
INTERVENTION-SPECIFIC APPENDIX

Conventional Lung-Protective Ventilation (LPV)

Current phase of evaluation for this intervention: Phase III

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BACKGROUND

Conventional lung-protective ventilation is defined based on the current SOC as specified in the clinical practice guidelines for management of mechanical ventilation in patients with acute respiratory distress syndrome sponsored by the American Thoracic Society.¹ These guidelines and the ventilation management strategy specified for this intervention are largely based on the ARDSnet ARMA trial² as implemented in more recent mechanical ventilation trials including LOVS,³ ExPRESS,⁴ and OSCILLATE.⁵ Given ongoing uncertainty about the optimal PEEP setting in AHRF, this protocol does not stipulate a particular PEEP strategy and recommends PEEP setting according to local site usual practice.

SAMPLE SIZE AND SITES

Sample size is not fixed for this intervention. Enrolment will continue perpetually until a different intervention is shown to be superior in phase III evaluation to any other ventilation strategy in the domain.

Because it represents current SOC, LPV will be implemented at all sites participating in this domain.

PATIENT STATES AND ELIGIBILITY CONSIDERATIONS

Patients from any state noted in the main domain protocol may be enrolled into this intervention arm. However, depending on what other arms a site is participating in, enrollment may be limited to fewer states (i.e. if no other intervention arm at a site is enrolling patients in the ECLS state, then patients in the ECLS state would not be enrolled into the LPV arm either). 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 LPV 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).

LPV INTERVENTION 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.

Intervention Management - LPV	
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 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)	Adjusted according to local site practice*
Fraction of inspired oxygen (FiO ₂)	Adjusted to maintain peripheral oxygen saturation $\geq 90\%$
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 _{oc}) 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 (ΔP_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 VT still above target, transition to a volume-cycled mode of ventilation. In a volume-cycled mode, if P_{plat} < 30 and dyssynchrony occurs, may increase VT in 1mL/kg increments to 7 or 8 mL/kg PBW if P_{plat} remains ≤ 30 cmH₂O. 4. If necessary, administer sedation to maintain target tidal

	volume
Adjustment for severe respiratory acidosis (pH<7.15) with respiratory rate adjusted to maximum of 35 breaths per minute	Clinician may treat with intravenous bicarbonate. 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 $\Delta P \geq 15$ cm H ₂ O	No adjustments
Adjustment for plateau airway pressure above target	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 FiO ₂ requirement).
Adjustment for dynamic transpulmonary $\Delta P_L > 23$ 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. Note: sedation target applies, unless clinically indicated (which includes increasing sedation to control tidal volume, if necessary).

*In centres participating in the CAV intervention, the PEEP and FiO₂ should be set according to one of the two PEEP FiO₂ tables (high or low) that are already routinely used in that centre as part of their SOC

Discontinuing the intervention

The intervention 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) FiO₂ ≤ 0.4
 - c) PEEP ≤ 8 cm H₂O
 - d) SpO₂ ≥ 90%

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- 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.

REFERENCES

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3. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637-45.
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