Ventilator weaning in patients with prolonged mechanical ventilation

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1.0 PROTOCOL SUMMARY

Title:

Mechanical ventilator weaning in chronically ventilated patients

Objective:

To compare the success rate of two protocolized weaning programs in patients requiring prolonged mechanical ventilation (PMV). We will compare Pressure support ventilation (PSV) weaning protocol to the Therapist-implemented patient specific (TIPS) weaning protocol.

Patient population:

PMV patients admitted to Barlow respiratory Hospital (BRH), a long-term acute care hospital (LTACH) in Los Angeles, California, for ventilator weaning.

Protocol design:

Eligible patients will be randomly assigned to one of two ventilator weaning protocol paths: 1.PSV path. This protocol uses a daily schedule of gradual reduction of PSV combined with daily rests on mandatory ventilator mode. The PSV path is at least 14 days long. 2. TIPS path. This protocol uses a daily schedule of SIMV ventilation with gradual reduction of mandatory ventilator support followed by PSV weaning. The TIPS path is at least 21 days long.

Primary outcome:

Weaned from mechanical ventilation (MV) by 30 days from LTACH admission.

Time of completion:

Patients who can disconnect from MV for 3 consecutive days or have their tracheostomy decannulated will be considered weaned (“success”) and will have completed the protocol. Patient who cannot complete the ventilator weaning by 30 days will fail the protocol and complete the study.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Mechanical ventilation (MV) is a life-saving technology supporting approximately 300,000 hospitalized patients in the USA annually1. While initially designed for short-term care, it is estimated that 6% of all MV patient will require PMV beyond 21 days2. PMV is associated with increased mortality and the risk of death is approximately 55% in one year3,4. Data collected in Massachusetts suggest that the number of chronically ventilated patients continues to grow and may affect 7.6/100.000 people in the USA5. Many PMV patients are cared for in long-term acute care hospitals (LTACH)4, which specialize in ventilator weaning (weaning) of tracheostomized patients. Tracheostomies provide safe long-term artificial airway opening which allows slower weaning6. The daily cost of care for PMV patient in the LTACH is greater than $10,000 7,8. Despite the specialized care, only about 54% of patients are liberated from the ventilator9.While improving weaning success in the PMV population has critical clinical and societal implications, it is not known what is the best weaning modality for these patients3,10. Available literature has focused on patients with good tolerance for spontaneous breathing trials (SBT), but this likely represents only about 20% of all PMV patients3. In PMV patients, protocolized ventilator weaning using pressure support-based ventilator weaning have been recommended6 but it remains unclear what protocol is the most beneficial.

The overall objective of this study is to establish the weaning success rate in patients requiring PMV, who cannot tolerate SBT. We will compare two established weaning protocols: A. pressure support ventilation (PSV) weaning with daily rest periods11 and B. the Therapist-implemented patient specific (TIPS) weaning, which combines synchronized intermittent mandatory ventilation (SIMV) and PSV weaning10.

Our central hypotheses are 1. weaning success in PMV patients is related to preserved hemodynamical and respiratory stability during the weaning process rather than the method of ventilator weaning (the criteria for hemodynamical and respiratory stability is listed in Section 5.3) and 2. PSV weaning protocol path is non-inferior to TIPS weaning protocol path.

To test the central hypotheses and to attain the objective of this project we will pursue the following *Specific Aims*:

* Scientific aim 1. Compare the success rate of PSV and TIPS weaning paths in a randomized, non-blinded clinical trial. At the time of completion the study will be able to answer the question if the PSV path is non-inferior to the TIPS path in ventilator weaning.
* Scientific aim 2. Compare the number of tracheotomy decannulations between the two ventilator weaning paths during hospitalization. Tracheostomy decannulation is an established marker of the resolution of severe hypoxemic respiratory failure12. At the completion of the study we will be able assess if one or other weaning path is superior in providing sustained resolution of the respiratory failure.
* Scientific aim 3. In this exploratory aim we will evaluate if time to speaking valve use, intensive care unit transfers, hospital length of stay, in-hospital and 90-day mortality and change in the Functional Status Score for the Intensive Care Unit (FSS-ICU) defers between the two weaning protocol paths.

3.0 BACKGROUND AND RATIONALE

Background

PMV is an important public health problem affecting 18,000 to 39,000 people in the USA2,13. PMV is defined by patients requiring at least 6 hours of positive pressure MV beyond 21 days2, but it encompasses a wide variety of disease severity with significant outcome differences. Following acute care hospitalization patients with continued MV need are often transferred to LTACHs for continued ventilator weaning14 and they represent the most severely ill PMV patients. The most common factors that challenge PMV weaning in the LTACH are: 1. poor baseline functional status, 2. severe course of underlying acute illness, 3. hemodynamic instability 4. variable expertise in mechanical ventilator weaning by treatment team and 5. the need for complex long term care. Most PMV patients in the LTACH have a tracheostomy tube for chronic mechanical ventilation which further complicates weaning15. Because of the complexity of care, outcomes of ventilator weaning in the LTACH are poor and most patients die within 1 year4,9. PMV weaning success is often measured by discontinuation of mechanical ventilation, but tracheostomy decannulation is probably the more important event, which signifies the resolution of severe respiratory failure. It is estimated that only about 35-59% of PMV patients are decannulated at the LTACH, but this is based on small observational studies and the true success rate of decannulation is not known16,17.

Significance

While MV weaning has been extensively studied in acute care hospital intensive care units11 there is lack of strong scientific evidence how to apply this knowledge to the PMV patients. Jubran et al. studied PSV weaning in LTACH patients and compared their success rate to unassisted breathing trials. This study focused on patients who were able to sustain unassisted breathing measured with spontaneous breathing trial (SBT).3 Unfortunately, the majority of PMV patients who arrive for ventilator weaning to the LTACH cannot sustain unassisted breaths and fail SBT. In clinical practice at our institution10 and elsewhere,9 these patients participate in TIPS or PSV weaning programs. Other ventilator weaning modalities have been considered largely experimental due to technical and safety concerns in this patient population6. Despite the common use of these ventilator weaning programs, they have not been compared for weaning and tracheostomy decannulation success. Currently, it is purely the clinician’s decision which method is chosen. We believe by studying the success of the ventilator programs in a clinical trial we will be able to learn about their benefits and also critically evaluate the challenges that hinder the overall ventilator weaning success.

Brief description of weaning programs

1. TIPS weaning. This ventilator weaning program starts with SIMV ventilation with a set respiratory rate of 10 to allow close evaluation of hemodynamic stability. The mandatory respiratory rate is then reduced daily for 4 days to allow assessment of spontaneous rate. If the patient remains hemodynamically stable, the weaning program continues with PSV weaning performed for 5 days while reducing the pressure support daily. If a patient is able to able to tolerate low pressure support, the patient is disconnected from the ventilator daily for increasing periods of time. The minimum length of the TIPS weaning program is 21 days. While this program is longer, in theory, it allows the patient more sustained stability when off the ventilator. The program is detailed in Table 2.
2. PSV weaning. In the PSV weaning program, patients receive PSV ventilation for 12 hours daily then rest on the original mandatory ventilator settings. The pressure support is reduced daily for 6 consecutive days. If a patient is able to tolerate low pressure support, the patient is disconnected from the ventilator daily for increasing periods of time. The minimum length of the PSV weaning program is 14 days. This program follows the philosophy that daily aggressive weaning combined with nighttime rest results in sustained ventilator-free time. The program is detailed in Table 3.

Both protocols end if the patient is able to tolerate at least 72 hours of disconnect from the ventilator.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design:

To study the non-inferiority of the PSV path compared to the TIPS path in ventilator weaning, consented patients will be randomized in two groups after admission to BRH. Both groups will undergo a daily weaning protocol performed by a respiratory therapist. The program allows daily assessment for respiratory and hemodynamic function.

To achieve our primary aim we will assess the success rate of MV weaning rate in both groups daily. Weaning failure will be defined as hemodynamic or respiratory instability, which would prevent them with continuing with the weaning program.

To achieve our secondary aim, we will compare the in hospital tracheostomy decannulation rate between the two ventilator weaning groups.

To achieve our third aim, we will collect demographic, clinical, and hospital information. We will extract pre-admission data from available short-stay acute care hospitals (STACH) notes and collect data prospectively from the BRH electronic medical records (EMR). The list of collected parameters is shown in Table 4 in Section 7. The data will be used to generate hospital outcomes which will be compared between the two groups of patients. The list of secondary outcomes is shown in Table 1. These hospital outcomes have been previously used in clinical studies to assess ventilator weaning success4,18.

Table 1. List of hospital outcomes

|  |
| --- |
| 1. time to speaking valve use (days) |
| 1. intensive care unit transfer (yes/no) |
| 1. hospital length of stay (LOS, days) |
| 1. in-patient mortality (yes/no) |
| 1. 90-day mortality (yes/no) |
| 1. Functional Status Score for the Intensive Care Unit (FSS-ICU) score on admission and at discharge |

4.2 Intervention

**A.** **Study protocol** (Figure 1):

1. Patients will be considered for enrollment in the study within 72 hours of admission to BRH.
2. All BRH patients requiring positive pressure invasive mechanical ventilation (MV) undergo spontaneous breathing trial (SBT, pressure support ventilation (PS) 5cmH2O with 5cmH2O of positive end expiratory pressure, PEEP) per hospital policy within 24 hours of admission. If they pass the SBT, they will be eligible for cool aerosol trials (humidified, oxygenated air without positive pressure mechanical ventilation). These patients will be excluded from the study, except if they fail to tolerate cool aerosol within 24 hours and continue require continuous positive pressure ventilation. These patients can be considered for study enrollment the next day.
3. In the rare instance that a patient has an endotracheal tube on admission to BRH and continued MV is needed, a date for tracheostomy will be set. Patients following tracheostomy placement can participate in the study.
4. Parameters to preclude study enrollment are listed in the Exclusion criteria (Section 5.2).
5. All patients are admitted to monitored beds at BRH. Vital signs (heart rate, oxygen saturation and lead 2 electrocardiogram, respiratory rate and ventilator compliance) are continuously monitored. Blood pressure is measured every 6 hours. Hemodynamic and respiratory stability is assessed daily on these parameters by the nurse and the respiratory therapist. The list of hemodynamic and respiratory parameters with values that represent instability are listed in section 5.3.
6. On D0, if a patient is stable and required continued MV, the study team will approach the patient and/or the patient’s designated power of attorney (DPOA) for informed consent.
7. On D0, consented patients, now referred to as subjects, will be randomized to participate in the fast or slow path of ventilator weaning.
8. On D1, weaning starts. Hemodynamic and respiratory instability is assessed every day as in point 5. Unstable subjects will complete the study, but will be followed throughout their hospitalization at BRH for hospital outcomes. Further weaning can be attempted after stabilization outside of the study protocol per the hospital weaning program.
9. If a subject fails to progress to the next step of ventilator weaning, the same step can be repeated on 3 consecutive days and if possible can continue with the designated weaning path.
10. If a subject cannot progress beyond the same step after 3 consecutive days in the PSV path, he/she can continue with TIPS path step 1.
11. If a subject cannot progress beyond the same step after 3 consecutive days in the TIPS path, he/she will complete the study.
12. Both paths will consist of a MV and a cool aerosol (CA) trial parts. The length of the TIPS path is a minimum 21 steps and 14 steps for the PSV path. These usually refer to days, but subjects may progress up to 3 steps a day. The details of both path are shown in the “ventilator paths” section.
13. When a subject is transitioned from MV to CA, arterial blood gas (ABG), will be collected after 2hrs CA to ensure adequate oxygenation and to avoid elevated carbon dioxide levels.
14. Following completion of the study all subjects will be assessed for tracheostomy decannulation by pulmonology, speech pathology and respiratory therapy.

Figure 1. Study protocol

**B. Ventilator paths**

1. TIPS path (Table 2). In the TIPS path, subjects will complete a 21 step protocol. MV weaning is done with synchronized intermittent mandatory ventilation (SIMV) mode for 24 hrs. Patients will transition to this mode on the D1 after completion of SBT. The initial ventilator setup is PS 20 cmH2O PEEP 5cmH2O set RR 10/min. During the first 4 steps the backup rate will be lowered gradually from 8/min to 4/min (Step 1-4). Subsequently the PS will be reduced from 20 to 10 by each step (Step 5-9). SBT is performed in Step 10 with 1 hr. CA trials. ABG is performed in Step 11 with 2 hrs. of CA to assure respiratory stability. Respiratory stability is defined by pH > 7.30, paO2>55mmHg, pCO2<60 mmHg or no more than 10 mmHg change from admission baseline pCO2. This protocol has a slower increase in CA time slowly to allow observation for stability and reaches 24 hours by Step 19. Patients rest on SIMV PS=10 cmH2O PEEP=5cmgH2O, RR=4 (Step 9) setting during CA trial. Subjects can progress up to 3 steps daily, if deemed able by the respiratory therapist. The protocol completes when the patients is able to complete 72 hours of continuous CA time.

Table 2. TIPS path protocol.

|  |
| --- |
| Step 1. Transition from admission ventilator mode to SIMV PS=20 cmH2O PEEP=5cmH2O, RR=10 |
| Step 2. SIMV PS=20 cmH2O PEEP=5cmH2O RR=8 |
| Step 3. SIMV PS=20 cmH2O PEEP=5cm H2O RR=6 |
| Step 4. SIMV PS=20 cmH2O PEEP=5cm H2O RR=4 |
| Step 5. SIMV PS=18 cmH2O PEEP=5cm H2O RR=4 |
| Step 6. SIMV PS=16 cmH2O PEEP=5cm H2O RR=4 |
| Step 7. SIMV PS=14 cmH2O PEEP=5cm H2O RR=4 |
| Step 8. SIMV PS=12 cmH2O PEEP=5cm H2O RR=4 |
| Step 9. SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 10. 1 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 11. 2 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4. ABG is performed |
| Step 12. 4 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 13. 6 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 14. 8 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 15. 10 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 16. 12 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 17. 16 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 18. 20 hrs. CA rest on SIMV PS=10 cmH2O PEEP=5cm H2O RR=4 |
| Step 19. 24 hrs. CA |
| Step 20. 48 hrs. CA |
| Step 21. 72 hrs. CA- protocol completed |

Abbreviations: SIMV=synchronized intermittent mandatory ventilation, RR= respiratory rate, PS=pressure support, PEEP=positive end expiratory pressure, SBT= spontaneous breathing trial, ABG arterial blood gas, CA=cool aerosol. The same abbreviations are used in the subsequent tables.

1. PSV path (Table 3). In the PSV path subjects will complete a 14 step protocol. In this protocol gradual decrease of PS is used for 10-12 hrs. a day. PS is decreased from 20cm H2O to 10cmH2O with 5cmH2O PEEP applied (Step 1-6). Every weaning step is followed by rest on the same ventilator setting the patient had on admission. Starting Step 7, subjects will undergo daily SBT (1 hour 5cmH2O PS with 5cmH2O PEEP). If they pass, they will progress to CA trials (Step 8-14). ABG is performed after 2 hours of CA time in Step 7 to assure respiratory stability. Respiratory stability is defined by pH > 7.30, paO2>55mmHg, pCO2<60 mmHg or no more than 10 mmHg change from admission baseline pCO2. CA time will be extended by 4 hrs. in Step 8 to 14. Patients rest on the admission ventilator settings. Subjects can progress up to 3 steps daily, if deemed able by the respiratory therapist. The protocol completes when the patients is able to complete 72 hrs. of continuous CA time.

Table 3. PSV path protocol

|  |
| --- |
| Step1. PS=20cmH2O PEEP=cm5H2O Backup rate=10\* |
| Step 2. PS=18 cmH2O PEEP=5 cmH2O Backup rate=10 |
| Step 3. PS=16 cmH2O PEEP=5 cmH2O Backup rate=10 |
| Step 4. PS=14 cmH2O PEEP=5 cmH2O Backup rate=10 |
| Step 5. PS=12 cmH2O PEEP=5 cmH2O Backup rate=10 |
| Step 6. PS=10 cmH2O PEEP=5 cmH2O Backup rate=10 |
| Step 7. SBT, if passes, oxygenated Cool aerosol (CA) for 4 hrs. (keep O2 sat>90%), Perform ABG after 2 hrs.# |
| Step 8. SBT, if passes, CA for 8 hrs. |
| Step 9. SBT, if passes, CA for 12 hrs. |
| Step 10. SBT, if passes, CA for 16 hrs. |
| Step 11. SBT, if passes, CA for 20 hrs. |
| Step 12. SBT, if passes, CA for 24 hrs. |
| Step 13. CA for 48hrs |
| Step 14. CA for 72 hrs-protocol completed |

\* weaning protocol is performed for 10-12 hrs. daily and subjects rest on admission ventilator settings. # subjects rest on admission ventilator settings during CA trial.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

The study population consist of patients admitted to BRH main site for ventilator weaning. BRH main site is a 50-bed LTACH in Los Angeles, which specializes in ventilator weaning. Patients arrive to BRH from short-term acute care hospitals (STACH) in the greater Los Angeles area. Patients who required prolonged continuous positive pressure ventilation (greater than 21 days, PMV) will be invited to participate in the study. The majority of patients arrive with tracheostomy already placed for continued mechanical ventilation, but patients who arrive with endotracheal tube (ETT) can also participate as long as we can arrange for tracheostomy before the start of the study.

5.1 Subject Inclusion Criteria

1. Patients requiring positive pressure mechanical ventilation for at least 21 days prior to BRH admission and
2. Have a secure tracheostomy.

5.2 Subject Exclusion Criteria

1. Inability to obtain informed consent from patient or DPOA
2. Incarcerated patients
3. Patients with less than 3 months of life expectancy
4. Patients requiring vasopressor medication to stabilize blood pressure on admission
5. Systolic blood pressure less than 90mmHg on admission
6. Pulse less than 50 or greater than 130 beats per minute or change by more than 20 from baseline on admission
7. Respiratory rate greater than 35/min
8. Oxygen saturation less than 90%
9. PEEP>5cmH2O
10. Lung tidal volume less than 250ml despite MV support
11. At least one previous admission to BRH with unsuccessful ventilator liberation attempt
12. Length of Stay (LOS) at BRH less than 24hours
13. Patients pass spontaneous breathing trial (SBT) on D1 and eligible for cool aerosol, except if they fail SBT on D2 and require continued MV

5.3 Daily assessment for hemodynamic and respiratory stability

1. Patients requiring vasopressor medication to stabilize blood pressure
2. Systolic blood pressure less than 90mmHg
3. Pulse less than 50 or greater than 130 beats per minute or change by more than 20 change from baseline
4. Respiratory rate greater than 35/min on current MV settings
5. Oxygen saturation less than 90%
6. Lung tidal volume less than 250ml despite MV support

6.0 RECRUITMENT PLAN

All patients with PMV will be considered for study participation regardless of age, gender, race or ethnicity as long as informed consent can be obtained. There is no incentive to participate other than the results of this study may help to move forward the field of PMV and will benefit patients in the future. There is a sizable incarcerated population at BRH. We will exclude incarcerated patients because they and their DPOA will not be able to consent freely to the study.

On D0, patients and/or their DPOA will be approached for informed consent. Our intent is to recruit 300 patients with 150 patients in each path of the study.

**7.0 STATISTICAL CONSIDERATIONS**

7.1 Statistics

Primary analyses will be by intent to treat, but a secondary per protocol analysis will also be performed.

For the primary outcome, the proportion who are successfully weaned before 30 days on their original protocol, we will use Fisher’ exact test to carry out a non-inferiority test with a non-inferiority difference (Δ) of 15%. That is, we will test the null hypothesis that outcome under the PSV protocol is 15% or more worse than the outcome under TIPS protocol versus the one sided alternative that the outcome under PSV protocol is less than 15% worse.

Fisher’s exact test will also be used for comparing other secondary binary outcomes including tracheostomy decannulation (secondary aim), ICU transfer, inpatient mortality and 90-day mortality), using the usual null hypothesis of no difference. Proportions, differences in proportions and their corresponding 95% confidence bounds will be reported.

We will use the Kaplan-Meir method to compute time to event curves for time dependent hospital outcomes such as time to speaking valve use, time to successful completion of the weaning and time to transition from PSV to TIPS path. We will use the log rank test to compute p-values for comparing time to event curves. We will report full descriptive statistics by group (minimum, quartiles, mean, SD) for continuous outcomes such as hospital length of stay and FSS-ICU change and use the non-parametric Wilcoxon rank sum test to compute p-values since these outcomes do not have a normal distribution.

For covariate comparisons and adjustment we will report descriptive statistics by protocol group for age, gender, race/ethnicity, and baseline heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, ventilator tidal volume (Vt) and FSS-ICU to demonstrate that the randomization was successful, as expected. If needed we will carry out covariate adjusted comparisons using inverse propensity score weighting to carry out the adjustment and report both adjusted and unadjusted results. The propensity score, if needed, will be estimated using logistic regression using the baseline covariates above as predictors.

While we do not expect substantial dropouts or missing data, if there are dropouts or missing, we will use Cox proportional hazard regression to determine if time to dropping out is related to treatment group (TIPS or PSV), and baseline variables above. If there is no association, we will assume this is evidence for the dropouts to be at random (missing completely at random –MCAR). In this case, the methods above are known to give unbiased results. Otherwise, we will consider using multiple imputation if needed and compare estimates under multiple imputation versus estimates with complete data to see if this has a significant effect on the results

7.2 Sample size / power

The sample size is based on the primary outcome, the proportion successfully weaned on the original protocol by 24 days and is based on one sided non inferiority testing with a delta of 15%. From the study of Scheinhorn et al (6), we expect the success proportion in the TIPS group to be approximately 60%. Based on this, and assuming that there is no true difference between PSV and TIPS paths, a sample size of n=131 per group gives 80% power using a conservative two sided alpha=0.05 (one sided alpha=0.10). Therefore, our sample size of 150 per group should provide more than 80% power.

8.0 ASSESSMENT/EVALUATION PLAN

We will collect 4 groups of data from subjects. The detailed list is shown in Table 4. Study visit data collection overview is shown in the Appendix.

1. Preadmission and admission data will be collected for consented subjects on D0. Data will extracted from available STACH charts the BRH EMR by the study staff. Collected parameters are listed in Table 4, Column A and B.
2. Daily assessment data will be collected from D1 to discharge. Daily assessment parameters will be extracted from BRH EMR by the study staff. Collected parameters are listed in Table 4, Column C.
3. Discharge data will be collected upon discharge from BRH EMR by the study staff. Collected parameters are listed in Table 4, Column D.
4. Functional Status Score for the Intensive Care Unit (FSS-ICU) score will be calculated by the physical therapist on admission and at discharge. The data will be entered in the BRH EMR and collected by the study staff. The FSS-ICU score measures five basic abilities: a) the ability of rolling, b) transferring from lying to sitting, c) sitting at the edge of bed, d) transfer from sit to stand, and d) walking. Each task is scored on a 0 (no function) to 7 (independent performance) scale. The minimum combined score is 0 and the maximum is 35. The FSS-ICU score has been validated in both the ICU and the LTACH settings. Patients were evaluated by a physical therapist on admission and discharge, and the change in FSS-ICU score was used to access for functional change.
5. Tracheostomy decannulation evaluation. Decannulation will be discussed by the clinical team upon successful ventilator weaning and at least 72 hours of clinical stability on CA. The clinical team usually includes the speech pathologist, respiratory therapist and pulmonologist. The evaluation results will be entered in the BRH EMR and collected by the staff.
6. The 90-day post discharge mortality will be extracted from National Death Records.

Table 4. Data collection

|  |  |  |  |
| --- | --- | --- | --- |
| 1. **Preadmission data** | 1. **Admission data** | 1. **Daily assessment** | 1. **Discharge data** |
| **Demographic data** | admission date | hemodynamically stable (SBP>90, HR>50 and <120, RR>10 and <35 | discharge date |
| age | Hemodialysis need on admission | Assigned path: fast or slow? | Trach present (yes or no)? |
| gender | Admission Functional Status Score for the Intensive Care Unit (FSS-ICU) score | Study day? | Invasive mechanical ventilation (MV, yes or no)? |
| race | Endotracheal tube present | Study step? | If MV, mode, FiO2, RR, PEEP |
| ethnicity | Tracheostomy present | Okay to proceed to next step? | Discharge location: home, acute inpatient rehab (ARU) , skilled nursing facility (SNF), STACH readmission, dead) |
| **Chronic premorbid conditions (stable)** | hemodynamically stable (SBP>90, HR>60 and <120, RR>10 and <40 | Weaning failed (day) | If STACH readmission, provide reason |
| diabetes | Glasgow coma scale (GCS) | Study completion (day) | Hemodialysis on discharge (yes or no) |
| hypertension (HTN) | ventilator mode (pressure support, pressure control, volume control, synchronized intermittent mandatory ventilation) | Ventilator settings on the day of failure (mode, FiO2, RR, PEEP | FSS-ICU score on discharge |
| cerebrovascular accident (CVA) | FiO2 | Vt | BUN |
| coronary artery disease (CAD) | ventilator set rate | Oxygen saturation (O2sat) | Cr |
| chronic kidney disease (CKD) | spontaneous breathing rate | If fast path, moved to slow? | Plt |
| chronic hemodialysis (HD) | PEEP | If fast path and moved to slow, move date? |  |
| congestive heart failure (CHF) | Vt | Passy-Muir (speaking) valve use? |  |
| chronic obstructive lung disease (COPD) | SBP | Passy-Muir (speaking) valve time (hrs.) |  |
| pulmonary fibrosis (PF) | DBP | trach size |  |
| obesity (BMI>35) | HR | trach change (date) |  |
| neuromuscular disease | ABG | Swallow evaluation (date) |  |
| chronic malignancy | Cr | Swallow evaluation (pass or fail) |  |
| **acute premorbid condition on short-term acute care hospital (STACH) admission** | BUN | eligible for decannulation (date) |  |
| STACH admission date | Plt | decannulated (date) |  |
| cardiac arrest | Passy-Muir (speaking valve) use | Inpatient mortality (date) |  |
| vasopressor need | Feeding tube use | bronchoscopy need (yes or no) |  |
| sepsis |  | bronchoscopy date |  |
| acute kidney injury (AKI) |  | bronchoscopy reason |  |
| acute CVA |  | Intensive care unit (ICU) transfer |  |
| acute myocardial infarction (AMI) |  | ICU transfer date |  |
| acute hypoxemic respiratory failure |  | ICU transfer reason |  |
| pneumonia |  | cardiac arrest at BRH? |  |
| acute respiratory distress syndrome (ARDS) |  | Cardiac arrest date? |  |
| acute venous thromboembolism (VTE including deep venous thrombosis and pulmonary embolism) |  | vasopressor use |  |
| acute traumatic brain injury (TBI) |  | vasopressors start date |  |
| acute malignancy |  | new antibiotic use |  |
| acute gastrointestinal bleed |  | new antibiotic start date |  |
| acute liver failure |  | ICU discharge date |  |
| **preadmission respiratory condition** |  | ABG (during cool aerosol trial) |  |
| date of endotracheal intubation |  | SBP |  |
| date of tracheostomy |  | DBP |  |
| previous tracheostomy (yes or no)? |  | HR |  |
| **Laboratory data on STACH discharge** |  |  |  |
| Cr |  |  |  |
| BUN |  |  |  |
| PLT |  |  |  |

Abbreviations of vital signs and laboratory test no listed in previous tables: HR=heart rate, SBP= systolic blood pressure (mmHg), DPB=diastolic blood pressure (mmHg), O2 sat=oxygen saturation (%), FiO2=fractional inspired oxygen (%), Vt=ventilator tidal volume (ml), Cr=serum creatinine (mg/dl), BUN=serum blood urea nitrogen (mg/dl), Plt=platelet count (/mm3)

**9.0 ADVERSE EVENTS, SAFETY AND MONITORING**

There are four potential risk for adverse events:

1. Clinical deterioration. The study population consists of chronically critically ill patients with high risk of cardiopulmonary decompensation and death. Data from our team shows that inpatient mortality in the PMV population is approximately 14% (18). To protect the patient population, all BRH patients are continuously be monitored via telemetry for HR, O2 saturation and 1-lead EKG. Blood pressure is measured at least every 6 hours and as needed. Patients are followed by nurses and respiratory therapists 24 hours a day. These same rules apply to our study population. In the event of cardiopulmonary decompensation, the rapid response team or the physician on site is notified. BRH is staffed with onsite critical care trained physicians 24 hours a day. BRH also has a medical ICU for critical care. For determination of failed weaning, see Determination of failed weaning session.
2. Confidentiality. To avoid unauthorized access to study data: A. All personal and clinical data will be stored in a password protected database. B. Subjects will be assigned a code for identification which will be stored separately from the collected personal information. In case of breach of confidentiality the subjects and their DPOA will be notified and the study will halt.
3. Voluntary participation. Patients and/or their DPOA will be approached for consent to participate in the study. Only
4. Adverse events related to the study protocol. In case of hemodynamic and respiratory instability related to the ventilator protocol, the respiratory therapist will stop the weaning and the patient will be returned to the last safe ventilator setting.

To assure appropriate oversight the study team will contract with an independent data and safety monitoring board (DSMB). The clinical trial will also be listed at the clinicaltirals.gov website.

## **10. ASSESSMENT OF SAFETY**

## 10.1 Determination of failed weaning

To adequately assess patient well-being and avoid major side effects from mechanical ventilation weaning, criteria for early study completion were developed. The criteria listed will be continuously monitored throughout the study by hospital staff. If a study subject meets one of the criteria listed below on 3 consecutive days, the subject will be excluded from the trial. However after exclusion from the trial the subject will be followed by the study staff for the remaining hospitalization time at BRH to collect clinical information shown in Table 4.

1. Hemodynamic instability during ventilator weaning.
2. Patients requiring vasopressor medication to stabilize blood pressure
3. Systolic blood pressure less than 80mmHg
4. Pulse less than 50 or greater than 130 beats per minute or change by more than 20 from baseline on admission
5. Respiratory instability during ventilator weaning.
6. Respiratory rate greater than 35/min
7. Oxygen saturation less than 90%
8. PEEP>5cmH2O
9. Lung tidal volume less than 250ml despite MV support
10. Ventilator-patient dyssynchrony resulting in more than 2 discordant breaths per 10 seconds despite adjustment of ventilator pressure, flow or volume settings
11. On ABG, pH<7.30, paO2<55mmHg, pCO2 >60 mmHg or no more than 10 mmHg change from admission baseline pCO2.
12. New onset fever, identified as core temperature >101F
13. Acute gastrointestinal bleed, identified as melena or bright blood per rectum.
14. Agitation, defined as pulling on tubes and line risking self-harm despite soft restraints.
15. Significant decline in cognition defined by unresponsiveness to command, if the patient was previously responsive.
16. Significant airway bleed resulting in suctioning difficulty of the airway

If a patients meets one of the failed weaning criteria, the respiratory therapist will return the patient to full support ventilator support, alert the attending pulmonologist and a member of the study team.

# 10.2 Unanticipated Problems

The Office for Human Research Protection Program (OHRPP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

Unexpected in terms of nature, severity, or frequency given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (2) the characteristics of the subject population being studied; related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Given that the study population has by definition severely deranged physiology and laboratory

values and a high risk of death as a fundamental part of their underlying disease process,

abnormal laboratory values and deaths are not considered unanticipated problems for this

population. Rather, we will be tracking physiological parameters listed here and in Section 10.1 to identify deterioration possibly related to the study protocol:

1. Hemodynamic stability
2. Respiratory stability
3. New onset fever
4. Acute gastrointestinal bleed
5. Agitation
6. Decline in cognition
7. Significant airway bleeding

#### 10.3 Adverse Events

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

#### 10.4 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

* Results in death
* Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
* Results in intensive care unit hospitalization or prolongation of existing hospitalization
* Results in a persistent or significant disability or incapacity

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### 10.5 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after enrollment until 7 days later for non-serious AEs, and 30 days for SAEs. Events will be followed for outcome information until resolution or stabilization.

#### 10.6 Characteristics of an Adverse Event and Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

* + 1. Related (Possible, Probable, Definite)
       1. The event is known to occur with the study intervention.
       2. There is a temporal relationship between the intervention and event onset.
       3. The event abates when the intervention is discontinued.
       4. The event reappears upon a re-challenge with the intervention.
    2. Not Related (Unlikely, Not Related)

1. There is no temporal relationship between the intervention and event onset.
2. An alternate etiology has been established

#### 10.7 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

#### 10.8 Severity of Event

The following scale will be used to grade adverse events:

* + 1. Mild: no intervention required; no impact on activities of daily living (ADL)
    2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
    3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

#### 10.9 Unanticipated Problem Reporting to IRB

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

* + - appropriate identifying information for the research protocol, such as the title, investigator’s name, and the IRB project number;
    - a detailed description of the adverse event, incident, experience, or outcome;
    - an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
    - a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

* + - Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event.
    - Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
    - All unanticipated problems should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB’s receipt of the report of the problem from the investigator.

#### 10.10 Reporting of Serious Adverse Event

The study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

* + - Serious adverse events regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

#### 10.11 Halting Rules

Should any serious adverse events or repeated adverse events appear to be related to the study interventions, the PI will work with the IRB and Independent Safety Monitor Dr. Stella Cohen to determine the appropriateness of halting further enrollment in the study. Dr. Cohen and the PI of this study do not have a formal mentor / mentee relationship or other arrangement that would preclude objectivity.

## **11. STUDY OVERSIGHT**

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of an Independent Safety Monitor (ISM), Dr Stella Cohen, and performed on a quarterly basis. The ISM is independent of the study and will be available in real time to review and recommend appropriate action regarding adverse events and other safety issues.

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**10. APPENDIX**

# Study visit data collection overview

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Visit 1 Day 0 of admission** | **Visit 2 Day 1-21 daily assessment** | **Visit 3 study completion** | **Visit 4 discharge** |
| Informed Consent | **X** |  |  |  |
| Medical History (from previous hospital records) | **X** |  |  |  |
| Complete Physical Exam | **X** |  |  |  |
| Abbreviated Physical Exam |  | **X** | **X** | **X** |
| Height | **X** | **X** | **X** | **X** |
| Demographics | **X** |  |  |  |
| Weight | **X** | **X** | **X** | **X** |
| Vital Signs | **X** | **X** | **X** | **X** |
| Ventilator settings | **X** | **X** | **X** | **X** |
| O2 saturation | **X** | **X** | **X** | **X** |
| Ventilator liberation | **X** | **X** | **X** | **X** |
| Tracheostomy status | **X** | **X** | **X** | **X** |
| Laboratory data (BUN, Cr, Plt) | **X** | **X** | **X** | **X** |
| Randomization | **X** |  |  |  |
| Concomitant Medication Review (abx, vasopressors) | **X** | **X** | **X** | **X** |
| Adverse Experiences (ICU transfer, hemodynamical instability) |  | **X** |  |  |
| Death | **X** | **X** | **X** | **X** |