INTERVENTION-SPECIFIC APPENDIX

Standard high PEEP strategy ("PEEP-20")

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BACKGROUND AND RATIONALE

Given the complications, morbidity, and resource utilization associated with ECLS for severe acute hypoxemic respiratory failure (AHRF), it is critical to identify mechanical ventilation strategies that accelerate recovery of lung function and liberation from ECLS and mechanical ventilation. Emerging from the COVID-19 pandemic where a large number of patients required VV-ECLS for severe AHRF and in whom mortality was approximately 50-60%,[1] it has become clear that strategies to improve outcomes in these patients are urgently required.

Prior work has established that higher PEEP improves survival and accelerates recovery in AHRF. A network meta-analysis of various published PEEP titration strategies in AHRF (excluding VV-ECLS) demonstrated benefit from ventilation with higher PEEP.[2] This work changed clinical practice guideline recommendations published by multiple professional societies including the European Society of Intensive Care Medicine and the American Thoracic Society.[3,4]

Pre-clinical studies have shown that preventing lung collapse with higher PEEP may prevent lung injury and improve outcomes. In a porcine model of severe acute respiratory failure, a ventilation strategy that minimized lung collapse with higher PEEP (median PEEP of 15 mmHg) was associated with improved survival as well as improved respiratory mechanics. In contrast, a ventilation strategy that accepted alveolar collapse to minimize lung distension with lower PEEP (median PEEP of 7 mmHg) was associated with higher mortality and worse respiratory mechanics and gas exchange.[5]

Clinical studies suggest possible benefit from applying higher PEEP during VV-ECLS. Several small observational studies have found that higher levels of PEEP in patients on VV-ECLS for AHRF are associated with improved lung function (including compliance and mechanical power) and hemodynamics. By contrast, titration strategies that employed lower PEEP did not improve pulmonary mechanics.[6,7] Setting PEEP as high as 20 cmH_2O may best optimize lung and pulmonary system compliance while maintaining recruitability in patients with AHRF.[8] A higher PEEP ventilation strategy guided by transpulmonary pressure increased the proportion of patients successfully weaned from VV-ECLS and reduced the duration of VV-ECLS compared to a usual care "lung rest" ventilation strategy.[9] A retrospective analysis found that a high PEEP strategy (median 18 cmH_2O) increased liberation from VV-ECLS compared to a standard PEEP strategy (median 10 cmH_2O).[10]

Safety Profile.

When higher PEEP levels result in excessive lung stress and strain, this may result in lung injury and barotrauma (including pneumothorax, pneumomediastinum, or subcutaneous emphysema),[11] decreased venous return to the right heart due to increased intrathoracic

pressure[12] and systemic hypotension. However, the risks of many of these potentially adverse effects are low, as reported in the literature.[13] Furthermore, preventing lung collapse may have favorable hemodynamic effects and may actually be associated with improved right heart function.[12] Other studies have shown that when higher PEEP is used to prevent lung collapse, mean pulmonary artery pressure decreases[14] and cardiac output is not severely affected because alveolar recruitment is paralleled with simultaneous recruitment of the pulmonary vascular bed. This in turn favors an improvement in both right and left heart function, and thus minimizes the possible negative effects on hemodynamics.[12] These considerations motivate testing a standardized higher PEEP strategy.

In summary, emerging evidence suggests possible benefit from applying higher PEEP during VV-ECLS. It may improve survival and accelerate recovery in AHRF. The benefit of this approach will be tested in the Standard high PEEP strategy ("PEEP-20") intervention.

STANDARD HIGH PEEP STRATEGY ("PEEP-20") INTERVENTION MANAGEMENT

Following initiation of VV-ECLS, the intervention mechanical ventilation strategy will be applied, with PEEP set at 20 cm H_2O.

Management details that differ from Standard low PEEP strategy ("PEEP-10") (control arm) are **bolded** in the table below.

Patients will be managed according to the intervention protocol. Intervention should be initiated as soon as possible after randomization. Day 0 is the day of randomization and the intervention will end on Day 7, or until the patient succeeds a sweep gas off trial (SGOT), whichever comes first. Thereafter, patients will be managed according to clinician discretion.

Intervention Management - PEEP-20	
Mode of mechanical ventilation	Pressure Control Ventilation (PCV) or Pressure Support Ventilation (*PSV) mode
Tidal volume	N/A
Plateau airway pressure target	During controlled ventilation (Pocc = 0 cm H_2O) ≤25 cm H_2O
Inspiratory pressure	≤10 cm H_2O to achieve plateau airway pressure target
pH	Target ≥7.30
Set respiratory rate	10 breaths per minute
Positive end-expiratory pressure (PEEP)	**Set at 20 cm H_2O** **Once patients begin breathing and triggering the ventilator, PEEP will be adjusted to minimize respiratory effort (assessed by expiratory occlusion pressure, Pocc) while still**

	not exceeding 25 cm H_2O and not less than 10 cm H_2O. PEEP should be titrated up or down in increments of 2 cm H_2O, and Pocc re-measured after 3 minutes at each step. If the magnitude of inspiratory effort decreases, PEEP should be titrated further until effort begins to increase. **PEEP will also be decreased in steps of 2 cm H_2O as needed to mitigate hemodynamic compromise while adhering as closely as possible to the assigned protocol**
Fraction of inspired oxygen (FiO_2)	Set to 0.40 unless higher FiO_2 is required to maintain peripheral oxygen saturation (SpO2) ≥ 88%
Neuromuscular blockade	**<u>For the first 24 hours after initiating the intervention:</u> Neuromuscular blockade will be applied by a continuous infusion of neuromuscular blockade.** **<u>After 24 hours:</u> the continuation of neuromuscular blockade will be at the discretion of the treating clinician.**
Sedation targets	All patients receiving neuromuscular blockade will be treated with sedation to maintain RASS score at -5 (SAS of 1) throughout the duration of neuromuscular blockade. Sedation will be managed at the discretion of the treating clinicians, or as specified in another PRACTICAL domain protocol for patients that are co-enrolled. It is recommended that sedation is managed targeting light levels of sedation via targeted sedation or daily interruption, unless otherwise contraindicated, as per PADIS guidelines.

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