Providing Optimal PEEP During Mechanical Ventilation for Obese Patients using Esophageal Balloon

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Providing Optimal PEEP During Mechanical Ventilation for Obese Patients using Esophageal Balloon: Master Protocol

Complete Title:	Effect of Esophageal Pressure Measurement to Determine Optimal Positive End-expiratory Pressure Compared to Usual Care in Obese Patients Receiving Mechanical Ventilation
Short Title:	PROP OPEN - Providing Optimal PEEP During Mechanical Ventilation for Obese Patients using Esophageal Balloon
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Table of Contents

Abbreviation	Definition
PEEP	Positive end expiratory pressure
MV	Mechanical ventilation
ARDS	Acute respiratory distress syndrome
P_{tp}	Transpulmonary pressure
P_{es}	Esophageal Pressure
P_{aw}	Airway pressure
FiO_2	Fraction of inspired oxygen
SpO_2	Peripheral oxygen saturation
MICU	Medical intensive care unit
RASS	Richmond Agitation-Sedation Scale
CAM-ICU	Confusion Assessment Method for the ICU
SOFA	Sequential Organ Failure Assessment
APACHE	Acute Physiology and Chronic Health Evaluation
VFD	Ventilator-free days
LAR	Legally authorized representative

Protocol Synopsis

Study Title	Effect of Esophageal Pressure Measurement to Determine Optimal Positive End-expiratory Pressure Compared to Usual Care in Obese Patients Receiving Mechanical Ventilation
Funder	Departmental funds
Study Rationale	The use of positive end-expiratory pressure (PEEP) in mechanical ventilation is important to reduce the collapse of alveoli between breaths. This atelectasis increases the patient's work of breathing and impairs oxygenation. In addition, atelectrauma can lead to ventilator-induced lung injury through repetitive shear injury. There is a patient-specific response to PEEP titration, but PEEP titration is frequently not guided by individual patient data. Obese patients have less compliant chest walls, which increases the apparent airway pressure required to provide mechanical ventilation. Titration of PEEP to levels high enough to prevent atelectasis and improve chest wall compliance in these patients yields apparently unsafe pressures. Yet these pressures are not likely transmitted to the alveoli. In order to evaluate the pressure transmitted to the alveoli, one should consider the pleural pressure. Direct measurement of the pleural pressure is highly invasive and poses risk to the patient. However, estimation of the pleural pressure using an esophageal pressure monitor is significantly less invasive and provides an acceptable alternative for estimation of transpulmonary pressure (Ptp). Preliminary work by members of the research group evaluated time to wean from mechanical ventilation in obese patients requiring tracheostomy. Use of Ptp to guide PEEP choice resulted in a significant reduction in the median time to wean, from 14 days to 3.5 days ($p=0.012$). We propose that esophageal pressure measurement can guide optimal PEEP selection in obese patients who require mechanical ventilation and reduce their time on the ventilator.
Study Objective(s)	To evaluate whether esophageal pressure measurement to determine optimal PEEP in obese patients receiving mechanical ventilation can reduce time on the ventilator when compared to usual care.
Study Design	Randomized-controlled clinical trial. Patients will be enrolled within 4 days of mechanical ventilation and randomized 1:1 to titration of PEEP based on esophageal balloon pressures or based on the "High PEEP" ARDSnet PEEP/FiO2 table. All patients will have esophageal balloons placed with baseline measurement of Ptp. Patients randomized to the intervention arm will then undergo titration of PEEP based on Ptp measurements to achieve "Optimal PEEP," defined as end expiratory Ptp of 0 to +2 cm H_2O.

Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria: Obese adults (BMI ≥ 40) admitted to the medical ICU at UNC Hospitals or Vidant Medical Center at ECU with acute respiratory failure requiring mechanical ventilation. Exclusion Criteria: 1. Refusal to give consent by subject or LAR 2. Abdominal compartment syndrome 3. Chest tube for pneumothorax 4. Having been on a ventilator for >4 days 5. Suspicion of or known intracranial hypertension 6. Anticipated extubation within 24 hours 7. Chronic ventilator dependence 8. Condition that precludes placement of an esophageal balloon (esophageal or nasopharyngeal pathology preventing insertion of the esophageal balloon catheter, severe thrombocytopenia, or coagulopathy) 9. Incarceration 10. Not expected to survive >48 hours 11. Unable to obtain consent from subject or LAR 12. Unable to obtain consent due to a language barrier
Number Of Subjects	76 patients
Study Duration	Each subject's participation will last for up to 28 days. The entire study is expected to last about 12-24 months.
Study Phases	(1) Screening: Screening for eligibility and obtaining consent for enrollment. (2) Pre-Intervention: Esophageal balloon placed and baseline data collected. (3) Intervention: PEEP titrated to achieve Optimal PEEP in the intervention group. Ptp Measurements will be obtained daily and adjustments to PEEP will occur daily. (4) Subject Completion/Withdrawal: Study will conclude for each patient at 28 days after enrollment or hospital discharge.
Efficacy Evaluations	Primary evaluation measurements that will be used to assess the efficacy of the intervention are ventilator free days at day 28. Differences between control and intervention groups will be attributed to differences in PEEP management.
Safety Evaluations	Periodic review will be performed by the NC TraCS DSMB. They will review aggregate safety data after 25, 50, and 75% enrollment to ensure there are not safety differences between the groups in hypotension requiring vasopressors and development of pneumothorax. All patients will have

	continuous monitoring of HR, BP, and oxygenation per ICU protocol to monitor patient safety.
Statistical And Analytic Plan	This is a randomized, controlled trial to evaluate the effect of using Optimal PEEP based on an esophageal balloon measurement on duration of mechanical ventilation. We hypothesize that using Ptp to identify optimal PEEP will reduce time on the ventilator and therefore increase the ventilator free days at day 28. The primary outcome is the number of ventilator-free days, defined as the number of days alive and ventilator-free by day 28. Differences between the two groups in the primary outcome will be analyzed using independent t-tests and a linear regression model adjusting for BMI, abdominal girth, and Ptp.
DATA AND SAFETY MONITORING PLAN	The PI will be responsible for maintaining patient data and ensuring accuracy of the data collected. All patient data will be collected using REDCap through the NC TraCS system. REDCap allows for immediate data validation and range setting to reduce the likelihood of erroneous data entry. Data created for analysis will be de-identified and secured on a password protected UNC School of Medicine network hard drive. All investigators will be trained on completing the electronic case report form. Patient safety will be monitored with continuous cardiovascular monitoring by the critical care team. Subject stopping rules will be in place to end the study intervention, including refractory hypotension, development of pneumothorax, or changes in oxygenation or hemodynamics that the primary team feels may be related to changes in PEEP.

1 BACKGROUND AND RATIONALE

1.1 Introduction

This is a randomized, controlled trial evaluating the effect of “optimal PEEP” compared to standardized PEEP titration on duration of mechanical ventilation in obese adult patients with acute respiratory failure requiring mechanical ventilation.

1.2 Description of Intervention

All patients in both groups will have an esophageal balloon catheter inserted by a research investigator. The catheter will be inserted into their nare while upright (head of bed >30 degrees) to a depth slightly more than the estimated distance from the lower sternum to the back of the ear (typically around 60 cm). Gastric positioning will be confirmed with abdominal compression testing and the catheter then retracted 10 – 20cm into the lower esophagus. Placement will be confirmed with the presence of cardiac oscillations on the esophageal probe. The probe will then be secured to the patient’s nasal opening using tape. Pressures (Pes, Paw, and Ptp) are measured directly through the ventilator. Values of Paw, Pes, and Ptp will be collected daily in both groups. The waveforms of Paw, Pes, and Ptp will be visualized on the ventilator. Ptp is obtained from Paw – Pes. PEEP will be increased on the ventilator to achieve a Ptp between 0 and +2 cm H2O (“Optimal PEEP”). Measurements will be obtained daily and adjustments to PEEP will occur daily. PEEP will be reduced below Optimal PEEP in the setting of hemodynamic compromise (requiring increasing vasoactive medications for blood pressure support).

1.3 Relevant Literature and Data

The use of PEEP in mechanical ventilation is important to reduce the collapse of alveoli between breaths. This atelectasis increases the patient’s work of breathing and impairs oxygenation. In addition, atelectrauma can lead to ventilator-induced lung injury (VILI) through repetitive shear injury. (1) There is a patient-specific response to PEEP titration, but PEEP titration is frequently not guided by individual patient data. Obese patients have less compliant chest walls, which increases the apparent airway pressure required to provide mechanical ventilation. Titration of PEEP to levels high enough to prevent atelectasis and improve chest wall compliance in these patients yields apparently unsafe pressures. Yet these pressures are not likely transmitted to the alveoli. (2) In order to evaluate the pressure transmitted to the alveoli, one should consider the pleural pressure. Direct measurement of the pleural pressure is highly invasive and poses risk to the patient. However, estimation of the pleural pressure using an esophageal pressure monitor is significantly less invasive and provides an acceptable alternative for estimation of transpulmonary pressure (Ptp). (3–6) Preliminary work by members of the research group evaluated time to wean from mechanical ventilation in obese patients requiring tracheostomy. Use of Ptp to guide PEEP choice resulted in a significant reduction in the median time to wean, from 14 days to 3.5 days (p=0.012). (7) We propose that esophageal pressure measurement can guide optimal PEEP selection in obese patients who require mechanical ventilation and reduce their time on the ventilator.

2 STUDY OBJECTIVE

The overall purpose of the study is to evaluate the effect of using an esophageal balloon determined optimal PEEP management strategy on the duration of mechanical ventilation in obese adult patients with acute respiratory failure requiring mechanical ventilation.

2.1 Primary Objective

To determine if titration of PEEP to Optimal PEEP results in a reduction of the duration of mechanical ventilation in obese adults in a medical ICU.

3 INVESTIGATIONAL PLAN

3.1 Study Design

We will conduct an open label randomized controlled clinical trial to evaluate the impact of titration to Optimal PEEP compared to use of a standardized PEEP table on the duration of mechanical ventilation in obese patients with acute respiratory failure. Patients will be followed for 28 days to evaluate for ventilator-free days. Blinding of the clinical team will not be possible due to the differences in treatment approach, including the performance of spontaneous breathing trials.

3.2 Allocation to Treatment Groups

Patients will be randomized 1:1 in blocks of 2, 4, or 6 to Optimal PEEP vs High-PEEP ARDSnet PEEP/FiO2 table PEEP management. Randomization will be completed using the REDCap randomization module.

3.3 Study Duration, Enrollment and Number of Participants

Enrollment will continue until 38 participants have been enrolled in each group (76 participants total). The medical ICU (MICU) admits approximately 150 per month, 40-50% of whom require mechanical ventilation. Based on a previous evaluation of lung protective ventilation in our hospital, approximately 45% of our patients requiring mechanical ventilation have a BMI ≥40. Therefore, the MICU conservatively admits approximately 24 patients a month that meet inclusion criteria. Based on expected enrollment of at least 3-4 participants per month, the trial is expected to complete enrollment within 24 months. Each patient's participation will last 28 days or until death or hospital discharge.

3.4 Study Population

Inclusion Criteria: Obese adults (BMI ≥ 40) admitted to the MICU at UNC Hospital or the ICU at Vidant Medical Center ECU with acute respiratory failure requiring mechanical ventilation.

Exclusion Criteria:

1. Refusal to give consent by the subject or their LAR
2. Abdominal compartment syndrome
3. Chest tube for pneumothorax
4. Having been on a ventilator for >4 days
5. Suspicion of or known intracranial hypertension
6. Anticipated extubation within 24 hours
7. Chronic ventilator dependence
8. Condition that precludes placement of an esophageal balloon (esophageal or nasopharyngeal pathology preventing insertion of the esophageal balloon catheter, severe thrombocytopenia or coagulopathy)
9. Incarceration
10. Not expected to survive >48 hours
11. Unable to obtain consent from subject or LAR
12. Unable to obtain consent due to a language barrier

4 STUDY PROCEDURES

4.1 Screening/Enrollment

Daily screening of all intubated patients in the MICU at UNC Hospital and the ICU at Vidant Medical Center ECU will be conducted by the research team. Intubated patients will be evaluated for inclusion and exclusion criteria. For patients meeting inclusion criteria, the primary clinical team will then be approached for permission to enroll prior to approaching families of patients for enrollment.

4.2 Randomization, Concealment, and Blinding

Patients will be randomized 1:1 in random blocks of 2, 4, or 6 to optimal PEEP vs standard PEEP management. Allocation concealment will be performed through the REDCap randomization module. Due to the obvious treatment differences between the two groups, blinding of treatment group will be impossible. However, we will have one outcome assessor who will have access only to the data necessary to determine the primary outcome (VFD at 28-days), and this assessor will be blinded to treatment group using built-in REDCap tools.

4.3 Intervention procedures

All patients in both groups will have an esophageal balloon catheter inserted by a research investigator. The catheter will be inserted into their nare while upright (head of bed >30 degrees) to a depth slightly more than the estimated distance from the lower sternum to the back of the ear (typically around 60 cm). Gastric positioning will be confirmed with abdominal compression testing and the catheter then retracted 10 – 20cm into the lower esophagus. Placement will be confirmed with the presence of cardiac oscillations on the esophageal probe. The probe will then be secured to the patient's nasal opening using tape.

Pressures (Pes, Paw, and Ptp) are measured directly through the ventilator. Values of Paw, Pes, and Ptp will be collected daily in both groups.

4.4 Participant Completion/ Withdrawal

Participants will complete the study at the time of death or the conclusion of 28 days, whichever occurs first.

Early completion of the trial for each participant will occur if any of the following outcomes are met:

a. Patient or family withdraw consent for the study
b. The clinical team feels that the patient no longer meets appropriateness for the study
c. Patient develops and adverse effect felt possibly related to the intervention (refractory hypotension, nasopharyngeal bleeding, pneumothorax, etc)

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Measurements

Procedures for PEEP and FiO2 Titration

Both groups will have their FiO2 titrated based on results of the PaO2 from an arterial blood gas, if available, or SpO2 values if no arterial blood gas is obtained. PEEP titration will vary by group as below.

Setting PEEP in Intervention Group

The waveforms of Paw, Pes, and Ptp will be visualized on the ventilator. Ptp is obtained from Paw – Pes. PEEP will be increased on the ventilator to achieve a Ptp between 0 and +2 cm H2O (Optimal PEEP). Measurements will be obtained daily and adjustments to PEEP will occur daily. PEEP will be reduced below Optimal PEEP in the setting of hemodynamic compromise (requiring increasing vasoactive medications for blood pressure support).

Setting PEEP in Control Group

PEEP in the control group will be determined by High PEEP ARDSnet PEEP/FiO2 table. Titration of PEEP will occur when clinically indicated by PaO2 or SpO2, and FiO2. We chose the High PEEP table based on the clinical suspicion that obese patients may require higher PEEP levels on average than non-obese patients to balance the additional pressure of their chest wall. In addition, EPVent2, a study of esophageal balloon PEEP titration in patients with ARDS utilized the High PEEP table. Patients with moderate and severe ARDS benefit from higher levels of PEEP. (8)

Procedures for Assessment of Readiness for Extubation

Both groups will have a daily assessment of readiness for extubation performed by the Respiratory Therapist and bedside RN according to the standard clinical protocol. Criteria for both groups to undergo a spontaneous breathing trial (SBT) will be the following:

1) Not in prone position
2) No increased ICP
3) No active seizures
4) No alcohol withdrawal requiring escalating treatment
5) No active myocardial ischemia in discussion with nursing or physician
6) No unstable spine fractures
7) No free muscle flaps
8) FiO2 ≤ 50% and SpO2 ≥ 90%
9) Minute Ventilation < 15 L/min
10) Minimal vasopressors (norepinephrine < 5mcg/min or 0.05 mcg/kg/min, dopamine/dobutamine ≤ 5 mcg/kg/min)
11) HR < 140
12) RR ≤ 35
13) SBP > 90 and < 180

Failure of an SBT will be demonstrated if any of the following criteria are met:

1) SpO2 < 90% sustained ≥ 5 minutes
2) Spontaneous VT ≤ 4ml/kg IBW – sustained ≥ 5 minutes
3) Respiratory Rate ≥ 35/min
4) Rapid Shallow Breathing Index >105
5) Other signs of respiratory distress (distress = 2 or more)
6) HR > 140
7) Marked accessory muscle use
8) Abdominal paradox (belly breathing)
9) Diaphoresis

Failure of an SBT will be determined by the bedside RT based on current policy (PolicyStat ID: 4745433). If a patient fails an SBT, they will be returned to their previous ventilator settings until the next daily assessment. If the patient tolerates a 30-minute SBT, they will be returned to their previous ventilator settings for 60 minutes, then extubated to an appropriate oxygen delivery device. Ventilator settings during the SBT and extubation procedures will vary between groups as below. Blinding of the respiratory therapist determining eligibility for SBT to treatment arm will not be possible because of the differences between SBT protocols. However, the study team will make no determinations of readiness for extubation. If a member of the study team is on service during the time of potential enrollment, these patients will be excluded to avoid bias.

SBT and Extubation Procedure for Intervention Group

Patients in the Intervention group will undergo an SBT regardless of their PEEP level. The PEEP that generates a Ptp of 0 will be considered their optimal PEEP, and this will not be lowered for the SBT. The Intervention Group SBT will consist of a trial of a pressure support of 5 cm H2O and Optimal PEEP.

SBT and Extubation Procedure for Control Group

Patients in the Control group will undergo an SBT **when they reach a PEEP ≤8** cm H2O. This is the current standard of care based on the SBT protocol at UNC Hospitals. SBT and extubation prior to meeting these criteria will be based on primary medical team's discretion and will be recorded for analysis and safety tracking.

Procedures for ventilator weaning after tracheostomy

Any patient who fails to be eligible for extubation or fails extubation will be eligible for tracheostomy per usual unit protocol. The study team will play no part in the decision to proceed with tracheostomy for ventilator weaning. After tracheostomy, it is routine practice to forego SBT and proceed with trials of liberation from the ventilator with oxygen delivered by an aerosol tracheostomy collar ("trach collar trials" or TCT). The same criteria are used to perform a TCT as an SBT above. The two groups will have different approaches to TCT.

TCT Procedure common to both groups

TCT will proceed for up to 12 hours as tolerated by the patient. Interval mechanical ventilation will be provided using a control mode of mechanical ventilation (typically PRVC with 6-8 ml/kg of IBW tidal volume). After 2 successful 12-hour TCT, a subsequent 24-hour TCT will be performed with no plan for interval mechanical ventilation. If the patient tolerates >48 hours of time free from mechanical ventilation, they will be considered liberated from mechanical ventilation. If they fail the 24-hour TCT, they will be placed back on mechanical ventilation and a subsequent 24-hour trial will be performed the following day. This pattern will continue until the patient is successfully liberated from mechanical ventilation.

TCT Procedure for Intervention Group

Based on the use of optimal PEEP in this group, and the experience in the previous study protocol (7), we will place patients in the Intervention group on TCT **ONLY** with a speaking valve. This simulates the normal process of utilizing the upper airway to maintain lung inflation that is performed automatically when a patient does not have an artificial airway.

TCT Procedure for Control Group

The control group will be placed on TCT with no requirement for speaking valve. They may utilize a speaking valve if tolerated and desired, but there is no requirement as there is in the Intervention group.

5.2 Other measurements

Variable	Source	How Measured	Baseline	Daily	Completion
Outcomes					
Ventilator free days at day 28 (*Primary outcome*)	EMR	Days alive and free of the ventilator			X
Reintubation	EMR	Intubated within 72 hours of extubation		X	X
ICU Length of Stay	EMR	Days			X
Hospital Length of Stay	EMR	Days			X
Tracheostomy	EMR	Y/N			X
Extubation prior to meeting established criteria	EMR	Y/N			X
Highest RASS	EMR	-5 to +4 (single highest value used)	X	X	
Lowest RASS	EMR	-5 to +4 (single lowest value used)	X	X	
Exposures					
Esophageal pressure (Pes)	Ventilator	cm H2O	X	X	
Airway pressure (Paw)	Ventilator	cm H_2O	X	X	
Transpulmonary pressure (Ptp) (inspiratory and expiratory)	Ventilator	cm H_2O	X	X	
PEEP	Ventilator	cm H_2O	X	X	
Opioids	EMR	Continuous, bolus sch, bolus prn, oral sch, oral prn	X	X	
Propofol	EMR	Y/N	X	X	
Dexmedetomidine	EMR	Y/N	X	X	
Benzodiazepines	EMR	Continuous, bolus sch, bolus prn, oral sch, oral prn	X	X	
Antipsychotics	EMR	Sched, PRN	X	X	
Neuromuscular blockade	EMR	Y/N	X	X	
Corticosteroid use	EMR	Y/N	X	X	
Fluid Balance	EMR	Net fluid balance prior to extubation		X	
Safety Measures					
Vasopressor requirement	EMR	norepinephrine equivalents(9)	X	X	
Pneumothorax	EMR	Y/N	X	X	
Other Variables of Interest					
Age	EMR	Years	X		
Race/Ethnicity					
BMI	EMR	kg/m^2	X		
Partial Pressure of Oxygen (PaO_2)	EMR	mmHg	X	X	
Oxygen Saturation (SpO_2)	EMR	%	X	X	

PaO_2/FiO_2 ratio	Calculated	Number	X	X	
SpO_2/FiO_2 ratio	Calculated	Number	X	X	
Charlson Comorbidities	EMR	Y/N	X		
Waist circumference	EMR	cm	X		
CAM-ICU	EMR	Positive/Negative	X	X	
SOFA	EMR	Calculated	X		
COVID (y/n)	EMR	Y/N	X		

6 STATISTICAL CONSIDERATION

6.1 Primary Endpoint

The primary outcome is the number of ventilator-free days (VFD), defined as the number of days alive and ventilator-free by day 28. The assessment of the primary outcome will be conducted by a study team member after subject completion in the study. In order to minimize potential bias, this team member will be blinded to treatment arm assignment.

6.2 Statistical Methods

All continuous variables (see 5.2) will be described using mean and standard deviation, with associated 95% confidence intervals, or median with interquartile range as appropriate based on normality of distribution. All categorical variables will be described with frequency and percentage.

To determine if the optimal PEEP has an effect on the duration of mechanical ventilation compared to usual PEEP, the primary outcome will be analyzed with a 2-sided independent t-test. As secondary analysis, the associations between the primary outcome and exposures and demographic variables will be further analyzed using linear regression models.

The impact of optimal PEEP vs standardized PEEP titration will be assessed on all other variables with independent t-tests or chi-square tests as appropriate. All secondary outcomes, as described in 5.2, will be further analyzed with either linear regression models or logistic models, using demographic and exposure variables as predictors.

All tests will be 2-sided, and p-values < 0.05 will be considered significant. Tests with p-values above 0.05 will be considered inconclusive. Missing values will be ignored.

No interim analyses for efficacy or futility are planned, but interim analyses will be conducted for safety.

6.3 Sample Size and Power

We utilized preliminary data from earlier studies of mechanical ventilation in the obese to establish a baseline. With a mean duration of mechanical ventilation of 7 days with a standard deviation of 2.9 days, we expect the control group to have 21 ventilator free days. We estimate that we could reasonably see an effect in the intervention group that reduces the duration of mechanical ventilation by 3 days. With a power of 80% and alpha=0.05, we would need 16 patients per group, for a total of 32 patients. Would the effect be only a reduction of mechanical ventilation by 2 days, we would need 34 patients in each group for a total of 68 patients. Because the population in our study would be expected to have a lower mean duration of mechanical

ventilation, we anticipate we may find a smaller effect size. Including a possible 10% dropout, we will target a sample size of 76 (38 per group) to safely achieve our goals.

7 SAFETY MANAGEMENT

7.1 Risks to Human Subjects

The placement of the esophageal balloon catheter in carefully selected patients (see exclusion criteria above) confers a relatively small risk to the patient (such as trauma to the nasopharynx, esophageal irritation, stimulation of cough or vomiting). Adverse events possibly related to mechanical ventilation and PEEP titration will be defined as new development of pneumothorax and hypotension thought to be related to changes in mechanical ventilation. Despite these theoretical concerns, no adverse effects were seen in a small randomized trial using an esophageal balloon to titrate to optimal PEEP in patients with ARDS. (5)

7.2 Data and Safety Monitoring Plan

All participants will be continuously monitored by critical care nurses under the guidance of critical care physicians per individual ICU protocols.

Stopping rules and procedures

Subject stopping rules will be the development of any of the following after randomization:

- New pneumothorax
    - Pneumothorax is a known risk factor for all patients requiring mechanical ventilation with a case rate of <1% of all mechanically ventilated patients. In previous studies of optimal PEEP determination using esophageal balloon-guided pressure measurement, no pneumothoraces were observed. We believe the study procedures will be safe for both arms, and that the intervention arm will be at lower risk for this outcome. However, development of a pneumothorax will necessitate a chest tube and will invalidate the measurement of pleural pressure. Therefore the study procedures must be stopped.
- Epistaxis requiring intervention
    - In the event of epistaxis requiring packing or intervention, the esophageal balloon will be removed and the study subject's participation in the study will end.
- Hypotension
    - In the event a patient experiences a drop in mean arterial pressure (MAP) below 65 mm Hg or a significant change in vasoactive medication requirement (>10 mcg/min dose of norepinephrine equivalent), that is felt by the clinical ICU team to possibly be related to the intervention, the study subject's PEEP will be dropped by 2 cm H_2O every 5 minutes until the parameter returns to an acceptable range (as determined by the clinical ICU team) or until the PEEP reaches the pre-intervention level. The patient will remain on no higher than this new PEEP for the remainder of the study.

Adverse Event Reporting

All Adverse Events will be documented and graded using CTCAE grading, defined as any patient who develops one of the following (by CTCAE grading):

- grade 3-5 hypotension
- grade 2-5 pneumothorax
- grade 2-5 epistaxis

Screening for possible adverse events will occur daily. Each possible adverse event will be reviewed by a UNC critical care physician, independent of the study, within 72 hours of occurrence. The primary independent reviewer will be Adrian Austin, MD, MSCR; if he is on clinical service responsible for the study subject, then Jason Mock, MD, PhD will serve as the independent reviewer. After independent review, events considered to be probably or definitely related to the intervention will be submitted to the IRB for review. In addition, we will utilize a Data and Safety Monitoring Board to review aggregate safety data.

7.3 Data and Safety Monitoring Board (DSMB)

We will utilize the NC TraCS DSMB for additional regulatory monitoring of the study. The DSMB will review aggregate safety data after enrollment of 25, 50, and 75% of the study participants. There will be several criteria for evaluating safety and possible early stopping of the trial. Adverse events will be graded based on the CTCAE criteria listed above (7.2 AE Reporting).

1) Pneumothorax – If 2 out of 10, or if more than 10 enrolled, 20% out of enrolled subjects experience pneumothorax, then the study will be suspended until the DSMB can review the information and provide recommendations.

2) Hypotension – If 2 out of 10, or if more than 10 enrolled, 20% out of enrolled subjects experience refractory hypotension, then the study will be suspended until the DSMB can review the information and provide recommendations.

3) Death – If 8 out of 10, or if more than 10 enrolled, 60% out of enrolled subjects die, then the study will be suspended until the DSMB can review the information and provide recommendations.

There are no stopping rules for efficacy, as there will be no interim efficacy analyses. The study is only adequately powered to detect an efficacy difference if it were completed.

8 DATA COLLECTION AND MANAGMENT

All patient data will be collected using UNC REDCap through the NC TraCS system. REDCap allows for immediate data validation and range setting to reduce the likelihood of erroneous data entry. Data created for analysis will be de-identified and secured on a password protected UNC School of Medicine network hard drive. All investigators will be trained on completing the electronic case report form.

All data will be recorded on computerized case report forms via REDCap, which will be transferred (after de-identification, as follows) to a centralized database constructed and operated for this project by the UNC TraCS Clinical Research Data Management Service. This database system provides for secure web-based data entry with the data stored on servers that we maintain. The data is encrypted during transmission. The servers are located in a secure campus area with all the appropriate physical security measures in place. One ITS group manages the space where the servers are housed, but that

team does not have access or manage content on the servers. UNC-Chapel Hill's TraCS IT staff (a team of 5 and the research team will have access to data collected in this study, as standard for most University server spaces. Research teams are provided access at the user level, per site. Only the investigators and project manager will have access to aggregate data. The data is encrypted during transmission using industry standards of TSL 1.1 algorithms (including MD5, AES, etc). The web and database servers are monitored by the TraCS IT staff, patched frequently, and scanned by a third party vendor to ensure that they are protected against known vulnerabilities. The scanning application is the standard service for the entire campus. Access is by individual user id with User-level permissions that define only those records an individual is authorized to see and is restricted to the forms and/or functions that the user needs to have. The applications themselves are written using open source tools, and have also been scanned by campus security office to ensure that the applications also are protected from known exploits. The data is backed up to electronic media on a daily basis. The electronic media is secured by ITS stored in a secure area separate from the servers.

The UNC TraCS Clinical Research Data Management Service endeavors to preserve the privacy, confidentiality, and security of protected health information that may be part of health records or research datasets. Protected Health Information (PHI) is handled according to appropriate Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Regulations. Staff who work with PHI are required to complete appropriate HIPAA and other compliance training in accordance with institution policy.

9 RECRUITMENT STRATEGY

Potential participants will be identified from daily screening of intubated patients in the MICU of each study site by research personnel. After identification of potential participants, study team members will approach the critical care team for confirmation of appropriateness and permission to enroll participants. If the clinician is agreeable, a study team member will approach the legally authorized representative for explanation of the study.

The patients' decision-making surrogates will be primarily approached to consent for participation in this study as most mechanically ventilated patients are medically or clinically sedated and not able to have decision making capacity. The investigators and/or research coordinators will approach the surrogates individually after the patients are identified as being eligible for the study to provide an informed consent process. Full disclosure will be provided that enrollment in this study will be optional and not affect major treatment decisions.

10 CONSENT PROCESS

The recruitment team will approach the patient's legal next of kin. These conversations will occur in the patient care room of the intensive care unit or a private consultation room in/near the intensive care unit with a trained study team member. Study information will be reviewed with the patient's next of kin and a copy of the IRB approved consent form will be provided for review. After having the chance to consider the trial, a time will be scheduled for the consent process. For patients whom no legal next of kin is physically present, the study team will make contact via telephone. In instances where inpatient consenting is not possible, e-consentingmay be utilized per institutional and IRB approved guidelines.

Cognitive impairment is a common symptom of critical illness and mechanical ventilation. Patients requiring mechanical ventilation are also frequently given psychoactive medications

(sedatives and analgesics) for sedation and comfort. Due to these circumstances, consent from an appropriately informed legally authorized representative (LAR) will be used for any patient who is cognitively unable to consent for any reason upon examination by research staff. Screening for cognitive impairment during screening and enrollment will entail the administration of a CAM-ICU, orientation questions or other approved methods per institutional or IRB guidelines. Cognitive impairment confirmation should be documented by research staff in enrollment notes. Consideration of appropriate LAR will be given in order of descending priority as identified by respective State law. Consent will be obtained by the study personnel in a private area.

Research staff may be introduced to family members at the bedside by the ICU physician or will call the next of kin if family is not available at the bedside. The Legally Authorized Representative (LAR) will be identified and consented for enrollment. The LAR may be a family member or surrogate in order of priority or someone who holds valid power of attorney documentation. All subjects will be informed that research is voluntary and refusal does not jeopardize their medical care or university status in any kind of way. Research subjects will be followed according to HIPAA guidelines.

Patients will be followed for recovery of cognitive function, and they will undergo the same informed consent process during reconsent if/when they are able during the hospitalization.

11 PLANS FOR PUBLICATION

At the conclusion of the study, the data will be analyzed and reported in manuscript form for submission to relevant pulmonary and critical care journals, including but not limited to *American Journal of Respiratory and Critical Care Medicine*, *Chest*, *Critical Care*, and *Journal of Critical Care*. Data will also be used for further grant applications.

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Appendix – Tables

12.1 ARDSNet PEEP/FiO2 table

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24