A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in patients with cardiogenic shock managed with VA ECMO (REVERSE)

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Background

Veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) is indicated as a haemodynamic rescue strategy in decompensated acute or chronic heart failure presenting as cardiogenic shock 1. It has been used across aeitologies including post-myocardial infarction, dilated cardiomyopathy, acute myocarditis and in post-cardiotomy shock. VA ECMO has a number of effects on the circulation including improved end-organ perfusion and possibly improved coronary perfusion, and is a bridge to further therapies including permanent advanced mechanical circulatory support, cardiac transplantation and to cardiac recovery.

Left ventricular assist devices (LVADs) provide long-term mechanical circulatory support and also profoundly mechanically unload the left ventricle 2. Multiple clinical studies have documented cardiac recovery using LVAD therapy, with a rate between 10-60% in selected populations 2-8. A large body of basic science has documented the pivotal role of mechanical load in determining ventricular contractile performance across species (amongst others 9-19). Therefore both clinical data and basic laboratory studies support the notion that profound ventricular unloading may result in improved cardiac performance through a variety of mechanisms ranging from triggered de novo cardiomyocyte proliferation 10, subcellular calcium handling reverse remodeling 18, changes to the extracellular matrix of the heart 20, reverse remodeling of the neurohormal milleu 21, amongst many others 14, 22, 23.

One of the major deficiencies of peripheral VA-ECMO is its lack of left ventricular unloading, with associated pulmonary congestion, which can derail clinical improvement and hamper cardiac recovery. Indeed, percutaneous VA-ECMO increases LV afterload due to the retrograde blood flow, and because of the lack of venting, there may be progressive LV distension 24, 25. These conditions can result in a congested, pressure-overloaded ventricle, even in the absence of echocardiographic ventricular distension. This may be ameliorated with the addition of ventricular mechanical unloading using percutaneous therapies including the percutaneous left ventricular device, Impella CP.

On the platform of VA-ECMO, the addition of an Impella device to reduce ventricular loading results in improved survival and recovery of ventricular performance in the setting of cardiogenic shock 26. In a number of small studies, the use of additional means to unload the ventricle, principally Impella, results in cardiac recovery and less ventricular distension 27-29. In chronic heart failure, direct ventricular unloading is critical to cardiac recovery 5, 6, 8, 22.

Objectives:

The objective of this randomized study is to determine whether the addition of early direct ventricular unloading using Impella CP leads to higher rates of cardiac recovery, defined as

survival free from mechanical circulatory support, heart transplantation or inotropic support at thirty days. This study will also examine the clinical, biochemical, echocardiographic and radiologic effects of VA ECMO with and without the addition of Impella CP to directly vent the left ventricle to address adjunct important questions such as the effects on pulmonary congestion.

Proposed Methods

Patients at the The Hospital of The University of Pennsylvania and Penn Presbyterian Medical Center will be placed on VA ECMO for clinical deterioration to provide full circulatory support in the setting of cardiogenic shock. Following the institution of VA ECMO, eligible patients who enroll in the study will be randomized to either no LV venting (Control; 48 patients) or percutaneous LV venting with Impella CP (48 patients) 30, 31 .

Patients will be informed of and consented for the REVERSE study by a maximum of 12 hours from the time of ECMO institution. The patient will be screened for signs of termination/stabilization of shock and must have a grossly viable neurological status including intact brainstem reflexes and moving extremities to some extent.

Randomisation will occur at any point when these criteria have been met up to 12 hours from ECMO institution, and Impella CP will be inserted within 12 hours of randomization – at a maximum of 24 hours from time of ECMO institution. We will follow the agreed published inclusion and exclusion criteria for VA-ECMO at The University of Pennsylvania (attached), in addition to the study criteria specified as below.

Inclusion criteria

1. Cardiogenic shock: Including refractory to conventional therapy, including systolic BP < 90mm Hg, Cardiac Index < 1.8 or a cardiac index < 2.0 on moderate to high doses of inotropes and vasopressors for greater than 30 mins, or systemic signs of tissue hypoxia.
2. Post-acute myocardial infarction cardiogenic shock: excluding mechanical complications requiring surgical intervention after ECMO such as post-ischaemic VSD.
3. Drug overdose-induced cardiogenic shock.
4. Early graft failure: post orthotropic heart transplantation cardiogenic shock, excluding immediate intra-operative failure.
5. Acute on chronic cardiomyopathy with progressive shock and decompensation unresponsive to medical therapies.

Exclusion criteria

1. Neurological injury including recent cerebrovascular accident or suspected severe neurologic injury

2. Recent Significant Pulmonary Embolus
3. Moderate to severe aortic valve insufficiency
4. Ongoing significant sepsis
5. Severe pulmonary hypertension & shock
6. Hypothermia
7. Post-cardiotomy cardiogenic shock
8. Continuous CPR>20-30 minutes, except if neurological status is satisfactory
9. Transfer from outside hospital on VA ECMO or with history of CPR
10. Listed for cardiopulmonary transplantation or being evaluated for cardiopulmonary transplantation or permanent mechanical circulatory support
11. Known or suspected chronic heart failure with echocardiogram documenting LVEDD >6.5cm
12. Known or suspected chronic heart failure with echocardiogram documenting LVEF< 25%
13. Mechanical AVR
14. Presence of LV thrombus
15. Pre-existing Impella 2.5, CP, 3.5 or 5.0
16. Cardiogenic shock due to primary respiratory failure
17. Mechanical complications requiring surgical intervention after ECMO such as post-ischaemic VSD.
18. Severe AI
19. Severe liver failure
20. Active malignancy
21. Acute aortic dissection
22. Intracranial hemorrhage

Presence of a pre-existing intra-aortic balloon pump will not be an exclusion or cross-over criteria.

Cross-over between groups

In the presence of radiologic evidence of severe pulmonary congestion, cross-over from the non-vented to vented (Impella CP) arm will be allowed at the discretion of the PI. This consideration is made as the standard of clinical care is that in the presence of severe pulmonary oedema, most physicians would advocate addition of an LV vent (surgical or percutaneous) for VA ECMO patients.

Consent

Within 12 hours of institution of VA-ECMO, a legally authorized representative will be proxy consented for enrolment in this trial to include clinical and laboratory data collection and echo turn-down studies, and the primary intervention of LV venting with Impella CP. In patients who are awake and orientated, the patient will be consented. This will be conducted in compliance with Federal regulations including 45 CFR Part 46, HIPAA and ICH-GCP.

The consenting process will take account of the imperative of patient comfort and confidentiality. All discussions will be undertaken in a private room in the Heart and Vascular ICU suite.

ECMO

The standard ECMO set-up routinely used at the University of Pennsylvania will be employed. This typically involves a 22-25 French Venous cannula in the femoral vein and a 15 -19 French arterial cannula in the femoral artery. A distal arterial perfusion cannula is uniformly used, often a micropuncture 5-9 French perfusion cannula. Central aortic and venous cannulation will not be used. A centrifugal pump such as Maquet Rotaflow or Centrimag platform are used on a console with standard Maquet bioline heparin bonded cannulae and Quadrox D oxygenator.

The Impella CP system that provides a low profile through a 16 Fr sheath with flow up to 3.0-3.5L/min on a 15Fr motor pump setup. The maximum outer diameter of the Impella CP as it crosses the iliofemoral subclavian vessels is 5.8mm. In the absence of significant peripheral vascular disease, it will be inserted via femoral artery using the Seldinger or open surgical technique in the operating theatre or cardiac catheterisation lab under fluoroscopic guidance, with its position re-adjusted under echocardiographic guidance. The subclavian artery route is also well established and will be used when more appropriate than femoral access. Angiography will be used routinely to guide placement. The Impella CP catheter will be positioned near the LV apex with the distal end of the catheter between 3-4 cm from the aortic valve.

In addition, wherever possible, all patients will receive a Swann-Ganz catheter, which is the standard of care in the management of cardiogenic shock.

Randomization

Randomisation will be performed to aim for an equal number of patients with similar age, sex and aetiology of heart failure in both the control and treatment arms.

Anticoagulation

The standard University of Pennsylvania ECMO Anticoagulation protocol will be followed, as described below.

Initial Heparin Bolus

- 5,000 units IV upon initiation, prior to cannulation
- aPTT sent within 1 hour of initial Heparin bolus

Heparin Infusion

- Heparin infusion is initiated as per the CT / Anesthesia attending physician and will generally be started within 12 hours of ECMO initiation. Reasons for delay in Heparin initiation include:
  - Chest tube output >100ml/hr
  - Hypothermia
  - Elevated aPTT
  - Excessive bleeding at cannulation sites, pulmonary hemorrhage, nasopharyngeal/GI bleeding
  - Hematoma formation at puncture sites
- Initial Heparin infusion rate – 400-600 units/hr as per the Anesthesia/CT attending
- Send baseline aPTT before starting Heparin infusion
- aPTT sent every 4 hours or 4 hours after Heparin infusion dose change

- Infusion titration guidelines - Standard: goal PTT 56-70
- aPTT <40.0 – increase by 200 units/hr
- aPTT 40.0-55.9 – increase by 100 units/hr
- aPTT 56.0-70.9 no change
- aPTT 71.0-79.9 – decrease by 100 units/hr
- aPTT 80.0-89.9 – decrease by 200 units/hr
- aPTT 90.0 or greater – hold Heparin for one hour and recheck PTT
- If Heparin infusion increased 2 times without an increase in PTT may consider Heparin bolus 1000-2000 units IVP as per Anesthesia/CT attending and based on amount of bleeding.

- Infusion titration guidelines – Risk for bleeding: goal PTT 40-55
- aPTT <30.0 – increase by 200 units/hr
- aPTT 30.0-39.9 – increase by 100 units/hr
- aPTT 40.0-55.9 no change
- aPTT 60.0-69.9 – decrease by 100 units/hr
- aPTT 70.0-79.9 – decrease by 200 units/hr
- aPTT 80.0 or greater – hold Heparin for one hour and recheck PTT
- If Heparin infusion increased 2 times without an increase in PTT may consider Heparin bolus 1000-2000 units IVP as per Anesthesia/CT attending and based on amount of bleeding.
- If platelets drop below 50,000 or if platelets decrease more than 50% from baseline, heparin may need to be adjusted or discontinued. Provider team will examine platelet count daily and make adjustments as needed.

This will provide appropriate anticoagulation levels required/recommended by the Impella CP manufacturer.

Primary Endpoint

Proportion of subjects treated with this standardized ECMO protocol with either (i) no additional therapy or (ii) Impella CP for LV mechanical unloading who experience myocardial

recovery defined as: survival free from mechanical circulatory support, heart transplantation or inotropic support at thirty days.

Secondary Endpoints

1. Survival to hospital discharge.
2. Significant between-group differences in inotropic score, pulmonary compliance and radiologic measures of pulmonary congestion at 24-72 h.
3. Significant between-group differences in echocardiographic measurements, biochemical profile, and haemodynamics.
4. A single 5 ml blood sample will be taken at 3, 6, 9 and 12 months to identify biomarkers of cardiac recovery in addition to those defined below in Table 1.
5. Incidence of crossover

Baseline Data

- Date Informed Consent obtained
- Demographics (including age, gender, race, ethnicity)
- Medical and surgical history
- Diagnosis and history of present illness requiring ECMO
- Cardiopulmonary resuscitation history
- Vital signs (temperature, heart rate and rhythm, blood pressure [systolic, diastolic, mean])
- Height and weight
- NYHA class
- INTERMACS profile and modifiers
- Hemodynamics: Central Venous Pressure (CVP); Pulmonary Artery Pressures: Systolic (PAS), Diastolic (PAD) and Mean (PAM); Pulmonary Capillary Wedge Pressure (PCWP); Cardiac Output (CO); Cardiac Index (CI); mixed venous oxygen saturation (SVO2).
- Ventilator settings: mode of ventilation, tidal volume, respiratory rate, inspiratory/expiratory (I/E) rate (ratio), PEEP, ventilator FiO2 (%)
- Oxygenator FiO2 (%) and sweep gas flow rate (L/min)
- Distal pulse assessment including presence of distal perfusion cannula
- Critical care interventions/assessments, including: level of consciousness (LOC), Continuous Renal Replacement Therapy (CRRT) or dialysis, cardiopulmonary resuscitation (CPR), urine output, intubated, ventilator, pulmonary edema.
- Other mechanical support device in use; as applicable
- Routine medications and medications in last 24 hours (if different from routine): Anticoagulants/Antithrombins, Anti-platelets, Inhaled Vasodilators/Prostaglandins, Inotropes, Thrombolytics, Vasopressors
- Baseline laboratory test results (as available):

o Laboratory test results:

- White Blood Cell count (WBC), Red Blood Cell count (RBC), Hematocrit (HCT), hemoglobin (HGB), Platelet count (Plt), Blood Urea Nitrogen (BUN), Creatinine (CR), Total

Bilirubin (TBili), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lactic Dehydrogenase (LDH)

- o Coagulation laboratory test results:
- ⏛ Prothrombin Time/International ratio (PT/INR), Partial Thromboplastin Time (aPTT)
- o Serum lactate
- o Arterial blood gases (ABG):
- ⏛ pH, pO2, HCO3, pCO2 O2 sat

Peri-procedural data

- ECMO insertion procedure detail including: cannula type, cannulation sites, circuit components, duration of procedure and anticoagulation administered
- ECMO data: record initial settings for:
- o Pump speed (in revolutions per minute [rpm]) and flow (in liters per minute [L/min]) Oxygenator FiO2 (%) and sweep gas flow rate (L/min)
- Vital signs (temperature, heart rate and rhythm, blood pressure [systolic, diastolic, mean])
- Hemodynamics: Record first set of hemodynamics as soon as possible after ECMO insertion (or upon arrival in CTSICU):
- o CVP; Pulmonary Artery Pressures if available: PAS, PAD, PAM; PCWP; CO; CI; SVO2.
- Ventilator settings: mode of ventilation, tidal volume, respiratory rate, I/E rate (ratio), PEEP, ventilator FiO2 (%)
- Distal pulse assessment and details of distal perfusion cannula
- Critical care interventions/assessments, including: LOC, CRRT or dialysis, urine output, intubated, ventilator, pulmonary edema.
- Impella parameters: P speed, flow, alarms, heparin flow rate
- Medications: Anticoagulants/Antithrombins, Anti-platelets, Inhaled Vasodilators/Prostaglandins, Inotropes, Thrombolytics, Vasopressors
- Laboratory test results (as available):
- o Coagulation laboratory test results: record immediately prior to ECMO insertion, as soon as possible after ECMO institution (CTSICU):
- ⏛ PT/INR, aPTT
- Surgical and other procedures proximate to the ECMO starting
- Serious Adverse Events
- Transfusions (# packed RBC) meeting the definition of Major Bleeding or Major Vascular Adverse Event (record on Hematological/Vascular Event Details eCRF)
- Device observations

Core Data while on ECMO Support

- ECMO data: Record every 12 hours while on ECMO support and with each speed change. Record for any hemolysis event and include pump current speed (rpm) and flow (L/min), Oxygenator FiO2 (%) and sweep gas flow rate (L/min), transmembrane gradients

- Distal pulse assessment including distal perfusion cannulae
- Vital signs (temperature, heart rate and rhythm, blood pressure [systolic, diastolic, mean]) q1hour
- Hemodynamics: Record every hour while on ECMO support.
  - CVP; Pulmonary Artery Pressures: PAS, PAD, PAM; PCWP; CO; CI; SVO2.
- Ventilator settings: mode of ventilation, tidal volume, respiratory rate, I/E rate (ratio), PEEP, ventilator FiO2 (%)
- Critical care interventions/assessments daily, including: LOC, CRRT or dialysis, urine output, intubated, ventilator, pulmonary oedema.
- Impella parameters: P speed, flow, alarms, heparin flow rate
- Medications: Anticoagulants/Antithrombins, Anti-platelets, Inhaled Vasodilators/Prostaglandins, Inotropes, Thrombolytics, Vasopressors
- Laboratory test results (as available):
- Laboratory test results: Every 12 hours while on ECMO support:
- WBC, RBC , HCT, HGB, Plt, BUN, CR, TBili, AST, ALT, LDH
- Coagulation laboratory test results: Record every 2 hours for the first 6 hours and at 12 and 24 hours post-ECMO insertion; then every 24 hours while on ECMO support. Also record 6 hours following anticoagulation medication dose change.
  - PT/INR, aPTT
  - Serum lactate results (record available results) every 12 hours
  - ABG results: Record all available results for the first 24 hours post-ECMO institution, then every 12 hours while an oxygenator is in the circuit:
    - pH, pO2, HCO3, pCO2 O2 sat, include site of sampling
- Support interruption details (date and time interrupted and resumed; reason for interruption)
- Device component and/or extracorporeal circuit changes
- Surgical and other procedures
- Serious Adverse Events
- Transfusions (# packed RBC) meeting the definition of Major Bleeding or Major Vascular Adverse Event (record on Hematological/Vascular Event Details eCRF)
- Device observations

Data during turndown studies

- Date and time of each weaning attempt
- Turndown studies will involve ECMO weaning to 1 litre, modest inotropic support (epinephrine 0.05mcg/kg/min, milrinone 0.25mcg/kg/min)
- ECMO data: record at the beginning and end of each weaning attempt and with each speed change
  - Speed (rpm) and flow (L/min), Oxygenator FiO2 (%) and sweep gas flow rate (L/min)
- Impella parameters: P speed, flow, alarms, heparin flow rate
- Hemodynamics as above: record at the beginning and end of each weaning attempt and with each speed change
  - CO (L/min), SvO2 (%), MAP (mmHg), Oxygenator FiO2 (%) and sweep gas flow rate (L/min)

- Echocardiography to guide weaning:
  - Date and time; Ejection Fraction (EF) (%), LVEDD, LVESD
- Surgical and cardiac procedures
- Serious Adverse Events
- Device observations

Data at point of ECMO removal

- Date and time of ECMO removal
  - Duration of ECMO (number of ECMO support days)
- Cannula site hemostasis details
- Remaining devices
- Prior to ECMO removal, record:
  - ECMO speed (rpm) and flow (L/min), Oxygenator FiO2 (%) and sweep gas flow rate (L/min), transmembrane pressures etc
  - Hemodynamics:
    - CVP; Pulmonary Artery Pressures: PAS, PAD, PAM; PCWP; CO; CI; SVO2.
  - Ventilator settings: mode of ventilation, tidal volume, respiratory rate, I/E rate (ratio), PEEP, ventilator FiO2 (%)
  - Distal pulse assessment
  - Critical care interventions/assessments, including: LOC, CRRT or dialysis, urine output, intubated, ventilator, pulmonary edema.
  - Medications: Anticoagulants/Antithrombins, Anti-platelets, Inhaled Vasodilators/Prostaglandins, Inotropes, Thrombolytics, Vasopressors
  - Laboratory test results (as available):
    - Coagulation laboratory test results:
- PT/INR, aPTT
- Surgical and cardiac procedures performed
- Echocardiogram
- Serious Adverse Events (per 21 CFR 803 Medical Device Reporting) will be collected.
- Device observations

Discharge Data

- Date of hospital discharge
- Vital Signs (temperature, pulse, blood pressure [systolic, diastolic])
- NYHA Class
- ICD or resynchronization device placement prior to hospital discharge
- Durable VAD implant or cardiac transplant after ECMO removal
- SAEs after ECMO removal, only if SAE/injury/death directly attributable to ECMO (per 21 CFR 803 Medical Device Reporting).
- Length of hospital stay (total number of hospital days from admission to discharge)
- Length of ICU stay (number of ICU days)

- Final lab data as above
- Echocardiogram

All patients will be followed through removal of ECMO and at hospital discharge, 30 days (+/- 15 days) and 180 days (+/- 60 days) after initial ECMO institution.

Follow up outcomes include survival and exit strategy status (e.g. durable VAD implant, cardiac transplant).

Patients will be contacted by phone to collect survival and VAD or cardiac transplant status (data from the patient's medical record [chart review] may also be used, if available). Quality of life assessment with short form 36 questionairre will be completed.

REVERSE Long-Term follow-up

It is essential to assess the long-term durability of recovery in survivors of both the control and experimental arms of the study. We propose to follow up at 3, 6, 9 and 12 months. This includes a visit with a heart failure cardiologist for a clinical history and physical examination, SF-36 quality of life questionnaire, transthoracic echocardiogram. We would also draw a single sample of peripheral venous blood for storage in a heart failure biomarker bank. At six months, per the standard of care, patients would undergo submaximal cardiopulmonary exercise testing using six minute walk test with measurement of VO2 max (maximal oxygen consumption).

Significant Adverse Events
Serious Adverse Events (SAEs) and any unexpected SAEs will be collected from the time of ECMO insertion through removal and hospital discharge. All SAEs will be reported using modified INTERMACS adverse event (AE) categories. The INTERMACS AE definitions have been modified to exclude pediatrics and include SAEs related to extracorporeal mechanical assist devices, including percutaneous cannula insertion.

Serious Injury Definition:
An injury or illness that:
- Is life threatening;
- Results in permanent impairment of a body function or permanent damage to a body structure, or
- Necessitates medical or surgical intervention to preclude permanent* impairment of a body function or permanent damage to a body structure.

*Permanent means irreversible impairment or damage to a body structure or function excluding trivial impairment or damage.

INTERMACS Adverse Event Terms and Definitions (amended for relevance)

Major Bleeding

An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:

a. Death,
b. Re-operation,
c. Hospitalization,
d. Transfusion of red blood cells as follows:

If transfusion is selected, then apply the following rules:

During first 7 days post-insertion
• Adults (≥ 50 kg): ≥ 4U packed red blood cells (PRBC) within any 24 period during first 7 days post-insertion.

After 7 days post-insertion through to ECMO removal
• Any transfusion of packed red blood cells (PRBC) after 7 days following insertion with the investigator recording the number of units given. (record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Major Vascular Events
A Major Vascular Event related to the ECMO cannulation or Impella:
- Any new thoracic aortic dissection
- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (>2 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g. hypogastric artery occlusion causing visceral ischaemia or spinal artery injury causing neurological impairment)
- Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible organ damage

Cardiac Arrhythmias
Any documented arrhythmia that results in clinical compromise (e.g., diminished ECMO flow, associated with unstable hemodynamics, oliguria, syncope or requires treatment (drug therapy, defibrillation, cardioversion, ICD therapy [e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure) occurring during ECMO support. Cardiac arrhythmias are classified as 1 of 2 types:

1) Sustained ventricular arrhythmia resulting in clinical compromise or requiring drug treatment, defibrillation or cardioversion.
2) Sustained supraventricular arrhythmia resulting in clinical compromise or requiring drug treatment or cardioversion.

Pericardial Fluid Collection

A Pericardial Fluid Collection is the accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/ECMO output) and those without signs of tamponade.

Device Malfunction

Device Malfunction denotes a failure of one or more of the components of the ECMO circuit or Impella which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output) or death including:

1. Suspected or confirmed pump thrombus; visible or with the following:
a. Presence of hemolysis
b. Abnormal pump current
2. Urgent transplantation (immediate 1A listing for transplant)
3. Pump or controller replacement
4. Urgent Pump removal or transition to another temporary or durable support device
5. Death

Hemolysis

A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center post-implant and associated with clinical symptoms or findings of hemolysis or abnormal pump function. Major Hemolysis requires the presence of one or more of the following conditions:

- Hemoglobinuria (“tea-colored urine”)
- Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-VAD state)
- Hyperbilirubinemia (total bilirubin above 2 mg%, with predominately indirect component)
- Pump malfunction and/or abnormal pump parameters.

Hepatic Dysfunction

New onset of an increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the patient’s baseline values in the absence of other confounding conditions such as Right Ventricular dysfunction.

Major Infection
New onset of a clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection
Infection localized to any organ system or region (e.g. urinary tract infection) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous cannula site infection
A positive culture from the skin and/or tissue surrounding the cannula coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Sepsis
Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Neurological Dysfunction
Any new, temporary or permanent, focal or global neurologic dysfunction ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as a cerebrovascular event as defined below or as a non-vascular acute neurologic event. A neurologic event may be recognized by a clinically evident sign or symptom, or by clinically-silent electrographic seizure activity, or as a clinically silent lesion detected by surveillance neuroimaging. Each neurologic event should be classified by the clinical provider following complete neurologic assessment as one of the following event types:

a. Transient ischemic attack, defined as an acute transient neurologic deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI).

b. Ischemic stroke, defined as a new acute neurologic deficit (or acute encephalopathy***) of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit. Ischemic stroke should be sub classified as due to arterial-distribution ischemia or due to venous thrombosis.

c. Acute symptomatic intracranial hemorrhage, defined as new acute neurologic deficit (or acute encephalopathy***) attributable to Intracranial hemorrhage (ICH). ICH subtype should be specified as one or a combination of the following types: subarachnoid, intraventricular, parenchymal, subdural.

d. Clinically covert ischemic stroke or ICH: infarction or ICH seen by surveillance imaging, without clinical findings of stroke or ICH at the time of event recognition.

e. Hypoxic-Ischemic Encephalopathy: Acute new encephalopathy*** due to hypoxic-ischemic injury (HIE), manifest as clinically- evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.

f. Acute new encephalopathy*** due to other causes, manifest as clinically-evident signs or symptoms or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable causes other than stroke, ICH or HIE, as defined above. This category of "other" acute encephalopathy includes neurologic signs or symptoms or subclinical seizures found to be attributable to other conditions such as meningitis, toxic-metabolic or drug-related processes.

*** Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

Acute Renal Dysfunction
New onset of abnormal kidney function (from post-ECMO insertion through ECMO removal) requiring dialysis (including hemofiltration) in patients who did not require this procedure (or the procedure was not part of planned intervention for the disease course prior to ECMO insertion) or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL sustained over 48 hours.

Respiratory Failure
New onset of impairment of respiratory function (from post-ECMO insertion through removal) requiring reintubation, tracheostomy or ventilator support in patients who did not require this procedure (or the procedure was not part of planned intervention for the disease course prior to ECMO insertion). This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure
New symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.3 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmhg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD; implantation; or requiring inhaled nitric oxide

or inotropic therapy for a duration of more than 1 week at any time after ECMO insertion through removal.

Arterial Non-CNS Thromboembolism
An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) standard clinical and laboratory testing
2) operative findings
3) autopsy findings

This definition excludes neurological events.

Venous Thromboembolism Event
Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Other Serious Adverse Event
A serious event that causes clinically relevant changes in the patient's health (e.g. limb ischemia, skin breakdown resulting from immobility).

Data Collection Overview

Table 1 specifies in detail the data collected at various time points. These investigations are currently collected as the standard of clinical care.

Assessment	Base-line	ECMO Institution		On ECMO	ECMO Turndown		ECMO Removal	Dis-charge	30 Days	180 Days
Baseline data as above	X									
Vital Signs (Temp, heart rate/rhythm, B/P[S/D/M])	X	X	X	X	X	X				
NYHA Class	X			X						
INTERMACs Profile, Modifiers		X								
Hemodynamics	X1	X1	X1	X1	X1	If available	If available			
Ventilator Settings)	X3	X3	X3		X3					
Oxygenator FiO2 and Sweep Gas Flow Rate (if oxygenator in circuit)						X3	X3	X3	X3	

Distal Pulse Assessment	X	X	X2		X2						
Critical Care Interventions/ Assessments (LOC, urine output, CRRT/dialysis, Intubation, Ventilation, Pulmonary Edema)	X	X	X 2	X 2							
Other Mechanical Support; IABP parameters	X	X	X	X							
Medications	X 4	X 4	X 4	X 4	X 4						
Laboratory Tests (WBC, RBC, HCT, HGB, Platelets, BUN, Creatinine, Total Bilirubin, AST, ALT, LDH, lactate, ABG, Coag)	X	Q1-4 hour for 12 hours	X	X	X	X	X				
NIRS Microcirculation	X	X5									
Chest X ray with modified Murray index of pulmonary oedema	X	Daily	X	X	X						
ECMO procedure details (cannula type, cannulation sites, circuit components, duration of procedure, anticoagulation admin.)	X	X5									
ECMO parameters (speed, flow, FiO2, Sweep, transmembrane gradients and post-oxygenator gas) and Impella parameters	X	X 5	X5	X5							
Support Interruption details; Device component/circuit changes	X										
ECMO Removal details (cannula site hemostasis, any remaining devices)											
Echocardiogram (left ventricular end-diastolic diameter; degree of mitral regurgitation; LVEF; Degree of RV dysfunction: degree of Tricuspid regurgitation	X6	X6	X	X	X	X					
Surgical/Cardiac/Other Procedures	X	X	X	X	X10						
SAEs & Device Observations	X11	X11	X11	X11, 12	X11, 12						
Hospital and ICU LOS	X										
Survival	X	X	X								
Durable VAD, Cardiac Transplant	X	X	X								

1 Includes: SBP, DBP, MAP, CVP, PAS, PAD, PAM, PCWP, CO, CI, SVO2. Collect at baseline; then collect the first set of parameters as soon as possible after ECMO insertion (or on arrival to CTSICU); then every hour while on ECMO support and prior to ECMO removal. During weaning, record CO (L/min), SvO2 (%), MAP (mmHg) at the beginning and end of each weaning attempt and with each speed change.

2 Every 6 hours while on ECMO support and prior to ECMO removal. The time of Impella insertion will be carefully documented and will trigger restarting all data collection as if newly placed on VA ECMO.

3 Collect at baseline, then collect the first set of parameters as soon as possible after ECMO insertion (or upon arrival to CTSICU); then then every hours while on ECMO support.

4 Medications in the following categories will be collected: Anticoagulants/Antithrombins, Anti-platelets, Inhaled Vasodilators/Prostaglandins, Inotropes, Thrombolytics, Vasopressors. Record routine medications (meds) and meds within 24 hours prior to ECMO insertion; procedural meds at ECMO insertion; meds every 6 hours while on ECMO support and meds administered immediately after ECMO removal. For anticoagulant/antithrombin meds, record as soon as

possible after ECMO insertion (or upon arrival to CTSICU); then every 2 hours for the first 6 hours and at 12 and 24 hours post-ECMO insertion ; then every 24 hours while on ECMO support and prior to ECMO removal. Record additional med details for anticoagulation meds administered during the ECMO insertion procedure.
5 Every 12 hours, and at any speed change
6 Ideally pre-ECMO if possible, then following ECMO institution (within 24 hours), during turndown studies as dictated by ICU team, at 30 days and at discharge. Other echocardiograms may be ordered by clinical team as required.

Radiation exposure

This study does not involve any more chest x rays than is the current standard of care.

Management of ECMO platform

Multiple broad phases of mechanical unloading induced recovery have been described 8, 23. First, shock must be terminated. Early on, maximal unloading (and drug therapy) aims to induce maximal reverse remodeling. Later phases focus on inducing physiological hypertrophy, in their case, using clenbuterol with graded weaning of mechanical support as tolerated.

Following randomization to control or Impella (and institution of Impella), either at the time of ECMO institution or shortly after, a period of full haemodynamic support will be used to terminate and reverse systemic sequelae of shock, “Stabilisation”. This also is a powerful impetus for reverse remodeling, and may indeed mimic the effects of a number of cardiovascular pharmacologic approaches 12, 24-26. Termination of shock will be determined by substantive improvements in hemodynamics and associated sustained improvements in end organ function including lactate, renal and liver function.

Following this, the “recovery” phase when lactate is clearing, and end-organ function is improving, involves a period of partial support of varying extents will be used to iteratively re-load the LV. The benefits of partial support of the LV are emerging at the clinical and basic levels 27-29, and this phase promotes physiological hypertrophy with sequential re loading, culminating in de-cannulation. The extent of partial support and the undertaking of turndown studies (where ECMO support is weaned and haemodynamic and echocardiographic data are collected) will be agreed with the ICU and cardiac surgery attending responsible for the patient. The general guidelines will be to wean to maintain CVP, PA diastolic and mean arterial blood pressure at baseline ± 10% without requiring significant escalation of vasopressors or inotropes. Likewise the decision to proceed to decannulation will be made with ICU and cardiac surgery attending, but will generally be guided by haemodynamic, laboratory and echocardiographic stability on minimal support.

This can be defined broadly as the following features on a moderate dose of inotropic support:

Turndown at 1L, full anticoagulation:

- Echocardiogram LVEF>25
- CVP<15-18
- PAD <20 or Wedge <18
- CI>2.2
- Absence of greater than moderate MR
- MAP>65

Decannulation may proceed when the heart team believes the patient is able to support their circulation based on these factors. It may be necessary to phase removal of the devices so that ECMO is removed but Impella remains for a period of time. These decisions are at the discretion of the clinical team.

The P speed of Impella will be directed by the ICU team and generally between P2-P8 aiming for adequate venting of the LV on echocardiography with a decompressed ventricle, LVEDD<6cm in the absence of greater than moderate MR.

Removal of ECMO and Impella

To assure the highest standard of safety, ECMO decannulation and Impella removal will be performed in the operating room. While “pulling and holding pressure” has been used to remove Impella, this exposes patients to a higher risk of vascular injury or subsequent bleeding. Directly visualized removal and primary repair of the artery assures the patient leaves the operating room with an intact and working artery. This will be performed by either cardiac or vascular surgery depending on availability as both clinical groups are highly experienced in this procedure.

PHASE TIMEPOINT ECMO SUPPORT MEDICAL THERAPY GOALS DECISION NODE
P1
STABILIZATION Institution Full Inotropes & vasopressors

Moderate doses: epinephrine 0.05mcg/kg/hr, milrinone 0.25 mcg/kg/hr, dopamine 2-8mcg/kg/hr MAP> 60mmHg
Maintain ECMO flow at CI >2.2 L/min/m2 Has shock been terminated?
Appropriate for turndown studies?

Appropriate for partial support?

Evidence of cardiac recovery?
P2

RECOVERY Daily Partial support as agreed with ICU team and according to protoco
Weaning of inotropes and vasopressors Lactate falling and below 5 mmol/L with improving LFT and serum creatinine. Titration of pharmacologic support
Titration of ECMO support
P3
RECOVERED Daily Minimal support Minimal vasopressors & inotropes
Diuresis Turndown at 1L, full anticoagulation:

- echocardiogram LVEF>25,
- CVP<15-17
- PAD <20 or wedge< 18
- CI>2.2
- Absence of greater than moderate MR Appropriate for decannulation?

P4
DECANNULATION Day 1 post VA ECMO Inotropes, Vasopressors, Reverse remodeling agents as tolerated

ACE inhibitors
Beta blockers
Active monitoring of haemodynamics and end-organ function. Recovery stable?

Anticipated outcomes

This study will provide valuable data on the changes at multiple levels with full and iteratively reduced mechanical circulatory support. It will serve as a focused attempt to actively seek out cardiac recovery, with the working assumption that it could be possible in a majority of patients. It will serve to carefully document the consequences of full, then partial mechanical circulatory support on key haemodynamic and echocardiographic indices. Stored tissue samples will be used to investigate biologic markers of recovery. In summary it will provide data on the following questions

1. Is direct mechanical unloading of the ventricle using percutaneous LV venting an effective strategy for inducing cardiac recovery on VA-ECMO. This study is the first randomized test of this question.
2. What are the clinical, haemodynamic, imaging and biochemical changes in patients on VA ECMO managed with a recovery orientated strategy with full then partial, graded support. Retrospective analysis of these data will also provide new insights into identifying those patients with the greatest potential for cardiac recovery, using readily available indices.
3. At what rate can cardiac recovery be anticipated with a program which is aggressively monitoring for and promoting cardiac recovery. For example, at what rate can support be weaned following the general guidelines outlined.

4. From the above, what can be gleaned about the mechanisms and biomarker profile of cardiac recovery. Specifically, can we use biological data to define readiness to progress through phases of ECMO support with the intention of cardiac recovery. This includes, for example, early echocardiographic markers of cardiac recovery.

Conclusions

One of the major limitations to cardiac recovery is that it is not often the target outcome of mechanical circulatory support programs and there has not emerged a standard haemodynamic, echocardiographic or biologic profile to identify nor promote it. The VA ECMO platform with targeted LV unloading strategies provides a unique strategy to understand in unprecedented detail the conditions necessary for cardiac recovery and to identify its full potential.

References

1. Peura JL, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, John R, Kiernan MS, Mitchell JE, O'Connell JB, Pagani FD, Petty M, Ravichandran P, Rogers JG, Semigran MJ, Toole JM, American Heart Association Heart F, Transplantation Committee of the Council on Clinical C, Council on Cardiopulmonary CCP, Resuscitation, Council on Cardiovascular Disease in the Y, Council on Cardiovascular N, Council on Cardiovascular R, Intervention, Council on Cardiovascular S and Anesthesia. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American Heart Association. Circulation. 2012;126:2648-67.
2. Terracciano CM, Miller LW and Yacoub MH. Contemporary use of ventricular assist devices. Annu Rev Med. 2010;61:255-70.
3. Maybaum S, Mancini D, Xydas S, Starling RC, Aaronson K, Pagani FD, Miller LW, Margulies K, McRee S, Frazier OH and Torre-Amione G. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. Circulation. 2007;115:2497-505.
4. Terracciano CM, Hardy J, Birks EJ, Khaghani A, Banner NR and Yacoub MH. Clinical recovery from end-stage heart failure using left-ventricular assist device and pharmacological therapy correlates with increased sarcoplasmic reticulum calcium content but not with regression of cellular hypertrophy. Circulation. 2004;109:2263-5.
5. Birks EJ, Hall JL, Barton PJ, Grindle S, Latif N, Hardy JP, Rider JE, Banner NR, Khaghani A, Miller LW and Yacoub MH. Gene profiling changes in cytoskeletal proteins during clinical recovery after left ventricular-assist device support. Circulation. 2005;112:I57-64.
6. Birks EJ, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, Banner NR, Khaghani A and Yacoub MH. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med. 2006;355:1873-84.
7. Hall JL, Birks EJ, Grindle S, Cullen ME, Barton PJ, Rider JE, Lee S, Harwalker S, Mariash A, Adhikari N, Charles NJ, Felkin LE, Polster S, George RS, Miller LW and Yacoub MH. Molecular

signature of recovery following combination left ventricular assist device (LVAD) support and pharmacologic therapy. Eur Heart J. 2007;28:613-27.
8. Birks EJ, George RS, Hedger M, Bahrami T, Wilton P, Bowles CT, Webb C, Bougard R, Amrani M, Yacoub MH, Dreyfus G and Khaghani A. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. Circulation. 2011;123:381-90.
9. Oriyanhan W, Tsuneyoshi H, Nishina T, Matsuoka S, Ikeda T and Komeda M. Determination of optimal duration of mechanical unloading for failing hearts to achieve bridge to recovery in a rat heterotopic heart transplantation model. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2007;26:16-23.
10. Canseco DC, Kimura W, Garg S, Mukherjee S, Bhattacharya S, Abdisalaam S, Das S, Asaithamby A, Mammen PP and Sadek HA. Human ventricular unloading induces cardiomyocyte proliferation. J Am Coll Cardiol. 2015;65:892-900.
11. Klotz S, Burkhoff D, Garrelds IM, Boomsma F and Danser AH. The impact of left ventricular assist device-induced left ventricular unloading on the myocardial renin-angiotensin-aldosterone system: therapeutic consequences? Eur Heart J. 2009;30:805-12.
12. Frazier OH, Benedict CR, Radovancevic B, Bick RJ, Capek P, Springer WE, Macris MP, Delgado R and Buja LM. Improved left ventricular function after chronic left ventricular unloading. Ann Thorac Surg. 1996;62:675-81; discussion 681-2.
13. Bick RJ, Grigore AM, Poindexter BJ, Schnee PM, Nussmeier NA, Gregoric ID, Shah NA, Myers TJ, Buja LM and Frazier OH. Left ventricular unloading with an assist device results in receptor relocalization as well as increased beta-adrenergic receptor numbers: are these changes indications for outcome? Journal of cardiac surgery. 2005;20:332-6.
14. Ibrahim M, Rao C, Athanasiou T, Yacoub MH and Terracciano CM. Mechanical unloading and cell therapy have a synergistic role in the recovery and regeneration of the failing heart. Eur J Cardiothorac Surg. 2012;42:312-8.
15. Klotz S, Foronjy RF, Dickstein ML, Gu A, Garrelds IM, Danser AH, Oz MC, D'Armiento J and Burkhoff D. Mechanical unloading during left ventricular assist device support increases left ventricular collagen cross-linking and myocardial stiffness. Circulation. 2005;112:364-74.
16. Schwoerer AP, Neuber C, Schmechel A, Melnychenko I, Mearini G, Boknik P, Kirchhefer U, Schmitz W, Ehmke H, Eschenhagen T and El-Armouche A. Mechanical unloading of the rat heart involves marked changes in the protein kinase-phosphatase balance. Journal of molecular and cellular cardiology. 2008;45:846-52.
17. Ogletree-Hughes ML, Stull LB, Sweet WE, Smedira NG, McCarthy PM and Moravec CS. Mechanical unloading restores beta-adrenergic responsiveness and reverses receptor downregulation in the failing human heart. Circulation. 2001;104:881-6.
18. Ibrahim M, Navaratnarajah M, Siedlecka U, Rao C, Dias P, Moshkov AV, Gorelik J, Yacoub MH and Terracciano CM. Mechanical unloading reverses transverse tubule remodelling and normalizes local Ca(2+)-induced Ca(2+)release in a rodent model of heart failure. European journal of heart failure. 2012;14:571-80.
19. Drakos SG, Terrovitis JV, Nanas JN, Charitos EI, Ntalianis AS, Malliaras KG, Diakos N, Koudoumas D, Theodoropoulos S, Yacoub MH and Anastasiou-Nana MI. Reverse

electrophysiologic remodeling after cardiac mechanical unloading for end-stage nonischemic cardiomyopathy. Ann Thorac Surg. 2011;91:764-9.
20. Bruggink AH, van Oosterhout MF, de Jonge N, Ivangh B, van Kuik J, Voorbij RH, Cleutjens JP, Gmelig-Meyling FH and de Weger RA. Reverse remodeling of the myocardial extracellular matrix after prolonged left ventricular assist device support follows a biphasic pattern. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2006;25:1091-8.
21. Thompson LO, Skrabal CA, Loebe M, Lafuente JA, Roberts RR, Akgul A, Jones V, Bruckner BA, Thohan V, Noon GP and Youker KA. Plasma neurohormone levels correlate with left ventricular functional and morphological improvement in LVAD patients. The Journal of surgical research. 2005;123:25-32.
22. Ibrahim M and Yacoub MH. Bridge to recovery and weaning protocols. Heart failure clinics. 2014;10:S47-55.
23. Ibrahim M, Terracciano C and Yacoub MH. Can bridge to recovery help to reveal the secrets of the failing heart? Current cardiology reports. 2012;14:392-6.
24. Lim HS. The Effect of Impella CP on Cardiopulmonary Physiology During Venoarterial Extracorporeal Membrane Oxygenation Support. Artif Organs. 2017.
25. Seo T, Ito T, Iio K, Kato J and Takagi H. Experimental study on the hemodynamic effects of veno-arterial extracorporeal membrane oxygenation with an automatically driven blood pump on puppies. Artif Organs. 1991;15:402-7.
26. Pappalardo F, Schulte C, Pieri M, Schrage B, Contri R, Soeffker G, Greco T, Lembo R, Mullerleile K, Colombo A, Sydow K, De Bonis M, Wagner F, Reichenspurner H, Blankenberg S, Zangrillo A and Westermann D. Concomitant implantation of Impella(R) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. European journal of heart failure. 2017;19:404-412.
27. Cheng A, Swartz MF and Massey HT. Impella to unload the left ventricle during peripheral extracorporeal membrane oxygenation. ASAIO J. 2013;59:533-6.
28. Kawashima D, Gojo S, Nishimura T, Itoda Y, Kitahori K, Motomura N, Morota T, Murakami A, Takamoto S, Kyo S and Ono M. Left ventricular mechanical support with Impella provides more ventricular unloading in heart failure than extracorporeal membrane oxygenation. ASAIO J. 2011;57:169-76.
29. Koeckert MS, Jorde UP, Naka Y, Moses JW and Takayama H. Impella LP 2.5 for left ventricular unloading during venoarterial extracorporeal membrane oxygenation support. Journal of cardiac surgery. 2011;26:666-8.
30. von Segesser LK, Jegger D, Mucciolo G, Tozzi P, Mucciolo A, Delay D, Mallabiabarrena I and Horisberger J. The Smartcanula: a new tool for remote access perfusion in limited access cardiac surgery. Heart Surg Forum. 2005;8:E241-5.
31. von Segesser LK, Ferrari E, Delay D, Maunz O, Horisberger J and Tozzi P. Routine use of self-expanding venous cannulas for cardiopulmonary bypass: benefits and pitfalls in 100 consecutive cases. Eur J Cardiothorac Surg. 2008;34:635-40.