Entrainment-Based Mechanical Ventilation

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I. BACKGROUND AND SIGNIFICANCE

All currently available mechanical ventilation modes assume that patient-ventilator interaction is necessarily a "master-slave" or controller-follower relationship. In controlled mechanical ventilation, the ventilator takes control of the ventilatory rhythm irrespective of whether the patient is breathing or not. In the patient-triggered mechanical ventilation modes such as assist/control, pressure support ventilation, proportional assist ventilation, neutrally adjusted ventilator support), instead of the ventilator dictating the ventilatory rhythm (ventilator-based ventilation), patient triggering allows the patient to initiate the breath with the ventilator responding to the patients demand (patient-based ventilation) with the imposition of various support.

Entrainment-based mechanical ventilation (EMV) is a new mode of mechanical ventilation based on the classical physics theory of mutual entrainment between coupled oscillators. It takes advantage of the patient's powerful innate capacity to entrain 1:1 to the ventilator rhythm via the Herring-Breuer reflex, provided that the ventilator rhythm is close enough to the spontaneous breathing rhythm. This ability of the respiratory system to adapt to changes in the entrainment mechanism via habituation and desensitization of the Herring-Breuer reflex allows an even greater dynamic range of entrainment.

There are currently no publications available on entrainment-based mechanical ventilation (EMV), which is a novel mode of mechanical ventilation. However, EMV is grounded on our previous experimental studies in anesthetized animals demonstrating that the respiratory rhythm has an intrinsic neural mechanism to automatically synchronize with the ventilator via the classical Hering-Breuer inflation reflex and to adapt to changes in entrainment through associative learning (1). Many studies in anesthetized animals have shown that periodic lung inflation during controlled mechanical ventilation may entrain the respiratory rhythm to the ventilation frequency or some sub-harmonics close to the intrinsic respiratory frequency (1-4). In anesthetized animals such entrainment is abolished after bilateral vagotomy (5, 6) and impaired after vagal cooling (7) indicating that it is mediated primarily by pulmonary slowly adapting stretch receptors and secondarily by pulmonary rapidly adapting receptors and/or vagal C-fibers.

Entrainment of breathing to mechanical ventilation has also been robustly demonstrated in normal humans during wakefulness or non-REM sleep or under anesthesia (8, 9), and in subjects after lung transplant (10) suggesting that other respiratory-related afferents (such as those from the chest wall) may be recruited after vagotomy to maintain entrainment. Therefore, respiratory entrainment

to mechanical ventilation is a well-established physiological phenomenon based on well-known neural mechanisms, and has been safely demonstrated in normal human subjects and in patients.

Justification for the investigation

We anticipate that the results of the study will help to improve the interaction of patients with the mechanical ventilator thereby minimizing the risks of mechanical ventilation in future. We believe the potential benefits significantly outweigh the potential risks.

II. SPECIFIC AIMS

Entrainment-based mechanical ventilation (EMV) is a new mode of mechanical ventilation intended for use in the ICU to improve patient-ventilator synchrony and decrease patient respiratory effort by minimizing patient triggering during assist/control (A/C) ventilation. The aim of this study is to determine if EMV is a feasible and safe mode of ventilation.

Primary Outcome variable:

Total number of asynchronous breaths/hour during entrainment-based ventilation compared to baseline ventilation.

Secondary outcome variables:

Ventilation and oxygenation as well as general ventilatory and hemodynamic variables will be analyzed during entrainment-based ventilation and compared to baseline data.

III. SUBJECT SELECTION

PATIENT POPULATION

Our study is targeted to enroll 20 stable mechanically ventilated adult patients (of either sex) capable of triggering the ventilator and only requiring pressure support ventilation.

INCLUSION CRITERIA

- Adult (age ≥ 18), mechanically ventilated via endotracheal tube, of either sex
- Capable of triggering the ventilator
- Subject receiving pressure support ventilation (or assist/control pressure-limited mechanical ventilation) with less than or equal to 15 cm H_2O inspiratory pressure, or, if on volume-limited A/C, when switched to pressure-limited A/C with the inspiratory pressure set to match the tidal volume on volume-limited A/C, the resultant inspiratory pressure is less than or equal to 15 cm H_2O.
- Stable on the above-mentioned ventilatory support for at least 8 hours.
- Arterial line in place for obtaining arterial blood gases

EXCLUSION CRITERIA

Patients meeting any of the following at enrollment will be excluded:

- Requiring high inspiratory oxygen concentration (> 50%)**.**
- Requiring high ventilatory driving pressure (> 15 cm H_20 on pressure-support)
- High spinal cord injury
- Immunosuppressed, < 2 months after receiving chemotherapy or radiation therapy.
- Neuromuscular/ neurological disease of a progressive nature resulting in chronic ventilator dependence.
- High risk of mortality within 3 months (terminal stage of their disease).
- Unable to spontaneously trigger the ventilator for any reason.
- Not considered a candidate for weaning from ventilatory support
- Consented for another interventional study.
- Requiring deep sedation and analgesia [Richmond Agitation Sedation Scale -3 to -5 (RASS)]
- Hemodynamically unstable patients as defined by those requiring norepinephrine at a dose greater than 5 mcg/min or neosynephrine > 100 mcg/min or those with a mean arterial blood pressure < 55 or > 120 mmHg or those with a heart rate < 50 or > 140 bpm.
- Respiratory rate > 30 breaths/min
- Pregnancy

IV. METHODS

This is a prospective study designed to evaluate the ability of entrainment-based mechanical ventilation to provide synchronous mechanical ventilation to patients in the SICU, MICU, CCU and Cardiac and Neuro Surgery ICUs at the Brigham and Women's Hospital (BWH).

The study will be conducted under IDE G120235. The FDA Investigational Device Exemption (IDE) was received from the FDA for the use of this ventilation mode for this study, and has granted an approval to start the investigation with an enrollment of 20 patients.

Study design and procedures:

After obtaining informed consent a NICO® respiratory monitor (Philips Respironics or a similar real-time data monitor) will be placed between the artificial airway and the Y piece of the ventilator circuit. Baseline mechanical ventilation data with conventional pressure-limited assist/control ventilation mode will then be collected for a 4-hour period. The patients will then be transitioned to pressure-limited entrainment-based ventilation for a 4-hour period. Baseline ventilation monitoring will be carried out either immediately preceding or immediately following EMV in the same patient. The sequence of the control/baseline phase and the experimental phase of the study will be randomized.

During the observation study period, the basic ventilator settings will remain as prescribed during conventional mechanical ventilation. Any adjustment in basic ventilator settings will be up to the medical staff caring for the patient. During the entrainment-based ventilation period, a respiratory

therapist will set the ventilation modes, and a trained physician from our research team will monitor the patients per written checklist for comfort and compliance with the ventilator mode as well as collect data. In addition, the ventilator alarms and limits will be set appropriately preventing the airway pressure from increasing more than 5 cmH_2O above the set level or the respiratory rate or tidal volume from exceeding or decreasing below the patient average tidal volume or respiratory rate by more than 25%. Apnea backup ventilation will be set to activate after a 20 second apnea period.

Data collection:

Demographic data, weight, height, and past and current medical history will be recorded. Also hospital admission information, reasons of mechanical ventilation, mode of mechanical ventilation and settings, arterial blood gas, clinical laboratory (hematology/chemistry) values, and hemodynamic values will be recorded.

- A NICO® monitor (Philips Respironics) will continuously collect mechanical ventilation data, which will be downloaded to a laptop computer for later analysis. The data will include tidal volume (VT), Respiratory rate (RR), Positive end expiratory pressure (PEEP), peak pressure, mode of ventilation, F_IO_2, dynamic compliance and waveform of airway pressure and flow. Data regarding patient ventilator synchrony will be analyzed from data obtained during the 1hr of baseline ventilation, and from the 2nd hr and the last hr of entrainment based ventilation.
- Blood gas analysis will be performed at the 2nd hr and at end of the baseline ventilation period, 2nd hr and at the end of the entrainment-based ventilation period.
- Oxygen saturation and blood pressure will be recorded every 15 minutes (every 5 minutes in the first hour) until completion.
- ECG will be monitored continuously and recorded every 15 minutes (every 5 minutes in the first hour).
- Heart rate, paradoxical breathing, accessory muscle use, nasal flaring, will be continuously monitored throughout the study by the study staff present at the bedside throughout the procedures.

Safety criteria:

The following criteria will be used to identify failure of entrainment-based ventilation:

- RR > 35/min for > 5 min
- SpO_2 < 88% for 5 minutes and not corrected by suctioning or if SpO_2 < 80% at any time
- Pulse sustained < 50/min or > 120/min
- PH $\pm$ 0.05 units from baseline pH
- PCO_2 $\pm$ 10 mmHg from baseline PCO_2
- Mean arterial pressure sustained $\pm$ 20 mmHg from baseline pressure
- Ischemic changes on ECG

- New onset of paradoxical breathing, accessory muscle use, nasal flaring, etc.
- Agitation (RASS > +1), diaphoresis, persistent anxiety despite reassurance and requiring sedation.

Once any of these safety criteria are met, the patient will be placed back to the baseline ventilation mode and closely observed for return to the pre-intervention baseline. Any patient who does not return to a pre-intervention baseline within 5 minutes after return to baseline ventilator settings will be evaluated by the study doctor for possible adverse effects or serious adverse effects and the patient will not be given further EMV therapy. Such AEs or SAEs will be deemed *unknown related* UADE or USADE. The DSMB will review the data and any safety concerns along with the Investigator and Sponsor each time any adverse event or serious adverse event occurs regardless of whether such an event is device related or not. If three or more non-serious adverse events occur or if two serious adverse events occur or if any death occurs, the corresponding events will be deemed *possibly device related* and the study will be placed on hold and the DSMB will review all available data at the time of the hold. The FDA and IRBs would review and approve any and all modifications to the protocol in response to such a study hold. Unanticipated problems and adverse events that occur during the conduct of the study, after study completion, or after subject withdrawal or completion will be reported to the IRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem.

The first indications of any adverse events: such as bronchospasm, atelectasis, hypoxemia, barotraumas, pulmonary edema, prolonged mechanical ventilation, increased ventilatory requirements, pneumonia, pneumothorax, acute lung injury, ARDS, organ failure, MI, or death are abnormal cardiorespiratory responses meeting the above safety criteria will be reported to the IRB and FDA according to the guidelines. Serious adverse events will be defined as any of the previous adverse events that lead to death, or are life-threatening, or lead to persistent or significant disability/incapacity, prolongation of hospitalization or surgical procedures. We will monitor all subjects for any adverse events or serious adverse events for 48 hours after return to baseline mechanical ventilation and will specifically include each of the above-listed events or any other adverse events or serious adverse events in the case report forms.

Patient monitoring:

This study will be performed at the subject's bedside when the subject is stable. A standard ventilator (Puritan-Bennett 840) modified to provide entrainment-based ventilation will be used for the study. This ventilator is widely used at BWH. All ventilator alarms will be active. Before using the entrainment-based ventilation mode for this study it will be fully tested on a spontaneously breathing lung model. The ventilator will be fully reviewed by the biomedical engineer in the respiratory care department.

During the study period the study staff will constantly monitor the patient for adverse or serious adverse events. If any of the events listed in the safety criteria above occurs, the entrainment-based ventilation will be permanently discontinued and subject will be changed back to baseline or conventional ventilation. Also the study will be stopped if any SAEs occur.

The protocol calls for blood gas analysis at the 2nd hr and at the end of the EMV period. Therefore, changes in arterial pH and PCO_2 values from baseline will be assessed at those time intervals for

any violation of the safety criteria. Once any changes in these blood gas variables are found to violate the stated safety criteria, the patient will be immediately returned to the pre-intervention ventilator settings and closely observed for return to the pre-intervention baseline.
ECG will be monitored continuously and recorded every 15 minutes (every 5 minutes in the first hour). Mean arterial pressure will be recorded every 15 minutes (every 5 minutes in the first hour).

Once any ischemic changes on ECG or excessive changes in mean arterial pressure ($\pm$ 20 mm Hg from baseline) are detected, the patient will be immediately returned to the pre-intervention ventilator settings and closely observed for return to the pre-intervention baseline.

For all other safety criteria mentioned above (regarding pulse, paradoxical breathing, accessory muscle use, nasal flaring, etc.), the timeframes are similar to those for RR. Specifically, the patient will be monitored continuously and will be placed back to the baseline mode of ventilation if any of these safety criteria are violated for > 5 min.

Sedation management will be performed per BWH ICU sedation guidelines, with sedation targeted to Ricker Agitation Sedation Scale. For actively weaning patients, this is typically RASS 0 to -2. Since management of sedation is beyond the scope of this pilot study, we will record the sedation used and the RASS score every hour during the study and look for trends. Any patient with increased agitation (RASS > +1) during EMV will be placed back to the baseline mode of ventilation.

V. Statistical analysis

Our study is targeted to enroll at least 20 sequential mechanically ventilated patients. Baseline demographic and procedural variables will be analyzed statistically by plotting the 95% confidence intervals of each variable. With 20 patients we will have an 88% chance of seeing any complication (such as those defined by the safety criteria or any associated adverse event or serious adverse event) that occurs with a frequency of 10% or more. For feasibility evaluation, the total number of each type of asynchronous breaths/hour during entrainment-based ventilation will be averaged over the 4-hour experimental period and compared with those in the 4-hour baseline ventilation period. The 95% confidence intervals of the differences of each type of asynchrony between entrainment-based ventilation and baseline ventilation will be provided without formal inference of statistical significance.

Analysis of synchrony:

The following types of patient-ventilator asynchrony will be analyzed every hour over the 4-hour baseline period and 4-hour experimental period:

- *Trigger asynchrony* – Number of breaths/hour initiated by the patients that fail to trigger the ventilator to inspiration (identified by pressure, flow and or CO_2 ventilator graphics.
- *Breath initiation asynchrony* – Number of breaths/hour in which the initial airway pressure drops below baseline pressure for > 100 milliseconds prior to pressurization of the airway or a concave rise in airway pressure after triggering or an initial pressure increase that exceeds the set pressure level.

- *Breath termination asynchrony* – Number of breaths/hour in which airway pressure at the end of the pressure targeted breath increases above set level just prior to exhalation or a second breath is rapidly triggered (double triggering) during initial expiration or premature termination of breath with small tidal volume.
- *Rhythm asynchrony* – Number of breaths/hour in which ventilation is continuously patient-triggered (assist mode) or continuously ventilator-initiated (control mode) for more than 10 minutes.

VI. RISKS

Risk minimization

The EMV method is an extension of the well-established assist/control (A/C) ventilation mode and has minimal risk. Below is a description of the potential risks and their mitigation.

Risks to the patient

The EMV mode is safe because it works in a similar manner as the standard A/C mode of mechanical ventilation, which is a tried-and-true ventilation method. Like the A/C mode, the EMV mode will always be operating in either the "control" mode or the "assist" mode of ventilation. Any potential phase difference between patient initiated breaths and machine triggered breaths in the EMV mode will be similar to the phase difference normally encountered in the A/C mode.

The only difference between the EMV mode and the A/C mode is that in the conventional A/C mode the baseline ventilator frequency is normally pre-set at a conservative low value (10-15 bpm) and is fixed. So, when the patient's breathing frequency rises above the pre-set value because of increased respiratory needs, the patient will have to trigger the ventilator most of the time with "assisted" ventilation, increasing both the work of breathing due to the triggering and dependence on the triggering mechanism. In the EMV mode, however, once the patient begins triggering the ventilator most of the time, the ventilator baseline frequency will be adaptively augmented to match the patient frequency in order to decrease the occurrence of patient triggering thereby keeping patient effort at a minimum. The ventilator frequency will increase only when it is preceded by sufficient number of patient-triggered breaths. That means the ventilator frequency will never increase beyond the patient's needs. Once patient-triggering is not detected, the ventilator frequency will decrease gradually in subsequent breaths. Therefore, hyperventilation is highly unlikely. Furthermore, under volume-limited ventilation for both the EMV and A/C modes, tidal volume will not increase beyond the targeted value. Further protection against such unlikely hyperinflation and hyperventilation events will be provided by the built-in alarm system on the PB840 ventilator, which will go off whenever the tidal volume or ventilation goes beyond the corresponding upper and lower limits that are pre-set by the clinician.

Even though there should be no more risk to the patient than what the patient would already experience from mechanical ventilation, It is possible, but unlikely, that the entrainment ventilation could lead to bronchospasm, atelectasis, hypoxemia, barotraumas, pulmonary edema, prolonged mechanical ventilation, increased ventilatory requirements, pneumonia, pneumothorax,

acute lung injury, ARDS, organ failure, MI, or death, but these are also likely from the patient's underlying illness that caused the respiratory failure.

VII. MONITORING PROCEDURES

A three-member DSMB will be assembled and a charter drafted and approved by the members. The DSMB will monitor the quality of data (primary and secondary outcome variables) and the safety of the subjects (as per the safety criteria listed in the protocol) and ensure that the Physician Investigator and the Sponsor adhere to the IRB approved investigational plan. The DSMB will hold group meetings with Physician Investigator and his team initially after 1st subject is studied and thereafter after 5 subjects and 10 subjects. The DSMB will meet with the Sponsor during the same time interval to discuss the safety and monitoring of the study with Physician Investigator and his team.

If any of the safety criteria (or other unexpected problems involving risks to any subject) are identified by the Physician Investigator and his team, the subject will be reverted to conventional assist/control mode of mechanical ventilation promptly and the DSMB and Sponsor will be notified. Appropriate adjustments of the parameters of the entrainment-mode ventilation will be made by the Physician Investigator, the Sponsor and their teams as necessary to minimize the likelihood of recurrence of the adverse effects or problems. Any patient who does not return to a pre-intervention baseline within 5 minutes after return to baseline ventilator settings will be evaluated by the ICU team for possible adverse effects or serious adverse effects and the patient will not be given further EMV therapy. Such AEs or SAEs will be deemed *unknown related* UADE or USADE. The DSMB will review the data and any safety concerns along with the Investigator and Sponsor each time any adverse event or serious adverse event occurs regardless of whether such an event is device related or not. If three or more non-serious adverse events occur or if two serious adverse events occur or if any death occurs, the corresponding events will be deemed *possibly device related* and the study will be placed on hold and the DSMB will review all available data at the time of the hold. The FDA and IRBs would review and approve any and all modifications to the protocol in response to such a study hold.

Pursuant to 21 CRF 812.150(a) and (b), the Investigator will submit to the sponsor a report of any SAEs, SADEs, UADEs and USADEs no later than 10 working days after the Investigator first learns of the effect; the Sponsor in turn will report any UADSs or USADEs to the FDA within 10 working days after the sponsor first receives notice of the effect. In particular, the following provisions will be added to the study protocol:

a. In the unlikely event that subject death occurs, the investigator will notify the sponsor, the DSMB and the IRB in writing as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

b. The Investigator will:

(i) Report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
(ii) Submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at quarterly intervals.
(iii) Notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice will be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.
(iv) Report to the sponsor and the reviewing IRB within 5 working days after any use of the device without obtaining informed consent.
(v) Submit a final report to the sponsor and the reviewing IRB within 3 months after termination or completion of the investigation or the investigator's part of the investigation.

c. The sponsor will:

(i) Report the results of any unanticipated adverse device effect evaluation under 812.46(b) to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor will submit such additional reports concerning the effect as FDA requests.
(ii) Notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.
(iii) Notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
(iv) Submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.
(v) Submit semi-annual progress reports and annual reports to all reviewing IRB's and FDA.
(vi) Notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.
(vii) Notify FDA within 30 working days of the completion or termination of the investigation and submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination.

(viii) *S*ubmit to FDA a copy of any report by the investigator of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(ix) Submit to FDA a report of the IRB's determination that the device is a significant risk device, within 5 working days after the sponsor first learns of the IRB's determination.

VIII. BIBLIOGRAPHY

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