TITLE: ASSESSING VENTILATOR SAFETY IN PATIENTS ON PRESSURE SUPPORT VENTILATION

Short Title: ASOP

Duke IRB # Pro00106860
ClinicalTrials.gov: NCT05125952

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Clinical Protocol Synopsis

1. Title

Assessing Ventilator **S**afety in Patients **o**n **P**ressure-support Ventilation (**ASOP**)

2. Background

Ventilator-induced lung injury (VILI) is known to cause significant morbidity and mortality in patients with acute respiratory failure.[1] Lung injury caused by large tidal volumes ("volutrauma"), high pressures ("barotrauma"), repetitive airway collapse ("atelectrauma"), and large changes in transpulmonary pressure during a breath ("driving pressure") are all known to cause VILI.[2] Most studies on VILI have involved the effects of inappropriate (often excessive) mechanical ventilator settings. More recently, it has been noted that similar lung damage can be caused by large, patient generated, uncontrolled tidal volumes and driving pressures, which has been termed "self-induced lung injury," or SILI[3,4].These patient generated large tidal volumes may be disease induced (e.g. neurologic injury) or be driven by other factors (e.g. metabolic derangements, anxiety). Importantly, interactions of patient efforts with assisted/supported modes of mechanical ventilation may worsen this.

Pressure-support ventilation (PSV) is a common mechanical ventilation mode often used in patients with active inspiratory efforts to help reduce patient inspiratory work and improve comfort. PSV effectively allows spontaneously breathing patients to determine their breath flow-rate and breath duration, eliminating flow and cycle dyssynchrony.[5] However, pressure support ventilation does not allow for physicians to control tidal volume or driving pressure. The risk of SILI may thus be increased with PSV.

Assessing SILI risk during PSV should involve more than just measuring the delivered tidal volume and should also include the end inspiratory alveolar pressure (plateau pressure or Pplat) and the airway driving pressure (DP = Pplat-PEEP). However, these are difficult to assess during PSV. Several different methods have been proposed to address these challenges[7-9]. However, to date none of these methods have been compared to assess for concordance in their ability to indicate an increased risk of self-induced lung injury.

3. Focus of the Study and Specific Aim.

ASOP is a prospective cohort study comparing three methods for assessing risk of self-induced lung injury in patients with acute respiratory failure being managed with pressure-support ventilation.

Specific Aim: We will describe the relationship between three different assessment methods for risk of self-induced lung injury and compare them to a gold standard measurement. The "gold standard" for SILI risk will be a direct assessment of transpulmonary Pplat and DP using an esophageal balloon tipped catheter to measure esophageal pressure (Pes) as a surrogate for pleural pressure. We will compare these to three assessment techniques using only the conventional airway pressure monitor: a plateau pressure and DP calculation in pressure support ventilation, an airway occlusion test in pressure support ventilation, and a plateau pressure and

DP calculation in volume-control ventilation in each patient. Our central hypothesis is that these three techniques will give similar results to "gold standard".

4. Study Population

Inclusion Criteria:

- Adult patients (≥18) with acute respiratory failure receiving invasive mechanical ventilation
- Managed in pressure-support mode of ventilation

Exclusion Criteria:

- Actively undergoing a spontaneously awakening trial or SAT
- Patient or surrogate is unable to provide informed consent
- Currently pregnant
- Currently incarcerated
- Acute exacerbation of an obstructive lung disease
- Known esophageal varices or any other condition for which the attending physician deems an orogastric catheter to be unsafe
- Esophageal, gastric or duodenal surgical procedures within the last 6 months

5. Screening and Recruitment

Study staff will identify potentially eligible patients during the study period using medical records and lists maintained for clinical operations. If a potentially eligible patient is identified, their clinical team will be contacted to ensure that the patient is appropriate for inclusion in the study. If deemed appropriate for participation by the clinical team, the LAR will be approached for consent.

6. Process of obtaining informed consent

A member of the study team will obtain permission from the legally authorized representative for each patient. It is necessary to obtain consent from the LAR in the study population as these individuals will be sedated and on mechanical ventilation. However, once the subject becomes capable of giving consent, the study team will approach them for study re-consent. We will obtain consent via paper consent.

Paper consent process

1. The informed consent document is provided to the patient's LAR.

2. Research staff discuss the informed consent document with the LAR in person. This step confirms subject/LAR identity.
3. If the LAR decides to consent to participate, the LAR signs the informed consent document.
4. Research staff signs consent document confirming their participation in the informed consent process.
5. A copy of the consent is provided with two copies of the consent, on for the LAR and one for participant.
6. Original signed consent is stored in study folder. A copy of the signed consent is uploaded to EHR.

7. Data collection

All data will be collected by study staff either through review of electronic health record or via direct measurements at the patient bedside after study enrollment.

Data collected from the electronic health record at enrollment will include:

- Baseline sociodemographic data
- Admission height and weight
- Admission diagnosis
- Duration of mechanical ventilation prior to study enrollment
- APACHE II Illness score

Data collected at the patient bedside will included:

- Baseline ventilator variables including
    - PEEP
    - Pressure support above PEEP
    - Fraction of inspired oxygen (FiO_2)
    - Tidal Volume

- Study specific measurements
    - Transpulmonary plateau pressure during a volume control breath
    - Transpulmonary driving pressure during a volume control breath
    - Airway plateau pressure during a volume-control breath
    - Airway driving pressure during a volume-control breath
    - Airway plateau pressure during a pressure-support breath
    - Airway driving pressure during a pressure-support breath
    - Transpulmonary plateau pressure during a pressure support breath
    - Transpulmonary driving pressure during a pressure support breath
    - Airway plateau pressure during a pressure-support breath measured using a Respironics NM3 device
    - Airway driving pressure during a pressure-support breath measured using a Respironics NM3 device

- Dynamic change in airway pressure ("occlusion pressure") and transpulmonary pressure during an airway occlusion maneuver during a pressure support breath
- Respiratory effort as measured by the ventilator p(0.1).
- Change in tidal volume with a decrease in set pressure-support
- Change in airway and transpulmonary plateau pressure with decreased pressure support
- Change in airway and transpulmonary driving pressure with decreased pressure support

Data collected from the EHR after study specific measurements will include

- Total duration of mechanical ventilation in days
- Total duration of intensive care length of stay in days
- Total duration of hospital length in stay in days
- Survival to discharge

No data will be collected after the patient is discharged from the hospital.

8. Randomization

This is a cohort study and there will be no randomization of patients to a treatment or control. Due to possible bias based of order of methods assessed, we will randomize the order that each patient is tested, including the gold standard (A) and the three methods of interest (B, C and D). Randomization schema will be a simple randomization of the methods for each patient, where each patient will be assessed on all 4 methods. A list of method order will be created prior to study start with order consisting of (e.g. ABCD, BCDA, CDAB, etc).

9. ASOP procedures.

ASOP is a prospective cohort study comparing three methods for assessing risk of self-induced lung injury to a gold-standard measurement in patients with acute respiratory failure being managed with pressure-support ventilation.

The study will compare the following four methods for assessing risk for SILI during PSV:

1. The transpulmonary plateau and driving pressure during a volume control. This will be considered the gold standard measurement of both plateau and driving pressure.
2. The airway plateau and driving pressure during a volume control breath.
3. The airway plateau and driving pressure during a pressure support breath
    a. This variable will be measured in two ways. Once using an inspiratory hold on the Servo ventilator, and once using a Respironics NM3 device with VentAssist SoftWare.
4. The dynamic change in airway pressure and transpulmonary pressure during an end expiratory occlusion maneuver during a pressure support breath.

After enrollment, all baseline ventilator settings will be recorded (including PEEP, pressure support, tidal volume, and FiO2).

The patient will then be transitioned to a study ventilator with software needed to measure esophageal and transpulmonary pressure. A Respironics NM3 device with VentAssist software will be connected to the ventilator. With this ventilator, an inspiratory hold can be performed in pressure support ventilation, so a plateau pressure (P plat) and driving pressure (DP) in PSV mode will be recorded. For all measurements with an esophageal balloon, an orogastric catheter fitted with esophageal balloon will be placed, with placement validated using previously described techniques.[6] Flow cycling will be set to the minimal value.

The following study procedure will be followed for each patient participating (note: variable numbers correspond to those in research data form).

1) Record baseline demographic and clinical data in study data sheet.

2) Record baseline ventilator data in study data sheet
   a) Baseline PEEP
   b) Baseline Pressure support
   c) Baseline FiO2
   d) Baseline Respiratory rate
   e) Baseline Tidal volume
      i) Record 5 measurements in data sheet, calculate mean

3) Determine study maneuver order (from predetermined randomization of maneuvers).

4) Insert esophageal pressure catheter and confirm placement by Baydur maneuver. Attach NM3 device. Set flow cycling to the minimum amount.

5) Perform following maneuvers in predetermined order, and record associated variables/measurements. All measurements to be done with PEEP, PS, and FiO2 the same as baseline reading in section 2 as above.

   a) Static respiratory system driving pressure (*DPrs*), respiraptory system driving pressure as measured by NM3 monitor (DPrs-NM3), and transpulmonary driving pressure (*DPtp*) and p(0.1) using inspiratory hold in pressure-support ventilation
      i) Record PEEP from ventilator(a.1)
      ii) Record PEEP from NM3 monitor (a.2)
      iii) Record end expiratory esophageal pressure (a.3)
      iv) Perform inspiratory hold
         (1) Measure airway plateau pressure (a.4)
         (2) Measure end-inspiratory esophageal pressure (a.5)
      v) Record plateau pressure as measured from NM3 monitor (a.6)
      vi) Repeat for 5 total measurements of each variable
      vii) Calculate respiratory system driving pressure from ventilator (a7 = a.4 – a.1) for each recorded breath
      viii) Calculate respiratory system driving pressure from NM3 (DPrs-NM3) monitor (a.8 = a.6-a.2)

ix) Calculate transpulmonary driving pressure from ventilator and esophageal balloon ([a.4-a.5]-[a.1-a.3]) for each recorded breath
x) Record P(0.1) from ventilator for 5 breaths (a.10)

b) Measure dynamic respiratory system driving pressure (DPrs-dyn) and transpulmory driving pressure (DPtp-dyn)
   i) Record PEEP from ventilator (b.1)
   ii) Record PEEP from NM3 monitor (b.2)
   iii) Record end-expiratory esophageal pressure during a breath (b.3)
   iv) Record maximum airway pressure (b.4)
   v) Record maximum inspiratory esophageal pressure (b.5)
   vi) Record Airway plateau pressure from NM3 monitor (b.6)
   vii) Repeat for 5 total measurements of each variable
   viii) Calculate dynamic driving pressure across the respiratory system (*DPrs-dyn) (b.7* = b.4-b.1)
   ix) Calculate dynamic transpulmonary driving pressure (*DPtp-dyn) (b.8* = ([b.4-b.5]-[b.1-b.3])
   x) Calculate the dynamic driving pressure across the respiratory system from the NM3 monitor DPrs-Dyn-NM3 (b.6-b.2)

c) Measure airway occlusion test (AOC)
   i) Measure PEEP (c.1)
   ii) Measure end expiratory esophageal pressure (c.2)
   iii) Perform expiratory hold
      (1) Expiratory hold should be held for entirety of respiratory effort until airway pressure returns to baseline
         (a) Measure maximum negative deflection of airway pressure (c.3)
         (b) Measure maximum negative deflection of esophageal pressure (c.4)
   iv) Repeat 5 total measurements of each variable
   v) Calculate airway occlusion pressure (*AOC* = c.1-c.3) for each breath

d) Measure static respiratory system (*DPrs-vc*) and transpulmonary driving pressure (*DPtp-vc)* in volume control breath
   i) Change ventilator mode to SIMV (PSV+VC), with IMV breaths set in Volume control.
      (1) Set PSV settings identical to baseline settings recorded in section 2.
      (2) For VC breaths, volume set to average tidal volume calculated in section 2. subsection D.
      (3) Set rate of IMV breaths to 1/min
      (4) Set flow rate for VC breaths to minimum
   ii) Measure PEEP (d.1)
   iii) Measure end-expiratory esophageal pressure (d.2)
   iv) Measure airway plateau (d.3) during inspiratory hold
   v) Measure end-inspiratory esophageal pressure (d.4) during inspiratory hold
   vi) Repeat for 5 total measurements of each variable
   vii) Calculate respiratory system driving pressure (*DPrs*-vc = d.2-d.1)
   viii) Calculate transpulmonary plateau pressure (d.6 = d.2-d.4)

ix) Calculate driving pressure across the lung (*DPtp-vc*= d.6 –(d.1-d.3))

e) Measure change in airway plateau pressure and patient effort with decrease in Pressure-support.
   i) Ventilator will be returned to baseline settings
   ii) The set pressure support will be decreased by 5 cm of H_2O (to a minimum of 5 cm of H_2O)
   iii) The new tidal volume will be recorded (e.1)
   iv) Measure PEEP (e.2)
   v) Measure end-expiratory esophageal pressure (e.3)
   vi) Perform and inspiratory hold in pressure-support
      (1) Measure airway plateau pressure (e.4)
      (2) Measure end-inspiratory esophageal pressure (e.5)
   vii) Measure a P(0.1) (e.6)
   viii) Repeat for 5 total measurements of each variable
   ix) Calculate new static respiratory system driving pressure *(DPrs-new)* (e.7=e.4-e.2)
   x) Calculate new transpulmonary driving pressure *(DPl-new)* (e.8=[e.4-e.5]-[e.2-e.3])

f) Return all ventilator settings to baseline.

The order of performing these measurements will be randomized to minimize bias of the order of measurements.

All study specific measurements and maneuvers will be completed in one day. After completion of study measurements and maneuvers, the orogastric balloon will be removed.

A patient's EHR will be monitored until hospital discharge to collect previously mentioned study specific endpoints as described above.

Overall, we plan to enroll 25 patients.

10. Statistical design, analyses, sample size, and power

Statistical Design and Analysis Plan

Patient and clinical characteristics will be described overall using frequency and percent for categorical characteristics, and mean, standard deviation, median, and quartiles for continuous variables. Agreement statistics such as the intraclass correlation coefficient (ICC), Bland-Altman plots, and Cohen's kappa, will be used to assess agreement of measures between the gold-standard and the three methods of interest. A mixed-effects regression model will be used to determine the difference between each method and the gold-standard taking into account the randomization order with results presented as the least squares mean (LSM) difference with 95% confidence interval (CI). All analyses will be performed using SAS 9.4 (Cary, NC) and a p-value <0.05 will be considered statistically significant.

Sample Size and Power

This is a descriptive study. The 25-person sample size reflects the pragmatics of recruitment with available study staff and should provide adequate power to evaluate similarities given that each patient acts as his/her own control.

11. Subject Participation and Duration

Study specific measurements will take one day to complete. Patients will be followed until their discharge from the hospital.

12. Study Duration

We estimate that from the time enrollment opens it will require 1 year to complete all study activities.

13. Costs to the Subject

There are no costs to participants.

14. Compensation

There is no compensation for participation in this study.

15. IRB

Duke University Health System (DUHS) IRB will be utilized as the IRB of record for this project.

16. Risk-benefit assessment

The overall study is believed to be a minimal risk trial. All study maneuvers and measurements, including esophageal balloon placement, end-inspiratory holds, and end-expiratory holds, are all parts of routine clinical care. Minor discomfort may be associated with esophageal tube placement, end-inspiratory holds, and end-expiratory holds. Minor discomfort can also be associated with a breath hold used for changing ventilators. Actually changing ventilators is minimal risk, and is again common in clinical practice (i.e. patients are often placed on travel ventilators to travel to have imaging studies performed). All patients, as they will be mechanically ventilated, should be receiving or have available analgesic and/or sedating medications as part of routine clinical care that should mitigate the risk of discomfort.

Esophageal balloon placement and use can assist with ventilator management and may be used by the patients' treatment teams after study measurements are taken, which may be an indirect benefit to patients who otherwise would not have a orogastric balloon placed. Placement of the orogastric tube with an esophageal balloon rarely could cause esophageal injury. This is more often associated with long-term placement of the balloon, which will not occur in this stidy.

Additionally, as with any research, there is always a potential loss of confidentiality. Appropriate safeguards are in place to ensure confidentiality, as described in the RDSP. Participants' LAR can choose not to participate and continue receiving normal standard of care.

Recruitment and informed consent procedures

First, the Duke Institutional Review Board (IRB) will review and approve the study protocol before study initiation. Informed consent will be required from all participants or their legally authorized representative. Enrollment is completely voluntary.

Protections against risk

General oversight

There are several ongoing mechanisms for monitoring the occurrence of adverse events. First, all study patients will be directly monitored by trained clinical staff (either a physician, respiratory therapist, or both) during study measurements and maneuvers to assess for adverse events. After enrollment, patients' EHR will be monitored daily by study personnel, which will allow identification of any long-term adverse events associated with orogastric balloon placement.

Vulnerable populations. We will not enroll participants from vulnerable populations (e.g., imprisoned persons, minors).

17. Data & safety monitoring

Data Accuracy and Protocol Compliance.

The PI will supervise the study, including data management, data accuracy, and protocol compliance. The co-PI (Dr. Pratt) will be the chief data manager and will adhere to established federal and institutional safety and protection guidelines. To assure data accuracy, the co-PI will review data reports on a routine basis. These reports will show enrollment, missing data, and other values that are neither study ID- nor outcome-based.

Adverse events (AEs), serious adverse events, (SAEs) and unanticipated problems (UPs).

It is anticipated, in this study, for AEs to be extremely rare as all interventions are part of routine clinical care and are associated with minimal risk. However, since enrolled patients will be critically ill and experiencing acute respiratory failure, it is expected that patients will have a number of unrelated adverse health events during the course of their hospital stay.

Therefore, for this study, only adverse events related to study maneuvers and measurements and long-term esophageal balloon placement will be recorded.

Adverse events related to study maneuvers and measurements will include:

- A change in respiratory status requiring increasing ventilator support (e.g., a decrease in peripheral oxygen saturation requiring an increase in ventilator FiO_2).
- Hemodynamic instability requiring addition or up-titration of vasopressors.

Adverse events related to nasogastric balloon placement will include:

- Esophageal injury
- Upper gastrointestinal bleeding

Like AEs, it is not anticipated that SAEs will occur. However, for this study, an SAE would be defined as a death related to study procedures. All serious adverse events will be reported within the standard timelines required to the IRB as appropriate and when applicable.

As the study intervention is short, it is not expected that there will be any protocol deviations. Should protocol deviations or unanticipated problems occur, they will be discussed with the PI, documented, and reported to the IRB as appropriate and when applicable.

Period and Frequency for Event Assessment and Follow-Up

Protocol deviations and other unanticipated problems, as well as AEs and SAEs, will be recorded throughout the study and reported, as appropriate, to the IRB when applicable.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or until hospital discharge (for SAEs).

Characteristics of an Adverse or Serious Adverse Event
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.

Expectedness

The Study PI will be responsible for determining whether an event is expected or unexpected. An 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.

Severity

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

Reporting Procedures

Serious (fatal or life-threatening) SAEs that are unanticipated and that are related to the intervention will be reported to the IRB within 5 days of study staff's knowledge of the SAE.

Protocol Deviations and Other Unanticipated Problem Reporting

Incidents or events that meet the reporting criteria, as outlined by the Duke IRB, will be reported to the Duke IRB as needed.

The following will be included, at a minimum:

- A detailed description of the event, incident, experience, or outcome.
- 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.

Compliance regarding Adverse Event Reporting.

The study team will be required to document and report adverse events (including serious adverse events) to the Institutional Review Board (IRB), as appropriate and in line with institutional reporting criteria.

17. Privacy, Data Storage & Confidentiality

Privacy

The study team will closely safeguard participant privacy regarding protected health and personal information. A study ID number will be generated at the time of consent and will be maintained in a secure file (e.g., linker file) which will contain the participant. Further, names, birth dates, telephone numbers, and addresses will be stored securely as described in the RDSP and only accessible by delegated study team members.

Data Storage

We will use a secure REDCap database to collect and store all study-related information. Additionally, datasets will be stored on the secured Duke server \\duhs-vclin-nc1\dusom_biostats_fs\data\BiostatsCore\CRU\Pulmonology\\ for statistical analysis.

Confidentiality

Subjects will not be identified on any study reports. University firewalls, multiple passwords, and encryption programs protect the security of the electronic data, which will be housed on a highly secure Duke University server. All personal computers are located in lockable offices and are accessible only by frequently changed passwords. The server room is accessible only to designated University Systems Administrators.

References:

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