
INTERVENTION-SPECIFIC APPENDIX

Positive End-Expiratory Pressure (PEEP) Titration by Electrical Impedance Tomography (EIT)

Current phase of evaluation for this intervention: pilot/feasibility phase

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BACKGROUND AND RATIONALE

The optimal titration of positive end-expiratory pressure (PEEP) among patients with Acute Respiratory Distress Syndrome (ARDS) undergoing invasive mechanical ventilation remains to be determined, with current guidelines either making a conditional recommendation in favor of a high PEEP approach (1) or no recommendation. (2) Current approaches include high (3) and low PEEP (4) tables, best respiratory system compliance (5) and, more experimentally, driving pressure (6) or transpulmonary pressure. (7) Open lung ventilation using high PEEP levels may be detrimental (8) via volutrauma from overdistension, meanwhile completely avoiding any element of overdistension can be harmful by worsening atelectrauma, a repetitive opening and closing of lung units. (9) Ultimately, some tradeoff between lung overdistension and atelectrauma is required to best mitigate ventilator induces lung injury. (10)

Electrical impedance tomography (EIT) is a non-invasive means to assess and monitor gas distribution in patients' lungs. The overdistension collapse intercept (ODCL) determined by EIT represents the PEEP setting where there is an optimal tradeoff between avoiding overdistension while minimizing lung collapse. PEEP titration via the ODCL has been proposed as a potentially superior way to individualize PEEP in ARDS patients (11). Randomized trials are limited, although meta-analysis of available data suggest driving pressure and mechanical power are decreased when PEEP is titrated by the ODCL (12). This is significant as elevations in mechanical power and driving pressure are associated with increased mortality in patients with ARDS. (13) When considered overall, titration of PEEP by EIT does not result in a different PEEP level compared to usual care approaches such as high or low PEEP tables (11).

However, on a case-by-case basis PEEP titration by EIT may result in changing PEEP to either higher or lower levels than determined by PEEP tables (14,15), affording an opportunity for personalized medicine in this setting. PEEP titration by determining the lowest driving pressure is currently under study (<https://practicalplatform.org/domains/imvs>). PEEP titration by EIT may offer an approach superior to driving pressure as the optimal PEEP determined by EIT via the ODCL is frequently at variance with that determined by the lowest driving pressure, with 81% of patients in a series of 108 patients having either increases (n=25) or decreases (n=62) in PEEP following PEEP titration by that means. (16)

Pilot phase clinical trials are important in determining whether performing a large, definitive phase III clinical trial is warranted. EIT affords a unique opportunity to personalize PEEP titration in ARDS patients in a fashion potentially offering the best tradeoff between lung overdistension and collapse.

Relevant Preliminary Studies: We performed a randomized cross over trial which compared PEEP titration via the ODCL versus that obtained using a standard high PEEP table. (17) When

compared with PEEP titration via the high PEEP table PEEP titration via the ODCL intercept determined by EIT resulted in decreased mechanical power, peak airway pressure, plateau airway pressure and driving pressure, and in a decreased static respiratory system compliance. Our study was included in the meta-analysis cited above (12) which also demonstrated reductions in mechanical power and driving pressure in EIT patients when compared to PEEP titration by other means. Hence, by reducing mechanical power and driving pressure, PEEP titration via EIT has the potential to ameliorate lung injury, the endpoint being studied in this pilot trial.

In summary, as earlier work has indicated, PEEP titration using the ODCL determined by EIT decreases mechanical power and thereby could partially mitigate ventilator-induced lung injury, as reflected in a lower mLIS. The proposed study will be the first to prospectively explore the utility of EIT in management of ARDS patients and serve as an indication whether a subsequent, definitive phase III trial should be performed.

SAMPLE SIZE, SITES, AND DURATION

This intervention will be a randomization option for up to 8 centers participating in this domain with access to an EIT device.

We plan to enroll 25 patients into this intervention. Simulations of the primary outcome, protocol adherence, were used to determine the sample size. We generated correlated longitudinal binary data with AR(1) models, representing adherence data, with an expected adherence rate of 90%. The number of adherence assessments per patient was determined with empirical data (18). A sample size of 25 will allow us to estimate protocol adherence with a confidence interval of 82% to 95%, assuming a low correlation within patient observations. The lower bound of this confidence interval meets our threshold of 80% protocol adherence.

The duration of accrual is expected to be 12 months and, along with the rest of the domain patients, patients will be followed for 6 months after randomization.

PATIENT STATES AND ELIGIBILITY CONSIDERATIONS

Only patients in the low or high elastance state can be randomized to this intervention arm (ECLS patients will not be randomized to EIT). For sites participating in the EIT intervention, patients that do not meet the following criteria will not be randomized to the EIT arm. Presence of all of the following conditions:

1. $\text{PaO}_2/\text{FiO}_2$ (if available) < 200 mm Hg at randomization
 - If $\text{PaO}_2/\text{FiO}_2$ has not been measured, $\text{SpO}_2 \leq 97\%$ on $\text{FiO}_2 \geq 60\%$

2. Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules

These criteria also apply to control arm patients if a site is participating in the EIT arm and control arm only (site not participating in any of the other intervention arms).

Refer to the Current Interventions protocol supplement, and the site specific Eligibility Checklist for additional information.

STUDY SCHEMA ADDITIONS

Refer to the main domain protocol for the general study schema and description of procedures. There are no additional procedures required for EIT patients, unless otherwise identified in the Intervention Appendices applicable to each site (i.e. some procedures outlined in the Intervention Appendices are applicable to all patients enrolled at a site participating in that intervention, regardless of what arm they are randomized to).

EIT INTERVENTION MANAGEMENT

EIT assessment Schedule: Patients randomized to the EIT group will receive daily PEEP titration via the determination of the ODCL as determined via a decremental PEEP trial while being assessed by EIT. Assessments will occur after randomization (day 0) and every morning thereafter through and including day 9 after randomization provided the patient is alive and has persistent moderate-severe hypoxemia with the most recently measured $\text{PaO}_2/\text{FiO}_2 < 150$ mm Hg, the current $\text{SpO}_2 \leq 97\%$ on $\text{FiO}_2 \geq 50\%$, and a PEEP ≥ 10 cm H_2O .

Patients randomized to the EIT group must have the application of electrical impedance tomography assessment initiated within four hours of randomization.

If the patient's lung function improves so that they no longer meet criteria for EIT assessment, but then deteriorates so that they meet these criteria on or before day 9, the EIT assessment should be performed.

If a patient's condition deteriorates substantially such that a change in PEEP is deemed to be possibly clinically warranted, the EIT assessment procedure should be repeated.

Once patient is spontaneously breathing and after study day 9, patients will be managed by the Conventional Lung-Protective Ventilation (LPV) intervention protocol.

Clinical and physiological characteristics will be collected twice per day while the patient is receiving the intervention, and once per day after the intervention period is over while the patient remains in ICU or until Day 28 (whichever comes first).

Daily EIT Assessment Procedure

Before performing the EIT assessment procedure, both of the following should be confirmed:

1. Absence of respiratory effort. Perform an end-expiratory hold for up to 3 seconds (P_{occ} measurement) to confirm absence of respiratory effort (P_{occ} = 0 cm H₂O). If respiratory effort is present, judicious administration of sedation or neuromuscular blockade may be necessary to transiently silence respiratory muscle effort.
2. Cardiopulmonary stability. In the judgment of the clinicians, the patient does not have rapidly deteriorating hemodynamics or gas exchange that would make the recruitment-decremental PEEP titration procedure unsafe.

If these criteria are not met, then the EIT assessment should be postponed until cardiopulmonary stability is established and respiratory muscle effort is absent. If necessary, the EIT assessment procedure may be deferred to later in the day. If absolutely necessary, the assessment may be deferred to the following day.

Application of EIT device:

1. Patients receiving prone ventilation will be evaluated by EIT while prone
2. The EIT device will be placed at the level of the 5th intercostal space. After application a period of 5-10 minutes will be allowed for electrode stabilization and calibration.

Two Phase Process:

1. Recruitment Phase:
 - Pressure control ventilation mode will be applied with an inspiratory pressure of 15 cm H₂O. The respiratory rate and I:E ratio (if needed) will be adjusted to maintain a constant minute ventilation.
 - Safety assessment prior to recruitment maneuver: If the patient's initial PEEP is lower than 20 cm H₂O, a stepwise increase of 2-3 cm H₂O per minute will be applied until reaching 20 cm H₂O. If the patient develops new or worsening hemodynamic instability or persistent desaturation (SpO₂ < 88% for more than 60 seconds unresponsive to increased FiO₂), the recruitment maneuver will not be performed and the decremental PEEP titration will initiated at the highest PEEP tolerated. During the uptitration in PEEP, respiratory rate will be adjusted to maintain a constant minute volume
 - Recruitment maneuver: Inspiratory pressure of 15 cm H₂O and PEEP of 20 cm H₂O (i.e., peak inspiratory pressure 35 cm H₂O) will be applied for 5-10 breaths and then increased to a PEEP of 25 cm H₂O (i.e., peak inspiratory pressure of 40 cm H₂O) for 1 minute
2. Decremental PEEP:

- After completing the recruitment maneuver, the mode will be switched to volume control, with tidal volume set to 6 mL/kg predicted body weight or decreased if needed to maintain plateau airway pressure at or below 35 cm H₂O. Respiratory rate will be adjusted to maintain a constant minute volume.
- These settings will be maintained for 5 minutes until stabilization
- Then, every 60 seconds, PEEP will be reduced by 2 cm H₂O.
- PEEP will be reduced until one of the following occurs:
 1. Oxygen saturation < 88% for > 30 seconds.
 2. Unable to maintain SpO₂ ≥90% with increases in FiO₂
 3. PEEP = 5 cm H₂O
 4. Patient develops hemodynamic instability

EIT signal analysis will be performed by online analysis of over-distention and collapse on the EIT device.

The best EIT-PEEP is identified as that which demonstrates the best compromise in over-distension (OD) and and collapse (CL), as determine by the ODCL EIT variable.

VENTILATION MANAGEMENT

For the duration of the intervention period and as long as patients remain in hypoxemic respiratory failure, ventilator settings will be adjusted to the parameters in the table below.

Management details that differ from LPV (control arm) are **bolded** in the table below.

Intervention Management - EIT	
Mode of mechanical ventilation	Pressure-targeted or volume-cycled ventilation modes as per clinician preference (i.e. pressure control, volume control, pressure support, etc.)
Tidal volume	Initiated at 6 mL/kg (predicted body weight) Maintained at 6 mL/kg as much as possible unless pH and plateau airway pressure targets require changes in tidal volume Adjusted if needed according to criteria below, permitted range 4-8 mL/kg <i>For ECLS patients; Adjust according to usual site practice, tidal volume permitted to be less than 4 mL/kg in these patients</i>
Plateau airway pressure	Target of ≤30 cm H ₂ O
pH	Target >7.15

Respiratory rate	≤35 breaths per minute
Positive end-expiratory pressure (PEEP)	<p>During the intervention phase, PEEP should be set according to the optimal PEEP identified after the daily EIT titration procedure. This PEEP should be maintained for 24 hours, unless substantial clinical deterioration warrants a change in PEEP (which should prompt a repeat EIT assessment procedure).</p> <p>After the intervention phase, clinicians may titrate PEEP according to usual site practice.</p>
Fraction of inspired oxygen (FiO ₂)	Adjusted to maintain peripheral oxygen saturation ≥90%
Plateau pressure monitoring protocol	Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected twice daily on the CRF)
Driving pressure (ΔP) monitoring protocol	Recorded twice daily (not used for ventilator titration)
Expiratory occlusion pressure (P _{occ}) monitoring protocol	Recorded twice daily (not used for ventilator titration)
Airway occlusion pressure (P _{0.1})	Recorded twice daily (not used for ventilator titration)
Dynamic transpulmonary driving pressure (DP _L) monitoring protocol	Not measured in real time at bedside
Adjustment for tidal volume above target	<ol style="list-style-type: none"> 1. During controlled ventilation, ventilator support (inspiratory pressure or tidal volume) should be adjusted to maintain tidal volume at the specified target (unless required by plateau pressure or pH targets) 2. During assisted ventilation in a pressure-targeted mode, inspiratory pressure should be reduced to achieve the target tidal volume 3. If this is unsuccessful, transition to a volume-cycled mode of ventilation and/or, if necessary, administer sedation to maintain target tidal volume
Adjustment for severe respiratory acidosis (pH<7.15)	Clinician may treat with intravenous bicarbonate.

with respiratory rate adjusted to maximum of 35 breaths per minute	If pH remains below 7.15, tidal volume may be increased in 1 mL/kg increments to achieve pH target (under these conditions plateau pressure targets may be exceeded)
Adjustment for DP \geq 15 cm H ₂ O	No adjustments
Adjustment for plateau airway pressure above target	<ol style="list-style-type: none"> 1. Tidal volume will be reduced in 1 mL/kg increments as permitted by pH to a minimum of 4 mL/kg; respiratory rate will be increased to a maximum of 35 breaths per minute if needed to facilitate reductions in tidal volume 2. PEEP can be titrated downward as tolerated, provided oxygenation does not worsen significantly (i.e. increase in FiO₂ requirement).
Adjustment for dynamic transpulmonary DP _L >23 cm H ₂ O	No adjustments
Sedation target	The sedation regimen will be managed by the clinical team to target light levels of sedation (typically SAS 3 to 4 or RASS -2 to 0) via targeted sedation or daily interruption, unless otherwise indicated, as per PADIS guidelines. Judicious sedation may be administered to suppress respiratory effort for the EIT assessment procedures if needed.

Discontinuing the intervention

See intervention management section above for details regarding discontinuing the EIT assessments. After the EIT assessment period the patient continues with the LPV intervention protocol. Both phases are considered the intervention phase for this arm.

The protocol will be applied until one of the following criteria are met;

- 1) Death
- 2) Day 28 of mechanical ventilation
 - If re-intubated within the 28 days during the index hospitalization, resume intervention if the patient has hypoxemic respiratory failure (i.e. they do not meet the criteria for resolution of hypoxemic respiratory failure in #3 below)
- 3) No longer in hypoxemic respiratory failure. We define patients as no longer in hypoxemic respiratory failure when they meet ALL of the following criteria for at least 2 hours:
 - a) Patient triggering the ventilator continuously in an assisted mode of ventilation

- b) $FiO_2 \leq 0.4$
- c) $PEEP \leq 8$ cm H₂O
- d) $SpO_2 \geq 90\%$
- e) Inspiratory pressure (peak pressure – PEEP) ≤ 10 cm H₂O; or Pressure Support ≤ 10 cm H₂O
- f) Inhaled nitric oxide and/or extracorporeal membrane oxygenation have been discontinued

For the duration of the intervention period (noted in #2 above), if hypoxemic respiratory failure recurs (i.e. patients no longer meet these criteria for discontinuing the intervention for at least 2 hours), then ventilator settings should again be managed according to protocol as specified for this intervention.

- 4) If the goals of care are modified such that no escalations in ventilator support will be permitted

Once one of these criteria are met, ventilator settings will be managed according to clinician discretion, while still following the domain protocol for co-interventions including weaning practices, if applicable.

OUTCOMES AND STATISTICS

Intervention-Specific Study Population

The population for analysis of this intervention will be patients enrolled and randomized in the LPV arm and the EIT arm at sites participating in the EIT intervention for the duration of the period to which patients are being randomized to LDPVS.

Intervention-Specific Primary Outcome

The primary outcome is protocol adherence, which will be assessed in all patients randomized to the EIT intervention. Protocol adherence will be measured as a binary outcome daily, while patients are receiving EIT (up to day 9). Our target protocol adherence across patients is $\geq 80\%$.

Intervention-Specific Secondary Outcomes

- Modified Lung Injury Score (mLIS)
- Mechanical power
- Driving pressure

Proposed Type of Analyses

The primary outcome will be analyzed with a generalized linear mixed effects model with a random patient intercept. We will report average protocol adherence and its 95% confidence interval.

Otherwise, we will analyze data descriptively, presenting binary data as proportions and counts. We will present continuous data as means (standard deviations), or medians (interquartile ranges), as appropriate

Proposed Frequency of Analyses

Data including safety outcomes will be analyzed upon completion of the pilot RCT. SAEs will be reported to the principal investigators in real-time during the trial. SAEs and clinical outcomes will be reviewed by the DSMB as per the charter.

REFERENCES

1. Qadir N, Saheyta S, Munshi L et al. An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome: An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2024; 209:24-36.
2. Grasselli G, Calfee CS, Camporota L et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Int Care Med* 2023; 49:727-59.
3. Biel M, Meade M, Mercat A et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; 303:865-73.
4. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301-8.
5. Manga LS, Subira C, Wong A et al. Setting positive end-expiratory pressure: does the 'best compliance' concept really work? *Curr Opin Crit Care* 2024; 30:20-7.
6. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–55.
7. Beitler JR, Sarge T, Banner-Goodspeed et al. Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure–Guided Strategy vs an Empirical High PEEP-Fio₂ Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA* 2019; 321:846-57.
8. Cavalcanti AB, Suzumura EA, Laranjeira LN et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA* 2017; 318:1335-45.
9. Guldner A, Braune A, Ball L et al. Comparative Effects of Volutrauma and Atelectrauma on Lung Inflammation in Experimental Acute Respiratory Distress Syndrome. *Crit Care Med* 2016; 44:e854-65.
10. Sousa MLA, Katira BH, Bouch S et al. Limiting Overdistention or Collapse When Mechanically Ventilating Injured Lungs: A Randomized Study in a Porcine Model. *Am J Respir Crit Care Med* 2024; 209:1441-62.
11. Jimenez JV, Weirauch AJ, Cutler CA, Choi PJ, Hyzy RC. Electrical Impedance Tomography in Acute Respiratory Distress Management. *Crit Care Med* 2022; 50:1210-23.
12. Songsangvorn N, Xu Y, Lu C et al. Electrical impedance tomography-guided positive end-expiratory pressure titration in ARDS: a systematic review and meta-analysis. *Int Care Med* 2024; 50:617-31.

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13. Uerner M, Juni P, Hansen B et al. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. *Lancet Respir Med* 2020; 8:905-13.
 14. Gibot S, Conrad M, Courte G et al. Positive End-Expiratory Pressure Setting in COVID-19-Related Acute Respiratory Distress Syndrome: Comparison Between Electrical Impedance Tomography, PEEP/FiO₂ Tables, and Transpulmonary Pressure. *Front Med (Lausanne)* 2021; 22:8:720920
 15. Jimenez JV and Hyzy RC. Electrical Impedance Tomography and Optimal Positive End-Expiratory Pressure: Uncovering Latent Heterogeneity of Treatment Effect. *Am J Respir Crit Care Med* 2023:208:636-7.
 16. Jonkman AH, Alcalá GC, Pavlovsky B et al. Lung Recruitment Assessed by Electrical Impedance Tomography (RECRUIT): A Multicenter Study of COVID-19 Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2023; 208:25-38.
 17. Jimenez JV, Munroe E, Weirauch AJ, Fiorino K, Cutler CA, Nelson K, Labaki WW, Choi PJ, Standiford TJ, Prescott HC, Hyzy RC. Electrical impedance tomography-guided PEEP titration reduces mechanical power in ARDS: a randomized crossover pilot trial. *Crit Care* 2023; 27:21.
 18. Costa, Eduardo L V et al. Impact of extended lung protection during mechanical ventilation on lung recovery in patients with COVID-19 ARDS: a phase II randomized controlled trial. *Annals of intensive care* vol. 14,1 85. 8 Jun. 2024