Jason Beattie, PGY-1

Columbia Presbyterian Internal Medicine Program

CRC IRB Protocol, December 2010

Conventional Ventilatory Support versus Extracoporeal Membrane Oxygenation for Severe ARDS: a Trial within Multiple ECMO Centers

A. Study Purpose and Rationale

ECMO (extracorporeal membrane oxygenation) is a technology used in ICU settings to provide cardiopulmonary bypass that enables reduction of ventilatory settings while avoiding severe hypoxemia and hypercapnea; the potential harm of positive pressure ventilation in the forms of baro-trauma, volu-trauma and oxygen toxicity can potentially be avoided through this technology. Originally developed in the 1970s, ECMO has seen significant device improvements that may expand its future indications. At present, it is well proven in respiratory failure in neonates however its role in treating adults remains under question. A randomized controlled trial that definitively shows mortality benefit of ECMO as compared to standard intensive care therapy for adult patients with respiratory failure remains necessary.

Review of the Literature

RCTs in neonates provide convincing evidence for the use of ECMO, with a number needed to treat between three and four infants for a mortality benefit at 1 year[4]. In adults, three prior RCTs exist, two of which are dated studies that showed no benefit [1, 5]. The most recent RCT was the CESAR trial, in which adults in the UK with respiratory failure defined as a Murray Score >3 (see appendix 1) or pH <7.2 were randomized either to conventional therapy or to referral to one ECMO center. This trial showed a disability free survival benefit for ECMO center referral (63%mortality for standard therapy vs 47% in ECMO center referral group, p-0.03) (disability defined as severe disability—bedbound and unable to wash/dress self). Within the group randomized to referral to the ECMO center, only 75% of these patients ultimately received ECMO. Overall the study was limited in its ability to make conclusions regarding the benefit of ECMO itself rather than referral to an ECMO center. A RCT that investigates the mortality benefit of ECMO itself would provide more appropriate justification for the role of ECMO in adults with respiratory failure.

B. Study Design and Statistical Procedures

The proposed trial will be modeled largely after the recent CESAR trial with several important differences.

Firstly, a multi-center trial RCT involving solely ECMO centers would allow for recruitment of sufficient patients for statistical power, and would remove the potential confounding variable of the type of center encountered in the CESAR trial. This would more clearly characterize a survival benefit provided by ECMO itself.

Secondly, the study population will be narrowed to include solely the first definition of respiratory failure employed in the CESAR trial (Murray score >3). The pH <7.2 definition of respiratory failure will be eliminated, as inclusion of patients meeting this parameter who may or may not meet the first parameter potentially diversifies the study group in terms of disease process and pathophysiology to an extent that is difficult to predict. This study will focus on severe ARDS alone as defined by a Murray score >3, with or without hypercapneic respiratory failure.

Hypothesis

For patients with severe but potentially reversible hypoxemic respiratory failure (Murray score >3) secondary to ARDS admitted to a center with ECMO, ECMO will increase survival without severe disability at 6 months post-randomization by a proportion of 25% as compared to non-ECMO ICU management at these same centers (including vent management by a pulmonologist as well as ARDSnet protocol).

Methods

a. Conceptual and Operational Definitions:

Study outcome will be a composite outcome of survival without severe disability at 6 months. Severe disability will be defined as being bed-bound and unable to wash and dress oneself.

b. Study Design

The study will be a longitudinal, prospective, un-blinded, parallel-arm, multi-center, intention to treat, RCT, composed of centers with adult ECMO experience. Study subjects will include patients aged 18-65 admitted to these centers who are diagnosed with potentially reversible hypoxemic respiratory failure. Upon diagnosis with ARDS at the ECMO center, the components of the Murray score will be monitored every 2 hours. Once a Murray score >2.5 is obtained, the intensive care team will begin to profile the patient for the study and contact a study representative if the patient's consenting family member is willing to speak with them (the consenting family member will provide initial consent, then, once able the patient can choose whether or not to continue with the trial). Data collection for all study members will include demographics, diagnosis leading to ARDS, dates of hospitalization/ intubation/ extubation, dates of transfers/discharges, conditions at discharge, complications, cause of death, vent settings, blood gases, hemodynamic status, APACHE II, Murray lung score. Once a Murray score of 3.0 is obtained, the study subject will be randomized to conventional therapy or to ECMO. Given the large potential for other variables to significantly affect the primary outcome of mortality, randomization will be stratified in a fashion similar to that done in the CESAR trial. Stratification will be performed for age, hours of high P/high FiO2, and number of organs failed (see Appendix 2).

Conventional therapy will include ARDSnet protocol vent management strategy with vent strategies guided by a pulmonologist. Data collection for the conventional management group will include time course, complications, and success with fulfillment of ARDSnet protocol (low-

volume, low-pressure with Pplat<30). For the ECMO group, V-V ECMO with percutaneous cannulation will be used, with standardized lung rest vent settings (Ppk 20-25, Ppl 10-15, rate 10, FiO2 30%), and ECMO will be continued until lung recovery is deemed obtained or until apparent irreversible multi-organ failure is attained. Data collection for the ECMO group will include cannulation information, flow, sweep, and pressure rates, and complications information.

c. Statistical Analysis:

The estimated mortality for severe ARDS is 70% (NIH ARDS network database). As with the CESAR trial, an estimate of 10% severe disability in both trial arms will be used. For sample size calculation, Alpha will be set at 0.05 and Beta at 0.2. An effect size of a 25% proportional disability free survival benefit (70% mortality → 52.5 mortality, or 17% difference in mortality) is estimated, which mirrors the effect size observed in the CESAR trial; using chi square testing this equates to a n of 132 patients for each study group.

C. Study procedures:

Intubation

All patients in this study will have respiratory failure prior to randomization, such that intubation and mechanical ventilation will occur prior to the study.

ECMO placement and maintenance

V-V ECMO will be placed for all patients randomized to the ECMO group. This requires a surgeon placing large catheters into the neck, in to the internal jugular vein, through a small incision. This is a simple, brief surgical procedure requiring sedation and anesthesia. Once the ECMO catheter has been placed, sedation will be used in order to prevent the patient from awakening and removing or moving the ECMO catheter, which is sutured in place in the neck. The catheters placed in the neck will extract blood from the heart that will then be run through the ECMO circuit for the purpose of oxygenating the blood and removing carbon dioxide from the blood. The ECMO circuits consist of pumps, membrane oxygenators, and filters. Blood running through the ECMO circuit has an increased risk of clotting such that all patients put on ECMO will receive heparin in order to avoid clotting. The heparin used to avoid clotting creates an increased risk of bleeding. To ensure that the therapeutic effect of heparin is appropriate, coagulation studies will be performed using simple blood tests.

D. Study Drugs: N/A

E. Medical Devices:

ECMO device

The ECMO circuit includes a Stockert SIII servo-controlled roller pump, Medtronic tubing, Medtronic .8meter squared membrane oxygenator, Medtronic ECMOTherm heat exchanger, a Stockert SIII control desk with dual pressure monitors, and Transonics Systems HT110 bypass

flow meter. Stockert—Freiburg, Germany; Medtronic—Minneapolis, MN; Transonics—Ithaca, NY.

Ventilator

Puritan Bennett 840 ventilators will be used.

F. Study Questionnaires:

For the purpose of identifying the primary endpoint, a brief questionnaire will be completed via phone interview asking after the disability status of the patients 6 months after randomization. Two simple yes/no questions will be answered: is the patient bedbound? Is the patient able to dress and wash his/her self?

G. Study Subjects:

Patients for this study will include patients admitted by any means (either transferred patients or patients entering the hospital via the ED of the ECMO center hospitals) to the ECMO centers involved in the study. In all cases, ECMO will be initiated following randomization at the ECMO study center.

Inclusion criteria will include adult patients (18-65 yo) with severe but potentially reversible hypoxemic respiratory failure despite optimal conventional treatment at the same study centers providing ECMO. Respiratory failure as mentioned will be defined by Murray score >3.0

Exclusion criteria will include duration of high P (>30 cm Ppk) and/or high FiO2 (>0.8) ventilation for >7 days, intra-cranial bleeding or any other absolute contraindications to heparinization, hypoxemic respiratory failure not fulfilling ARDS definition or hypoxemic respiratory failure deemed irreversible by a study consultant, moribund patients deemed to have minimal chance for survival regardless of chosen intervention as defined by a study consultant. ARDS related hypoxemic respiratory failure implies acute onset of a potentially reversible pathophysiology for which 'lung rest' allowing for low pressure/low FiO2 vent settings may provide mortality benefit through avoidance of baro/volu-trauma and oxygen toxicity as well as avoidance of any degree of hypoxemia during the acute phase of disease; this is the rationale for excluding nonreversible and chronic hypoxemic respiratory failure.

H. Recruitment of Subjects:

As mentioned above, study subjects will be identified by ARDS diagnosis and by Murray score. Once an ARDS diagnosis is made, Murray score parameters will be monitored every 2 hours, and once Murray score is >2.5, the patient's primary intensivist will then ask after the consenting family member as to the willingness to speak with a study representative.

I. Confidentiality of Study Data

A unique code will be created for each study participant for identification purposes and for data collection. Data will be secured in a secure location, only accessible by investigators.

J. Potential Conflict of Interest: Unknown.

K. Location of Study: Studies will be conducted entirely within the critical care areas of participating ECMO centers.

L. Potential Risks:

All study subjects will be severely ill patients admitted to intensive care units and thus the risk of death and complications will be extremely high.

M. Potential Benefits:

A modernized high standard of intensive care will be provided to all subjects.

N. Alternative Therapies: N/A

O. Compensation to Subjects: none

P. Costs to Subjects: none

Q. Minors as Research Subjects: N/A

R. Radiation or Radioactive Substances: N/A

Appendix 1: Murray Score

0-4 severity index of ARDS (total points as per below divided by 4)

a) p/f (with FiO2 at 100% for 20 mins): >=300=0pts, 225-299=1pt, 175-224=2pts, 100-174=3, <100=4
-CXR: nl=0, 1 pt per quadrant

b) PEEP: <=5=0, 6-8=1, 9-11=2, 12-14=3, >=15=4

c) Compliance: (ml/cmH2O): >=80=0, 60-79=1, 40-59=2, 20-39=3, <=19=4

d) Number of quadrants with infiltr on CXR (1-4)

Appendix 2: Stratification guidelines

a) Age (18-30, 31-45, 46-65)

b) Hours of high P / high FiO2 ventilation (0-48, 49-168)

c) Number of organs failed (1-2 vs 3 or more); failure defined using SOFA score >=2

i. Resp—p/f: <400=1, <300=2, <200+vent=3, <100+vent=4

ii. CNS—GCS: 13-14=1, 10-12=2, 6-9=3, <6=4

iii. CV—MAP: <70=1, DA=2, DA>5 / epi<=0.1 / NE <=0.1 = 3, DA>15 / epi>0.1 / NE >0.1 = 4

iv. Liver—Bili: 1.2-1.9=1, 2-5.9=2, 6-11.9=3, >12=4

v. Coagulation—Plts: <150=1, <100=2, <50=3, <20=4

vi. Renal—CRE: 1.2-1.9=1,. 2-3.4=2, 3.5-4.9 or uop <500=3, <5 or UOP <200=4

References

1. Morris et al. Randomized Clinical Trial of Pressure-controlled Inverse Ratio Ventilation and Extracorporeal CO2 Removal for Adult Respiratory Distress Syndrome. American Journal of Respiratory and Critical Care Medicine. Vol 149, No 2. Feb 1994, 295-305.

2. Peek et al. Efficacy and Economic Assessment of Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR): a Multicentre Randomized Controlled Trial. The Lancet. Vol 374. Oct 17, 2009.

3. Peek et al. CESAR Study Protocol. BMC Health Services Research. 6:163. Dec 23, 2006.

4. UK Collaborative ECMO Group. The Collaborative UK ECMO Trial: Follow-up to 1 Year of Age. Pediatrics. Vol 101. No 4. April 1998.

5. Zapoi et al. Extracorporeal Membrane Oxygenation in Severe Acute Respiratory Failure: A Randomized Prospective Study. JAMA. Vol 242. No 20. Nov 16, 1979.