Detailed Protocol: Early insertion of Axillary Impella® for LV recovery in patients with veno-arterial extracorporeal membrane oxygenation

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

I. BACKGROUND AND SIGNIFICANCE (including progress report and preliminary studies).

a. Historical background
b. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research
c. Rationale behind the proposed research, and potential benefits to patients and/or society

Veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) is used as a rescue strategy for patients in acute hemodynamic deterioration such as cardiogenic shock and cardiopulmonary arrest with severe pulmonary congestion. VA ECMO is the fastest way to stabilize a patient with cardiogenic shock and improve end-organ perfusion, and is used as a bridge to recovery or further advanced therapies including durable implantable ventricular assist device or heart transplantation. However, one of the major disadvantages of peripheral VA-ECMO is that it provides no left ventricular unloading and increases left ventricular (LV) afterload secondary to the retrograde blood flow. Therefore, LV wall tension and myocardial oxygen demand may actually increase in the setting of VA ECMO.

The Impella device is a miniature rotary blood pump which can be inserted retrograde across the aortic valve. In this configuration, it withdraws blood from the LV and ejects it into the ascending aorta. It unloads the left ventricle, reducing LV wall tension and myocardial oxygen demand and increasing myocardial blood flow. The Impella 5.0 is an FDA approved pump designed for intermediate support in patients with severe, cardiogenic shock. The axillary positioning allows for early extubation and ambulation and is more stable than groin placement.

In present practice, the decision to place an Impella pump in VA-ECMO patients is based on the perceived need for direct LV unloading or when a bridge device is required to transition off ECMO support. Patients with peripheral VA ECMO are managed with inotropic agents at the beginning and once patients develop pulmonary edema mechanical LV unloading is considered electively. The advantage of LV unloading with Impella has been demonstrated in recent studies.[1,2] We also reported that concomitant implantation of Impella with VA ECMO for LV unloading resulted in improved survival and recovery of ventricular performance in patients with cardiogenic shock.[3] Compared to delayed elective LV unloading, early LV unloading could lead to decreased pulmonary edema, improved oxygenation delivery to the myocardium, increased chance of LV recovery and improved survival.

The objective of this prospective study is to assess whether the early direct ventricular unloading using axillary Impella leads to higher rates of cardiac recovery, defined as survival free from mechanical circulatory support, heart transplantation or inotropic support at thirty days, compared with the conventional, elective placement of Impella after developing significant pulmonary congestion.

II. SPECIFIC AIMS (Research Objectives)

a. Specify objectives and hypotheses to be tested in the research project

The purpose of this study is to assess the outcomes of early placement of axillary Impella for LV unloading and LV recovery in patients with VA ECMO. We hypothesize that the early LV unloading and ambulation might increase the chance of LV recovery, shorten the length of ECMO support and ICU length of stay, and decrease ECMO related complications.

III. SUBJECT SELECTION

a. Inclusion/exclusion criteria
b. Source of subjects and recruitment methods

This prospective, single-arm trial will include all consecutive patients undergoing cannulation of peripheral VA ECMO at the Massachusetts General Hospital from April 2019 to March 2020. Approximately 20 subjects are anticipated to be enrolled during this time. No one population will be excluded from the study.

Inclusion:

- Age ≥18
- Impaired LV systolic function with ≤35% of LVEF
- Enlarged LV with ≥50mm of LVEDD on echocardiogram

Exclusion:

- Non-cardiac etiology
- Surgically correctable cardiac abnormality
- Recent significant pulmonary embolism
- Severe pulmonary hypertension
- Acute aortic dissection
- Presence of mechanical aortic valve prosthesis
- Presence of left ventricle thrombus
- Pre-existing Impella 5.0
- Critical aortic stenosis
- Uncorrectable system malperfusion under ECMO support
- Significant cerebrovascular accident

IV. SUBJECT ENROLLEMNT

a. Methods of enrollment, including procedures for patient registration and/or randomization
b. Procedures for obtaining informed consent (including timing of consent process)
c. Treatment assignment, and randomization (if applicable)

Potential study subjects will be identified only after they have been deemed eligible and appropriate for VA-ECMO therapy.

The primary specialist/healthcare provider who is known to the potential subject and has firsthand knowledge of the patient's medical history will give approval for his/her patient to be contacted for research purposes. The primary specialist/healthcare provider will introduce the study and obtain the patient's/family's permission to be contacted by study staff verbally. When a subject is a patient of one

the Investigators, it will be made clear to the subject that participation in the study is entirely voluntary and that their decision will not affect their care now or in the future.

The Investigator will explain the research study to the potential subject in detail including the purpose of the research, procedures, risks and potential benefits, right to withdraw, alternative care and confidentiality. Subjects will be given a copy of the consent form to review to ensure the subject is able to understand the study. Potential subjects will be encouraged to speak with friends/family and/or other healthcare providers about research participation. Subjects are told that the PI will also be available to discuss the study.

Whenever possible, our research team will ask a physician co-investigator (not the treating physician) to re-contact the potential subject after the Investigator has presented the study. We will offer potential subjects the opportunity to ask additional questions and raise concerns. We will assure the subject understands the study procedures, risks/benefits, and opt-out with someone other than their treating physician.

Once a subject decides to participate, a licensed physician investigator will obtain informed consent from the subject. The consent discussion between the investigator and patient participant will be documented in the research record. Subjects will be given a copy of their signed consent form. The original signed consent form will be retained in the study binder. A copy of the signed consent form will be filed in the subject's medical record. Should the participant have additional questions, a licensed physician investigator will be offered (and made available) to discuss the consent questions.

Typically, individuals on ECMO will be incapacitated due to their hemodynamic instability and sedation. If it is determined that a potential subject is not competent to give consent or in the event of patient incapacity by sedation/intubation/clinical acuity, the PHRC preferred order of surrogates will be followed:

a. Court appointed guardian;
b. Health care proxy/person with durable power of attorney; or
c. Spouse, adult child, parent, adult sibling, or another close family member

A physician Investigator will approach the surrogate using the same process as outlined in obtaining consent for all subjects. The study will be explained in full to the surrogate, including the purpose of the research, procedures, risks and benefits, right to withdraw, alternative care and confidentiality. We will ensure and document that the surrogate understands that his/her decisions should be based on substituted judgment. If a potential subject did not previously express a view, the surrogate should make the decision based on the potential subject's best interests. We will explain the difference between standard of care and research.

Phone consent will be considered if a subject is not competent to give consent or is incapacitated and a surrogate is not present at the time of ECMO initiation. When surrogate phone consent is obtained, the Investigator will assure the surrogate has a copy of the consent form (sent via fax or email) during the phone discussion. Emails sent outside Partners will be sent securely by encryption per Partners policy, unless the subject agrees to allow non-secure email transmission. The phone consent discussion will

reflect the same process as if conducted in person. If the surrogate agrees, he/she will sign the consent form and return it to the physician investigator via fax or email. Upon receipt, the consent form will be signed by the physician investigator who spoke with the surrogate by phone and a copy of the consent form (with both signatures) will be returned to the surrogate. Consent discussions by phone will be documented in the research records.

If surrogate consent is obtained, the basis of the determination of the subject's lack of capacity will be documented in the research records, along with a description of the relationship of the surrogate.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured (e.g. laboratory tests, x-rays, and other testing)
b. Drugs to be used (dose, method, schedule of administration, dose modifications, toxicities), include Toxicity Grading Scale (if applicable)
c. Devices to be used
d. Procedures/surgical interventions, etc.
e. Data to be collected and when the data is to be collected

All enrolled patients will undergo surgical placement of Impella via axillary artery within 48 hours after peripheral VA ECMO initiation and be managed with early extubation and ambulation strategy.

After Impella placement, there will be no research procedures performed. Subjects will receive standard of care and the subject's progress will be documented throughout the 30 days study follow-up. The data obtained from the electronic medical record in EPIC at MGH will be reviewed throughout the study.

The following documentation will be obtained: demographic data and health/medical reports/results, including history/physical, problem list, operative/procedure notes, medications, and laboratory/imaging results. Specific data fields include vital signs, ventilation settings, type/setting and duration of mechanical support, inotrope use, transfusions, fluid balance, and echocardiogram results, and CXR results.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study (e.g. data collection sheets).
b. Study endpoints
c. Statistical methods
d. Power analysis (e.g. sample size, evaluable subjects, etc.)

The primary outcome of this study will be survival at 30 days. Prespecified secondary end points will include the rate of death from cardiovascular causes, NYHA functional class, LV function (assessed by echocardiography), and the rate of stroke, neurological functional status, acute kidney injury, vascular complications, and bleeding.

The enrolled subjects (early Impella) would be compared with patients who underwent current elective placement of Impella after cannulation of VA ECMO (elective Impella) in the past two years. Student's t-test (for continuous variables) or Fisher exact test (for categorical variables) will be used for between-

group comparisons. The primary endpoint in the data analysis is binary: 30-day survival. The null hypothesis of no difference between early Impella and elective Impella will be tested using logistic regression. The secondary endpoint, the rate of death from cardiovascular causes, NYHA functional class, LV function, and the rate of stroke, neurological functional status, acute kidney injury, vascular complications, and bleeding, will be addressed using competing risks hazard regression models. This is a pilot study for the future multicenter study. If this study demonstrates no inferiority or any significant superiority, we will proceed to do multicenter prospective study. Power analysis will be assessed based on the result of this preliminary study.

VII. RISKS AND DISCOMFORTS (Stratify by common and uncommon)

a. Complications of surgical and non-surgical procedures, etc.
b. Drug side effects and toxicities
c. Device complications/malfunctions
d. Psychosocial (non-medical risks)
e. Radiation risks (statement provided by Radiation Safety Committee)

There is a risk of complications associated with the surgical procedure of Impella placement, which include infection, bleeding, thrombosis/embolism, stroke, arrhythmia, LV injury/perforation, limb malperfusion, and others. However, there is no additional risk to the subjects compared with standard care, since mechanical LV unloading for dilated impaired LV is a part of standard treatment and the timing to place Impella is the only difference of the study procedure from standard care. Only cardiac surgeons certified for Impella 5.0 placement will perform the surgical Impella placement.

The risk to privacy is a minimal risk and obtaining data will not affect the rights or welfare of subjects. All pertinent information regarding the subjects in this study is documented within the electronic medical record in EPIC. Clinical data for this study will be collected from EPIC by IRB-approved researchers listed on the protocol. Only authorized personnel will have access to identifiable data. The electronic data will be stored in a password protected fashion on an internal secure server, accessible only through a Partners encrypted device with anti-virus software. Paper-based data will be stored in a locked and secure office. Neither identifiable nor non-identifiable data will be sent outside Partners or to Partners researchers not listed on the protocol. Data will be used only for clinical outcome research. Patient identifiers be removed from the data and destroyed after all data has been collected, the study has been completed, or all regulatory obligations have been met. Only de-identified datasets will be retained after this point.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals
b. Potential benefits to society (e.g. increased understanding of disease process, etc.)

Our previous retrospective study showed that the group of concomitant implantation of Impella with VA ECMO for LV unloading improved survival compared with patients in VA ECMO without Impella. Early LV unloading could lead to decreased pulmonary edema, improved myocardial oxygenation,

increased chance of LV recovery and improved survival, especially for the study population with dilated impaired LV.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data
b. Safety monitoring (e.g. Data Safety Monitoring Board, etc.)
c. Outcomes monitoring
d. Adverse event reporting guidelines

During the course of the trial, the PI will oversee the conduct of the trial and will review study documents for completeness and accuracy as well as compliance with the study protocol and applicable regulations. The PI is ultimately responsible for protecting the safety and welfare of all subjects.

The PI is responsible for reviewing all laboratory, imaging and procedural reports for clinical significance. It is the PI's responsibility to determine if any reports are significant or meet the guidelines for adverse event and/or serious adverse event reporting for both the sponsor and the IRB.

Safety data will be continuously monitored and reviewed in order to quickly identify any unforeseen risks to subjects. The physician investigator will perform regular, internal reviews of all adverse events. Events will be reported to the IRB per the outlined requirements and a summary of the safety data will be sent the IRB at the time of the annual renewal. Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

All serious adverse events (SAEs) will be assessed by the principal investigator, documented and reported to the IRB according to PHRC guidelines. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

X. REFERENCES

1. Schrage B, Burkhoff D, Rübsamen N, et al. Unloading of the Left Ventricle During Venoarterial Extracorporeal Membrane Oxygenation Therapy in Cardiogenic Shock. JACC Heart Fail. 2018;6(12):1035-1043. doi: 10.1016/j.jchf.2018.09.009.

2. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. Eur J Heart Fail. 2017 Mar;19(3):404-412. doi: 10.1002/ejhf.668.

3. Fiedler AG, Dalia A, Axtell AL, et al. Impella Placement Guided by Echocardiography Can Be Used as a Strategy to Unload the Left Ventricle During Peripheral Venoarterial Extracorporeal Membrane Oxygenation. *J Cardiothorac Vasc Anesth*. 2018;32(6):2585-2591. doi:10.1053/j.jvca.2018.05.019