

Form "EAST Multicenter Study Proposal"

Study Title	A Prospective, Randomized Trial of Airway Pressure Release Ventilation in Severly Injured Trauma Patients
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Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined	<p>There is abundant data demonstrating that severely injured trauma patients are at risk for developing ARDS. A prospective study by Hudson et al et al showed that if a combination of any two of the following risk factors were identified (pulmonary contusion, multiple fractures, and multiple transfusions), the incidence of ARDS was 40.3% (1). It was noted that as the severity of injury worsened and as the need for blood product transfusion increased, the incidence of ARDS did as well (1). Furthermore, mortality was significantly higher in those trauma patients that developed ARDS when compared to those that did not (58% vs 12.9%) (1). More recent data suggests that the mortality of ARDS associated with trauma patients has decreased over the past twenty five years, however, the morbidity, length of stay and hospital length of stay continues to be significantly higher in that patient population (4,19).</p>
Primary aim	<p>Using the ventilator to prevent ARDS is a strategy that has not, until recently, been considered as we have known for some time that mechanical ventilation inherently produces lung injury. An animal study applied APRV to pigs immediately following fecal peritonitis and ischemic injury. This group found that the lung architecture in the APRV group was maintained without histologic findings of ARDS as opposed to those in the conventional ventilation group. This was the first study suggesting that a preemptive use of a ventilatory strategy could be used prophylactically for ARDS (26). Animal data in rats with normal lungs showed reduced histopathologic changes in those who were pre-emptively placed on APRV. In fact, none of the rats pre-emptively placed on APRV had P:F ratio less than 300 suggesting that early APRV could prevent known ventilator induced lung injury (14). A recent systematic review showed that with early APRV use, the incidence of ARDS and associated mortality was decreased as compared with that of traditional ventilation (12). This systematic review only included small retrospective case series however.</p> <p>The primary aim of this study is to test the hypothesis that early APRV (within 6 hrs of admission) reduces mortality in severely injured trauma patients at risk for developing respiratory failure and ARDS.</p>

- 1) To test the hypothesis that early APRV will decrease the incidence of ARDS in severely injured trauma patients in acute respiratory failure and at risk for ARDS.
- 2) To test the hypothesis that early APRV will decrease number of ventilator days in severely injured trauma patients in acute respiratory failure and at risk for ARDS.

Secondary aims

3) To test the hypothesis that early APRV will decrease the incidence of renal failure in severely injured trauma patients in acute respiratory failure.

5) To test the hypothesis that early APRV will decrease number of ICU days in severely injured trauma patients in acute respiratory failure and at risk for ARDS.

Inclusion Criteria

Patients that are intubated prior to or following admission after sustaining a traumatic injury with an injury severity score greater than sixteen (indicating a severely injured trauma patient), a chest abbreviated injury score greater than 2 (indicating severe chest injury), and having received two liters of crystalloid/colloid prior to enrollment. Patients will be enrolled within six hours of intubation. Only those patients who remain intubated for 48 hours will be included. and those extubated prior will be dropped from the study.

Exclusion Criteria

Exclusion criteria include known or suspected pregnancy, patients who are prisoners, evidence of intracranial hypertension, a history of COPD, and any condition requiring paralytics or deep sedation thus preventing spontaneous breathing. Patients that are initially intubated, but then extubated within 48 hrs will also be excluded from the study.

After randomization, the patient will be placed on either standard low tidal volume ventilation which will be the control group or the study group with APRV settings. Those patients in the study group will be started on settings as outlined in the protocol (see below) and when appropriate, will be weaned off of APRV to BiPAP and evaluated for extubation.

Initial Settings

-Pt will be placed on volume control with tidal volumes of 6mL/kg to determine the plateau pressures.

-P high will be set at three above the plateau pressure , not to exceed 30cm H₂O.

-P low will be set at 0cm H₂O

-T high will be set at 4s

-T low will be set at 0.4s

-FiO₂ will be set to 100%

Therapeutic Interventions

Weaning

-Weaning of FiO₂ will begin immediately and addressed every thirty minutes, maintaining oxygen saturations >92%.

-Once FiO₂ is at 40%, all patients will be assessed for ventilator weaning every 4 hours by monitoring oxygen saturations and ABGs.

-If sats are >92% and/or pO₂>60, the P high will be decreased by 2cm H₂O.

-If pH>7.2, pCO₂ 60, the T high will be increased by 1s.

-Once P high is 10 and T high is 15 for 3 hours, patients will have their sedation/analgesic drips turned off in anticipation of spontaneous breathing trial.

-At 4 hours, a spontaneous breathing trial will be performed for 30-60 minutes.

-If pt meets all criteria for extubation (cough, gag, cuff leak, GCS>8) extubation will be performed within 30 minutes of completion of the SBT.

-If pt does not meet criteria for extubation, they will be placed back to the previous APRV settings and continue the weaning process.

Trouble shooting

-If ventilator changes are made aside from weaning protocol, an ABG should be drawn 1 hour after to confirm resolution of gas disturbance.

-Once stabilized, they will continue on the weaning protocol with an ABG every 4 hours.

Hypoxia:

-For sats <92% or pO₂60, decrease T high 0.5s and increase P high 1cm H₂O.

Hypocapnea:

-Increase T high by 0.5s

Primary Outcome

The primary outcome will be 28 day mortality.

Secondary outcomes will include, development of ARDS as described by the Berlin Criteria (16), number of ventilator days, number of ICU and hospital days, and incidence of renal failure as defined by the Kidney Disease Improving Global Outcomes Clinical Practice Guidelines (KDIGO, 2012) (an increase in SCr by >0.3 mg/dL within 48 hours, an increase in SCr to >1.5 times baseline which has occurred in the previous 7 days, urine volume <0.5mL/kg/hr for six hours) (27), and cardiovascular failure as determined by quantity and duration of vasopressors and inotropes.

Secondary Outcomes

Berlin Criteria include respiratory distress within 1 week of a known clinical insult, bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules, respiratory failure not fully explained by cardiac failure or fluid overload.

List specific variables to be collected & analyzed

Baseline demographic data will be collected on all patients, including admission physiologic variables (heart rate, blood pressure, initial ventilator settings), injury severity score, and additional patient comorbidities.

Outcome variables include: Mortality, development of ARDS, ventilator days, ICU days, hospital days, incidence of renal failure, duration of vasopressor use.

Outline the data collection plan and statistical analysis plan succinctly

The sample size is determined on the primary outcome. According to a systematic review, early APRV was associated with lower incidence of in-hospital mortality (3.9% vs 14.1%) compared to conventional model ventilation (12). We plan to recruit patients until we reach at least 186 patients in study and control group to achieve a power of 90%. Patients not complying with study protocol will be supplemented by additional recruitment to meet the final sample requirement. We will analyze the data on intent to treat basis and where possible, patients with incomplete data will be included in secondary analysis.

The primary outcome (i.e. 28 days mortality rate) will be examined by Fisher's exact test. On the secondary outcomes, Fisher's exact test will be also used on binary outcome variables, including ARDS incidence rate and acute renal failure incidence rate, and t test will be used on continuous outcome variables, including length of ventilator use, ICU stay, and total hospital stay. The statistical software Stata (College station, TX) will be used in all statistical analyses.

Data collection will be performed by our study coordinator

All patients admitted to the SNICU at the University of Iowa who sustained a traumatic injury will be screened for eligibility. For patients meeting eligibility criteria, study information will be shared with the family. Because patients will be unable to consent for themselves, surrogate consent will be sought from a legally authorized representative and once able, patients will be asked to give their consent.

The intensivist on call in each bay of the SNICU will serve as an independent physician to monitor for adverse events. Adverse events such as barotrauma and primary respiratory acidosis with a pH less than 7.2 will be specifically looked for. Interim analysis will be performed after 186 patients are enrolled. This interim analysis will not include efficacy analyses, and the significance of the primary outcome will not be adjusted for multiple comparisons. Any adverse events will be reported and the intensivists will be able to stop the study at any point should safety concerns exist.

Outline consent procedures here, if applicable

Succinctly outline a risk/benefit analysis

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2. Salim, Ali; Martin, Matthew; Constantinou, Constantinou et al; Acute Respiratory Distress Syndrome in the Trauma Intensive Care Unit. *Arch Surg* 2006;141:655-658.
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4. Bakowitz, Magdalena; Bruns, Brandon; McCunn, Maureen: Acute Lung Injury and the Acute Respiratory Distress Syndrome in the Injured Patient. *Trauma, Resuscitation and Emergency Medicine* 2012; 20:54.
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7. Navarrete-Navarro, Pedro; Rivera-Fernandez, Ricardo; Ricon-Ferrari, Ma Dolores et al: Early markers of acute respiratory distress syndrome development in severe trauma patients. *J Crit Care* 2006;21:253-258.

Include a brief listing of key references

8. Plurad, David; Martin, Mathew; Green, Donald: The Decreasing Incidence of Late Posttraumatic Acute Respiratory Distress Syndrome: the Potential Role of Lung Protective Ventilation and Conservative Transfusion Practice. *J Trauma* 2007;63:1-8.
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12. Andrews, Penny; Shiber, Joseph; Jaruga-Killeen, Ewa et al: Early application of airway pressure release ventilation may reduce mortality in high risk trauma patients: A systematic review of observational trauma ARDS literature. *J Trauma Acute Care Surg* 2013;75(4):635-641.
13. Rasanen, Jukka; Downs, John; Stock, Christine: Cardiovascular Effects of Conventional Positive Pressure Ventilation and Airway Pressure Release Ventilation. *CHEST* 1988;93(5):911-915.
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15. Ashbaugh, David; Bigelow, Boyd; Petty, Thomas et al: Acute Respiratory Distress in Adults. *The Lancet* 1967.