**American Association for the Surgery of Trauma**

**Multi-Institutional Trial Committee**

**New Proposal Application Form**

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**Title of Proposal:** The Impact of Venovenous Extracorporeal Membrane Oxygenation on Trauma Patient Outcomes: Should We Cannulate?

**Hypothesis:** We hypothesize that trauma patients in acute respiratory failure who are managed with venovenous extracorporeal membrane oxygenation (VV-ECMO) will demonstrate improved mortality when compared to similar patients who are treated with conventional ventilatory methods.

**Type of Study: Retrospective**

**Background-**

**Define the Knowledge Gap that Study Addresses:**

Acute respiratory distress syndrome (ARDS) is a significant cause of morbidity and mortality in trauma patients (1), with an incidence of 8.4% according to a systematic review by Pfeifer et al. in 2017. Trauma patients sustaining thoracic injuries, traumatic brain injuries (TBI), and those patients undergoing massive transfusion are particularly susceptible to developing ARDS (1, 3) with a staggering incidence of 10 to 25% reported in the setting of thoracic trauma in particular (4). Although the incidence of ARDS due to over-resuscitation has declined, it remains a common complication in the setting of TBI, thoracic trauma, and pneumonia, and its associated mortality continues to increase over time (5, 6). Tignanelli et al. reviewed over 800,000 Trauma Quality Improvement Program (TQIP) patients between 2010 and 2014 and observed an increase in ARDS-related mortality from 18% to 21% over that time period (6). Specific risk factors that were associated with an increased mortality included a lower initial Glasgow Coma Scale (GCS), higher initial injury severity score (ISS), male sex, and older age (6). This study helped highlight a critical need for more effective treatment strategies.

Extracorporeal membrane oxygenation (ECMO) was first described by Hill et al. in 1971 when it was used to treat a trauma patient with acute respiratory failure. ECMO has the ability to provide both respiratory and circulatory support by oxygenating venous blood extracorporeally and returning it back to the body via a pump (8). When considering VV-ECMO specifically, multiple randomized controlled trials such as the CESAR and EOLIA trials have shown improvements in mortality when ECMO is used in non-trauma patients (9, 10).

While ECMO use in non-trauma patients is well described and continues to expand, its use in the setting of post-traumatic respiratory failure is more controversial as patient outcomes have been variable and formal guidelines are lacking (11). When looking at patient outcomes, Chen et al. found that between 2006 and 2010, while ECMO usage increased 1.68-fold in trauma patients, survival decreased from 75.8% to 62% at the conclusion of the study. However, in 2016, Robba et al. reviewed several case series detailing the use of ECMO in trauma and noted a survival of 87%. The following year, a National Trauma Data Bank (NTDB) study noted an overall survival of 64% (14). Guttman et al. analyzed the American College of Surgeons (ACS) TQIP database and found that from 2012-2016 the average growth rate of ECMO per year was 24%. However, this same study noted that patients receiving ECMO had a higher mortality than non-ECMO patients (32% vs. 19%) (15). Most recently, in 2021, Henry et al. published an ACS TQIP based study from 2013 to 2016. This study included 97 patients managed with ECMO and found on univariate analysis that ECMO patients had lower in-hospital mortality (23% vs. 50%, p < 0.001) but demonstrated higher rates of complications (p < 0.005) when compared to patients managed with conventional ventilatory strategies (16).

The variability in outcomes and the lack of formal guidelines underscore the need for further research in this area with a critical knowledge gap. Currently, most existing studies are single center with limited sample sizes. Furthermore, there is no data detailing whether social determinants of health impact access to ECMO or cannulation practices.

This study aims to address these gaps by evaluating the impact of VV-ECMO on patients who have sustained blunt or penetrating trauma and who have subsequently developed acute respiratory failure across multiple centers.

**Study Aim(s)-**

**Primary Aim:** To compare the morbidity and mortality of trauma patients with acute respiratory failure managed with VV-ECMO to similar patients managed with conventional ventilatory strategies.

**Secondary Aim:** To determine both the optimal timing for VV-ECMO cannulation in order to maximize survival benefits and to identify the patient populations that are most likely and least likely to benefit from VV-ECMO.

**Tertiary Aim:** To determine if a patient’s geographic proximity to an urban, level 1 trauma center and social determinants of health impact the likelihood of VV-ECMO cannulation.

**Proposed Study Population-**

**Inclusion Criteria:**

-Patients >/= 18 years of age presenting between January 1, 2014 and December 31, 2023 who developed severe acute respiratory failure (ARF) post-trauma and were managed with VV-ECMO. Severe ARF is defined as meeting any of the following criteria: PaO2:FiO2 < 80 mmHg for > 6 hours, PaO2:FiO2 < 50 mmHg for > 3 hours, or pH <7.25 with PaCO2 > 60 mmHg for > 6 hours (17).

-Control group: patients >/= 18 years of age who developed severe ARF post-trauma but were managed with conventional ventilatory strategies. Severe ARF is defined as meeting any of the following criteria: PaO2:FiO2 < 80 mmHg for > 6 hours, PaO2:FiO2 < 50 mmHg for > 3 hours, or pH <7.25 with PaCO2 > 60 mmHg for > 6 hours (17).

**Exclusion Criteria:**

-Patients < 18 years, pregnant women, incarcerated patients.
-Patients who developed ARF but who did not meet any of the following criteria: PaO2:FiO2 < 80 mmHg for > 6 hours, PaO2:FiO2 < 50 mmHg for > 3 hours, or pH <7.25 with PaCO2 > 60 mmHg for > 6 hours .
-Patients with a diagnosis of cardiogenic shock requiring cannulation with venoarterial (VA) ECMO or those who required conversion from VV to VA-ECMO.
-Patients who died within the first 24 hours after admission.

**Outcome Measures-**

**Primary Outcome:** The primary outcome is in-hospital mortality.

**Secondary Outcome(s):** Secondary outcomes include both hospital and intensive care unit lengths of stay, ventilator days, timing of ECMO initiation and decannulation, infectious complications, venous thromboembolic events, unplanned operations, unplanned intubations, and 30-day mortality.

**Data Collection Variables:**

Variables to be collected include:

Hospital specific data: zip code of hospital, trauma center level, number of beds, team who cannulates for ECMO, unit where ECMO patients are managed, number of cannulations in last 10 years in both trauma and non-trauma patients.

Demographic data: age, gender, race, patient’s home address, insurance status, employment status, zip code of where trauma occurred, and comorbidities including diabetes mellitus, hypertension, hyperlipidemia, myocardial infarction, congestive heart failure, cerebrovascular accident, coronary artery disease, peripheral vascular disease, chronic kidney disease, liver cirrhosis, chronic obstructive pulmonary disease, venous thromboembolism, current malignancy, steroid use, drug abuse, alcohol abuse, dementia, and bleeding disorder.

Admission physiology: mechanism of injury, initial blood pressure, heart rate, body temperature, respiratory rate, mean arterial pressure, initial GCS, ISS, abbreviated injury scale for each body region, initial lab values including hemoglobin, hematocrit, creatinine, calcium, lactate, INR, pH, PaO2, PaCO2, bicarbonate, base deficit, and ED interventions including intubation in the ED, vasopressor support, arterial line placement, and central line placement.

Management data: units of whole blood, packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate given within the first 24 hours of admission, TXA, MTP activation, injury list and severity, operative interventions (list of procedures performed), time to first operative intervention (hours), time to intubation (hours), time to tracheostomy (hours), time to diagnosis of severe ARF (hours), cause of ARF, time to ECMO team consultation (hours), reason why patient was/was not cannulated, time to cannulation (hours), time to decannulation (hours), location of cannulas, anticoagulation, vasopressor support initiation and duration (hours), continuous renal replacement therapy initiation and duration (hours), presence of and timing of placement of a Swan Ganz catheter, presence of and timing of placement of a FloTrac sensor, antibiotic usage, timing and duration of respiratory adjuncts including prone positioning, neuromuscular blockade, steroids, and inhaled pulmonary vasodilators.

Hospital course physiology: lab values including hemoglobin, hematocrit, creatinine, calcium, lactate, INR, pH, PaO2, PaCO2, bicarbonate, base deficit, FiO2, fluid balance, and ventilator mode/settings will be collected at the following time points: diagnosis of severe ARF, ECMO team consultation, ECMO cannulation, and ECMO decannulation.

Complications: cardiac arrest, myocardial infarction, acute kidney injury, cerebrovascular accident, venous thromboembolic events, surgical site infections, sepsis, ventilator associated pneumonia, central line associated blood stream infection, cannula related complications including cannulation site bleeding, limb ischemia, and cannula dislodgement, unplanned intubation, unplanned return to the operating room, and unplanned readmission to the ICU. All complications will have an associated hospital day to determine if they occurred before or after ECMO cannulation.

Outcomes data: hospital, and ICU length of stay, total ventilator days, discharge disposition, in-hospital mortality, 30, 60, and 90-day mortality, transition to comfort focused measures/palliation, cause of death, all-cause readmission within 30 days.

**Planned Duration of Study:** 2 years.

**Center Participation Goal:** 20 centers **Patient Recruitment Goal:** 400

**Power Analysis Performed: Yes** [x]  **No** [ ]

**Plan for Statistical Analysis:** Standardized, retrospective data will be collected from each patient from January 1, 2014 through December 31, 2023. De-identified patient data will be entered into a REDCap database. Patients will then be grouped based on whether severe ARF developed within the first 72 hours of admission or if it developed later in the hospital course. Descriptive statistics will be reported as the mean +/- standard deviation for continuous normally distributed data or median [IQR] for skewed data. Frequencies will be used for categorical variables. Continuous variables will be compared using student’s t-test and/or Mann Whitney U test and categorical variables will be compared using Chi-squared tests. In order to account for inter-hospital variation in ECMO practices and to strengthen any causal inference, instrument variable analysis will be performed using the geographic location of where the trauma occurred as the instrument to better estimate the causal effect of ECMO on patient mortality. Statistical significance will be set at p<0.05.

**Power analysis:** Henry et al. found that trauma patients managed with VV-ECMO demonstrated a 23% in-hospital mortality versus 50% seen in patients managed with conventional ventilatory strategies. Using this data, the study will require a total sample size of 196 patients (98 in each cohort) to achieve an alpha of 0.05 and 80% power.

**Define How Findings from this Multi-Center Study Will Serve as the Foundation for Future Studies or Future Funded Research:**

To our knowledge, this multicenter trial will be the largest cohort study in the literature evaluating the impact of VV-ECMO on trauma patient outcomes and the first to address trauma patient’s social determinants of health and geographic constraints on ECMO utilization. Unlike previous single-center case series, or those studies utilizing databases with limited data points, our hope is that this study will provide robust data to identify specific patient populations that would most benefit and least benefit from VV-ECMO and will also help determine the optimal timing for cannulation. Findings from this study will serve as the basis for future research and will potentially influence the development of formal guidelines for ECMO use in the setting of trauma.

**Does Study Require Informed Consent, Describe Rationale:**

No informed consent will be required as this is a retrospective chart review and all data will be de-identified.

**Database Development-**

**Do you have independent funding?: Yes** [ ]  **No** [x]

**Does your study require upload of imaging studies?: Yes** [ ]  **No** [x]

**If the cost of development of your database exceeds the allotted financial support from AAST, are you able/willing to fund the difference?: Yes** [x]  **No** [ ]

**Key References-**

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