Preventing cardiovascular collaPse with Administration of fluid Resuscitation before Endotracheal intubation: The PrePARE Trial

Version 1.2

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1.0 Study Summary

Title: Preventing cardiovascular collapse with Administration of fluid Resuscitation during Endotracheal intubation: The PrePARE Randomized Controlled Trial
- A multi-center, randomized trial of fluid loading to prevent cardiovascular collapse during endotracheal intubation of critically ill adults.

Study Sites: LSU New Orleans/University Medical Center New Orleans ICUs, Ochsner Medical Center Jefferson Campus MICU, Vanderbilt Medical Center Nashville ICUs and Emergency Department, University of Washington Harborview Medical Center ICUs, University of Alabama Birmingham MICU, Lahey Medical Center MICU, Lincoln Medical Center Emergency Department

Background: Severe complications are common during endotracheal intubation of critically ill patients. One of the most common complications, a post-procedural decrease in blood pressure, is associated with increased resource utilization and poor clinical outcomes. Fluid loading, a rapid infusion of 500 milliliters of a intravenous crystalloid solution beginning prior to the start of the procedure, may prevent a decrease in blood pressure, but effectiveness data are lacking. Currently, pre-intubation fluid loading occurs sporadically, with significant provider practice variation. We propose a randomized trial to compare fluid loading versus none to prevent cardiovascular collapse after endotracheal intubation of critically ill adults.

Primary Aim:
- To compare the effect of fluid loading versus none on cardiovascular collapse (composite endpoint) among critically ill adults undergoing endotracheal intubation

Primary Hypothesis:
- Fluid loading will reduce the rate of cardiovascular collapse among critically ill adults undergoing endotracheal intubation

Inclusion Criteria:
1. Patient is admitted to a participating study unit
2. Planned procedure is endotracheal intubation and planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Administration of sedation (with or without neuromuscular blockade) is planned

Exclusion Criteria:
1. Operator feels fluid loading is absolutely indicated or contraindicated in the patient
2. Urgency of intubation precludes safe performance of study procedures
3. Prisoners
4. Pregnant Patients

5. <18 years of age

Consent: Given that (1) fluid loading is already an arbitrarily used approach to endotracheal intubation used in half of critically ill adults, (2) there no established risk or benefit with either approach, and (3) providers will exclude patients from this trial for whom they feel either fluid loading or no fluid loading is required for safe care, this trial poses no increased risk beyond usual ICU care to the patients. Over 90% of patients undergoing endotracheal intubation in the ICU cannot consent for the procedure itself, therefore it is impractical to obtain informed consent for research prior to the procedure. Given the minimal risk interventions and impractability of informed consent, a waiver of informed consent will be requested.

Randomization: Using opaque envelopes available in the patient care areas, participants will be randomized 1:1 to fluid loading or none.

Study Interventions:

- **Fluid Loading:**
  - **Fluid Loading** – (1) 500 milliliters of an intravenous crystalloid solution of the operator's choosing will be (2) infused at any time after randomization and prior to the administration of procedural medications from (3) above the level of the central or peripheral intravenous or intraosseus access used and allowed to infuse by gravity and (4) stopped after 500 mL have infused. All intravenous infusions preceding the decision to perform endotracheal intubation will not be altered.
  - **No Fluid Loading** – No intravenous fluids are started after the decision is made to perform endotracheal intubation. All intravenous infusions preceding the decision to perform endotracheal intubation will not be altered.

Primary Endpoint (All endpoints are collected non-invasively and are already a part of clinical data obtained in usual ICU care at the bedside or in the medical record):

- One or more of the following items indicating cardiovascular collapse:
  - Death within 1 hour of intubation
  - Cardiac arrest within 1 hour of intubation
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
  - New or increased vasopressor between induction and 2 minutes following intubation

Secondary Endpoints:

- Each of the individual items in the composite primary endpoint

- Additional fluids given to either group and started between induction and 2 minutes after intubation
- Lowest systolic blood pressure between induction and 2 minutes after intubation
- Lowest arterial oxygen saturation between induction and 2 minutes after intubation
- Incidence of hypoxemia (oxygen saturation <90%) and severe hypoxemia (oxygen saturation <80%) between induction and 2 minutes after intubation; incidence of desaturation (defined by decrease in oxygen saturation of >3%); change in saturation from induction to lowest oxygen saturation
- ICU-free days
- Ventilator-free days
- In-hospital mortality

Safety Endpoints:

- Lowest oxygen saturation in the 24 hours after intubation; highest fraction of inspired oxygen in the 24 hours after intubation; highest positive end-expiratory pressure in the 24 hours after intubation
- Cumulative diuretic dose (in furosemide equivalents) on the day of enrollment and from enrollment through three days after enrollment
- Vasopressor-free days
- Cumulative intravenous fluid administration from enrollment through three days after enrollment

2.0 Background

Endotracheal intubation is common in the care of critically ill patients (1-3). Complications of airway management in this setting are frequently encountered and may be associated with an increased risk of death (1, 2, 4, 5). The prevention of complications during urgent and emergent endotracheal intubation is a key focus for airway management research (4, 6, 7). Post-intubation hypotension (PIH), a common complication of endotracheal intubation in the critically ill (4), may be prevented by a bolus of intravenous fluid prior to the start of the procedure, but this approach has not been examined in a prospective trial.

2.1 Complications of Endotracheal Intubation of the Critically Ill

The emergent endotracheal intubation of critically ill patients is associated with an increased risk of complications compared to the intubation of patients in the OR (8). Approximately 30% of emergent endotracheal intubations in the ICU are associated with complications, including: hypotension, hypoxia, failed intubation, esophageal intubation, airway trauma, aspiration, cardiac arrest, and death (4, 8, 9). PIH, which occurs in as many as 46% of critically ill adults during endotracheal intubation (4, 10), is associated with an increased risk of mortality double that of ICU patients who do not experience procedural hypotension (10, 11). PIH is thought to be due to three potential mechanisms, all of which may respond to an intervention which increases preload with intravenous fluid: 1. procedural medication-induced hypotension, 2. pre-existing hemodynamic instability and increased venous capacitance due to decreased circulating catecholamines, and 3. decreased venous return secondary to positive pressure applied to the thoracic cavity.

2.2 Potential Mechanisms of Post-intubation Hypotension in the Critically Ill

Procedural medication-induced hypotension. In an effort to facilitate rapid placement of an endotracheal tube in the trachea, sedating and neuromuscular blocking medications are often chosen by the operator to relax the muscles of the upper airway and perform the procedure in a comfortable fashion for the patient (12, 13). Propofol and benzodiazepines, commonly selected sedatives to facilitate endotracheal intubation, are commonly associated with PIH. The mechanism by which propofol induces hypotension is thought to be related the medication's ability to venodilate and decrease preload. In a study of adults undergoing intubation, propofol caused a decrease in systolic blood pressure and increase in venous compliance measured by forearm occlusive plethysmography compared to control patients (14). Additionally, propofol may have a depressive effect on the myocardium and reduce cardiac index beyond an isolated decrease in preload (15). Decreased preload due to venodilation and a possible decrease in myocardial contractility are contributors to propofol-associated PIH observed in multiple studies of endotracheal intubation (15-18). The use of

midazolam for procedural sedation also results in PIH in critically ill adults (19, 20). Even newer sedative agents used in rapid sequence intubation, such as etomidate and ketamine, can result in venodilation and PIH. Increasing preload via the administration of an intravenous crystalloid fluid bolus prior to the administration of procedural medications may reduce the incidence of PIH associated with these medications.

Pre-existing Hemodynamic Instability. Even after treatment of critical illness has begun, critically ill adults often experience further clinical deterioration and require endotracheal intubation (21-23). In a recent randomized trial of endotracheal intubation in critically ill adults conducted by our group, prior to the start of the procedure patients had severe physiologic derangements resulting in a median APACHE II score of 22 and around 25% of patients were in shock (21, 22). Specifically, an increase in the APACHE II score by 1 point is associated with a 2% increased risk of PIH (24). Even in the absence of pre-existing shock, in a study of critically ill adults undergoing endotracheal intubation, a pre-procedure shock index (heart rate divided by systolic blood pressure) of ≥ 0.8 was strongly predictive of the development of PIH (11). Additionally, increasing pre-procedure shock index is also associated with complete cardiovascular collapse resulting in cardiac arrest (25). These shock and "pre-shock" states seen in critically ill adults are often, in part, a result of decreased preload due to hypovolemia and are often treated by the administration of intravenous fluids (26-29). Patients with shock and "pre-shock" may be dependent on circulating catecholamines to sustain blood pressure. With decreased levels of catecholamines after induction, increased venous capacitance may decrease preload, cardiac output, and mean arterial blood pressure. Again, increasing preload by the pre-procedure administration of intravenous crystalloids may improve the physiologic derangements commonly seen in critically ill adults and prevent PIH.

The New Application of Positive Pressure to the Thoracic Cavity. Venous return to the right atrium is dependent on the pressure gradient created between the predominantly positive pressure, extrathoracic anatomic sites and the predominantly negative pressure in the thoracic cavity. The application of positive pressure to the thoracic cavity by mechanical ventilation reduces venous return to the right atrium and can cause PIH in hypovolemic patients with reduced preload. Additionally, in one observational study of critically ill adults with traumatic injuries and presumed hypovolemia, intubation and positive pressure ventilation was independently associated with the new development of hypotension and increased mortality (30). Intravenous infusion of a crystalloid fluid prior to the application of positive intrathoracic pressure may increase extrathoracic pressure, increase preload, and prevent PIH in critically ill adults.

2.3 Existing Evidence on the Use of Fluid Loading to Prevent Post-Intubation Hypotension

There are no randomized trials of intravenous fluid administration to prevent PIH in critically ill adults. Fluid loading has been studied indirectly in one observational study of using a pre-procedure checklist for endotracheal intubation of critically ill adults (4). In this "before-and-after" study, observational data were collected both 6 months before and after the institution

of a pre-procedure checklist. One item on this checklist was "fluid loading" defined as an intravenous infusion of 500 milliliters of isotonic saline or 250 milliliters of a starch-based fluid in the absence of cardiogenic pulmonary edema started prior to the procedure. Prior to instituting the checklist, operators performed fluid loading in 49% of patients. During the checklist phase, use of fluid loading increased to 75% and the incidence of severe cardiovascular collapse decreased from 26% to 15%. These data support the hypothesis that fluid loading may prevent PIH; however the observational nature of this study prevents us from invoking a causal relationship. Additionally, the ten-item checklist also included other interventions which may explain a decrease in PIH, such as using only etomidate or ketamine for procedural sedation and starting an intravenous norepinephrine infusion for low measured blood pressures. As a result of a lack of evidence around this intervention and concerns about fluid loading contributing to volume overload and hypoxemia, observational studies have shown that operators use fluid loading arbitrarily in about 50% of critically ill adults undergoing endotracheal intubation (4, 31).

3.0 Rationale, Aims, and Hypotheses

In order to determine the impact of fluid loading on procedural and clinical outcomes of endotracheal intubation of critically ill patients, a randomized trial is needed.

Study Aims:

- **Primary:**
  - To compare the effect of fluid loading compared with none on a composite of cardiovascular collapse experienced by critically ill adults undergoing endotracheal intubation
- **Secondary:**
  - To evaluate the effect of the same intervention in the same population on clinical outcomes (ventilator-free days, ICU-free days, and in-hospital mortality), severe hypoxia, and airway management characteristics (first pass success, grade of view, time to completion of intubation, additional devices, additional operators)

Study Hypotheses:

- **Primary:**
  - In critically ill adults undergoing endotracheal intubation, fluid loading will reduce the incidence of cardiovascular collapse among critically ill adults undergoing endotracheal intubation

- **Secondary:**

- Fluid loading will increase the lowest systolic blood pressure measured between procedural medication administration and 2 minutes after endotracheal intubation without affecting other procedural, physiologic, and clinical outcomes

4.0 Study Description

In order to address the aims outlined above, we propose a randomized, parallel-group trial evaluating the impact of fluid loading to decrease cardiovascular collapse during and after endotracheal intubation in critically ill adults. Patients admitted to the study sites who are deemed by their clinical team to require intubation and fulfill inclusion criteria without meeting exclusion criteria will be enrolled and randomly assigned to fluid loading versus none. All other decisions regarding airway management will remain at the discretion of the treating provider. Data will be collected at the time of intubation and prospectively from the medical record in order to determine the effect of the assigned intervention on short- and long-term outcomes. All data are collected non-invasively and are already a part of clinical data obtained in usual ICU care at the bedside or in the medical record. No additional data will be collected that is not observed at the bedside or obtained from the medical record.

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria:

We will include airway management events in which:

1. Patient is admitted to participating study unit
2. Planned procedure is endotracheal intubation and planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Administration of sedation with or without neuromuscular blockade is planned
4. Age ≥ 18 years old

5.2 Exclusion Criteria:

We will exclude airway management events in which:

1. Operator believes fluid loading to be absolutely indicated or contraindicated for the safe care of the patient
2. Urgency of intubation precludes safe performance of study procedures
3. Pregnancy
4. Prisoners
5. Age < 18 years old

6.0 Enrollment/Randomization

6.1 Study Sites: Intensive Care Units at University Medical Center New Orleans (UMCNO), Vanderbilt University Medical Center in Nashville (VUMC) MICU and Emergency Department, University of Washington Harborview Medical Center, University of Alabama Birmingham, Lahey Medical Center, Lincoln Medical Center Emergency Department

6.2 Study Population: The study population will be all critically ill adults for whom the clinical team has decided to perform endotracheal intubation using sedation with or without neuromuscular blockade. Patients will be excluded only if the operator feels: 1. Additional intravenous fluids in the form of fluid loading is absolutely indicated or contraindicated, or 2. The urgency of the intubation would make performing the study procedures unsafe. Patients will be included regardless of gender, race, weight or body mass index, initial oxygen saturation, anticipated grade of view, and other clinical factors. Patients enrolled in this trial may also be enrolled in other ongoing clinical trials. Specifically, a trial with similar eligibility criteria examining the effect of ventilation between induction and laryngoscopy on per-intubation desaturation, the PreVent trial (Preventing Hypoxemia With Manual Ventilation During Endotracheal Intubation Trial; ClinicalTrials.gov Identifier: NCT03026322), may co-enroll a portion of patients in the PrePARE trial. For any trial co-enrolling with the current trialthat focuses on outcomes of endotracheal intubation, we will formally record study group assignment for both trials and perform a formal statistical test for interaction.

6.3 Enrollment: All patients will be enrolled at the time the clinical team decides that intubation is required and the patient meets inclusion but no exclusion criteria.

6.4 Consent:

Fluid loading or the absence of additional fluid administration are both commonly used approaches during endotracheal of critically ill adults in current practice (4, 32, 33). In prior observational studies of critically ill adults undergoing endotracheal intubation, clinicians have opted to administer a fluid bolus prior to induction in approximately 50% of patients, with significant variability by provider and practice environment (4, 31). Currently, there are no randomized trials or evidence-based guidelines to support the choice between fluid loading or none for the endotracheal intubation of critically ill adults.

Because both approaches to peri-intubation fluid management being studied are (1) commonly used as a part of routine care, (2) are interventions the patient would arbitrarily be exposed to even if not participating in the study, and (3) are acceptable options from the perspective of the clinical provider (otherwise patient is excluded), we feel the study meets criteria for minimal risk.

Additionally, obtaining informed consent in the study would be impracticable. Endotracheal intubation of acutely ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows discussion of risks and benefits in less than 10% of airway management events in the ICU.

Because the study poses minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

6.5 Randomization:

Computerized randomization using permuted blocks of two, four, or six will be conducted in order to generate a series of study assignments deliberately exceeding the planned enrollment number. Study assignments will be stratified by study site, placed in opaque randomization envelopes, and will be available to operators in the ICUs. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study. Once it has been determined by the treating team that (1) intubation is required, (2) sedation with or without neuromuscular blockade will be used, and (3) urgency of the intubation does not preclude safe performance of study procedures, the operator will open the next consecutively numbered envelope and follow the assignment of either fluid loading or no fluid loading.

7.0 Study Procedures

7.1 Study Interventions

7.1.1 Fluid Loading

The PrePARE study will affect only the initiation of fluid bolus administration for the prevention of cardiovascular collapse between enrollment and two minutes after completion of endotracheal intubation. The study will NOT affect fluid administration initiated prior to enrollment, fluid administration initiated after two minutes after completion of intubation, or fluid bolus administration for the treatment of cardiovascular collapse. This study will not protocolize any other aspect of endotracheal intubation such as choice of induction agent and neuromuscular blocker, patient position, choice of laryngoscopy – all of which will be determined by the treating clinicians.

Once the envelope is opened and group assignment is known, the clinical team will either start fluid loading or not anytime prior to the administration of procedural medications. Although the patient must be either receiving fluid loading or not at the time of initiation of procedural medications, if difficulties with airway management are encountered, the provider may revise the fluid management strategy at any time thereafter in order to ensure safe performance of the procedure.

In patients randomized to <u>fluid loading</u>, the bedside nurse will obtain 500 milliliters of a crystalloid fluid of the operator's choosing, connect this volume to intravenous infusion tubing, and attach the tubing to any intravenous catheter or intraosseous device. The crystalloid fluid

will then be placed above the level of the intravenous or intraosseous device and allowed to infuse by gravity. At any time after the initiation of fluid loading, the operator can choose to begin the procedure by administering procedure-related medications. Fluid loading will continue until all 500 milliliters are infused. Infusions present prior to the decision to perform endotracheal intubation will not be altered by the current study.

In patients randomized to no fluid loading, no additional intravenous crystalloid administration will be initiated by the study between enrollment and two minutes after completion of endotracheal intubation. Infusions present prior to the decision to perform endotracheal intubation will not be affected by the study and their management will be deferred to the treating clinician. Treating clinicians may initiate a fluid bolus at any time for the treatment of cardiovascular collapse (not considered a protocol violation). Treating clinicians may also initiate a fluid bolus at any time if felt to be mandatory for the safe treatment of the patient (if between enrollment and two minutes after completion of intubation and in the absence of cardiovascular collapse this will be recorded as a protocol violation).

8.2 Data Collection

All data are collected non-invasively and are already a part of clinical data obtained in usual ICU care at the bedside or in the medical record. No additional data will be obtained beyond that which is obtained by bedside observation and from the electronic medical record.

Baseline: Age, gender, height, weight, race, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, mean arterial pressure and vasopressor use prior to intubation, noninvasive ventilator use, highest FiO_2 delivered in prior 6 hours, lowest oxygen saturation in prior six hours, pH, PaO_2, $PaCO_2$, indication for intubation, reintubation, preoxygenation technique, operator experience will be collected from the medical record.

Peri-procedural: Date and time of sedative and/or neuromuscular blocker administration, saturation at time of sedative and/or neuromuscular blocker administration, sedative, neuromuscular blocker, device used for pre-oxygenation prior to medication administration, ventilation between induction and laryngoscopy, tube characteristics, route, laryngoscope type and size, total number of attempts, tube tape level, confirmation of placement technique, airway grade, airway difficulty, rescue device use, need for additional operators, mechanical complications (esophageal intubation, aspiration, airway trauma), arrhythmia requiring therapy, and patient positioning. Lowest arterial oxygen saturation, lowest systolic blood pressure, vasopressor administration, time to intubation, presence of additional personnel, and other key peri-procedural outcomes will be collected by a trained, independent observer not affiliated with the performance of the procedure.

0-24 hours: Post-intubation imaging, post intubation shock or cardiac arrest, SaO_2, FiO_2, PEEP, and systolic and mean arterial pressures up to 24 hours after intubation will be collected from the medical record.

In-Hospital Outcomes: Total cumulative fluid adminstration in the ICU after randomization, total cumulative furosemide dose in the ICU and during hospitalization after randomization, date of extubation (ventilator-free days), date of ICU discharge (ICU-free days), and date of death will be collected from the medical record.

8.3 Outcome Measures

Primary Endpoint:

- Cardiovascular collapse – a composite endpoint defined as one or more of the following:
  - Death within 1 hour of intubation
  - Cardiac arrest within 1 hour of intubation
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after completion of intubation
  - New or increased vasopressor receipt between induction and 2 minutes after completion of intubation

Secondary and Tertiary Endpoints:

Secondary Outcomes

1. The incidence of each component of the cardiovascular collapse composite endpoint
2. Additional fluids given to either group and started between induction and 2 minutes after intubation
3. Lowest systolic blood pressure between induction and two minutes after intubation; change in systolic blood pressure from induction to lowest systolic blood pressure
4. Lowest oxygen saturation between induction and 2 minutes after completion; Incidence of severe hypoxia between induction and 2 minutes following intubation – defined as new arterial oxygen saturation of <80%
5. Time from administering induction medications to successful endotracheal intubation
6. Lowest systolic blood pressure adjusting for systolic blood pressure at induction
7. Cumulative ICU furosemide administration from enrollment to three days after enrollment
8. Cumulative ICU fluid adminstration from enrollment to three days after enrollment
9. Cormack-Lehane grade of view on first attempt

10. Incidence of "first pass success" defined as "placement of an endotracheal tube in the trachea after the first insertion of the laryngoscope into the oral cavity without the use of any other devices"
11. Number of attempts required for successful tube placement
12. Incidence of need for additional intubating equipment, second operator
13. Incidence of post-intubation tube malposition on CXR
14. Incidence of fluid administration outside of the study
15. Cumulative furosemide administration from enrollment through hospital discharge or death

Tertiary outcomes

1. In-hospital mortality
2. Ventilator-free days (VFDs)
3. ICU-free days (ICUFDs)
4. Vasopressor-free days

ICU-free days to 28 days after enrollment will be defined as the number of midnights alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit before 28 days. If the patient is admitted to an intensive care unit service at day 28 or dies prior to day 28, ICU-free days will be 0.

Ventilator-free days to day 28 will be defined as the number of midnights alive and with unassisted breathing to day 28 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0.

8.0 Risks and Benefits:

In patients for whom the treating team has decided endotracheal intubation is required, there are currently no established risks or benefits to intubation with or without fluid loading. Patients randomized to the fluid loading group may be at increased risk of developing pulmonary edema and those randomized to the no fluid loading group may be at increased risk of cardiovascular collapse. However, previous studies of endotracheal intubation of critically ill adults suggest that in routine care, operators arbitrarily decide to use fluid loading in approximately 50% of patients. Therefore, patients would be exposed to either pulmonary edema or procedural hypotension in routine practice. In addition, the exclusion criteria would

exclude patients in whom the treating provider felt that peri-procedural fluid loading was needed to prevent hypotension or was contraindicated due to the risk of developing pulmonary edema. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients requiring endotracheal intubation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective airway management for critically ill patients.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

9.0 Safety Monitoring and Adverse Events:

9.1 Safety Monitoring

This study will take place in the environment of an intensive care unit or emergency department at the time of a procedure required for routine clinical care. Thus, at the time of the study intervention, the patient will have in the room a critical care- or emergency medicine-trained physician, a nurse trained in critical care, and usually a respiratory therapist in addition to continuous invasive or non-invasive monitoring. Additionally, study personnel will be readily available to answer questions at any time during the study course. Even after randomization, if any healthcare provider participating in the intubation procedure believes that the study interventions cannot be performed for the safe performance of the procedure, the study intervention is halted and the patient is intubated in the manner which the clinical team judges to be safest.

A Data and Safety Monitoring Board (DSMB) will oversee the trial. Interim analyses for safety and efficacy will be conducted as described in the Statistical Analysis section of the protocol.

9.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation where a participant is administered an intervention that does not necessarily have to have a causal relationship with the intervention. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

A serious adverse event (SAE) is defined as any unexpected and untoward medical occurrence that is probably or possibly related to the study and meets any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe). Life-threatening cardiovascular complications, as defined as the primary endpoint of this trial, will be prospectively and systematically collected as the outcome. As such, these events will not be reported as SAEs. Similarly, life-threatening severe hypoxia will also be systematically collected as a secondary endpoint and will therefore not be reported as an SAE.
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the clinical team or bedside nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events. **Serious and unexpected adverse events potentially associated with study interventions will be recorded in a case report form in the study record and reported to the IRB and DSMB within 7 calendar days in accordance with IRB policy.** As endotracheal intubation in the critical care setting is known to be independently associated with numerous adverse events including hypoxemia, aspiration, esophageal intubation, airway trauma, failed attempts at intubation, pneumothorax, pneumomediastinum, hypotension, severe bradycardia, cardiac arrest, and death, these events will be recorded as study outcomes and monitored by the Data and Safety Monitoring Board at the semi-annual DSMB meetings to determine if a preponderance of adverse events in one study group merits consideration of stoppage of the trial. However, in the absence of an imbalance of the above events between study groups, these events are expected in the routine performance of the airway management procedure and will not be individually reported to the IRB and DSMB as serious and unexpected adverse events, unless the investigators or clinical team believe the event was related to the study intervention.

As an additional safety measure, the exclusion criteria specifically state that airway management events in which urgency precludes performance of study or the operator foresees a potential need for or contraindication to manual ventilation between induction and intubation will not be included in the trial so all airway management events studied will be those in which the treating clinical team felt equipoise between the interventions being examined. Further, only the conditions at the initiation of the airway management event are

proscribed by the study protocol and if at any time during the procedure the operator chooses to employ an alternative airway management strategy they are free to do so.

In addition, a DSMB containing at least one clinical investigator experienced in monitoring and conducting clinical trials in critically ill patients will oversee the study. In addition to assisting the PI with monitoring the trial for safety, the DSMB will also perform the interim analyses described in the statistical methods. If the data meet the stopping rules for efficacy at the interim analysis, the DSMB will communicate a recommendation to stop the trial at that time. In addition, the DSMB will also be available to review unexpected serious adverse events in a timely manner. They will be asked to be available for rapid access by the investigators in the case of the need to evaluate unexpected serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of unexpected serious adverse events, the DSMB will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues.

10.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11.0 Statistical Considerations

Sample Size Determination:

In a previous before-and-after observational study (4) which incorporated preemptive intravenous fluid loading to prevent cardiovascular collapse during endotracheal intubation in critically ill adults, the rate of life-threatening cardiovascular collapse was approximately 25% in the control arm and 15% in the preemptive intravenous fluid loading arm (an absolute risk reduction of 10% and a relative risk reduction of 40%). Randomization of a total of 500 patients

(250 patients per group) will provide 80% power to detect the same 10% difference in cardiovascular collapse between groups with an alpha of 0.05.

Statistical Analysis:

Analysis principles

- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All hypothesis tests will be two sided, with an α of 0.05 unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.
- Subgroup analyses will be performed irrespective of treatment efficacy.

Trial profile:

We will present a Consolidated Standards of Reporting Trials diagram as Figure 1 to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:

To assess randomization success, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for intubation; Active illnesses at the time of intubation; Severity of Illness (APACHE II score); Respiratory status pre-intubation; Airway management procedure (Preoxygenation technique, Saturation at
time of induction, Induction medication, Neuromuscular blocker, Laryngoscope
type).

Primary Analyses:

Unadjusted test of treatment effect.

The primary endpoint will be the categorical variable of cardiovascular collapse. The difference between the two groups will be compared using the Pearson $\chi 2$ test. All other comparisons will be considered secondary analyses.

Secondary Analyses:

Per-Protocol Analysis of Primary Outcome.

In addition to the intention-to-treat analysis, we will conduct a per protocol analysis of the primary outcome comparing patients in which the enitre volume of crystalloid was infused to patients who received no fluid loading.

Analysis of Secondary and Tertiary Outcomes.

We will conduct unadjusted analyses examining the treatment effect of fluid loading on each of the pre-specified secondary and tertiary outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the Fischer exact test.

Subgroup Analyses.

We will conduct unadjusted analyses examining the treatment effect of fluid loading on life-threatening cardiovascular complications in each of the pre-specified subgroups. Data will be presented as odds ratios and 95% confidence intervals for categorical variables and as mean differences and 95% confidence intervals for continuous variables.

Modeling to Examine Potential Interactions

We will test for heterogeneity of treatment effect across each of the prespecified subgroups using multivariable regression with the primary outcome as the dependent variable, study group and the subgroup of interest as independent variables along with relevant confounders, and a cross-product interaction term. Subgroup variables which are continuous will not be artificially dichotomized. Significance will be determined by p value for the interaction term.

Modeling to Examine Potential Confounding Factors.

We will develop a multiple regression model with the primary outcome as the dependent variable and study group and relevant confounders included as independent variables.

Presentation of Statistics

Continuous variables will be described as mean and standard deviation or median and 25th percentile – 75th percentile or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as percentage and number. All between-group comparisons with continuous variables will be performed using Mann-Whitney U tests and Fisher's exact test for categorical variables. Kaplan-Meier curves and log-rank tests will be used to analyze time-to-event comparisons between groups.

Interim Analysis

The DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 250 patients. The stopping boundary for efficacy will be met if the P value for the difference between groups in the primary outcome is 0.003 or less. Assuming a 25% event rate of life-threatening cardiovascular collapse in the control arm, this stopping boundary would stop the trial for any relative risk reduction greater than 58%. Should the trial not meet this stopping point, but still have the same relative risk reduction for the second half of the patients enrolled, at most 18 additional patients would be at risk for developing life-threatening cardiovascular collapse due to not stopping the trial early. Use of this conservative stopping boundary ($P \leq 0.003$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the relatively large number targeted for enrollment, the interim analysis will also evaluate the trial for futility. A futility stopping boundary of $P > 0.60$ will be used for stopping the trial for futility. If the control arm has the anticipated 25% incidence of life-threatening cardiovascular collapse, this means the trial would be stopped for futility at the interim analysis if the relative risk reduction was 12% or less (equivalent to an absolute risk reduction less than 3%).

The DSMB will be asked to formally evaluate the safety of the trial at the interim analysis. As the theoretical risk of the intervention is acute pulmonary edema requiring increased ventilatory support, the primary determination of safety will be based on the highest fraction of inspired oxygen and highest positive end-expiratory pressure between 6 and 24 hours after intubation. If (1) the P value for the difference between study groups in both of these physiologic variables is less than 0.001, (2) the difference between groups in both physiologic variables is concordant in direction with the point estimate for in-hospital mortality, AND (3) the P value for the difference between study groups in in-hospital mortality is less than 0.1, it is recommended that the study be stopped early for safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety. Finally, the DSMB will have the ability to monitor the rate of the primary outcome in the control group at the interim analysis and can ask that the study be re-powered if the rate of the primary outcome is different from our original estimate of 25%.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway

management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

14.0 References

1. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114:42–48.
2. Simpson GD, Ross MJ, McKeown DW, Ray DC. Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;108:792–799.
3. Leibowitz AB. Tracheal intubation in the intensive care unit: extremely hazardous even in the best of hands. *Crit Care Med* 2006;34:2497–2498.
4. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, Verzilli D, Jonquet O, Eledjam J-J, Lefrant J-Y. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med* 2010;36:248–255.
5. Griesdale DEG, Bosma TL, Kurth T, Isac G, Chittock DR. Complications of endotracheal intubation in the critically ill. *Intensive Care Med* 2008;34:1835–1842.
6. van Zundert A, Pieters B, Doerges V, Gatt S. Videolaryngoscopy allows a better view of the pharynx and larynx than classic laryngoscopy. *Br J Anaesth* 2012;109:1014–1015.
7. Jabre P, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltramini A, Gamand P, Albizzati S, Perdrizet D, Lebail G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant J-Y, Bollaert P-E, Megarbane B, Ricard J-D, Anguel N, Vicaut E, Adnet F, KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009;374:293–300.
8. Cook TM, Woodall N, Harper J, Benger J, Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *Br J Anaesth* 2011;106:632–642.
9. Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: a justification for incorporating the ASA Guidelines in the remote location. *J Clin Anesth* 2004;16:508–516.
10. Green RS, Turgeon AF, McIntyre LA, Fox-Robichaud AE, Fergusson DA, Doucette S, Butler MB, Erdogan M, Canadian Critical Care Trials Group (CCCTG). Postintubation hypotension in intensive care unit patients: A multicenter cohort study. *J Crit Care* 2015;30:1055–1060.
11. Heffner AC, Swords DS, Nussbaum ML, Kline JA, Jones AE. Predictors of the complication of postintubation hypotension during emergency airway management. *J Crit Care* 2012;27:587–593.
12. Walz JM, Zayaruzny M, Heard SO. Airway management in critical illness. *Chest*

2007;131:608–620.
13. Natt BS, Malo J, Hypes CD, Sakles JC, Mosier JM. Strategies to improve first attempt success at intubation in critically ill patients. In: Asai T, editor. *Br J Anaesth* 2016;aew061.doi:10.1093/bja/aew061.
14. Muzi M, Berens RA, Kampine JP, Ebert TJ. Venodilation contributes to propofol-mediated hypotension in humans. *Anesth Analg* 1992;74:877–883.
15. Möller Petrun A, Kamenik M. Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. *Br J Anaesth* 2013;110:388–396.
16. Shah SB, Chowdhury I, Bhargava AK, Sabbharwal B. Comparison of hemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels. *J Anaesthesiol Clin Pharmacol* 2015;31:180–185.
17. Kaushal RP, Vatal A, Pathak R. Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass. *Ann Card Anaesth* 2015;18:172–178.
18. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, Bodian CA. Predictors of hypotension after induction of general anesthesia. *Anesth Analg* 2005;101:622–8– table of contents.
19. Choi YF, Wong TW, Lau CC. Midazolam is more likely to cause hypotension than etomidate in emergency department rapid sequence intubation. *Emerg Med J* 2004;21:700–702.
20. Davis DP, Kimbro TA, Vilke GM. The use of midazolam for prehospital rapid-sequence intubation may be associated with a dose-related increase in hypotension. *Prehosp Emerg Care* 2001;5:163–168.
21. Janz DR, Semler MW, Lentz RJ, Matthews DT, Assad TR, Norman BC, Keriwala RD, Ferrell BA, Noto MJ, Shaver CM, Richmond BW, Zinggeler Berg J, Rice TW, Facilitating EndotracheaL intubation by Laryngoscopy technique and apneic Oxygenation Within the ICU Investigators and the Pragmatic Critical Care Research Group. Randomized Trial of Video Laryngoscopy for Endotracheal Intubation of Critically Ill Adults. *Crit Care Med* 2016;doi:10.1097/CCM.0000000000001841.
22. Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, Keriwala RD, Ferrell BA, Noto MJ, McKown AC, Kocurek EG, Warren MA, Huerta LE, Rice TW, FELLOW Investigators and the Pragmatic Critical Care Research Group. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med* 2016;193:273–280.
23. Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, Calfee CS. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016;44:120–129.
24. Perbet S, De Jong A, Delmas J, Futier E, Pereira B, Jaber S, Constantin J-M. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the

ICU: a multicenter observational study. *Crit Care* 2015;19:257.
25. Heffner AC, Swords DS, Neale MN, Jones AE. Incidence and factors associated with cardiac arrest complicating emergency airway management. *Resuscitation* 2013;84:1500–1504.
26. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683–1693.
27. Semler MW, Rice TW. Sepsis Resuscitation: Fluid Choice and Dose. *Clin Chest Med* 2016;37:241–250.
28. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R, SPLIT Investigators, ANZICS CTG. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *JAMA* 2015;314:1701–1710.
29. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent J-L, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013. pp. 580–637.
30. Shafi S, Gentilello L. Pre-hospital endotracheal intubation and positive pressure ventilation is associated with hypotension and decreased survival in hypovolemic trauma patients: an analysis of the National Trauma Data Bank. *J Trauma* 2005;59:1140–5–discussion 1145–7.
31. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal J-M, Guitton C, Allaouchiche B, Paugam-Burtz C, Constantin J-M, Lefrant J-Y, Leone M, Papazian L, Asehnoune K, Maziers N, Azoulay E, Pradel G, Jung B, Jaber S, AzuRéa Network for the Frida-Réa Study Group. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187:832–839.
32. Boyd JH, Forbes J, Nakada T-A, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39:259–265.
33. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575.

Tracking of Protocol Versions:

Version 1.0 – Initial Submission (11/16/2016)

Version 1.1 – Revisions after initial meeting with DSMB (1/25/17)

- The planned approach to co-enrollment in other clinical trials was specified. A plan to perform a test of interaction when co-enrollment occurred with another intervention airway management trial was specified. Registration information was provided for the PreVent trial, for which there is anticipated to be co-enrollment.
- The plan to provide all study outcomes, adverse events, and serious adverse events to the DSMB at each of the semi-annual DSMB meetings was clarified. The plan to collect anticipated adverse events as outcomes and report to the IRB and DSMB within 7 days only those which are unexpected and potentially related to the study intervention was clarified.
- At the request of the DSMB, the stopping criteria for safety at the interim analysis were clarified to eliminate the oxygen saturation criteria, specify a *P* value for the difference in mortality between groups, and eliminate the ventilator-free days criterion.

Version 1.2

- Amendment is to add Lincoln Medical Center Emergency Department as an enrolling site following receipt of IRB approval from their local institutional review board