Effort of breathing guided ventilator management for children: a pilot study

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1. Introduction

Children have a disproportionately high rate of respiratory related illness and death[1]. While breathing tubes and mechanical ventilators are lifesaving supportive therapies, children have significantly higher short-term morbidity related to mechanical ventilation. These include higher rates of nosocomial infections, complications such as upper airway obstruction (UAO) after extubation (removal of the breathing tube), exposure, tolerance and withdrawal from sedatives and analgesics used during mechanical ventilation, ventilator induced respiratory muscle weakness, and significant increases in healthcare costs. They may develop long term morbidity with neurodevelopmental impairment from inflammation associated with ventilator associated lung injury, prolonged exposure to sedatives, functional impairment, and in some cases death from complications related to mechanical ventilation [2-6].

Shortening the amount of time children spend on mechanical ventilation would significantly reduce this morbidity. There is a wealth of data that clinicians wean ventilators too slowly for many patients[2, 7, 8]. At the same time, extubation failure rates may be as high as 20 - 50% in some neonates and infants, arguing that current tools inadequately gauge who is ready for extubation. Finally, 40% of neonates and infants are managed with non-invasive ventilation after extubation, and are often left on this therapy days longer than needed due to lack of evidence based methods to wean this support.

The key physiologic principle that drives weaning from mechanical ventilation surrounds effort of breathing. The clinical surrogates for effort of breathing are based on clinical examination, are subjective, and have high inter-rater variability. Direct measurement of effort of breathing is possible using minimally invasive techniques with naso-esophageal tubes, spirometers, and respiratory inductance plethysmogrpahy (RIP) bands. We have strong preliminary data from a completed NIH funded investigation here at CHLA (CCI-11-00210) involving > 400 mechanically ventilated children (neonates to adolescent) that objective measures of effort of breathing may aid clinical decision making regarding readiness for extubation, detecting and managing complications after extubation such as upper airway obstruction (UAO), and titrating noninvasive ventilation support. We have recently applied for RO1 award to conduct a follow up study which would be a randomized controlled trial comparing an objective measure of effort of breathing (esophageal manometry) guided approach to a more conventional ventilator protocol, incorporating current evidence. Our hypothesis is that this protocol will lead to faster ventilator weaning, by preserving diaphragm and other respiratory muscle strength. To do this, we plan to incorporate physiologic measurements and calculations which will be displayed as part of a software program we have developed, provide recommendations to the clinicians who will ultimately accept or reject the protocol recommendations, and provide feedback as to why

they rejected the recommendations. This pilot study will help test the acceptability of our study protocols with bedside providers, , ensure the user interfaces and recommendations are easy to follow, demonstrate the feasibility of performing repeated diaphragm ultrasound measurements, and help determine the potential effect size of the intervention to determine ultimate sample size calculations.

2. Background literature

Typical Course of Mechanical Ventilation

The typical course of mechanical ventilation for both adults and children can be divided into acute, convalescent, and weaning phases. During the acute phase of illness while on mechanical ventilation, the goals are minimizing work of breathing, ensuring adequate gas exchange and oxygen delivery, and minimizing potential injury from the way the ventilator is managed [8]. The convalescent phase represents a period of relative stability, but ventilator reductions (or weaning) have not begun. The weaning phase is variable, and represents the time frame through which ventilator support is reduced until the breathing tube is removed (extubation). However, weaning may continue after extubation when patients are placed on non-invasive ventilation, and ultimately the patient may fail weaning, and require re-intubation. This may be from unresolved respiratory, cardiovascular, neuromuscular, or central nervous system disease, but may also be a direct consequence of complications of endotracheal intubation, including upper airway obstruction (UAO). Currently, clinical assessment of disease stability, and effort of breathing is used to determine which phase the patient is in, and ultimately when it is time to begin weaning, how quickly to wean, when to extubate the patient, and whether the patient is failing extubation. For the most part, this assessment of EOB has largely been based upon subjective clinical assessment [8].

Several studies in pediatrics have demonstrated two important phenomena to highlight the potential room for improvement in ventilator weaning strategies: (1) patients with unplanned extubation often do not fail extubation (suggesting they could have been extubated sooner than the clinicians had planned to extubate them) and (2) extubation failure rates based on clinical assessment and decision making regarding extubation readiness range from 8-50%. This implies that current clinical assessment tools are inadequate at predicting who is likely to fail extubation. Moreover, previous studies on pediatric mechanical ventilation weaning have highlighted that nearly half of the patients are ready for extubation simply after they have had close to 24 hours in the convalescent phase of ventilation, and do not need a prolonged weaning phase [7].

Measurement of work or effort of breathing

The most important metric to consider in the clinical context of respiratory disease is work or effort of breathing: how the patient responds to the changes in pressure, resistance, and flow to maintain ventilation and oxygenation. In physics, the term "work" is used to characterize the concept of force applied over a distance (or pressure across a volume). In the clinical setting, work of breathing can be calculated from the curve of esophageal pressure versus tidal volume. The work per breath can be computed from the area enclosed by an esophageal pressure-tidal volume curve. However, the term "work" does not entirely characterize the effort necessary for a patient to breathe as it does not take into account the duration of contraction nor the energy required for isometric contractions of the respiratory muscles

To more accurately describe the concept of patient energy expenditure, the better term to use is "effort" of breathing (EOB). While dependent upon the mechanical properties of the respiratory system, effort of breathing is more specifically an assessment of the load opposing respiratory muscle contraction. Metrics of EOB describe the activity of respiratory muscles and are useful tools for the evaluation of breathing efforts. Fundamentally, sustained periods of increased EOB eventually lead to respiratory muscle fatigue and ultimately respiratory failure. As such, therapeutic interventions, such as intubation and mechanical ventilation, are targeted at reducing EOB. Resolution or normalization of EOB is hallmark for determining how to decrease ventilator support as mechanical ventilation is weaned.

One of the most widely accepted methods for evaluating EOB in the pediatric population is pressure.rate product (PRP). It is an effective tool to measure effort of breathing as it takes into account the product of respiratory rate and change in esophageal pressure required to maintain adequate gas exchange. It takes into account both isometric and productive contractions of the respiratory muscles and serves as an estimate of the energy cost of the work of breathing because oxygen consumption by muscle is proportional to the integral of muscle tension with respect to time. We have used PRP at CHLA for numerous clinical studies on both invasively and non-invasively ventilated patients [9-13] [14]. We also have extensive experience with PRP measurements on animals [15] [16].

Preliminary Data from CHLA (unpublished): From the most recent set of investigations we have done at CHLA using an interim analysis on 350 children in our PICU and CTICU (CCI-11-00210), we have found that effort of breathing values obtained prior to extubation while on minimal ventilator support are predictive of weaning failure- particularly for the use of non-invasive ventilation after extubation. Moreover, effort of breathing values just after extubation,

as well as the change in this value from the intubation value, is predictive of re-intubation. These values appear more predictive than current evidence based methods (Rapid Shallow Breathing Index), and clinical estimation of extubation readiness. This forms the rationale for the proposed study to use PRP based measures to study weaning and extubation readiness.

Evidence based protocols

While clinical judgment forms the basis for most current weaning strategies and ventilator management during even the acute phase of illness, there are evidence based guidelines that have been developed, largely from data from adults with acute respiratory distress syndrome [8, 17]. We have developed a suite of tools to implement the evidence based guidelines for ventilator management, both for the acute phase of ventilation, and for weaning, using a modification of the adult-based guidelines. These protocols have been funded through grants from the National Institutes of Health (R21 PI Newth and Sward), and have been vetted through the NIH funded Collaborative Pediatric Critical Care Research Network.

Preliminary Data from CHLA (published): We have previously demonstrated using data from our own institution, that clinicians frequently do not follow evidence based guidelines regarding ventilator management, and there are potentially lost opportunities to improve our ventilator management by complying with current best evidence[17]. These protocols will form the basis for ventilator management as part of this study, and effort of breathing calculations will be added on top of these existing guidelines. The suite of software tools simply gather data from the available clinical data at the bedside (laboratory feeds, ventilator connections), determine what the current best-evidence would suggest be done for the patient based on these parameters, and make a recommendation to the clinician. Ultimately, the clinician will determine whether to accept or reject the recommendation, and provide an explanation for why the recommendation was rejected to eventually improve the adherence to the protocol.

Transpulmonary pressure

While implementing current evidence based guidelines has the potential to reduce length of mechanical ventilation and minimize risk of ventilator induced lung injury, there is the potential to improve on the current best evidence through optimization of ventilator support during the acute phase of illness. Transpulmonary pressure based titration of ventilator settings has demonstrated utility in the management of adult patients with ARDS to improve oxygenation [18]. *Preliminary Data from CHLA (unpublished):* We have preliminary data here as part of another approved study (CCI-13-00370) that there may be differences between clinician chosen ventilator settings, and recommendations based on transpulmonary pressure. However, what is unclear and impossible to ascertain with the previous study design, is whether there would be a

difference between ventilator settings recommended by Trans-Pulmonary Pressure (with the use of esophageal manometry), and the current best evidence based guidelines. Our preliminary data demonstrates that TPP measurements are simple to obtain, may be different than clinically chosen values for, in particular, Positive End Expiratory Pressure (PEEP), and that changing PEEP values to normalize TPP is safe, with no significant change in cardiac output or oxygen delivery.

Upper Airway Obstruction

Preliminary Data from CHLA (published and unpublished): Our preliminary data suggests close to 25% of children have upper airway obstruction (UAO) after extubation. Those with UAO have a fourfold higher rate of re-intubation than those without UAO. Moreover, there is an extremely high rate of variability in the clinical assessment of UAO [19], with practitioners frequently disagreeing on the presence of UAO (kappa values 0.2-0.4). We have developed an objective parameter to gauge UAO severity which integrates esophageal manometry and RIP signals. This parameter is displayed on the software to aid in decision-making, along with the integrated waveforms from RIP and esophageal manometry for clinical interpretation. In preliminary analysis of the 350 patients included in the UAO study, this objective parameter predicts re-intubation from UAO with an area under the curve of the Receiver operating plot of 0.92. This provides support that this objective measure has excellent ability to discriminate risk for re-intubation from UAO, and may identify a group of patients at risk for extubation failure, in which more aggressive management is warranted. This parameter can be made available at the bedside, as part of the software package we have developed, to aid in clinical decision-making.

Software (Stage of development and validation):

There are two pieces of software which will be used in this pilot study. Neither of the software suites are specifically FDA approved. However, they have been developed iteratively and tested relatively extensively at times during clinical care and as part of already approved investigations.

1. CDS tool for implementing evidence based guidelines. This tool has been developed in Microsoft Access over the past 8 years. It has been refined numerous times to keep consistent with current best evidence in the management of pediatric ventilation, both for the acute and weaning phase of ventilation. Dr. Newth has received NIH grants to iterate on this protocol (the evidence based recommendations), and they have been modified through the Collaborative Pediatric Critical Care Research Network. The software receives automated feeds from our electronic data resources in real time- and when an evaluation is due; it will pull in data and make a recommendation. The recommendations

are transparent- and the physicians can drill down to the rules to understand why the recommendation was made. The physicians (or their surrogate- the respiratory therapist if working under orders from the physicians) can then accept or reject the recommendation. If the recommendation is rejected, they will be asked to provide feedback as to why. We have used this tool intermittently for clinical care for the last 4-5 years, at the discretion of the attending physicians on service, using it on over 40 patients to date. The tool will also be used to remind clinicians that an evaluation is due by blinking on a laptop screen at the bedside every 2 hours, or with a new blood gas. This tool will be used as soon as consent is obtained for the study. As part of the rules of the tool, once patients are breathing spontaneously and on modest ventilator support, it asks the providers if a spontaneous breathing trial is indicated. If the answer is yes, then the second piece of software will be added for the weaning phase (See flow diagram below). While this tool has been developed in Microsoft Access, to support better integration with the clinical workflow in the ICU, it has been migrated to a web-based platform. This enables it to be used on devices that have web-connectivity, and can interface with the current VDI systems in the ICU.

2. Monitoring software integrating esophageal manometry, spirometry, and RIP signals. This software package has been developed extensively over the last 3 years as part of Dr. Khemani's NIH funded investigation. It is a data capturing tool, enabling signals to be post-processed for the sake of interpretation for the NIH funded UAO study. The device (Bicore II) is FDA approved through 510K equivalence, as are all the sensors. These have been used in the ongoing UAO study with no complications. However, the software package (Polybench, Applied Biosignals) is capable of real time and near-real time display of data and calculations. These have been crucial during the UAO study to ensure the data being captured was reliable and representative of the patient state. There have been 2 biomedical engineering students who have worked extensively on the user interface and software module, to enable real-time calculations. This has involved over 40 different iterations and modifications to ensure its accuracy in calculations and clinical interpretability. It is judged against an FDA approved post-processing program (Vivosense, Vivonetics Corp, San Diego CA)- on calculations of effort of breathing, calibration of Respiratory Inductance Plethysmography, assessment of Upper Airway Obstruction with Flow-Pressure Plots and Konno-Mead Plots. In using this module on close to 400 patients thus far we have found it to be accurate against the post- processing program. For the sake of the UAO study, after completing a standardized assessment, the clinicians were given access to the data displayed from the UAO module to assist their clinical decision making. However, decisions made in response to the information were

not tracked, as that was not the intention of the study. Nor were there any specific protocol recommendations for management based on the calculations in the tool. For this proposed study, the clinicians would have ready access to the tool for assistance with clinical decision making regarding weaning, and post-extubation management. Based on effort of breathing calculations within the tool, there will be specific recommendations regarding weaning or no weaning. The effort of breathing guided protocol rules will be incorporated in the CDS tool above and ultimately the clinician will decide whether or not to wean by evaluating the patient, and knowing the effort of breathing trend since the last evaluation. If the clinician elects not to wean when the protocol recommends a wean, they will record why using the tool above.

3. Purpose of this study

Study Objectives

1. To refine the esophageal manometry based effort of breathing weaning protocol so that it can be used easily, and can attain high protocol adherence for eventual use in a randomized controlled trial.
2. To demonstrate that integration of these two pieces of software together can be used safely to provide recommendations for ventilator management, and measure protocol adherence.
3. To determine the potential magnitude of reduction in length of mechanical ventilation afforded by using such a weaning tool, to help determine estimated sample size for a future randomized controlled trial.
4. To obtain data regarding the potential difference between Transpulmonary pressure guided PEEP management and management recommended by current best evidence using a PEEP/FiO2 titration table, for eventual use in a clinical trial.
5. To refine the esophageal manometry based effort of breathing protocol for weaning non-invasive ventilation after extubation.
6. To determine the feasibility and reproducibility of diaphragm ultrasound measurements amongst providers.

4. Research Design and Methods

Study Overview

This is a single center prospective trial in the 24 bed multidisciplinary medical-surgical pediatric intensive care unit (PICU) at Children's Hospital Los Angeles. All patients intubated and mechanically ventilated with an anticipated length of intubation > 48 hours will be eligible. Specific inclusion and exclusion criteria are delineated below.

5. Eligibility and Recruitment

Inclusion Criteria

All patients intubated and mechanically ventilated in our Pediatric ICU with an anticipated length of intubation > 48 hours will be eligible. The primary attending physician taking care of the patient must approve the patient for participation in the study before they are approached for consent.

Exclusion Criteria

Patients will be excluded if they have a corrected gestational age less than 37 weeks or contraindications to nasoesophageal catheter placement (nasopharyngeal or esophageal abnormalities) or RIP bands (abdominal wall defects such as omphalocele). Patients with lower airway obstruction (asthma or bronchiolitis), confirmed by ventilator spirometry (standard practice in ICU) will also be excluded because the evidence based guidelines do not specifically address these patient populations.

6. Methods and Procedures

Recruitment and Informed Consent Process

All mechanically ventilated patients will be screened daily for potential eligibility. Parents or guardians will be asked to sign all consent forms as all the patients meeting criteria for the study will be either too young for the study, or sedated while on a mechanical ventilator. These forms include the consent form for the study, the HIPAA Waiver, and the experimental subject's Bill of Rights. The study will be explained to parents using non-medical language in the primary language of the parents using an interpreter as needed. Parents will have the opportunity to ask questions and voice concerns, and will be given the opportunity to withdraw from the study at any time.

Study Treatments

Schematic illustrations are displayed in Figures 1-5. After consent, an esophageal catheter will be placed. The CDS tool for ventilator management will be placed at the bedside (on a laptop computer) for each enrolled patient, and recommendations regarding changing ventilator support will be provided to the clinicians every 2 hours or with a new arterial blood gas. Clinician decisions and changes to the ventilator with respect to each recommendation will be tracked. PEEP and FiO2 management is based on current best evidence. Twice a day, transpulmonary pressure measurement will be obtained (a. on the current PEEP/FiO2 combination- as recommended by the current best evidence and b. PEEP will be changed to make transpulmonary pressure zero). TPP measurements are obtained through an expiratory and inspiratory hold on the ventilator while the patient is not breathing significantly spontaneously. This methodology will be identical to what is already approved as part of another ongoing investigation at CHLA (CCI-13-00370). This data will be tracked to help generate a new protocol based on TPP. PEEP will be returned to the previous level after TPP calculations are complete. Once the patient meets criteria for spontaneous breathing (see flow diagram below, Figure 1), they will enter the effort of breathing weaning arm of the study.

In this weaning arm of the study, there will first be an oxygenation test to ensure the patient can tolerate lower levels of PEEP and FiO2 in preparation for weaning. If they fail, they will go back to the previous ventilator settings and an oxygenation test will not be repeated again for 24 hours. If they pass, they will go to a 2 hour Spontaneous breathing trial. Esophageal manometry, spirometry, and Respiratory Inductance Plethysmography (RIP) bands will be in place. If they pass based on clinical criteria as well as guidance from the esophageal manometry protocol regarding effort of breathing and other pieces of extubation failure (such as direction of the Konno Meade plot as an indication of neuromuscular weakness) the recommendation will be to extubate. If the clinician elects not to extubate, the reasons will be tracked.

If patients fail the SBT, they will be placed on the previous PEEP (prior to oxygenation test) and PS equal to the delta P (PIP-PEEP) on the previous ventilator support. The protocol will then make recommendations every 2 hours regarding weaning based on whether PRP has been in a range to wean, or a range to go back up on support (Figure 2). Clinicians will ultimately decide whether or not to accept these recommendations, and again reasons for rejection will be tracked. Once the patient achieves PS level of $\leq$ 8 cmH20, another SBT on CPAP will be recommended. If it has been 24 hours since the last SBT, regardless of PRP, another SBT will also be recommended. The clinician will chose whether or not to accept or reject the recommendation, and again reasons for rejection will be tracked. If the patient passes the SBT, the recommendation will be for extubation. If the patient fails the SBT, PS will be returned to its

previous level. No SBT recommendation will be made between 10pm-6am, so that extubation will take place at accepted times for extubation in our ICUs.

The PRP targets for weaning versus increasing support are based on analysis of the existing data from patients on PS and CPAP just prior to extubation, who were enrolled in the UAO study. From this data, over 90% of the patients who were extubated successfully had a PRP on PS < 250, and a PRP on CPAP < 400. Hence, the recommendations will be to wean PS if PRP is < 250, to maintain PS if PRP is between 250 and 400, and to increase PS if PRP is > 400. Ultimately, the clinician will make the final determination regarding whether or not to make the wean, or to extubate the patient.

The decision to begin non-invasive ventilation after extubation will be left to the clinician. NIV management will be per clinician choice, and we will not implement a NIV protocol.

Diaphragm ultrasound measurements will occur daily, and will be conducted by two providers who will remain blinded to each-other's measurements. We will place an ultrasound probe over the right hemi-diaphragm just lateral to the nipple line between and compute Diaphragm Contractile Activity (DCA). DCA is obtained by measuring the thickness of the right hemi diaphragm and calculating the percent difference between diaphragm thickness on inspiration and exhalation. 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.

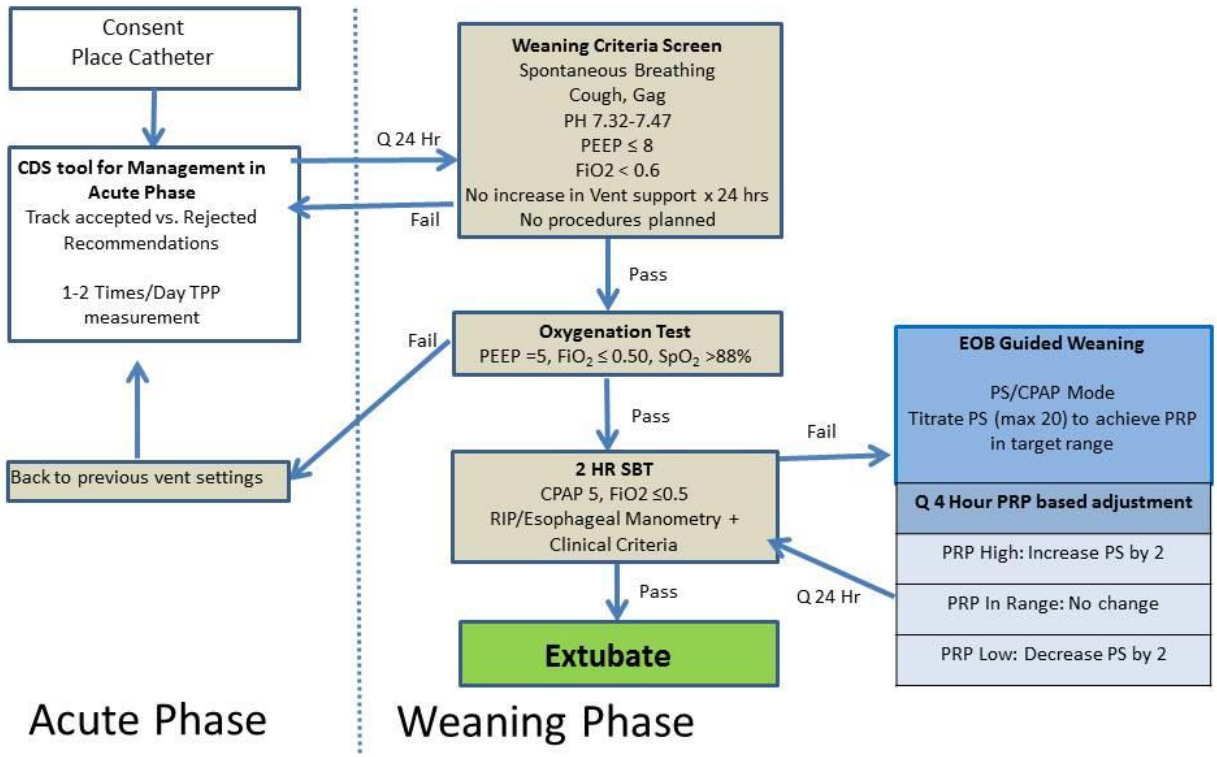

Figure 1: High Level view of Flow Diagram of Study

Study Outcomes

The following study outcomes will be followed for each of the proposed study objectives.

1. Objective: To refine the esophageal manometry based effort of breathing weaning protocol so that it can be used easily, and can attain high protocol adherence for eventual use in a randomized controlled trial. Outcome: protocol adherence for each

recommendation, as well as qualitative data on the reasons for rejection of the recommendation. This will guide refinement of the protocol.

2. Objective: To demonstrate that integration of these two pieces of software together can be used safely to provide recommendations for ventilator management. Outcome: PRP values used to generate each recommendation will be tracked, and raw data will be recorded at least twice daily to compare calculated PRP values from the software program to the post-processing program we currently use for the UAO study. Will also track reasons for rejecting recommendations (above), specifically targeting any recommendations which were rejected because of perceived problems with the software or calculations (incorrect data etc).
3. Objective: To determine the potential magnitude of reduction in length of mechanical ventilation afforded by using such a weaning tool, to help determine estimated sample size for a future randomized controlled trial. Outcomes: The primary outcome is the total length of ventilation (invasive and non-invasive). Secondary outcomes include length of invasive ventilation, length of non-invasive ventilation, re-intubation rates, use of inhaled medications to treat UAO, use of steroids for UAO, post-extubation ICU length of stay. Sedation level will be tracked as this is a potential confounding variable, as well as fluid balance, details about endotracheal tubes, use of blood pressure medications, as well as procedures.
4. Objective: To obtain data regarding the potential difference between Transpulmonary pressure guided PEEP management and management recommended by current best evidence using a PEEP/FiO2 titration table. Outcomes: TPP values on evidence based protocol determined PEEP, and that which would be needed to make TPP zero. This will be used to guide the development of another ventilator protocol based on TPP for eventual use in a randomized controlled trial.
5. Objective: To determine the reproducibly of diaphragm ultrasound measurements between a trained provider with experience in ultrasound (M. Elkunovich), and the other study investigators. Outcome: inter-observer variability in DCA and Diaphragm thickness measurements between study investigators and Dr. Elkunovich. This will serve as feasibility data and training to ensure that the other investigators can perform these measurements for follow up studies. After an initial training phase, each provider will be required to perform a minimum of 8 simultaneous measurements against Dr. Elkunovich, with DCA and DTe measurements required to be within +/- 10% of Dr. Elkunovich's values.

Methods of Data Collection

Data will be comprised of demographic and outcomes, as well as raw study measurements and protocol adherence and recommendations. During data collection, patient identifiers will be maintained to ensure accurate data from multiple sources. Once the patient has completed the study, data which needs to be extracted onto data collection sheets, raw data measurements and protocol adherence will be coded. Individual data collection forms will be maintained for each patient with a study number and no identifying patient information. A separate coded sheet linking the patient and study number will be maintained separate from the data collection forms. With the exception of the coded sheet, all other patient identifiers will be removed from study data. Data will be kept on a password-protected computer and any printouts will be stored in a locked cabinet in the office of the investigators. Ultrasound images will be annotated in real time, and stored per-provider, uploaded wirelessly through the Qpath system (which is used for clinical point of care ultrasounds).

Study Termination

The endpoints of the study for individual patients will occur 48 hours afterextubation. . The bands and esophageal catheter will be removed 1 hour after extubation for study purposes. However, if the clinical team would like to use the catheter or bands for ongoing patient management, it can be left in place but will no longer be considered a study specific intervention. The patient will be followed for 48 hours to track therapies and re-intubation.

7. Analysis and Sample Size

In performing sample size calculations for the eventual proposed RCT, with an anticipated 1 day reduction in effort of breathing between intervention and control groups, the expected number of patients will range from 300-700 patients per arm. For this reason, the eventual study would need several years to complete, or be performed as a multi-center RCT. Estimates of treatment effect generated from this study will help refine these estimates.

For this pilot study, the requested sample size is 40. The sample size has been increased from the initial 20 to 40 to accommodate the changes in the CDS tool platform, the protocol changes to the effort of breathing algorithm, and the diaphragm ultrasound measurements. We believe this sample size is necessary to test all of the stated objectives. By objective

1. Refining esophageal manometry protocol: It is anticipated that 40% of patients will pass the initial SBT. This means that 10-12 patients will be left to test the protocol. Each patient should generate 10-20 recommendations on the weaning protocol, giving approximately 100 recommendations to test. Based on preliminary analysis of the 20

included patients to date, and in discussions with the bedside providers, we have modified the esophageal manometry protocol to allow for 3 ranges of adjustment, rather than 2. It is believed that this will improve adherence, while still meeting the physiologic principles of titration of ventilator support to maintain effort of breathing. The subsequent 20 patients would then be used to test if the revised protocol attains high adherence.

2. Software pieces: Each patient should receive at least 24 recommendations on the CDS portion of the protocol and for those that fail the SBT, another 10-20 recommendations on the weaning protocol. We have migrated the CDS tool out of Microsoft Access, making it available in a web-browser to improve compatibility with clinical care. The rules of the protocol have not changed. The additional analysis will be to confirm that users can follow the new user interface. This should afford enough data to test the reliability of the software. From the 10-12 patients who are enrolled in the weaning protocol, at least 2 time points will be available to compare PRP values between the software tool and the post-processing program, allowing > 20 points for direct comparison.

3. Magnitude of reduction: It is anticipated that the expected duration of MV for those with anticipated lengths > 48 hours ranges from 5-7 days on average, with a wide range. While it is unlikely that we will have a definitive answer about the magnitude of effect, approximately 20 patients should provide data to get a reliable estimate of mean and standard deviation for length of ventilation to use in future calculations.

4. TPP separation: It is anticipated that 20 patients should yield a minimum of 60 TPP measurements (average 3/patient) which can be used to identify a potential separation between PEEP recommended by the protocol, and that which would be recommended by normalizing TPP. From the preliminary data we have to date (approximately 9 patients), there appears to be an average separation of 2 cmH_20 between clinician chosen PEEP and PEEP at TPP, although the variation is large. However, most of the time clinician chosen PEEP is below the evidence based recommendations. If we can demonstrate that for at least 50% of the observations (95% Confidence Interval 40-60%) there would be a separation of at least 2 cmH_20, it would facilitate development of a protocol. To achieve this level of confidence, we would need a minimum of 50 observations.

5. NIV protocol: It is anticipated that 40% of patients who are extubated will be placed on NIV after extubation. This means that 10-12 patients will be left to test the protocol. Each patient should generate 10-20 recommendations on the NIV weaning protocol, giving approximately 100 recommendations to test.

6. Ultrasound: For each provider the mean bias and precision of DCA and Dte measurements will be compared against Dr. Elkhunovich's with the requirements that the mean bias be no more than 10% , with precision in the range of +/- 20%.

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