Title: Identifying and Preventing Ventilator Induced Diaphragm Dysfunction in Children

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REDVENT

(**R**eal-time **E**ffort **D**riven **VENT**ilator management)

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A Introduction

A1 Study Abstract

Nearly half of mechanically ventilated (MV), critically ill adults develop ventilator-induced respiratory muscle weakness (particularly of the diaphragm), which impairs successful weaning from MV, often leads to re-intubation, and is associated with higher post-ICU mortality. Respiratory muscle weakness is associated with extubation failure in critically ill children. However, we lack crucial information on the mechanisms and timing of this weakness, its importance for ventilator weaning, and its potential prevention through promoting more physiologic levels of patient effort of breathing during MV.

This study is a Phase II controlled clinical trial that will obtain comprehensive, serial assessments of respiratory muscle strength and architecture to understand the evolution of ventilator-induced respiratory muscle weakness in critically ill children, and test whether a novel computer-based approach (Real-time Effort Driven ventilator management (REDvent)) can preserve respiratory muscle strength and reduce time on MV. REDvent offers systematic recommendations to reduce controlled ventilation during the acute phase of MV, and uses real-time measures from esophageal manometry to adjust supported ventilator pressures such that patient effort of breathing remains in a normal range during the ventilator weaning phase. This phase II clinical trial is expected to enroll 300 children with pulmonary parenchymal disease, anticipated to be ventilated > 48 hrs. Patients will be randomized to REDvent-acute vs. usual care for the acute phase of MV (interval from intubation to first spontaneous breathing trial (SBT)). Patients in either group who fail their first Spontaneous Breathing Trial (SBT), will also be randomized to REDvent-weaning vs. usual care for the weaning phase of MV (interval from first SBT to passing SBT). The primary clinical outcome is length of weaning (time from first SBT until successful passage of an SBT or extubation (whichever comes first)). Mechanistic outcomes surround multi-modal serial measures of respiratory muscle capacity (PiMax), load (resistance, compliance), effort (esophageal manometry), and architecture (ultrasound) throughout the course of MV. Upon completion, this study will provide important information on the pathogenesis and timing of respiratory muscle weakness during MV in children and whether this weakness can be mitigated by promoting more normal patient effort during MV via the use of REDvent. This will form the basis for a larger, Phase III multi-center study, powered for key clinical outcomes such as 28-day Ventilator Free Days.

A2 Protocol Summary

Title: Real-time Effort Driven Ventilator Management (REDvent)

Phase: Phase II

Funding: NIH/NHLBI R01HL124666

Committees: Steering Committee, Institutional Data and Safety Monitoring Board

Background and Significance: Nearly half of critically ill patients on MV develop respiratory muscle weakness, particularly of the diaphragm. In adults, this weakness leads to the inability to resume unassisted ventilation after the acute illness has resolved, prolongs the weaning phase of MV, and contributes to extubation failure. [1-11] However, in critically ill children, we lack crucial information about the importance of ventilator-induced respiratory muscle weakness during weaning, the means to prevent it, and whether it is influenced by maturational changes in respiratory mechanics and diaphragm histology that occur throughout infancy and childhood.[12]

Consistent with the pediatric literature,[4] our preliminary data has shown that usual care ventilation in children is associated with minimal patient effort of breathing; [13, 14] known to be a major risk factor for ventilator-induced diaphragm weakness in adults.[5] To reduce this weakness, we developed a computer-based approach (Real-time Effort Driven ventilator management (REDvent)), which recommends systematic reductions in controlled ventilation during the acute phase of MV and uses real-time measures to adjust supported ventilator pressures to maintain patient effort of breathing during the weaning phase. Through a Phase I trial, we demonstrated that patients managed with REDvent spent fewer days on MV than historical controls, and bedside providers could easily implement REDvent. Our central hypothesis is that REDvent use will reduce ventilator-induced respiratory muscle weakness, leading to shorter time on MV by enhancing the patient's capacity for effective, unsupported ventilation and by facilitating MV weaning.

Study Aims:
SA1: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV (Primary outcome).

SA2: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes.

SA3: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness.

Study Design: Single-center randomized controlled trial (150 children per arm) using REDvent (intervention arm) as compared with usual care ventilator management including a standardized daily SBT (control arm). Acute phase randomization will occur upon study enrollment, and patients who fail the first SBT will undergo a weaning phase randomization. We will obtain serial measurements of respiratory system capacity, load, effort of breathing, and diaphragm architecture throughout the course of MV.

Inclusion Criteria:

1. Children > 1 month (>44 weeks CGA) and ≤ 18 years of age AND

2. Supported on mechanical ventilation with pulmonary parenchymal disease (i.e., pneumonia, bronchiolitis, Pediatric Acute Respiratory Distress Syndrome (PARDS)) with Oxygen Saturation Index (OSI) ≥ 5 or Oxygenation Index (OI) ≥) AND
3. Who are within 48 hours of initiation of invasive mechanical ventilation (allow for up to 72 hours for those transferred from another institution)

Exclusion Criteria:

1. Contraindications to use of an esophageal catheter (i.e. severe mucosal bleeding, nasal encephalocele, transphenoidal surgery) OR
2. Contraindications to use of RIP bands (i.e. omphalocele, chest immobilizer or cast) OR
3. Conditions precluding diaphragm ultrasound measurement (i.e. abdominal wall defects, pregnancy) OR
4. Conditions on enrollment that preclude conventional methods of weaning (i.e., status asthmaticus, severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal Life Support (ECLS), intubation for UAO, tracheostomy, DNR, severe chronic respiratory failure, spinal cord injury above lumbar region, cyanotic heart disease (unrepaired or palliated)) OR
5. Primary Attending physician refuses (will be cleared with primary attending before approaching the patient).

A high level overview is presented in Figure 1.

Acute Phase: The acute phase is defined as the time from intubation until the patient meets weaning criteria,[15, 16] passes the initial oxygenation test (decrease PEEP to 5 cmH_2O and FiO_2 to 0.5, maintains SpO2 > 90%), and undergoes a Spontaneous Breathing Trial (SBT).

1. Intervention Arm (REDvent-acute): Patients will be managed with pressure control plus pressure support ventilation using a computerized decision support tool that will recommend changes to ventilator settings approximately every 4 hr (with or without a new blood gas). If the patient is spontaneously breathing, it will incorporate real-time measures of effort of breathing (esophageal manometry) to keep it in a target range.
2. Control Arm (Control-acute): Ventilator management will be per usual care until the patient meets weaning criteria and passes the oxygenation test.

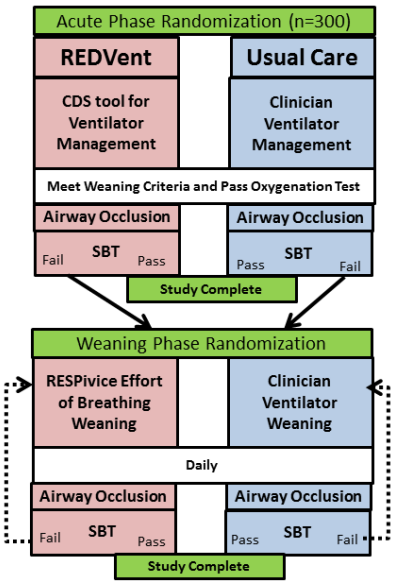

Figure 1: Study Schematic

Weaning Phase: The weaning phase is defined as the time from the first Spontaneous Breathing Trial (SBT) until the patient successfully passes an SBT or is extubated (whichever comes first). Patients who pass the initial SBT at the end of the acute phase will not undergo weaning phase randomization.

1. Intervention Arm (REDvent-weaning): Patients will be managed in a pressure support/CPAP mode of ventilation with assessments or changes to the level of

pressure support every 4 hours, targeting maintaining effort of breathing (esophageal manometry) in a normal range. An SBT will be conducted daily, and the weaning phase will continue until the patient passes the SBT.

2. Control Arm (Control-weaning): Ventilator management will be per usual care. An SBT will be conducted daily, and the weaning phase will continue until the patient passes the SBT.

Endpoints:

Primary:

- Duration of Weaning (Time from first attempted SBT until SBT passage or extubation [whichever comes first])

Secondary

- Ventilator Free Days
- Extubation Failure
- Pre-specified and Unanticipated Adverse Events
- ICU, Hospital, and 90 Day Mortality
- Esophageal Manometry: Maximal Inspiratory Pressure During Airway Occlusion (ePiMax)
- Airway Pressure: Maximal Inspiratory Pressure During Airway Occlusion (aPiMax)
- Diaphragm Ultrasound: Change in diaphragm thickness on Exhalation (Dte)
- Respiratory Inductance Plethysmography: Phase angle (PA)

Analysis Plan and Sample Size Justification:

Aim 1: The primary outcome is weaning duration. Sample size has been determined to adequately power 3 separate comparative analyses: (a) REDvent-acute versus Acute Phase control (b) REDvent-weaning phase versus Weaning Phase control (c) REDvent both phases versus control both phases. Power is based on 2 planned methods for analysis: cox proportional hazard ratios for multivariable analysis and univariate analysis with an independent t-test using log transformation (as needed) to account for the expected distribution of weaning duration. For all three of the planned comparisons above, with the proposed sample size we would be adequately powered (>0.8) to detect a difference in weaning duration of ≥ 1 day, or a hazard ratio of ≥ 1.4 between groups. The secondary outcomes are ventilator free days and extubation failure. Directly comparing control only patients to REDvent only patients, with an expected standard deviation for VFDs between 5 to 9 days, we will be able to detect a 2-day change in VFDs between groups with a power between 0.35 and 0.82. Re-intubation rates are expected to be 10%, allowing us to confirm that REDvent is not inferior to usual care in regards to re-intubation with a non-inferiority margin of 0.10 with a power of 0.8 and alpha of 0.05.

Aim 2: The primary outcome of this aim is weaning duration. For respiratory muscle strength we will compare the first measured aPiMax (after resolution of the acute phase, before the first SBT), the trajectory and value of the daily aPiMax during the weaning phase prior to extubation, the lowest and highest measured aPiMax, and aPiMax on the day of extubation against weaning duration. For analysis, aPiMax will be dichotomized at 30 cmH2O, and weaning duration will be compared between patients with aPiMax > 30 versus ≤ 30 cmH2O using a t-test with or without log-transformation, or Mann-Whitney U test, depending on the distribution. From our preliminary data, we anticipate at least 35% of patients (n=84) will have aPiMax ≤ 30 cmH2O. Based on a similar power analysis as presented above, this would allow us to determine whether low aPiMax

is associated with a ≥ 1-day increase in weaning duration, with an alpha of 0.05 and power of 0.8. We will perform identical analysis for ePiMax. Diaphragm Thickness analysis will compound daily ultrasound measures to detect the relative change in diaphragm thickness from study day 1 until passage of an SBT. We will compare the change in thickness after resolution of the acute phase (on the day of the first SBT) against weaning duration, in a similar manner as proposed above for aPiMax. In addition to weaning duration, we will also examine whether the respiratory measures taken just prior to or during each SBT are associated with the patient passing the SBT. For example with aPiMax and ePiMax, we will examine if there is a dose response relationship between PiMax measured just before the SBT and the rate of passage of the subsequent SBT.

Aim 3: The primary outcome of this aim is aPiMax < 30 cmH2O.The analysis will focus on determining whether the degree of patient effort of breathing is independently associated with the development of respiratory muscle weakness. For the acute phase, we will generate a time-weighted average PRP during the acute phase and graph it against aPiMax at the first SBT. We will subsequently dichotomize aPiMax at the first SBT and compare mean time weighted average PRP in the acute phase between aPiMax groups (> 30 vs. ≤ 30 cmH2O). For the weaning phase, we will graph the changes in aPiMax throughout the weaning phase (from first failed SBT until successful SBT) against time-weighted average PRP, with the anticipation that low PRP will be associated with either further reductions in aPiMax, or no improvement, while PRP in the physiologic range of 150-400 will be associated with improvement in aPiMax. We will subsequently dichotomize aPiMax (at 30 cm H2O) at the time of successful passage of an SBT and compare time-weighted average PRP in the weaning phase between aPiMax groups. Subsequently, we will build a multivariable logistic regression model on the outcome of aPiMax ≤ 30 cmH2O to determine if time-weighted PRP in the acute phase, weaning phase or both have an independent association with preserving aPiMax, after controlling for confounding variables.

Monitoring: The study will one planned interim analysis at 150 patients, with no rules planned for early stopping, given the low risk nature of this study and the high degree of physiologic data collected. In addition, there will be an early safety check after approximately 50 patients are enrolled, to review rates of adverse events between groups. There will be review of adverse events by the DSMB during scheduled meetings twice a year, or as requested.

A3 Primary Hypothesis and Specific Aims

Our central hypothesis is that REDvent use will reduce ventilator-induced respiratory muscle weakness, leading to shorter time on MV by enhancing the patient's capacity for effective, unsupported ventilation and by facilitating MV weaning. This will be specifically tested with 3 complementary specific aims:

SA1: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV (Primary outcome). We expect that patients randomized to receive REDvent-acute will either pass their first SBT or experience a shorter duration of weaning when compared to usual care. In addition, patients randomized to receive REDvent-weaning will experience a shorter duration of weaning compared to usual care. Secondary outcomes include 28-day Ventilator Free Days and extubation failure.

SA2: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes. We expect that diminished respiratory muscle strength (low PiMax), and diaphragm atrophy (ultrasound) will be prevalent after resolution of the acute phase of MV, and the combination of high respiratory load (or effort) with low PiMax will be a major factor leading to prolonged weaning and weaning failure (failure of SBT).

SA3: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness. We expect that after controlling for confounding variables like age, diagnosis, sedation, use of neuromuscular blockade, and other risk factors for neuromuscular weakness, children who maintain normal effort of breathing in the acute or weaning phases will have higher respiratory muscle capacity as measured by PiMax.

B Background

B1 Prior Literature and Studies

Children supported by mechanical ventilators in intensive care units contribute to over $5 billion dollars a year in US healthcare costs.[17, 18] Efficient methods to optimize ventilator support in children are lacking, resulting in some children being on ventilators longer than necessary.[16] Each additional day of ventilation leads to added health risks such as exposure to medications that may harm the developing brain, higher risk of infection, and critical illness acquired weakness leading to long-term impairment in patient quality of life.[17, 19-25] Mechanical ventilation (MV) of critically ill adults frequently leads to acquired respiratory muscle weakness, particularly of the diaphragm, which is a major factor contributing to extra days on MV.[1, 2] Mechanisms responsible for ventilator-induced diaphragm weakness relate to the underlying disease status of the patient, the severity of inflammation, the use of therapies like neuromuscular blockade and corticosteroids, the degree of protein catabolism, and the degree of diaphragm contraction during MV.[1, 5, 6, 8-10, 26] Accumulating data indicate that > 50 % of critically ill adults who are on MV > 72 hours have thinning of the diaphragm (based on ultrasound) within the first few days of MV, [5] and there is a dose response relationship between diaphragm atrophy and increasing ventilator driving pressure.[5] Moreover, low diaphragm contractile activity leads to atrophy, while diaphragm thickness is preserved when contractile activity during MV is normal (i.e., patient maintains normal work of breathing).[27]

Many adult studies have demonstrated architectural changes to the diaphragm which occur throughout the course of mechanical ventilation, but these changes may not directly translate into weakness.[5, 7] Respiratory muscle weakness can be objectively measured as the inability to generate sufficient changes in airway or esophageal pressure with maximal diaphragm contraction (PiMax), either voluntarily or through external stimulation of the phrenic nerve. However, there are limited data quantifying the time frame and degree to which these direct measures of respiratory muscle weakness (PiMax) become impaired during MV, although evidence suggests that low PiMax at extubation is associated with longer lengths of MV and higher mortality in adults.[8, 28] Single direct measures of respiratory muscle strength may be misleading. Experts in the field of pulmonary function testing of the respiratory muscles recommend serial measurements, combining multiple techniques to obtain the most comprehensive view of the respiratory muscles. This approach has been used when investigating other causes of diaphragm dysfunction, [29] but such a systematic, multi-modal approach has not been applied to study ventilator induced diaphragm dysfunction in critically ill patients.

B2 Rationale for this Study

Few data are available regarding the prevalence of ventilator induced diaphragm weakness and the risk factors for its development in children, although the respiratory muscles of the infant and newborn are more susceptible to weakness and fatigue than

those of older children because of crucial differences in diaphragm histology.[12, 30] However, the pathophysiology of ventilator-induced diaphragm weakness supports in children, as in adults, that ventilator management in both acute and weaning phases of MV contribute to diaphragm weakness.[4, 11] During the acute phase of MV, the goals are to maintain safe gas exchange, reduce excessive patient work of breathing, and prevent ventilator-induced lung injury through lung protective ventilation. While prolonged periods of high effort of breathing should be avoided because they worsen gas exchange, compromise oxygen delivery and potentiate ventilator induced lung injury, MV is often too highly controlled, resulting in minimal to no patient effort of breathing[4] and minimal changes of the ventilator settings. Consistent with other investigations [31], we have found that practitioners do not make changes to promote lung protective ventilation [32, 33] and do not reduce high ventilator settings over 50% of the time when managing MV without an explicit protocol, even in circumstances of respiratory alkalosis and over-ventilation.[33] Ventilator driving pressures are often higher than necessary and respiratory alkalosis prevents meaningful patient effort during the acute phase of MV. This strategy results in high rates of fully controlled mechanical ventilation and directly leads to diaphragm weakness. [34 35-38]

When critical illness has stabilized, weaning towards extubation in current practice involves slow, gradual reductions of ventilator pressures until spontaneous breathing trials (SBTs) are performed,[16, 39] although routine SBTs are only performed in < 25% of MV children. [33, 39] While practitioners frequently have the patient initiate ventilator breaths (spontaneous breathing) during weaning, the ventilator performs most of the required work of breathing. In general, during usual care ventilator management, patient breathing effort during both acute and weaning phases of MV is well below the normal physiologic range that would be expected if their lungs were healthy and off a ventilator. [4, 5] This sub-physiologic patient effort potentiates diaphragm weakness.

We hypothesize that maintaining patient effort of breathing closer to a normal, physiologic range will protect against diaphragm weakness. In pediatrics, there has been little work developing methods to promote early return to more natural breathing in this physiologic range. For adults, there are a few commercially available closed-loop ventilation weaning systems that provide an estimate of effort of breathing, and concurrently reduce ventilator support during weaning. Such systems have been shown to reduce length of MV by 20-40% over conventional weaning, [40] with supportive pilot data in older children. [41] Unfortunately, current closed-loop weaning tools are not available for most children, and these strategies are not initiated until the weaning phase of MV, allowing respiratory muscle weakness to develop during the acute phase of illness. [5, 42] New methods to continuously measure effort or work of breathing to guide ventilator management in young children are needed.

Through the use of technology systems developed specifically for children, we seek to determine whether a physiology-based ventilator management approach can prevent acquired respiratory muscle weakness in children, thus facilitating MV weaning and earlier recovery from critical illness. [43] The approach promotes the safe reduction in controlled ventilation during the acute phase of MV and early return to spontaneous breathing with maintenance of normal patient effort of breathing in the weaning phase (Real-time Effort Driven ventilator management (REDvent)). Through this study, we seek to understand the importance of respiratory muscle weakness in both the acute and weaning phases of MV in children, quantify the importance of patient effort of breathing for the development of respiratory muscle weakness, and determine whether REDvent can shorten ventilator weaning time. This study will improve our understanding of the pathogenesis of ventilator-induced diaphragm weakness in children and determine

whether computer-driven management prevents this weakness and leads to improved patient outcomes.

B3 Preliminary Data

B.3.1 Patient effort of breathing is generally very low with usual care ventilation: Dr. Khemani led a study of 409 mechanically ventilated children (77% consent rate) in which respiratory parameters were measured using esophageal manometry and respiratory inductance plethysmography [44] near extubation (K23 HL103785, PI Khemani). From secondary analysis of that data, we found that Pressure Rate Product (PRP, a direct measure of patient effort of breathing derived from esophageal manometry) on the day of extubation under what is considered minimal respiratory support (PS of 10/5 cmH20) was nearly 2.5 fold lower (median 90 (50, 140)) than PRP post-extubation (median 220 (120, 320)).[13, 14,39] Other pediatric investigators have demonstrated frequent periods of no detectable diaphragm effort during conventional ventilation, with electrical activity of the diaphragm 3 times lower during MV than it was at ICU discharge. [4] Thus, current ventilator strategies do not maintain normal patient effort and may contribute to respiratory muscle weakness. We have also shown that there is a normal range for effort of breathing that can be maintained by adjusting ventilator support. 75% of patients from our cohort who did well after extubation (i.e., no re-intubation, no need for post-extubation noninvasive ventilation) had a PRP from 150 to 400. These cut points appear to work across the entire pediatric age spectrum (neonate to 18 years), and form the basis for the "optimal range" that will be used for titration in this application.

B.3.2 REDvent management protocol: The computerized decision support (CDS) tool used by REDvent-acute is an electronic protocol that makes recommendations at user-set time intervals to adjust both ventilation (ventilator pressure or tidal volume and ventilator rate) and oxygenation (Positive End Expiratory Pressure and FiO2) to promote lung protective ventilation during the acute phase of MV. It implements a pediatric modification of the Acute Respiratory Distress Syndrome Network protocol,[45] (R21HD061870, PI Newth). We have demonstrated that pediatric critical care practitioners agree on the recommendations generated by the modified protocol.[46, 47] The CDS tool has been extensively tested in our ICU to provide explicit recommendations, and has built-in reporting features to measure protocol adherence. REDvent-weaning recommends adjusting supported ventilator pressures based on real-time direct measures of effort of breathing using RESPivice. RESPivice is an open-loop patient monitor that incorporates an esophageal manometry catheter and Respiratory Inductance Plethysmography Bands (RIP Bands) connected to a hardware box that passes signals to a laptop computer. [48, 49] The esophageal manometry catheter (which has an integrated feeding tube) is used for continuous effort of breathing calculations and RIP bands allow for measurement of phase angle (a measure of thoraco-abdominal asynchrony), and can be calibrated to measure flow or volume after extubation. [49]

B.3.3 Phase I trial using REDvent protocols: To test the feasibility of REDvent in MV children, Dr. Khemani led an open label, intervention only Phase I study enrolling 20 children <18 yr of age with pulmonary parenchymal disease and an anticipated intubation of > 48 hours (83% consent rate). Details of the REDvent management protocol are summarized in Figure 2. The acute phase of ventilator management was

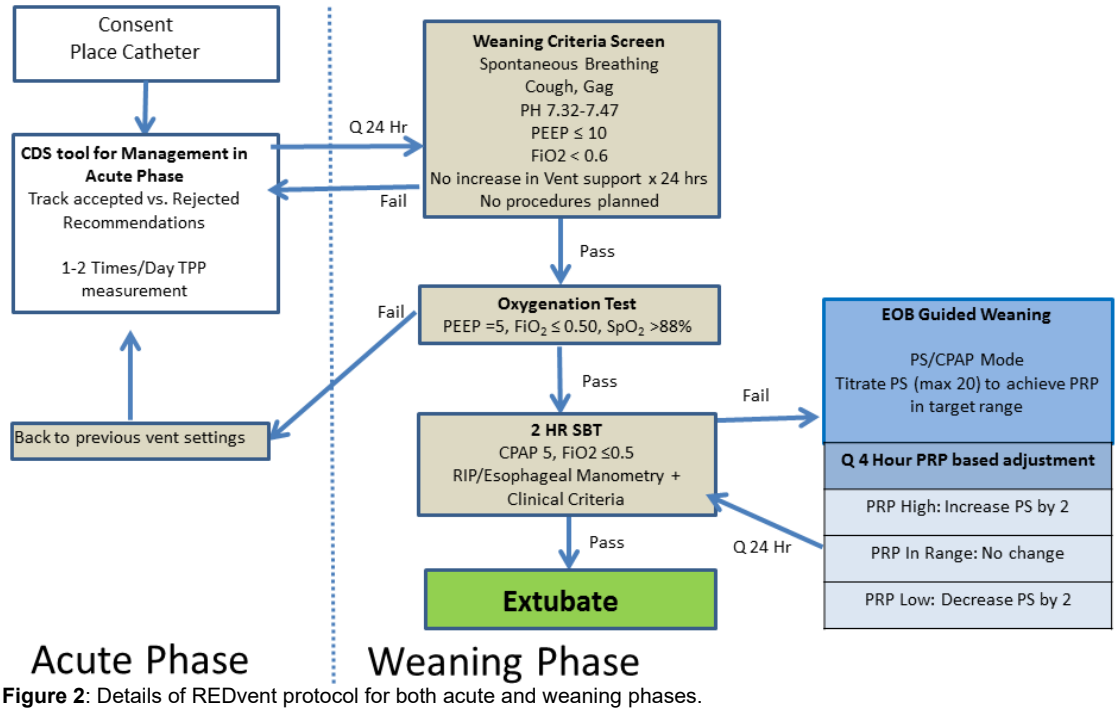

Figure 2: Details of REDvent protocol for both acute and weaning phases.

controlled by the CDS tool with a ventilator recommendation generated every 4 hr, or with a new blood gas value. If a blood gas was not available at the 4 hr interval, then non-invasive parameters (pulse oximetry and end-tidal CO2) were used to provide estimates for the adequacy of oxygenation and ventilation based on prediction models we have previously validated. [50] When patients met weaning criteria (no increase in ventilator support for 24 hr, spontaneous breathing, PEEP ≤ 10 cmH2O, FiO2 ≤ 60%), they had an oxygenation test (decease PEEP to 5, Fio2 ≤ 0.5, maintain SpO_2 > 88%). If they passed the oxygenation test, they were then given a SBT on CPAP of 5 cmH_2O and then extubated (i.e. both clinical and effort of breathing criteria were met). If they failed the SBT, they were initiated on the effort of breathing part of the study and pressure support was added to PEEP to maintain PRP in the target range. After patient 15, we modified the weaning protocol to allow 3 ranges for adjustment (Figure 2) to better fit with clinical practice and improve adherence. Every 4 hr, a recommendation was given to adjust pressure support by 2 cmH_2O to keep PRP in the target range (200-400) . The SBT and extubation evaluation were performed every 24 hr.

B.3.4 <u>The protocol has the potential to shorten duration of ventilation:</u> We have completed the Phase I study described above. During the acute phase, 698/966 recommendations were accepted (73% adherence). During the weaning phase 136/187 (73%) recommendations were accepted. However, after the protocol modification for the weaning phase, 96% of the recommendations were followed. Over 40 ***bedside*** respiratory therapists have used the acute and weaning protocols. A study respiratory therapist has been providing initial training of the bedside RT. In addition the study RT or PI has been available during the day and as needed by phone at night. Specific training sheets have been developed, overnight support by research personnel was generally minimal, and no safety concerns were identified. MV is generally weaned steadily in both acute and weaning phases. As the Phase I study did not have a control group, we used matched historical controls that were similar with respect to age and

initial hypoxemia severity, with a similar percentage of immune compromise, sepsis and pneumonia patients between groups. Patients treated with REDvent had larger changes in Peak Inspiratory Pressure and Ventilator Rate per day in the acute phase as compared with historical controls. REDvent was associated with approximately 2 fewer days on MV (25% reduction) compared to historical controls (p=0.36, Table 1). While not statistically significant due to the small sample size, **REDvent appears to lead to faster MV weaning**.

Table 1: Comparison between REDvent and historical controls	REDvent (n=19)	Matched Controls (n=90)
Matching Variables		
Age (years)	9.2 (3.2,12.3)	7.0 (0.9,14.2)
Oxygen Saturation Index (OSI)	15.9 (10.6,16.2)	14.1 (9.6,19.4)
High Frequency Oscillator (HFO)	17%	17%
Immune Compromised	39%	32%
Pneumonia	50%	58%
Sepsis	38%	39%
Outcomes		
Daily Change PIP Acute Phase	4 (2,5)	1.5 (1,3)
Daily Change Vent Rate Acute Phase	3 (0,4)	1 (0,2)
Length of MV (days)	**6.5 (4.9,8.7)**	**8.4 (4.5,13.9)**

B.3.5 Ventilator-induced respiratory muscle weakness is common in children, leading to failed extubation: Accurate quantification of the severity of diaphragm dysfunction is understudied, particularly in pediatrics. While diaphragm ultrasound can provide corroborative data about architectural changes, ultrasound does not directly measure strength. [3, 5, 7, 51, 52] Single measures of respiratory muscle strength (airway or esophageal PiMax) measured with maximal voluntary efforts during airway occlusion are regarded as the most appropriate tests in adults.[29] To specifically examine diaphragm strength (isolated from the intercostal muscles), two simultaneous pressure transducers (one in the esophagus and one in the stomach) can be used to calculate trans-diaphragmatic pressure. [29, 53] When patients are intubated, there is divergence in the literature as to whether maximal voluntary efforts can be guaranteed,[26, 29, 54-57] prompting investigators to use twitch stimulation of the phrenic nerve through electrical or magnetic coils with resultant measures of airway or esophageal pressure,[29, 58] . Although this technique has been applied in a very limited capacity in young children, it has high variability and limited reproducibility. [59-64]

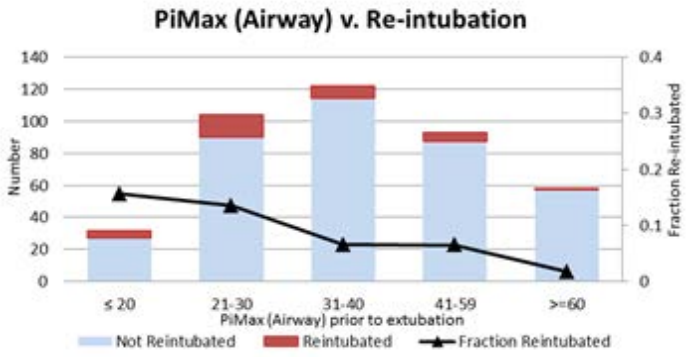

Figure 3: Re-intubation rates increase in a dose response fashion as a function of low aPiMax.

An analysis of the 409 patients enrolled in our previous study suggested that low PiMax (both airway (aPiMax) and esophageal (ePiMax)) measured during airway occlusion while the child is breathing spontaneously, was associated with re-intubation. [65] A trained provider (research respiratory therapist or study PI) performed airway occlusion maneuvers to measure both aPiMax and ePiMax, ensuring that the child was at end-exhalation and that the airway remained occluded for at minimum 3 consecutive breaths, but most of the time at least 5,[57] just before extubation. Measures of respiratory system capacity were obtained prior to extubation during airway occlusion, and measures of respiratory effort were obtained

both before and after extubation. Of the 409 patients, 34 were re-intubated within 48 hours (8.3%). Prior to extubation, re-intubation risk factors included lower aPiMax, and longer length of ventilation. After extubation, post-extubation upper airway obstruction (UAO), high respiratory effort or load (Pressure Rate Product (PRP), Pressure Time Product (PTP), Tension Time Index (TTI)) and high Phase Angle (PA) were associated with re-intubation. Because patients in this study had already passed SBTs, they generally had near normal compliance (low load), so pre-extubation respiratory effort was not associated with re-intubation. When looking specifically at measures of respiratory muscle capacity prior to extubation, there was a dose response relationship between lower aPiMax and re-intubation risk (Figure 3). Children with aPiMax ≤ 30 cmH_2O accounted for 33% of all extubated patients, but were responsible for 56% of all failed extubations (19/34). Thus, aPiMax alone is a marker of re-intubation risk (AUC 0.66 (0.57, 0.75).

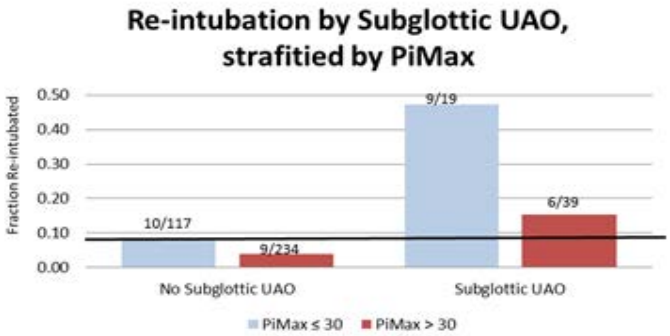

Figure 4: When children with low aPiMax develop high respiratory load (such as from post extubation UAO), they have very high re-intubation rates. Solid line is population average.

Nevertheless, combining aPiMax with measures of respiratory effort (after extubation) such as PRP better predicted re-intubation risk (AUC 0.77). For children with diminished respiratory muscle capacity (aPiMax ≤ 30 cmH_2O), re-intubation rates were always higher than the population average, and they became accelerated as effort increased (PRP>500). Children with maintained respiratory muscle capacity (aPiMax >30 cmH_2O) could tolerate moderate to high levels of load after extubation (PRP 500-1000), and re-intubation rates did not exceed the population average unless effort was very high (PRP > 1000). Post-extubation subglottic UAO was the most common reason for high respiratory muscle load after extubation, and when children with diminished respiratory muscle capacity (aPiMax ≤ 30 cmH_2O) had subglottic UAO after extubation, their re-intubation rates were 5.7 times higher than the population average (47.5% vs. 8.3%, Figure 4). The rate of aPiMax ≤ 30 cmH_2O was slightly higher for neonates (47%) compared to the other age groups, although this was not statistically significant (p=0.12; 30% infants (1-24 months), 30 % child age (2-11 years) and 34% adolescents (11-18 years)). Multivariable risk factors for re-intubation include primary intubation for neurologic disease, lower aPiMax, UAO post-extubation, higher PEEP before extubation, higher PRP after extubation, and lower height (AUC 0.823). This demonstrates that **respiratory muscle weakness contributes to extubation failure,** and maintaining respiratory muscle strength will likely reduce re-intubation rates even when respiratory load after extubation is high. These data further support **the hypothesis that children with respiratory muscle weakness will have more trouble weaning from MV** when respiratory load (compliance, resistance) may still be high**.**

B.3.6 Summary of Preliminary Data: We have demonstrated that 35% of MV children have respiratory muscle weakness at the time of extubation, making them 3 times more likely to be re-intubated, and nearly 6 times more likely to fail when respiratory load is high.[65, 66] We have also shown that current ventilator management in children likely exacerbates the development of respiratory weakness by lowering patient

effort of breathing well below normal physiologic values.[13, 14] To promote maintaining patient effort of breathing in a normal range we have developed and demonstrated the feasibility of having bedside providers use a computer-based ventilator management system throughout the entire course of MV. Patients managed with this system experienced a median 2 day reduction in the length of MV compared to historical controls. Together these data justify the next phase of this program of research, to test whether this ventilator management approach can lead to improved clinical outcomes in a robust randomized clinical trial, and to characterize the mechanisms underlying this improvement through detailed, serial assessments of the respiratory muscles.

C Study Objectives

C1 Primary Aim

SA1: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV. We expect that patients randomized to receive REDvent-acute will either pass their first SBT or experience a shorter duration of weaning when compared to usual care. In addition, patients randomized to receive REDvent-weaning will experience a shorter duration of weaning compared to usual care. Secondary outcomes include 28-day Ventilator Free Days and extubation failure.

C2 Secondary Aims

SA2: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes. We expect that diminished respiratory muscle strength (low PiMax), and diaphragm atrophy (ultrasound) will be prevalent after resolution of the acute phase of MV, and the combination of high respiratory load (or effort) with low PiMax will be a major factor leading to prolonged weaning and weaning failure (failure of SBT).

SA3: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness. We expect that after controlling for confounding variables like age, diagnosis, sedation, use of neuromuscular blockade, and other risk factors for neuromuscular weakness, children who maintain normal effort of breathing in the acute or weaning phases will have higher respiratory muscle capacity as measured by PiMax.

C3 Rationale for the Selection of Outcome Measures

C.3.1. Clinical outcome measures:

1. Primary Outcome – Weaning Duration
   Weaning duration is defined as the time from the first spontaneous breathing trial (SBT) until successful passage of an SBT or successful extubation (whichever comes first). Successful extubation is defined as removal of the endotracheal tube without re-intubation for at least 24 hours. SBT passage will be based on objective criteria, based on previous publications.

   a. Criteria for SBT passage: SBTs will be performed when weaning criteria are met, and the patient passes the oxygenation test (maintenance of SpO2 > 90% with FiO2 ≤ 0.5 and PEEP ≤ 5 cmH20). SBTs will be performed on CPAP ≤ 5 cmH_2O, for 2 hours duration. The following criteria represent rules for study defined SBT failure at any time point during the 2 hour SBT.

Variable	Failure within 2 hours
pH (arterial or capillary)	< 7.32
End tidal CO2	↑10 mmHg from baseline
Oxygenation	FiO2 >0.5 and SpO2 <90% on PEEP

	=5 cmH20
HR	↑ > 40 BPM over baseline
Rapid Shallow Breathing Pattern (RSBI) (bpm/ml/kg)	≥ 12
Pressure.Rate.Product (PRP)	>500
Retractions	Moderate or Severe

b. Rationale for passing SBTs vs. extubation in defining weaning duration: SBTs systematically assess the patient's readiness to resume unassisted ventilation, while extubation can be delayed after SBT passage (due to respiratory secretions, procedures, etc.). For this reason, SBT passage or successful extubation (whichever comes first) will define the end of the weaning phase. If a patient passes an SBT but is not extubated within 6 hr, ventilator management until extubation will continue as per the group to which the patient has been randomized for the current phase of ventilation. However the length of weaning for the primary outcome measure will be calculated as the time the patient passed the SBT. If a patient does not pass the SBT, but the clinical team elects to extubate the child (or the child has an unplanned extubation), and the child is not re-intubated within 24 hours, then the length of weaning for the primary outcome measure will be calculated as the time the patient was extubated.

2. Duration of Invasive Mechanical Ventilation (IMV)- Secondary Outcome
Duration of invasive ventilation is the number of days and hours that the patient is intubated (from insertion to removal), censored 60 days after study enrollment. For calculations, removal of the ETT will be calculated as the first time the tube is continuously absent for at least 24 hours. Re-intubation after 24 hours and subsequent periods of invasive mechanical ventilation within 60 days of study enrollment will be summed together to represent total duration of IMV.

3. Duration of Non-Invasive Mechanical Ventilation (NIV) after extubation– Secondary Outcome
Duration of non-invasive ventilation after extubation is defined as the number of days and hours that the patient is on oro-nasal mask CPAP with minimal pressure of 5 cmH20, or Bi-Level ventilation (at any pressure) after extubation, censored 60 days after study enrollment. For calculations, the end of Non-Invasive Ventilation will be calculated as oro-nasal mask CPAP (minimal 5 cmH20) or BIPAP as continuously absent for at least 24 hours. Resumption of NIV after 24 hours and subsequent periods of non- invasive mechanical ventilation within 60 days of study enrollment will be summed together to represent total duration of NIV after extubation.

4. Duration of Non-Invasive Mechanical Ventilation (NIV) before intubation– Secondary Outcome
Duration of non-invasive ventilation before intubation is defined as the number of days and hours that the patient is on oro-nasal mask CPAP with minimal pressure of 5 cmH20, or Bi-Level ventilation (at any pressure) prior to intubation. This is necessary to correctly compute ventilator free days. For calculations, the patient must have been on Non-Invasive Ventilation in the 24 hours prior to intubation.

5. Duration of Non-Invasive Respiratory Support (NRS) after extubation- Secondary Outcome
   Non-invasive respiratory support includes: High Flow Nasal Cannula (HFNC) or nasal-only modes of non-invasive ventilation (CPAP or Nasal IMV or BiPAP). It does not include oxygen therapy via face mask, nasal cannula, oxygen hood, or blow by oxygen alone. Duration of NRS after extubation is defined as the number of days and hours that the patient is on NRS after extubation, censored at 60 days after study enrollment. For calculations, the end of NRS will be calculated as NRS being continuously absent for at least 24 hours. Resumption of NRS after 24 hours and subsequent periods of NRS within 60 days of study enrollment will be summed together to represent total duration of NRS after extubation.

6. Re-intubation within 48 hours of extubation- Secondary Outcome
   Re-intubation will be defined as re-insertion of the endotracheal tube within 48 hours of the initial extubation.

7. Re-intubation within 7 days of extubation- Secondary Outcome
   Re-intubation will be defined as re-insertion of the endotracheal tube within 7 days of the initial extubation.

8. Ventilator Free Days- Secondary Outcome
   Because the acute phase of ventilation is often long and less predictable, weaning duration was chosen as the primary outcome because there is more variability in Ventilator Free Days (VFDs) than in weaning duration. However VFDs is a secondary outcome. VFDs will be calculated at 28 and 60 days, defined as total number of days after initiation of MV in which the patient is alive and not on ventilation. The components of length of mechanical ventilation used for VFD calculations include length of IMV (2 above), length of NIV after extubation (3 above) and length of NIV prior to intubation (4) above. Patients who die within the 28 or 60 days will have 0 28 or 60 Day VFDs respectively.

9. Use and duration of rescue therapies - Secondary Outcomes
   We will track daily whether the patient received any of the following "rescue therapies" which are frequently used for ARDS management: inhaled nitric oxide, High Frequency Oscillatory Ventilation, Prone Positioning, Extra Corporeal Life Support, Corticosteroids for lung disease/ARDS, Continuous Neuromuscular Blockade, Airway Pressure Release Ventilation.

C.3.2 Physiologic outcome measures: Our primary physiologic outcome surrounds respiratory muscle weakness. Previous research has highlighted the importance of using multiple assessments of respiratory muscles, as single tests may be misleading. [67] We will use esophageal manometry, airway pressure, and diaphragm ultrasound to evaluate direct and indirect measures of respiratory muscle strength.

1. Respiratory Muscle Strength (aPiMax- Primary Outcome; ePiMax – Secondary Outcome)**:**
   a. Physiologic measures of strength include airway and esophageal pressure during airway occlusion (aPiMax and ePiMax, respectively). Primary analysis is planned using aPimax (calculated as maximal change in airway pressure at end exhalation during airway occlusion for 3-5 breaths). Secondary analysis will use

ePimax (calculated as maximal change in esophageal pressure at end exhalation during airway occlusion for 3-5 breaths). Measurements will be obtained daily after the patient passes the oxygenation test.

b. Rationale: We found aPiMax better predicted re-intubation than ePiMax in our preliminary data. We believe that this is due to more artifacts in the esophageal pressure signal during airway occlusion, which are not present with airway pressure. To isolate diaphragm weakness, a second balloon catheter would be necessary to calculate trans-diaphragm pressure. However, this is not practical for repeated use in children and no double-balloon catheters are commercially available for infants. A second catheter in an already small esophagus may alter the signals further, and impede clinical care if the catheter is left in place. While we will measure both airway and esophageal PiMax, we plan to use aPiMax as the primary marker of respiratory system capacity. Our previous study evaluated PiMax parameters only at extubation, but we are confident the technique can be applied earlier (i.e., just prior to SBTs), and have obtained them successfully as part of our pilot study. Early in the course of MV, patients may be more sedated than they are at the time of extubation (but are still breathing spontaneously), but we have successfully measured both airway and esophageal PiMax in patients who are considerably more sedated, and in deeply sedated rhesus monkeys.[48] Sedated patients still produce reliable PiMax measurements when using our methodology, particularly when 5 occluded breaths are used. We will also calculate P0.1 (change in airway or esophageal pressure in the first 0.1 seconds of a breath attempt) which can be used to identify if sedation is affecting the results of the PiMax measurements. All PiMax procedures will be recorded for post-processing analysis.

2. Diaphragm Architecture**:** Serial measurements from diaphragm ultrasound will be performed daily to assess changes in diaphragm thickness during exhalation (Dte) during both acute and weaning phases. [3, 5-8, 26, 52, 68-73] For the acute phase, the main diaphragm ultrasound outcome is: change in diaphragm thickness from study initiation until the end of the acute phase. For the weaning phase it is: change in diaphragm thickness from the end of the acute phase until the end of the weaning phase. Because diaphragm ultrasound is non-invasive, it has advantages although it has not been validated against direct measures of respiratory muscle strength or weaning outcomes. We will attempt such a validation with this study, but have not selected it as the primary physiologic endpoint for that reason.

D Study Design

D1 Overview or Design Summary

We propose a single-center randomized controlled trial (150 children per arm) using REDvent (intervention arm) as compared with usual care ventilator management including a standardized daily SBT (control arm). Acute phase randomization will occur upon study enrollment, and patients who fail the first SBT will undergo a weaning phase randomization. We will obtain serial measurements of respiratory system capacity, load, effort of breathing, and diaphragm architecture throughout the course of MV.

D2 Subject Selection

D.2.1 Inclusion Criteria

1. Children > 1 month (at least 44 weeks Corrected Gestational Age) and ≤ 18 years of age AND
2. Supported on mechanical ventilation for pulmonary parenchymal disease (i.e., pneumonia, bronchiolitis, Pediatric Acute Respiratory Distress Syndrome (PARDS)) with Oxygen Saturation Index (OSI) ≥ 5 or Oxygenation Index (OI) ≥4 [74] AND
3. Who are within 48 hours of initiation of invasive mechanical ventilation (allow for up to 72 hours for those transferred from another institution)

D.2.2 Exclusion Criteria

1. Contraindications to use of an esophageal catheter (i.e. severe mucosal bleeding, nasal encephalocele, transphenoidal surgery) OR
2. Contraindications to use of RIP bands (i.e. omphalocele, chest immobilizer or cast) OR
3. Conditions precluding diaphragm ultrasound measurement (i.e. abdominal wall defects, pregnancy) OR
4. Conditions precluding conventional methods of weaning (i.e., status asthmaticus, severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal Life Support (ECLS), intubation for UAO, tracheostomy, DNR, severe chronic respiratory failure, spinal cord injury above lumbar region, cyanotic heart disease (unrepaired or palliated)) OR
5. Primary Attending physician refuses (will be cleared with primary attending before approaching the patient).

D2.3 Screening and Eligibility

Screening will occur daily to identify eligible patients. An automated report has been generated to facilitate screening which calculates the oxygen saturation index, oxygenation index, PF ratio, and SF ratio for all patients on mechanical ventilation in the ICU. Patients who have had qualifying hypoxemia (OSI >5 or OI >4) in the previous 24 hours will have their chart reviewed to determine complete eligibility based on meeting all inclusion criteria and no exclusion criteria.

D3 Study Interventions

The study intervention includes both acute and weaning phase components. A high level view of the study is summarized in figure 5 below.

D.3.1 Acute Phase: The acute phase is defined as the time from intubation until the patient meets weaning criteria,[15, 16] and passes the initial oxygenation test (decrease PEEP to 5 cmH_2O and FiO_2 to 0.5, Figure 6)**.**

D.3.2 Acute Phase, Intervention Arm (REDvent-acute): Patients will be managed with pressure control plus pressure support ventilation with the CDS tool that will recommend changes to ventilator settings every 4 hr or with a new blood gas. The computerized decision support (CDS) tool used by REDvent-acute is an electronic

protocol that makes recommendations at to adjust both ventilation (ventilator pressure or tidal volume and ventilator rate) and oxygenation (Positive End Expiratory Pressure and FiO2) to promote lung protective ventilation during the acute phase of MV. Details of the rules behind the actual protocols are in section I. PEEP/FiO2 is based on a PEEP/FiO2 table adapted from the Acute Respiratory Distress Syndrome Network protocol,[45] (R21HD061870, PI Newth). Ventilation is changed based on pH range, Peak Inspiratory Pressure, and Ventilator Rate. When the patient is breathing spontaneously during the acute phase, the Pressure.Rate.Product (PRP) is incorporated into the algorithm. The pH based recommendations are followed if increasing support is recommended. If the pH based recommendation is to decrease support, it will only do so if the PRP is below 200. If the PRP is between 200-400, support is maintained. If the PRP is above 400, the protocol will recommend increasing driving pressure (Delta P) by 2 cm H20, to a max of 35 cmH20. The use of High Frequency Oscillatory (HFO) Ventilation as a rescue therapy will be left to the bedside clinicians, but HFO management will continue to be protocolized using the HFOV CDS tool (expected use: 10-15% in this cohort). This protocol has a MAP/FiO2 table, and also recommends alterations in Amplitude and Hertz based on pH. Details of the rules of the protocols are in section I.

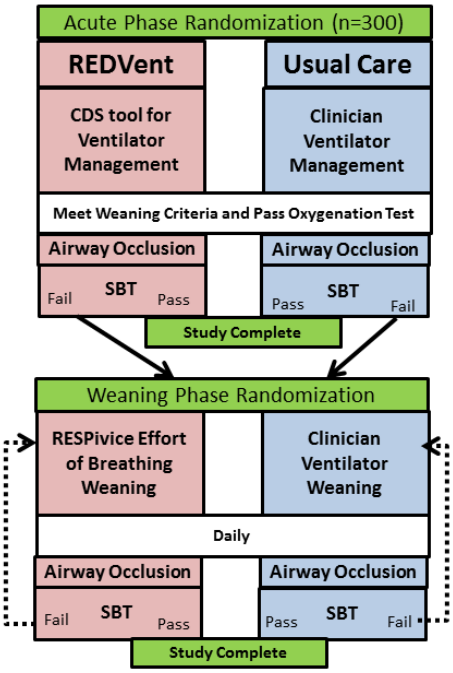

Figure 5: High level view of study interventions for both arms, during acute and weaning phases

D.3.3 Acute Phase, Control Arm: Ventilator management will be per usual care until the patient meets weaning criteria and passes the oxygenation test (Figure 6).

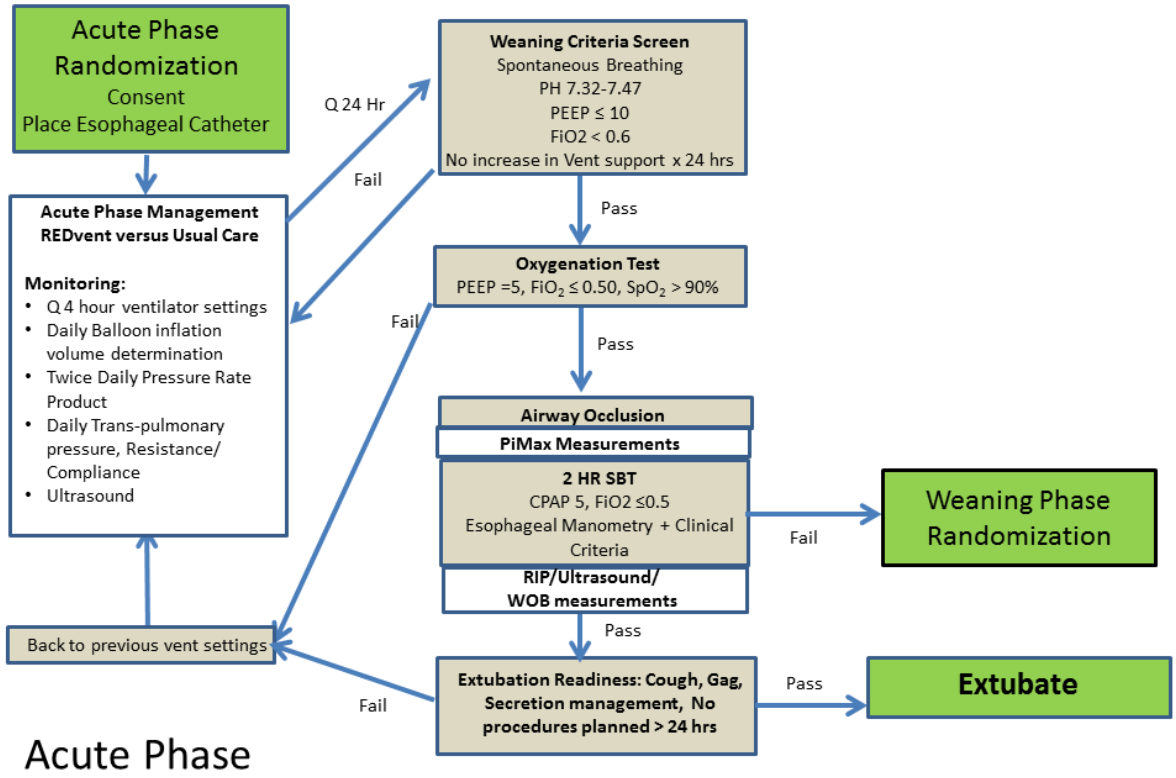

Figure 6: Acute Phase schematic, both arms

D.3.4 Acute Phase Monitoring, both arms: Patients will be fitted with an esophageal manometry catheter, will undergo diaphragm ultrasound measurements, and will be connected to RIP bands during SBTs. Once the patient passes the oxygenation test, an airway occlusion maneuver will be performed to measure neuromuscular strength, followed by a SBT. Daily SBTs are required and will be performed between 9 and 11 AM on CPAP of 5 cmH_2O. The primary study outcome (length of the weaning phase) is defined as the time from initiation of the first SBT until successful passing of an SBT (or extubation, whichever comes first). We will use validated objective criteria to define successful passing of the SBT, and track delays in extubation (> 6 hr between SBT passing and extubation). These criteria are based on our previous publications and are detailed in the description of the primary outcome above, and again below. [16, 75] Patients who fail the initial SBT will move on to the weaning phase, and will undergo the weaning phase randomization to allocate treatment or control arms for weaning management.

D.3.5 Spontaneous Breathing Trials and success/failure

Variable	Failure within 2 hours
pH (arterial or capillary)	< 7.32
End tidal CO2	↑10 mmHg from baseline
Oxygenation	FiO2 >0.5 and SpO2 <90% on PEEP = 5 cmH20
HR	↑ > 40 BPM over baseline
Rapid Shallow Breathing Pattern (RSBI) (bpm/ml/kg)	≥ 12
Pressure.Rate.Product (PRP)	>500
Retractions	Moderate or Severe Retractions

For the outcome of SBT passage, if any of the above criteria are met during the 2 hour SBT, the patient will be labeled as failing the SBT for study purposes. Once any of these failure criteria are met, the respiratory therapist will alert the clinical team. The clinical team may choose to stop the SBT, in which case the patient will be returned to the previous ventilator settings, and weaning phase randomization will occur. If the patient is randomized to REDvent-weaning, they will be placed in PS/CPAP mode and pressure support will be titrated to achieve PRP between 200-400 (to max of 20). PEEP may be adjusted between 5 and 10 cmH20. The clinical team may alternatively choose to continue the SBT or to extubate the patient. If the patient is extubated, post-extubation management (and subsequent re-intubation management) will be usual care. If the patient is not extubated but the SBT is terminated by the clinical team, then weaning phase randomization will occur at that point.

Monitoring during the SBT will include placement of Respiratory Inductance Plethysmography (RIP) bands and a spirometer. Vital signs, physiologic measurements, and data from RIP and esophageal manometry will be recorded every 30 minutes during the SBT. A study ultrasound to measure diaphragm contractile activity will occur approximately 15 minutes into the SBT.

If the patient successfully passes the SBT, extubation readiness criteria will be confirmed (i.e. cough, gag, handling secretions, no procedures planned). If the patient meets extubation readiness criteria, the recommendation will be for extubation to the clinical team. If the patient does not meet extubation readiness criteria, they return to acute phase management (to whichever group they were randomized), and another SBT will be repeated 24 hours later. If a recommendation for extubation was given but actual extubation is delayed beyond 6 hours, the reasons will be recorded on the case report forms, and the acute phase intervention will be resumed. If the patient is extubated as recommended, the esophageal catheter and RIP bands will remain in place for 1 hour after extubation to monitor post-extubation effort of breathing.

If the patient fails the SBT, they will go on to the weaning phase randomization.

D.3.6 Weaning Phase: The weaning phase is defined as the time from the first SBT until the patient successfully passes an SBT.

D.3.7 Weaning Phase, Intervention Arm (REDvent-weaning): The weaning phase in the intervention arm uses esophageal manometry and a custom built hardware and software package for effort of breathing guided management. The patient will be placed in a pressure support mode of ventilation and PRP will be monitored continuously, adjusting pressure support (to a max of 20 cmH20) every 4 hr to maintain PRP in the target range (Figure 7). Effort of Breathing guided management will continue until the patient passes a SBT. The esophageal balloon is inflated to a daily prescribed volume every 4 hours prior to assessment, based on an optimal filling volume algorithm. The median PRP over 10-20 breaths during calm periods of breathing (i.e. not agitated, not recently suctioned etc) is inputted into the computer decision support tool, which subsequently generates the recommendation regarding changing the level of pressure support.

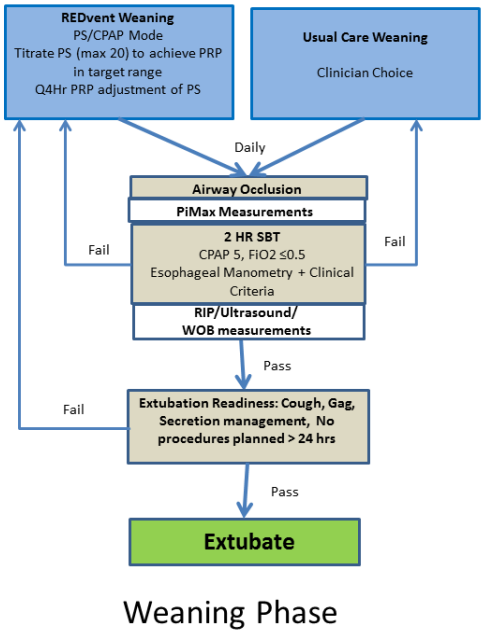

Figure 7: Weaning Phase schematic, both arms

D.3.8 Weaning Phase, Control Arm: Ventilator management will be per usual care until the patient passes a SBT.

D.3.9 Weaning Phase, Monitoring both groups: In both groups, a daily airway occlusion maneuver and SBT will be performed, with the same rules above in section D.3.5 regarding SBT passage and monitoring.

D.3.10 Post-extubation Management: The decision to use non-invasive ventilation and other post-extubation management will not be protocolized, regardless of study arm. Patients who are re-intubated after a planned extubation (regardless of study arm) will subsequently receive usual care ventilation. The esophageal catheter and RIP bands will be removed 1 hour after extubation.

D.3.11 Suspension of Weaning Phase: Suspension of the weaning phase is permitted for up to 12 hours for situations such as procedures, increased need for sedation preventing adequate spontaneous breathing, transient increase in ventilator support etc. As soon as the patient appropriately meets weaning criteria (based on weaning criteria screen Figure 6), the weaning phase intervention is resumed.

D.3.12 Failure of the Weaning Phase: If the weaning phase is suspended for > 12 hours and the patient no longer meets weaning criteria at the 12 hour mark (Figure 6), then the acute phase of management and monitoring is resumed. The patient will be managed as per their pre-assigned acute phase group (i.e. REDvent-acute or usual care). Once weaning criteria are met, an SBT will again be performed. If the patient fails the SBT, then the weaning phase intervention to which they were previously randomized (REDvent-weaning or usual care) is resumed. The frequency with which weaning failure occurs in both arms will be tracked as an adverse event.

D.3.13 Termination of study interventions at 28 days: If the patient has not passed the SBT by day 28 after enrollment, study interventions and daily measurements will be terminated. All ventilator management will be as per usual care. Clinical outcomes will continue to be followed.

D.3.14 Post Enrollment exclusion criteria: Patients who develop exclusion criteria after study enrollment that preclude continuation of the study interventions (i.e. use of ECLS, new condition requiring removal of esophageal catheter) will have the study protocol and measurements terminated, but clinical outcomes will continue to be followed and analysis will be as per intention to treat. For patients who are made allow natural death status during the study, parents will be given the option to either continue the study protocol, or withdraw from the study. Clinical outcomes will continue to be followed. Patients who develop a condition which may preclude calculation of secondary

outcomes (i.e. diaphragm ultrasound or RIP bands) will continue to receive study interventions, and all planned study measurements which can reasonably be obtained.

D4 Measurement of Study Variables

Demographics, clinical variables, and outcomes will be measured as detailed in the table below (data collection timeline). To ensure the adequacy of randomization and understand the risk factors that may contribute to neuromuscular weakness and weaning failure, we will gather detailed, serial data for variables that may be related to weaning duration and development of neuromuscular weakness.[1, 5, 6, 8-10, 26] These variables are based upon our recent consensus-based guidelines for clinical trials in children with pediatric ARDS. [76] Identical measurements of respiratory parameters will occur for all patients enrolled in the study (regardless of study arm) (1) serially during both acute and weaning phases, (2) during airway occlusion prior to SBTs, and (3) during SBTs (Table below).

D.4.1 Serial respiratory measurements during acute and weaning phases: We will measure patient effort of breathing twice daily with esophageal manometry (using Pressure Rate Product [PRP] and Pressure Time Product [PTP]) and once daily using diaphragm ultrasound (using Diaphragm Contractile Activity [DCA]), during the acute and weaning phases in both arms. DCA is obtained by measuring the thickness of the right hemi-diaphragm and calculating the percent difference between diaphragm thickness on inspiration and exhalation. Diaphragm ultrasound measurements will be performed independently by 2 practitioners, one of whom is specifically trained in acute care ultrasound. We will also use ultrasound to measure diaphragm thickness on exhalation and monitor how this changes serially over time as a measure of the architecture of the diaphragm. Finally, we will measure respiratory load (resistance, compliance) daily using spirometry. The clinical team will remain blinded to the results of these measurements in both arms.

D.4.2. Spontaneous Breathing trial respiratory measurements during Airway Occlusion: Prior to each SBT, we will perform a standardized airway occlusion maneuver to measure neuromuscular capacity with aPiMax (airway) and ePiMax (esophageal), as described in the Preliminary Data. In addition, during airway occlusion we will measure DCA (as above) [5, 7, 51, 52], to provide complementary data to PiMax. The clinical team will remain blinded to the results of these measurements in both arms.

D.4.3 Weaning trial measurements during SBTs: During SBTs, respiratory effort and capacity will be measured with PRP, PTP, inspiratory pressure from esophageal manometry (Pi), Pi/ePiMax, Tension Time Index (TTI), Phase angle (PA), and DCA. Patients will be monitored continuously during the SBT, and all of these measures will be recorded at the beginning of the SBT, and then every 30 minutes (for 5 minute periods) to monitor respiratory muscle endurance over time. The PRP measurements will be shared with the clinical team in both arms because they will be used to help define passage of SBTs (as above). Clinical providers will remain blinded to the results of the other measurements in both arms.

Data Collection timeline	Enroll-ment	Acute (Daily)	Weaning (Daily)	SBT	Post-Extubation
Demographics (age, race, gender, past medical history, primary diagnoses, comorbidities, PRISM-III-12 severity of illness scores, height, weight)	■				
Clinical Variables (total dose of sedatives, analgesics, highest/lowest/modal sedation scores, pain scores, corticosteroids, aminoglycosides, fluid balance, caloric and protein intake, hypoxemia markers, dead space markers, ventilator type and settings (q6h), blood gasses (all), inotropes/vasopressors, organ failure scores (PELOD), procedures)	■	■	■		
Effort of Breathing and Respiratory Load					
Esophageal Manometry: PRP, PTP, TTI, Pi		■	■	■	■
Respiratory Inductance Plethysmography [44]: Phase Angle (PA)				■	■
Ultrasound: Diaphragm Contractile Activity (DCA)		■	■	■	
Spirometry**:** Resistance, Dynamic and Static Compliance		■	■		
Respiratory Muscle Strength (during airway occlusion)					
Esophageal Manometry: Esophageal PiMax (ePiMax)				■	
Airway Pressure: Airway PiMax (aPiMax)				■	
Ultrasound: DCA during airway occlusion				■	
Diaphragm Architecture (Thickness on Exhalation)	■	■	■		
Outcomes (Weaning Duration, VFDs and components, re-intubation, Non-Invasive Ventilation use and duration, ICU, Hospital, 90-day mortality)					■

D.4.4 Rationale for respiratory measures: Previous research has highlighted the importance of using multiple assessments of respiratory muscles, as single tests may be misleading. [67] We will use four classes of respiratory monitoring: esophageal manometry, diaphragm ultrasound, RIP, and ventilator/clinical data. Our primary interest is respiratory muscle strength, which is best characterized during airway occlusion with PiMax. PiMax measurements will be done as soon as the acute phase has resolved, and daily during the weaning phase, because PiMax is not feasible to measure during the acute phase of MV because patients may be too unstable to tolerate airway occlusion. Serial measurements from diaphragm ultrasound can and will be performed daily to assess changes in diaphragm architecture during both acute and weaning phases [3, 5-8, 26, 52, 68-73]. Because diaphragm ultrasound is non-invasive, it has advantages although it has not been validated against direct measures of respiratory muscle strength or weaning outcomes. We will attempt such a validation with this study. We anticipate DCA and PRP will provide complementary information regarding patient effort. To isolate diaphragm weakness, a second balloon catheter would be necessary to calculate trans-diaphragm pressure. However, this is not practical for repeated use in children and no double-balloon catheters are commercially available for infants. A second catheter in an already small esophagus may alter the signals further, and impede clinical care if the catheter is left in place. While this leaves open the possibility of intercostal muscles contributing to the weakness, we will complement these data with architectural changes to the diaphragm on ultrasound.

D5 Co-Interventions

Sedation: Sedation management will be controlled in both arms targeting a State Behavioral Scale, based on the sedation protocol used in the NHLBI funded RESTORE clinical trial. [75] This scale is being implemented for routine use in the Pediatric Intensive Care unit. Each day the clinical team will select an SBS target on morning rounds, based on the status of the patient. The level of sedation and SBS score will be monitored every 4 hours in each group. Generally acceptable SBS targets range from -2 to 0. For the acute phase management, the suggested SBS target is -2, and for the weaning phase of ventilation the SBS target is -1. A nurse guided protocol is not currently in place for automatic adjustment of sedation to meet the SBS target, but the nurse will administer as needed medications to meet the SBS target if it is above target, and will consult with the MD to decrease sedation if the SBS is below target.

Inhaled Nitric Oxide: Inhaled Nitric Oxide is frequently used for clinical care in our intensive care unit for children with ARDS. Like High Frequency Oscillatory Ventilation and other rescue therapies, the decision to begin inhaled nitric oxide will be left to the discretion of the clinical team. However, for patients in REDvent Acute, inhaled nitric oxide is built into the computerized protocol management of PEEP/FiO2. Consistent with the ICU protocol for nitric oxide weaning, once FiO2 is reduced to 0.6, if oxygenation is adequate or high, weaning of nitric oxide will be recommended (see section I for details).

Quadriceps Ultrasound: Critically ill patients lose strength and muscle mass when in the intensive care unit, which may contribute to long term functional impairment. While functional assessment and strength testing is most accurate, they are difficult to do in children, or on sedated, non-cooperative patients. Ultrasound can measure muscle thickness and echogenicity, and can document progression of muscle atrophy.[3] The quadriceps femoris muscle group is most commonly measured, with a demonstrated relationship between strength and quadriceps femoris muscle thickness. Adult studies have documented that the quadriceps muscle thickness and cross sectional area decreases through the ICU course, correlates with length of stay and muscle strength and, less consistently, function at discharge. In most studies, ultrasound has high accuracy and inter-rater reliability. In children, the literature on quadriceps muscle thickness measurement by ultrasound is limited to comparing normal children to those with neuromuscular disease. While the proposed REDvent intervention is specifically targeting prevention of diaphragm atrophy, critical illness itself can lead to atrophy of other muscles. As such, in addition to measuring the change in diaphragm thickness daily, we will also measure the change in quadriceps muscle thickness daily, to help understand whether REDvent can modulate quadriceps muscle atrophy, of if the degree of quadriceps muscle atrophy has an interaction with the potential benefit of REDvent on diaphragm atrophy or strength. In each patient while supine with their feet pointing up, we will measure quadriceps muscle thickness at two points, in the midsaggital plane for each thigh. Like diaphragm ultrasound measurements, multiple providers will obtain measurements daily, to ensure reproducibility and inter rater reliability.

D6 Statistical Considerations

D.6.1. Randomization Strategy and Blinding

Consenting subjects will be **block randomized** to intervention or control arms for the acute phase based on age group: infant (30 days -365 days), child (366 days to ≤8 years), and older child/ adolescent (9-18 years); and immune suppression. For study purposes immune suppressed patients will be defined as: patients with congenital or acquired conditions (including medications) which result in marked inability to respond to antigenic stimuli. Examples of immune suppression include: oncologic disease with recent chemotherapy or radiation, congenital immunodeficiency, HIV, rheumatologic condition on chemotherapy, allogeneic or autologous stem cell transplant, solid organ transplant, or any other condition in which immunosuppressive medications are prescribed. Block randomization will be based on random block sizes of 4, 6 and 8 within the strata above, and loaded into opaque envelopes by the statistician for the study team to determine treatment arm at the time of randomization. Weaning phase randomization will be block randomized by REDvent-acute phase group, age, and immunosuppressed status using the same methodology. Although **blinding** is not possible given the open label nature of the intervention, analysis will be blinded to treatment groups, and performed by an independent statistician.

D.6.2 Rationale for Randomization Strategy: Age stratified randomization is necessary because *age is an important biological variable* likely to confound the relationship between respiratory muscle weakness and length of weaning. This will ensure an equal age distribution amongst treatment groups. Age groups are based upon accepted pediatric definitions, and have been used in numerous other pediatric RCTs. Neonates (< 1 month) have been excluded because they are often managed with different ventilator strategies and because normal values for PiMax are lower in neonates [63, 64]. Immunosuppression is a known risk factor which affects duration of ventilation and weaning, and an imbalance in immunosuppression between groups has been shown to significantly confound previous pediatric mechanical ventilation studies. The additional weaning phase randomization is necessary because we anticipate an imbalance of the number of patients who will be extubated after the acute phase between REDvent-acute and control groups. Acute phase management may have a sustained effect on neuromuscular strength that will affect the duration of weaning. To understand whether the REDvent strategy during the weaning phase can prevent prolonged weaning, risk factors for prolonged weaning (which may be different based on acute phase management) need to be rebalanced with a second randomization. Ultimately, this will allow us to determine the independent utility of REDvent-acute and REDvent-weaning components.

D.6.3 Preparation of the Analysis Data Set

Datasets for analyses consist only of data for which all queries have been resolved. In addition to data management steps to reduce error in data acquisition and entry, a biostatistical cleaning will focus on inconsistencies, missing data and outliers in variables related to the derivation of key outcomes. These activities will be ongoing throughout the study and will involve both the data management team and the biostatistics team.

Preplanned construction of new variables will be conducted in accordance with the study hypotheses and analysis plans. Variable transformation may be required for interpretive and statistical purposes. With respect to the primary outcome of weaning duration, patients who do not progress to the weaning phase within 28 days (i.e. death, prolonged severe illness) will not be included in analysis of the primary outcome, but will be considered for secondary outcomes.

D.6.4 Statistical Analysis Plan

For all variables, descriptive statistics will be calculated, including means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Data will be examined for skewness, outliers, and systematic missing data. Transformations will be undertaken as needed. Comparisons of demographic and baseline variables will be obtained by treatment group.

D.6.4.1 SA 1 Analysis Plan: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV (Primary outcome).

Primary analysis and sample size: The primary outcome for this aim is weaning duration. Because we seek to understand whether REDvent-acute and/or REDvent weaning have an independent effect on length of weaning, we propose a sample size to adequately power 3 separate comparative analyses: **(a)** REDvent-acute versus Acute Phase control **(b)** REDvent-weaning phase versus Weaning Phase control **(c)** REDvent both phases versus control both phases. We expect up to 13% mortality before the first SBT based on our Preliminary Data. These patients will not be included in the analysis for the primary outcome. From our pilot data (REDvent in both acute and weaning phases), the duration of the weaning phase in the intervention arm was 2.2 days, compared to 4 days in historical controls with a standard deviation of 2.1 days in the intervention arm and 2.8 days in the historical controls.

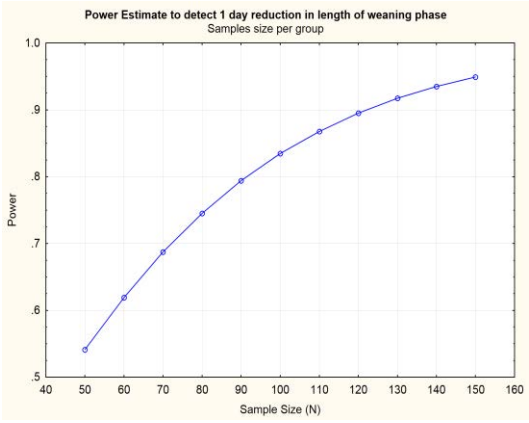

Figure 8: Power curve for a 1 day reduction in weaning

Comparison (a) REDvent-acute versus control**:** A 1-day reduction in length of weaning is considered clinically significant (less sedative exposure, fewer nosocomial infections, lower healthcare costs). With a sample size of 300 patients (150 per arm), up to 13% mortality and 7% attrition or incorrect randomization, a minimum of 240 patients (120 per arm) will be available for analysis of the acute phase. Power is based on 2 planned methods for analysis: cox proportional hazard ratios for multivariable analysis and univariate analysis with an independent t-test using log transformation (as needed) to account for the expected distribution of weaning duration. For univariate analysis using the assumptions above, we would be able to detect a ≥ 1-day reduction in weaning duration with an alpha of 0.05 and power of 0.9 (Figure 7). For the cox proportional hazard model, we would be able to detect a relative hazard ratio of 1.5 (ratio between control/intervention group) with a power of 0.9 or a hazard ratio of 1.4 with a power of 0.8.

Comparison (b) REDvent-weaning versus control: Patients who fail the initial SBT will undergo the weaning phase randomization. From our pilot data, approximately 25% of patients exposed to the intervention passed the initial SBT, corroborating previous studies. [15] Thus, at least 180 patients (90 per arm) will receive weaning phase interventions. Using the same assumptions as above, we will be able to detect a ≥ 1 day reduction in the length of the weaning phase (Figure 8), or a hazard ratio of 1.5 with an alpha of 0.05 and power of 0.8. Patients who do not pass the SBT by 28 days post the

weaning phase randomization will be censored for analysis, as study interventions and daily monitoring will end on day 29.

Comparison (c) REDvent versus control both phases: We will get an assessment of the cumulative effect of the intervention by comparing patients who received both REDvent-acute and REDvent weaning to patients who received only usual care in both phases. Because the rates of passage of the first SBT will differ between groups, there will not be an equal number of patients exposed to REDvent only as control only. Based on the assumptions above, we anticipate that of the 240 patients included in the analysis of weaning duration, 78 will be REDvent only, 72 will be control only, and 90 will be mixed. As such, the expected sample size comparing REDvent only to control only would allow us to detect a ≥ 1.1- day reduction in weaning duration with a hazard ratio of 1.6 with a power of 0.8 and alpha of 0.05; or a ≥ 1.3- day reduction in weaning duration with a hazard ratio of 1.6 with a power of 0.9.

All patients will be analyzed in the groups to which they were randomized for weaning duration, following intention to treat principles (allow for up to 7% incorrect allocation or attrition). Clinical variables (data collection table) will be tracked and compared between intervention and control groups for all 3 of the planned analyses (a-c). If there is an imbalance in any variable that may confound the relationship between weaning duration and REDvent, we will build a multivariable cox proportional hazard model to ensure that the measured treatment effect on weaning duration is retained after multivariable adjustment.

Secondary Outcomes for SA 1: The 28 and 60 Day Ventilator Free Days (28D VFD, 60D VFD) will be secondary outcomes of this aim. Groups for VFD analysis will be based on any exposure to the intervention (acute or weaning) because some patients will never undergo a weaning phase randomization (i.e. died or were extubated right after the acute phase). If patients who died as well as those who dropped out are included in the VFD analysis, with the assumptions above regarding expected passing rate of SBTs, the estimated distribution of patients in 3 distinct groups will be: (a) REDvent only (n=108); (b) REDvent and control (n=90); (c) control only (n=102). We anticipate children in the REDvent only arm will have the most 28 D VFDs (anticipation 22), and those in the control only arm the least (anticipation 20). Directly comparing control only patients to REDvent only patients, with an expected standard deviation for VFDs between 5 to 9 days, we will be able to detect a 2-day change in VFDs between groups with a power between 0.35 and 0.82. Re-intubation rates are expected to be 10%, allowing us to confirm that REDvent is not inferior to usual care in regards to re-intubation with a non-inferiority margin of 0.10 with a power of 0.8 and alpha of 0.05. Finally, to ensure that REDvent is promoting greater patient effort of breathing and that the intervention does not alter clinical practice in the usual care arm, we will compare time weighted average values for direct measures of patient effort of breathing (PRP, PTP, Diaphragm Contractile Activity), and ventilator settings between intervention and control groups, and monitor the separation between groups over the time of the study.

D.6.4.2 SA2 Analysis Plan: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes.

Analysis and Sample Size: The primary outcome of this aim is weaning duration (as defined above). For this analysis, we will compare how each respiratory measure detailed in the data collection table relates to weaning duration. For respiratory muscle strength we will compare the first measured aPiMax (after resolution of the acute phase, before the first SBT), the trajectory and value of the daily aPiMax during the weaning

phase prior to extubation, the lowest and highest measured aPiMax, and aPiMax on the day of extubation against weaning duration. For analysis, aPiMax will be dichotomized at 30 cmH2O (based on our preliminary data), and weaning duration will be compared between patients with aPiMax > 30 versus ≤ 30 cmH2O using a t-test with or without log-transformation, or Mann-Whitney U test, depending on the distribution. From our preliminary data, we anticipate at least 35% of patients (n=84) will have aPiMax ≤ 30 cmH2O. Based on a similar power analysis as presented above, this would allow us to determine whether low aPiMax is associated with a ≥ 1-day increase in weaning duration, with an alpha of 0.05 and power of 0.8. We will perform identical analysis for ePiMax.

Diaphragm Thickness analysis will compound daily ultrasound measures to detect the relative change in diaphragm thickness from study day 1 until passage of an SBT. We will compare the change in thickness after resolution of the acute phase (on the day of the first SBT) against weaning duration, in a similar manner as proposed above for aPiMax. For analysis, diaphragm thickness will be tested as a continuous variable (with Spearman's or Pearson's Correlation), but also categorized into 3 groups (loss of > 10% in thickness, maintenance of thickness (-10% to +10%), and increase in size of > 10%) to account for the potential ill effects of diaphragm hypertrophy (expected in about 10% of patients), using Analysis of Variance (ANOVA) to compare weaning duration between groups. We will characterize how diaphragm thickness changes daily during the weaning phase compared to the thickness on study day 1, as well as the daily thickness compared to that on the day of the first SBT. This will be used to determine whether patients whose trajectory of diaphragm atrophy continues during the weaning phase have a longer weaning duration compared to those who maintain diaphragm thickness or have increased thickness during the weaning phase. We anticipate high correlation between aPiMax and diaphragm atrophy, such that the proportion of patients with > 10% loss in diaphragm thickness will be similar to the proportion of those with aPiMax ≤ 30 cmH2O, resulting in the same sample size that yield adequate power, as above.

Respiratory load (resistance and compliance), effort (PRP, PTP) and combination measures of capacity, load or effort (TTI, Diaphragm Contractile Activity, Phase Angle) will be measured daily during or just before SBTs, as detailed in the data collection table. Analysis of each of these measures against the primary outcome will mimic what is presented above for aPiMax and Diaphragm thickness, with correlation for continuous variables, as well as categorization into distinct ranges for ANOVA.

Secondary Outcomes, SBT failure: In addition to weaning duration, we will also examine whether the respiratory measures in the data collection table taken just prior to or during each SBT are associated with the patient passing the SBT. For example with aPiMax and ePiMax, we will examine if there is a dose response relationship between PiMax measured just before the SBT and the rate of passage of the subsequent SBT (e.g., similar to Figure 3). In addition, we will compare mean or median values for aPiMax between patients who pass versus fail the SBT using a t-test or MWU test. Finally, we will examine aPiMax as a continuous variable to determine its ability to discriminate passage of the subsequent SBT using the Area Under the Curve (AUC) of the Receiver operating Characteristic Plot (ROC). Similar analysis will be done for all other respiratory measures in Table 2, and we will compare the AUCs (using a Chi-squared test) for each individual respiratory parameter against the others to identify which of these tests have the highest sensitivity, specificity, and overall discrimination of SBT failure. We will subsequently generate multivariate logistic regression models to identify which combination of these measures of capacity, architecture, load, and effort retain an independent association with SBT failure. Because SBTs will be repeated daily, we will use a hierarchical logistic regression model to control for repeated measures from

each patient as well as controlling for the other potential confounding variables detailed in the data collection table. We anticipate that 240 patients will undergo SBT testing, and 90% of these patients will pass the SBT within 28 days of the weaning phase randomization. As such, we would be able to include at least 20 variables in a multivariable hierarchical logistic regression model. Finally, we will determine whether common "phenotypes" for weaning failure can be determined. We anticipate four possible phenotypes by combining information from all available measures of capacity, load, effort, and architecture. Based on our preliminary data, we anticipate that patients with high load will be more likely to fail weaning, but that this effect will be more pronounced if they have diminished respiratory muscle capacity. We hypothesize that the rates of passage of the SBT will increase incrementally from phenotype 1 to 4: (1) Diminished capacity, high load and effort; (2) Normal capacity, high load and effort; (3) Diminished capacity, low load and effort; (4) Normal capacity, low load and effort. These phenotypes are exploratory; thus, no power analysis is provided.

D.6.4.3 SA3 Analysis Plan: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness.

Analysis and Sample Size: The primary outcome of this aim is aPiMax < 30 cmH2O.The analysis will focus on determining whether the degree of patient effort of breathing is independently associated with the development of respiratory muscle weakness. PRP will be the primary measure of effort of breathing, and will be measured twice daily in both acute and weaning phases. Secondary measures of effort of breathing include DCA and PTP. For the acute phase, we will generate a time- weighted average PRP during the acute phase and graph it against aPiMax at the first SBT, anticipating a positive correlation (higher average PRP values associated with higher aPiMax). We will subsequently dichotomize aPiMax at the first SBT and compare mean time weighted average PRP in the acute phase between aPiMax groups (> 30 vs. ≤ 30 cmH2O). For the weaning phase, we will graph the changes in aPiMax throughout the weaning phase (from first failed SBT until successful SBT) against time-weighted average PRP, with the anticipation that low PRP will be associated with either further reductions in aPiMax, or no improvement, while PRP in the physiologic range of 150-400 will be associated with improvement in aPiMax. We will subsequently dichotomize aPiMax (at 30 cm H2O) at the time of successful passage of an SBT and compare time-weighted average PRP in the weaning phase between aPiMax groups. Subsequently, we will build a multivariable logistic regression model on the outcome of aPiMax ≤ 30 cmH2O to determine if time-weighted PRP in the acute phase, weaning phase or both have an independent association with preserving aPiMax, after controlling for confounding variables (data collection table). We anticipate that 35% of patients (at least 80) will have aPiMax ≤ 30 cmH2O, allowing for inclusion of at least 9 variables in the multivariable model. Secondary goals are to characterize other variables that retain an independent association with low aPiMax, which are likely to include age group, use and dose of neuromuscular blockade, driving pressure during the acute phase of ventilation, sepsis, corticosteroids and use of aminoglycoside antibiotics.

D.6.5 Dissemination plan and data archiving

The results of this clinical trial will be critically important to disseminate to critical care clinicians, both pediatric and adult. In the final two years of the study the Steering Committee will develop the strategic plan for the comprehensive presentation and

publication of the study findings. The biostatistician will assist Dr. Khemani and Steering Committee members to prepare abstracts and papers for presentation at the annual meetings of American Thoracic Society (ATS), Society of Critical Care Medicine (SCCM), the European Society of Pediatric and Neonatal Intensive Care (ESPNIC). Dr. Khemani will provide the mechanical ventilation subgroup of the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) network an update on the clinical trial twice yearly to maintain disciplinary interest in the study. In addition to primary publication targeted at high priority journals, we anticipate numerous secondary publications in critical care, physiology, and respiratory journals. Final data sets and statistical analyses will be archived and a public use dataset will be made available as per NIH recommendations.

D7 Data and Instrument Management

A significant portion of the data management infrastructure and protocols have been developed with previous studies, and we will capitalize on this by modifying existing protocols to be relevant to this study. The devices and software have been used extensively, and we will follow existing protocols to maintain calibration, quality control, and accuracy of all study devices. A vast majority of the data (ventilator settings, blood gas values, and many of the variables in the data collection table) will be collected through automated electronic feeds. A trained study data collector will use data extracts from the electronic feeds in conjunction with data in the electronic health care record to populate study specific case report forms. Data collection will occur in real-time, to enable primary source verification. Respiratory measurements will be entered into web-based case report forms at the time of study measurements. In addition, raw data from esophageal manometry and RIP will be recorded during each measurement for a minimum of 5 minutes, and the calculations will be post-processed by trained research personnel to verify the real-time data entry. Ultrasound images will be interpreted in real-time and calculations entered into the web-based case report form. In addition, all ultrasound images will be uploaded to a secure server for source data verification and can be de-identified. We will develop a series of algorithms to confirm the validity of entered data, and will perform detailed queries of entered data monthly.

To ensure data safety and reliability, server back-up procedures will be executed daily to back up all electronic study related materials, which include database, Word documents, statistical programs, and files. Access to the data management system is strictly prohibited and requires user authentication. Authorized users include data-entry personnel, research coordinators, the PI, the database programmer, and biostatisticians. Any hard copies of eCRFs with subject ID codes will be stored in locked file cabinets, accessible by authorized staff only. Identifiable subject data, such as contact information and medical record numbers, will be stored separately and securely, and will not be entered into the electronic database.

All application software will be hosted securely on the Children's Hospital Los Angeles Network, which is protected by several firewalls and security is monitored and audited regularly.

D8 Quality Control Procedures

D.8.1 Training

Training materials detailing study protocols have been created and used for the Phase I study, and an order set has been created in our electronic health-care record system.

Research respiratory therapists and data collectors will be directly trained by the PI and the Lead Research Respiratory Therapist (J. Hotz). Detailed training of all bedside staff will occur before beginning the study, as well as in real-time with each patient enrollment, using a similar model as the Phase I study.

D.8.2. Development of Case Report Forms

Case report forms will be modified from successfully implemented CRFs we have used for the pilot study, as well as a large observational study on Pediatric Acute Respiratory Distress Syndrome (PARDIE study). Form design features include the selection of valid, reliable measurements, development and testing of reliability measures, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open ended questions), smooth flow (clear skip patterns) to reduce missing data. Members of the Steering Committee will sign off on eCRFs before implementation.

D9 Anticipated Problems and Solutions

D.9.1 What if enrollment is slow? We are confident we can meet enrollment targets at CHLA alone and will monitor this with targeted and actual enrollment graphs. If enrollment is slower than anticipated, we will add UCLA Children's Hospital as a satellite ICU. This is another PICU 15 miles away with at least 100 eligible patients per year. Through previous funding from the Collaborative Pediatric Critical Care Research Network, we share research infrastructure and resources, and have combined efforts (functioning as one site) for over 30 different clinical studies. [77-83]

D.9.2 What if aPiMax is not associated with weaning duration? We believe that a real strength of this application relies on the multitude of direct and indirect measures of respiratory system capacity, load, and effort, which we will associate with highly clinically relevant weaning outcomes. While we anticipate aPiMax will be the best measure of strength, the multitude of other measurements concomitantly made will allow using alternative measures to aPiMax to assess strength (such as ePiMax, diaphragm contractile activity during occlusion, diaphragm thickness, or phase angle). Our analysis will allow us to determine which of these parameters has the strongest association with clinical outcomes.

D.9.3 Non-compliance with the intervention study protocol? We are confident we will maintain high protocol compliance, as we have demonstrated in the pilot study. We have iteratively refined the protocol such that adherence to weaning phase recommendations exceeds 90%. The acute phase recommendations generally exceed 75%, which we view as acceptable. The protocol is intended to provide a framework for ventilator decisions and is not intended to replace clinician's judgment. For this reason it has been implemented as open loop. The degree of protocol adherence will be tracked electronically, as part of the CDS tool itself. If adherence is lower than anticipated, then detailed analysis of the reasons for protocol rejection (tracked with every recommendation) will be reviewed, and a protocol modification will be considered.

D.9.4. Changes in clinical practice in the ICU during this time period? The impact of changes in pediatric critical care management is expected to affect both groups equally so should not bias treatment group comparisons.

D10 Study Timeline and Milestone accrual Policy

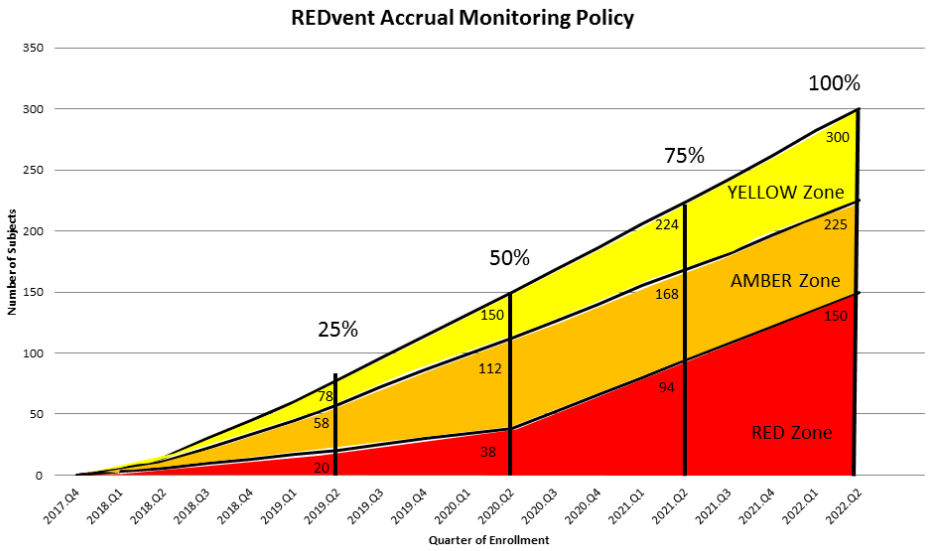

Figure 1: REDvent milestone accrual plan. Planned assessment at the end of Q2.2019 (25% expected patients enrolled), end of Q2.2020 (50%), end of Q2 2021 (75%). Numbers next to intersection of bars represent threshold number of patients required to be enrolled at that time point to move out of given zone.

The Milestone Accrual figure above details targeted enrollment over the course of the study. The Yellow, Amber, and Red zone each have corrective action associated with it, as part a separate milestone accrual plan with NHLBI.

E Human Subjects Considerations

E1 Ethical Considerations

The human subjects for this study are infants and children who are intubated and mechanically ventilated in intensive care unit. It is anticipated that 300 endotracheally intubated children will be enrolled in the study. The age of children will range from one month (≥ 44 weeks Post Conceptual Age) to 18 years. All participants enrolled in the study will be critically ill, requiring mechanical ventilation through an endotracheal tube. The main risk of participation in this study is the placement of an esophageal catheter for measurements of esophageal pressure. While esophageal catheters (or nasogastric feeding tubes) are routinely used in children who are mechanically ventilated (it is the norm for all endotracheally intubated children to have a feeding tube, either nasogastric, orogastric, gastric, or jejunal), because this additional catheter is part of the research protocol, it is likely to be considered greater than minimal risk. However the study does provide potential for significant benefit for the patient, and as such the benefits generally outweigh the risks. Use of this catheter has been approved on multiple occasions with appropriate informed consent. The ultrasound measurements and RIP bands are non-invasive and pose minimal risk to the patient.

The hardware (device) is minimal risk and has been used on a variety of studies. All sensors (esophageal catheter, RIP, and spirometry) have appropriate clearance through FDA approval or 510K equivalence for use in children, and have been used in our previous investigations. The two pieces of the software (tool to help interpret raw signals from the sensors), and the CDS ventilator management protocol have both previously been deemed non-significant risk because they are primarily implemented in an open-loop application, incorporate current evidence based guidelines (computer CDS protocol), or have been iteratively tested against FDA approved post-processing programs as part of our previous investigations. Moreover, clinicians are free to reject protocol recommendations, and to that end this data is to be used simply as an adjunct to clinical assessment, rather than a replacement.

E2 Subject Recruitment Plans and Consent Process

The subjects of this study are critically ill infants and children who will not be able to consent for their own participation in this study. One or both parents will be informed about the study and given an opportunity to voluntarily give their consent/permission for their child to participate. Assent of child subjects will not be possible because they are critically ill, intubated on a ventilator, and sedated. Thus, assent will be waived. Families or guardians of any endotracheally intubated and mechanically ventilated child who meet inclusion and do not meet exclusion criteria will be approached for consent. Consent will be attained by the study investigator, co-investigator, or research nurse. Consent will be documented on a consent form, and stored in a study binder, identified by patient number. This binder will be stored in a locked cabinet in the office of the site principal investigator.

E3 Risks and Benefits

E.3.1 Risks:

1. Placement of the esophageal catheter. While this procedure is very well tolerated, there is a very small risk for bleeding, incorrect placement into the lungs or other body cavities, or damage to the esophagus, stomach, or nasal or oral mucosa. Patients at high risk of bleeding (thrombocytopenia, coagulopathy, mucositis), will not be included in the study.
2. Small amount of discomfort when placing the esophageal catheter, although nearly all patients will be receiving analgesia and sedation as part of mechanical ventilation. Intermittent doses of already prescribed sedative or analgesia medications may be administered to minimize pain during placement.
3. A particular computer generated recommendation may not be correct for the patient at that time, and the clinicians may choose not to follow them.
4. There is potential of accidental release of confidential information.
5. There is a possibility of transient fall in oxygen levels during airway occlusion maneuvers, although patients will be pre-oxygenated as per ICU standard practices prior to measurement, and patients must pass the oxygenation test prior to performing these measurements.

E.3.2 Potential Benefits to Subjects

There is the prospect of direct benefit to subjects in both arms. For the intervention arm, using the intervention tool has the potential to significantly shorten length of assisted breathing, lower re-intubation rates, increase Ventilator Free Days (VFDs), shorten ICU and hospital length of stay, and reduce exposure to sedatives and analgesics. Patients in the control arm also have potential to benefit as enrollment in the study will prompt more consistent use of evidence based weaning guidelines including a daily Spontaneous Breathing Trial. This may also result in more days free of ventilators compared to those not enrolled in the study.

E.3.4 Importance of the Knowledge to Be Gained

Completion of this study will elucidate important information on the pathogenesis and timing of respiratory muscle weakness during MV in children, and whether this weakness can be mitigated by promoting more normal patient effort during MV. These data can lead to immediate change in practice by implementing mechanical ventilation strategies that promote more patient effort of breathing. They will also form the basis to determine whether a larger, Phase III multi-center study of REDvent is indicated, which would focus on key clinical outcomes such as 28-day Ventilator Free Days. Given that the risks to the study participants are small, the information gathered will shape the design of future trials and will improve our understanding of diaphragm weakness in mechanically ventilated children in the ICU.

E.3.5 Procedures to minimize risk

All patients will be extensively monitored in the intensive care unit throughout the duration of the study. This will include close monitoring of cardio-respiratory parameters including heart rate, temperature, blood pressure, oxygen saturation, respiratory rate, and work of breathing. Intensive care unit physicians, nurses, and respiratory therapists will be present during the entire study, and will intervene as necessary should any treatment be indicated. In addition, to protect confidentiality of data, study forms will only be labeled with a unique number identifier, which can only be

linked to identifiable information only through a key with access restricted to the PI or research coordinator.

E4 Early Withdrawal of Subjects

The subject may be withdrawn from the study by the (1) study investigator or (2) the parent or legal guardian at any time after consent. The primary attending physician can also request that the principal investigator consider withdrawal of the patient from the study if they believe the study is no longer in the best interest of the patient.

E.4.1 When and How to Withdraw Subjects

Subjects can be withdrawn by the parents at any time, simply by requesting that the principal investigator withdraw the patient. The study investigator may withdraw the patient from the study if he or she believes that this is necessary to protect the health of the child, if the condition of the child changes such that continuation in the study poses additional risks, or if the child experiences an adverse event which changes the risk benefit profile of continuing in the study.

E.4.2 Data Collection and Follow-up for Withdrawn Subjects

If consent is withdrawn for participation in the research by the parent/guardian, then data collection will cease. Parents will be asked if we can keep existing data and follow clinical outcomes for intention to treat analysis. However, if they wish, existing data will be destroyed. If the study investigator withdraws the patient, then existing data will be preserved, and clinical outcome data detailed in section C.3.1. will continue to be collected to enable intention to treat analysis.

F Data Safety Monitoring Plan and Board

Please see separate Data Safety and Monitoring Plan and Data Safety and Monitoring Board Charter. An institutional DSMB has been created for this study.

The Data Safety Monitoring Plan details expected adverse events, with expected rates of occurrence.

G References

1. Daniel Martin A, Smith BK, Gabrielli A. Mechanical ventilation, diaphragm weakness and weaning: a rehabilitation perspective. Respiratory Physiology & Neurobiology 2013; 189:377-83.
2. Di Mussi R, Spadaro S, Mirabella L, et al. Impact of prolonged assisted ventilation on diaphragmatic efficiency: NAVA versus PSV. Critical Care (London, England) 2016; 20:1.
3. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 2014; 69:423-7.
4. Emeriaud G, Larouche A, Ducharme-Crevier L, et al. Evolution of inspiratory diaphragm activity in children over the course of the PICU stay. Intensive Care Medicine 2014; 40:1718-26.
5. Goligher EC, Fan E, Herridge MS, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. American Journal of Respiratory & Critical Care Medicine 2015; 192:1080-8.
6. Heunks LM, Doorduin J, van der Hoeven JG. Monitoring and preventing diaphragm injury. Current Opinion in Critical Care 2015; 21:34-41.
7. Matamis D, Soilemezi E, Tsagourias M, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Medicine 2013; 39:801-10.
8. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. Critical Care (London, England) 2013; 17:R120.
9. Hooijman PE, Beishuizen A, Witt CC, et al. Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. American Journal of Respiratory & Critical Care Medicine 2015; 191:1126-38.
10. Sieck GC. Muscle weakness in critical illness. American Journal of Respiratory & Critical Care Medicine 2015; 191:1094-6.
11. Wolf GK, Walsh BK, Green ML, Arnold JH. Electrical activity of the diaphragm during extubation readiness testing in critically ill children. Pediatric Critical Care Medicine 2011; 12:e220-4.
12. Keens TG, Bryan AC, Levison H, Ianuzzo CD. Developmental pattern of muscle fiber types in human ventilatory muscles. Journal of Applied Physiology: Respiratory, Environmental & Exercise Physiology 1978; 44:909-13.
13. Khemani R, Flink R, Morzov R, Ross P, Newth C. Its not like breathing through a straw: Effort of breathing on CPAP most accurately estimates post-extubation effort in children. American Journal of Respiratory and Critical Care Medicine 2013; suppl 2013.187.1:A3682.
14. Khemani RG, Hotz J, Morzov R, et al. Pediatric extubation readiness tests should not use pressure support. Intensive Care Medicine 2016; 42:1214-22.
15. Randolph AG, Wypij D, Venkataraman ST, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA 2002; 288:2561-8.
16. Newth CJ, Venkataraman S, Willson DF, et al. Weaning and extubation readiness in pediatric patients. Pediatric Critical Care Medicine 2009; 10:1-11.

17. Odetola FO, Clark SJ, Freed GL, Bratton SL, Davis MM. A national survey of pediatric critical care resources in the United States. Pediatrics 2005; 115:e382-6.
18. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. Critical Care Medicine 2010; 38:1947-53.
19. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Critical Care Medicine 2005; 33:1266-71.
20. Seymour CW, Martinez A, Christie JD, Fuchs BD. The outcome of extubation failure in a community hospital intensive care unit: a cohort study. Critical Care (London, England) 2004; 8:R322-7.
21. Anand KJ, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics 2010; 125:e1208-25.
22. Kurachek SC, Newth CJ, Quasney MW, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Critical Care Medicine 2003; 31:2657-64.
23. Rossi C, Simini B, Brazzi L, et al. Variable costs of ICU patients: a multicenter prospective study. Intensive Care Medicine 2006; 32:545-52.
24. Sachdeva RC, Jefferson LS, Coss-Bu J, et al. Effects of availability of patient-related charges on practice patterns and cost containment in the pediatric intensive care unit. Critical Care Medicine 1996; 24:501-6.
25. Randolph AG, Gonzales CA, Cortellini L, Yeh TS. Growth of pediatric intensive care units in the United States from 1995 to 2001. Journal of Pediatrics 2004; 144:792-8.
26. Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. American Journal of Respiratory & Critical Care Medicine 2013; 187:20-7.
27. Umbrello M, Formenti P, Longhi D, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Critical Care (London, England) 2015; 19:161.
28. Medrinal C, Prieur G, Frenoy E, et al. Respiratory weakness after mechanical ventilation is associated with one-year mortality - a prospective study. Critical Care (London, England) 2016; 20:231.
29. ATS, ERS. ATS/ERS Statement on Respiratory Muscle Testing. American Journal of Respiratory and Critical Care Medicine 2002; 166:518-624.
30. Keens TG, Ianuzzo CD. Development of fatigue-resistant muscle fibers in human ventilatory muscles. American Review of Respiratory Disease 1979; 119:139-41.
31. Santschi M, Jouvet P, Leclerc F, et al. Acute lung injury in children:therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med 2010; 11:681-689.
32. Newth CJ, K S, RG K, JM D. Variability In Usual Care Mechanical Ventilation For Pediatric Acute Lung Injury. American Journal of Respiratory and Critical Care Medicine 2014; 189:A2613.
33. Khemani RG, Sward K, Morris A, Dean JM, Newth CJL, (CPCCRN) NCPCCRN. Variability in usual care mechanical ventilation for pediatric acute lung injury: the potential benefit of a lung protective computer protocol. Intensive Care Medicine 2011; 37:1840-1848.
34. Jaber S, Jung B, Matecki S, Petrof BJ. Clinical review: ventilator-induced diaphragmatic dysfunction--human studies confirm animal model findings! Critical Care (London, England) 2011; 15:206.

35. Falk DJ, Deruisseau KC, Van Gammeren DL, Deering MA, Kavazis AN, Powers SK. Mechanical ventilation promotes redox status alterations in the diaphragm. Journal of Applied Physiology 2006; 101:1017-24.
36. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. New England Journal of Medicine 2008; 358:1327-35.
37. Powers SK, DeCramer M, Gayan-Ramirez G, Levine S. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Critical Care (London, England) 2008; 12:191.
38. Futier E, Constantin JM, Combaret L, et al. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Critical Care (London, England) 2008; 12:R116.
39. Mhanna MJ, Anderson IM, Iyer NP, Baumann A. The use of extubation readiness parameters: a survey of pediatric critical care physicians. Respiratory Care 2014; 59:334-9.
40. Burns KE, Lellouche F, Lessard MR, Friedrich JO. Automated weaning and spontaneous breathing trial systems versus non-automated weaning strategies for discontinuation time in invasively ventilated postoperative adults. Cochrane Database of Systematic Reviews 2014; 2:CD008639.
41. Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J. Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial. Intensive Care Medicine 2013; 39:919-25.
42. Rose L, Schultz MJ, Cardwell CR, Jouvet P, McAuley DF, Blackwood B. Automated versus non-automated weaning for reducing the duration of mechanical ventilation for critically ill adults and children. Cochrane Database of Systematic Reviews 2013; 6:CD009235.
43. Khemani R, Schneider J, Morzov R, Markovitz B, Newth CJ. Pediatric Upper Airway Obstruction: Interobserver variability is the road to perdition. Journal of Critical Care 2013; 28:490-7.
44. Pandharipande PP, Shintani AK, Hagerman HE, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. Critical Care Medicine 2009; 37:1317-21.
45. ARDSnet. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. New England Journal of Medicine 2000; 342:1301-8.
46. Sward K, CJL N, RG K, JM D. Data-driven knowledge base evaluation: Translating an adult CDS tool for use in pediatric care (Abstract). Journal of the American Medical Informatics Association (JAMIA) 2015; 2015 Annual conference
47. Sward K, Newth CJ, Page K, Dean JM. Pediatric Intensivist Attitudes About a Ventilator Management Computer Protocol. C57. NEWS FROM THE NICU AND PICU: American Thoracic Society, 2015:A4772-A4772.
48. Khemani R, Flink R, Hotz J, Ross P, Ghuman A, Newth CJ. Respiratory inductance plethysmography calibration for pediatric upper airway obstruction: an animal model. Pediatric Research 2015; 77:75-83.
49. Khemani RG, Hotz J, Morzov R, et al. Risk Factors for Pediatric Post-Extubation Upper Airway Obstruction Using a Physiology Based Tool. Am J Respir Crit Care Med 2015.

50. Khemani RG, Celikkaya EB, Shelton CR, et al. Algorithms to estimate PaCO2 and pH using noninvasive parameters for children with hypoxemic respiratory failure. Respiratory Care 2014; 59:1248-57.
51. Baldwin CE, Paratz JD, Bersten AD. Diaphragm and peripheral muscle thickness on ultrasound: intra-rater reliability and variability of a methodology using non-standard recumbent positions. Respirology 2011; 16:1136-43.
52. Vivier E, Mekontso Dessap A, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Medicine 2012; 38:796-803.
53. Benditt JO. Esophageal and gastric pressure measurements. Respiratory Care 2005; 50:68-75.
54. Gozal D, Shoseyov D, Keens TG. Inspiratory pressures with CO2 stimulation and weaning from mechanical ventilation in children. American Review of Respiratory Disease 1993; 147:256-61.
55. Harikumar G, Egberongbe Y, Nadel S, et al. Tension-time index as a predictor of extubation outcome in ventilated children. American Journal of Respiratory & Critical Care Medicine 2009; 180:982-8.
56. Wen AS, Woo MS, Keens TG. How many maneuvers are required to measure maximal inspiratory pressure accurately. Chest 1997; 111:802-7.
57. Harikumar G, Moxham J, Greenough A, Rafferty GF. Measurement of maximal inspiratory pressure in ventilated children. Pediatric Pulmonology 2008; 43:1085-91.
58. Watson AC, Hughes PD, Louise Harris M, et al. Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Critical Care Medicine 2001; 29:1325-31.
59. Dimitriou G, Greenough A, Moxham J, Rafferty GF. Influence of maturation on infant diaphragm function assessed by magnetic stimulation of phrenic nerves. Pediatric Pulmonology 2003; 35:17-22.
60. Luo YM, Hart N, Mustfa N, et al. Reproducibility of twitch and sniff transdiaphragmatic pressures. Respiratory Physiology & Neurobiology 2002; 132:301-6.
61. Man WD, Luo YM, Mustfa N, et al. Postprandial effects on twitch transdiaphragmatic pressure. European Respiratory Journal 2002; 20:577-80.
62. Polkey MI, Kyroussis D, Hamnegard CH, et al. Paired phrenic nerve stimuli for the detection of diaphragm fatigue in humans. European Respiratory Journal 1997; 10:1859-64.
63. Rafferty GF, Greenough A, Dimitriou G, et al. Assessment of neonatal diaphragm function using magnetic stimulation of the phrenic nerves. American Journal of Respiratory & Critical Care Medicine 2000; 162:2337-40.
64. Rafferty GF, Mustfa N, Man WD, et al. Twitch airway pressure elicited by magnetic phrenic nerve stimulation in anesthetized healthy children. Pediatric Pulmonology 2005; 40:141-7.
65. Sekayan T, Hotz J, Flink R, Iyer NP, Newth CJ, Khemani R. Risk Factors for pediatric extubation failure: the importance of respiratory muscle strength. Critical Care Medicine 2017; Abstact 2017 Conference:14.
66. Lafortune M, Kamerkar A, Hotz J, Morzov R, Newth CJ, Khemani R. Risk Factors for Pediatric Noninvasive Ventilation Failure using Physiologic and Clinial Measures (abstract). C27 News from the NICU and PICU: American Thoracic Society, 2016:7300.

67. Steier J, Kaul S, Seymour J, et al. The value of multiple tests of respiratory muscle strength. Thorax 2007; 62:975-80.
68. Scott CB, Nickerson BG, Sargent CW, Dennies PC, Platzker AC, Keens TG. Diaphragm strength in near-miss sudden infant death syndrome. Pediatrics 1982; 69:782-4.
69. Zambon M, Cabrini L, Beccaria P, Zangrillo A, Colombo S. Ultrasound in critically ill patients: focus on diaphragm. Intensive Care Medicine 2013; 39:986.
70. Rehan VK, Laiprasert J, Nakashima JM, Wallach M, McCool FD. Effects of continuous positive airway pressure on diaphragm dimensions in preterm infants. Journal of Perinatology 2001; 21:521-4.
71. Rehan VK, Laiprasert J, Wallach M, Rubin LP, McCool FD. Diaphragm dimensions of the healthy preterm infant. Pediatrics 2001; 108:E91.
72. Rehan VK, McCool FD. Diaphragm dimensions of the healthy term infant. Acta Paediatrica 2003; 92:1062-7.
73. Rehan VK, Nakashima JM, Gutman A, Rubin LP, McCool FD. Effects of the supine and prone position on diaphragm thickness in healthy term infants. Archives of Disease in Childhood 2000; 83:234-8.
74. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Group ftPALICC. Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference. Pediatric Critical Care Medicine 2015; 16:S23-S40.
75. Curley MA, Wypij D, Watson RS, et al. Protocolized Sedation vs. Usual Care in Pediatric Patients Mechanically Ventialted for Acute Respiratory Failure. JAMA 2015; 313:379-389.
76. Valentine SL, Nadkarni VM, Curley MA, Pediatric Acute Lung Injury Consensus Conference G. Nonpulmonary treatments for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatric Critical Care Medicine 2015; 16:S73-85.
77. Carcillo JA, Dean JM, Holubkov R, et al. The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial. Pediatric Critical Care Medicine 2012; 13:165-73.
78. Newth CJ, Meert KL, Clark AE, et al. Fatal and near-fatal asthma in children: the critical care perspective. Journal of Pediatrics 2012; 161:214-21.e3.
79. Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. Pediatric Critical Care Medicine 2013; 14:356-65.
80. Moler FW, Silverstein FS, Meert KL, et al. Rationale, timeline, study design, and protocol overview of the therapeutic hypothermia after pediatric cardiac arrest trials. Pediatric Critical Care Medicine 2013; 14:e304-15.
81. Pollack MM, Holubkov R, Funai T, et al. Relationship between the functional status scale and the pediatric overall performance category and pediatric cerebral performance category scales. JAMA Pediatrics 2014; 168:671-6.
82. Dalton HJ, Garcia-Filion P, Holubkov R, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. Pediatric Critical Care Medicine 2015; 16:167-74.
83. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. New England Journal of Medicine 2015; 372:1898-908.

H Ventilation Protocols (Intervention group)

Acute phase management is based on SIMV pressure control/pressure support mode of ventilation. Oxygenation targets are 88-93% during the acute phase, and PEEP and FiO2 are managed as per the PEEP/FiO2 tables on the subsequent pages. If inhaled nitric oxide is used by the clinical team, then rules for weaning nitic oxide have been built into the protocol, as detailed below. Ventilation management during the acute phase uses pH, ventilator rate, and PIP to suggest changes to embrace permissive hypercapnia. When the patient is breathing spontaneously, rules regarding Pressure Rate Product are also implemented, to keep work of breathing in a physiologic range.

If High frequency oscillatory ventilation is used for patients randomized to RED-vent Acute, then HFOV rules have been created. There is no requirement to transition to HFOV, but it will be permitted for rescue therapy. Similar to the conventional ventilation, Oxygenation is managed with a MAP/FiO2 table, with rules for inhaled nitric oxide if used. Ventilation adjusts Hz, Amp based on pH. There are no PRP based rules during HFOV, since most patients are not spontaneously breathing. There are recommendations for minimal therapy with HFOV, when conversion back to conventional ventilation should be considered, although the clinical team will ultimately make the decision regarding conversion back to conventional ventilation.

Details of the protocols are summarized on the following pages.

Pressure Control: Ventilation table

PIP

pH	<=28	29-35	>35
> 7.45	↓ Δ P by 2 ↓ VR by 20%	↓ Δ P by 2	↓ Δ P by 4
7.30-7.45	↓ Δ P by 2 ↓ VR by 10%	↓ Δ P by 2	↓ Δ P by 2
7.15-7.29 (VR < Max)	↑ Δ P by 2 ↑ VR by 20%	↑ VR by 20%	↓ Δ P by 2 ↑ VR by 20%
7.15-7.29 (VR >= Max)	↑ Δ P by 4	No change to Δ P Or VR Consider Bicarb if PCO2 <25	↓ Δ P by 2 Consider Bicarb if PCO2 <25
< 7.15 (VR < Max)	↑ Δ P by 4 ↑ VR by 20%	↑ Δ P by 2 ↑ VR by 20%	↑ VR by 20% Consider Bicarb if PCO2 <25
< 7.15 (VR >= Max)	↑ Δ P by 4 Consider Bicarb if PCO2 <25	↑ Δ P by 2 Consider Bicarb if PCO2 <25	No change to Δ P Or VR Consider Bicarb if PCO2 <25

Green cells: If the patient is breathing spontaneously, the PRP is used to make the following recommendations based on PRP range: Low, Middle, High.

PRP Range

Low	Middle	High
Standard recommendation	No change to ventilation support	If , PIP <35 and PS < 20 ↑ Δ P by 2 ↑ PS by 2 Else, consult MD

Note: Default max VR (Ventilator Rate) is 35, however patients with evidence of lower airway obstruction will have this reduced to 24.

Pressure Control: Oxygenation (Low)
PaO2 < 55, SpO2 < 88%

PEEP \ FiO2	0.25	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	1.0
5	Inc. FiO2 by 0.05	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3
8	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
10	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
12	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
14	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
16	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
18	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2
20	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2
22	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2
24	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Maximal Therapy

- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
- For weaning of inhaled nitric oxide, if FiO2 ≤ 0.6 and an FiO2 wean would normally be recommended, this recommendation is replaced with a recommendation to decrease inhaled nitric oxide until it is discontinued.

Pressure Control: Oxygenation (Middle)
PaO2 55-68, SpO2 88-93%

PEEP \ FiO2	0.25	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	1.0
5	No Changes	No Changes	No Changes	No Changes	Inc. PEEP 3	Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3
8	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	No Changes	Inc. PEEP 2	Inc. PEEP 2	Inc. PEEP 2	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
10	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	No Changes	No Changes	No Changes	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
12	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	Inc. PEEP 2	Inc. PEEP 2	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
14	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	No Changes	No Changes	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
16	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2	Inc. FiO2 0.05	No Changes	No Changes	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
18	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes
20	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes
22	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes
24	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes

- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
- For weaning of inhaled nitric oxide, if FiO2 ≤ 0.6 and an FiO2 wean would normally be recommended, this recommendation is replaced with a recommendation to decrease inhaled nitric oxide until it is discontinued.

Pressure Control: Oxygenation (High)
PaO2 >68, SpO2 > 93%

PEEP \ FiO2	0.25	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	1.0
5	Minimal Therapy Maintain	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
8	Dec. PEEP by 3	Dec. PEEP by 3	Dec. PEEP by 3	Dec. PEEP by 3	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
10	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
12	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 by 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
14	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
16	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05	Dec. FiO2 0.05
18	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 by 0.05	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05
20	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2
22	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2
24	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2

- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
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HFOV: Ventilation

pH

Amplitude (Amp)	< 7.15	7.15 -7.29	7.30-7.45	>7.45
< 50	↑ Amp by 10 ↓ Hz by 0.5 Consider IV Bicarb	↑ Amp by 10	↑ Hz by 0.5 [If at max Hertz, consider CMV]	↓ Amp by 5 ↑ Hz by 1.0 (If at max Hertz, ↓ Amp by 5)
50-70	↑ Amp by 10 ↓ Hz by 0.5 Consider IV Bicarb	↑ Amp by 10	↑ Hz by 0.5 [If at max Hertz, ↓ Amp by 5]	↓ Amp by 5 ↑ Hz by 0.5 (If at max Hertz, ↓ Amp by 10)
> 70	↑ Amp by 5 ↓ Hz by 1.0 [If at max Amp , ↓ Hz by 1.5] Consider IV Bicarb	↑ Amp by 5 ↓ Hz by 0.5 [If at max Amp , ↓ Hz by 1.0]	↓ Amp by 5 ↑ Hz by 0.5 [If at max Hz, ↓ Amp by 10]	↓ Amp by 10 ↑ Hz by 0.5 [If at max Hz, ↓ Amp by 15]

Hertz (Hz) range 3-15

HFOV: Oxygenation (Low)
PaO2 >68, SpO2 > 93%

MAP \ FiO2	0.25	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	1.0
18	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
20	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
22	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
24	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
26	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
28	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
30	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
32	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
34	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
36	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
38	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2
40	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Maximal Therapy

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HFOV: Oxygenation (Middle)
PaO2 55-68, SpO2 88-93%

MAP \ FiO2	0.25	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	1.0
18	Minimal Therapy	Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2
20	Dec. MAP 2	No Change	Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
22	Dec. MAP 2 Inc. FiO2 0.05	No Change	Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 3	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
24	Dec. MAP 2 Inc. FiO2 0.05	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 3	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
26	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
28	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
30	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
32	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
34	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
36	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
38	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2
40	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	No Change	No Change

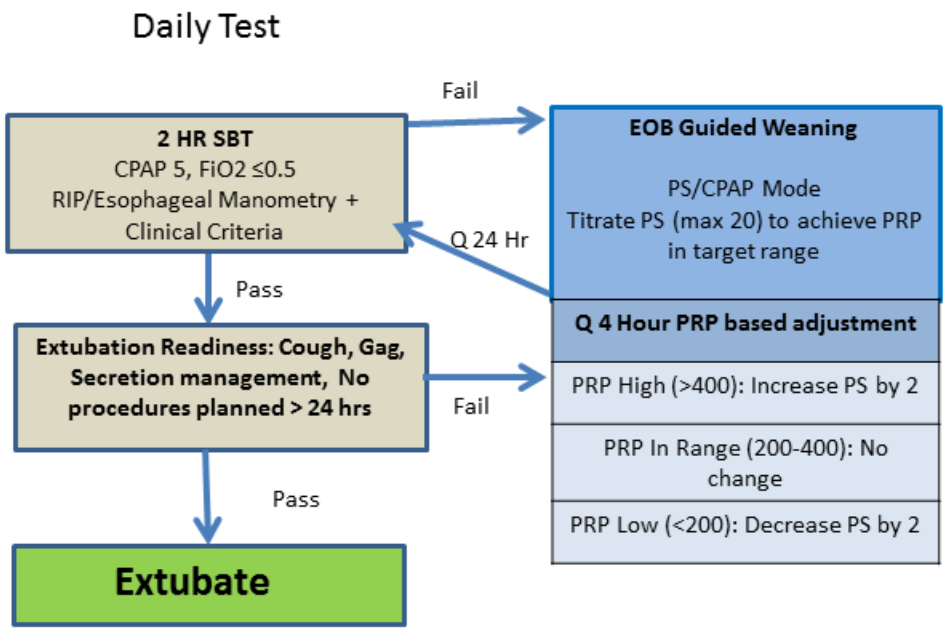
- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
- For weaning of inhaled nitric oxide, if FiO2 ≤ 0.6 and an FiO2 wean would normally be recommended, this recommendation is replaced with a recommendation to decrease inhaled nitric oxide until it is discontinued.

HFOV: Oxygenation (High)
PaO2 < 55, SpO2 < 88%

MAP \ FiO2	0.25	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	1.0
18	Minimal Therapy	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
20	No Change	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
22	No Change	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
24	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
26	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
28	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
30	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
32	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
34	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
36	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
38	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05
40	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2

- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
- For weaning of inhaled nitric oxide, if $FiO_2 \leq 0.6$ and an FiO_2 wean would normally be recommended, this recommendation is replaced with a recommendation to decrease inhaled nitric oxide until it is discontinued.

Weaning Phase Protocol



- During weaning phase, PEEP ≤ 10 cmH_2O, FiO_2 ≤ 0.6, PS ≤ 20 cmH_2O. PEEP and FiO_2 management can be changed within PEEP range of 5-10 cmH_2O and FiO_2 from 0.21-0.6 by the clinical team.
- Suspension of the weaning phase is permitted for up to 12 hours for situations such as procedures, increased need for sedation preventing adequate spontaneous breathing, or other circumstances requiring transient need for increase in ventilator support etc. As soon as the patient appropriately meets weaning criteria (spontaneous breathing, pH 7.32-7.47, PEEP ≤ 10 cmH_2O, FiO_2 ≤ 0.6), the weaning phase intervention is resumed.
- If the weaning phase is suspended for > 12 hours and the patient no longer meets weaning criteria, the acute phase intervention will be resumed, until the patient again meets weaning criteria. This will be labeled weaning failure, and tracked in both arms.

REDVENT

(**R**eal-time **E**ffort **D**riven **VENT**ilator management)

NIH/NHLBI R01HL134666 and NIH/NHLBI 1R01HL164397 - 01A1
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A Introduction

A1 Study Abstract

Nearly half of mechanically ventilated (MV), critically ill adults develop ventilator-induced respiratory muscle weakness (particularly of the diaphragm), which impairs successful weaning from MV, often leads to re-intubation, and is associated with higher post-ICU mortality. Respiratory muscle weakness is associated with extubation failure in critically ill children. However, we lack crucial information on the mechanisms and timing of this weakness, its importance for ventilator weaning, and its potential prevention through promoting more physiologic levels of patient effort of breathing during MV.

This study is a Phase II controlled clinical trial that will obtain comprehensive, serial assessments of respiratory muscle strength and architecture to understand the evolution of ventilator-induced respiratory muscle weakness in critically ill children, and test whether a novel computer-based approach (Real-time Effort Driven ventilator management (REDvent)) can preserve respiratory muscle strength and reduce time on MV. REDvent offers systematic recommendations to reduce controlled ventilation during the acute phase of MV, and uses real-time measures from esophageal manometry to adjust supported ventilator pressures such that patient effort of breathing remains in a normal range during the ventilator weaning phase. This phase II clinical trial is expected to enroll 276 children with pulmonary parenchymal disease, anticipated to be ventilated > 48 hrs. Patients will be randomized to REDvent-acute vs. usual care for the acute phase of MV (interval from intubation to first spontaneous breathing trial (SBT)). Patients in either group who fail their first Spontaneous Breathing Trial (SBT), will also be randomized to REDvent-weaning vs. usual care for the weaning phase of MV (interval from first SBT to passing SBT). The primary clinical outcome is length of weaning (time from first SBT until successful passage of an SBT or extubation (whichever comes first)). Mechanistic outcomes surround multi-modal serial measures of respiratory muscle capacity (PiMax), load (resistance, compliance), effort (esophageal manometry), and architecture (ultrasound) throughout the course of MV. Upon completion, this study will provide important information on the pathogenesis and timing of respiratory muscle weakness during MV in children and whether this weakness can be mitigated by promoting more normal patient effort during MV via the use of REDvent. This will form the basis for a larger, Phase III multi-center study, powered for key clinical outcomes such as 28-day Ventilator Free Days.

A2 Protocol Summary

Title: Real-time Effort Driven Ventilator Management (REDvent)

Phase: Phase II

Funding: NIH/NHLBI R01HL124666

Committees: Steering Committee, Institutional Data and Safety Monitoring Board

Background and Significance: Nearly half of critically ill patients on MV develop respiratory muscle weakness, particularly of the diaphragm. In adults, this weakness leads to the inability to resume unassisted ventilation after the acute illness has resolved, prolongs the weaning phase of MV, and contributes to extubation failure. [1-11] However, in critically ill children, we lack crucial information about the importance of ventilator-induced respiratory muscle weakness during weaning, the means to prevent it, and whether it is influenced by maturational changes in respiratory mechanics and diaphragm histology that occur throughout infancy and childhood.[12]

Consistent with the pediatric literature,[4] our preliminary data has shown that usual care ventilation in children is associated with minimal patient effort of breathing; [13, 14] known to be a major risk factor for ventilator-induced diaphragm weakness in adults.[5] To reduce this weakness, we developed a computer-based approach (Real-time Effort Driven ventilator management (REDvent)), which recommends systematic reductions in controlled ventilation during the acute phase of MV and uses real-time measures to adjust supported ventilator pressures to maintain patient effort of breathing during the weaning phase. Through a Phase I trial, we demonstrated that patients managed with REDvent spent fewer days on MV than historical controls, and bedside providers could easily implement REDvent. Our central hypothesis is that REDvent use will reduce ventilator-induced respiratory muscle weakness, leading to shorter time on MV by enhancing the patient's capacity for effective, unsupported ventilation and by facilitating MV weaning.

Study Aims:
SA1: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV (Primary outcome).

SA2: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes.

SA3: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness.

Study Design: Single-center randomized controlled trial (138 children per arm) using REDvent (intervention arm) as compared with usual care ventilator management including a standardized daily SBT (control arm). Acute phase randomization will occur upon study enrollment, and patients who fail the first SBT will undergo a weaning phase randomization. We will obtain serial measurements of respiratory system capacity, load, effort of breathing, and diaphragm architecture throughout the course of MV.

Inclusion Criteria:

1. Children > 1 month (>44 weeks CGA) and ≤ 21 years of age AND

2. Supported on mechanical ventilation with pulmonary parenchymal disease (i.e., pneumonia, bronchiolitis, Pediatric Acute Respiratory Distress Syndrome (PARDS)) with Oxygen Saturation Index (OSI) ≥ 5 or Oxygenation Index (OI) ≥) AND
3. Who are within 48 hours of initiation of invasive mechanical ventilation (allow for up to 72 hours for those transferred from another institution)

Exclusion Criteria:

1. Contraindications to use of an esophageal catheter (i.e. severe mucosal bleeding, nasal encephalocele, transphenoidal surgery) OR
2. Contraindications to use of RIP bands (i.e. omphalocele, chest immobilizer or cast) OR
3. Conditions precluding diaphragm ultrasound measurement (i.e. abdominal wall defects, pregnancy) OR
4. Conditions on enrollment that preclude conventional methods of weaning (i.e., status asthmaticus, severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal Life Support (ECLS), intubation for UAO, DNR, severe chronic respiratory failure, spinal cord injury above lumbar region, cyanotic heart disease (unrepaired or palliated)) OR
5. Primary Attending physician refuses (will be cleared with primary attending before approaching the patient).

A high level overview is presented in Figure 1.

Acute Phase: The acute phase is defined as the time from intubation until the patient meets weaning criteria,[15, 16] passes the initial oxygenation test (decrease PEEP to 5 cmH_2O and FiO_2 to 0.5, maintains SpO2 > 90%), and undergoes a Spontaneous Breathing Trial (SBT).

1. Intervention Arm (REDvent-acute): Patients will be managed with pressure control plus pressure support ventilation using a computerized decision support tool that will recommend changes to ventilator settings approximately every 4 hr (with or without a new blood gas). If the patient is spontaneously breathing, it will incorporate real-time measures of effort of breathing (esophageal manometry) to keep it in a target range.
2. Control Arm (Control-acute): Ventilator management will be per usual care until the patient meets weaning criteria and passes the oxygenation test.

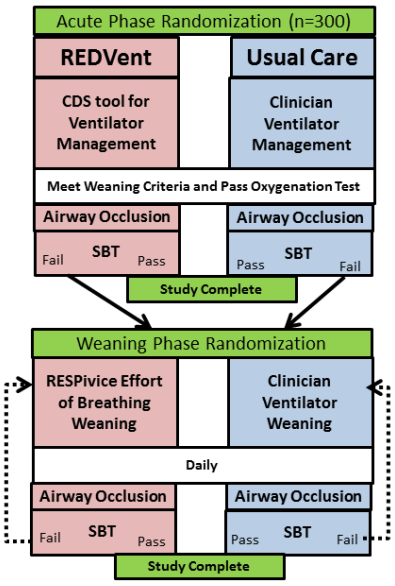

Figure 1: Study Schematic

Weaning Phase: The weaning phase is defined as the time from the first Spontaneous Breathing Trial (SBT) until the patient successfully passes an SBT or is extubated (whichever comes first). Patients who pass the initial SBT at the end of the acute phase will not undergo weaning phase randomization.

1. Intervention Arm (REDvent-weaning): Patients will be managed in a pressure support/CPAP mode of ventilation with assessments or changes to the level of

pressure support every 4 hours, targeting maintaining effort of breathing (esophageal manometry) in a normal range. An SBT will be conducted daily, and the weaning phase will continue until the patient passes the SBT.

2. Control Arm (Control-weaning): Ventilator management will be per usual care. An SBT will be conducted daily, and the weaning phase will continue until the patient passes the SBT.

Endpoints:

Primary:

- Duration of Weaning (Time from first attempted SBT until SBT passage or extubation [whichever comes first])

Secondary

- Ventilator Free Days
- Extubation Failure
- Pre-specified and Unanticipated Adverse Events
- ICU, Hospital, and 90 Day Mortality
- Esophageal Manometry: Maximal Inspiratory Pressure During Airway Occlusion (ePiMax)
- Airway Pressure: Maximal Inspiratory Pressure During Airway Occlusion (aPiMax)
- Diaphragm Ultrasound: Change in diaphragm thickness on Exhalation (Dte)
- Respiratory Inductance Plethysmography: Phase angle (PA)

Analysis Plan and Sample Size Justification:

Aim 1: The primary outcome is weaning duration. Sample size has been determined to adequately power 3 separate comparative analyses: (a) REDvent-acute versus Acute Phase control (b) REDvent-weaning phase versus Weaning Phase control (c) REDvent both phases versus control both phases. Power is based on 2 planned methods for analysis: cox proportional hazard ratios for multivariable analysis and univariate analysis with an independent t-test using log transformation (as needed) to account for the expected distribution of weaning duration. For all three of the planned comparisons above, with the proposed sample size we would be adequately powered (>0.8) to detect a difference in weaning duration of ≥ 1 day, or a hazard ratio of ≥ 1.4 between groups. The secondary outcomes are ventilator free days and extubation failure. Directly comparing control only patients to REDvent only patients, with an expected standard deviation for VFDs between 5 to 9 days, we will be able to detect a 2-day change in VFDs between groups with a power between 0.35 and 0.82. Re-intubation rates are expected to be 10%, allowing us to confirm that REDvent is not inferior to usual care in regards to re-intubation with a non-inferiority margin of 0.10 with a power of 0.8 and alpha of 0.05.

Aim 2: The primary outcome of this aim is weaning duration. For respiratory muscle strength we will compare the first measured aPiMax (after resolution of the acute phase, before the first SBT), the trajectory and value of the daily aPiMax during the weaning phase prior to extubation, the lowest and highest measured aPiMax, and aPiMax on the day of extubation against weaning duration. For analysis, aPiMax will be dichotomized at 30 cmH2O, and weaning duration will be compared between patients with aPiMax > 30 versus ≤ 30 cmH2O using a t-test with or without log-transformation, or Mann-Whitney U test, depending on the distribution. From our preliminary data, we anticipate at least 35% of patients (n=84) will have aPiMax ≤ 30 cmH2O. Based on a similar power analysis as presented above, this would allow us to determine whether low aPiMax

is associated with a ≥ 1-day increase in weaning duration, with an alpha of 0.05 and power of 0.8. We will perform identical analysis for ePiMax. Diaphragm Thickness analysis will compound daily ultrasound measures to detect the relative change in diaphragm thickness from study day 1 until passage of an SBT. We will compare the change in thickness after resolution of the acute phase (on the day of the first SBT) against weaning duration, in a similar manner as proposed above for aPiMax. In addition to weaning duration, we will also examine whether the respiratory measures taken just prior to or during each SBT are associated with the patient passing the SBT. For example with aPiMax and ePiMax, we will examine if there is a dose response relationship between PiMax measured just before the SBT and the rate of passage of the subsequent SBT.

Aim 3: The primary outcome of this aim is aPiMax < 30 cmH2O.The analysis will focus on determining whether the degree of patient effort of breathing is independently associated with the development of respiratory muscle weakness. For the acute phase, we will generate a time-weighted average PRP during the acute phase and graph it against aPiMax at the first SBT. We will subsequently dichotomize aPiMax at the first SBT and compare mean time weighted average PRP in the acute phase between aPiMax groups (> 30 vs. ≤ 30 cmH2O). For the weaning phase, we will graph the changes in aPiMax throughout the weaning phase (from first failed SBT until successful SBT) against time-weighted average PRP, with the anticipation that low PRP will be associated with either further reductions in aPiMax, or no improvement, while PRP in the physiologic range of 150-400 will be associated with improvement in aPiMax. We will subsequently dichotomize aPiMax (at 30 cm H2O) at the time of successful passage of an SBT and compare time-weighted average PRP in the weaning phase between aPiMax groups. Subsequently, we will build a multivariable logistic regression model on the outcome of aPiMax ≤ 30 cmH2O to determine if time-weighted PRP in the acute phase, weaning phase or both have an independent association with preserving aPiMax, after controlling for confounding variables.

Monitoring: The study will one planned interim analysis at 138 patients, with no rules planned for early stopping, given the low risk nature of this study and the high degree of physiologic data collected. In addition, there will be an early safety check after approximately 50 patients are enrolled, to review rates of adverse events between groups. There will be review of adverse events by the DSMB during scheduled meetings twice a year, or as requested.

A3 Primary Hypothesis and Specific Aims

Our central hypothesis is that REDvent use will reduce ventilator-induced respiratory muscle weakness, leading to shorter time on MV by enhancing the patient's capacity for effective, unsupported ventilation and by facilitating MV weaning. This will be specifically tested with 3 complementary specific aims:

SA1: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV (Primary outcome). We expect that patients randomized to receive REDvent-acute will either pass their first SBT or experience a shorter duration of weaning when compared to usual care. In addition, patients randomized to receive REDvent-weaning will experience a shorter duration of weaning compared to usual care. Secondary outcomes include 28-day Ventilator Free Days and extubation failure.

SA2: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes. We expect that diminished respiratory muscle strength (low PiMax), and diaphragm atrophy (ultrasound) will be prevalent after resolution of the acute phase of MV, and the combination of high respiratory load (or effort) with low PiMax will be a major factor leading to prolonged weaning and weaning failure (failure of SBT).

SA3: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness. We expect that after controlling for confounding variables like age, diagnosis, sedation, use of neuromuscular blockade, and other risk factors for neuromuscular weakness, children who maintain normal effort of breathing in the acute or weaning phases will have higher respiratory muscle capacity as measured by PiMax.

B Background

B1 Prior Literature and Studies

Children supported by mechanical ventilators in intensive care units contribute to over $5 billion dollars a year in US healthcare costs.[17, 18] Efficient methods to optimize ventilator support in children are lacking, resulting in some children being on ventilators longer than necessary.[16] Each additional day of ventilation leads to added health risks such as exposure to medications that may harm the developing brain, higher risk of infection, and critical illness acquired weakness leading to long-term impairment in patient quality of life.[17, 19-25] Mechanical ventilation (MV) of critically ill adults frequently leads to acquired respiratory muscle weakness, particularly of the diaphragm, which is a major factor contributing to extra days on MV.[1, 2] Mechanisms responsible for ventilator-induced diaphragm weakness relate to the underlying disease status of the patient, the severity of inflammation, the use of therapies like neuromuscular blockade and corticosteroids, the degree of protein catabolism, and the degree of diaphragm contraction during MV.[1, 5, 6, 8-10, 26] Accumulating data indicate that > 50 % of critically ill adults who are on MV > 72 hours have thinning of the diaphragm (based on ultrasound) within the first few days of MV, [5] and there is a dose response relationship between diaphragm atrophy and increasing ventilator driving pressure.[5] Moreover, low diaphragm contractile activity leads to atrophy, while diaphragm thickness is preserved when contractile activity during MV is normal (i.e., patient maintains normal work of breathing).[27]

Many adult studies have demonstrated architectural changes to the diaphragm which occur throughout the course of mechanical ventilation, but these changes may not directly translate into weakness.[5, 7] Respiratory muscle weakness can be objectively measured as the inability to generate sufficient changes in airway or esophageal pressure with maximal diaphragm contraction (PiMax), either voluntarily or through external stimulation of the phrenic nerve. However, there are limited data quantifying the time frame and degree to which these direct measures of respiratory muscle weakness (PiMax) become impaired during MV, although evidence suggests that low PiMax at extubation is associated with longer lengths of MV and higher mortality in adults.[8, 28] Single direct measures of respiratory muscle strength may be misleading. Experts in the field of pulmonary function testing of the respiratory muscles recommend serial measurements, combining multiple techniques to obtain the most comprehensive view of the respiratory muscles. This approach has been used when investigating other causes of diaphragm dysfunction, [29] but such a systematic, multi-modal approach has not been applied to study ventilator induced diaphragm dysfunction in critically ill patients.

B2 Rationale for this Study

Few data are available regarding the prevalence of ventilator induced diaphragm weakness and the risk factors for its development in children, although the respiratory muscles of the infant and newborn are more susceptible to weakness and fatigue than

those of older children because of crucial differences in diaphragm histology.[12, 30] However, the pathophysiology of ventilator-induced diaphragm weakness supports in children, as in adults, that ventilator management in both acute and weaning phases of MV contribute to diaphragm weakness.[4, 11] During the acute phase of MV, the goals are to maintain safe gas exchange, reduce excessive patient work of breathing, and prevent ventilator-induced lung injury through lung protective ventilation. While prolonged periods of high effort of breathing should be avoided because they worsen gas exchange, compromise oxygen delivery and potentiate ventilator induced lung injury, MV is often too highly controlled, resulting in minimal to no patient effort of breathing[4] and minimal changes of the ventilator settings. Consistent with other investigations [31], we have found that practitioners do not make changes to promote lung protective ventilation [32, 33] and do not reduce high ventilator settings over 50% of the time when managing MV without an explicit protocol, even in circumstances of respiratory alkalosis and over-ventilation.[33] Ventilator driving pressures are often higher than necessary and respiratory alkalosis prevents meaningful patient effort during the acute phase of MV. This strategy results in high rates of fully controlled mechanical ventilation and directly leads to diaphragm weakness. [34 35-38]

When critical illness has stabilized, weaning towards extubation in current practice involves slow, gradual reductions of ventilator pressures until spontaneous breathing trials (SBTs) are performed,[16, 39] although routine SBTs are only performed in < 25% of MV children. [33, 39] While practitioners frequently have the patient initiate ventilator breaths (spontaneous breathing) during weaning, the ventilator performs most of the required work of breathing. In general, during usual care ventilator management, patient breathing effort during both acute and weaning phases of MV is well below the normal physiologic range that would be expected if their lungs were healthy and off a ventilator. [4, 5] This sub-physiologic patient effort potentiates diaphragm weakness.

We hypothesize that maintaining patient effort of breathing closer to a normal, physiologic range will protect against diaphragm weakness. In pediatrics, there has been little work developing methods to promote early return to more natural breathing in this physiologic range. For adults, there are a few commercially available closed-loop ventilation weaning systems that provide an estimate of effort of breathing, and concurrently reduce ventilator support during weaning. Such systems have been shown to reduce length of MV by 20-40% over conventional weaning, [40] with supportive pilot data in older children. [41] Unfortunately, current closed-loop weaning tools are not available for most children, and these strategies are not initiated until the weaning phase of MV, allowing respiratory muscle weakness to develop during the acute phase of illness. [5, 42] New methods to continuously measure effort or work of breathing to guide ventilator management in young children are needed.

Through the use of technology systems developed specifically for children, we seek to determine whether a physiology-based ventilator management approach can prevent acquired respiratory muscle weakness in children, thus facilitating MV weaning and earlier recovery from critical illness. [43] The approach promotes the safe reduction in controlled ventilation during the acute phase of MV and early return to spontaneous breathing with maintenance of normal patient effort of breathing in the weaning phase (Real-time Effort Driven ventilator management (REDvent)). Through this study, we seek to understand the importance of respiratory muscle weakness in both the acute and weaning phases of MV in children, quantify the importance of patient effort of breathing for the development of respiratory muscle weakness, and determine whether REDvent can shorten ventilator weaning time. This study will improve our understanding of the pathogenesis of ventilator-induced diaphragm weakness in children and determine

whether computer-driven management prevents this weakness and leads to improved patient outcomes.

B3 Preliminary Data

B.3.1 Patient effort of breathing is generally very low with usual care ventilation: Dr. Khemani led a study of 409 mechanically ventilated children (77% consent rate) in which respiratory parameters were measured using esophageal manometry and respiratory inductance plethysmography [44] near extubation (K23 HL103785, PI Khemani). From secondary analysis of that data, we found that Pressure Rate Product (PRP, a direct measure of patient effort of breathing derived from esophageal manometry) on the day of extubation under what is considered minimal respiratory support (PS of 10/5 cmH20) was nearly 2.5 fold lower (median 90 (50, 140)) than PRP post-extubation (median 220 (120, 320)).[13, 14,39] Other pediatric investigators have demonstrated frequent periods of no detectable diaphragm effort during conventional ventilation, with electrical activity of the diaphragm 3 times lower during MV than it was at ICU discharge. [4] Thus, current ventilator strategies do not maintain normal patient effort and may contribute to respiratory muscle weakness. We have also shown that there is a normal range for effort of breathing that can be maintained by adjusting ventilator support. 75% of patients from our cohort who did well after extubation (i.e., no re-intubation, no need for post-extubation noninvasive ventilation) had a PRP from 150 to 400. These cut points appear to work across the entire pediatric age spectrum (neonate to 21 years), and form the basis for the "optimal range" that will be used for titration in this application.

B.3.2 REDvent management protocol: The computerized decision support (CDS) tool used by REDvent-acute is an electronic protocol that makes recommendations at user-set time intervals to adjust both ventilation (ventilator pressure or tidal volume and ventilator rate) and oxygenation (Positive End Expiratory Pressure and FiO2) to promote lung protective ventilation during the acute phase of MV. It implements a pediatric modification of the Acute Respiratory Distress Syndrome Network protocol,[45] (R21HD061870, PI Newth). We have demonstrated that pediatric critical care practitioners agree on the recommendations generated by the modified protocol.[46, 47] The CDS tool has been extensively tested in our ICU to provide explicit recommendations, and has built-in reporting features to measure protocol adherence. REDvent-weaning recommends adjusting supported ventilator pressures based on real-time direct measures of effort of breathing using RESPivice. RESPivice is an open-loop patient monitor that incorporates an esophageal manometry catheter and Respiratory Inductance Plethysmography Bands (RIP Bands) connected to a hardware box that passes signals to a laptop computer. [48, 49] The esophageal manometry catheter (which has an integrated feeding tube) is used for continuous effort of breathing calculations and RIP bands allow for measurement of phase angle (a measure of thoraco-abdominal asynchrony), and can be calibrated to measure flow or volume after extubation. [49]

B.3.3 Phase I trial using REDvent protocols: To test the feasibility of REDvent in MV children, Dr. Khemani led an open label, intervention only Phase I study enrolling 20 children <18 yr of age with pulmonary parenchymal disease and an anticipated intubation of > 48 hours (83% consent rate). Details of the REDvent management protocol are summarized in Figure 2. The acute phase of ventilator management was

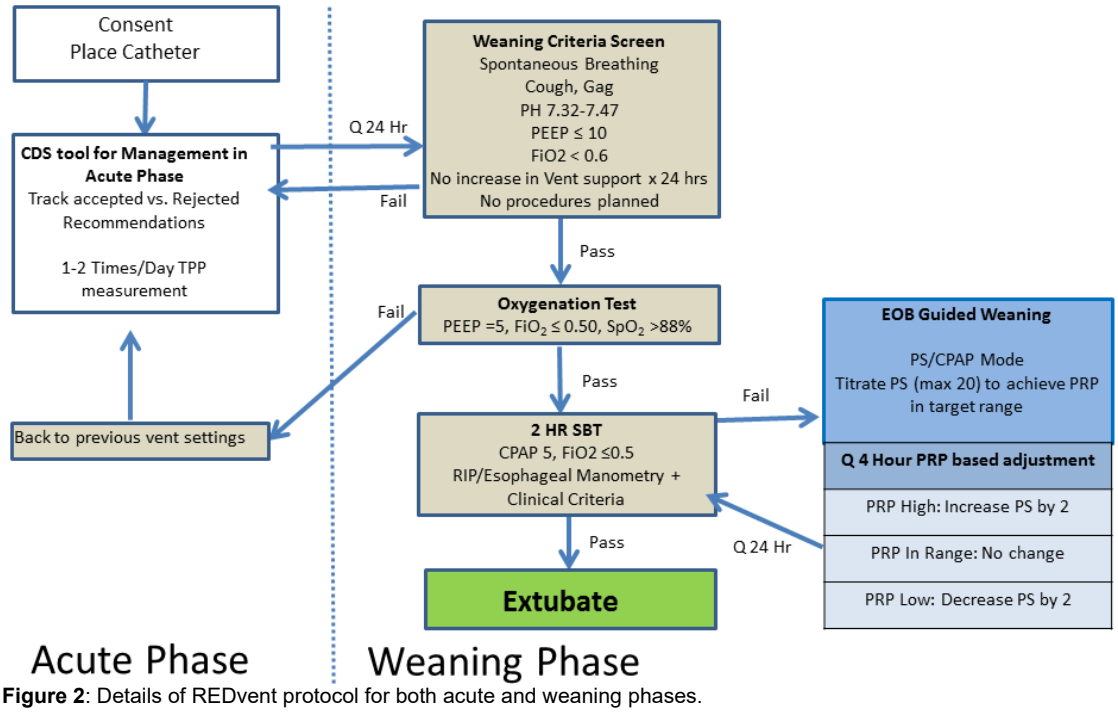

Figure 2: Details of REDvent protocol for both acute and weaning phases.

controlled by the CDS tool with a ventilator recommendation generated every 4 hr, or with a new blood gas value. If a blood gas was not available at the 4 hr interval, then non-invasive parameters (pulse oximetry and end-tidal CO2) were used to provide estimates for the adequacy of oxygenation and ventilation based on prediction models we have previously validated. [50] When patients met weaning criteria (no increase in ventilator support for 24 hr, spontaneous breathing, PEEP ≤ 10 cmH2O, FiO2 ≤ 60%), they had an oxygenation test (decease PEEP to 5, Fio2 ≤ 0.5, maintain SpO_2 > 88%). If they passed the oxygenation test, they were then given a SBT on CPAP of 5 cmH_2O and then extubated (i.e. both clinical and effort of breathing criteria were met). If they failed the SBT, they were initiated on the effort of breathing part of the study and pressure support was added to PEEP to maintain PRP in the target range. After patient 15, we modified the weaning protocol to allow 3 ranges for adjustment (Figure 2) to better fit with clinical practice and improve adherence. Every 4 hr, a recommendation was given to adjust pressure support by 2 cmH_2O to keep PRP in the target range (200-400) . The SBT and extubation evaluation were performed every 24 hr.

B.3.4 <u>The protocol has the potential to shorten duration of ventilation:</u> We have completed the Phase I study described above. During the acute phase, 698/966 recommendations were accepted (73% adherence). During the weaning phase 136/187 (73%) recommendations were accepted. However, after the protocol modification for the weaning phase, 96% of the recommendations were followed. Over 40 ***bedside*** respiratory therapists have used the acute and weaning protocols. A study respiratory therapist has been providing initial training of the bedside RT. In addition the study RT or PI has been available during the day and as needed by phone at night. Specific training sheets have been developed, overnight support by research personnel was generally minimal, and no safety concerns were identified. MV is generally weaned steadily in both acute and weaning phases. As the Phase I study did not have a control group, we used matched historical controls that were similar with respect to age and

initial hypoxemia severity, with a similar percentage of immune compromise, sepsis and pneumonia patients between groups. Patients treated with REDvent had larger changes in Peak Inspiratory Pressure and Ventilator Rate per day in the acute phase as compared with historical controls. REDvent was associated with approximately 2 fewer days on MV (25% reduction) compared to historical controls (p=0.36, Table 1). While not statistically significant due to the small sample size, **REDvent appears to lead to faster MV weaning**.

Table 1: Comparison between REDvent and historical controls	REDvent (n=19)	Matched Controls (n=90)
Matching Variables		
Age (years)	9.2 (3.2,12.3)	7.0 (0.9,14.2)
Oxygen Saturation Index (OSI)	15.9 (10.6,16.2)	14.1 (9.6,19.4)
High Frequency Oscillator (HFO)	17%	17%
Immune Compromised	39%	32%
Pneumonia	50%	58%
Sepsis	38%	39%
Outcomes		
Daily Change PIP Acute Phase	4 (2,5)	1.5 (1,3)
Daily Change Vent Rate Acute Phase	3 (0,4)	1 (0,2)
Length of MV (days)	**6.5 (4.9,8.7)**	**8.4 (4.5,13.9)**

B.3.5 Ventilator-induced respiratory muscle weakness is common in children, leading to failed extubation: Accurate quantification of the severity of diaphragm dysfunction is understudied, particularly in pediatrics. While diaphragm ultrasound can provide corroborative data about architectural changes, ultrasound does not directly measure strength. [3, 5, 7, 51, 52] Single measures of respiratory muscle strength (airway or esophageal PiMax) measured with maximal voluntary efforts during airway occlusion are regarded as the most appropriate tests in adults.[29] To specifically examine diaphragm strength (isolated from the intercostal muscles), two simultaneous pressure transducers (one in the esophagus and one in the stomach) can be used to calculate trans-diaphragmatic pressure. [29, 53] When patients are intubated, there is divergence in the literature as to whether maximal voluntary efforts can be guaranteed,[26, 29, 54-57] prompting investigators to use twitch stimulation of the phrenic nerve through electrical or magnetic coils with resultant measures of airway or esophageal pressure,[29, 58] . Although this technique has been applied in a very limited capacity in young children, it has high variability and limited reproducibility. [59-64]

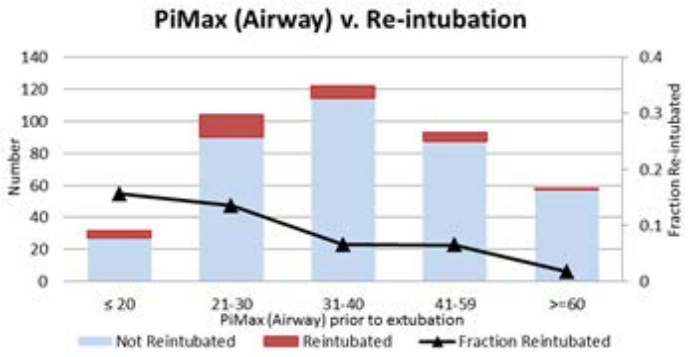

Figure 3: Re-intubation rates increase in a dose response fashion as a function of low aPiMax.

An analysis of the 409 patients enrolled in our previous study suggested that low PiMax (both airway (aPiMax) and esophageal (ePiMax)) measured during airway occlusion while the child is breathing spontaneously, was associated with re-intubation. [65] A trained provider (research respiratory therapist or study PI) performed airway occlusion maneuvers to measure both aPiMax and ePiMax, ensuring that the child was at end-exhalation and that the airway remained occluded for at minimum 3 consecutive breaths, but most of the time at least 5,[57] just before extubation. Measures of respiratory system capacity were obtained prior to extubation during airway occlusion, and measures of respiratory effort were obtained

both before and after extubation. Of the 409 patients, 34 were re-intubated within 48 hours (8.3%). Prior to extubation, re-intubation risk factors included lower aPiMax, and longer length of ventilation. After extubation, post-extubation upper airway obstruction (UAO), high respiratory effort or load (Pressure Rate Product (PRP), Pressure Time Product (PTP), Tension Time Index (TTI)) and high Phase Angle (PA) were associated with re-intubation. Because patients in this study had already passed SBTs, they generally had near normal compliance (low load), so pre-extubation respiratory effort was not associated with re-intubation. When looking specifically at measures of respiratory muscle capacity prior to extubation, there was a dose response relationship between lower aPiMax and re-intubation risk (Figure 3). Children with aPiMax ≤ 30 cmH_20 accounted for 33% of all extubated patients, but were responsible for 56% of all failed extubations (19/34). Thus, aPiMax alone is a marker of re-intubation risk (AUC 0.66 (0.57, 0.75).

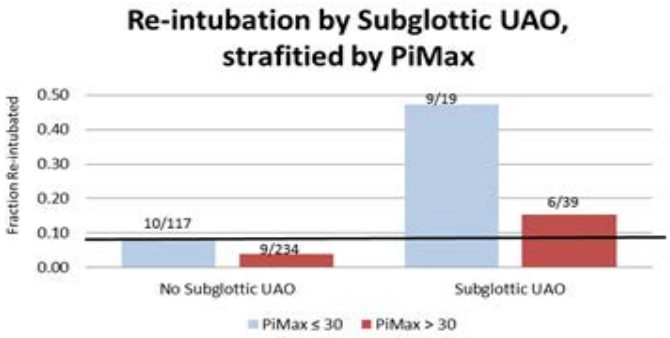

Figure 4: When children with low aPiMax develop high respiratory load (such as from post extubation UAO), they have very high re-intubation rates. Solid line is population average.

Nevertheless, combining aPiMax with measures of respiratory effort (after extubation) such as PRP better predicted re-intubation risk (AUC 0.77). For children with diminished respiratory muscle capacity (aPiMax ≤ 30 cmH_2O), re-intubation rates were always higher than the population average, and they became accelerated as effort increased (PRP>500). Children with maintained respiratory muscle capacity (aPiMax >30 cmH_2O) could tolerate moderate to high levels of load after extubation (PRP 500-1000), and re-intubation rates did not exceed the population average unless effort was very high (PRP > 1000). Post-extubation subglottic UAO was the most common reason for high respiratory muscle load after extubation, and when children with diminished respiratory muscle capacity (aPiMax ≤ 30 cmH_2O) had subglottic UAO after extubation, their re-intubation rates were 5.7 times higher than the population average (47.5% vs. 8.3%, Figure 4). The rate of aPiMax ≤ 30 cmH_2O was slightly higher for neonates (47%) compared to the other age groups, although this was not statistically significant (p=0.12; 30% infants (1-24 months), 30 % child age (2-11 years) and 34% adolescents (11-18 years)). Multivariable risk factors for re-intubation include primary intubation for neurologic disease, lower aPiMax, UAO post-extubation, higher PEEP before extubation, higher PRP after extubation, and lower height (AUC 0.823). This demonstrates that **respiratory muscle weakness contributes to extubation failure,** and maintaining respiratory muscle strength will likely reduce re-intubation rates even when respiratory load after extubation is high. These data further support **the hypothesis that children with respiratory muscle weakness will have more trouble weaning from MV** when respiratory load (compliance, resistance) may still be high**.**

B.3.6 Summary of Preliminary Data: We have demonstrated that 35% of MV children have respiratory muscle weakness at the time of extubation, making them 3 times more likely to be re-intubated, and nearly 6 times more likely to fail when respiratory load is high.[65, 66] We have also shown that current ventilator management in children likely exacerbates the development of respiratory weakness by lowering patient

effort of breathing well below normal physiologic values.[13, 14] To promote maintaining patient effort of breathing in a normal range we have developed and demonstrated the feasibility of having bedside providers use a computer-based ventilator management system throughout the entire course of MV. Patients managed with this system experienced a median 2 day reduction in the length of MV compared to historical controls. Together these data justify the next phase of this program of research, to test whether this ventilator management approach can lead to improved clinical outcomes in a robust randomized clinical trial, and to characterize the mechanisms underlying this improvement through detailed, serial assessments of the respiratory muscles.

C Study Objectives

C1 Primary Aim

SA1: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV. We expect that patients randomized to receive REDvent-acute will either pass their first SBT or experience a shorter duration of weaning when compared to usual care. In addition, patients randomized to receive REDvent-weaning will experience a shorter duration of weaning compared to usual care. Secondary outcomes include 28-day Ventilator Free Days and extubation failure.

C2 Secondary Aims

SA2: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes. We expect that diminished respiratory muscle strength (low PiMax), and diaphragm atrophy (ultrasound) will be prevalent after resolution of the acute phase of MV, and the combination of high respiratory load (or effort) with low PiMax will be a major factor leading to prolonged weaning and weaning failure (failure of SBT).

SA3: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness. We expect that after controlling for confounding variables like age, diagnosis, sedation, use of neuromuscular blockade, and other risk factors for neuromuscular weakness, children who maintain normal effort of breathing in the acute or weaning phases will have higher respiratory muscle capacity as measured by PiMax.

C3 Rationale for the Selection of Outcome Measures

C.3.1. Clinical outcome measures:

1. Primary Outcome – Weaning Duration
   Weaning duration is defined as the time from the first spontaneous breathing trial (SBT) until successful passage of an SBT or successful extubation (whichever comes first). Successful extubation is defined as removal of the endotracheal tube without re-intubation for at least 24 hours. For tracheostomy patients, extubation is defined as removal of positive pressure mechanical ventilation without re-initiation for at least 24 hours. SBT passage will be based on objective criteria, based on previous publications.

   a. Criteria for SBT passage: SBTs will be performed when weaning criteria are met, and the patient passes the oxygenation test (maintenance of SpO2 > 90% with FiO2 ≤ 0.5 and PEEP ≤ 5 cmH20). SBTs will be performed on CPAP ≤ 5 cmH_2O, for 2 hours duration. The following criteria represent rules for study defined SBT failure at any time point during the 2 hour SBT.

Variable	Failure within 2 hours
pH (arterial or capillary)	< 7.32

End tidal CO2	↑10 mmHg from baseline
Oxygenation	FiO2 >0.5 and SpO2 <90% on PEEP =5 cmH20
HR	↑ > 40 BPM over baseline
Rapid Shallow Breathing Pattern (RSBI) (bpm/ml/kg)	≥ 12
Pressure.Rate.Product (PRP)	>500
Retractions	Moderate or Severe

b. Rationale for passing SBTs vs. extubation in defining weaning duration: SBTs systematically assess the patient's readiness to resume unassisted ventilation, while extubation can be delayed after SBT passage (due to respiratory secretions, procedures, etc.). For this reason, SBT passage or successful extubation (whichever comes first) will define the end of the weaning phase. If a patient passes an SBT but is not extubated within 6 hr, ventilator management until extubation will continue as per the group to which the patient has been randomized for the current phase of ventilation. However the length of weaning for the primary outcome measure will be calculated as the time the patient passed the SBT. If a patient does not pass the SBT, but the clinical team elects to extubate the child (or the child has an unplanned extubation), and the child is not re-intubated within 24 hours, then the length of weaning for the primary outcome measure will be calculated as the time the patient was extubated.

2. Duration of Invasive Mechanical Ventilation (IMV)- Secondary Outcome
Duration of invasive ventilation is the number of days and hours that the patient is intubated (from insertion to removal), censored 60 days after study enrollment. For calculations, removal of the ETT will be calculated as the first time the tube is continuously absent for at least 24 hours. For tracheostomy patients, the end of intubation is defined as removal of positive pressure mechanical ventilation without re-initiation for at least 24 hours. Re-intubation after 24 hours and subsequent periods of invasive mechanical ventilation within 60 days of study enrollment will be summed together to represent total duration of IMV.

3. Duration of Non-Invasive Mechanical Ventilation (NIV) after extubation– Secondary Outcome
Duration of non-invasive ventilation after extubation is defined as the number of days and hours that the patient is on oro-nasal mask CPAP with minimal pressure of 5 cmH20, or Bi-Level ventilation (at any pressure) after extubation, censored 60 days after study enrollment. For calculations, the end of Non-Invasive Ventilation will be calculated as oro-nasal mask CPAP (minimal 5 cmH20) or BIPAP as continuously absent for at least 24 hours. Resumption of NIV after 24 hours and subsequent periods of non- invasive mechanical ventilation within 60 days of study enrollment will be summed together to represent total duration of NIV after extubation.

4. Duration of Non-Invasive Mechanical Ventilation (NIV) before intubation– Secondary Outcome
Duration of non-invasive ventilation before intubation is defined as the number of days and hours that the patient is on oro-nasal mask CPAP with minimal

pressure of 5 cmH20, or Bi-Level ventilation (at any pressure) prior to intubation. This is necessary to correctly compute ventilator free days. For calculations, the patient must have been on Non-Invasive Ventilation in the 24 hours prior to intubation.

5. Duration of Non-Invasive Respiratory Support (NRS) after extubation- Secondary Outcome
   Non-invasive respiratory support includes: High Flow Nasal Cannula (HFNC) or nasal-only modes of non-invasive ventilation (CPAP or Nasal IMV or BiPAP). It does not include oxygen therapy via face mask, nasal cannula, oxygen hood, or blow by oxygen alone. Duration of NRS after extubation is defined as the number of days and hours that the patient is on NRS after extubation, censored at 60 days after study enrollment. For calculations, the end of NRS will be calculated as NRS being continuously absent for at least 24 hours. Resumption of NRS after 24 hours and subsequent periods of NRS within 60 days of study enrollment will be summed together to represent total duration of NRS after extubation.

6. Re-intubation within 48 hours of extubation- Secondary Outcome
   Re-intubation will be defined as re-insertion of the endotracheal tube within 48 hours of the initial extubation. For tracheostomy patients, re-intubation is defined as re-initiation of positive pressure mechanical ventilation within 48 hours of discontinuation.

7. Re-intubation within 7 days of extubation- Secondary Outcome
   Re-intubation will be defined as re-insertion of the endotracheal tube within 7 days of the initial extubation. For tracheostomy patients, re-intubation is defined as re-initiation of positive pressure mechanical ventilation within 7 days of discontinuation.

8. Ventilator Free Days- Secondary Outcome
   Because the acute phase of ventilation is often long and less predictable, weaning duration was chosen as the primary outcome because there is more variability in Ventilator Free Days (VFDs) than in weaning duration. However VFDs is a secondary outcome. VFDs will be calculated at 28 and 60 days, defined as total number of days after initiation of MV in which the patient is alive and not on ventilation. The components of length of mechanical ventilation used for VFD calculations include length of IMV (2 above), length of NIV after extubation (3 above) and length of NIV prior to intubation (4) above. Patients who die within the 28 or 60 days will have 0 28 or 60 Day VFDs respectively.

9. Use and duration of rescue therapies - Secondary Outcomes
   We will track daily whether the patient received any of the following "rescue therapies" which are frequently used for ARDS management: inhaled nitric oxide, High Frequency Oscillatory Ventilation, Prone Positioning, Extra Corporeal Life Support, Corticosteroids for lung disease/ARDS, Continuous Neuromuscular Blockade, Airway Pressure Release Ventilation.

C.3.2 Physiologic outcome measures: Our primary physiologic outcome surrounds respiratory muscle weakness. Previous research has highlighted the importance of using multiple assessments of respiratory muscles, as single tests may be misleading. [67] We

will use esophageal manometry, airway pressure, and diaphragm ultrasound to evaluate direct and indirect measures of respiratory muscle strength.

1. Respiratory Muscle Strength (aPiMax- Primary Outcome; ePiMax – Secondary Outcome)**:**
   a. Physiologic measures of strength include airway and esophageal pressure during airway occlusion (aPiMax and ePiMax, respectively). Primary analysis is planned using aPimax (calculated as maximal change in airway pressure at end exhalation during airway occlusion for 3-5 breaths). Secondary analysis will use ePimax (calculated as maximal change in esophageal pressure at end exhalation during airway occlusion for 3-5 breaths). Measurements will be obtained daily after the patient passes the oxygenation test.
   b. Rationale: We found aPiMax better predicted re-intubation than ePiMax in our preliminary data. We believe that this is due to more artifacts in the esophageal pressure signal during airway occlusion, which are not present with airway pressure. To isolate diaphragm weakness, a second balloon catheter would be necessary to calculate trans-diaphragm pressure. However, this is not practical for repeated use in children and no double-balloon catheters are commercially available for infants. A second catheter in an already small esophagus may alter the signals further, and impede clinical care if the catheter is left in place. While we will measure both airway and esophageal PiMax, we plan to use aPiMax as the primary marker of respiratory system capacity. Our previous study evaluated PiMax parameters only at extubation, but we are confident the technique can be applied earlier (i.e., just prior to SBTs), and have obtained them successfully as part of our pilot study. Early in the course of MV, patients may be more sedated than they are at the time of extubation (but are still breathing spontaneously), but we have successfully measured both airway and esophageal PiMax in patients who are considerably more sedated, and in deeply sedated rhesus monkeys.[48] Sedated patients still produce reliable PiMax measurements when using our methodology, particularly when 5 occluded breaths are used. We will also calculate P0.1 (change in airway or esophageal pressure in the first 0.1 seconds of a breath attempt) which can be used to identify if sedation is affecting the results of the PiMax measurements. All PiMax procedures will be recorded for post-processing analysis.

2. Diaphragm Architecture**:** Serial measurements from diaphragm ultrasound will be performed daily to assess changes in diaphragm thickness during exhalation (Dte) during both acute and weaning phases. [3, 5-8, 26, 52, 68-73] For the acute phase, the main diaphragm ultrasound outcome is: change in diaphragm thickness from study initiation until the end of the acute phase. For the weaning phase it is: change in diaphragm thickness from the end of the acute phase until the end of the weaning phase. Because diaphragm ultrasound is non-invasive, it has advantages although it has not been validated against direct measures of respiratory muscle strength or weaning outcomes. We will attempt such a validation with this study, but have not selected it as the primary physiologic endpoint for that reason.

D Study Design

D1 Overview or Design Summary

We propose a single-center randomized controlled trial (138 children per arm) using REDvent (intervention arm) as compared with usual care ventilator management including a standardized daily SBT (control arm). Acute phase randomization will occur upon study enrollment, and patients who fail the first SBT will undergo a weaning phase randomization. We will obtain serial measurements of respiratory system capacity, load, effort of breathing, and diaphragm architecture throughout the course of MV.

D2 Subject Selection

D.2.1 Inclusion Criteria

1. Children > 1 month (at least 44 weeks Corrected Gestational Age) and ≤ 21 years of age AND
2. Supported on mechanical ventilation for pulmonary parenchymal disease (i.e., pneumonia, bronchiolitis, Pediatric Acute Respiratory Distress Syndrome (PARDS)) with Oxygen Saturation Index (OSI) ≥ 5 or Oxygenation Index (OI) ≥4 [74] AND
3. Who are within 48 hours of initiation of invasive mechanical ventilation (allow for up to 72 hours for those transferred from another institution)

D.2.2 Exclusion Criteria

1. Contraindications to use of an esophageal catheter (i.e. severe mucosal bleeding, nasal encephalocele, transphenoidal surgery) OR
2. Contraindications to use of RIP bands (i.e. omphalocele, chest immobilizer or cast) OR
3. Conditions precluding diaphragm ultrasound measurement (i.e. abdominal wall defects, pregnancy) OR
4. Conditions precluding conventional methods of weaning (i.e., status asthmaticus, severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal Life Support (ECLS), intubation for UAO, DNR, severe chronic respiratory failure, spinal cord injury above lumbar region, cyanotic heart disease (unrepaired or palliated)) OR
5. Primary Attending physician refuses (will be cleared with primary attending before approaching the patient).

D2.3 Screening and Eligibility

Screening will occur daily to identify eligible patients. An automated report has been generated to facilitate screening which calculates the oxygen saturation index, oxygenation index, PF ratio, and SF ratio for all patients on mechanical ventilation in the ICU. Patients who have had qualifying hypoxemia (OSI >5 or OI >4) in the previous 24 hours will have their chart reviewed to determine complete eligibility based on meeting all inclusion criteria and no exclusion criteria.

D3 Study Interventions

The study intervention includes both acute and weaning phase components. A high level view of the study is summarized in figure 5 below.

D.3.1 Acute Phase: The acute phase is defined as the time from intubation until the patient meets weaning criteria,[15, 16] and passes the initial oxygenation test (decrease PEEP to 5 cmH_2O and FiO_2 to 0.5, Figure 6).

D.3.2 Acute Phase, Intervention Arm (REDvent-acute): Patients will be managed with pressure control plus pressure support ventilation with the CDS tool that will recommend changes to ventilator settings every 4 hr or with a new blood gas. The computerized decision support (CDS) tool used by REDvent-acute is an electronic protocol that makes recommendations at to adjust both ventilation (ventilator pressure or tidal volume and ventilator rate) and oxygenation (Positive End Expiratory Pressure and FiO2) to promote lung protective ventilation during the acute phase of MV. Details of the rules behind the actual protocols are in section I. PEEP/FiO2 is based on a PEEP/FiO2 table adapted from the Acute Respiratory Distress Syndrome Network protocol,[45] (R21HD061870, PI Newth). Ventilation is changed based on pH range, Peak Inspiratory Pressure, and Ventilator Rate. When the patient is breathing spontaneously during the acute phase, the Pressure.Rate.Product (PRP) is incorporated into the algorithm. The pH based recommendations are followed if increasing support is recommended. If the pH based recommendation is to decrease support, it will only do so if the PRP is below 200. If the PRP is between 200-400, support is maintained. If the PRP is above 400, the protocol will recommend increasing driving pressure (Delta P) by 2 cm H20, to a max of 35 cmH20. The use of High Frequency Oscillatory (HFO) Ventilation as a rescue therapy will be left to the bedside clinicians, but HFO management will continue to be protocolized using the HFOV CDS tool (expected use: 10-15% in this cohort). This protocol has a MAP/FiO2 table, and also recommends alterations in Amplitude and Hertz based on pH. Details of the rules of the protocols are in section I.

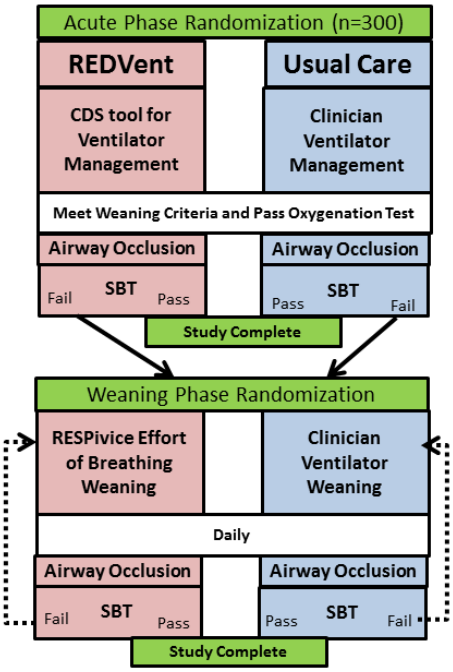

Figure 5: High level view of study interventions for both arms, during acute and weaning phases

D.3.3 Acute Phase, Control Arm: Ventilator management will be per usual care until the patient meets weaning criteria and passes the oxygenation test (Figure 6).

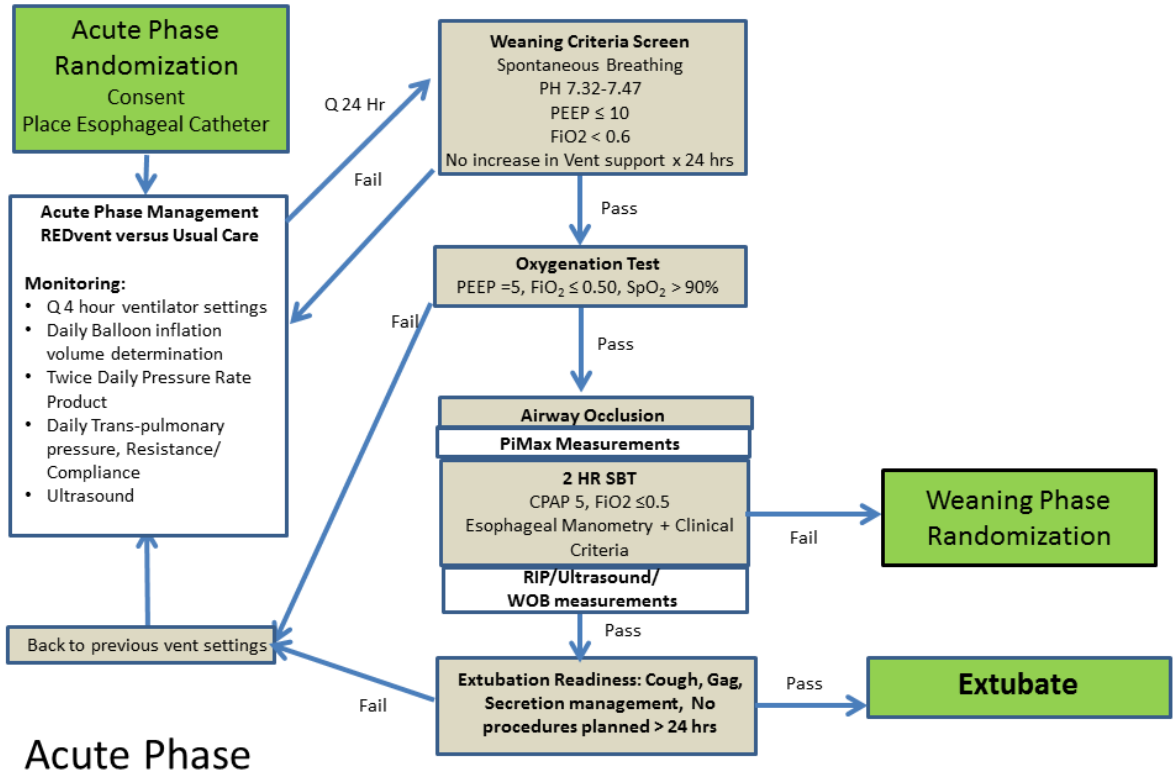

Figure 6: Acute Phase schematic, both arms

D.3.4 Acute Phase Monitoring, both arms: Patients will be fitted with an esophageal manometry catheter, will undergo diaphragm ultrasound measurements, and will be connected to RIP bands during SBTs. Volumetric capnography with an airway flow sensor will be placed at the end of the endotracheal tube to measure Carbon dioxide concentration, tidal volume, and airway pressures.

Once the patient passes the oxygenation test, an airway occlusion maneuver will be performed to measure neuromuscular strength, followed by a SBT. Daily SBTs are required and will be performed between 9 and 11 AM on CPAP of 5 cmH_2O. The primary study outcome (length of the weaning phase) is defined as the time from initiation of the first SBT until successful passing of an SBT (or extubation, whichever comes first). We will use validated objective criteria to define successful passing of the SBT, and track delays in extubation (> 6 hr between SBT passing and extubation). These criteria are based on our previous publications and are detailed in the description of the primary outcome above, and again below. [16, 75] Patients who fail the initial SBT will move on to the weaning phase, and will undergo the weaning phase randomization to allocate treatment or control arms for weaning management.

D.3.5 Spontaneous Breathing Trials and success/failure

Variable	Failure within 2 hours
pH (arterial or capillary)	< 7.32
End tidal CO2	↑10 mmHg from baseline
Oxygenation	FiO2 >0.5 and SpO2 <90% on PEEP = 5 cmH20
HR	↑ > 40 BPM over baseline
Rapid Shallow Breathing Pattern (RSBI) (bpm/ml/kg)	≥ 12

Pressure.Rate.Product (PRP)	>500
Retractions	Moderate or Severe Retractions

For the outcome of SBT passage, if any of the above criteria are met during the 2 hour SBT, the patient will be labeled as failing the SBT for study purposes. Once any of these failure criteria are met, the respiratory therapist will alert the clinical team. The clinical team may choose to stop the SBT, in which case the patient will be returned to the previous ventilator settings, and weaning phase randomization will occur. If the patient is randomized to REDvent-weaning, they will be placed in PS/CPAP mode and pressure support will be titrated to achieve PRP between 200-400 (to max of 20). PEEP may be adjusted between 5 and 10 cmH20. The clinical team may alternatively choose to continue the SBT or to extubate the patient. If the patient is extubated, post-extubation management (and subsequent re-intubation management) will be usual care. If the patient is not extubated but the SBT is terminated by the clinical team, then weaning phase randomization will occur at that point.

Monitoring during the SBT will include placement of Respiratory Inductance Plethysmography (RIP) bands and a spirometer. Vital signs, physiologic measurements, and data from RIP and esophageal manometry will be recorded every 30 minutes during the SBT. A study ultrasound to measure diaphragm contractile activity will occur approximately 15 minutes into the SBT.

If the patient successfully passes the SBT, extubation readiness criteria will be confirmed (i.e. cough, gag, handling secretions, no procedures planned). If the patient meets extubation readiness criteria, the recommendation will be for extubation to the clinical team. If the patient does not meet extubation readiness criteria, they return to acute phase management (to whichever group they were randomized), and another SBT will be repeated 24 hours later. If a recommendation for extubation was given but actual extubation is delayed beyond 6 hours, the reasons will be recorded on the case report forms, and the acute phase intervention will be resumed. If the patient is extubated as recommended, the esophageal catheter and RIP bands will remain in place for 1 hour after extubation to monitor post-extubation effort of breathing.

If the patient fails the SBT, they will go on to the weaning phase randomization.

D.3.6 Weaning Phase: The weaning phase is defined as the time from the first SBT until the patient successfully passes an SBT.

D.3.7 Weaning Phase, Intervention Arm (REDvent-weaning): The weaning phase in the intervention arm uses esophageal manometry and a custom built hardware and software package for effort of breathing guided management. The patient will be placed in a pressure support mode of ventilation and PRP will be monitored continuously, adjusting pressure support (to a max of 20 cmH20) every 4 hr to maintain PRP in the target range (Figure 7). Effort of Breathing guided management will continue until the patient passes a SBT. The esophageal balloon is inflated to a daily prescribed volume every 4 hours prior to assessment, based on an optimal filling volume algorithm. The median PRP over 10-20 breaths during calm periods of breathing (i.e. not agitated, not recently suctioned etc) is inputted into the computer decision support tool, which subsequently generates the recommendation regarding changing the level of pressure support.

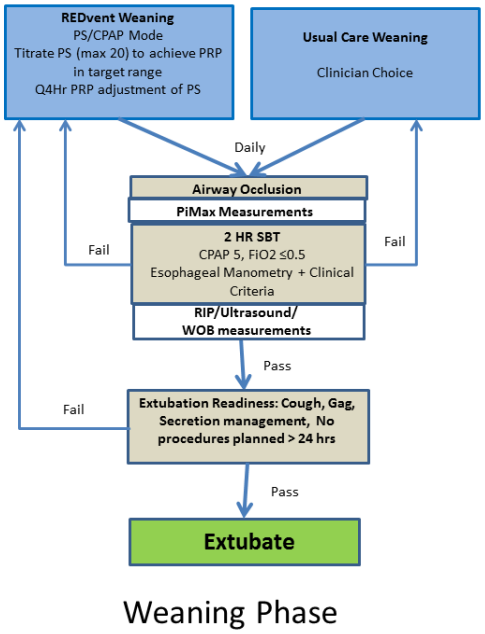

Figure 7: Weaning Phase schematic, both arms

D.3.8 Weaning Phase, Control Arm: Ventilator management will be per usual care until the patient passes a SBT.

D.3.9 Weaning Phase, Monitoring both groups: In both groups, a daily airway occlusion maneuver and SBT will be performed, with the same rules above in section D.3.5 regarding SBT passage and monitoring.

D.3.10 Post-extubation Management: The decision to use non-invasive ventilation and other post-extubation management will not be protocolized, regardless of study arm. Patients who are re-intubated after a planned extubation (regardless of study arm) will subsequently receive usual care ventilation. The esophageal catheter and RIP bands will be removed 1 hour after extubation.

D.3.11 Suspension of Weaning Phase: Suspension of the weaning phase is permitted for up to 12 hours for situations such as procedures, increased need for sedation preventing adequate spontaneous breathing, transient increase in ventilator support etc. As soon as the patient appropriately meets weaning criteria (based on weaning criteria screen Figure 6), the weaning phase intervention is resumed.

D.3.12 Failure of the Weaning Phase: If the weaning phase is suspended for > 12 hours and the patient no longer meets weaning criteria at the 12 hour mark (Figure 6), then the acute phase of management and monitoring is resumed. The patient will be managed as per their pre-assigned acute phase group (i.e. REDvent-acute or usual care). Once weaning criteria are met, an SBT will again be performed. If the patient fails the SBT, then the weaning phase intervention to which they were previously randomized (REDvent-weaning or usual care) is resumed. The frequency with which weaning failure occurs in both arms will be tracked as an adverse event.

D.3.13 Termination of study interventions at 28 days: If the patient has not passed the SBT by day 28 after enrollment, study interventions and daily measurements will be terminated. All ventilator management will be as per usual care. Clinical outcomes will continue to be followed.

D.3.14 Post Enrollment exclusion criteria: Patients who develop exclusion criteria after study enrollment that preclude continuation of the study interventions (i.e. use of ECLS, new condition requiring removal of esophageal catheter) will have the study protocol and measurements terminated, but clinical outcomes will continue to be followed and analysis will be as per intention to treat. For patients who are made allow natural death status during the study, parents will be given the option to either continue the study protocol, or withdraw from the study. Clinical outcomes will continue to be followed. Patients who develop a condition which may preclude calculation of secondary

outcomes (i.e. diaphragm ultrasound or RIP bands) will continue to receive study interventions, and all planned study measurements which can reasonably be obtained.

D4 Measurement of Study Variables

Demographics, clinical variables, and outcomes will be measured as detailed in the table below (data collection timeline). To ensure the adequacy of randomization and understand the risk factors that may contribute to neuromuscular weakness and weaning failure, we will gather detailed, serial data for variables that may be related to weaning duration and development of neuromuscular weakness.[1, 5, 6, 8-10, 26] These variables are based upon our recent consensus-based guidelines for clinical trials in children with pediatric ARDS. [76] Identical measurements of respiratory parameters will occur for all patients enrolled in the study (regardless of study arm) (1) serially during both acute and weaning phases, (2) during airway occlusion prior to SBTs, and (3) during SBTs (Table below).

D.4.1 Serial respiratory measurements during acute and weaning phases: We will measure patient effort of breathing twice daily with esophageal manometry (using Pressure Rate Product [PRP] and Pressure Time Product [PTP]) and once daily using diaphragm ultrasound (using Diaphragm Contractile Activity [DCA]), during the acute and weaning phases in both arms. DCA is obtained by measuring the thickness of the right hemi-diaphragm and calculating the percent difference between diaphragm thickness on inspiration and exhalation. Diaphragm ultrasound measurements will be performed independently by 2 practitioners, one of whom is specifically trained in acute care ultrasound. We will also use ultrasound to measure diaphragm thickness on exhalation and monitor how this changes serially over time as a measure of the architecture of the diaphragm. Finally, we will measure respiratory load (resistance, compliance) daily using spirometry. The clinical team will remain blinded to the results of these measurements in both arms.

D.4.2. Spontaneous Breathing trial respiratory measurements during Airway Occlusion: Prior to each SBT, we will perform a standardized airway occlusion maneuver to measure neuromuscular capacity with aPiMax (airway) and ePiMax (esophageal), as described in the Preliminary Data. In addition, during airway occlusion we will measure DCA (as above) [5, 7, 51, 52], to provide complementary data to PiMax. The clinical team will remain blinded to the results of these measurements in both arms.

D.4.3 Weaning trial measurements during SBTs: During SBTs, respiratory effort and capacity will be measured with PRP, PTP, inspiratory pressure from esophageal manometry (Pi), Pi/ePiMax, Tension Time Index (TTI), Phase angle (PA), and DCA. Patients will be monitored continuously during the SBT, and all of these measures will be recorded at the beginning of the SBT, and then every 30 minutes (for 5 minute periods) to monitor respiratory muscle endurance over time. The PRP measurements will be shared with the clinical team in both arms because they will be used to help define passage of SBTs (as above). Clinical providers will remain blinded to the results of the other measurements in both arms.

Data Collection timeline	Enroll-ment	Acute (Daily)	Weaning (Daily)	SBT	Post-Extubation
Demographics (age, race, gender, past medical history, primary diagnoses, comorbidities, PRISM-III-12 severity of illness scores, height, weight, quality of life score)					
Clinical Variables (total dose of sedatives, analgesics, highest/lowest/modal sedation scores, pain scores, corticosteroids, aminoglycosides, fluid balance, caloric and protein intake, hypoxemia markers, dead space markers, ventilator type and settings (q6h), blood gasses (all), inotropes/vasopressors, organ failure scores (PELOD), procedures)					
Effort of Breathing and Respiratory Load					
Esophageal Manometry: PRP, PTP, TTI, Pi					
Respiratory Inductance Plethysmography [44]: Phase Angle (PA)					
Ultrasound: Diaphragm Contractile Activity (DCA)					
Spirometry**:** Resistance, Dynamic and Static Compliance					
Respiratory Muscle Strength (during airway occlusion)					
Esophageal Manometry: Esophageal PiMax (ePiMax)					
Airway Pressure: Airway PiMax (aPiMax)					
Ultrasound: DCA during airway occlusion					
Diaphragm Architecture (Thickness on Exhalation)					
Outcomes (Weaning Duration, VFDs and components, re-intubation, Non-Invasive Ventilation use and duration, ICU, Hospital, 90-day mortality, quality of life score)					

D.4.4 Rationale for respiratory measures: Previous research has highlighted the importance of using multiple assessments of respiratory muscles, as single tests may be misleading. [67] We will use four classes of respiratory monitoring: esophageal manometry, diaphragm ultrasound, RIP, and ventilator/clinical data. Our primary interest is respiratory muscle strength, which is best characterized during airway occlusion with PiMax. PiMax measurements will be done as soon as the acute phase has resolved, and daily during the weaning phase, because PiMax is not feasible to measure during the acute phase of MV because patients may be too unstable to tolerate airway occlusion. Serial measurements from diaphragm ultrasound can and will be performed daily to assess changes in diaphragm architecture during both acute and weaning phases [3, 5-8, 26, 52, 68-73]. Because diaphragm ultrasound is non-invasive, it has advantages although it has not been validated against direct measures of respiratory muscle strength or weaning outcomes. We will attempt such a validation with this study. We anticipate DCA and PRP will provide complementary information regarding patient effort. To isolate diaphragm weakness, a second balloon catheter would be necessary to calculate trans-diaphragm pressure. However, this is not practical for repeated use in children and no double-balloon catheters are commercially available for infants. A second catheter in an already small esophagus may alter the signals further, and impede clinical care if the catheter is left in place. While this leaves open the possibility of intercostal muscles contributing to the weakness, we will complement these data with architectural changes to the diaphragm on ultrasound.

D5 Co-Interventions

Sedation: Sedation management will be controlled in both arms targeting a State Behavioral Scale, based on the sedation protocol used in the NHLBI funded RESTORE clinical trial. [75] This scale is being implemented for routine use in the Pediatric Intensive Care unit. Each day the clinical team will select an SBS target on morning rounds, based on the status of the patient. The level of sedation and SBS score will be monitored every 4 hours in each group. Generally acceptable SBS targets range from -2 to 0. For the acute phase management, the suggested SBS target is -2, and for the weaning phase of ventilation the SBS target is -1. A nurse guided protocol is not currently in place for automatic adjustment of sedation to meet the SBS target, but the nurse will administer as needed medications to meet the SBS target if it is above target, and will consult with the MD to decrease sedation if the SBS is below target.

Inhaled Nitric Oxide: Inhaled Nitric Oxide is frequently used for clinical care in our intensive care unit for children with ARDS. Like High Frequency Oscillatory Ventilation and other rescue therapies, the decision to begin inhaled nitric oxide will be left to the discretion of the clinical team. However, for patients in REDvent Acute, inhaled nitric oxide is built into the computerized protocol management of PEEP/FiO2. Consistent with the ICU protocol for nitric oxide weaning, once FiO2 is reduced to 0.6, if oxygenation is adequate or high, weaning of nitric oxide will be recommended (see section I for details).

Quadriceps Ultrasound: Critically ill patients lose strength and muscle mass when in the intensive care unit, which may contribute to long term functional impairment. While functional assessment and strength testing is most accurate, they are difficult to do in children, or on sedated, non-cooperative patients. Ultrasound can measure muscle thickness and echogenicity, and can document progression of muscle atrophy.[3] The quadriceps femoris muscle group is most commonly measured, with a demonstrated relationship between strength and quadriceps femoris muscle thickness. Adult studies have documented that the quadriceps muscle thickness and cross sectional area decreases through the ICU course, correlates with length of stay and muscle strength and, less consistently, function at discharge. In most studies, ultrasound has high accuracy and inter-rater reliability. In children, the literature on quadriceps muscle thickness measurement by ultrasound is limited to comparing normal children to those with neuromuscular disease. While the proposed REDvent intervention is specifically targeting prevention of diaphragm atrophy, critical illness itself can lead to atrophy of other muscles. As such, in addition to measuring the change in diaphragm thickness daily, we will also measure the change in quadriceps muscle thickness daily, to help understand whether REDvent can modulate quadriceps muscle atrophy, of if the degree of quadriceps muscle atrophy has an interaction with the potential benefit of REDvent on diaphragm atrophy or strength. In each patient while supine with their feet pointing up, we will measure quadriceps muscle thickness at two points, in the midsaggital plane for each thigh. Like diaphragm ultrasound measurements, multiple providers will obtain measurements daily, to ensure reproducibility and inter rater reliability.

D6 Statistical Considerations

D.6.1. Randomization Strategy and Blinding

Consenting subjects will be **block randomized** to intervention or control arms for the acute phase based on age group: infant (30 days -365 days), child (366 days to ≤8 years), and older child/ adolescent (9-21 years); and immune suppression. For study purposes immune suppressed patients will be defined as: patients with congenital or acquired conditions (including medications) which result in marked inability to respond to antigenic stimuli. Examples of immune suppression include: oncologic disease with recent chemotherapy or radiation, congenital immunodeficiency, HIV, rheumatologic condition on chemotherapy, allogeneic or autologous stem cell transplant, solid organ transplant, or any other condition in which immunosuppressive medications are prescribed. Block randomization will be based on random block sizes of 4, 6 and 8 within the strata above, and loaded into opaque envelopes by the statistician for the study team to determine treatment arm at the time of randomization. Weaning phase randomization will be block randomized by REDvent-acute phase group, age, and immunosuppressed status using the same methodology. Although **blinding** is not possible given the open label nature of the intervention, analysis will be blinded to treatment groups, and performed by an independent statistician.

D.6.2 Rationale for Randomization Strategy: Age stratified randomization is necessary because *age is an important biological variable* likely to confound the relationship between respiratory muscle weakness and length of weaning. This will ensure an equal age distribution amongst treatment groups. Age groups are based upon accepted pediatric definitions, and have been used in numerous other pediatric RCTs. Neonates (< 1 month) have been excluded because they are often managed with different ventilator strategies and because normal values for PiMax are lower in neonates [63, 64]. Immunosuppression is a known risk factor which affects duration of ventilation and weaning, and an imbalance in immunosuppression between groups has been shown to significantly confound previous pediatric mechanical ventilation studies. The additional weaning phase randomization is necessary because we anticipate an imbalance of the number of patients who will be extubated after the acute phase between REDvent-acute and control groups. Acute phase management may have a sustained effect on neuromuscular strength that will affect the duration of weaning. To understand whether the REDvent strategy during the weaning phase can prevent prolonged weaning, risk factors for prolonged weaning (which may be different based on acute phase management) need to be rebalanced with a second randomization. Ultimately, this will allow us to determine the independent utility of REDvent-acute and REDvent-weaning components.

D.6.3 Preparation of the Analysis Data Set

Datasets for analyses consist only of data for which all queries have been resolved. In addition to data management steps to reduce error in data acquisition and entry, a biostatistical cleaning will focus on inconsistencies, missing data and outliers in variables related to the derivation of key outcomes. These activities will be ongoing throughout the study and will involve both the data management team and the biostatistics team.

Preplanned construction of new variables will be conducted in accordance with the study hypotheses and analysis plans. Variable transformation may be required for interpretive

and statistical purposes. With respect to the primary outcome of weaning duration, patients who do not progress to the weaning phase within 28 days (i.e. death, prolonged severe illness) will not be included in analysis of the primary outcome, but will be considered for secondary outcomes.

D.6.4 Statistical Analysis Plan

For all variables, descriptive statistics will be calculated, including means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Data will be examined for skewness, outliers, and systematic missing data. Transformations will be undertaken as needed. Comparisons of demographic and baseline variables will be obtained by treatment group.

D.6.4.1 SA 1 Analysis Plan: To determine if REDvent acute and/or weaning phase protocols can shorten the duration of weaning from MV (Primary outcome).

Primary analysis and sample size: The primary outcome for this aim is weaning duration. Because we seek to understand whether REDvent-acute and/or REDvent weaning have an independent effect on length of weaning, we propose a sample size to adequately power 3 separate comparative analyses: **(a)** REDvent-acute versus Acute Phase control **(b)** REDvent-weaning phase versus Weaning Phase control **(c)** REDvent both phases versus control both phases. We expect up to 12% mortality before the first SBT based on our Preliminary Data. These patients will not be included in the analysis for the primary outcome. From our pilot data (REDvent in both acute and weaning phases), the duration of the weaning phase in the intervention arm was 2.2 days, compared to 4 days in historical controls with a standard deviation of 2.1 days in the intervention arm and 2.8 days in the historical controls.

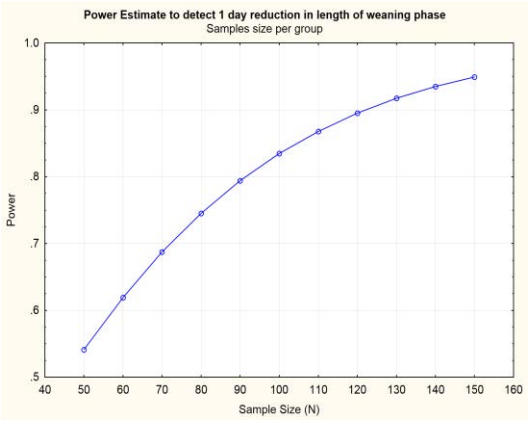

Figure 8: Power curve for a 1 day reduction in weaning

Comparison (a) REDvent-acute versus control**:** A 1-day reduction in length of weaning is considered clinically significant (less sedative exposure, fewer nosocomial infections, lower healthcare costs). With a sample size of 276 patients (138 per arm), up to 12% mortality and 1% attrition or incorrect randomization, a minimum of 240 patients (120 per arm) will be available for analysis of the acute phase. Power is based on 2 planned methods for analysis: cox proportional hazard ratios for multivariable analysis and univariate analysis with an independent t-test using log transformation (as needed) to account for the expected distribution of weaning duration. For univariate analysis using the assumptions above, we would be able to detect a ≥ 1-day reduction in weaning duration with an alpha of 0.05 and power of 0.9 (Figure 7). For the cox proportional hazard model, we would be able to detect a relative hazard ratio of 1.5 (ratio between control/intervention group) with a power of 0.9 or a hazard ratio of 1.4 with a power of 0.8.

Comparison (b) REDvent-weaning versus control: Patients who fail the initial SBT will undergo the weaning phase randomization. From our pilot data, approximately 25% of patients exposed to the intervention passed the initial SBT, corroborating previous studies. [15] Thus, at least 180 patients (90 per arm) will receive weaning phase interventions. Using the same assumptions as above, we will be able to detect a ≥ 1 day

reduction in the length of the weaning phase (Figure 8), or a hazard ratio of 1.5 with an alpha of 0.05 and power of 0.8. Patients who do not pass the SBT by 28 days post the weaning phase randomization will be censored for analysis, as study interventions and daily monitoring will end on day 29.

Comparison (c) REDvent versus control both phases: We will get an assessment of the cumulative effect of the intervention by comparing patients who received both REDvent-acute and REDvent weaning to patients who received only usual care in both phases. Because the rates of passage of the first SBT will differ between groups, there will not be an equal number of patients exposed to REDvent only as control only. Based on the assumptions above, we anticipate that of the 240 patients included in the analysis of weaning duration, 78 will be REDvent only, 72 will be control only, and 90 will be mixed. As such, the expected sample size comparing REDvent only to control only would allow us to detect a ≥ 1.1- day reduction in weaning duration with a hazard ratio of 1.6 with a power of 0.8 and alpha of 0.05; or a ≥ 1.3- day reduction in weaning duration with a hazard ratio of 1.6 with a power of 0.9.

All patients will be analyzed in the groups to which they were randomized for weaning duration, following intention to treat principles (allow for up to 1% incorrect allocation or attrition). Clinical variables (data collection table) will be tracked and compared between intervention and control groups for all 3 of the planned analyses (a-c). If there is an imbalance in any variable that may confound the relationship between weaning duration and REDvent, we will build a multivariable cox proportional hazard model to ensure that the measured treatment effect on weaning duration is retained after multivariable adjustment.

Secondary Outcomes for SA 1: The 28 and 60 Day Ventilator Free Days (28D VFD, 60D VFD) will be secondary outcomes of this aim. Groups for VFD analysis will be based on any exposure to the intervention (acute or weaning) because some patients will never undergo a weaning phase randomization (i.e. died or were extubated right after the acute phase). If patients who died as well as those who dropped out are included in the VFD analysis, with the assumptions above regarding expected passing rate of SBTs, the estimated distribution of patients in 3 distinct groups will be: (a) REDvent only (n=108); (b) REDvent and control (n=90); (c) control only (n=102). We anticipate children in the REDvent only arm will have the most 28 D VFDs (anticipation 22), and those in the control only arm the least (anticipation 20). Directly comparing control only patients to REDvent only patients, with an expected standard deviation for VFDs between 5 to 9 days, we will be able to detect a 2-day change in VFDs between groups with a power between 0.35 and 0.82. Re-intubation rates are expected to be 10%, allowing us to confirm that REDvent is not inferior to usual care in regards to re-intubation with a non-inferiority margin of 0.10 with a power of 0.8 and alpha of 0.05. Finally, to ensure that REDvent is promoting greater patient effort of breathing and that the intervention does not alter clinical practice in the usual care arm, we will compare time weighted average values for direct measures of patient effort of breathing (PRP, PTP, Diaphragm Contractile Activity), and ventilator settings between intervention and control groups, and monitor the separation between groups over the time of the study.

D.6.4.2 SA2 Analysis Plan: To determine if changes to direct measures of respiratory muscle strength, load, effort, and architecture throughout the duration of MV are related to weaning outcomes.

Analysis and Sample Size: The primary outcome of this aim is weaning duration (as defined above). For this analysis, we will compare how each respiratory measure detailed in the data collection table relates to weaning duration. For respiratory muscle

strength we will compare the first measured aPiMax (after resolution of the acute phase, before the first SBT), the trajectory and value of the daily aPiMax during the weaning phase prior to extubation, the lowest and highest measured aPiMax, and aPiMax on the day of extubation against weaning duration. For analysis, aPiMax will be dichotomized at 30 cmH2O (based on our preliminary data), and weaning duration will be compared between patients with aPiMax > 30 versus ≤ 30 cmH2O using a t-test with or without log-transformation, or Mann-Whitney U test, depending on the distribution. From our preliminary data, we anticipate at least 35% of patients (n=84) will have aPiMax ≤ 30 cmH2O. Based on a similar power analysis as presented above, this would allow us to determine whether low aPiMax is associated with a ≥ 1-day increase in weaning duration, with an alpha of 0.05 and power of 0.8. We will perform identical analysis for ePiMax.

Diaphragm Thickness analysis will compound daily ultrasound measures to detect the relative change in diaphragm thickness from study day 1 until passage of an SBT. We will compare the change in thickness after resolution of the acute phase (on the day of the first SBT) against weaning duration, in a similar manner as proposed above for aPiMax. For analysis, diaphragm thickness will be tested as a continuous variable (with Spearman's or Pearson's Correlation), but also categorized into 3 groups (loss of > 10% in thickness, maintenance of thickness (-10% to +10%), and increase in size of > 10%) to account for the potential ill effects of diaphragm hypertrophy (expected in about 10% of patients), using Analysis of Variance (ANOVA) to compare weaning duration between groups. We will characterize how diaphragm thickness changes daily during the weaning phase compared to the thickness on study day 1, as well as the daily thickness compared to that on the day of the first SBT. This will be used to determine whether patients whose trajectory of diaphragm atrophy continues during the weaning phase have a longer weaning duration compared to those who maintain diaphragm thickness or have increased thickness during the weaning phase. We anticipate high correlation between aPiMax and diaphragm atrophy, such that the proportion of patients with > 10% loss in diaphragm thickness will be similar to the proportion of those with aPiMax ≤ 30 cmH2O, resulting in the same sample size that yield adequate power, as above.

Respiratory load (resistance and compliance), effort (PRP, PTP) and combination measures of capacity, load or effort (TTI, Diaphragm Contractile Activity, Phase Angle) will be measured daily during or just before SBTs, as detailed in the data collection table. Analysis of each of these measures against the primary outcome will mimic what is presented above for aPiMax and Diaphragm thickness, with correlation for continuous variables, as well as categorization into distinct ranges for ANOVA.

Secondary Outcomes, SBT failure: In addition to weaning duration, we will also examine whether the respiratory measures in the data collection table taken just prior to or during each SBT are associated with the patient passing the SBT. For example with aPiMax and ePiMax, we will examine if there is a dose response relationship between PiMax measured just before the SBT and the rate of passage of the subsequent SBT (e.g., similar to Figure 3). In addition, we will compare mean or median values for aPiMax between patients who pass versus fail the SBT using a t-test or MWU test. Finally, we will examine aPiMax as a continuous variable to determine its ability to discriminate passage of the subsequent SBT using the Area Under the Curve (AUC) of the Receiver operating Characteristic Plot (ROC). Similar analysis will be done for all other respiratory measures in Table 2, and we will compare the AUCs (using a Chi-squared test) for each individual respiratory parameter against the others to identify which of these tests have the highest sensitivity, specificity, and overall discrimination of SBT failure. We will subsequently generate multivariate logistic regression models to identify which combination of these measures of capacity, architecture, load, and effort

retain an independent association with SBT failure. Because SBTs will be repeated daily, we will use a hierarchical logistic regression model to control for repeated measures from each patient as well as controlling for the other potential confounding variables detailed in the data collection table. We anticipate that 240 patients will undergo SBT testing, and 90% of these patients will pass the SBT within 28 days of the weaning phase randomization. As such, we would be able to include at least 20 variables in a multivariable hierarchical logistic regression model. Finally, we will determine whether common "phenotypes" for weaning failure can be determined. We anticipate four possible phenotypes by combining information from all available measures of capacity, load, effort, and architecture. Based on our preliminary data, we anticipate that patients with high load will be more likely to fail weaning, but that this effect will be more pronounced if they have diminished respiratory muscle capacity. We hypothesize that the rates of passage of the SBT will increase incrementally from phenotype 1 to 4: (1) Diminished capacity, high load and effort; (2) Normal capacity, high load and effort; (3) Diminished capacity, low load and effort; (4) Normal capacity, low load and effort. These phenotypes are exploratory; thus, no power analysis is provided.

D.6.4.3 SA3 Analysis Plan: To determine if patient effort of breathing during both acute and weaning phases of MV is independently associated with the development of respiratory muscle weakness.

Analysis and Sample Size: The primary outcome of this aim is aPiMax < 30 cmH2O.The analysis will focus on determining whether the degree of patient effort of breathing is independently associated with the development of respiratory muscle weakness. PRP will be the primary measure of effort of breathing, and will be measured twice daily in both acute and weaning phases. Secondary measures of effort of breathing include DCA and PTP. For the acute phase, we will generate a time- weighted average PRP during the acute phase and graph it against aPiMax at the first SBT, anticipating a positive correlation (higher average PRP values associated with higher aPiMax). We will subsequently dichotomize aPiMax at the first SBT and compare mean time weighted average PRP in the acute phase between aPiMax groups (> 30 vs. ≤ 30 cmH2O). For the weaning phase, we will graph the changes in aPiMax throughout the weaning phase (from first failed SBT until successful SBT) against time-weighted average PRP, with the anticipation that low PRP will be associated with either further reductions in aPiMax, or no improvement, while PRP in the physiologic range of 150-400 will be associated with improvement in aPiMax. We will subsequently dichotomize aPiMax (at 30 cm H2O) at the time of successful passage of an SBT and compare time-weighted average PRP in the weaning phase between aPiMax groups. Subsequently, we will build a multivariable logistic regression model on the outcome of aPiMax ≤ 30 cmH2O to determine if time-weighted PRP in the acute phase, weaning phase or both have an independent association with preserving aPiMax, after controlling for confounding variables (data collection table). We anticipate that 35% of patients (at least 80) will have aPiMax ≤ 30 cmH2O, allowing for inclusion of at least 9 variables in the multivariable model. Secondary goals are to characterize other variables that retain an independent association with low aPiMax, which are likely to include age group, use and dose of neuromuscular blockade, driving pressure during the acute phase of ventilation, sepsis, corticosteroids and use of aminoglycoside antibiotics.

D.6.5 Dissemination plan and data archiving

The results of this clinical trial will be critically important to disseminate to critical care clinicians, both pediatric and adult. In the final two years of the study the Steering Committee will develop the strategic plan for the comprehensive presentation and publication of the study findings. The biostatistician will assist Dr. Khemani and Steering Committee members to prepare abstracts and papers for presentation at the annual meetings of American Thoracic Society (ATS), Society of Critical Care Medicine (SCCM), the European Society of Pediatric and Neonatal Intensive Care (ESPNIC). Dr. Khemani will provide the mechanical ventilation subgroup of the Pediatric Acute Lung Injury and Sepsis Investigator (PALISI) network an update on the clinical trial twice yearly to maintain disciplinary interest in the study. In addition to primary publication targeted at high priority journals, we anticipate numerous secondary publications in critical care, physiology, and respiratory journals. Final data sets and statistical analyses will be archived and a public use dataset will be made available as per NIH recommendations.

D7 Data and Instrument Management

A significant portion of the data management infrastructure and protocols have been developed with previous studies, and we will capitalize on this by modifying existing protocols to be relevant to this study. The devices and software have been used extensively, and we will follow existing protocols to maintain calibration, quality control, and accuracy of all study devices. A vast majority of the data (ventilator settings, blood gas values, and many of the variables in the data collection table) will be collected through automated electronic feeds. A trained study data collector will use data extracts from the electronic feeds in conjunction with data in the electronic health care record to populate study specific case report forms. Data collection will occur in real-time, to enable primary source verification. Respiratory measurements will be entered into web-based case report forms at the time of study measurements. In addition, raw data from esophageal manometry and RIP will be recorded during each measurement for a minimum of 5 minutes, and the calculations will be post-processed by trained research personnel to verify the real-time data entry. Ultrasound images will be interpreted in real-time and calculations entered into the web-based case report form. In addition, all ultrasound images will be uploaded to a secure server for source data verification and can be de-identified. We will develop a series of algorithms to confirm the validity of entered data, and will perform detailed queries of entered data monthly.

To ensure data safety and reliability, server back-up procedures will be executed daily to back up all electronic study related materials, which include database, Word documents, statistical programs, and files. Access to the data management system is strictly prohibited and requires user authentication. Authorized users include data-entry personnel, research coordinators, the PI, the database programmer, and biostatisticians. Any hard copies of eCRFs with subject ID codes will be stored in locked file cabinets, accessible by authorized staff only. Identifiable subject data, such as contact information and medical record numbers, will be stored separately and securely, and will not be entered into the electronic database.

All application software will be hosted securely on the Children's Hospital Los Angeles Network, which is protected by several firewalls and security is monitored and audited regularly.

D8 Quality Control Procedures

D.8.1 Training

Training materials detailing study protocols have been created and used for the Phase I study, and an order set has been created in our electronic health-care record system. Research respiratory therapists and data collectors will be directly trained by the PI and the Lead Research Respiratory Therapist (J. Hotz). Detailed training of all bedside staff will occur before beginning the study, as well as in real-time with each patient enrollment, using a similar model as the Phase I study.

D.8.2. Development of Case Report Forms

Case report forms will be modified from successfully implemented CRFs we have used for the pilot study, as well as a large observational study on Pediatric Acute Respiratory Distress Syndrome (PARDIE study). Form design features include the selection of valid, reliable measurements, development and testing of reliability measures, pre-testing of forms, formatting of forms to ensure clarity (standard conventions for coding close-ended questions, minimal use of open ended questions), smooth flow (clear skip patterns) to reduce missing data. Members of the Steering Committee will sign off on eCRFs before implementation.

D9 Anticipated Problems and Solutions

D.9.1 What if enrollment is slow? We are confident we can meet enrollment targets at CHLA alone and will monitor this with targeted and actual enrollment graphs. If enrollment is slower than anticipated, we will add UCLA Children's Hospital as a satellite ICU. This is another PICU 15 miles away with at least 100 eligible patients per year. Through previous funding from the Collaborative Pediatric Critical Care Research Network, we share research infrastructure and resources, and have combined efforts (functioning as one site) for over 30 different clinical studies. [77-83]

D.9.2 What if aPiMax is not associated with weaning duration? We believe that a real strength of this application relies on the multitude of direct and indirect measures of respiratory system capacity, load, and effort, which we will associate with highly clinically relevant weaning outcomes. While we anticipate aPiMax will be the best measure of strength, the multitude of other measurements concomitantly made will allow using alternative measures to aPiMax to assess strength (such as ePiMax, diaphragm contractile activity during occlusion, diaphragm thickness, or phase angle). Our analysis will allow us to determine which of these parameters has the strongest association with clinical outcomes.

D.9.3 Non-compliance with the intervention study protocol? We are confident we will maintain high protocol compliance, as we have demonstrated in the pilot study. We have iteratively refined the protocol such that adherence to weaning phase recommendations exceeds 90%. The acute phase recommendations generally exceed 75%, which we view as acceptable. The protocol is intended to provide a framework for ventilator decisions and is not intended to replace clinician's judgment. For this reason it has been implemented as open loop. The degree of protocol adherence will be tracked electronically, as part of the CDS tool itself. If adherence is lower than anticipated, then detailed analysis of the reasons for protocol rejection (tracked with every recommendation) will be reviewed, and a protocol modification will be considered.

D.9.4. Changes in clinical practice in the ICU during this time period? The impact of changes in pediatric critical care management is expected to affect both groups equally so should not bias treatment group comparisons.

D10 Study Timeline and Milestone accrual Policy

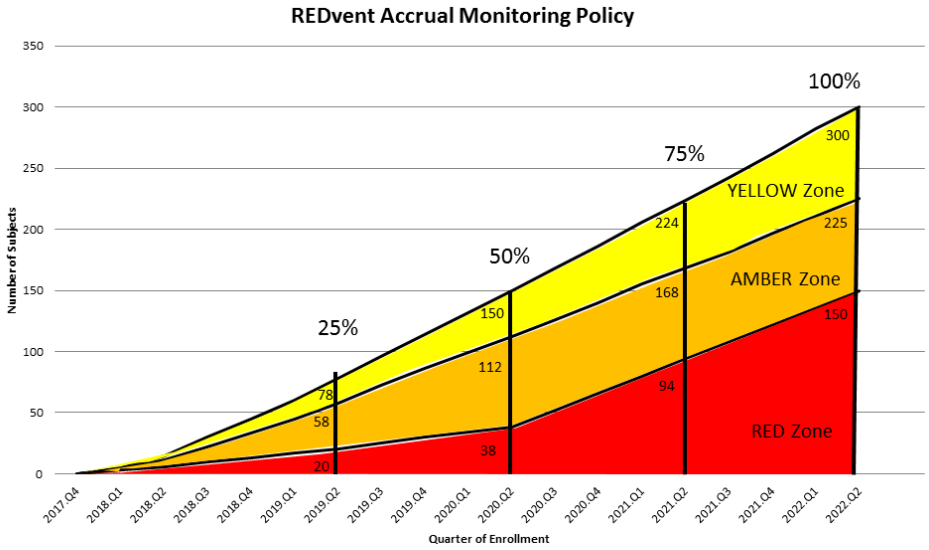

Figure 1: REDvent milestone accrual plan. Planned assessment at the end of Q2.2019 (25% expected patients enrolled), end of Q2.2020 (50%), end of Q2 2021 (75%). Numbers next to intersection of bars represent threshold number of patients required to be enrolled at that time point to move out of given zone.

The Milestone Accrual figure above details targeted enrollment over the course of the study. The Yellow, Amber, and Red zone each have corrective action associated with it, as part of a separate milestone accrual plan with NHLBI. In Q2 2019, enrollment crossed into the yellow zone on the milestone accrual plan. In discussions with NHLBI and the DSMB, a new milestone accrual plan has been created.

The revised milestone accrual plan has been reviewed and approved by the DSMB and NHLBI. Initial estimates of mortality and attrition were 13% and 7%, respectively, allowing for 20% of patients not meeting the primary outcome measure. Based on enrolled patients as of 08/16/2019, no patients have withdrawn from the study, and the overall mortality is 11.8%. As a result, the overall sample size estimate has been revised using 13% of patients who will not meet the primary outcome, rather than 20%. Target study enrollment of 300 total patients has been dropped to 276. The A-priori determination of 240 patients meeting the primary outcome measure has not changed.

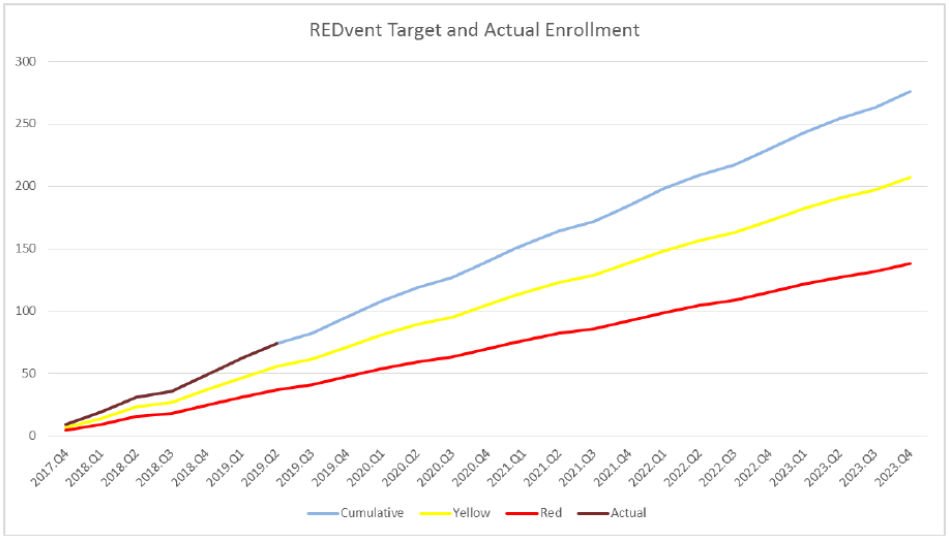

Figure 8: Revised Milestone Accrual Plan

E Human Subjects Considerations

E1 Ethical Considerations

The human subjects for this study are infants and children who are intubated and mechanically ventilated in intensive care unit. It is anticipated that 276 intubated children will be enrolled in the study. The age of children will range from one month (≥ 44 weeks Post Conceptual Age) to 21 years. All participants enrolled in the study will be critically ill, requiring mechanical ventilation through an endotracheal or tracheal tube. The main risk of participation in this study is the placement of an esophageal catheter for measurements of esophageal pressure. While esophageal catheters (or nasogastric feeding tubes) are routinely used in children who are mechanically ventilated (it is the norm for all endotracheally intubated children to have a feeding tube, either nasogastric, orogastric, gastric, or jejunal), because this additional catheter is part of the research protocol, it is likely to be considered greater than minimal risk. However the study does provide potential for significant benefit for the patient, and as such the benefits generally outweigh the risks. Use of this catheter has been approved on multiple occasions with appropriate informed consent. The ultrasound measurements and RIP bands are non-invasive and pose minimal risk to the patient. There are no known risks associated with the use of volumetric capnography.

The hardware (device) is minimal risk and has been used on a variety of studies. All sensors (esophageal catheter, RIP, and spirometry) have appropriate clearance through FDA approval or 510K equivalence for use in children, and have been used in our previous investigations. The two pieces of the software (tool to help interpret raw signals from the sensors), and the CDS ventilator management protocol have both previously been deemed non-significant risk because they are primarily implemented in an open-loop application, incorporate current evidence based guidelines (computer CDS protocol), or have been iteratively tested against FDA approved post-processing programs as part of our previous investigations. Moreover, clinicians are free to reject protocol recommendations, and to that end this data is to be used simply as an adjunct to clinical assessment, rather than a replacement.

E2 Subject Recruitment Plans and Consent Process

The subjects of this study are critically ill infants and children who will not be able to consent for their own participation in this study. One or both parents will be informed about the study and given an opportunity to voluntarily give their consent/permission for their child to participate. Assent of child subjects will not be possible because they are critically ill, intubated on a ventilator, and sedated. Thus, assent will be waived. Families or guardians of any intubated and mechanically ventilated child who meet inclusion and do not meet exclusion criteria will be approached for consent. Consent will be attained by the study investigator, co-investigator, or research nurse. Consent will be documented on a consent form, and stored in a study binder, identified by patient number. This binder will be stored in a locked cabinet in the office of the site principal investigator.

E3 Risks and Benefits

E.3.1 Risks:

1. Placement of the esophageal catheter. While this procedure is very well tolerated, there is a very small risk for bleeding, incorrect placement into the lungs or other body cavities, or damage to the esophagus, stomach, or nasal or oral mucosa. Patients at high risk of bleeding (thrombocytopenia, coagulopathy, mucositis), will not be included in the study.
2. Small amount of discomfort when placing the esophageal catheter, although nearly all patients will be receiving analgesia and sedation as part of mechanical ventilation. Intermittent doses of already prescribed sedative or analgesia medications may be administered to minimize pain during placement.
3. A particular computer generated recommendation may not be correct for the patient at that time, and the clinicians may choose not to follow them.
4. There is potential of accidental release of confidential information.
5. There is a possibility of transient fall in oxygen levels during airway occlusion maneuvers, although patients will be pre-oxygenated as per ICU standard practices prior to measurement, and patients must pass the oxygenation test prior to performing these measurements.

E.3.2 Potential Benefits to Subjects

There is the prospect of direct benefit to subjects in both arms. For the intervention arm, using the intervention tool has the potential to significantly shorten length of assisted breathing, lower re-intubation rates, increase Ventilator Free Days (VFDs), shorten ICU and hospital length of stay, and reduce exposure to sedatives and analgesics. Patients in the control arm also have potential to benefit as enrollment in the study will prompt more consistent use of evidence based weaning guidelines including a daily Spontaneous Breathing Trial. This may also result in more days free of ventilators compared to those not enrolled in the study.

E.3.4 Importance of the Knowledge to Be Gained

Completion of this study will elucidate important information on the pathogenesis and timing of respiratory muscle weakness during MV in children, and whether this weakness can be mitigated by promoting more normal patient effort during MV. These data can lead to immediate change in practice by implementing mechanical ventilation strategies that promote more patient effort of breathing. They will also form the basis to determine whether a larger, Phase III multi-center study of REDvent is indicated, which would focus on key clinical outcomes such as 28-day Ventilator Free Days. Given that the risks to the study participants are small, the information gathered will shape the design of future trials and will improve our understanding of diaphragm weakness in mechanically ventilated children in the ICU.

E.3.5 Procedures to minimize risk

All patients will be extensively monitored in the intensive care unit throughout the duration of the study. This will include close monitoring of cardio-respiratory parameters including heart rate, temperature, blood pressure, oxygen saturation, respiratory rate, and work of breathing. Intensive care unit physicians, nurses, and respiratory therapists will be present during the entire study, and will intervene as necessary should any treatment be indicated. In addition, to protect confidentiality of data, study forms will only be labeled with a unique number identifier, which can only be

linked to identifiable information only through a key with access restricted to the PI or research coordinator.

E4 Early Withdrawal of Subjects

The subject may be withdrawn from the study by the (1) study investigator or (2) the parent or legal guardian at any time after consent. The primary attending physician can also request that the principal investigator consider withdrawal of the patient from the study if they believe the study is no longer in the best interest of the patient.

E.4.1 When and How to Withdraw Subjects

Subjects can be withdrawn by the parents at any time, simply by requesting that the principal investigator withdraw the patient. The study investigator may withdraw the patient from the study if he or she believes that this is necessary to protect the health of the child, if the condition of the child changes such that continuation in the study poses additional risks, or if the child experiences an adverse event which changes the risk benefit profile of continuing in the study.

E.4.2 Data Collection and Follow-up for Withdrawn Subjects

If consent is withdrawn for participation in the research by the parent/guardian, then data collection will cease. Parents will be asked if we can keep existing data and follow clinical outcomes for intention to treat analysis. However, if they wish, existing data will be destroyed. If the study investigator withdraws the patient, then existing data will be preserved, and clinical outcome data detailed in section C.3.1. will continue to be collected to enable intention to treat analysis.

F Data Safety Monitoring Plan and Board

Please see separate Data Safety and Monitoring Plan and Data Safety and Monitoring Board Charter. An institutional DSMB has been created for this study.

The Data Safety Monitoring Plan details expected adverse events, with expected rates of occurrence.

G References

1. Daniel Martin A, Smith BK, Gabrielli A. Mechanical ventilation, diaphragm weakness and weaning: a rehabilitation perspective. Respiratory Physiology & Neurobiology 2013; 189:377-83.
2. Di Mussi R, Spadaro S, Mirabella L, et al. Impact of prolonged assisted ventilation on diaphragmatic efficiency: NAVA versus PSV. Critical Care (London, England) 2016; 20:1.
3. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 2014; 69:423-7.
4. Emeriaud G, Larouche A, Ducharme-Crevier L, et al. Evolution of inspiratory diaphragm activity in children over the course of the PICU stay. Intensive Care Medicine 2014; 40:1718-26.
5. Goligher EC, Fan E, Herridge MS, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. American Journal of Respiratory & Critical Care Medicine 2015; 192:1080-8.
6. Heunks LM, Doorduin J, van der Hoeven JG. Monitoring and preventing diaphragm injury. Current Opinion in Critical Care 2015; 21:34-41.
7. Matamis D, Soilemezi E, Tsagourias M, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Medicine 2013; 39:801-10.
8. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. Critical Care (London, England) 2013; 17:R120.
9. Hooijman PE, Beishuizen A, Witt CC, et al. Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients. American Journal of Respiratory & Critical Care Medicine 2015; 191:1126-38.
10. Sieck GC. Muscle weakness in critical illness. American Journal of Respiratory & Critical Care Medicine 2015; 191:1094-6.
11. Wolf GK, Walsh BK, Green ML, Arnold JH. Electrical activity of the diaphragm during extubation readiness testing in critically ill children. Pediatric Critical Care Medicine 2011; 12:e220-4.
12. Keens TG, Bryan AC, Levison H, Ianuzzo CD. Developmental pattern of muscle fiber types in human ventilatory muscles. Journal of Applied Physiology: Respiratory, Environmental & Exercise Physiology 1978; 44:909-13.
13. Khemani R, Flink R, Morzov R, Ross P, Newth C. Its not like breathing through a straw: Effort of breathing on CPAP most accurately estimates post-extubation effort in children. American Journal of Respiratory and Critical Care Medicine 2013; suppl 2013.187.1:A3682.
14. Khemani RG, Hotz J, Morzov R, et al. Pediatric extubation readiness tests should not use pressure support. Intensive Care Medicine 2016; 42:1214-22.
15. Randolph AG, Wypij D, Venkataraman ST, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA 2002; 288:2561-8.
16. Newth CJ, Venkataraman S, Willson DF, et al. Weaning and extubation readiness in pediatric patients. Pediatric Critical Care Medicine 2009; 10:1-11.

17. Odetola FO, Clark SJ, Freed GL, Bratton SL, Davis MM. A national survey of pediatric critical care resources in the United States. Pediatrics 2005; 115:e382-6.
18. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. Critical Care Medicine 2010; 38:1947-53.
19. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Critical Care Medicine 2005; 33:1266-71.
20. Seymour CW, Martinez A, Christie JD, Fuchs BD. The outcome of extubation failure in a community hospital intensive care unit: a cohort study. Critical Care (London, England) 2004; 8:R322-7.
21. Anand KJ, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics 2010; 125:e1208-25.
22. Kurachek SC, Newth CJ, Quasney MW, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Critical Care Medicine 2003; 31:2657-64.
23. Rossi C, Simini B, Brazzi L, et al. Variable costs of ICU patients: a multicenter prospective study. Intensive Care Medicine 2006; 32:545-52.
24. Sachdeva RC, Jefferson LS, Coss-Bu J, et al. Effects of availability of patient-related charges on practice patterns and cost containment in the pediatric intensive care unit. Critical Care Medicine 1996; 24:501-6.
25. Randolph AG, Gonzales CA, Cortellini L, Yeh TS. Growth of pediatric intensive care units in the United States from 1995 to 2001. Journal of Pediatrics 2004; 144:792-8.
26. Doorduin J, van Hees HW, van der Hoeven JG, Heunks LM. Monitoring of the respiratory muscles in the critically ill. American Journal of Respiratory & Critical Care Medicine 2013; 187:20-7.
27. Umbrello M, Formenti P, Longhi D, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Critical Care (London, England) 2015; 19:161.
28. Medrinal C, Prieur G, Frenoy E, et al. Respiratory weakness after mechanical ventilation is associated with one-year mortality - a prospective study. Critical Care (London, England) 2016; 20:231.
29. ATS, ERS. ATS/ERS Statement on Respiratory Muscle Testing. American Journal of Respiratory and Critical Care Medicine 2002; 166:518-624.
30. Keens TG, Ianuzzo CD. Development of fatigue-resistant muscle fibers in human ventilatory muscles. American Review of Respiratory Disease 1979; 119:139-41.
31. Santschi M, Jouvet P, Leclerc F, et al. Acute lung injury in children:therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med 2010; 11:681-689.
32. Newth CJ, K S, RG K, JM D. Variability In Usual Care Mechanical Ventilation For Pediatric Acute Lung Injury. American Journal of Respiratory and Critical Care Medicine 2014; 189:A2613.
33. Khemani RG, Sward K, Morris A, Dean JM, Newth CJL, (CPCCRN) NCPCCRN. Variability in usual care mechanical ventilation for pediatric acute lung injury: the potential benefit of a lung protective computer protocol. Intensive Care Medicine 2011; 37:1840-1848.
34. Jaber S, Jung B, Matecki S, Petrof BJ. Clinical review: ventilator-induced diaphragmatic dysfunction--human studies confirm animal model findings! Critical Care (London, England) 2011; 15:206.

35. Falk DJ, Deruisseau KC, Van Gammeren DL, Deering MA, Kavazis AN, Powers SK. Mechanical ventilation promotes redox status alterations in the diaphragm. Journal of Applied Physiology 2006; 101:1017-24.
36. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. New England Journal of Medicine 2008; 358:1327-35.
37. Powers SK, DeCramer M, Gayan-Ramirez G, Levine S. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Critical Care (London, England) 2008; 12:191.
38. Futier E, Constantin JM, Combaret L, et al. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Critical Care (London, England) 2008; 12:R116.
39. Mhanna MJ, Anderson IM, Iyer NP, Baumann A. The use of extubation readiness parameters: a survey of pediatric critical care physicians. Respiratory Care 2014; 59:334-9.
40. Burns KE, Lellouche F, Lessard MR, Friedrich JO. Automated weaning and spontaneous breathing trial systems versus non-automated weaning strategies for discontinuation time in invasively ventilated postoperative adults. Cochrane Database of Systematic Reviews 2014; 2:CD008639.
41. Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J. Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial. Intensive Care Medicine 2013; 39:919-25.
42. Rose L, Schultz MJ, Cardwell CR, Jouvet P, McAuley DF, Blackwood B. Automated versus non-automated weaning for reducing the duration of mechanical ventilation for critically ill adults and children. Cochrane Database of Systematic Reviews 2013; 6:CD009235.
43. Khemani R, Schneider J, Morzov R, Markovitz B, Newth CJ. Pediatric Upper Airway Obstruction: Interobserver variability is the road to perdition. Journal of Critical Care 2013; 28:490-7.
44. Pandharipande PP, Shintani AK, Hagerman HE, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. Critical Care Medicine 2009; 37:1317-21.
45. ARDSnet. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. New England Journal of Medicine 2000; 342:1301-8.
46. Sward K, CJL N, RG K, JM D. Data-driven knowledge base evaluation: Translating an adult CDS tool for use in pediatric care (Abstract). Journal of the American Medical Informatics Association (JAMIA) 2015; 2015 Annual conference
47. Sward K, Newth CJ, Page K, Dean JM. Pediatric Intensivist Attitudes About a Ventilator Management Computer Protocol. C57. NEWS FROM THE NICU AND PICU: American Thoracic Society, 2015:A4772-A4772.
48. Khemani R, Flink R, Hotz J, Ross P, Ghuman A, Newth CJ. Respiratory inductance plethysmography calibration for pediatric upper airway obstruction: an animal model. Pediatric Research 2015; 77:75-83.
49. Khemani RG, Hotz J, Morzov R, et al. Risk Factors for Pediatric Post-Extubation Upper Airway Obstruction Using a Physiology Based Tool. Am J Respir Crit Care Med 2015.

50. Khemani RG, Celikkaya EB, Shelton CR, et al. Algorithms to estimate PaCO2 and pH using noninvasive parameters for children with hypoxemic respiratory failure. Respiratory Care 2014; 59:1248-57.
51. Baldwin CE, Paratz JD, Bersten AD. Diaphragm and peripheral muscle thickness on ultrasound: intra-rater reliability and variability of a methodology using non-standard recumbent positions. Respirology 2011; 16:1136-43.
52. Vivier E, Mekontso Dessap A, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Medicine 2012; 38:796-803.
53. Benditt JO. Esophageal and gastric pressure measurements. Respiratory Care 2005; 50:68-75.
54. Gozal D, Shoseyov D, Keens TG. Inspiratory pressures with CO2 stimulation and weaning from mechanical ventilation in children. American Review of Respiratory Disease 1993; 147:256-61.
55. Harikumar G, Egberongbe Y, Nadel S, et al. Tension-time index as a predictor of extubation outcome in ventilated children. American Journal of Respiratory & Critical Care Medicine 2009; 180:982-8.
56. Wen AS, Woo MS, Keens TG. How many maneuvers are required to measure maximal inspiratory pressure accurately. Chest 1997; 111:802-7.
57. Harikumar G, Moxham J, Greenough A, Rafferty GF. Measurement of maximal inspiratory pressure in ventilated children. Pediatric Pulmonology 2008; 43:1085-91.
58. Watson AC, Hughes PD, Louise Harris M, et al. Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Critical Care Medicine 2001; 29:1325-31.
59. Dimitriou G, Greenough A, Moxham J, Rafferty GF. Influence of maturation on infant diaphragm function assessed by magnetic stimulation of phrenic nerves. Pediatric Pulmonology 2003; 35:17-22.
60. Luo YM, Hart N, Mustfa N, et al. Reproducibility of twitch and sniff transdiaphragmatic pressures. Respiratory Physiology & Neurobiology 2002; 132:301-6.
61. Man WD, Luo YM, Mustfa N, et al. Postprandial effects on twitch transdiaphragmatic pressure. European Respiratory Journal 2002; 20:577-80.
62. Polkey MI, Kyroussis D, Hamnegard CH, et al. Paired phrenic nerve stimuli for the detection of diaphragm fatigue in humans. European Respiratory Journal 1997; 10:1859-64.
63. Rafferty GF, Greenough A, Dimitriou G, et al. Assessment of neonatal diaphragm function using magnetic stimulation of the phrenic nerves. American Journal of Respiratory & Critical Care Medicine 2000; 162:2337-40.
64. Rafferty GF, Mustfa N, Man WD, et al. Twitch airway pressure elicited by magnetic phrenic nerve stimulation in anesthetized healthy children. Pediatric Pulmonology 2005; 40:141-7.
65. Sekayan T, Hotz J, Flink R, Iyer NP, Newth CJ, Khemani R. Risk Factors for pediatric extubation failure: the importance of respiratory muscle strength. Critical Care Medicine 2017; Abstact 2017 Conference:14.
66. Lafortune M, Kamerkar A, Hotz J, Morzov R, Newth CJ, Khemani R. Risk Factors for Pediatric Noninvasive Ventilation Failure using Physiologic and Clinial Measures (abstract). C27 News from the NICU and PICU: American Thoracic Society, 2016:7300.

67. Steier J, Kaul S, Seymour J, et al. The value of multiple tests of respiratory muscle strength. Thorax 2007; 62:975-80.
68. Scott CB, Nickerson BG, Sargent CW, Dennies PC, Platzker AC, Keens TG. Diaphragm strength in near-miss sudden infant death syndrome. Pediatrics 1982; 69:782-4.
69. Zambon M, Cabrini L, Beccaria P, Zangrillo A, Colombo S. Ultrasound in critically ill patients: focus on diaphragm. Intensive Care Medicine 2013; 39:986.
70. Rehan VK, Laiprasert J, Nakashima JM, Wallach M, McCool FD. Effects of continuous positive airway pressure on diaphragm dimensions in preterm infants. Journal of Perinatology 2001; 21:521-4.
71. Rehan VK, Laiprasert J, Wallach M, Rubin LP, McCool FD. Diaphragm dimensions of the healthy preterm infant. Pediatrics 2001; 108:E91.
72. Rehan VK, McCool FD. Diaphragm dimensions of the healthy term infant. Acta Paediatrica 2003; 92:1062-7.
73. Rehan VK, Nakashima JM, Gutman A, Rubin LP, McCool FD. Effects of the supine and prone position on diaphragm thickness in healthy term infants. Archives of Disease in Childhood 2000; 83:234-8.
74. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Group ftPALICC. Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference. Pediatric Critical Care Medicine 2015; 16:S23-S40.
75. Curley MA, Wypij D, Watson RS, et al. Protocolized Sedation vs. Usual Care in Pediatric Patients Mechanically Ventialted for Acute Respiratory Failure. JAMA 2015; 313:379-389.
76. Valentine SL, Nadkarni VM, Curley MA, Pediatric Acute Lung Injury Consensus Conference G. Nonpulmonary treatments for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatric Critical Care Medicine 2015; 16:S73-85.
77. Carcillo JA, Dean JM, Holubkov R, et al. The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial. Pediatric Critical Care Medicine 2012; 13:165-73.
78. Newth CJ, Meert KL, Clark AE, et al. Fatal and near-fatal asthma in children: the critical care perspective. Journal of Pediatrics 2012; 161:214-21.e3.
79. Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. Pediatric Critical Care Medicine 2013; 14:356-65.
80. Moler FW, Silverstein FS, Meert KL, et al. Rationale, timeline, study design, and protocol overview of the therapeutic hypothermia after pediatric cardiac arrest trials. Pediatric Critical Care Medicine 2013; 14:e304-15.
81. Pollack MM, Holubkov R, Funai T, et al. Relationship between the functional status scale and the pediatric overall performance category and pediatric cerebral performance category scales. JAMA Pediatrics 2014; 168:671-6.
82. Dalton HJ, Garcia-Filion P, Holubkov R, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. Pediatric Critical Care Medicine 2015; 16:167-74.
83. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. New England Journal of Medicine 2015; 372:1898-908.

H Secondary Analyses Related to Patient Ventilator Asynchrony

Summary and Rationale

Mechanically ventilated children often have patient-ventilator asynchrony (PVA) although this is incompletely characterized in the literature and infrequently recognized at the bedside. When a ventilated patient has spontaneous effort, the ventilator attempts to synchronize with the patient, but PVA represents a mismatch between what the patient wants and what the ventilator delivers. PVA is common in ventilated adults and is associated with longer duration of ventilation, increased risk of infection, lung injury, diaphragm dysfunction, and adverse neurocognitive effects. While there are many types of PVA, they are not equally harmful or prevalent. Therapeutic strategies should focus on the most harmful forms of PVA. Although we still don't know which PVA subtypes are truly most harmful, Double Cycled (DC) breaths (where a second breath is delivered before the first breath is complete) have the strongest biological plausibility for harm, because DC induces lung stress, strain, ventilator induced lung injury and eccentric contraction of the diaphragm.

PVA is understudied in children, even though it may be more common and goes largely unrecognized even by highly trained clinicians. Moreover, existing pediatric studies have failed to identify a clear relationship between PVA and worse clinical outcomes, although these studies have not focused on the highest risk patients (such as those with Acute Respiratory Distress Syndrome (ARDS)), have used different definitions for PVA and its subtypes, and have been inadequately powered to evaluate the relationship between PVA subtypes and outcome. As part of this additional analyses under the REDvent study, we seek to fill crucial knowledge and implementation gaps including: (1) harmonizing how PVA is measured and defined, (2) identifying the most harmful PVA subtypes and the patients at risk, and (3) using innovative and accurate bedside tools to improve the recognition of PVA. We will leverage the expertise and preliminary data from three premier pediatric research groups who have the expertise to use precise methods to capture the patient's neural respiratory effort, which is crucial to correctly identify PVA subtypes. We will perform detailed secondary analysis of existing waveforms and clinical data from over 350 children, including all children enrolled in the REDvent study. We will use causal inference and mediation approaches to evaluate the relationship between PVA subtypes and clinical and mechanistic outcomes by leveraging data from the randomized controlled REDvent trial where PVA rates and subtypes likely differ between intervention and control groups.

Three existing datasets will be used as part of model and definition development, and data from the REDvent trial has more extensive clinical outcome and mechanistic data and will be used for additional analyses. Each dataset will contain one of three direct measures of patient neural respiratory effort (Pes, Children's Hospital Los Angeles; Edi, St. Justine Children's Hospital; sEMG, Beatrix Children's Hospital). The data which will be used for analysis has already been collected as part of the parent studies, or is planned for collection for the remaining patients in the REDvent trial.

Specific Aims

Asynchrony Specific Aim 1) To identify the frequency and risk factors for PVA and its subtypes in ventilated children, with a specific focus on DC breaths. **Hypothesis**: PVA subtypes related to inadequate ventilator support (flow undershoot and premature cycling) and reverse triggering will be the most common causes of DC breaths, with risk factors related to respiratory drive and ventilator settings. **Study Design:** Secondary analysis of waveforms and clinical data from anonymous datasets and data from the REDvent clinical trial.

Asynchrony Specific Aim 2: To determine if a ventilator strategy in children with ARDS that promotes spontaneous breathing and physiologic levels of patient effort results in different rates and subtypes of PVA, and if PVA mediates the relationship between this intervention and clinical or mechanistic outcomes. **Hypothesis:** (a) REDvent intervention patients will have a different distribution of PVA subtypes than usual care patients which will partially mediate the relationship between REDvent intervention and outcome. (b) DC breaths will be associated with worse clinical and mechanistic outcomes. **Study Design:** Secondary analysis of waveforms and clinical data from the REDvent clinical trial.

Asynchrony Specific Aim 3) To develop and test a clinical decision support system using machine learning techniques to automatically identify common forms of PVA in children. **Hypothesis**: (a) Machine learning models using waveforms available on all mechanical ventilators will accurately identify PVA subtypes compared to gold standard annotations which include measures of neural drive. (b) Algorithms can be optimized for high sensitivity and low false alert rates to identify children with frequent PVA. **Study Design:** Secondary analysis of waveforms and clinical data from anonymous datasets and data from the REDvent clinical trial.

Data Management and aggregation

Data from CHLA will be coded for analysis. Data from other sites may be coded or anonymous, but if it is coded the key will stay at the individual site. The data to be shared does not include any protected health information. It will include the respiratory waveforms gathered on each of the study monitors, as well as demographic and clinical information to inform the analyses proposed below. Data will be transferred from participating institutions via One Drive through Children's Hospital Los Angeles and will be loaded onto a CHLA research server for analysis. Researchers at all 3 institutions will be able to view anonymous data on the CHLA research server and annotate waveforms to facilitate completion of this project, but will not be able to download or export the data directly.

Preliminary Data, Analysis Plan, and Sample Size Justification by Specific Aim

Asynchrony Specific Aim 1) To identify the frequency and risk factors for PVA subtypes in ventilated children, with a specific focus on DC breaths. **Hypothesis**: PVA subtypes related to inadequate ventilator support (flow undershoot and premature cycling) and reverse triggering will be the most common causes of DC breaths, with risk factors related to respiratory drive and ventilator settings.

Preliminary Data

PVA subtype definitions in children which use a measure of neural effort can be developed with high inter-rater reliability. We performed a detailed literature review to identify definitions for PVA applicable to children. There were no consistent definitions that included a measure of neural respiratory effort for all PVA subtypes. Definitions were modified to include esophageal manometry and were tested for inter-rater reliability amongst 2 independent readers using a set of 50 patient recordings from the REDvent dataset (Figure 2). While there are slight differences based on asynchrony subtype, kappa values were > 0.83 for all asynchrony subtypes which occurred at rates > 1% of breaths. **As part of this proposal, our three research groups will collaborate to harmonize these definitions and incorporate Edi and sEMG.**

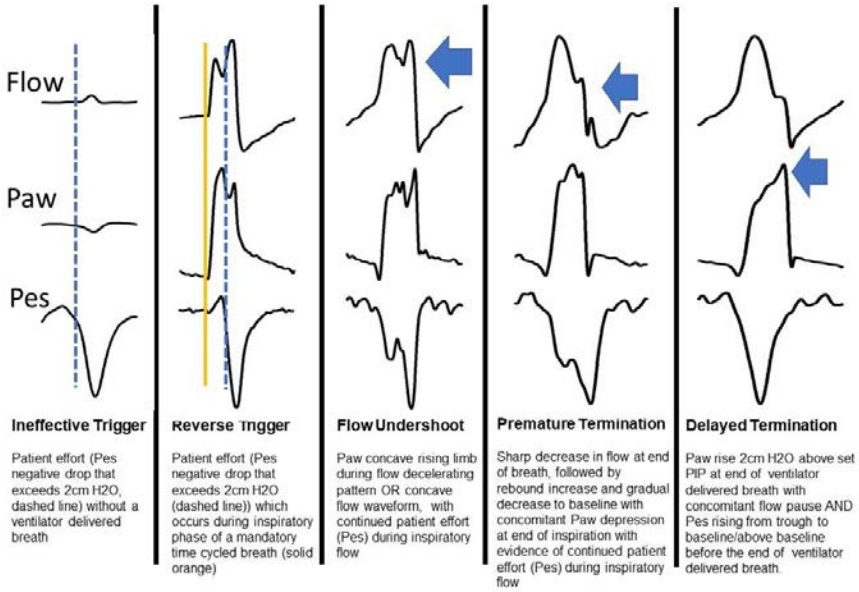

Figure 2. PVA subtype examples with operational definitions based on Pes as the measure of neural respiratory drive.

Nearly 30% of breaths are asynchronous, with a number of distinct PVA subtypes identified in children. Each of our groups have conducted observational studies on subsets of mechanically ventilated children, using our own definitions for PVA and its subtypes. In an ARDS population with Pes (preliminary analysis of 65 patients and 54,284 breaths from the REDvent cohort at CHLA), 28.7% of breaths had some form of asynchrony, with 63/65 (95.4%) patients demonstrating at least one episode of PVA. The predominant asynchrony subtypes were flow undershoot (13.8%), delayed termination (7.4%), premature termination (5.1%), and reverse trigger (1.9%). Double cycled breaths occurred 3% of the time (see below). In a mixed cohort of 74 children at Beatrix Children's Hospital that used sEMG, 33% of breaths had some form of asynchrony. The predominant asynchrony subtypes were ineffective trigger (68%) followed by delayed termination (19%). DC breaths occurred 4% of the time. In a mixed cohort of 62 children at St. Justine Children's hospital that used Edi, 27% of breaths had some form of asynchrony. The predominant asynchrony subtypes were trigger delay (9%), ineffective efforts (10%) and premature termination (4%). DC breaths occurred 1% of the time. There are high rates of PVA amongst ventilated children, with differences in PVA subtypes based on institution, technique of measurement of neural effort, and disease state. These findings underscore the need to have common operational definitions for PVA subtypes which can incorporate different methods to measure neural effort, with a diverse, heterogeneous sample of ventilated children from multiple institutions.

Double Cycle (DC) occurs in approximately 3% of breaths, with underlying asynchrony subtypes nearly equally split between Reverse Trigger and Premature

Termination/Flow Undershoot. A DC breath occurs when the ventilator delivers a second breath before the patient has fully exhaled. This is particularly injurious because it leads to very high tidal volumes and risk of volutrauma (strain), in addition to high transpulmonary pressure and barotrauma (stress). [21,22,24,48-51,60] In the REDvent cohort, 3.0% of breaths were DC, with at least one DC breath occurring in 46/65 (70.8%) patients. The most common PVA associated with DC breaths was reverse trigger (52.5%). High patient effort with flow undershoot/premature termination was also very common (45.2%, combined for analysis), while auto trigger (1.2%) was rare. Rates of DC breaths were similar in cohorts from St. Justine (1%) and Groningen (4%), but the underlying PVA subtype was not characterized.

Understanding the underlying PVA will inform the therapeutic strategy: The two predominant forms of PVA leading to DC breaths are Reverse Trigger (RT) and flow undershoot/ premature termination. This has not been explicitly articulated in the literature[35,38,61] and has crucial therapeutic implications. This can represent a paradigm shift in PVA therapeutics, because the most common clinical approach to eliminate DC breaths involves adjusting the trigger sensitivity on the ventilator. This will likely only be effective for auto-triggering, the rarest cause of DC breaths in our preliminary data. We recently identified that patients were more likely to have RT when the set ventilator rate was close to the patient's neural respiratory rate.[53] This fits with the physiologic concepts of respiratory entrainment. We have reported recent cases of patients with consistent 1:1 patterns of RT with intermittent DC (Figure 3a). In this example, the patient's neural respiratory rate and set ventilator rate were identical at 21 breaths per minute. By reducing the set ventilator rate by 6, we were able to abolish the RT (Figure 3b).[62] We have seen similar manipulations work in other children with RT, although this does not appear to work in all patients. This case emphasizes the importance of identifying the pathogenesis of DC breaths, as targeting the intervention to RT ultimately abolished the underlying PVA and its subsequent effects. In contrast, if the DC breaths are from flow undershoot/premature termination, then strategies involve increasing ventilator support, prolonging inspiratory time, or reducing respiratory drive with sedation or neuromuscular blockade.

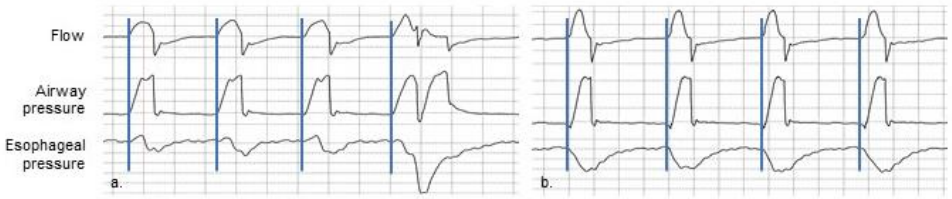

Figure 3. Manipulations to the ventilator targeting reverse trigger PVA (a). where patient effort (esophageal pressure) begins after ventilator insufflation (airway pressure). We were able to abolish the PVA and its subsequent DC breaths (b.) by lowering the ventilator rate.

Methods and analysis plan to complete aim 1

Standardization of definitions across neural effort type and annotation of datasets: The definitions for PVA subtype will be extended to include sEMG and Edi. The software system we have developed for breath annotation is cloud-based, enabling collaboration across multiple sites. All waveform files will be coded with a unique study number and stripped of identifying information. An initial set of 10 illustrative files from each dataset will be used to harmonize the definitions. Subsequently, inter-rater reliability of the definitions will be tested using a dataset of 60 patient files (20 with each method of neural effort) which will be independently annotated by a minimum of two investigators, and kappa values per PVA subtype and neural effort measurement will be

generated. If a kappa value is > 0.8 (as per preliminary data above), then the PVA subtype will be considered to have high reliability. If kappa is < 0.8, breaths with disagreement will be reviewed and definitions modified or clarified as necessary. An additional 20 files (targeting that neural effort measure) will again be read by a minimum of two investigators, and the process repeated until all relevant kappa values are > 0.8 for PVA subtypes which occur at a frequency > 1%. After inter-rater reliability is established, one trained reader will annotate future files. If there is uncertainty about a particular breath, it will be reviewed as part of a weekly meeting to arrive at a final annotation. If a particular breath type is unable to achieve a kappa >0.8, then all potential breaths of that breath type will also be reviewed at a team meeting.

Analysis of PVA subtypes leading to DC breaths, and identification of risk factors: Each dataset contains detailed diagnostic data, demographics, ventilator settings, and medication data. Using data from existing datasets, all patients and all days of ventilation will be analyzed to describe the frequency of PVA subtypes leading to DC breaths. For each DC breath (anticipated 3% of all breaths), one of three underlying PVA subtypes will be annotated (Reverse Trigger, Flow Undershoot/Premature Termination, Auto-trigger, Figure 4). Flow undershoot and premature termination represent the same physiologic concepts of inadequate ventilator support, so they will be combined for analysis of DC breaths. We anticipate that RT and Flow Undershoot/Premature Termination will continue to comprise > 95% of the causes of DC and will be the primary focus of analysis. We will evaluate ventilator and patient specific risk factors for PVA subtypes which lead to DC.

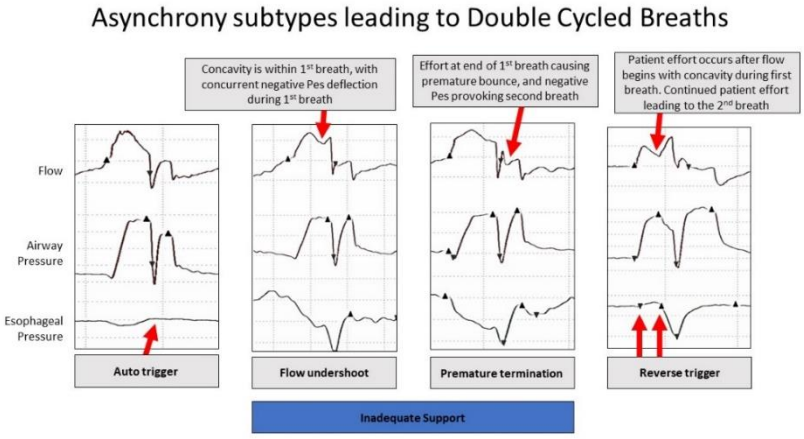

Figure 4. Asynchrony subtypes leading to DC breaths. Flow undershoot/ premature termination represent inadequate ventilator support for the patient's respiratory drive, while Reverse trigger leading to DC occurs when patient effort begins after lung insufflation. Auto trigger is relatively rare and occurs when a second breath is delivered with no patient effort.

Sample Size and Power: From existing datasets, we are anticipating having over 1,000,000 breaths for analysis, from 371 patients, with more than 1,000 patient days. Based on our preliminary data, 3% of breaths are DC, and 70% of patients have at least one episode of DC. This should give us a minimum of 30,000 DC breaths from 260 patients. This will permit inclusion of dozens of variables in the risk factor analyses, although we anticipate between 3-5 in each model. Analysis will be conducted on the breath and on the patient level.

The goal of the breath level model is to understand why DC occurs when a specific PVA subtype is present. We will create two prediction models, one to identify risk factors for DC related to RT and one to identify DC related to flow undershoot/premature termination. Variables considered in the breath-by-breath model include parameters with biological plausibility to be in the causal pathway for the PVA subtype or DC including ventilator mode (including NAVA), respiratory rate, ventilator rate (RRvent), spontaneous or neural respiratory rate (RRneural) and neural

initiation and termination, peak inspiratory pressure (PIP), Tidal Volume, PEEP, inspiratory time, and an estimate for patient effort (ΔPes, peak Edi, or sEMG). We will first perform univariate analysis on the predictor variables of interest, stratified by DC versus non-DC in each of the subtypes. Mixed logistic regression models will then be created to first control for patient level effects with repeated measurements per patient, retaining variables with an independent association with DC breaths.

The goal of the patient level model is to identify patients who are at high risk for DC. Because RT and flow undershoot/ premature termination are the PVA subtypes which lead to DC over 95% of the time, variables for consideration will focus on risk factors for each of these PVA subtypes, in addition to risk factors for DC specifically. Univariable analysis will examine the Spearman's correlation between the frequency of DC breaths per patient in each PVA subtype category and static patient related variables of interest such as **age, gender**, height, body weight, risk factors and severity of lung injury, blood gas data, sedation and analgesia (cumulative dose of drugs, pain and sedation scale). In addition, median values for respiratory parameters from breath-by-breath analysis over the entire 30-minute recording will also be used. Subsequently, patients will be categorized into groups based on the frequency of DC breaths from each subtype. Those with DC occurring in more than 5% of breaths will be labeled DC patients for analysis. Our preliminary data supports this occurs in approximately 20% of patients. Subsequently, mixed logistic regression models will be created to identify the patient specific factors associated with DC, stratified by each of the PVA subtypes.

Specific Aim 2: To determine if a ventilator strategy in children with ARDS that promotes spontaneous breathing and physiologic levels of patient effort results in different rates and subtypes of PVA, and if PVA mediates the relationship between this intervention and clinical or mechanistic outcomes. **Hypothesis:** (a) REDvent intervention patients will have a different distribution of PVA subtypes than usual care patients which will partially mediate the relationship between REDvent intervention and outcome. (b) PVA subtypes which lead to DC breaths will be associated with clinical and mechanistic outcomes. **Study Design:** Secondary analysis of waveforms and clinical data from the REDvent clinical trial.

Preliminary Data

The relationship between PVA and clinical outcomes is complex because PVA is more likely to occur in patients with more spontaneous breathing. A conventional ventilator management strategy for patients with ARDS promotes controlled ventilation with high degrees of sedation or neuromuscular blockade with low rates of spontaneous breathing early during ventilation, followed by spontaneous breathing

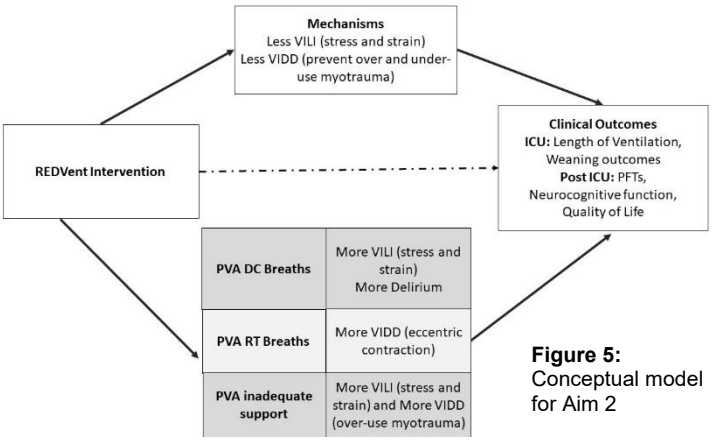

Figure 5: Conceptual model for Aim 2

when evaluating for readiness for ventilator liberation.[21] These patients may have lower rates of PVA because they are not permitted to breathe spontaneously until the ARDS is largely resolved, but they may have longer length of ventilation because of the lack of spontaneous breathing. A balanced lung and diaphragm protective strategy, like what is being tested in the REDvent trial, promotes spontaneous breathing earlier during ventilation. We hypothesize that this will result in shorter time on ventilation by reducing the rates of over and under assistance myotrauma (VIDD) as well as more lung protection (VILI).[22,24,45] However, earlier spontaneous breathing may result in a higher overall rate of PVA in REDvent versus control patients, but a different distribution of PVA subtypes. Because REDvent targets physiologic levels of respiratory effort, it is likely that the under-assistance related causes of PVA which lead to double cycling (flow undershoot/premature termination) will occur less frequently. However, the lung protective component of REDvent frequently uses a higher ventilator rate than usual care, which may make Reverse Trigger more common, with double cycling. **It is therefore highly plausible that PVA frequency and subtype may mediate the relationship between REDvent intervention and outcome (Figure 5).** It is therefore important to understand when the benefits of spontaneous breathing related to prevention of diaphragm atrophy are outweighed by any additional risks related to PVA. The analytic framework must consider these potentially competing principles. Adult data confirms associations between PVA (and its subtypes) and adverse clinical outcomes. [12-16] Nevertheless, human studies have not confirmed mechanistic pathways involved, although pre-clinical data support these proposed mechanisms of injury. [64-67] While this study will primarily establish associations, a mediation approach (see below) to the analysis allows for causal inference and specifically leverages the **randomized** nature of the REDvent trial. To decouple these effects, when analyzing the relationship between PVA variables and length of ventilation, we stratify or control for the time to spontaneous breathing.

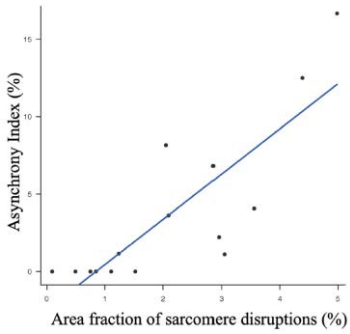

Figure 6: Relationship between Asynchrony index and sarcomere disruption of the diaphragm in a rabbit model for PVA

<u>Preclinical data confirms that PVA leads to VIDD and VILI.</u> Several mechanistic studies, including published analysis by our group, confirms that PVA leads to VIDD and VILI.[64-67] In a rabbit model, we identified that VIDD was reduced with a ventilation strategy promoting spontaneous breathing using pressure support ventilation compared to controlled ventilation, but that this injury could be further reduced with Neutrally Adjusted Ventilatory Assist (NAVA) by reducing the rates of PVA.[67] Interestingly, diaphragmatic injury from over-assistance myotrauma (common during controlled ventilation without spontaneous breathing) resulted in atrophy, while diaphragmatic injury from PVA was mediated by sarcomere disruption. There was a dose response relationship between Asynchrony Index and fraction of sarcomere disruptions in the diaphragm (Figure 6). Both sarcomere disruption and atrophy result in functional impairments seen in VIDD, albeit with different mechanisms.

PVA subtypes are associated with clinical and mechanistic outcomes.

Preliminary analysis from 65 patients in the REDvent dataset evaluated the association between PVA rates on the first day of spontaneous breathing and outcomes. While the sample size from this preliminary data is under-powered, it highlights the potential magnitude of effect we may see with the larger sample size in this application. We have not conducted group-based comparison (REDvent versus control), as study investigators need to remain blinded to group-based analyses until completion of REDvent (Dec 2023). Flow undershoot represents inadequate support on the ventilator and not surprisingly was associated with longer length of ventilation (p<0.05, Figure 7a) perhaps through hypertrophy of the diaphragm (Dte increased), although this analysis is limited by sample size with only 7/65 patients in the hypertrophy group (p=0.4, Figure 7b). Moreover, patients who had DC breaths had higher rates of delirium, as measured by the Cornell Assessment of Pediatric Delirium (CAPD) screener (p< 0.01, Figure 7c). This may relate to agitation from PVA which manifests with the same symptoms as delirium, or it may be that delirium itself makes it harder for patients to synchronize with the ventilator. Children with reverse trigger received higher doses of opioids (p<0.01, Figure 7d), which re-enforces that alteration of neural respiratory rate (suppressed with opioids) may make RT more common.

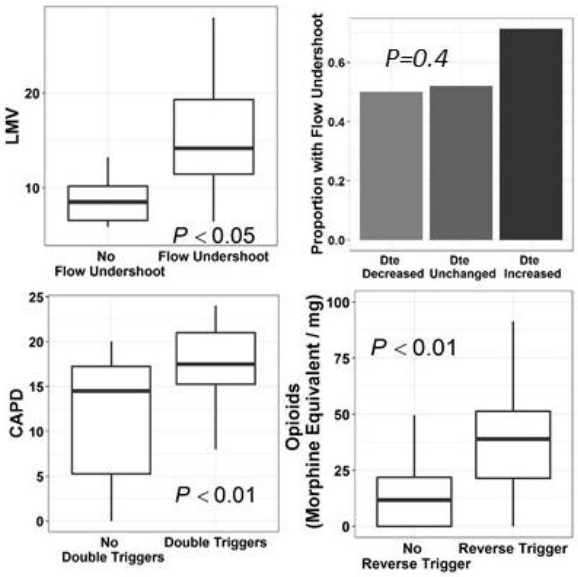

Figure 7: (a, top left) Length of ventilation (days) is higher in children with flow undershoot forms of PVA when spontaneous breathing does not occur until after the 3rd day of ventilation (b, top right) Diaphragm hypertrophy may be more likely to occur in children with flow-undershoot forms of PVA (c, bottom left) Delirium scores are higher in children with high rates of Double Cycled breaths. (d, bottom right) Reverse Trigger patients receive higher doses of opioids.

Methods and Analysis Hypothesis A: Here we seek to test whether the REDvent intervention results in different rates and subtypes of PVA than usual care. This type of analysis is perfectly suited to secondary analysis of a randomized trial, where the intervention is striving to promote more spontaneous breathing with a downstream influence on PVA. This would not be possible to do with an observational cohort, because of inherent selection bias in which patients are permitted to have more spontaneous breathing. We believe the forms of asynchrony which lead to DC breaths (flow undershoot/premature cycling) and reverse trigger may be different in REDvent versus control patients. This aim will use all available patients with spontaneous breathing in the REDvent dataset (expected 235). For each patient day with spontaneous breathing, PVA subtypes will be analyzed. The proportion of breaths which fall into a particular PVA subtype will be expressed in addition to global asynchrony index, calculated as the total number of asynchronous breaths over the total number of breaths.[30] Because rates of PVA may vary from day to day, analysis will focus on both an area under the curve of PVA over all days (calculated as the total number of asynchronous breaths over the total number of breaths available for analysis) in addition

to the highest rate of PVA on any day for each patient, by PVA subtype. PVA and PVA subtype rates per patient will be expressed as a continuous variable and compared between REDvent and usual care patients using a Mann Whitney U test given it is not expected to be normally distributed. PVA subtypes which are different between REDvent and control patients will be considered for mediation analysis (below).

The REDvent study will evaluate wither the REDvent intervention results in improvement in length of mechanical ventilation (clinical outcome), as well as mechanistic outcomes (PiMax and Diaphragm Atrophy). The impact of REDvent group on time to event variables (i.e. length of ventilation) will be analyzed with competing risk regression (competing risk of death), continuous outcomes (i.e. PiMax) with linear regression, and dichotomous variables (i.e. mortality) with logistic regression. In mediation analysis we will add the PVA subtypes which are different between REDvent and control patients to multivariable models. The PVA subtype will be considered a mediator if it changes the parameter estimate of the REDvent intervention by more than 20%. If the PVA subtype significantly strengthens the association between REDvent intervention and outcomes, then therapeutic trials which seek to decrease that PVA subtype maybe beneficial (e.g Reverse Trigger). In contrast, if controlling for PVA subtype weakens the association between REDvent and outcome, then strategies to mitigate that type of PVA may be more harmful (e.g. Flow Undershoot). This approach allows us to simultaneously evaluate the potential benefits of a lung and diaphragm protective strategy and understand the extent to which PVA subtypes which are different between intervention and control groups affects outcomes. This type of causal inference analysis is possible because of the randomized nature of the REDvent trial in which the intervention is likely to affect PVA rates and subtypes.

Sample Size and Power: We anticipate 235 patients available for analysis, with a median time from first day of spontaneous breathing to extubation of 4 days. Using a proposed mediation analysis with a conservative estimate for a partial "r" of 0.3 of the PVA variable with the mediator outcome, a partial "r" of 0.3 for the mediator outcome with the clinical variable, then we would have a power of 0.84 to detect the overall effect estimate in the mediation model.

Methods and Analysis Hypothesis B: Here we seek to understand which PVA subtypes and frequency are independently associated with clinical or mechanistic outcomes. The primary clinical outcome is length of mechanical ventilation after the first day of spontaneous breathing. This is the primary outcome because the relationship between PVA rates and length of ventilation is confounded by time to first day of spontaneous breathing, as discussed above. Patients who have highly controlled ventilation without spontaneous breathing for several days inherently cannot develop PVA, as there is no significant patient effort. Secondary short-term clinical outcomes include length of mechanical ventilation, length of the weaning phase of mechanical ventilation (time from first spontaneous breathing trial until extubation), 90-day mortality and re-intubation. Secondary longer-term clinical outcomes include pulmonary function, neurocognitive function, and health related quality of life for the 2 years after ICU discharge amongst survivors. Mechanistic outcomes will focus on pathways of injury hypothesized to be associated with PVA, summarized by PVA subtype in Table 2.

PVA Subtype	Mechanistic Pathway	Variables to be considered
"Inadequate Support": Flow Undershoot or Premature Cycling	VILI, VIDD (Over-use)	Transpulmonary Pressure, Tidal Volume, Resolution of Organ Dysfunction, Resolution of Lung Injury, PiMax, Diaphragm Thickness
Reverse Trigger	VIDD (Eccentric Contraction), Delirium, Excess Sedation	PiMax, Diaphragm Thickness, Cornell Assessment of Pediatric Delirium, Cumulative Dose of Sedatives and Opioids
Double Cycle (All causes)	VILI	Transpulmonary Pressure, Tidal Volume, Resolution of Organ Dysfunction, Resolution of Lung Injury
Asynchrony Index (All PVA)	Delirium, Excess Sedation	Cornell Assessment of Pediatric Delirium, State Behavioral Scale, FLACC Score, Cumulative Dose of Sedatives and Opioids

Table 2: Analytic Plan with PVA variable of interest, mediation variables to be investigated, and hypothesized mechanistic pathway.

Univariable analysis will focus on the relationship between the PVA variables above and clinical and mechanistic outcomes. Nearly all the variables of interest are continuous, so analyses will focus on strength of association and dose response. Nonparametric or parametric correlations will explore the relationships between continuous variables. The primary clinical outcome of length of ventilation after the first day of spontaneous breathing will be modelled with a competing risk regression to look at time to extubation against the competing risk of death. This type of model is necessary rather than traditional survival analysis or linear regression because both death and prolonged ventilation are undesired outcomes, and some proportion of children (likely 5-10%) will die even after the first day of spontaneous breathing. We have successfully used this framework in previous investigations.[68-72] We will then add in variables which may confound the relationship between PVA and clinical outcomes including demographic factors (age, co-morbidities), severity of initial lung injury, diagnostic data and medications. Similar analyses will be repeated all clinical and mechanistic outcomes. For mechanistic analysis (table 2), within each of the proposed mechanisms (VILI, VIDD, Delirium), the variable with the strongest association with PVA (or its subtype) will be included as the outcome variable.

Specific Aim 3) To develop and test a clinical decision support system using machine learning techniques to automatically identify common forms of PVA in children. **Hypothesis**: (a) Machine learning models using waveforms available on all mechanical ventilators will accurately identify PVA subtypes compared to gold standard annotations which include measures of neural drive. (b) Algorithms can be optimized for high sensitivity and low false alert rates to identify children with frequent PVA.

Preliminary Data

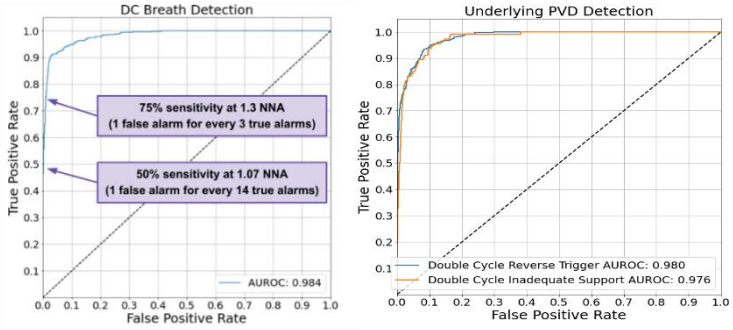

Figure 8: (a, left) The machine learning model has outstanding discrimination of double cycled breaths (b, right.) and the individual PVA subtypes leading to DC breaths

Machine learning methods can detect DC breaths and the PVA subtypes leading to DC. We have been developing a machine learning framework using Spectral Analysis with a Convolutional Neural Network to detect PVA subtypes. Details about the methods used (and intend to employ here) are described below. Preliminary models were trained on 34, validated on 13 and tested on 18 patients from the REDvent dataset. Gold standard annotations were provided using the methods and data described in SA 1. The machine learning model (a Convolutional Neural Network) **was trained using flow and airway pressure alone**, although the gold standard annotations (from humans) also used esophageal pressure. When evaluating the performance of the models in the test set (18 patients, >49,000 breaths) to detect DC, the model was very accurate with an Area Under the Cure (AUC) of the Receiver Operating Curve (ROC) of 0.984 (Figure 8a). This would be able to detect 50% of all DC breaths, with a false alarm rate of 1 in 14, or 75% of all DC breaths, with a false alarm rate of 1 in 3. Furthermore, when evaluating the underlying asynchrony subtype responsible for the DC breath, the models accurately distinguished between Flow Undershoot/ Premature Cycling and Reverse Trigger, with AUCs > 0.97 (Figure 8b).

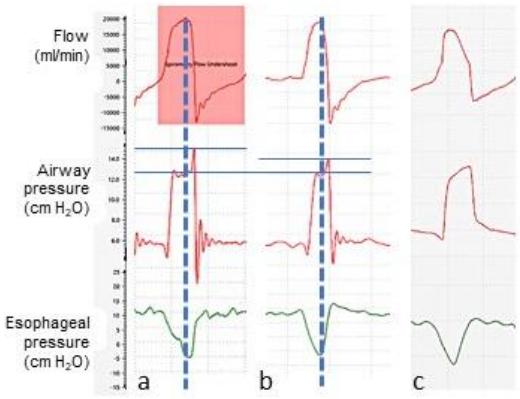

Figure 9: (a) Flow-undershoot detected by both human annotators and the machine learning algorithm with concave rising limb of flow, rise in airway pressure (horizontal lines) and falling esophageal pressure with airway pressure plateau (dotted line). (b) Flow-undershoot by machine learning algorithm but did not meet thresholds required by human annotators, although still represents same physiologic phenomena. (c) normal breath

Machine Learning Methods may be more accurate than highly trained clinicians. We have identified that these machine learning methods are also accurate at identifying Flow Undershoot/Premature termination and Reverse Trigger even when not associated with a Double Cycled Breath. We applied the methods on 13 patient files in the validation set (REDvent dataset only). Out of 10,326 breaths, the gold standard (human)

method labeled 1,926 (18.65%) of breaths as Flow Undershoot and 251 (2.43%) of breaths as Premature Termination. The machine learning methods identified 1486/1926 (77.14%) of the breaths which were labeled as Flow Undershoot by the gold standard method, and 176/251 (70.11%) of the breaths that were labeled as Premature Termination. Interestingly, the machine learning method also identified 1,993 breaths as Flow Undershoot and 987 breaths as Premature Termination which were not initially labeled as such by the expert readers. Several of these files were subsequently re-reviewed by the expert readers, and in nearly all cases, the patterns detected by the machine learning algorithms did in fact demonstrate the correct physiologic phenomena, although they did not meet the exact threshold criteria used for the definitions. (Figure 9). **This highlights that these methods may be more sensitive than the human eye.** Additional training of these algorithms to adjust threshold values that balance sensitivity and specificity between the more overt versus subclinical forms of flow undershoot, in addition to developing algorithms to identify the other forms of PVA will be a focus for the approach.

Methods: On a high level, a spectral tensor is used as input to a Convolutional Neural Network (CNN) model, which generates predictions that show the likelihood of a breath having asynchrony, with a specific asynchrony subtype. CNN are widely used in computer vision tasks[73], which make them appropriate for this application. Our group has extensive experience with machine learning models in the ICU environment.[74-80] The methods are based on analysis of three contiguous breaths, called a breath triplet with the breath of interest being the central breath (Figure 10). Breath triplets are generated from the two readily available clinical waveforms (flow spirometry and airway pressure). Each triplet is labeled with the asynchrony types associated with its central breath. A sliding Discrete Fourier Transform (DFT) is used to transform each of the waveforms of a triplet into two spectrograms: one with the power spectral density (PSD), which measures the energy of sinusoids in each channel, and another containing phase, which measures the angular shift of the sinusoids. This results in four spectral images for each triplet (Figure 10). Methods are employed to remove noise[81] and the spectrograms are aggregated in a stack to create a 4-channel image. This is analogous to the typical input used in CNNs, a three channel (RGB) image, except each channel corresponds to a single generated spectrogram as opposed to a color. Very subtle changes and patterns in the airway pressure and flow channels can be more readily apparent in their spectral representation than in their raw waveforms. CNNs, which are state-of-the-art in image processing, can accurately and efficiently recognize patterns in stacks of spectrograms. This powerful combination of spectrograms and CNNs is what makes our machine learning technique superior to automation-based approaches (i.e. hard coding the rulesets). Further, the technique can be ventilator agnostic.

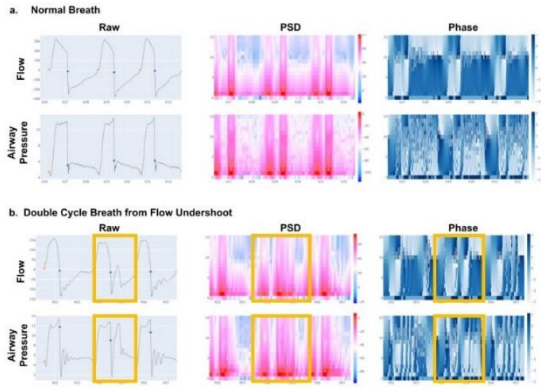

Figure 10: Example of a synchronous breath (a) compared to an asynchronous breath (b) and the spectral tensor conversions for each, with the DC breath highlighted in orange.

Analysis Plan: The existing datasets from all 3 institutions will be combined and patients will be randomly assigned to one of three datasets for derivation (50%), validation (25%), and final testing (25%).

Hypothesis a (algorithm development and testing): We anticipate having nearly 1,000,000 breaths for analysis from existing datasets (500,000 training, 250,000

validation and 250,000 in the final test set). Our models will first concentrate on DC breaths using the methods described above. Machine learning experts will work with the clinical team to review breaths in the validation set which have been classified as a certain PVA subtype, but which were not labeled the same way by human annotators (using one of 3 gold standard measures of neural effort). We anticipate many of the PVA annotations by the machine learning algorithm will represent "sub-clinical" PVA, where the breaths are representative of a specific type of PVA, but do not meet the threshold determined by the clinical reviewers. Models will be fine-tuned to differentiate "sub-clinical" from more overtly "clinical" PVA. Final performance will be assessed using the test set only once to ensure an unbiased estimate of the ability of the model to discriminate DC breaths and synchronous breaths. The performance of the models will be assessed using AUROC to assess the overall ability of the model to discriminate between DC breaths and other breaths. Additionally, the recall of the model at various levels of Number Needed to Alert (1.01, 1.1, 1.5, 2) will be analyzed to understand the potential clinical utility. Similar analysis will then follow to identify the underlying PVA subtype leading to the DC breath, and finally to identify other forms of asynchrony, independent of whether it results in a DC breath.

Hypothesis b (development of a clinical alert to identify when PVA is occurring with high frequency). To improve the recognition of PVA and support trials focused on PVA prevention, it is necessary to have real-time tools which balance the benefits of identification of potentially injurious forms of PVA against false alarms. The focus of this sub-aim is to develop a decision support system to continuously read in flow and airway pressure waveforms, apply the machine learning algorithms, provide relevant summary data about PVA frequency and subtypes, and potentially alert clinicians when patients have high rates of dangerous forms of PVA. We will build the relevant pipelines necessary for these systems, using raw waveform data from the three different hospitals. We will develop alert algorithms to identify patients who are having frequent PVA, while minimizing false alarms. This will mimic the real-world deployment scenario of detecting PVA on a new patient (not previously seen). The system and alert algorithms will be developed and internally validated from the data available in the existing datasets, evaluating sliding windows of 30-60 breaths to identify patients that exceed thresholds for PVA subtypes during that window (i.e. > 20% of breaths are flow undershoot in that window). This is important because it may not be possible (or desired) to eliminate all forms of PVA, particularly if the PVA event is rare. The unintended consequence of adjusting ventilator settings to eliminate one form of PVA, may result in other forms of PVA, or other consequences such as over-assistance of the patient. We will adjust the alert thresholds to optimize detection of true PVA events, against false alarm rates, with the goal of maintaining false alarm detection as low as possible (i.e. less than 5%). As seen in the preliminary data with DC breaths, *on the individual breath level*, our false alarm rate is 1/3-1/14 when sensitivity is in the 50-75% range. We anticipate the requirement for a certain number (or percentage) of breaths to be classified as a certain PVA subtype will greatly improve the sensitivity and specificity for identifying patients with frequent PVA.

Additional References for PVA

1. Ramirez II, Arellano DH, Adasme RS, et al. Ability of ICU Health-Care Professionals to Identify Patient-Ventilator Asynchrony Using Waveform Analysis. Respir Care 2017;62(2):144-149. (In eng). DOI: 10.4187/respcare.04750.
2. Vignaux L, Grazioli S, Piquilloud L, et al. Optimizing patient-ventilator synchrony during invasive ventilator assist in children and infants remains a difficult task*. Pediatr Crit Care Med 2013;14(7):e316-25. (In eng). DOI: 10.1097/PCC.0b013e31828a8606.
3. Piquilloud L, Jolliet P, Revelly JP. Automated detection of patient-ventilator asynchrony: new tool or new toy? Crit Care 2013;17(6):1015. (In eng). DOI: 10.1186/cc13122.
4. Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? Respir Care 2011;56(1):25-38. (In eng). DOI: 10.4187/respcare.01009.
5. Kondili E, Akoumianaki E, Alexopoulou C, Georgopoulos D. Identifying and relieving asynchrony during mechanical ventilation. Expert Rev Respir Med 2009;3(3):231-43. (In eng). DOI: 10.1586/ers.09.13.
6. Chen CW, Lin WC, Hsu CH, Cheng KS, Lo CS. Detecting ineffective triggering in the expiratory phase in mechanically ventilated patients based on airway flow and pressure deflection: feasibility of using a computer algorithm. Crit Care Med 2008;36(2):455-61. (In eng). DOI: 10.1097/01.CCM.0000299734.34469.D9.
7. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. Intensive Care Med 2006;32(1):34-47. (In eng). DOI: 10.1007/s00134-005-2828-5.
8. Nilsestuen JO, Hargett KD. Using ventilator graphics to identify patient-ventilator asynchrony. Respir Care 2005;50(2):202-34; discussion 232-4. (In eng).
9. Mellott KG, Grap MJ, Munro CL, et al. Patient ventilator asynchrony in critically ill adults: frequency and types. Heart & Lung 2014;43(3):231-43. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't) (In English). DOI: https://dx.doi.org/10.1016/j.hrtlng.2014.02.002.
10. Vignaux L, Vargas F, Roeseler J, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Medicine 2009;35(5):840-6. (Multicenter Study) (In English). DOI: https://dx.doi.org/10.1007/s00134-009-1416-5.
11. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Medicine 2006;32(10):1515-22. (Research Support, Non-U.S. Gov't) (In English). DOI: https://dx.doi.org/10.1007/s00134-006-0301-8.
12. Ge H, Duan K, Wang J, et al. Risk Factors for Patient-Ventilator Asynchrony and Its Impact on Clinical Outcomes: Analytics Based on Deep Learning Algorithm. Front Med (Lausanne) 2020;7:597406. (In eng). DOI: 10.3389/fmed.2020.597406.
13. Sousa MLA, Magrans R, Hayashi FK, Blanch L, Kacmarek RM, Ferreira JC. Predictors of asynchronies during assisted ventilation and its impact on clinical outcomes: The EPISYNC cohort study. J Crit Care 2020;57:30-35. (In eng). DOI: 10.1016/j.jcrc.2020.01.023.

14. Blanch L, Villagra A, Sales B, et al. Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med 2015;41(4):633-41. (In eng). DOI: 10.1007/s00134-015-3692-6.
15. Goligher EC, Dres M, Patel BK, et al. Lung and Diaphragm-Protective Ventilation. Am J Respir Crit Care Med 2020 (In eng). DOI: 10.1164/rccm.202003-0655CP.
16. Martos-Benítez FD, Domínguez-Valdés Y, Burgos-Aragüez D, et al. Outcomes of ventilatory asynchrony in patients with inspiratory effort. Rev Bras Ter Intensiva 2020;32(2):284-294. (In eng|spa). DOI: 10.5935/0103-507x.20200045.
17. Khemani RG, Hotz JC, Klein MJ, et al. A Phase II randomized controlled trial for lung and diaphragm protective ventilation (Real-time Effort Driven VENTilator management). Contemp Clin Trials 2020;88:105893. (In eng). DOI: 10.1016/j.cct.2019.105893.
18. Hotz JC, Bornstein D, Kohler K, et al. Real-Time Effort Driven Ventilator Management: A Pilot Study. Pediatr Crit Care Med 2020;21(11):933-940. (In eng). DOI: 10.1097/PCC.0000000000002556.
19. Khemani RG, Smith L, Lopez-Fernandez YM, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med 2019;7(2):115-128. (In eng). DOI: 10.1016/S2213-2600(18)30344-8.
20. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. Critical Care Medicine 2010;38(10):1947-53.
21. Goligher EC, Dres M, Patel BK, et al. Lung- and Diaphragm-Protective Ventilation. Am J Respir Crit Care Med 2020;202(7):950-961. (In eng). DOI: 10.1164/rccm.202003-0655CP.
22. Goligher EC, Brochard LJ, Reid WD, et al. Diaphragmatic myotrauma: a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure. Lancet Respir Med 2019;7(1):90-98. (In eng). DOI: 10.1016/S2213-2600(18)30366-7.
23. Yoshida T, Amato MBP, Kavanagh BP, Fujino Y. Impact of spontaneous breathing during mechanical ventilation in acute respiratory distress syndrome. Curr Opin Crit Care 2019;25(2):192-198. (In eng). DOI: 10.1097/MCC.0000000000000597.
24. Schepens T, Goligher EC. Lung- and Diaphragm-protective Ventilation in Acute Respiratory Distress Syndrome: Rationale and Challenges. Anesthesiology 2019;130(4):620-633.
25. Glau CL, Conlon TW, Himebauch AS, et al. Progressive Diaphragm Atrophy in Pediatric Acute Respiratory Failure. Pediatric Critical Care Medicine 2018;19(5):406-411. (In English). DOI: https://dx.doi.org/10.1097/PCC.0000000000001485.
26. Goligher EC, Dres M, Fan E, et al. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. American Journal of Respiratory & Critical Care Medicine 2018;197(2):204-213. (In English). DOI: https://dx.doi.org/10.1164/rccm.201703-0536OC.
27. Heunks LM, Doorduin J, van der Hoeven JG. Monitoring and preventing diaphragm injury. Current Opinion in Critical Care 2015;21(1):34-41. (In English). DOI: http://dx.doi.org/10.1097/MCC.0000000000000168.
28. Bulleri E, Fusi C, Bambi S, Pisani L. Patient-ventilator asynchronies: types, outcomes and nursing detection skills. Acta Biomed 2018;89(7-S):6-18. (In eng). DOI: 10.23750/abm.v89i7-S.7737.

29. Di Mussi R, Spadaro S, Mirabella L, et al. Impact of prolonged assisted ventilation on diaphragmatic efficiency: NAVA versus PSV. Crit Care 2016;20:1. (In eng). DOI: 10.1186/s13054-015-1178-0.
30. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Asynchrony index in pressure support ventilation (PSV) versus neurally adjusted ventilator assist (NAVA) during non-invasive ventilation (NIV) for respiratory failure: systematic review and meta-analysis. Intensive Care Medicine 2016;42(11):1813-1815. (Letter) (In English). DOI: https://dx.doi.org/10.1007/s00134-016-4508-z.
31. Vasconcelos RoS, Melo LH, Sales RP, et al. Effect of an automatic triggering and cycling system on comfort and patient-ventilator synchrony during pressure support ventilation. Respiration 2013;86(6):497-503. (In eng). DOI: 10.1159/000353256.
32. de la Oliva P, Schuffelmann C, Gomez-Zamora A, Villar J, Kacmarek RM. Asynchrony, neural drive, ventilatory variability and COMFORT: NAVA versus pressure support in pediatric patients. A non-randomized cross-over trial. Intensive Care Medicine 2012;38(5):838-46. (Clinical Trial Comparative Study Research Support, Non-U.S. Gov't) (In English). DOI: https://dx.doi.org/10.1007/s00134-012-2535-y.
33. Musante G, Schulze A, Gerhardt T, et al. Proportional assist ventilation decreases thoracoabdominal asynchrony and chest wall distortion in preterm infants. Pediatric Research 2001;49(2):175-80. (Research Support, Non-U.S. Gov't) (In English). DOI: https://dx.doi.org/10.1203/00006450-200102000-00008.
34. Jarreau PH, Moriette G, Mussat P, et al. Patient-triggered ventilation decreases the work of breathing in neonates. American Journal of Respiratory & Critical Care Medicine 1996;153(3):1176-81. (Clinical Trial Comparative Study Randomized Controlled Trial) (In English). DOI: https://dx.doi.org/10.1164/ajrccm.153.3.8630564.
35. Liao KM, Ou CY, Chen CW. Classifying different types of double triggering based on airway pressure and flow deflection in mechanically ventilated patients. Respir Care 2011;56(4):460-6. (In eng). DOI: 10.4187/respcare.00731.
36. Robinson BR, Blakeman TC, Toth P, Hanseman DJ, Mueller E, Branson RD. Patient-ventilator asynchrony in a traumatically injured population. Respir Care 2013;58(11):1847-55. (In eng). DOI: 10.4187/respcare.02237.
37. de Haro C, Magrans R, López-Aguilar J, et al. Effects of sedatives and opioids on trigger and cycling asynchronies throughout mechanical ventilation: an observational study in a large dataset from critically ill patients. Crit Care 2019;23(1):245. (In eng). DOI: 10.1186/s13054-019-2531-5.
38. de Haro C, López-Aguilar J, Magrans R, et al. Double Cycling During Mechanical Ventilation: Frequency, Mechanisms, and Physiologic Implications. Crit Care Med 2018;46(9):1385-1392. (In eng). DOI: 10.1097/CCM.0000000000003256.
39. Blokpoel RGT, Burgerhof JGM, Markhorst DG, Kneyber MCJ. Trends in Pediatric Patient-Ventilator Asynchrony During Invasive Mechanical Ventilation. Pediatr Crit Care Med 2021;22(11):993-997. (In eng). DOI: 10.1097/PCC.0000000000002788.
40. Blokpoel RG, Burgerhof JG, Markhorst DG, Kneyber MC. Patient-Ventilator Asynchrony During Assisted Ventilation in Children. Pediatric Critical Care Medicine 2016;17(5):e204-11. (In English). DOI: https://dx.doi.org/10.1097/PCC.0000000000000669.
41. Mortamet G, Larouche A, Ducharme-Crevier L, et al. Patient-ventilator asynchrony during conventional mechanical ventilation in children. Ann Intensive Care 2017;7(1):122. (In eng). DOI: 10.1186/s13613-017-0344-8.

42. Goligher EC, Fan E, Herridge MS, et al. Evolution of Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort. American Journal of Respiratory & Critical Care Medicine 2015;192(9):1080-8. (In English). DOI: http://dx.doi.org/10.1164/rccm.201503-0620OC.
43. Khemani RG, Hotz JC, Sward KA, Newth CJL. The role of computer-based clinical decision support systems to deliver protective mechanical ventilation. Curr Opin Crit Care 2020;26(1):73-81. (In eng). DOI: 10.1097/MCC.0000000000000688.
44. Spinelli E, Mauri T, Beitler JR, Pesenti A, Brodie D. Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions. Intensive Care Med 2020;46(4):606-618. (In eng). DOI: 10.1007/s00134-020-05942-6.
45. Schepens T, Dres M, Heunks L, Goligher EC. Diaphragm-protective mechanical ventilation. Curr Opin Crit Care 2019;25(1):77-85. (In eng). DOI: 10.1097/MCC.0000000000000578.
46. Aquino Esperanza J, Sarlabous L, de Haro C, et al. Double and multiple cycling in mechanical ventilation: Complex events with varying clinical effects. Med Intensiva (Engl Ed) 2020;44(7):449-451. (In eng|spa). DOI: 10.1016/j.medin.2019.06.004.
47. Figueroa-Casas JB, Montoya R. Effect of Tidal Volume Size and Its Delivery Mode on Patient-Ventilator Dyssynchrony. Ann Am Thorac Soc 2016;13(12):2207-2214. (In eng). DOI: 10.1513/AnnalsATS.201605-362OC.
48. Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D. Respiratory Drive in Critically Ill Patients. Pathophysiology and Clinical Implications. Am J Respir Crit Care Med 2020;201(1):20-32. (In eng). DOI: 10.1164/rccm.201903-0596SO.
49. Dianti J, Angriman F, Ferreyro BL, et al. Association of Mortality with Neuromuscular Blockade Differs according to Baseline Diaphragm Thickness. Am J Respir Crit Care Med 2020;202(12):1717-1720. (In eng). DOI: 10.1164/rccm.202004-1157LE.
50. van Haren F, Pham T, Brochard L, et al. Spontaneous Breathing in Early Acute Respiratory Distress Syndrome: Insights From the Large Observational Study to UNderstand the Global Impact of Severe Acute Respiratory FailurE Study. Crit Care Med 2019;47(2):229-238. (In eng). DOI: 10.1097/CCM.0000000000003519.
51. 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(1):346. (In eng). DOI: 10.1186/s13054-019-2617-0.
52. Shimatani T, Yoon B, Hotz JC, Khemani RG. Reply: Not All Breaths That Follow a Ventilator Cycle Are Reverse Triggering. Ann Am Thorac Soc 2021;18(7):1264-1266. (In eng). DOI: 10.1513/AnnalsATS.202103-322LE.
53. Shimatani T, Yoon B, Kyogoku M, et al. Frequency and Risk Factors for Reverse Triggering in Pediatric Acute Respiratory Distress Syndrome during Synchronized Intermittent Mandatory Ventilation. Ann Am Thorac Soc 2021;18(5):820-829. (In eng). DOI: 10.1513/AnnalsATS.202008-1072OC.
54. Turbil E, Guérin C, Schwebel C, Terzi N. Reverse Triggering: Sometimes It Is Not Only the Diaphragm. Am J Respir Crit Care Med 2020;201(7):e24-e25. (In eng). DOI: 10.1164/rccm.201907-1358IM.
55. Shimatani T, Yoon B, Kyogoku M, et al. Frequency and Risk Factors for Reverse Triggering in Pediatric ARDS during Synchronized Intermittent Mandatory

Ventilation. Ann Am Thorac Soc 2020 (In eng). DOI: 10.1513/AnnalsATS.202008-1072OC.
56. Mauri T, Yoshida T, Bellani G, et al. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. Intensive Care Med 2016;42(9):1360-73. (In eng). DOI: 10.1007/s00134-016-4400-x.
57. Akoumianaki E, Maggiore SM, Valenza F, et al. The application of esophageal pressure measurement in patients with respiratory failure. American Journal of Respiratory & Critical Care Medicine 2014;189(5):520-31. (In eng). DOI: 10.1164/rccm.201312-2193CI [doi].
58. Thille AW, Cabello B, Galia F, Lyazidi A, Brochard L. Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. Intensive Care Medicine 2008;34(8):1477-86. (Randomized Controlled Trial Research Support, Non-U.S. Gov't) (In English). DOI: https://dx.doi.org/10.1007/s00134-008-1121-9.
59. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Group ftPALICC. Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference. Pediatric Critical Care Medicine 2015;16(5_suppl):S23-S40. (In English). DOI: 10.1097/pcc.0000000000000432.
60. Marini JJ, Rocco PRM, Gattinoni L. Static and Dynamic Contributors to Ventilator-induced Lung Injury in Clinical Practice. Pressure, Energy, and Power. Am J Respir Crit Care Med 2020;201(7):767-774. (In eng). DOI: 10.1164/rccm.201908-1545CI.
61. Mirabella L, Cinnella G, Costa R, et al. Patient-Ventilator Asynchronies: Clinical Implications and Practical Solutions. Respir Care 2020;65(11):1751-1766. (In eng). DOI: 10.4187/respcare.07284.
62. Shimatani T, Yoon B, Hotz JC, Khemani RG. Reply: Not All Breaths that Follow a Ventilator Cycle Are Reverse Triggering. Ann Am Thorac Soc 2021 (In eng). DOI: 10.1513/AnnalsATS.202103-322LE.
63. de Wit M, Pedram S, Best AM, Epstein SK. Observational study of patient-ventilator asynchrony and relationship to sedation level. J Crit Care 2009;24(1):74-80. (In eng). DOI: 10.1016/j.jcrc.2008.08.011.
64. Heulitt MJ, Clement KC, Holt SJ, Thurman TL, Jo CH. Neurally triggered breaths have reduced response time, work of breathing, and asynchrony compared with pneumatically triggered breaths in a recovering animal model of lung injury. Pediatr Crit Care Med 2012;13(3):e195-203. (In eng). DOI: 10.1097/PCC.0b013e318238b40d.
65. Wood SM, Thurman TL, Holt SJ, Bai S, Heulitt MJ, Courtney SE. Effect of ventilator mode on patient-ventilator synchrony and work of breathing in neonatal pigs. Pediatric Pulmonology 2017;52(7):922-928. (In English). DOI: https://dx.doi.org/10.1002/ppul.23682.
66. Wu XY, Yin JJ, Yu JQ, Zheng RQ. [Effect of different mechanical ventilation modes on patient-ventilator synchrony and diaphragm function in rabbit model of acute respiratory distress syndrome]. Zhonghua Yi Xue Za Zhi 2020;100(21):1662-1667. (In chi). DOI: 10.3760/cma.j.cn112137-20191113-02469.
67. Shimatani T, Shime N, Nakamura T, Ohshimo S, Hotz J, Khemani RG. Neurally adjusted ventilatory assist mitigates ventilator-induced diaphragm injury in rabbits. Respir Res 2019;20(1):293. (In eng). DOI: 10.1186/s12931-019-1265-x.
68. Bhalla AK, Klein MJ, Emeriaud G, et al. Adherence to Lung-Protective Ventilation Principles in Pediatric Acute Respiratory Distress Syndrome: A Pediatric Acute

Respiratory Distress Syndrome Incidence and Epidemiology Study. Critical Care Medicine 2021;April. DOI: 10.1097/ccm.0000000000005060.
69. Bhalla AK, Yehya N, Mack WJ, Wilson ML, Khemani RG, Newth CJL. The Association Between Inhaled Nitric Oxide Treatment and ICU Mortality and 28-Day Ventilator-Free Days in Pediatric Acute Respiratory Distress Syndrome. Crit Care Med 2018;46(11):1803-1810. (In eng). DOI: 10.1097/CCM.0000000000003312.
70. Yehya N, Harhay MO, Klein MJ, et al. Predicting Mortality in Children With Pediatric Acute Respiratory Distress Syndrome: A Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Study. Crit Care Med 2020 (In eng). DOI: 10.1097/CCM.0000000000004345.
71. Yehya N, Thomas NJ, Khemani RG. Risk Stratification Using Oxygenation in the First 24 Hours of Pediatric Acute Respiratory Distress Syndrome. Crit Care Med 2018;46(4):619-624. (In eng). DOI: 10.1097/CCM.0000000000002958.
72. Yehya N, Bhalla AK, Thomas NJ, Khemani RG. Alveolar Dead Space Fraction Discriminates Mortality in Pediatric Acute Respiratory Distress Syndrome. Pediatr Crit Care Med 2016;17(2):101-9. (In eng). DOI: 10.1097/PCC.0000000000000613.
73. Simonyan K, Zisserman A. Very Deep Convolutional Networks for Large-Scale Image Recognition.
74. Aczon MD, Ledbetter DR, Laksana E, Ho LV, Wetzel RC. Continuous Prediction of Mortality in the PICU: A Recurrent Neural Network Model in a Single-Center Dataset. Pediatr Crit Care Med 2021;22(6):519-529. (In eng). DOI: 10.1097/PCC.0000000000002682.
75. Ho LV, Aczon M, Ledbetter D, Wetzel R. Interpreting a recurrent neural network's predictions of ICU mortality risk. J Biomed Inform 2021;114:103672. (In eng). DOI: 10.1016/j.jbi.2021.103672.
76. Winter MC, Day TE, Ledbetter DR, et al. Machine Learning to Predict Cardiac Death Within 1 Hour After Terminal Extubation. Pediatr Crit Care Med 2021;22(2):161-171. (In eng). DOI: 10.1097/PCC.0000000000002612.
77. Laksana E, Aczon M, Ho L, Carlin C, Ledbetter D, Wetzel R. The impact of extraneous features on the performance of recurrent neural network models in clinical tasks. J Biomed Inform 2020;102:103351. (In eng). DOI: 10.1016/j.jbi.2019.103351.
78. Carlin CS, Ho LV, Ledbetter DR, Aczon MD, Wetzel RC. Predicting individual physiologically acceptable states at discharge from a pediatric intensive care unit. J Am Med Inform Assoc 2018;25(12):1600-1607. (In eng). DOI: 10.1093/jamia/ocy122.
79. Wetzel RC, Aczon M, Ledbetter DR. Artificial Intelligence: An Inkling of Caution. Pediatr Crit Care Med 2018;19(10):1004-1005. (In eng). DOI: 10.1097/PCC.0000000000001700.
80. Ho LV, Ledbetter D, Aczon M, Wetzel R. The Dependence of Machine Learning on Electronic Medical Record Quality. AMIA Annu Symp Proc 2017;2017:883-891. (In eng).
81. Zhuang J, Tang T, Ding Y, et al. AdaBelief Optimizer: Adapting Stepsizes by the Belief in Observed Gradients. NeurIPS 2020; 2020.

I Ventilation Protocols (Intervention group)

Acute phase management is based on SIMV pressure control/pressure support mode of ventilation. Oxygenation targets are 88-93% during the acute phase, and PEEP and FiO2 are managed as per the PEEP/FiO2 tables on the subsequent pages. If inhaled nitric oxide is used by the clinical team, then rules for weaning nitic oxide have been built into the protocol, as detailed below. Ventilation management during the acute phase uses pH, ventilator rate, and PIP to suggest changes to embrace permissive hypercapnia. When the patient is breathing spontaneously, rules regarding Pressure Rate Product are also implemented, to keep work of breathing in a physiologic range.

If High frequency oscillatory ventilation is used for patients randomized to RED-vent Acute, then HFOV rules have been created. There is no requirement to transition to HFOV, but it will be permitted for rescue therapy. Similar to the conventional ventilation, Oxygenation is managed with a MAP/FiO2 table, with rules for inhaled nitric oxide if used. Ventilation adjusts Hz, Amp based on pH. There are no PRP based rules during HFOV, since most patients are not spontaneously breathing. There are recommendations for minimal therapy with HFOV, when conversion back to conventional ventilation should be considered, although the clinical team will ultimately make the decision regarding conversion back to conventional ventilation.

Details of the protocols are summarized on the following pages.

Pressure Control: Ventilation table

pH \ PIP	<=28	29-35	>35
> 7.45	↓ Δ P by 2 ↓ VR by 20%	↓ Δ P by 2	↓ Δ P by 4
7.30-7.45	↓ Δ P by 2 ↓ VR by 10%	↓ Δ P by 2	↓ Δ P by 2
7.15-7.29 (VR < Max)	↑ Δ P by 2 ↑ VR by 20%	↑ VR by 20%	↓ Δ P by 2 ↑ VR by 20%
7.15-7.29 (VR >= Max)	↑ Δ P by 4	No change to Δ P Or VR Consider Bicarb if PCO2 <25	↓ Δ P by 2 Consider Bicarb if PCO2 <25
< 7.15 (VR < Max)	↑ Δ P by 4 ↑ VR by 20%	↑ Δ P by 2 ↑ VR by 20%	↑ VR by 20% Consider Bicarb if PCO2 <25
< 7.15 (VR >= Max)	↑ Δ P by 4 Consider Bicarb if PCO2 <25	↑ Δ P by 2 Consider Bicarb if PCO2 <25	No change to Δ P Or VR Consider Bicarb if PCO2 <25

Green cells: If the patient is breathing spontaneously, the PRP is used to make the following recommendations based on PRP range: Low, Middle, High.

PRP Range

Low	Middle	High
Standard recommendation	No change to ventilation support	If , PIP <35 and PS < 20 ↑ Δ P by 2 ↑ PS by 2 Else, consult MD

Note: Default max VR (Ventilator Rate) is 35, however patients with evidence of lower airway obstruction will have this reduced to 24.

Pressure Control: Oxygenation (Low)
PaO2 < 55, SpO2 < 88%

PEEP \ FiO2	0.25	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	1.0
5	Inc. FiO2 by 0.05	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3	Inc. PEEP by 3
8	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
10	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
12	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
14	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
16	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2	Inc. PEEP by 2
18	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2	Inc. PEEP by 2
20	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2
22	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. PEEP by 2
24	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Maximal therapy

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Pressure Control: Oxygenation (Middle)
PaO2 55-68, SpO2 88-93%

PEEP \ FiO2	0.25	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	1.0
5	No Changes	No Changes	No Changes	No Changes	Inc. PEEP 3	Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3	Dec. FiO2 0.05 Inc. PEEP 3
8	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	No Changes	Inc. PEEP 2	Inc. PEEP 2	Inc. PEEP 2	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
10	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	No Changes	No Changes	No Changes	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
12	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	Inc. PEEP 2	Inc. PEEP 2	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
14	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes	No Changes	No Changes	Dec. FiO2 0.05 Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
16	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2	Inc. FiO2 0.05	No Changes	No Changes	Inc. PEEP 2	Dec. FiO2 0.05 Inc. PEEP 2
18	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes	No Changes
20	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes	No Changes
22	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes
24	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Dec. PEEP 2 Inc. FiO2 0.05	Inc. FiO2 0.05	Inc. FiO2 0.05	No Changes

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Pressure Control: Oxygenation (High)
PaO2 >68, SpO2 > 93%

PEEP \ FiO2	0.25	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	1.0
5	Minimal Therapy Maintain	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
8	Dec. PEEP by 3	Dec. PEEP by 3	Dec. PEEP by 3	Dec. PEEP by 3	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
10	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
12	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 by 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
14	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05	Dec. FiO2 0.05
16	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05	Dec. FiO2 0.05
18	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 by 0.05	Dec. PEEP by 2	Dec. PEEP by 2	Dec. FiO2 0.05
20	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2
22	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2
24	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2	Dec. PEEP by 2

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HFOV: Ventilation

pH

Amplitude (Amp)	< 7.15	7.15 -7.29	7.30-7.45	>7.45
< 50	↑ Amp by 10 ↓ Hz by 0.5 Consider IV Bicarb	↑ Amp by 10	↑ Hz by 0.5 [If at max Hertz, consider CMV]	↓ Amp by 5 ↑ Hz by 1.0 (If at max Hertz, ↓ Amp by 5)
50-70	↑ Amp by 10 ↓ Hz by 0.5 Consider IV Bicarb	↑ Amp by 10	↑ Hz by 0.5 [If at max Hertz, ↓ Amp by 5]	↓ Amp by 5 ↑ Hz by 0.5 (If at max Hertz, ↓ Amp by 10)
> 70	↑ Amp by 5 ↓ Hz by 1.0 [If at max Amp , ↓ Hz by 1.5] Consider IV Bicarb	↑ Amp by 5 ↓ Hz by 0.5 [If at max Amp , ↓ Hz by 1.0]	↓ Amp by 5 ↑ Hz by 0.5 [If at max Hz, ↓ Amp by 10]	↓ Amp by 10 ↑ Hz by 0.5 [If at max Hz, ↓ Amp by 15]

Hertz (Hz) range 3-15

HFOV: Oxygenation (Low)
PaO2 >68, SpO2 > 93%

MAP \ FiO2	0.25	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	1.0
18	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
20	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
22	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
24	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
26	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
28	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
30	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
32	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
34	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
36	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2	Inc. MAP by 2
38	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. MAP by 2	Inc. MAP by 2
40	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Inc. FiO2 by 0.05	Maximal Therapy

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HFOV: Oxygenation (Middle)
PaO2 55-68, SpO2 88-93%

MAP \ FiO2	0.25	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	1.0
18	Minimal Therapy	Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 2
20	Dec. MAP 2	No Change	Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
22	Dec. MAP 2 Inc. FiO2 0.05	No Change	Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP by 2	Dec. FiO2 0.05 Inc. MAP by 3	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
24	Dec. MAP 2 Inc. FiO2 0.05	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 3	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
26	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
28	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
30	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
32	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
34	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
36	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2	Inc. MAP 2	Dec. FiO2 0.05 Inc. MAP 2
38	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	Dec. MAP 2	No Change	No Change	Inc. MAP 2
40	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2 Inc. FiO2 0.05	Dec. MAP 2	No Change	No Change

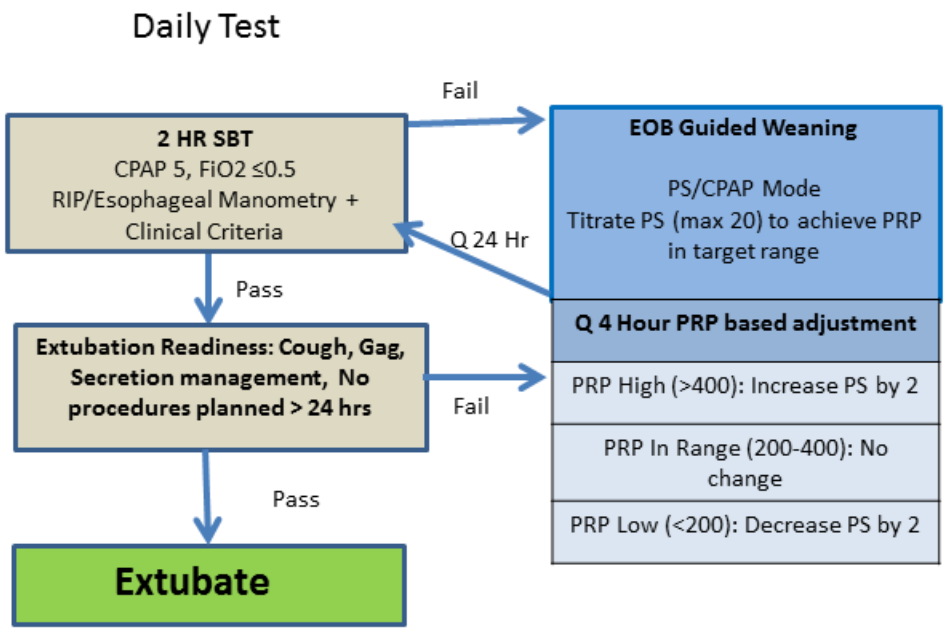
- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
- For weaning of inhaled nitric oxide, if FiO2 ≤ 0.6 and an FiO2 wean would normally be recommended, this recommendation is replaced with a recommendation to decrease inhaled nitric oxide until it is discontinued.

HFOV: Oxygenation (High)
PaO2 < 55, SpO2 < 88%

MAP \ FiO2	0.25	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	1.0
18	Minimal Therapy	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
20	No Change	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
22	No Change	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
24	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
26	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
28	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
30	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
32	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
34	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
36	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05	Dec. FiO2 by 0.05
38	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. FiO2 by 0.05
40	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2	Dec. MAP by 2

- For patients on inhaled nitric oxide, escalation of iNO is per the clinical team.
- For weaning of inhaled nitric oxide, if $FiO_2 \leq 0.6$ and an FiO_2 wean would normally be recommended, this recommendation is replaced with a recommendation to decrease inhaled nitric oxide until it is discontinued.

Weaning Phase Protocol



- During weaning phase, PEEP ≤ 10 cmH_20, FiO_2 ≤ 0.6, PS ≤ 20 cmH_20. PEEP and FiO_2 management can be changed within PEEP range of 5-10 cmH_20 and FiO_2 from 0.21-0.6 by the clinical team.
- Suspension of the weaning phase is permitted for up to 12 hours for situations such as procedures, increased need for sedation preventing adequate spontaneous breathing, or other circumstances requiring transient need for increase in ventilator support etc. As soon as the patient appropriately meets weaning criteria (spontaneous breathing, pH 7.32-7.47, PEEP ≤ 10 cmH_20, FiO_2 ≤ 0.6), the weaning phase intervention is resumed.
- If the weaning phase is suspended for > 12 hours and the patient no longer meets weaning criteria, the acute phase intervention will be resumed, until the patient again meets weaning criteria. This will be labeled weaning failure, and tracked in both arms.

The table below summarizes all protocol changes and the dates the amendments were approved by the Children's Hospital Institutional Review Board. Changes related to conduct of the trial (modifications of inclusion and exclusion criteria, sample size etc) were approved by the DSMB and NHLBI. Minor changes related to additional surveys or additional funding for secondary analysis are also included in the table below but did not result in substantive changes to the conduct of the trial.

Amendment Date	Summary of Changes
10/10/2018	Exclusion criteria revised to allow inclusion of patients with tracheostomy without home mechanical ventilation. Protocol change approved by NHLBI and DSMB to help increase enrollment to stay aligned with milestone accrual plan.
5/30/2019	Inclusion of Health-Related Quality of Life questions (surveys) at ICU admit and Discharge (additional funding received)
10/14/2019	Sample size reduced from 300 to 276. Inclusion of Phillips NM3 volumetric capnography device (ancillary study funding). Protocol change approved by NHLBI and DSMB.
3/18/2020	COVID-19 related changes including allowing up to 72 hours from intubation for enrollment of all patients (previously restricted to those admitted from an outside ICU). This was to facilitate recruitment while staying compliant with institutional protocols related to COVID-19. Protocol change approved by NHLBI and DSMB.
08/08/2020	Addition of survey related to Vaping/Smoking exposure (ancillary study funding)
11/17/2022	Age range for inclusion increased from 18 to 21 years of age. Protocol change approved by NHLBI and DSMB to help increase enrollment to stay aligned with milestone accrual plan.
03/28/2023	Details added regarding secondary analysis related to patient-ventilator asynchrony (additional funding obtained).

REDvent Statistical Analysis Plan (Fall 2019)

Inclusion Criteria

1. Children > 1 month (at least 44 weeks corrected gestational age) and ≤18 years of age AND
2. Supported on MV for pulmonary parenchymal disease (radiographic evidence of alveolar or interstitial opacifications with a clinical risk factor for lung disease e.g. pneumonia, acute respiratory distress syndrome, aspiration, etc.) with Oxygen Saturation Index (OSI= (FiO_2 * Mean Airway Pressure*100)/SpO_2) ≥ 5 or Oxygenation Index (OI= FiO_2 * Mean Airway Pressure*100)/PaO_2)) ≥4 [1] AND
3. Within 48 hours of initiation of invasive MV (up to 72 for those transferred from another hospital)

Exclusion Criteria

1. Contraindications to an esophageal catheter (i.e. severe mucosal bleeding, nasal encephalocele, trans-sphenoidal surgery) OR
2. Contraindications to use of Respiratory Inductance Plethysmography (RIP) bands (i.e. omphalocele, chest immobilizer or cast) OR
3. Conditions precluding diaphragm ultrasound measurement (i.e. abdominal wall defects, pregnancy) OR
4. Conditions precluding conventional methods of weaning (i.e., status asthmaticus, severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal Life Support (ECLS), limitation of care, severe chronic respiratory failure, spinal cord injury above lumbar region, cyanotic heart disease (unrepaired or palliated) OR
5. Primary Attending physician refusal

Randomization Strategy and Blinding

For the acute phase, subjects will be block randomized to either arm in a 1:1 allocation ratio, stratified by age group: infant (30 days -365 days), child (366 days to ≤8 years), and older child/ adolescent (9-18 years); and immune suppression (congenital or acquired conditions that result in marked inability to respond to antigenic stimuli). Block randomization will use random block sizes of 4, 6 and 8 within the strata above. Weaning phase randomization is block randomized by acute phase group and age, using the same methodology. Although blinding is not possible given the open label nature of the intervention, analysis will be blinded to treatment groups. Randomization schema will be loaded into the central REDCAP database by the unblinded statistician.

Statistical Analysis Plan

Baseline characteristics at the time of randomization will be computed for each treatment group (REDvent and usual care) and within each phase (Acute and Weaning). For all analyses, assumptions for data distribution will be assessed, and normalizing transformations of the data or nonparametric analysis will be performed as necessary. The mean and standard deviation will be reported for normally distributed continuous variables, and the median and interquartile ranges will be reported for non-normally distributed continuous variables. Given this is an RCT, we anticipate balanced baseline characteristics. To evaluate this, we will calculate effect sizes for measures of central tendency (Cohen d, Cramer v) across groups. For non-parametric variables, effect sizes defined for the Mann-Whitney U will be calculated to produce r. For frequency counts and percentages the rate ratio will be evaluated to calculate the effect size. Variables that have more than a small effect size ($d > 0.2$, $v > 0.01$, or $r > 0.1$,

categorical effect size>1.2) indicate potential imbalances in baseline characteristics between groups. These variables will be included in sensitivity analyses after the primary ITT analyses are performed or included as covariates using multivariable models.

Retention, adherence, and missing data will be compared across groups. High levels of missing data are not anticipated given the nature of the study. If the missing data are determined to be related to the outcome (not missing at random) or related to group or a covariate (missing at random), we will explore the impact of these biases in sensitivity analyses after the primary ITT analyses using multiple imputation processes. Our primary approach to imputing missing data is the Markov Chain Monte Carlo (MCMC) simulation. Statistical Analysis Software (SAS) procedures will be used.

The primary analysis seeks to address if there are differences in length of weaning between: 1) REDvent-acute compared to usual care acute, 2) REDvent-weaning compared to usual care-weaning, and 3) REDvent-acute and weaning (combined) compared to usual care acute and weaning (combined). Analyses of these aims will follow the ITT principle. The primary analyses will compare median weaning duration between groups using a Mann-Whitney U test, or a t-test with transformation as necessary. The effect size (r) will also be computed to assess the magnitude of treatment effect. If imbalances in baseline characteristics are found between or across randomized treatment groups, a Cox proportional hazard model will be performed to adjust for covariates. The estimates (mean, median, or hazard ratio) and the associated 95% confidence interval, as well as the p-values, will be presented for interpretation.

Power analysis: For the primary outcome (weaning duration), a 1-day change in length of weaning is considered clinically significant. It is anticipated that up to 20% of patients may not achieve the primary outcome (successful passage of an SBT or extubation due to death or dropout); these patients will not be included in the primary outcome analysis but will be included in secondary outcomes. We are targeting an overall sample size of 300 patients, with a minimum of 240 patients (120 per arm) available for analysis of the primary outcome. Using the planned statistical tests above, this sample size would be able to detect a ≥ 1-day change in weaning duration with a two-sided alpha of 0.05 and power of 0.9, or a relative hazard ratio of 1.5 (ratio between control/intervention group) with a power of 0.9 or a hazard ratio of 1.4 with a power of 0.8. Patients who fail the initial SBT will undergo the weaning phase randomization. From our pilot data, approximately 25% of patients exposed to the intervention passed the initial SBT. Anticipating 180 patients (90 per arm) will receive weaning phase interventions, there will be adequate power to detect a ≥ 1 day change in the length of the weaning phase, or a hazard ratio of 1.5 with an alpha of 0.05 and power of 0.8 in the weaning phase.

The analytic approach for secondary aims and outcomes such as mortality and ventilator free days will follow those described above. For categorical data, a $\chi 2$ or Fisher's exact test will be used to compare difference between groups. Logistic regression will be used to assess binary outcomes, and a multinomial/ordinal logistic regression will be used for categorical outcomes (> 2 categories) while adjusting for covariates. To assess the association between 2 continuous variables, a Pearson or Spearman correlation will be used, and analysis of covariance (ANCOVA) will be used to adjust for covariates. Generalized Estimating Equations (GEE) or mixed effect models will be used when necessary to analyze repeated measures. Because of the physiologic nature of the study with a Phase II design, multiple comparisons adjustment is not planned for secondary outcomes. Analyses will be performed using the appropriate recent version of the SAS statistical software (SAS Institute Inc., Cary, NC).

In order to increase precision around the effect estimates for the primary and secondary aims and to reflect the stratified sampling, all analyses will be adjusted for block randomization variables.[2] For acute phase these are age group (infant, child, and adolescent) and whether or not the subject was immunocompromised. For the weaning phase this is acute phase randomization grouping and age group. In addition, variables thought to be potential confounders on the relationship between intervention and outcome with large differences between groups (standardized effect sizes as detailed above) will also be included in all adjusted analyses. Unadjusted analyses will be presented to summarize data; all primary and secondary outcomes will present adjusted analyses controlling for age category, immunosuppression and imbalanced baseline variables.

Model assumptions and fit for multiple linear regression (with or without log transformation) will be assessed visually for normality of residuals as well as variance inflation factor and difference in betas (DFBETAS) for influential points. Model fit for binary multiple logistic regression will be assessed with Pearson Chi-square and deviance. Firth's penalized likelihood method will be used in subgroup analyses when event rates are small to reduce bias in the parameter estimates.[3] When using negative binomial regression, model fit will be assessed for over and underdispersion with the scaled Pearson Chi-square/deviance and influential points assessed as previously described. The proportional hazards assumption will be assessed when using Cox proportional hazards modeling using graphical approaches ("log-log" figures and Kaplan-Meier curves) for each covariate.

A detailed outline of each outcome's analysis approach to control for blocking variables and confounders is given in the Table 1. Pre-specified comparisons of interest are REDvent acute vs. usual care acute, REDvent weaning vs. usual care weaning, and four group combination: 1) REDVent acute + REDvent weaning 2) REDvent acute + usual care weaning 3) Usual care acute + usual care weaning 4) usual care acute + REDvent weaning. The four group combinations comparisons are exploratory and will only be considered if there are noted differences between both acute and weaning phase interventions.

References

1. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, et al. Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference. *Pediatric Critical Care Medicine*. Jun 01 2015;16(5_suppl):S23-S40. doi:10.1097/PCC.0000000000000432
2. Holmberg MJ, Andersen LW. Adjustment for Baseline Characteristics in Randomized Clinical Trials. *JAMA*. Dec 06 2022;328(21):2155-2156. doi:10.1001/jama.2022.21506
3. Firth D. Bias Reduction of Maximum Likelihood Estimates. Biometrika 1993. p. 27-38.

Table 1: Detailed analytic plan for each outcome variable

Variable	Description	Imputation & Exclusion	Initial Analytic Approach	Misc. Notes
Length of Weaning (primary outcome)	Time from first attempted SBT until successful SBT passage or extubation, whichever comes first. Successful extubation is removal without re-intubation or death for at least 24 hours.	Patients no longer undergo SBTs after the 28 day intervention but they will be clinically assessed for extubation and will be followed up to 90 days. If a patient remains intubated at 90 days their length of weaning becomes 90 days. Patients who never attempt an SBT are excluded. Patients who attempt an SBT but never pass an SBT and die within 24 hours of extubation are excluded.	Cox proportional hazards model controlling for blocking variables and confounders. Proportional hazards assumption will be assessed.	Expect 20% exclusion rate for this outcome. Patients who pass the SBT will have a length of weaning of around 2 hours (SBT duration). Length of weaning will be expressed in days and will take on values of 0.0833 (2 hours) to 90 days. The adjusted hazard ratio and 95% C.I. will be presented for REDvent vs. usual care.
IMV duration in survivors (Secondary Outcome)	Time from start of index intubation to successful liberation. Successful liberation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of extubation are excluded.	Log transformed multiple linear regression controlling for blocking variables and confounders.	IMV duration will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.

NIV duration after extubation (secondary outcome)	Duration of non-invasive ventilation after extubation is defined as the number of days and hours that the patient is on oro-mask CPAP or Bi-level ventilation after successful extubation. Successful extubation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of IMV or who never receive NIV post-extubation are excluded. Patients who die while on NIV will have their death date as end of NIV duration.	Log transformed multiple linear regression controlling for blocking variables and confounders.	NIV duration will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.
NRS duration after extubation (secondary outcome)	Duration of NRS after extubation is defined as the number of days and hours that the patient is on NRS after successful liberation. End of NRS is defined as absent continuously for at least 24 hours. Successful extubation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of IMV or who never receive NRS post-extubation are excluded. Patients who die while on NRS will have their death date as end of NIV duration.	Log transformed multiple linear regression controlling for blocking variables and confounders.	NRS duration will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.
Re-intubation within 48 hours of extubation (secondary outcome)	Binary variable for re-insertion of endotracheal tube within 48 hours of initial extubation.	Patients who remain on IMV for their index intubation or die within 48 hours of index extubation are excluded.	Multivariable logistic regression for the event re-intubation = yes. Adjusting for blocking variables and confounders.	Binary yes/no variable. Adjusted odds ratio for re-intubation with 95% C.I. for REDvent vs. Usual care will be presented.

28-day ventilator free days (secondary outcome)	Number of days between index intubation and 28-days post-index intubation in which patient is alive and not on IMV.	No exclusions.	Competing risks regression adjusting for blocking variables and confounders. Censoring indicators: 0=those who do not die but are not extubated within 28 days 1=those that have successful liberation within 28-days 2=those that die within 28-days	If patient is re-intubated within 24 hours of extubation the time in between intubations is not counted towards VFDs. If a patient in extubated for >24 hours and then subsequently re-intubated they get credit for those days without IMV. Values are 0 to 28 days. Adjusted hazard ratio and 95% C.I. will be presented.
PiMax on day of 1st SBT (secondary outcome)	PiMax value on the day the 1st SBT was performed.	Patient with values >100 will be truncated to 100. Exclude patients who never attempted an SBT in the 28-days study period.	Multiple linear regression adjusting for blocking variables and confounders.	Adjusted mean difference with 95% C.I. will be presented for REDvent vs. Usual care.
PiMax on day of extubation (secondary outcome)	PiMax value on the day of extubation. Restricted to those who met primary outcome (SBT passage or successful extubation).	Exclude patients who died within 24 hours of extubation or remained intubated at 90 days.	Multiple linear regression adjusting for blocking variables and confounders.	Adjusted mean difference with 95% C.I. will be presented for REDvent vs. Usual care.
ICU mortality (secondary outcome)	Yes/no binary variable for did patient die in the ICU.	No exclusions	Multivariable logistic regression controlling for blocking variables and confounders.	Adjusted odds ratios for death in REDvent vs. Usual care with 95% C.I. will be presented.
90-day mortality (secondary outcome)	Yes/no binary variable for did patient die in the hospital and within 90 days.	No exclusions	Multivariable logistic regression controlling for blocking variables and confounders.	Adjusted odds ratios for death in REDvent vs. Usual care with 95% C.I. will be presented.

Time to 1st SBT (secondary outcome)	Number of days from start of index intubation to either first SBT or successful extubation, whichever came first. Successful extubation defined as no death or re-intubation within 24 hours of extubation.	Exclude patients who never had an SBT or never successfully extubated in study observation period.	Log transformed multiple linear regression controlling for blocking variables and confounders.	Time will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.
Time to 1st SBT passage (secondary outcome)	Number of days from start of index intubation to either first SBT passage or successful extubation, whichever came first. Successful extubation defined as no death or re-intubation within 24 hours of extubation.	Exclude patients who never had an SBT or never successfully extubated in study observation period.	Log transformed multiple linear regression controlling for blocking variables and confounders.	Time will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.
Decline in PCPC from baseline to ICU discharge	Change in PCPC defined as baseline minus ICU discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in PCPC).	Patients who did not survive to ICU discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in PCPC from baseline to ICU discharge with 95% C.I. for REDvent vs. usual care will be presented.
Decline in POPC from baseline to ICU discharge	Change in POPC defined as baseline minus ICU discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in POPC).	Patients who did not survive to ICU discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in POPC from baseline to ICU discharge with 95% C.I. for REDvent vs. usual care will be presented.

Improvement in FSS from baseline to ICU discharge	Change in FSS defined as baseline minus ICU discharge value. This change was grouped into ordinal categories: no change/improvement (change of ≥0), 1-2 point decline, and >2 point decline.	Patients who did not survive to ICU discharge were excluded.	Proportional odds logistic regression controlling for blocking variables and confounders. Ordered on the probability towards improvement.	Adjusted odds for the improvement (change going towards positive) with 95% C.I. for REDvent vs. usual care.
Decline in PCPC from baseline to hospital discharge	Change in PCPC defined as baseline minus hospital discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in PCPC).	Patients who did not survive to hospital discharge (censored at 90 days) discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in PCPC from baseline to hospital discharge with 95% C.I. for REDvent vs. usual care will be presented.
Decline in POPC from baseline to hospital discharge	Change in POPC defined as baseline minus hospital discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in POPC).	Patients who did not survive to hospital discharge (censored at 90 days) discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in POPC from baseline to hospital discharge with 95% C.I. for REDvent vs. usual care will be presented.
Improvement in FSS from baseline to hospital discharge	Change in FSS defined as baseline minus hospital discharge value. This change was grouped into ordinal categories: no change/improvement (change of ≥0), 1-2 point decline, and >2 point decline.	Patients who did not survive to hospital discharge (censored at 90 days) discharge were excluded.	Proportional odds logistic regression controlling for blocking variables and confounders. Ordered on the probability towards improvement.	Adjusted odds for the improvement in FSS (change going towards positive) with 95% C.I. for REDvent vs. usual care.

REDvent Statistical Analysis Plan Final with Summary of Changes (July 2024)

Inclusion Criteria

1. Children > 1 month (at least 44 weeks corrected gestational age) and ≤ 21 years of age AND
2. Supported on MV for pulmonary parenchymal disease (radiographic evidence of alveolar or interstitial opacifications with a clinical risk factor for lung disease e.g. pneumonia, acute respiratory distress syndrome, aspiration, etc.) with Oxygen Saturation Index (OSI= (FiO_2 * Mean Airway Pressure*100)/SpO_2) ≥ 5 or Oxygenation Index (OI= FiO_2 * Mean Airway Pressure*100)/PaO_2)) ≥4 [1] AND
3. Within 72 hours of initiation of invasive MV

Exclusion Criteria

1. Contraindications to an esophageal catheter (i.e. severe mucosal bleeding, nasal encephalocele, trans-sphenoidal surgery) OR
2. Contraindications to use of Respiratory Inductance Plethysmography (RIP) bands (i.e. omphalocele, chest immobilizer or cast) OR
3. Conditions precluding diaphragm ultrasound measurement (i.e. abdominal wall defects, pregnancy) OR
4. Conditions precluding conventional methods of weaning (i.e., status asthmaticus, severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal Life Support (ECLS), limitation of care, severe chronic respiratory failure, spinal cord injury above lumbar region, cyanotic heart disease (unrepaired or palliated) OR
5. Primary Attending physician refusal

Randomization Strategy and Blinding

For the acute phase, subjects will be block randomized to either arm in a 1:1 allocation ratio, stratified by age group: infant (30 days -365 days), child (366 days to ≤8 years), and older child/ adolescent (9-18 years); and immune suppression (congenital or acquired conditions that result in marked inability to respond to antigenic stimuli). Block randomization will use random block sizes of 4, 6 and 8 within the strata above. Weaning phase randomization is block randomized by acute phase group and age, using the same methodology. Although blinding is not possible given the open label nature of the intervention, analysis will be blinded to treatment groups. Randomization schema was loaded into the central REDCAP database by the unblinded statistician. Patients were consented for the study by one of the study investigators, and randomization in the central REDCAP database was conducted by one of the research respiratory therapists or study investigators. Prior to randomization, blocking strata variables were double checked with a second member of the study team or the primary attending physician.

Statistical Analysis Plan

Additional details are also available in the published study protocol.[2] Baseline characteristics at the time of randomization will be computed for each treatment group (REDvent and usual care) and within each phase (Acute and Weaning). For all analyses, assumptions for data distribution will be assessed, and normalizing transformations of the data or nonparametric analysis will be performed as necessary. The mean and standard deviation will be reported for normally distributed continuous variables, and the median and interquartile ranges will be reported for non-normally distributed continuous variables. Given this is an RCT, we anticipate balanced baseline characteristics. To evaluate this, we will calculate effect sizes for measures of central tendency (Cohen d, Cramer v) across groups. For non-parametric

variables, effect sizes defined for the Mann-Whitney U will be calculated to produce r. For frequency counts and percentages the rate ratio will be evaluated to calculate the effect size. Variables that have more than a small effect size (d > 0.2, v > 0.01, or r > 0.1, categorical effect size>1.2) indicate potential imbalances in baseline characteristics between groups. These variables will be included in sensitivity analyses after the primary ITT analyses are performed or included as covariates using multivariable models.

Retention, adherence, and missing data will be compared across groups. High levels of missing data are not anticipated given the nature of the study. If the missing data are determined to be related to the outcome (not missing at random) or related to group or a covariate (missing at random), we will explore the impact of these biases in sensitivity analyses after the primary ITT analyses using multiple imputation processes. Our primary approach to imputing missing data is the Markov Chain Monte Carlo (MCMC) simulation. Statistical Analysis Software (SAS) procedures will be used.

The primary analysis seeks to address if there are differences in length of weaning between: 1) REDvent-acute compared to usual care acute, 2) REDvent-weaning compared to usual care-weaning, and 3) REDvent-acute and weaning (combined) compared to usual care acute and weaning (combined). Analyses of these aims will follow the ITT principle. The primary analyses will compare median weaning duration between groups using a Mann-Whitney U test, or a t-test with transformation as necessary. The effect size (r) will also be computed to assess the magnitude of treatment effect. If imbalances in baseline characteristics are found between or across randomized treatment groups, a Cox proportional hazard model will be performed to adjust for covariates. The estimates (mean, median, or hazard ratio) and the associated 95% confidence interval, as well as the p-values, will be presented for interpretation.

Power analysis: For the primary outcome (weaning duration), a 1-day change in length of weaning is considered clinically significant. It is anticipated that up to 20% of patients may not achieve the primary outcome (successful passage of an SBT or extubation due to death or dropout); these patients will not be included in the primary outcome analysis but will be included in secondary outcomes. We are targeting an overall sample size of 300 patients, with a minimum of 240 patients (120 per arm) available for analysis of the primary outcome. Using the planned statistical tests above, this sample size would be able to detect a ≥ 1-day change in weaning duration with a two-sided alpha of 0.05 and power of 0.9, or a relative hazard ratio of 1.5 (ratio between control/intervention group) with a power of 0.9 or a hazard ratio of 1.4 with a power of 0.8. Patients who fail the initial SBT will undergo the weaning phase randomization. From our pilot data, approximately 25% of patients exposed to the intervention passed the initial SBT. Anticipating 180 patients (90 per arm) will receive weaning phase interventions, there will be adequate power to detect a ≥ 1 day change in the length of the weaning phase, or a hazard ratio of 1.5 with an alpha of 0.05 and power of 0.8 in the weaning phase.

The analytic approach for secondary aims and outcomes such as mortality and ventilator free days will follow those described above. For categorical data, a $\chi 2$ or Fisher's exact test will be used to compare difference between groups. Logistic regression will be used to assess binary outcomes, and a multinomial/ordinal logistic regression will be used for categorical outcomes (> 2 categories) while adjusting for covariates. To assess the association between 2 continuous variables, a Pearson or Spearman correlation will be used, and analysis of covariance (ANCOVA) will be used to adjust for covariates. Generalized Estimating Equations (GEE) or mixed effect models will be used when necessary to analyze repeated measures. Because of the physiologic nature of the study with a Phase II design,

multiple comparisons adjustment is not planned for secondary outcomes. Analyses will be performed using the appropriate recent version of the SAS statistical software (SAS Institute Inc., Cary, NC).

In order to increase precision around the effect estimates for the primary and secondary aims and to reflect the stratified sampling, all analyses are adjusted for block randomization variables.[3] For acute phase these are age group (infant, child, and adolescent) and whether or not the subject was immunocompromised. For the weaning phase this is acute phase randomization grouping and age group. In addition, variables thought to be potential confounders on the relationship between intervention and outcome with large differences between groups (standardized effect sizes as detailed above) will also be included in all adjusted analyses. Unadjusted analyses will be presented to summarize data; all primary and secondary outcomes will present adjusted analyses controlling for age category, immunosuppression and imbalanced baseline variables. Potential confounders will be assessed for multicollinearity and if present, the confounder with the highest biological plausibility to impact the effect of the intervention on the outcome will be selected for inclusion as a model covariate.

Model assumptions and fit for multiple linear regression (with or without log transformation) will be assessed visually for normality of residuals as well as variance inflation factor and difference in betas (DFBETAS) for influential points. Model fit for binary multiple logistic regression will be assessed with Pearson Chi-square and deviance. Firth's penalized likelihood method will be used in subgroup analyses when event rates are small to reduce bias in the parameter estimates.[4] When using negative binomial regression, model fit will be assessed for over and underdispersion with the scaled Pearson Chi-square/deviance and influential points assessed as previously described. The proportional hazards assumption will be assessed when using Cox proportional hazards modeling using graphical approaches ("log-log" figures and Kaplan-Meier curves) for each covariate. Repeated measures analysis for ventilator settings, lung mechanics, and respiratory measures will be assessed with linear mixed models and generalized linear mixed models that include a variable for time from randomization to control for correlation of values within each patient using the first-order autoregressive structure. The robust sandwich estimators for standard errors will be used to reduce heteroscedasticity when appropriate.

A detailed outline of each outcome's analysis approach to control for blocking variables and confounders is given in the Table 1. Pre-specified comparisons of interest are REDvent acute vs. usual care acute, REDvent weaning vs. usual care weaning, and four group combination: 1) REDVent acute + REDvent weaning 2) REDvent acute + usual care weaning 3) Usual care acute + usual care weaning 4) usual care acute + REDvent weaning. The four group combinations comparisons are exploratory and will only be considered if there are noted differences between both acute and weaning phase interventions.

October 2019- new milestone accrual plan

After the first 75 patients were enrolled in the study a new milestone accrual plan was created to account for the increase in the percentage of patients meeting the primary outcome. Previously, it was assumed 20% of patients would not meet the outcome, however, data after 75 patients revealed this was 13% and the total sample size requirement was adjusted down from 300 to 276 patients. The number of patients targeted per group to meet the primary outcome was unchanged, at 120 per group. This updated milestone accrual plan was reviewed and accepted by the NLHBI and DSMB.

January 2023 - Change in primary analysis for length of weaning

Blinded, non-inferential summary statistics and distributions were assessed for the length of weaning outcome by the primary statistician as part of the data cleaning process. It was revealed that length of weaning might not be optimally analyzed as a continuous variable because SBTs were conducted once a day, with most patients passing their SBT within the first three days. In addition, enrollment had been affected by the COVID-19 pandemic and a new milestone accrual plan was requested by the NHLBI. As the observed distribution appeared more count-like, the primary analysis model was changed to Poisson or Negative binomial regression to better fit the data and satisfy assumptions. This decision was made by the senior biostatistician who was blinded to the randomization groups.

The sample size was re-estimated based on a minimum detectable difference for a reduction in the number of weaning days in the REDvent-acute vs. usual care-acute group using negative binomial regression. This yielded a minimal sample size of 230 patients to detect a reduction of 0.36 to 0.75 days when usual care had an average number of weaning days between 1 and 4, respectively with a power of 80%. This estimate of 230 patients accounted for the 13% loss in those meeting the primary outcome. This updated sample size estimate was reviewed and accepted by the NHLBI and DSMB. Based on this, the milestone accrual plan was revised, and enrollment was planned to continue through March 2024 with a target sample size between 230-276.

May 2024 – Change in primary analysis for length of weaning and PiMax

Data collection and cleaning were completed at the end of May 2024. During the analysis phase, the unblinded statistician checked assumptions and diagnostics for the primary analysis using negative binomial for outcome length of weaning. During this process two influential outliers were discovered in the usual care group who had attempted a SBT but never had a successful SBT; these two patients remained on IMV at 90 days. These patients were eligible for the primary outcome analysis, so were not removed from analysis, however, they were very influential and biased the estimate for the difference in length of weaning days.

Three sensitivity analyses were proposed to address these outliers: 1) truncate length of weaning to 28 days (instead of 90) using log transformed multiple linear regression, 2) categorize length of weaning into clinically relevant groups and conduct a proportional odds logistic regression model, and 3) revert back to the Cox proportional hazards model and censor patients at 28 days. Each of these sensitivity analyses adjusted for the same blocking variables and confounders used in the pre-specified negative binomial regression model. The truncation approaches failed because the assumptions of both log transformed linear regression and time to event analysis were not met. Residuals were highly skewed in linear regression even after truncation and log-transformation. The PH assumption was violated when adjusting for blocking variables when running the Cox proportional hazards model. The proportional odds logistic regression model categorized length of weaning as follows <0.5 day, 0.5 to <1.5, 1.5 to <2.5, 2.5 to <4.5, 4.5 to <7.5, and ≥7.5 days. Patients who had a long length of weaning were therefore in the highest category of ≥7.5 days. The proportional odds model uses a rank-based non-parametric approach to model the probability of a lower ordered value, or in our case, a lower length of weaning which can be thought of a latent continuous variable bucketed into meaningful cutoffs. This model also allowed interpretation of the intervention effect on length of weaning in a stepwise manner, which is more representative of what happens clinically with daily SBTs and does not require that the difference between categories be equal. The proportional odds assumption for each independent variable was assessed graphically using their empirical cumulative logits and overall with the score Chi-square test.[5-7]

Because the pre-specified plan was to use a negative binomial model, those findings have been presented in the main results, but because the model does not appropriately fit the data due to the highly influential outliers, the conclusions and abstract results reflect the more appropriate proportional odds model. This model was agreed upon by the study statistical team and DSMB statisticians in June 2024 at the final DSMB meeting.

PiMax was planned to be modeled with linear regression, with truncation of values >100. In the analysis, no transformation could satisfy the assumptions of linear regression, with poor model diagnostics and non-normality of residuals. PiMax was therefore modeled with the proportional odds model given the non-parametric nature of the data. No specific categories were created for PiMax, but instead it was treated as a rank-based variable with comparisons of ranks between groups, adjusting for blocking variables and confounders (oxygenation index). The model allowed us to compare the odds of a higher PiMax ranking for the REDvent vs. usual care groups. Table 1 has been revised and now presents the description of all outcome variables, initial planned analyses, and modifications to initial proposed analyses and the timing of those changes. In addition, since all outcomes are presented as adjusted analyses, Table 2 details the four main modeling approaches used in these analyses, and interpretation of the model intervention parameter estimates.

References

1. Khemani RG, Smith LS, Zimmerman JJ, et al. Pediatric Acute Respiratory Distress Syndrome: Definition, Incidence, and Epidemiology: Proceedings From the Pediatric Acute Lung Injury Consensus Conference. *Pediatric Critical Care Medicine*. Jun 01 2015;16(5_suppl):S23-S40. doi:10.1097/PCC.0000000000000432
2. Khemani RG, Hotz JC, Klein MJ, et al. A Phase II randomized controlled trial for lung and diaphragm protective ventilation (Real-time Effort Driven VENTilator management). *Contemp Clin Trials*. Jan 2020;88:105893. doi:10.1016/j.cct.2019.105893
3. Holmberg MJ, Andersen LW. Adjustment for Baseline Characteristics in Randomized Clinical Trials. *JAMA*. Dec 06 2022;328(21):2155-2156. doi:10.1001/jama.2022.21506
4. Firth D. Bias Reduction of Maximum Likelihood Estimates. Biometrika 1993. p. 27-38.
5. Koch G, Amara I, Singer J. *A Two-Stage Procedure for the Analysis of Ordinal Categorical Data*. Biostatistics: Statistics in Biomedical, Public Health, and Environmental Science. 1985.
6. Harrell F. Resources for Ordinal Regression Models. Statistical Thinking 2023.
7. Harrell F. Equivalence of Wilcoxon Statistic and Proportional Odds Model. Statistical Thinking 2022.

Table 1: Detailed analytic plan for each outcome variable, including any changes which were made to the analytic approach and when those changes were made.

Variable	Description	Imputation & Exclusion	Initial Analytic Approach	Misc. Notes	Changes to Analytic Plan
Length of Weaning (primary outcome)	Time from first attempted SBT until successful SBT passage or extubation, whichever comes first. Successful extubation is removal without re-intubation or death for at least 24 hours.	Patients no longer undergo SBTs after the 28 day intervention but they will be clinically assessed for extubation and will be followed up to 90 days. If a patient remains intubated at 90 days their length of weaning becomes 90 days. Patients who never attempt an SBT are excluded. Patients who attempt an SBT but never pass an SBT and die within 24 hours of extubation are excluded.	Cox proportional hazards model controlling for blocking variables and confounders. Proportional hazards assumption will be assessed.	Expect 20% exclusion rate for this outcome. Patients who pass the SBT will have a length of weaning of around 2 hours (SBT duration). Length of weaning will be expressed in days and will take on values of 0.0833 (2 hours) to 90 days. The adjusted hazard ratio and 95% C.I. will be presented for REDvent vs. usual care.	**October 2019-** Expected exclusion rate adjusted to 13% **January 2023-** Revised analytic plan to reflect data distribution as count variable with SBTs daily. Over-dispersed for Poisson so plan to use negative binomial model. **May 2024-** During analysis, 2 patients with very long length of weaning found to have large effect on adjusted Incidence Rate Ratio for negative binomial model. Revised to a non-parametric Proportional Odds Logistic Regression.
IMV duration in survivors (Secondary Outcome)	Time from start of index intubation to successful liberation. Successful liberation is defined as no death or re-intubation within 24 hours of extubation.	Patients who are intubated past 90 days of index intubation are imputed as 90 days. Patients who die within 24 hours of extubation are excluded.	Log transformed multiple linear regression controlling for blocking variables and confounders.	IMV duration will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.	None

Received NIV after extubation (secondary outcome)	Yes/no binary variable for receiving oro-mask CPAP or Bi-level ventilation after successful extubation. Successful extubation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of IMV or remain on IMV at 90 days are not included.	Multivariable logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for receiving NIV post-extubation with 95% C.I. for REDvent vs. Usual care will be presented.	**January 2024** added as necessary component to interpret length of NIV after extubation more appropriately.
NIV duration after extubation (secondary outcome)	Duration of non-invasive ventilation after extubation is defined as the number of days and hours that the patient is on oro-mask CPAP or Bi-level ventilation after successful extubation. Successful extubation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of IMV or who never receive NIV post-extubation are excluded. Patients who remain on NIV at 90 days will have 90 days imputed. Patients who die while on NIV will have their death date as end of NIV duration	Log transformed multiple linear regression controlling for blocking variables and confounders.	NIV duration will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.	None

Received Non-invasive respiratory support (NRS) post-extubation (secondary outcome)	Yes/no binary variable for receiving NRS after successful extubation. NRS includes: High Flow Nasal Cannula (HFNC) or nasal-only modes of non-invasive ventilation (CPAP or Nasal IMV or BiPAP Successful extubation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of IMV or remain on IMV at 90 days are not included.	Multivariable logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for receiving NRS post-extubation with 95% C.I. for REDvent vs. Usual care will be presented.	**January 2024** added as necessary component to interpret length of NRS after extubation more appropriately.
NRS duration after extubation (secondary outcome)	Duration of NRS after extubation is defined as the number of days and hours that the patient is on NRS after successful liberation. End of NRS is defined as absent continuously for at least 24 hours. Successful extubation is defined as no death or re-intubation within 24 hours of extubation.	Patients who die within 24 hours of IMV or who never receive NRS post-extubation are excluded. Patients who remain on NRS at 90 days will have 90 days imputed. Patients who die while on NRS will have their death date as end of NIV duration.	Log transformed multiple linear regression controlling for blocking variables and confounders.	NRS duration will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.	None
Re-intubation within 48 hours of extubation (secondary outcome)	Binary variable for re-insertion of endotracheal tube within 48 hours of initial extubation.	Patients who remain on IMV for their index intubation or die within 48 hours of index extubation are excluded.	Multivariable logistic regression for the event re-intubation = yes. Adjusting for blocking variables and confounders.	Binary yes/no variable. Adjusted odds ratio for re-intubation with 95% C.I. for REDvent vs. Usual care will be presented.	None

28-day ventilator free days (secondary outcome)	Number of days between index intubation and 28-days post-index intubation in which patient is alive and not on IMV.	No exclusions.	Competing risks regression adjusting for blocking variables and confounders. Censoring indicators: 0=those who do not die but are not extubated within 28 days 1=those that have successful liberation within 28-days 2=those that die within 28-days	If patient is re-intubated within 24 hours of extubation the time in between intubations is not counted towards VFDs. If a patient in extubated for >24 hours and then subsequently re-intubated they get credit for those days without IMV. Values are 0 to 28 days. Adjusted hazard ratio and 95% C.I. will be presented.	**January 2023**- Updated competing risk regression to negative binomial model to align with analysis plan for primary outcome and because the variable is a count of the number of days. Negative binomial also treats death and those on IMV for 28 days as the same (zero VFDs). This aligns with the hypothesis that the influence of the treatment variable is on the days of ventilation, and we do not expect any treatment effect for death.
PiMax on day of 1st SBT (secondary outcome)	PiMax value on the day the 1st SBT was performed.	Patient with values >100 will be truncated to 100. Exclude patients who never attempted an SBT in the 28-days study period.	Multiple linear regression adjusting for blocking variables and confounders.	Adjusted mean difference with 95% C.I. will be presented for REDvent vs. Usual care.	**June 2024-** unable to satisfy assumptions of linear regression with any transformation. Modeled as non-parametric proportional odds logistic regression.

PiMax on day of extubation (secondary outcome)	PiMax value on the day of extubation. Restricted to those who met primary outcome (SBT passage or successful extubation).	Patient with values >100 will be truncated to 100. Exclude patients who died within 24 hours of extubation or remained intubated at 90 days.	Multiple linear regression adjusting for blocking variables and confounders.	Adjusted mean difference with 95% C.I. will be presented for REDvent vs. Usual care.	**June 2024-** unable to satisfy assumptions of linear regression with any transformation. Modeled as non-parametric proportional odds logistic regression.
ICU mortality (secondary outcome)	Yes/no binary variable for did patient die in the ICU.	No exclusions	Multivariable logistic regression controlling for blocking variables and confounders.	Adjusted odds ratios for death in REDvent vs. Usual care with 95% C.I. will be presented	None
90-day mortality (secondary outcome)	Yes/no binary variable for did patient die in the hospital and within 90 days.	No exclusions	Multivariable logistic regression controlling for blocking variables and confounders.	Adjusted odds ratios for death in REDvent vs. Usual care with 95% C.I. will be presented.	None
Time to 1st SBT (secondary outcome)	Number of days from start of index intubation to either first SBT or successful extubation, whichever came first. Successful extubation defined as no death or re-intubation within 24 hours of extubation.	Patients who never received an SBT and were successfully extubated after 31 days (time from start of IMV to end of protocol) were truncated to 31 days.	Log transformed multiple linear regression controlling for blocking variables and confounders.	Time will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.	None
Time to 1st SBT passage (secondary outcome)	Number of days from start of index intubation to either first SBT passage or successful extubation, whichever came first. Successful extubation defined as no death or re-intubation within 24 hours of extubation.	Patients who never passed an SBT and were successfully extubated after 31 days (time from start of IMV to end of protocol) were truncated to 31 days.	Log transformed multiple linear regression controlling for blocking variables and confounders.	Time will be expressed in days. Adjusted mean difference and 95% C.I. for REDvent vs. usual care will be back transformed with exp(estimate) and interpreted as a relative change.	None

Decline in PCPC from baseline to ICU discharge	Change in PCPC defined as baseline minus ICU discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in PCPC).	Patients who did not survive to ICU discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in PCPC from baseline to ICU discharge with 95% C.I. for REDvent vs. usual care will be presented.	**April 2024**- Evaluated possibility of using continuous variable but was highly skewed with little variability so it was dichotomized.
Decline in POPC from baseline to ICU discharge	Change in POPC defined as baseline minus ICU discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in POPC).	Patients who did not survive to ICU discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in POPC from baseline to ICU discharge with 95% C.I. for REDvent vs. usual care will be presented.	**April 2024**- Evaluated possibility of using continuous variable but was highly skewed with little variability so it was dichotomized.
Improvement in FSS from baseline to ICU discharge	Change in FSS defined as baseline minus ICU discharge value. This change was grouped into ordinal categories: no change/improvement (change of ≥0), 1-2 point decline, and >2 point decline.	Patients who did not survive to ICU discharge were excluded.	Proportional odds logistic regression controlling for blocking variables and confounders. Ordered on the probability towards improvement.	Adjusted odds for the improvement (change going towards positive) with 95% C.I. for REDvent vs. usual care.	**April 2024**- Evaluated possibility of using continuous variable but was highly skewed with little variability so it was grouped into categories.
Decline in PCPC from baseline to hospital discharge	Change in PCPC defined as baseline minus hospital discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in PCPC).	Patients who did not survive to hospital discharge (censored at 90 days) discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in PCPC from baseline to hospital discharge with 95% C.I. for REDvent vs. usual care will be presented.	**April 2024**- Evaluated possibility of using continuous variable but was highly skewed with little variability so it was dichotomized.

Decline in POPC from baseline to hospital discharge	Change in POPC defined as baseline minus hospital discharge value. This change was dichotomized into a change of ≥0 (no change or increased) vs. change of <0 (decline in POPC).	Patients who did not survive to hospital discharge (censored at 90 days) discharge were excluded.	Multiple logistic regression controlling for blocking variables and confounders.	Adjusted odds ratio for the outcome decline in POPC from baseline to hospital discharge with 95% C.I. for REDvent vs. usual care will be presented.	**April 2024**- Evaluated possibility of using continuous variable but was highly skewed with little variability so it was dichotomized.
Improvement in FSS from baseline to hospital discharge	Change in FSS defined as baseline minus hospital discharge value. This change was grouped into ordinal categories: no change/improvement (change of ≥0), 1-2 point decline, and >2 point decline.	Patients who did not survive to hospital discharge (censored at 90 days) discharge were excluded.	Proportional odds logistic regression controlling for blocking variables and confounders. Ordered on the probability towards improvement.	Adjusted odds for the improvement in FSS (change going towards positive) with 95% C.I. for REDvent vs. usual care.	**April 2024**- Evaluated possibility of using continuous variable but was highly skewed with little variability so it was grouped into categories.

Table 2: Outcome variables, modelling approaches, and interpretation of models

Model Name	Outcomes	Methods	Interpretation
Negative Binomial Model	Length of Weaning (initial plan- revised); Ventilator Free Days	Count variables with adjustment for blocking variables and confounders. Model assumptions and methods to evaluate model fit: Pearson Chi-square/deviance for over and under-dispersion, DFBETAS and variance inflation factor.	Raw estimate and 95% C.I. for REDvent vs. usual care exponentiated to obtain Incidence Rate Ratio with 95% CI. Patients in the REDvent group had a decreased rate of length of weaning by x% compared to usual care after adjusting for blocking variables and confounders.
Logistic regression	First SBT success; re-intubation, NIV/NRS use post extubation; ICU and 90 day mortality; decline in PCPC or POPC;	Binary outcomes with adjustment for blocking variables and confounders. Firth's penalized likelihood method was used in subgroup analyses when event rates were small to reduce bias in the parameter estimates.	Odds Ratio with 95% CI. Patients in the REDvent group had higher odds (if OR>1) of achieving the outcome than usual care after adjustment for blocking and confounding variables.
Linear Regression	Days to first SBT and SBT passage; length of IMV; length of NRS/NIV post extubation; ICU Length of Stay; Hospital Length of Stay	Continuous outcomes with adjustment for blocking variables and confounders. Residuals evaluated for normality, homoscedasticity. DFBETAS and variance inflation factors assessed for influence of observations. Log transformation of the outcome used when appropriate.	Relative change (slope) of regression coefficient with 95% confidence interval. Patients in the REDvent group had a reduction in length of IMV by x compared to usual care. If log transformation used the estimate for the adjusted mean difference and 95% C.I. on the log scale were exponentiated. Outcome decreased by x% in the REDvent group compared to usual care.
Proportional Odds Logistic Regression	Length of weaning, PiMax variables, Functional Status Scale	Proportional odds assumption checked for each covariate with empirical cumulative logit figures for parallel slopes, also overall using the score Chi-square test (null hypothesis is that there is no evidence of non-proportional odds).	Odds were ordered appropriately depending on the outcome (length of weaning= odds lower length of weaning, PiMax= odds of higher PiMax, FSS= odds of higher change in PiMax). The odds of decreased length of weaning in the REDvent group vs. usual care, while controlling for blocking variables and confounders.

Summary of Changes and timeline for REDvent SAP.

Full details are provided in the final SAP with the rationale for changes in the text, and a summary of the changes in the table.

Date	Summary of changes
November 2017	Initial protocol approved and enrollment began. Basic SAP detailed in initial study protocol, with ongoing work with statistical team to develop each outcome and analytic approach in fully detailed SAP.
Fall 2019	Full detailed SAP developed with definitions for all outcome variables and detailed analytic plan for each outcome variable.
October 2019	Target Sample size reduced from 300 to 276 based on number of patients meeting primary outcome
January 2023	Analytic plan for primary outcome variable changed to align with count like distribution of data. Power analysis reconsidered, minimum sample size revised to 230, with target between 230-276.
January 2024	Mock tables finalized with all specified outcomes. Added use of NIV and NRS as count variables in addition to the duration variables to aid interpretation of duration.
April/May 2024	Primary outcome found to be highly influenced by few observations with count-model approach (negative binomial). Revised to proportional odds approach. Consideration of modeling FSS/POPC/PCPC as continuous but data too sparse and stuck with ordinal/dichotomous.
June 2024	PiMax variables did not satisfy assumptions of linear regression with transformation- changed to proportional odds regression. Clarification and articulation of methods used to assess for co-linearity, assessment of model assumptions, and interpretation of output of each of the models.