



EAST MULTICENTER STUDY PROPOSAL

(Proposal forms must be completed in its entirety, incomplete forms will not be considered)

GENERAL INFORMATION

Study Title: Early Use of High Frequency Oscillatory Ventilation in Patients with Severe Thoracic Injury.

Primary investigator / Senior researcher:
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Co-primary investigator:

BACKGROUND AND SIGNIFICANCE

Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined:

Trauma patients are at high risk of pulmonary decompensation due to multiple factors, including thoracic injury, aspiration pneumonitis, Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury and Fat Emboli Syndrome. Management of patients relies heavily on conventional low-volume ventilatory strategies. These approaches may prove inadequate and rescue modes may include high-frequency oscillatory ventilation (HFOV), in addition to adjuncts such as prone positioning, nitric oxide and extracorporeal membrane oxygenation. Since there are no well-defined criteria to predict need for more aggressive ventilatory strategies, use of these modalities is dependent on physician preference and may occur too late in the clinical course for success.

High-frequency oscillatory ventilation as a rescue therapy has been an area of intense interest over the last decade. Multiple retrospective studies have indicated improved oxygenation with the use of HFOV. No studies, either prospective or retrospective, have demonstrated a survival benefit with this mode of therapy. These studies have largely focused on patients with ARDS in the medical ICU, however, and the few studies including surgical patients have rarely included a significant number of trauma patients. Though research has indicated that HFOV may be more successful when employed earlier in the patient's course, HFOV tended to be employed as a rescue therapy and was rarely utilized early. Therefore, the use of HFOV early in the ICU stay for patients at high risk of pulmonary decompensation is poorly understood.

The specific aims of this multicenter study are:

Primary aim:

To determine safety and efficacy of immediate use of the HFOV in trauma patients suffering severe injuries to the thoracic region.

Secondary aims:

To determine if oxygenation is improved and ventilator days are decreased with early use of HFOV.

EXPERIMENTAL DESIGN/METHODS

Inclusion Criteria:

Patients age 16 -70 suffering either blunt or penetrating injury. Patients must require intubation within the first 48 hours.

Patients must meet one of the following criteria for inclusion :

1. Severe thoracic injury as identified by a lung AIS \geq , a chest wall AIS \geq 3 or 4 or more adjacent rib fractures

or

2. ARDS within 24 hours of intubation – defined as PaO₂/FIO₂ \leq 200mmHg, bilateral pulmonary infiltrates and no evidence of left atrial distention

Exclusion Criteria:

Aside from patients who fail to meet the inclusion criteria, any patient who dies within 72 hours of admission will be excluded. Use of ECMO will end study participation and patients will be analyzed in their randomized group for intention to treat.

Therapeutic Interventions:

Patients who meet criteria and from whom consent is obtained (or from legally authorized representative) will be randomized to conventional ventilation or HFOV.

Conventional ventilation may include any of the following modes of ventilatory management : SIMV, A/C, APRV, CPAP. Patients in this group will be managed at the discretion of the treating physician. Use of HFOV is also at the discretion of the clinician, if they wish to proceed to this strategy as a rescue therapy later in the patient's course. Participation in the study will be considered complete when the patient has maintained a PaO₂/FIO₂ $>$ 200mmHg for 48 continuous hours or upon patient death.

Patients randomized to HFOV will be transitioned to this mode of ventilation immediately after randomization. Nitric oxide will be used concurrently with the oscillator. Initiation will include a recruitment maneuver and initial mPaw (mean airway pressure) settings will be 5 cm H₂O higher than mPaw on the conventional ventilator. Subsequent adjustments to the HFOV will be at the discretion of the clinician, though the protocol by Fessler et al. will be provided for reference if needed. Paralytics will be recommended upon initiation of HFOV but discontinuation is encouraged after the first few hours and is at clinician discretion after that. Patients will continue on the oscillator until the

PaO₂/FIO₂ > 200mmHg for 48 hours and the mPaw is ≤ 24 cm H₂O. Participation will be considered complete when one of the following criteria is met:

- 1) PaO₂/FIO₂ > 200mmHg for 48 hours off of the HFOV on a conventional mode of ventilation
- 2) Patient death
- 3) Patient is removed from HFOV based on clinician recommendation

Serial arterial blood gas measurements will be recommended every 6 hours for the first two days of the study and at least twice daily after that. A daily CXR is recommended.

Outcomes Measures:

Primary Outcome:

Ventilator free days (day 1 to 28)

Secondary Outcomes:

Secondary outcomes of this study are mortality and oxygenation during study inclusion

Variables:

List the specific variables to be collected and analyzed here. For organization, it is useful to divide these into categories for consideration. Examples of categories might include: Demographics, Admission physiology, Management variables, Surgical variables, Outcomes

Demographics: age, gender, mechanism of injury, comorbidities (focusing on lung disease), smoking history, injury severity score, AIS for lung and chest wall (if appropriate)

Physiologic Parameters: time to intubation, admission HR, SBP/DBP (MAP), O₂ saturation, respiratory rate. Admission hemoglobin and hematocrit, arterial blood gas values (pH, CO₂, O₂, bicarbonate, base deficit), serum lactate, admission PaO₂/FIO₂ ratio (if available)

At study inclusion : arterial blood gas values, PaO₂/FIO₂ ratio, hemoglobin/hematocrit, HR, SBP/DBP (MAP), respiratory rate, oxygen saturation.

Conventional ventilator settings. Initial HFOV settings if patient randomized to that arm

Study data points :

Day 1-2 – every six hour arterial blood gas values, PaO₂/FIO₂ ratio, hemoglobin /hematocrit, HR, SBP/DBP (MAP), respiratory rate, oxygen saturation. Ventilator settings

Day 3 – study completion – twice daily arterial blood gas values, PaO₂/FIO₂ ratio, hemoglobin /hematocrit, HR, SBP/DBP (MAP), respiratory rate, oxygen saturation. Ventilator settings

Management variables: data will be collected on surgical procedures required (and date of procedure), need for tracheostomy, infectious complications (VAP, bacteremia, UTI, empyema), occurrence of

pneumothorax (and need for tube thoracostomy), ICP's if a patient has an ICP monitor (at placement of the ICP monitor and at study inclusion, q6hr for days 1-2 of the study and bid for days 3-end). Further data points to be collected will be need for adjuncts in ventilatory management including:

- nitric oxide in conventional ventilator patients
- prone positioning
- cuff deflation in HFOV

Outcomes: ventilator days, ICU LOS, hospital LOS, death (and time to death), presumed cause of death, discharge location

Data Collection and Statistical Analysis:

Outline the data collection plan and statistical analysis plan succinctly here

Data will be collected on a standard excel spreadsheet. We will likely try to utilize a data entry tool similar to that utilized by the AAST multicenter trials website to make data entry easy and standardized.

Demographic and admission variables will be compared with student's t-test, Chi-square test or Wilcoxon Rank Sum test depending on the nature of the variables. Key outcome variables will be assessed with a multivariable logistic regression. A stepwise logistic regression will be used, with variables have a p-value < 0.2 included in this analysis. Statistical significance in the final model will be attributed to p-values < 0.05.

Consent Procedures:

This is a prospective trial involving therapeutic interventions. Whenever possible, the patient will be consented for inclusion prior to intubation. When not possible, the patient's legally authorized representative will be asked to provide consent. Patients may be withdrawn later if consent is rescinded by either the legally authorized representative or by the patient.

Risk/ Benefit Analysis:

HFOV is a standard ventilatory method that has been shown to be safe in both pediatric and adult patients. Though the current practice tends to use this strategy as a rescue mode, there is no indication in the literature that early use is harmful to patients. Therefore, there are risks in both groups of the study to include barotrauma, pneumothorax, hypercarbia, hypoxia and death. Benefits related to the HFOV group may include decreased barotrauma and shorter ventilatory requirement.

Instructions for submitting data collection tools:

All data submissions should be entered through the EAST Multicenter Trial Taskforce website portal. Instructions can be found on the EAST website. The data collection sheet located under the Multicenter Trial Taskforce heading for this study can be utilized to record the data, and then the information transferred to the portal entry system. For any questions regarding this study, please contact the PI.

References:

Include a brief listing of key references here:

1. Fessler HE, Derdak S, Ferguson ND et al. "A Protocol for High-Frequency Oscillatory Ventilation in Adults: Results from a Roundtable Discussion." *Critical Care Medicine* 2007; 35(7): 1649-54.
2. Chan KPW, Stewart TE & Mehta S. "High-Frequency Oscillatory Ventilation for Adult Patients with ARDS." *Chest* 2007; 131: 1907-16.
3. Young D, Lamb SE, Shah S et al. "High-Frequency Oscillation for Acute Respiratory Distress Syndrome." *New England Journal of Medicine* 2013; 368: 806-13.
4. O'Rourke J, Sheeran P, Heaney M et al. "Effects of Sequential Changes From Conventional Ventilation to High-Frequency Oscillatory Ventilation at Increasing Mean Airway Pressures in an Ovine Model of Combined Lung and Head Injury." *European Journal of Anaesthesiology* 2007; 24: 454-63.
5. Eastman A, Holland D, Higgins J et al. "High-Frequency Percussive Ventilation Improves Oxygenation in Trauma Patients with Acute Respiratory Distress Syndrome: A Retrospective Review." *The American Journal of Surgery* 2006; 192: 191-5.
6. Salim A, Miller K, Dangleben D et al. "High-Frequency Percussive Ventilation: An Alternative Mode of Ventilation for Head-Injured Patients with Adult Respiratory Distress Syndrome." *Journal of Trauma* 2004; 57: 542-6.
7. Kao KC, Tsai YH, Wu YK et al. "High Frequency Oscillatory Ventilation for Surgical Patients with Acute Respiratory Distress Syndrome." *Journal of Trauma* 2006; 61: 837-43.
8. Briggs S, Goettler CE, Schenarts PJ et al. "High-Frequency Oscillatory Ventilation as a Rescue Therapy for Adult Trauma Patients." *American Journal of Critical Care* 2009; 18: 144-8.
9. The ARDS Definition Task Force. "Acute Respiratory Distress Syndrome: The Berlin Definition." *Journal of the American Medical Association* 2012; 307(23): 2526-33.