratio
- Pplat
- Driving pressure
- Cst and Cdyn
- C20/dyn

3.2 Biomarker Endpoints

- IL-6
- IL-8
- sRAGE
- SP-D
- Angiopoetin-2
- VWF

3.3 Monocyte Endpoints

- Monocyte phenotyping for HLA-DR expression
- Single cell confocal Raman microscopy of circulating and lung monocyte/macrophage
- Unbias metagenomic RNA-Seq mRNA quantitation in BAL macrophages

4 Study Population and Enrollment

4.1 Number/Source/Screening

The trial will accrue 20 patients over a 1 to 2 year interval. Patients will be recruited from the emergency departments and the critical care medicine unit (CCMU). The overall strategy is to screen and enroll early, every newly intubated, acutely ill medical patient, using clinically obtained blood gases.

4.2 Inclusion Criteria

1. Age $\geq$ 18 years
2. Endotracheal ventilation for $\leq$ 1 week (168 hours)
3. Presence of all of the following conditions for $\leq$ 72 hours
   i. PaO2/FiO2 < 150 with PEEP $\geq$ 5 cm H2O for $\geq$ 30 min.
   OR, IF ABG NOT AVAILABLE
   SpO2/FiO2 ratio that is equivalent to a PaO2/FiO2 < 150 with PEEP > 8 cm H2O (Appendix G), and a confirmatory SpO2/FiO2 ratio between 1-6 hours after the initial SpO2/FiO2 ratio determination
   ii. respiratory failure not fully explained by cardiac failure or fluid overload

4. Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules for ≤ 1 week (168 hours)
5. All criteria listed in (3) developed within 1 week of a known clinical insult or new or worsening respiratory symptoms

The 72-hour enrollment time window begins when criteria 1-4 are met. Criteria may be met at either the University of Michigan Hospital or a referring hospital.

4.3 Exclusion Criteria

1. Lack of informed consent
2. Known pregnancy
3. ECMO
4. Severe chronic respiratory disease requiring home oxygen therapy or ventilation
5. Calculated BMI of greater than 50
6. Severe chronic liver disease defined as a Child-Pugh score of 12-15
7. Prior bone marrow transplantation or present chemotherapy induced neutropenia
8. Expected duration of mechanical ventilation of < 48 hours
9. Decision to withhold life-sustaining treatment
10. Moribund patient not expected to survive 24 hours
11. Diffuse alveolar hemorrhage from vasculitis
12. Burns > 40% total body surface or burns on the thorax
13. Unwillingness to utilize the ARDS Network 6 ml/kg IBW ventilation protocol
14. Neurologic conditions with risk of intracranial hypertension
15. ARDS criteria met for > 48 hours
16. Contraindications to using EIT (Presence of a pacemaker or AICD, inability to place the belt (presence of surgical wounds dressing, thoracic or spinal cord trauma, recent thoracic surgery, etc), undrained pneumothorax or BPF)
17. Platelet count < 50 K/uL

See Appendix A for specific exclusion criteria definitions.

4.4 Randomization, and Study Initiation Time Window

All patients must be randomized within 72 hours of meeting inclusion criteria. The window for randomization begins at the time of meeting all inclusion criteria, regardless of patient location.

4.5 Informed Consent

Informed consent will be obtained from each patient or legally authorized representative (LAR) prior to enrollment in the trial. No study procedures will be done prior to obtaining informed consent.

Permission to approach patients and/or LARs will be requested from the attending physicians. All patients meeting inclusion criteria will be entered on a screening log. If the patient is not enrolled, the screening log will include information explaining why

enrollment did not occur (e.g., exclusion criteria, attending physician denial, patient refusal).

4.6 Randomization

Randomization assignment will be made via sealed envelopes. Twenty envelopes have been prepared containing the randomization selection – ten stating "EIT first" and ten stating "Usual Care First." These envelopes have been shuffled and stored in a larger envelope. After obtaining a signed and dated informed consent, a sealed envelope will be selected and opened to reveal the randomization assignment.

5 Study Procedures

5.0 Study Design:

Single-center, prospective, 2-arm, unblinded, randomized, cross-over clinical trial.

5.1. Study Initiation

At the time of randomization all study subjects will be receiving the standard University of Michigan ARDS protocol high PEEP arm (Appendix B). All patients will receive lung protective ventilation (LPV), attempting to achieve a plateau pressure (Pplat) $\leq$ 30 cm H2O with tidal volume by ideal body weight being allowed as high as 8 cc/kg and as low as 4 cc/kg in so doing.

Following randomization patients will undergo a mini-BAL according the methodology undertaken by Ranieri and colleagues [16] prior to institution of the protocol arm.

5.1.2 Mini-BAL Procedure

After the administration of sedation, consisting of an increase in the baseline amount of propofol or midazolam already being administered, local anesthesia will be administered by instilling 1-3 cc aliquots of 2% lidocaine via the endotracheal tube port. The use of local anesthesia is optional and will only be administered if deemed necessary by the clinician or RT.

1. FiO2 will be increased to 1.0 ten (10) minutes prior to the start of the procedure.
   - Mini-BAL will not be performed if the P/F ratio is < 100 or the imputed S/F (Appendix G) ratio is less than 89. [17]
   - Mini-BAL will not be performed if the platelet count < 50 K/uL.
2. Sedation with appropriate increases in propofol or midazolam will be made prior to insertion of the catheter.
3. When diffuse infiltrates are seen on chest radiography, the mini-BAL catheter will be directed toward the right middle or lower lobes. When an area of localized pulmonary infiltrate is present the mini-BAL catheter will be directed toward the lower lobe of the opposite lung.
4. A Halyard mini-BAL catheter will be inserted into the endotracheal tube and blindly advanced to the area noted above in #3.

5. Lavage with two aliquots of 40 cc sterile isotonic saline will be performed. Fluid from the first aliquot will be discarded.
6. A third lavage will be performed if less than 30 cc is recovered from the first two aliquots.
7. The procedure will be terminated for a saturation <89% for >1 minute following the administration of any aliquot.
8. The non-discarded BAL fluid will be put on ice and transported to Dr. Standiford's laboratory for cytokine for IL-6, IL-8, TNFR1, sRAGE, SP-D, Angiopoentin-2, and VWF.

5.1.3 Usual Care First Group

1. Following completion of the initial mini-BAL, patients in the Usual Care First group will continue to receive mechanical ventilation according to the University of Michigan ARDS protocol High-PEEP arm (Appendix C). Confirmation will be made to assure compliance with the High-PEEP table.
2. Approximately six hours after randomization a second mini-BAL will be performed (5.1.2 above).
3. Following completion of the second mini-BAL procedure Usual Care First patients will crossover and receive PEEP titration by EIT (see 5.1.5 below) for an additional 14-18 hours at which time a third mini-BAL will be performed. The protocol will end after the third mini-BAL has been performed and the patient will return to mechanical ventilation PEEP titration via the University of Michigan ARDS protocol high PEEP arm. All ventilator management will return to the clinical team.

5.1.4 Electrical Impedance Tomography (EIT) First Group

1. Following completion of the initial mini-BAL, patients in the EIT first group will have best PEEP determined by EIT (see 5.1.5 below).
2. Approximately six hours after randomization a second mini-BAL will be performed (5.1.2 above).
3. Between initial PEEP setting and the 2nd mini-BAL, ventilator management will follow the University of Michigan ARDS protocol, with the exception that PEEP will be left at the EIT determined level and only FiO2 adjusted for oxygenation issues. If FiO2 reaches 1.0, the clinical team will use their discretion to manage PEEP.
4. Following completion of the second mini-BAL procedure EIT first patients will crossover and receive PEEP titration by the University of Michigan ARDS treatment protocol using the high PEEP table for an additional 14-18 hours at which time a third mini-BAL will be performed. The protocol will end after the third mini-BAL has been performed and the patient will continue to be receive mechanical ventilation PEEP titration via the University of Michigan ARDS protocol high PEEP arm. All ventilator management will return to the clinical team.

5.1.5 EIT PEEP Titration

Electrical impedance tomography (EIT) is a non-invasive, non-radioactive, bedside imaging tool. EIT entails the use of a belt like apparatus which is placed circumferentially around a patient's chest. A small, imperceptible current is applied and regional voltages are subsequently measured to determine ventilation related impedance changes across the thoracic cross section created by the belt. Reconstruction algorithms are then utilized to generate real time tomographic images on a breath by breath basis. The Drager Pulmovista 500, which is commercially available in Europe and Canada will be used for the generation of EIT images (Appendix D).

In a review of the recent EIT literature, we found 7 studies [18-22] using the Drager EIT device in adults to either provide feedback on the effects of PEEP or to determine a specific level to set PEEP (see Appendix E). All 7 studies are observational in design, ranging in sample size from 10 to 39 patients. Five were studies of patients with ARDS. The methods used in most of these studies provided a breathing pattern at a modest pressure level (recruitment maneuver) to open the maximum number of lung units for that pressure and then gradually reduced the end-expiratory pressure (decremental PEEP) to observe the patterns of variation in ventilation.

The most common EIT variables used to assess PEEP include:

1. Regional compliance: it is analogous to dynamic compliance, but rather than using a change in tidal volume in the numerator, it uses the tidal impedance variation (TIV). Also, dynamic and static compliance are global measurements, while EIT regional compliance reflects the compliance in each of the four regions of interest (generally dorsal, medial-dorsal, medial-ventral and ventral)
2. EELI (end-expiratory lung impedance): it is analogous to the end-expiratory lung volume or functional residual capacity (FRC)
3. ODCL (overdistension-collapse): this index estimates the percentage and location of lung overdistension and atelectasis (collapse) during a decremental PEEP trial
4. GI (global inhomogeneity) index: this quantifies the ventilation distribution in the lungs and provides information on the degree of homogeneity of lung ventilation
5. COV (center of ventilation): it reflects the distribution of regional ventilation in a dependent-to-non-dependent direction

Patient preparation:

1. The patient should be sedated adequately to suppress respiratory effort.
2. The EIT belt will be placed at the level of the 5^{th} intercostal space. A period of 5-10 minutes will be allowed for electrode stabilization and calibration.

PEEP Titration Procedure:

1. The procedure involves two phases: a recruitment phase followed by a gradual reduction in the end-expiratory pressure phase (Decremental PEEP).

2. Recruitment Phase: Pressure control with a drive pressure of 15 cm H2O and PEEP of 20 cm H2O (ie, 35/20) will be applied for 5-10 breaths and then increased to a PEEP of 25 cm H2O (ie, 40/25) for 1 minute.
3. Decremental PEEP: In volume control, VT will be set to 6 mL/kg PBW and PEEP to 20. Every 5-10 minutes, PEEP will be reduced by 2 cm H2O. PEEP will be reduced until one of the following occurs: 1) drop in EELI in any region during the stabilization period by >10%, 2) PEEP = 5 cm H2O, or 3) patient develops hemodynamic instability or SpO2 <88%.
4. The best EIT-PEEP is identified as that which demonstrates the best compromise in over-distension (OD) and collapse (CL), as determine by the ODCL EIT variable.

5.1.6 Rescue Procedures

If PaO2 ≥ 55 mmHg or SpO2 ≥ 88% with FIO2 of 1.0 cannot be maintained or if acidosis is severe and cannot be controlled, and alternate therapies (rescue procedures) can be employed. Rescue procedures will be chosen according to the University of Michigan ARDS protocol (Appendix C), and may include repeated recruitment maneuvers, prone positioning, neuromuscular blockade, inhaled nitric oxide, inhaled epoprostenol sodium, airway pressure release ventilation, high frequency ventilation, or ECMO.

5.1.7 Other Aspects of Care

All other aspects of care such as fluids, antibiotics etc. will be determined by the clinical team caring for the patient.

6 Data Collection

6.1 Background Assessments

1. Demographic and Admission Data (including age, sex, race)
2. Pertinent Medical History and Physical Examination (including Charlson co-morbidity score)
3. Height; gender; measured Body Weight (mBW); calculated predicted body weight (PBW); body mass index (BMI)
4. Time on ventilator prior to enrollment
5. Risk factors for ARDS (sepsis, aspiration, trauma, pneumonia, drug overdose, other)
6. Ever smoker (>100 cigarettes in lifetime)?
    a. If Yes, current smoker?
    b. If ever smoker, estimate pack years [Pack years = (# packs per day) x (number of years smoked)]
    c. If former smoker, when quit?

6.2 Baseline Assessments

The following information will be recorded during the 24-hour interval preceding randomization. If more than one value is available for this 24-hour period, the value closest to the time of randomization will be recorded. If no values are available from the 24 hours prior to randomization, then values will be measured post randomization but prior to study initiation.

1. History and physical examination
2. Vital signs: heart rate (beats / min), systemic systolic and diastolic BP (mmHg), body temperature (^{0}C)
3. Ventilator mode, rate, minute ventilation, tidal volume, FiO_2, PEEP, Pplat, Ppeak, and Pmean
4. Arterial blood gas (PaO_2, $PaCO_2$, SaO_2, pH) and SpO_2
5. Frontal Chest Radiograph – radiographic lung injury score (# of quadrants)
6. Administration of the following medications (name)
   (a) Sedatives
   (b) Analgesics
   (c) Vasopressors
   (d) Corticosteroids
7. Presumed site of infection, if sepsis is the etiology of ARDS
8. APACHE II score, including the acute physiology components
9. APACHE II demographics plus history of: hypertension, prior myocardial infarction, congestive heart failure, peripheral vascular disease, prior stroke with sequelae, dementia, chronic pulmonary disease, arthritis, peptic ulcer disease
10. SOFA Score: Cardiovascular, renal, respiratory, hepatic, and hematology organ function will be assessed using the SOFA methodology as described in Appendix H.

6.3 Assessments During Study

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 at the times shown in the Time-Events schedule (Appendix F).

It is expected that setting PEEP using EIT will take between 20-40 minutes and 5-10 minutes using the High-PEEP table. To standardize the time from new PEEP exposure until inflammatory mediators are obtained, time 0 is defined as the time at which the PEEP setting is finally established. Hour 6 is subsequently six hours after PEEP is initially established and the time of the 2nd mini-BAL. Time 0 resets at the point of crossover, as the time at which the new PEEP level is established. (see Appendix F)

Safety assessment during the mini-BAL

1. Heart rate, blood pressure and SpO2 will be continuously monitored

Hour 0 of First group (following initial PEEP setting):

1. Ventilator mode, rate, minute ventilation, tidal volume, FiO_2, PEEP, Pplat, Ppeak, Pmean, total-PEEP
2. EIT data
3. Heart rate, systemic systolic and diastolic BP, SpO2

Hour 1 of First group:

1. Arterial blood gas (pH, PaCO2, PaO2, SaO2), if collected for standard of care
2. SpO2

Hour 6 of First group:

1. Immediately before the mini-BAL
    a. Ventilator mode, rate, minute ventilation, tidal volume, FiO_2, PEEP, Pplat, Ppeak, Pmean, total-PEEP
    b. EIT data
    c. Heart rate, systemic systolic and diastolic BP, SpO2
2. Safety assessment during the mini-BAL
    a. Heart rate, blood pressure and SpO2 will be continuously monitored
3. Immediately following the mini-BAL, the patient will crossover to the other PEEP titration method

Hour 0 of Crossover group (following initial PEEP setting):

1. Ventilator mode, rate, minute ventilation, tidal volume, FiO_2, PEEP, Pplat, Ppeak, and Pmean, total-PEEP
2. EIT data
3. Heart rate, systemic systolic and diastolic BP, SpO2

Hour 1 of Crossover group:

1. Arterial blood gas (pH, PaCO2, PaO2, SaO2), if collected for standard of care
2. SpO2

Hour 14 to 18 of Crossover group:

1. Immediately before the mini-BAL
    a. Ventilator mode, rate, minute ventilation, tidal volume, FiO_2, PEEP, Pplat, Ppeak, and Pmean, total-PEEP
    b. EIT data
    c. Heart rate, systemic systolic and diastolic BP, SpO2
2. Safety assessment during the mini-BAL
    a. Heart rate, blood pressure and SpO2 will be continuously monitored
3. Immediately following the mini-BAL, the patient will be placed on standard University study ventilator settings and the study will conclude

7 Statistical Considerations

This study will compare the physiologic and biomarker endpoints from various time points: Usual care first and EIT first groups will be compared with each other at baseline and between groups at 6 hours. The 6-hour crossover point will yield a comparison between groups 14-18 hours later, at the completion of the protocol as well as a comparison between groups from the 6-hour crossover point. Quantitative, normally distributed variables such as cytokine levels and P/F ratio will be tested via t-test. Quantitative, non-normally distributed variables such as driving pressure and plateau will be tested via Mann Whitney test. Categorical variables, such as cause of ARDS will be tested via Chi-square.

8 Data Collection

The research coordinators will collect data and record it either on paper data sheets or in a custom-designed computer database.

9 Risk Assessment

This study involves randomization to usual care or PEEP titration by EIT, and then crossover to the other arm. All patients will receive a high PEEP strategy during the usual care arm of the protocol. In addition, mini-BAL will be performed at three time points during the protocol on each subject.

9.1 Risks of mini-BAL

Study subjects will be assessed before, during and for 15 minutes after the mini-BAL. Potential complications of the Mini-BAL procedure include pneumothorax, bronchial hemorrhage, vagal reflex, bronchial irritation, and transient arterial hypoxemia. Prior to performing mini-BAL the study subject's FiO2 will be increased to 1.0 ten (10) minutes prior to the start of the procedure. Mini-BAL will not be performed if the P/F ratio is < 100 or the imputed S/F ratio is less than 89. Mini-BAL will not be performed if the platelet count < 50 K/uL. During performance of the mini-BAL the procedure will be terminated for a saturation <89% sustained for greater than 1 minute following the administration of any aliquot. The early termination of the mini-BAL, based on the above criteria, will be reported as an adverse event.

9.2 Risks of High PEEP

Historical risks include pneumothorax and hypotension. However, no significant differences in pneumothorax or barotrauma, nor vasopressor use or circulatory and other organ failures were noted in randomized trials save for the ART trial, which used a decremental PEEP approach following an aggressive high pressure, long duration recruitment maneuver. This was felt to be largely accountable to the aggressive recruitment maneuver, which will not be used as part of this protocol.[25] Recruitment maneuvers in both groups (if required in the High-PEEP group during routine management) will be performed in accordance with University of Michigan protocol

(Appendix I). High-PEEP management will also follow our standard University of Michigan guidelines for clinical practice.

9.3 Risk of Death

It is unlikely that one treatment arm may lead to more deaths; mortality will be monitored during the course of the 24-hour study, but is not a clinical outcome of this trial.

9.4 Minimization of Risks

Federal regulations at 45 CFR 46.111(a)(1) require that risks to subjects are minimized by using procedures which are consistent with sound research design. Oxygen saturations and arterial blood gases, if indicated, will be monitored during the mini-BAL procedures. We will use a high PEEP protocol based on those used in multiple large clinical trials, that were shown safe, feasible, and of potential clinical benefit for the intended population or moderate to severe ARDS. The DSMB will be reviewing data as outlined above and will examine not only efficacy but safety (inclusive of mortality) and will reserve the right to halt the study at any time.

9.5 Potential Benefits

Study subjects may or may not receive any direct benefits from their participation in this study. High PEEP has been shown to improve oxygenation in ARDS, to be safe in multiple large trials, and of potential benefit in moderate-severe ARDS. This approach is routinely chosen by most clinicians. Titration of PEEP by EIT, if anything, should be safer than using the customary PEEP table insofar as it provides real time insight into whether lung zones are being over ventilated and manifesting tidal hyperinflation.

9.6 Risks in Relation to Anticipated Benefits

Federal regulations at 45 CFR 46. 111 (a)(2) require that “the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.” Based on the preceding assessment of risks and potential benefits, the risks to subjects are reasonable in relation to anticipated benefits.

Procedures – Mini-BAL can result in transient worsening of hypoxemia. This is usually transient in nature. Mini-BAL will not be performed for a P/F ratio <100 or an S/F ratio <89 and will be terminated for a S/F ratio of <89 for more than one minute. Mini-BAL can result in lung irritation and bleeding. Mini-BAL will not be performed if platelets < 50 K/uL.

Treatments – High PEEP is routinely used in clinical practice. The EIT belt is noninvasive and minimally discomforting to wear. There is potential for benefit to society and individual patients should EIT prove to be result in less lung inflammation and a large clinical trial were to demonstrate clinical benefit.

10 Human Subjects

Each study participant or a legally authorized representative must sign and date an informed consent form. Institutional review board approval will be required before any subject is entered into the study.

10.1 Selection of Subjects

10.1.1 Equitable Selection of Subjects

Federal regulations at 45 CFR 46(a)(3) require the equitable selection of subjects. The Emergency department and Critical Care Medicine Unit will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. No protocol-specific tests nor procedures will be performed as part of the screening process. If any subjects meet criteria for study enrollment, then the attending physician will be asked for permission to approach the patient or his/her LAR for informed consent. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice.

10.1.2 Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of a type of treatment for patients with ARDS. Due to the nature of ARDS and its risk factors (e.g., sepsis, trauma), the vast majority of these patients will have impaired decision-making capabilities. This study cannot be conducted if limited to enrolling only those subjects with retained decision-making capacity. Hence, subjects recruited for this trial are not being unfairly burdened with involvement in this research simply because they are easily available.

10.2 Informed Consent

Federal regulations 45 CFR 46.111(a)(5) require that informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR). As we will enroll critically ill, intubated patients, we anticipate almost all consents will be from the subject's LAR, and thus the remainder of this section will focus on LARs. The investigator is responsible for ensuring that the LAR understands the risks and benefits of participating in the study, and answering any questions the LAR may have throughout the study and sharing any new information in a timely manner that may be relevant to the LAR's willingness to continue the subject's participation in the trial. The consenter will make every effort to minimize coercion. All study participants or their LARs will be informed of the objectives of the study and the potential risks. The informed consent document will be used to explain the risks and benefits of study participation to the LAR in simple terms before the patient is entered into the study, and to document that the LAR is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The investigator is responsible for ensuring that informed consent is given by each LAR. This includes obtaining the

appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures.

10.3 Withdrawal of Consent

Patients may withdraw or be withdrawn (by the patient or LAR) from the trial at any time without prejudice. Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use their data has also been withdrawn.

10.4 Identification of Legally Authorized Representatives

Many of the patients approached for participation in this research protocol will invariably have limitations of decision-making abilities due to their critical illness. Hence, most patients will not be able to provide informed consent. Accordingly, informed consent will be sought from the potential subject's legally authorized representative.

Regarding proxy consent, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a legally authorized representative (LAR) as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." OHRP defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for subject participation in the research.

According to a previous President's Bioethics Committee (National Bioethics Advisory Committee), an investigator should accept as an LAR…a relative or friend of the potential subject who is recognized as an LAR for purposes of clinical decision making under the law of the state where the research takes place (National Bioethics Advisory Commitee (NBAC), 1998). Finally, OHRP has opined in their determination letters that a surrogate could serve as a LAR for research decision making if such an individual is authorized under applicable state law to provide consent for the "procedures" involved in the research study (Office of Human Research Protections (OHRP), 2002).

10.5 Justification of Surrogate Consent

According to the Belmont Report, respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that person with diminished autonomy are entitled to protection. One method that serves to protect subjects is restrictions on the participation of subjects in research that presents greater than minimal risks. Commentators and Research Ethics Commissions have held the view that it is permissible to include incapable subjects in greater than minimal risk research as long as there is the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits ***similar*** to that available in the clinical setting (Dresser, 1999). Several U.S. task forces have deemed it is permissible to include incapable subjects in research. For example, the American

College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment." (American College of Physicians, 1989). Finally, the National Bioethics Advisory Committee (NBAC) stated that an IRB may approve a protocol that presents greater than minimal risk but offers the prospect of direct medical benefits to the subject, provided that…the potential subject's LAR gives permission…" (National Bioethics Advisory Committee (NBAC), 1998)

Consistent with the above ethical sensibilities regarding the participation of decisionally incapable subjects in research and the previous assessment of risks and benefits in the previous section, the present trial presents a balance of risks and potential direct benefits that is ***similar*** to that available in the clinical setting, with the exception of the additional blood draws.

10.6 Additional Safeguards for Vulnerable Subjects

The present research will involve subjects who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that additional safeguards be included to protect the rights and welfare of these subjects. Such safeguards might include, but are not limited to: a) assessment of the potential subject's capacity to provide informed consent, b) requirement for subject's assent, c) the availability of the LAR to monitor the subject's subsequent participation and withdrawal from the study; d) augmented consent processes.

10.7 Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, study related data and reports will identify subjects by a coded number only. Only the study research teams will have access to the codes. All records will be kept in a secure password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained in a locked cabinet inside a locked office. Clinical information will not be released without the written permission of the patient.

11 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. The Investigators will determine daily if any clinical adverse experiences occur during the period from enrollment through the end of the protocol, 24 hours after enrollment.

The following adverse events will be collected in the adverse event case report forms:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study procedures

- Adverse events that lead to permanent discontinuation of the study procedures

A clinical trial adverse event is any untoward medical event associated with the use of a drug or study procedure in humans, whether or not it is considered related to a drug or study procedure.

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

Clinical Outcomes
Routine clinical outcomes of ARDS are exempt from adverse event reporting unless the investigator deems the event to be related to the conduct of study procedures. The following are examples of events that will be considered clinical outcomes:

- Death related to ARDS or a sequela of ARDS based on the interpretation of the investigator.
- Cardiovascular events: the need for vasoactive drugs or fluids for hypotension or hypotension.
- Respiratory events: decreased PaO_2/FiO_2, hypoxia, worsening acute respiratory distress syndrome, or respiratory failure, unless related to performance of the mini-BALs.
- Hepatic events: hepatic injury or liver dysfunction that leads to an increase from baseline in the serum level of bilirubin.
- Renal events: renal failure, renal insufficiency, or renal injury that leads to an increase from baseline in serum creatinine.
- Hematologic/coagulation events: coagulopathy, disseminated intravascular coagulation, thrombocytopenia, or thrombocytosis.
- Systemic inflammatory response syndrome related criteria: tachypnea, tachypnea, leukocytosis, leukopenia, hypothermia, hyperthermia, tachycardia, or bradycardia that does not meet the definition of severe and prolonged.

Note: Arrhythmias such as atrial fibrillation, heart block, ventricular tachycardia or ventricular fibrillation are not considered clinical outcomes and should be recorded as adverse events if they are serious events, are considered by the investigator to be related to study protocol, or lead to discontinuation of the protocol.

Serious Adverse Events
Serious adverse event collection begins after the patient or surrogate has signed informed consent. If a patient experiences a serious adverse event after consent, but prior to protocol initiation, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert the principal investigator or his designee of any **serious and study procedure related** adverse event within 24 hours of investigator awareness of the event.

A serious adverse event is any adverse event that results in one of the following outcomes and is not classified as a clinical outcome of ARDS using the definitions noted above:

- Death that is not related to ARDS or a sequela of ARDS or death that is considered by the investigator to be related to study procedures
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity

Important medical events that may not result in death or be life-threatening may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention.

Data Safety Monitoring Board

This study will use a DSMB to regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations. Three members of the Division of Pulmonary and Critical Care Medicine, Division of Acute Care Surgery and/or Division of Emergency Critical Care who are not involved in this project will independently review this study on a semi-annual basis.

APPENDICES

A. Exclusion Definitions

1. Child-Pugh Score (Pugh, 1973)

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

2. Severe Chronic Respiratory Disease

Any of the following is considered severe chronic respiratory disease and excludes a patient from being eligible for enrollment:

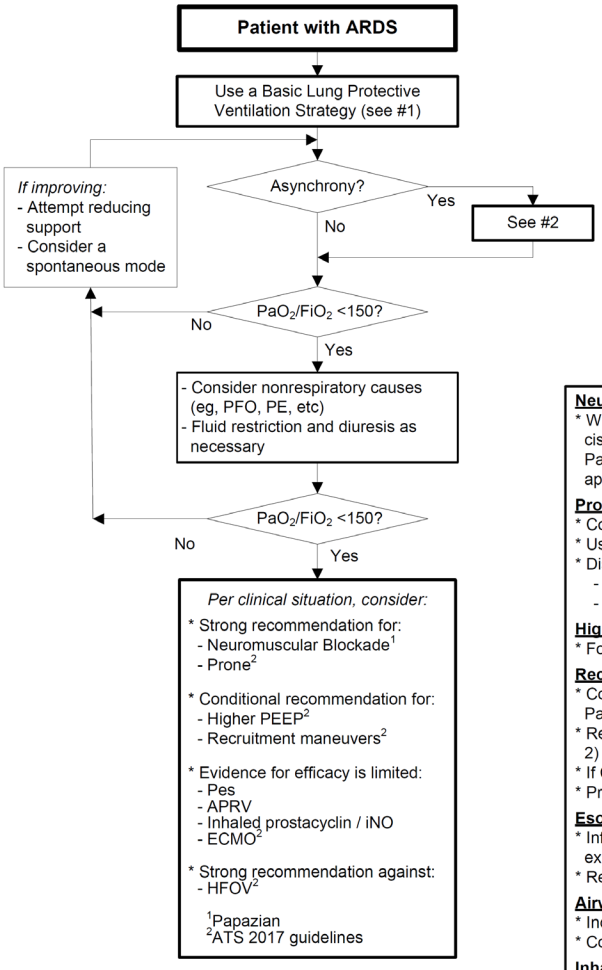
a. FEV_1 less than 20 ml/kg PBW (e.g. 1.4 L for a 70 kg person), or
b. FEV_1/VC less than 50% predicted, or
c. Chronic hypercapnia ($PaCO_2$ greater than 45 mmHg) and/or chronic hypoxemia (PaO_2 less than 55 mmHg) on F_IO_2 = 0.21, or
d. Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration, or
e. Hospitalization within the past six months for respiratory failure in patients with chronic respiratory disease. ($PaCO_2$ greater than 50 mmHg or PaO_2 less than 55 mmHg or O_2-Sat < 88% on FiO_2 = .21).
f. 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 greater than 40 mmHg), or ventilator dependency.

B. Flowchart of Management of EIT Study Groups

C. ARDS Ventilator Management Strategies

Overview of ARDS Ventilator Management Strategies

University Hospital Respiratory Care
Michigan Medicine, Ann Arbor MI



1: Basic Lung Protective Ventilation

- ARDS Network ventilation strategy:
  a. Use VCV or PCV, targeting VT 6 mL/kg PBW
  b. Maintain Pplat ≤30 cm H_2O
     - Reduce VT to 5 or 4 mL/kg if necessary
  c. PEEP/FiO_2 per table (see bottom of page)
- Consider maintaining driving pressure ≤15 cm H_2O
- If consolidation is asymmetrical, consider placing 'good lung' in dependent position

2: Pt-Vent Asynchrony

* Consider minor ventilator adjustments (eg, flow rate & pattern, inspiratory pause)
* Assess potential to treat with pharmacologic agents (eg. sedation, NMB agents), especially in pt with severe ARDS and strong respiratory drive
* For double-triggering, consider increasing VT 1 mL/kg (max 8 mL/kg), provided Pplat ≤30 cm H_2O
* For flow asynchrony, consider a variable flow pressure breath mode of ventilation:
  - Volume targeted PC (PRVC, VC+, Autoflow)
  - Pressure control, pressure support

Neuromuscular Blockade

* When started w/i 36 hrs of diagnosis, short course (~48 hrs) of cisatracurium associated with improved mortality in pts with PaO_2/FiO_2 <150 (Papazian); a shorter period may be appropriate if patient improves quickly; awaiting ROSE results

Prone Positioning

* Consider after initial 12-24 hrs of stabilization
* Use 16 hr/day (generally 4 pm to 10 am)
* Discontinue when:
  - Instability in prone position
  - Supine x 4 hr, PaO_2/FiO_2 >150 on FiO_2 ≤0.60 & PEEP ≤10

Higher PEEP

* For pts with PaO_2/FiO_2 <150, consider higher PEEP table

Recruitment Maneuvers

* Consider for patients with clear de-recruitment, negative Ptp or PaO_2/FiO_2 <150
* Recommend PCV with: 1) 40/20-25 for 1-3 min (as tolerated) or 2) delta-P of 15 and increase PEEP by 5 up to PIP of 40
* If CPAP method used, limit to 15-30 seconds
* Provider should be at bedside if pressures >40 cm H2O used

Esophageal Pressure (Pes) Guided Therapy

* Informs of transpulmonary end-inspiratory (Ptp-plat) and end-expiratory (Ptp-PEEP) pressures
* Requires AVEA ventilator & placement of Pes catheter

Airway Pressure Release Ventilation (APRV)

* Increases Pmean with lower Pplat; lacks outcomes benefit
* Concern for P-SILI in pt with strong respiratory drive

Inhaled Nitric Oxide (iNO)

* Start at 10 ppm
* If positive response (improved oxygenation) or brought in by Survival Flight:
  - Maintain at 10 ppm and reduce FiO_2 down to 0.7, then titrate iNO down, or
  - Consider Veletri or iloprost, per Respiratory Care Policy
* If no response, discuss with team to consider stopping

NOTE: *iNO is a very costly drug compared to alternatives*

Extracorporal Membrane Oxygenation (ECMO)

* Absolute contraindications: irreversible pulmonary process
* Evaluate, but lower survival if on vent 7-10 days pre-ECMO

High Frequency Oscillatory Ventilation (HFOV)

* Strong recommendation against routine use; may have benefit if PaO_2/FiO_2 <64; goal is to increase Pmean

FiO_2/PEEP Tables

Lower PEEP/Higher FiO2 table

Step:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FiO2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20	22	24

Higher PEEP/ Lower FiO2 table (from ROSE study)

Step:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FiO2	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.0
PEEP	5	5	8	10	12	14	16	16	18	20	20	20	20	22	22	22	24

Consider Lower PEEP for patients with low PEEP-responsiveness potential (ie, P/F ≥150); Higher PEEP if higher PEEP-responsiveness potential (P/F <150) or BMI >35

See page 2 for general comments & recommended reading

Updated: 7/11/18

GENERAL COMMENT

Low VT and minimizing Pplat is the only ventilation strategy with a high level of evidence of mortality benefit in ARDS. Therefore, a lung protective ventilation strategy (LPVS) following the ARDS Network strategy (using pressure or volume ventilation) to limit VT (target 6 mL/kg; reduce to 5 or 4 for high Pplat, 7 or 8 for double-triggering) and Pplat (≤30 cm H2O) should be the initial and primary strategy for all ARDS patients.

RECOMMENDED READING

Guidelines or Reviews on ARDS Management:

1. Fan E, et al. Am J Respir Crit Care Med 2017;195:1253-1263 [ATS CPG on mechanical ventilation in ARDS]
2. Fan E, Slutsky AS. JAMA 2018;319:698-710 [Update on ARDS management, contains flow diagram]
3. Narendra DK, et al. Chest 2017;152:867-879 [Update on ARDS management, contains flow diagram]

Setting VT:

* Standard is targeting 6 mL/kg PBW & limit Pplat ≤30 cm H_2O; drive pressure (ie, keep <15) may be more important than VT or Pplat

1. The ARDS Network. NEJM 2004; 342(19):1301-1308 [Pivotal ARDS RCT, 861 pts, reduced mortality with 6 mL/kg IBW & Pplat ≤30, is current standard of care]
2. Amato MBP, et al. NEJM 2015;372:747-755 [Secondary analysis of 9 RCTs showing that drive pressure is strongly associated with survival, VT and Pplat were not]
3. Sahetya SK, et al. Am J Respir Crit Care Med 2017;196:1519-1525 [Review on VT selection in ARDS, includes transpulmonary pressure, drive-P, lung strain, etc]

PEEP

* For most pts the Lower PEEP table should be used. For pts with ARDS & P/F <150 and/or those with high Ppl, the Higher PEEP table should be considered

1. Briel M, et al. JAMA 2010; 303:865-873 [Patient-level meta-analysis; higher PEEP associated with improved mortality in subgroup of patients with PaO_2/FiO_2 <200 (moderate & severe ARDS), suggested harm of high PEEP in mild ARDS (PaO_2/FiO_2 >200]
2. Maiolo G, et al. Am J Respir Crit Care Med 2018;197:1586-1595 [Majority of ARDS is moderate (PaO_2/FiO_2 101-200); using PaO_2/FiO_2 of 150, study suggests that 150-200 is similar to mild ARDS and <150 like severe ARDS. Provides evidence for using higher PEEP, as well as prone and NMBA in those with PaO_2/FiO_2 <150]
3. Chiumello D, et al. Crit Care Med 2014;42:252-264 [Cross-over on 51 ARDS pts of 4 PEEP methods; only High PEEP table (LOV) provided PEEP proportional to degree of lung recruitment (vs Pes/Ptp, stress index, EXPRESS]

Neuromuscular Blockade (NMB)

* Despite all 3 positive NMB trials being from the same group, 48 hrs of cisatracurium is reasonable for ARDS pts with P/F <150, certainly if <120

1. Papazian L, et al. NEJM 2010; 363:1107-1116 [ACURASYS RCT, showed improved survival in group given NMB (cisatricurium) for first 48 hr of management, without increasing muscle weakness]
2. Slutsky AS. NEJM 2010; 363:1176-1180 [Papazian editorial hypothesizing that NMB may reduce VILI by reducing asynchrony]
3. Bourenne J, et al. Ann Transl Med 2017;5:291 [Review of sedation and NMB agents in ARDS]
4. Steingrub JS, et al. Crit Care Med 2014;42:90-96 [Propensity-matched analysis of 1818 septic pts who received NMB; NMB associated with 31.9% mortality vs 38%]

Prone Positioning (PP)

* PP improves respiratory mechanics and hemodynamics which improve both oxygenation and RV function; is associated with lower inflammatory mediator levels.

1. Guerin C, et al. N Engl J Med 2013; 368:2159-2168 [RCT, demonstrated reduced mortality in ARDS patients with PaO_2/FiO_2 <150; PP >16 hrs/d]
2. Beitler JR, et al. Intensive Care Med 2014;40:332-341 [Meta-analysis; suggests that when studies stratified by VT size, PP associated with reduced mortality in low VT studies (≤8 mL/kg PBW by baseline)]
3. Dickenson S, Park PK, Napolitano LM. Crit Care Clin 2011; 27:511-523 [Review; describes UM method of prone positioning]

Esophageal Pressure (Pes) Monitoring

* Pes and transpulmonary pressure (Ptp) monitoring helps set PEEP to a positive end-expiratory Ptp and allows assessment of end-inspiratory Ptp vs absolute Pplat

1. Talmor D, et al. NEJM 2008; 359:2095-2104 [Small RCT, improved oxygenation and compliance in Pes-guided PEEP group; underpowered for mortality]
2. Mauri T, et al. Intensive Care Med 2016;42:1360-1373 [Review covering all important issues on esophageal manometry]

Recruitment Maneuvers (RM)

* Reserved for pts with clear de-recruitment, negative Ptp or P/F <150. A PC RM is better tolerated than CPAP. Use with caution and NOT routinely to all pts.

1. Hess D. Respir Care 2015;60:1688-1704 [Review of recruitment maneuvers and PEEP titration]
2. Goligher EC, et al. Ann Am Thorac Soc 2017;14 (Suppl 4):S304-S311 [Meta-analysis (6 RCT, 1423 pt); RM associated with mortality benefit, improved oxygenation, less use of rescue therapy, no increase in barotrauma or hemodynamic compromise]
3. Cavalcanti B. JAMA 2017;318:1335-1345 [ART open lung (OL) RCT (RM of 60/45, changed to 50/35 after 2 cardiac arrests; decremental PEEP begin at 23); OL associated with higher 28-d mortality (55.3 vs 49.3%), increased pneumothorax requiring drainage and barotrauma, fewer VFD's; no diff in ICU or hospital mortality]
4. Bhattacharjee S, et al. J Intensive Care 2018;6:35 [Meta-analysis that includes recent ART study; concludes no mortality or duration (ICU, hospital) benefit]

Airway Pressure Release Ventilation

* Other than Zhao, over 15 RCTs have NOT shown superiority of APRV vs conventional MV. Concern exists about strong resp drive and P-SILI in severe ARDS.

1. Habashi NM. Crit Care Med 2005; 33(Suppl): S228-S240 [Classic review of APRV describing how to initiate and manage]
2. Zhou Y, et al. Intensive Care Med 2017;43:1648-1659 [RCT (138 ARDS pts); early application of APRV associated with improved oxygenation and respiratory mechanics, decreased Pplat and reduced duration of ventilation and ICU stay; trend toward lower ICU mortality (19.7 vs34.3%, p=0.053)]
3. Jain SV, et al. Intensive Care Med 2016;4:11 [Review of 30-yr evolution of APRV; describes importance of setting T-low to 75% of PEFR]
4. Yoshida T, et al. Am J Respir Crit Care Med 2016:195:985-992 [Review of spont breathing, concern of high respiratory drive & excessive transpulmonary pressure

Inhaled Nitric Oxide and Inhaled Prostacyclin

* iNO improves oxygenation, reduces shunt thru PFO, helps safe transport to UM, no mortality benefit, is associated with AKI, costly (>$2000/d not reimbursed)

1. Puri N, Dellinger RP. Crit Care Clin 2011; 27:561-587 [Review of iNO and inhaled prostacyclin in ARDS]
2. Afshari A, et al. Anesth Analg 2011; 112:1411-1421 [Meta-analysis of iNO; iNO improved oxygenation, no mortality benefit, may cause renal damage]

ECMO

* Rescue therapy for severe hypoxemic RF (ARDS w/ P/F <60 on >80% O2) after medical and MV optimized (incl NMB, PEEP, fluid/HD). Consider early consult.

1. Peek GJ, et al. Lancet 2009; 374:1351-1361 [CESAR RCT, suggests transfer to ECMO center for care is associated with improved outcome]
2. Park PK, Napolitano LM, Bartlett RH. Crit Care Clin 2011; 27:627-646 [Review of ECMO in ARDS]
3. Combes A, et al. NEJM 2018; 378:1965-1975 [EOLIA RCT; inclusion: P/F <50 x3 hrs, or <80 x6 hrs, or pH <7.25 w/ $PaCO_2$ >60 x6 hrs; lower trend in 60-d mortality w/ECMO (35 vs 46% (RR 0.76; 95% CI 0.55 to 1.04, p=0.09)), crossover to ECMO in 28% of control, had higher mortality (57%)]

HFOV

* Harmful in mild and moderate ARDS; may be beneficial in very severe (P/F<64) ARDS

1. Ferguson ND, et al. N Engl J Med 2013; 368(9):795-805 [OSCILLATE RCT of 548 severe ARDS pts; mortality for HFOV=47%, control=35%]
2. Young D, et al. N Engl J Med 2013; 368(9):806-813 [OSCAR RCT of 795 severe ARDS patients; no mortality difference (41.7 vs 41.1%)]
3. Meade MO, et al. Am J Respir Crit Care Med 2017;196:727-733 [Patient-level meta-analysis (4 RCT, 1552 pt); HFOV increases mortality for most ARDS patients, may improve survival in patients with severe hypoxemia (ie PaO_2/FiO_2 <64); barotrauma higher with HFOV]

Updated 7/11/18

E. EIT Studies

Adult Studies using Dräger Pulmovista EIT to assess PEEP

(as of 7/31/18)

Author, Year	Design	Patients	EIT best PEEP	Other PEEP method(s)	Protocol	EIT Measures	Outcome
Heines, 2018	Observ-ational; describe clinical practice	ARDS (n=39)	Best compromise in OD vs CL (Costa)	Physician preference	- PCV constant IP; - (RM) Incremental PEEP (to 18-20) - Decremental PEEP by 2 cmH2O steps; stop when loss in EELI (derecruitment), RM, decr until EELI loss in dependent area - Do offline analysis	EELI, offline analysis: ODCL-like,	- EIT acquisition feasible in all pts; no complications with trials, - set vs EIT PEEP same (11.7 vs 11.3), but variable individual agreement - 28% of pts was a diff by ≥4 cm (cln relevant), 38% same - after set to EIT PEEP increased C and P/F (in both <4 and those ≥4, so RM?)
Karsten, 2017	Observ-ational	Mild to Moderate ARDS (n=15)	Used both ODCL and COV index (i.e., 2 Best EIT)	Cdyn (lowest PEEP associated with highest C)	- VC w/ 7 ml/kg IBW - (RM) Incremental PEEP, starting at 0 to 15 in 5 mbar steps Q4 min, if PIP=40 not reached PEEP increased to 20 and 25. - Decremental PEEP in 2 mbar steps from 15 to 5 Q4 min.	ODCL, COV index	- Best PEEP by COV resulted in lower PEEP than Best PEEP compliance, - Best PEEP per ODCL was higher than based on compliance. - The best compliance did not correspond to PEEP with least overdistension and collapse. (Mean PEEP: $BestPEEP_{COV}$ < $BestPEEP_{compl}$ <$BestPEEP_{ODCL}$)
Franchineau, 2017	Observ-ational	Severe ARDS on ECMO (n=15)	Best compromise betw CL and OD; CL of ≤15% with lowest % OD	N/A	- PC w/ delta-P=14, PEEP 20 (34/20) x20 min - Decremental PEEP from 20 to 0 (if tol), by 5 Q20 min; (no RM pretrial)	ODCL; EELI, delta-impedance	- EIT PEEP was 15, 10 and 5, in 7, 6 and 2 pts respectively; 20 and 0 never selected - High PEEP associated with more OD (50% in some) and lower CL lower PEEP associated with CL (>70% in some) - Wide variability of CL and OD among the 5 PEEP levels suggests need for EIT - tidal vol distribution w/decr PEEP trial decreases in medial-dorsal and dorsal and increases in medial ventral and ventral
Eronia, 2017	Observ-ational	ARDS (N=16)	delta EELI (variation)	Lower PEEP table	- Baseline x 20 min: ARDSNet protocol (VC, 6, <30, lower PEEP table, f to pH7.3-7.45, etc.) - RM 40x40, if Delta EELI change >10%, RM 40x40, increase PEEP 2 measure delta EELI again (max PEEP=18) - Also measurements at EIT-PEEP +2	- Regional compliance (Vt%/100*compliance), - Alveolar hyperdistension and collapse, - Amount of recruited volume	- 14 of 16 could get good data; mean 48 min to complete study - EIT-PEEP higher than table-PEEP (13 vs 9) - P/F increased and drive-pressure reduced with EIT-PEEP - calculated that EXPRESS PEEP would be 20.6 vs EIT_PEEP (13.1) - Regional alv OD and CL reduced in dependent and increased in non-dependent
Long, 2015	Observ-ational	ARDS (n=18)	Level to prevent sign CL w/o obvious OD	Baseline PEEP/FiO2 method not specific, just to SpO2 >90%	- Baseline (VC w/6 mL/kg (5 or 4 for Pplat), Pplat≤30, PEEP/FiO2 for SpO2 >90%) x10-15 min - ZEEP: PEEP=0, FiO2=1.0, x3-5 min - RM: PEEP to 15 x2 min, if Pplat<40, to 20 x2 min - Decremental: 20 to 5 by 3 Q5-10 min - 2 groups based on RM PaO2+PaCO2 on 100%: Responders(R) >400 vs Non-responders (NR) <400	- % recruited pixels - % OD pixels - GI-TV and GI-FRC	- 18 pts, 10 male, 12 w/pneumonia, - 13 responders (pneumonia in 35 (R) vs 80% (NR), p=0.062) - No diff in ZEEP P/F; PEEP-15: P/F 302 vs 104; PEEP-20: 369 vs 121 - In R: PEEP mainly increased recruitment in dependent and OD in nondependent. PEEP alleviated global inhomogeneity of VT and EELV. - PEEP levels w/o significant CL and OD were identified individually
Blankman, 2014	Observ-ational	Post cardiac surgery (n=12)	PEEP with minimal lung collapse & minimal OD	- Cdyn - P/F	- Ventilated on PC with constant delta-P, I:E, f, FiO2 throughout study - RM: delta-P=20 while PEEP increased from 5 to 20, by 5 so that 40/20, held for 40 sec - Decremental: delta-P=10 and PEEP=15 x15 min, then drop by 5 to 0 Q10-20 min	- TIV - VSA - COV - GI index - Regional compliance - ITV index (new)	- Cdyn and P/F had highest value at 10 and 15 PEEP - Max values for TIV, regional C and VSA in nonresponders was 5, in responders was 15 - GI index lowest at 10, while COV and RVD index was 15 PEEP - Concluded ITV index was comparable to Cdyn to indicate "best PEEP"
Zhao, 2010	Observ-ational	Periop (n=10)	Lowest GI index	- Cdyn (least sq.); - Intra-tidal compliance-volume curve	- VC (10 mL/kg), f-12, 1:1.5, 100% - Incremental PEEP, 0 to 28 by 2, each for 10 breaths	GI index	- PEEP values for 3 methods: EIT-GI: 12.2; Cdyn:11.4; compliance-volume: 12.2 - Feasible and reasonable to use GI index to select PEEP with respect to ventilation homogeneity

F. Time-Event Schedule

Clock example	Study hour	Procedures	Vent data	EIT data	HR/ BP	SpO2	ABG	Cytokines	Comments
closest	BL, pre	**BL Assess**	**X**		**X**	**X**	**X**		
8:00		**BAL#1**			**X**	**X**		**X**	BAL procedure time ~30 min
8:30	0	**Set PEEP #1**	**X**	**X**	**X**	**X**			Set EIT ~20-40 min vs table ~5-10 min
9:30	1					X	**X**		ABG 1 H after setting PEEP
10:30	2								
11:30	3								
12:30	4								
13:30	5								
	pre BAL	**Assessment**	**X**	**X**	**X**	**X**	**X**		
14:30	6	**BAL #2**			**X**	**X**		**X**	BAL procedure time ~30 min
15:00	0	**Set PEEP #2**	**X**	**X**	**X**	**X**			
16:00	1					X	**X**		ABG 1 H after setting PEEP
17:00	2								
18:00	3								
19:00	4								
20:00	5								
21:00	6								
22:00	7								
23:00	8								
0:00	9								
1:00	10								
2:00	11								
3:00	12								
4:00	13								
5:00	14								BAL #3, anytime between hr 14-18
6:00	15								
7:00	16								
8:00	17								
9:00	pre-BAL	**Assessment**	**X**	**X**	**X**	**X**	**X**		
9:00	18	**BAL #3**			**X**	**X**		**X**	BAL procedure time ~30 min

Data Collected:	
Ventilator:	mode, set VT, RRset, RRtot, VE, FiO2, PEEP, Ppeak, Pplat, Pmean, PEEPtot,
vent calcs:	drive-P, Cst, Cdyn,
EIT:	delta-EELI, ODCL; COV, GI Index, Regional compliance
ABG:	pH, PaCO2, PaO2, SaO2, BE, HCO3 (if collected for standard of care)
Cytokines:	per protocol

Definition of Time: **Time 0** is when PEEP is established
Time 6 is 6 hours after PEEP is set
Reset time frames at cross-over

G. Imputed PaO_2/FiO_2

SPO2	FiO2														
	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

The table is used when an ABG is not available to calculate the PaO_2/FiO_2. Instead, the SpO_2 and FiO_2 are used to impute what the PaO_2/FiO_2 might be. The following conditions must be met:

1. SpO_2 between 80-96%
2. SpO_2 should be measured at least 10 minutes after any FiO_2 change
3. PEEP must be $\geq$8 cm H_2O
4. An adequate pulse oximetry waveform tracing is present

H. **SOFA Scoring System**

SOFA Score	0	1	2	3	4
Respiration[A] PaO_2/FiO_2 (mmHg) or imputed P/F using SaO_2/FiO_2	>400	<400	<300	<200	<100
Coagulation Platelets $10_3/mm_3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular[B] Hypotension	No hypotension	MAP<70	Dopamine </= 5 or dobutamine (any)	Dopamine >5 or norepineprine </= 0.1	Dopamine >15 or norepinephrine >0.1
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

A: Values for scores 3 and 4 are with respiratory support

B: Adrenergic agents administered for at least one hour (doses given in mcg/kg/min)

I. Recruitment Maneuver Policy (on file)

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