INTERVENTION-SPECIFIC APPENDIX

Driving Pressure-Limited Ventilation (DPL)

Current phase of evaluation for this intervention: Phase III

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BACKGROUND AND RATIONALE

The modern era of Vt-limited lung-protective ventilation was ushered in by the publication of the ARDSnet RCT two decades ago.[1] Since that time, mechanistic studies and practice-changing RCTs have substantially advanced our understanding of the pathophysiology of acute hypoxemic respiratory failure (AHRF). These advances suggest that a driving pressure-limited ventilation strategy may be superior to conventional lung-protective ventilation.

With current Vt-limited ventilation, patients with high respiratory system elastance remain at high risk of ventilator-induced lung injury (VILI). In AHRF, the size of the aerated lung available for ventilation varies widely. Respiratory system elastance (the inverse of compliance) reflects the aerated lung volume; patients with small aerated lung volume have higher elastance ("stiffness") and are at higher risk of excessive and injurious lung stress from the tidal volume. CT imaging studies have shown that a third of patients exhibited hyperinflation of the lung at "protective" Vt (6 mL/kg predicted body weight), resulting in increased pulmonary inflammation.[2] Driving pressure (ΔP), the elastic pressure generated by inflating the respiratory system with the Vt, reflects the stress applied to the lung. ΔP remains high in many patients even when Vt is in the protective range, especially in those with high respiratory system elastance.

Targeting ΔP for lung-protective ventilation may be superior to conventional Vt-limited ventilation. Compared to Vt, ΔP more accurately reflects lung stress and strain during mechanical ventilation, the key determinants of VILI. Hence, scaling Vt based on ΔP will prevent excess lung stress and strain. ΔP is more strongly associated with mortality than Vt and this association persists over time.[3,4] The effect of lowering Vt on mortality was greater in patients with more severe lung injury as reflected by higher elastance and higher ΔP.[5] Decreases in ΔP following ventilator changes are associated with improved mortality.[6] These and other studies suggest an inflection point for the association between ΔP and mortality near 15 cm H_2O. ΔP is easily measured directly from the ventilator by simple, routinely performed maneuvers. On this basis, we hypothesize that targeting ΔP <15 cm H_2O (a "driving pressure-limited" ventilation strategy, DPL) will prevent injurious lung stress, reduce VILI, and improve survival, especially in patients with high elastance.

In patients with low elastance and higher aerated lung volume, limiting Vt for lung-protective ventilation is unlikely to benefit and may be harmful. Limiting Vt to 4-8 mL/kg PBW was not associated with mortality benefit when elastance was low.[5] In fact, limiting Vt may be harmful for some patients: it can worsen atelectasis, hypoxemia, work of breathing, and dyspnea, and exacerbate patient-ventilator dyssynchrony. To limit Vt, patient respiratory effort must often be suppressed using heavy sedation. This can impair hemodynamics and gas exchange and cause rapid disuse atrophy of the diaphragm, resulting in diaphragm dysfunction and prolonged mechanical ventilation. Prolonged ventilation, in turn, contributes to intensive care unit (ICU)-

acquired weakness, death, and long-term disability. Heavy sedation may also increase the risk of delirium and long-term cognitive dysfunction. In patients with low elastance, a ΔP-limited approach would allow Vt to be increased in many patients while maintaining ΔP<15 cm H_2O to avoid VILI. This could alleviate dyspnea and sedation requirements, facilitate spontaneous breathing to prevent diaphragm atrophy, enhance early mobilization, reduce ICU-acquired weakness, promote liberation from the ventilator, and improve long-term quality of life and functional status.

A new non-invasive technique allows us to easily detect high ΔP due to patient breathing effort. A simple ventilator-based technique (expiratory occlusion pressure, Pocc) can measure the patient's respiratory effort and this information can be used to compute the lung-distending pressure (dynamic transpulmonary ΔP).[7] Pocc can be measured at regular intervals to ensure that dynamic transpulmonary ΔP is maintained within safe limits when patients are spontaneously breathing. Observational evidence suggests that a dynamic transpulmonary ΔP of 23 cm H_2O is correlated to a static airway driving pressure of 15 cm H_2O, suggesting that this value be used to define a safe upper limit for lung-distending pressure during assisted ventilation.

Evidence from systematic reviews. A systematic review of observational studies found that higher ΔP was associated with higher mortality (pooled risk ratio, 1.44, 95% CI 1.11-1.88). A separate systematic review found a similar association.[8]

Safety Profile. As with conventional lung-protective ventilation, lowering Vt to limit ΔP carries a potential risk of hypercapnic acidosis. A recent trial reported a low risk of severe acidosis (6%) when applying ultra-low Vt in moderate or severe ARDS patients.[9] A pilot RCT of a ΔP-limited strategy found no evidence for a heightened risk of severe acidosis.[10]

In summary, emerging evidence suggests that a ΔP-limited ventilation strategy is likely superior to current practice. It may reduce mortality in patients with high respiratory system elastance and may accelerate liberation from mechanical ventilation in patients with low respiratory system elastance. The development of the Pocc technique enables detection and prevention of potential lung injury from excess patient breathing effort. The benefit of this approach will be tested in the DPL intervention.

SAMPLE SIZE AND SITES

Sample size is not fixed for this intervention and will continue until a statistical conclusion is reached about superiority, equivalence, futility, or inferiority in phase III. In the current domain with a dual comparison at phase II, statistical conclusions will be reached based on superiority and futility of DPL compared to LPV. The triggers for statistical conclusion will apply in each state after a minimum of 500 patients have been enrolled in that state. Plausible sample size requirements for this design were evaluated by simulating a range of plausible treatment effects. Based on these simulations, a maximum sample size of 1,000 patients randomized to each of the DPL or LPV interventions in each of the two relevant platform-defined states (low elastance, high elastance; maximum total of 4,000 patients) will give ≥80% power to conclude superiority of the ΔP-limited strategy when the treatment effect is equal to or greater than an odds ratio of 1.30 (consistent with clinically important benefit). These simulations also demonstrate that the risk of incorrectly concluding superiority (Type I error) under the null effect scenario (OR = 1.0) is acceptably low (≤5%) given this maximum planned sample size.

Approximately 80 centres are planned to participate in this intervention across a broad network of collaborating networks in Canada (Canadian Critical Care Trials Group, CCCTG), the United States (Society of Critical Care Medicine Discovery Network, others), Ireland (Irish Critical Care Clinical Trials Network), Australia (Australia/New Zealand Intensive Care Society Clinical Trials Network), Saudi Arabia (Saudi Critical Care Trials Group), Italy, Spain, Argentina, and other countries.

DPL 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. When patients are not making respiratory efforts (Pocc = 0) the primary target variable will be $\Delta P \leq 15$ cm H_2O. When patient efforts are contributing (Pocc < 0) the primary target variable will be dynamic transpulmonary driving pressure (ΔP_L) of 23 cm H_2O or lower.

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

Intervention Management - DPL	
Mode of mechanical ventilation	Pressure-targeted or volume-cycled ventilation modes as per clinician preference (e.g. pressure control, volume control, pressure support, etc.)
Tidal volume	**During controlled ventilation (Pocc = 0 cm H_2O): adjusted to maintain $\Delta P \leq 15$ cm H_2O** **During assisted ventilation (Pocc < 0 cm H_2O): adjusted to maintain dynamic transpulmonary $\Delta P \leq 23$ cm H_2O**
Plateau airway pressure	**Target of ≤35 cm H_2O**
pH	Target >7.15
Respiratory rate	**≤40 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 (SpO2) ≥ 90% , unless otherwise specified by this protocol
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	**Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected twice daily on the CRF)**
Expiratory occlusion pressure (Pocc) monitoring protocol	**Measured at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution, collected twice daily on the CRF)**
Dynamic transpulmonary driving pressure (ΔP_L) monitoring protocol	**Computed in real time at each routine ventilation assessment (approximately every 4 hours although timing may vary by institution). If Pocc = 0 cm H_2O, ΔPL cannot be estimated and does not apply.**
Adjustment for severe respiratory acidosis (pH<7.15) with respiratory rate adjusted to maximum of 40 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 airway ΔP >15 cm H_2O during controlled ventilation (Pocc = 0 cm H_2O)	**1) PEEP will be titrated upward or downward to determine whether ΔP can be reduced by optimizing compliance** **2) Tidal volume will be decreased as permitted by pH; respiratory rate will be increased to a maximum of 40 breaths per minute if needed to permit reductions in tidal volume**
Adjustment for plateau airway pressure above target during controlled ventilation (Pocc = 0 cm H_2O)	**1) PEEP will be titrated downward as tolerated, provided oxygenation does not worsen significantly (i.e. increase in FiO2 requirement) and ΔP does not increase to ≥15 cm H_2O.** **2) Tidal volume will be reduced as permitted by pH; respiratory rate will be increased to a maximum of 40 breaths per minute if needed to permit reductions in tidal volume**
Adjustment for dynamic transpulmonary ΔP_L>23 cm H_2O during assisted ventilation (Pocc <0 cm H_2O)	**1) *If patients transition to ECLS state after randomization and are currently receiving ECLS;* increase sweep gas flow in increments of 2 L/min to a maximum of 10 L/min and assess dynamic transpulmonary ΔPL at each step. Stop when limited by pH (> 7.5) or hypocapnia (PaCO2 < 30 mm Hg)** **2) PEEP will be titrated upward or downward to determine whether dynamic transpulmonary ΔP can be reduced by optimizing compliance and respiratory effort** **3) Inspiratory pressure/flow will be decreased as permitted by pH and tidal volume limits *(can be skipped if the patient's respiratory effort is already significantly elevated (i.e., Pocc more negative than –20 cm H_2O)*** **4) If Pocc is more negative than –20 cm H_2O, FiO_2 will be increased by 20% to increase PaO_2 to assess whether this reduces respiratory drive and effort** **5) If pH < 7.3, consider bicarbonate infusion** **6) Sedation will be increased when deemed necessary by the clinicians to reduce respiratory effort in order to reduce dynamic transpulmonary ΔP to acceptable limits** **7) Consider neuromuscular blockade if dynamic transpulmonary ΔP_L remains above target because of persistently excessive respiratory effort despite deep sedation**
Sedation targets	**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.** **During assisted ventilation, if dynamic transpulmonary ΔP_L exceeds 23 cm H_2O due to excessive respiratory effort, and this cannot be resolved by adjusting the ventilator, the clinical team will be directed to adjust sedation according to their best**

	judgment to reduce respiratory effort and achieve dynamic transpulmonary ΔP_L target. Sedation to apnea (Pocc = 0 cm H_2O) is permitted if necessary to achieve targets.

Discontinuing the intervention

The intervention will be applied until <u>one</u> 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 ≤ 8 cm H_2O
    d) SpO2 ≥90%
    e) Inspiratory pressure (peak pressure – PEEP) ≤10 cm H_2O; or Pressure Support ≤10 cm H_2O
    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

1. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. 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.

2. Terragni PP, Rosboch G, Tealdi A, et al. Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome. American journal of respiratory and critical care medicine 2007;175:160-6.

3. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747-55.

4. Urner M, Juni P, Hansen B, Wettstein MS, Ferguson ND, Fan E. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. Lancet Respir Med 2020;.

5. Goligher EC, Costa ELV, Yarnell CJ, et al. Effect of Lowering Vt on Mortality in Acute Respiratory Distress Syndrome Varies with Respiratory System Elastance. Am J Respir Crit Care Med 2021;203:1378-85.

6. Yehya N, Hodgson CL, Amato MP, et al. Response to Ventilator Adjustments for Predicting ARDS Mortality: Driving Pressure versus Oxygenation. Annals of the American Thoracic Society 2020;.

7. Bertoni M, Telias I, Urner M, et al. A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. Crit Care 2019;23:346-0.

8. Aoyama H, Pettenuzzo T, Aoyama K, Pinto R, Englesakis M, Fan E. Association of Driving Pressure With Mortality Among Ventilated Patients With Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. Crit Care Med 2018;46:300-6.

9. Richard JC, Marque S, Gros A, et al. Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients. Intensive Care Med 2019;45:1590-8.

10. Pereira Romano ML, Maia IS, Laranjeira LN, et al. Driving Pressure-limited Strategy for Patients with Acute Respiratory Distress Syndrome. A Pilot Randomized Clinical Trial. Annals of the American Thoracic Society 2020;17:596-604.