The Left Ventricular Assist Device Off or On Pump Implantation Study: A single-center randomized trial (LVAD-ON-OFF)

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Protocol Title:	The Left Ventricular Assist Device Off or On Pump Implantation Study: A single-center randomized trial (LVAD-ON-OFF)
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Population:	140 stage D adult heart failure patients that are treated at CAHF and are approved for left ventricular assist device therapy
Number of Sites:	1
Study Duration:	4 Years
Subject Duration:	1 Year

TABLE OF CONTENTS

Contents

BACKGROUND

The left ventricular assist device (LVAD) has evolved into a standard therapy for patients with advanced heart failure (HF) (1-3). Continuous-flow (CF) devices, such as the HeartMate II (Thoratec Corp, Pleasanton, CA), HeartWare (HeartWare Inc, Framingham, MA), and the most recent HeartMate III (Thoratec Corp, Pleasanton, CA) have significantly improved patient survival and quality of life ((2, 4, 5). Compared with pulsatile devices, CF-LVADs are smaller, quieter, and easier to implant. The improvement of survival over time has resulted in the more widespread adoption of this therapy; however, device-related adverse events persist and include infections, bleeding, and thromboembolic events (TE). Despite advances, many patients still suffer significant morbidity in association with the implantation procedure itself. Two currently approved devices that are widely used due to their favorable risk-benefit profile are HeartWare (HVAD) and HeartMate III. Both have been approved by the Federal Drug Administration (FDA) for use as a bridge-to-transplant (BTT) or destination therapy (DT) . Traditionally, LVAD implantation is performed with the help of a cardiopulmonary bypass (CPB) circuit. LVAD implantation without the use of CPB, a so-called "off-pump" procedure has been published (6). Because of the intrapericardial implant position and the smaller pump volume, the HVAD and HeartMate III can be safely and most successfully implanted without the use of CPB (7-13). There are controversial opinions regarding the indication of this technique, with respect to LVAD patient selection, results, benefits and disadvantages. In the literature, the data have been compared in retrospective non-randomized single or multicenter studies, case reports and case series, and the results report advantages for either method, which often brings more confusion than clarification (14). At present, there are no data from prospective and randomized studies about the risks and benefits of CPB use in LVAD patients. Therefore, we aim to delineate the impact an off-pump LVAD implantation on patient outcomes.

Cardiopulmonary bypass

The CPB circuit is commonly called "the pump", and it allows the surgeon to perform cardiac surgery on an arrested heart, under optimal visualization. It has been used worldwide in millions of patients; however, the use of CPB during cardiac surgery is associated with complications, such as atrial fibrillation (15, 16), increased pulmonary vascular resistance, stroke and neurocognitive dysfunction (17), renal dysfunction, increased need for blood transfusions, activation of inflammatory mediators, platelet activation, and coagulopathy (18), and about 2% perioperative mortality. Overall, the rates of

these complications are considerable, and these events are largely attributed to the CPB itself and to the aortic cannulation and cross-clamping required with CPB (19).

The patient population that requires LVAD implantation often has evidence of end-organ dysfunction, including liver congestion, renal insufficiency and pulmonary edema. LVAD placement under CPB often exacerbates these pre-existing conditions, resulting in post-operative coagulopathy, bleeding and worsening right heart failure.

Off-pump LVAD surgery

To avoid deleterious consequences of CPB, cardiac surgeons have designed heart stabilizers to allow them to perform cardiac surgery on a beating heart without using CPB. Off-pump cardiac surgery does not require hypothermia, aortic cannulation, or cross-clamping of the ascending aorta. Some studies, including a retrospective analysis of our center data (20), have suggested that off-pump LVAD implantation is associated with a significant reduction in blood transfusions, length of stay in hospital and intensive care unit (ICU) stay (20). Decreased numbers of blood products offer important benefits, especially in the BTT patient population (21). Although the risk of known viral transmission is currently low, stored red blood cells do not function normally, and each unit contains activated inflammatory cells and mediators. These changes cause limited oxygen release, impaired microcirculatory flow, and immune suppression. A number of studies have observed decreased survival associated with transfusions in trauma, coronary artery bypass grafting, and ICU stays. However, these studies were retrospective and had insufficient power to detect moderate but important differences in the incidence of right ventricular dysfunction and allo-antibody formation.

Based on our surgical team's previous experience with off-pump implantation of Jarvik 2000 (Jarvik Heart, Inc., New York, NY) in animals (22) and humans (23), we started implanting HVADs without CPB in 2011 (11). Our goal was to implant HVAD off-CPB when possible. The decision to implant an LVAD on-CPB was made intraoperatively if patient developed hemodynamic instability during positioning of the heart. We have previously showed that LVAD implantation without the use of CPB helps to minimize post-operative complications without hemodynamic compromise or excessive bleeding during implantation (6).

Left Ventricular Assist Devices and Right Ventricular Dysfunction

Outcomes after LVAD implantation are critically dependent on right ventricular (RV) function. This means that the ability of the RV to keep up with the improved blood flow following LVAD greatly effects how well a person does following surgery. It is understood that a high pulmonary artery (PA) pressure (pressure in the blood vessel that takes blood from the right side of the heart to the lungs) measured before surgery, indicates that a higher risk of right heart failure (RHF) exists after LVAD implantation. Development of RHF in LVAD patients has a direct effect on mortality and is associated with a prolonged ICU stay and hospital admission (24). RHF in LVAD patients leads to increased morbidity and is associated with worse outcomes after cardiac transplantation (25). Despite improvements in surgical and medical management the incidence of RHF after LVAD implantation has plateaued at approximately 20-30% (26). The intra-operative technique used during LVAD implantation may play a role in the preservation of RV function. Cross-clamping and cardioplegia may compromise RV contractility (27).

Left Ventricular Assist Devices and Coagulation-Fibrinolysis Changes during On-Pump and Off-Pump LVAD implantation

Patients undergoing implantation of CF-LVADs have a higher incidence of thrombotic and bleeding complications. Previous investigators found higher leukocyte counts, more neutrophil activation (28), and increased cytokine activation (29) in on-pump surgeries compared with off-pump cardiac surgeries. Recently, it was also demonstrated that the complement system is less activated by off-pump surgery (30). CPB activates platelets and coagulation factors, which causes impairment of hemostasis (31). The exact extent of hemostatic and fibrinolytic derangements in off-pump versus on-pump LVAD implantation is unknown.

Overall hemostasis potential (OHP) in plasma is a global functional test for assessing hemostatic potential and predicting clinical outcomes (bleeding, thrombosis). OHP in plasma is a newly developed laboratory method based on spectrophotometric measurement of the area under the curve for fibrin activation in citrated plasma samples (32). It is potentially useful for a rapid, and simple, bedside evaluation of patients with hemostatic dysfunction.

Other techniques for similar determinations, such as thromboelastography, require special equipment. With thromboelastography, the measurements should be performed on whole-blood samples within eight hours after sampling, and frozen samples cannot be used. Moreover, the observation time is up to several hours if the whole hemostatic process, especially the fibrinolysis part, is monitored. In contrast,

a global hemostatic assay for determination of overall hemostatic potential in plasma is inexpensive and relatively rapid. Estimation of OHP, coagulation, and fibrinolysis potential is finished in 40 minutes. With the exception of a common kinetic microplate reader, no special equipment is necessary for a global hemostatic assay. In addition, this technique is also useful for research purposes because frozen samples may be used.

There has not been a randomized study that has compared OHP in patients undergoing on-pump versus off-pump LVAD implantation. We speculate that with measurement of the OHP, it will be possible to better monitor the anticoagulant effects of antithrombotic drugs and prevent thrombotic and bleeding events. Further, by measuring the OHP, we might be able to stratify patients in different risk groups for thrombotic and bleeding complications.

Immunologic effects of LVAD after On-Pump versus Off-Pump LVAD implantation

LVADs have been implicated as one of the key causes of allosensitization in patients awaiting cardiac transplantation. Contemporary data on allosensitization triggered by CF-LVADs are limited, and whether allosensitization attributes to CF-LVADs affects outcomes after transplant remains controversial (33). In a recent study, an adjusted multivariable Cox regression analysis included the variables of LVAD implantation, leukocyte-filtered packed red blood cell and platelet transfusion, and sex; it found that LVAD implantation was the only independent predictor of sensitization (34). Significant allosensitization developed in 22% of the patients who received LVADs, with calculated panel reactive antibodies (PRA) > 10%.

The effect of on-pump versus off-pump implantation has not been studied, yet. However, several investigators found reduced blood loss or less need for transfusions after off-pump cardiac surgery (35). The reduction of the number of transfusions with off-pump LVAD surgery could potentially attenuate the development of antibodies to blood products that would make future transfusions and heart transplantation less difficult.

METHODS

STUDY DESIGN AND PATIENTS

LVAD-ON-OFF is a single center, two-arm, parallel-group, individually randomized (1:1) controlled trial with blinded outcome assessment (at 30 days, 6 months and 1 year) which aims to compare adverse events after off-pump versus on-pump LVAD implantation.

Prior to surgery, all consecutive patients scheduled for LVAD implantation will be screened for inclusion into the study. If the patient fulfills the inclusion criteria for the study, he/she will be approached and the study will be described. If the patient agrees to participate, he /she will be given written, informed consent for inclusion in the study. Baseline demographic and clinical characteristics of patients, echocardiographic parameters, hemodynamic data from right heart catheterization and blood samples will be collected. These procedures are a part of standard of care procedures, so the patients will not suffer any discomfort or additional cost due to the inclusion in the study. However, patients will be asked to provide additional blood samples for advanced hemostatic assays and panel reactive antibodies. Randomization is done intraoperatively as detailed later. In cases where the patient will not be eligible for inclusion into the study prior to randomization (e.g. if during the heart positioning the patient becomes hemodynamically instable and the CPB will a priory have to be used), the additionally collected blood samples will be discarded. The operation is initiated by a standard procedure and all postoperativey management will be completed according to institution protocols and standard of care medical guidelines.

Randomization will be done with the help of the REDCap (REDCap electronic data capture tools hosted at UTHealth) (36), a software program that contains a randomization module using stratified randomization (by type of LVAD therapy).

The primary hypothesis is that off-pump LVAD surgery compared with on-pump LVAD surgery reduces a composite outcome of right ventricular dysfunction, thrombotic complications and survival in the short term (30 days) and that these benefits are maintained at long term (1 year). The secondary hypothesis is that off-pump LVAD surgery compared with on-pump LVAD surgery reduces OHP leading to lower complement activation and reduced immune allosensitization in the short term (30 days) and at long term (1 year).

Inclusion criteria

- Adult (≥ 18 years of age)
- The patient has had a diagnosis of end stage heart failure, NYHA class III or IV HF for a minimum of 90 days prior to screening.
- The patient has guideline-directed medical therapy according to ACC/AHA/ESC HF guidelines
- The patient has an Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score of 1-3.

- LVAD placement is intended as a BTT or DT with either HVAD or HeartMate III LVAD.
- The patient is able to sign informed consent form and Release of Medical Information Form.
- The patients is willing and able to participate in scheduled follow-up appointments.

Exclusion criteria

Subjects will not be enrolled into this study if they meet ANY of the following criteria:

- The patient requires concomitant surgery for left ventricular or atrial appendage closure or the patient has severe aortic insufficiency, mitral stenosis, or severe tricuspid regurgitation.
- The patient has an intracardiac thrombus or other mass diagnosed by echocardiography, left ventriculogram, or other imaging.
- Planned insertion of RV support device (either temporary or permanent).
- The patient has suffered an acute cardiovascular event such as acute coronary syndrome (ST elevation myocardial infarction (STEMI) or Non-ST elevation myocardial infarction (NSTEMI), or unstable angina), or underwent any cardiac surgery or interventional cardiac or peripheral vascular procedure within 30 days prior to LVAD implantation.
- The patient has had ischemic or hemorrhagic stroke as diagnosed by CT or MRI within 90 days prior to study enrollment.
- The patient had prior heart or other organ transplantation, or surgically implanted LVAD or cardiac shunt.
- The patient will likely need an immediate heart transplant due to hemodynamic instability.
- The patient has had a known active malignancy or treatment for cancer within the past year except for localized prostate cancer, cervical carcinoma in situ, breast cancer in situ, or non-melanoma skin cancer that has been definitively treated.
- The patient has history of any malignancy where expected survival is less than two years. Past medical history of cancer is not exclusionary as long as subject has been disease-free for at least one years since the time of diagnosis and treatment.
- Patient has a severe co-morbidity (current need for hemodialysis or current GFR ≤20 mL/minute/1.73 m2 estimated by MDRD calculation; hepatic impairment defined as liver function tests (ALT, AST, alkaline phosphatase) >3x Upper Limit of Normal within 30 days prior to LVAD implantation or known objectively confirmed intrinsic liver disease (e.g., cirrhosis, chronic hepatitis B or hepatitis C virus infection)).

- The patient has a known bleeding diathesis or thrombocytopenia defined as platelet count <50,000 platelets/µL.
- The patient has peri/postpartum cardiomyopathy, or is a pregnant or lactating woman, or a woman of child-bearing age not using a suitable method of contraception.
- The patient, who in the absence of an ICD (or any implanted device capable of defibrillation), has a history of malignant ventricular arrhythmia or sustained ventricular tachycardia (VT), with sustained VT demonstrated by QRS complexes wider than 120 milliseconds, lasting more than 30 seconds, and with a rate of more than 100 beats per minute on screening ECG or other data supporting this diagnosis.
- Recent history of psychiatric disease, including drug or alcohol abuse, that is likely to impair, in the opinion of the investigator, the subject's ability to comply with protocol-mandated procedures.
- Participation in any other clinical investigation that is likely to confound study results or affect study outcome

DEFINITION OF OUTCOME MEASURES

Primary Outcome Measures

Occurrence of the composite outcome of moderate or severe RV dysfunction (perioperative right heart failure), severe renal dysfunction requiring renal replacement therapy, thrombotic complications or death from any cause within 30 days post LVAD implantation, defined as:

- **Perioperative RV failure** is defined by the INTERMACS scoring as the need for intravenous inotropes for >14 days post-operatively or a right ventricular assist device (RVAD) (37). Right ventricular function will be measured by tricuspid annular plane systolic excursion (TAPSE) values assessed using echocardiography prior to implantation (baseline), 14 (+/- 2 days) days post-implant, 30-days post-implant, 6-months and 1-year post-implant. Additionally, we will collect also hemodynamic evidence of RV dysfunction with: a right-atrial pressure (RAP): pulmonary capillary wedge pressure (PCWP) ratio of ≥ 0.67.
- **A thrombotic complication** is defined as any thromboembolic event (transient ischemic attack or stroke objectively confirmed with computed tomography) or confirmed pump thrombus as previously done (38). A suspected pump thrombosis event in which a thrombus is confirmed in

the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This will be reported via direct visual inspection (documented by a photograph if available) on pump removal or by sending the pump back to manufacturer for evaluation. Any pump explanted for suspected device thrombosis will be sent back to manufacturer for analysis. All pump thrombosis events will be adjudicated by an independent committee, the Research Review Committee which is described below in the Data and Safety Monitoring Section.

- For patients who will **die in the hospital within 30 days**, the cause of death will be confirmed by postmortem examination performed by a pathologist who will be unaware of the study assignments.

Secondary Outcome Measures

1. Need for blood product transfusion within 48-hours post LVAD implantation
2. Operative safety outcomes: incidence of 30-day mortality (from the day of surgery to 30 days [+/- 3 days]), chest tube output in the first post-operative 24 hours, rate of post-operative re-exploration for bleeding
3. Incidence of allosensitization at 30-days, 6-months and 12-months post-LVAD implantation. Allosensitization is defined as calculated panel reactive antibody (cPRA) > 10%.
4. Readmission for heart failure (follow-up 1 year)
5. OHP, overall coagulation potential and overall fibrinolytic potential in the perioperative period
6. Major bleeding defined as an episode of suspected internal or external bleeding that results in one or more of the following: death, re-operation, hospitalization, transfusion of red blood cells according to INTERMACS definition.

Other Outcome Measures

1. Duration of surgery (skin incision to skin closure)
2. Duration of postoperative mechanical ventilation (length of time from intubation until patient is extubated)
3. Length of ICU stay (length of time from ICU admission from surgery until ICU discharge)
4. Length of hospital stay (length of time from surgery to hospital discharge)
5. Incidence of renal dysfunction defined by INTERMACS criteria
6. Incidence of 30-day mortality (from the day of surgery to 30 days [+/- 3 days])
7. Incidence of post-operative mortality within 6 months and 1 year

8. Device-related complications totaled at 30-days, 6-months and 12-months post-LVAD implantation.
9. Duration and amount of intraoperative and postoperative inhaled nitric oxide use

COLLECTION OF BASIC DATA/PATIENT CHARACTERISTICS

During the screening process the electronic medical record of the patient will be used to ascertain baseline demographic, clinical characteristics, echocardiographic parameters, and hemodynamic data from right heart catheterization to determine eligibility. Once enrolled, this data will be entered into case report forms and blood samples will be collected as described later.

The following **demographic and clinical characteristics of enrolled participants** will be recorded at baseline (within 48 hours of LVAD implantation):

- age (years)
- birth sex
- race/ethnicity (white/Caucasian, black/African-American, Native American, Asian, Hispanic, Mixed, Other, Not Disclosed)
- etiology of heart failure (ischemic cardiomyopathy, non-ischemic cardiomyopathy)
- blood pressure, heart rate and EKG data
- height (cm) and weight (kg)
- body mass index (BMI) (kg/m^2) will be calculated by taking patient's weight in kilograms and dividing it by patient's height (in meters) squared
- body surface area (BSA) (m^2) will be calculated using the formula of DuBois and DuBois (BSA = [0.425 weight x 0.725 height] x 0.007184), where the weight is in kilograms and the height is in centimeters.
- risk factors for cardiovascular diseases and comorbidities (arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, chronic renal insufficiency, chronic obstructive pulmonary disease)
- type and dosage of cardiovascular medications will be evaluated, including a beta-blocker, angiotensin convertase enzyme (ACE) inhibitor, angiotensin II receptor antagonists (sartan), statins, antidiabetic drugs and diuretics, as well as drugs for treatment of PA hypertension. Information on preoperative antiplatelet and anticoagulant treatment will be obtained.
- duration of LVAD support defined as BTT or DT

- INTERMACS status
- duration of home therapy with milrinone
- type and duration of preoperative mechanical circulatory support (ECMO, intra-aortic balloon pump [IABP], Impella, CentriMag LVAD, TandemHeart)

Per standard of care, every subject receives **a transthoracic echocardiogram (TTE)** within 48 hours prior to LVAD implantation (baseline). These preoperative echocardiograms are reviewed and compared with echocardiograms at 30 (+/- 5) days, 6-months and 1-year post-LVAD implantation. The echocardiograms will be performed by staff cardiologists at UTHealth/Memorial Hermann Hospital-TMC and are regularly scheduled per standard of care. The staff cardiologists will not be aware of the treatment assignment of enrolled patients.

For each subject, the following echocardiographic parameters will be pulled from the electronic medical record and transferred to case report forms:

- left ventricular end-systolic diameter (LVESD)
- left ventricular end-diastolic diameter (LVEDD)
- left ventricular (LV) ejection fraction
- severity of mitral regurgitation (MR) based on a graded system
- RV ejection fraction (RVEF),
- RV end-diastolic dimension (RVEDD),
- RV end-systolic diameter (LVESD)
- RV stroke work index (RVSWI),
- tricuspid annular plane systolic excursion (TAPSE)
- severity of tricuspid regurgitation (TR)

Right heart catheterization is another standard diagnostic procedure for LVAD patients. The test evaluates the hemodynamics of LVAD patients. Right heart catheter hemodynamic variables are analyzed pre-LVAD implantation and compared with 30 (+/- 5) days, 6-months and 1-year post-LVAD implantation values as regularly scheduled care. All procedures will be performed by staff cardiologists at UTHealth/Memorial Hermann Hospital-TMC, who will not be aware of the treatment assignments.

For each subject, the following hemodynamic measurements will be pulled from the electronic medical record and transferred to case report forms:

- central venous pressure (CVP),
- pulmonary artery pressures (PAP): systolic and diastolic PAP,
- pulmonary capillary wedge pressure (PCWP),
- cardiac index (CI)
- pulmonary vascular resistance (PVR)
- right-atrial pressure (RAP)
- RAP: pulmonary capillary wedge pressure (PCWP) ratio

Laboratory parameters: Per standard of care, blood for routine biochemical and coagulation markers will be taken at prior to surgery (within 48 hours) and at follow-up visits (30 days, 6 months, 1 year). The electronic medical record will be used to ascertain the results of the following laboratory tests:

- complete blood count
- blood glucose
- hemoglobin A1c
- total cholesterol
- LDL cholesterol
- HDL cholesterol
- triglycerides
- creatinine
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- total bilirubin
- albumin
- pre-albumin
- lactate,
- lactate dehydrogenase (LDH)
- prothrombin time (PT)
- activated plasma thromboplastin time (aPTT)

From this information the international normalized ratio (INR) will be calculated and recorded on case report forms.

PERIOPERATIVE VARIABLES

The medical record will be used to ascertain the following variables

- length of ICU stay
- length of hospital stay (LOS)
- total surgery time

- time-on-mechanical ventilation
- time on the CPB (min) (for “on pump” group only)
- number and type of concomitant cardiac procedures
- pharmacologic vasoactive and inotropic support (average daily dosage and duration of dobutamine, dopamine, epinephrine, norepinephrine and milrinone)
- duration and amount of perioperative use of inhaled nitric oxide
- total amount of bleeding (estimated based on mL of blood in the suction tank and gauzes in the operation room [each immersed gauze will be considered as 20 mL of blood] based on the evaluation by the anesthesiologist at the end of the operation)
- blood loss through the thoracic drains
- amount of received blood product units intraoperatively and in the 48-hours postoperatively will be recorded:
    - red blood cells (units)
    - fresh frozen plasma (units)
    - platelets (units)
    - cryoprecipitate (units)
- all postoperative complications following LVAD procedures
    - fever (defined as a body temperature above 38˚C)
    - reoperation due to local infection
    - dehiscence or bleeding
    - sepsis
    - pneumonia
    - venous thromboembolism
    - acute coronary events in the first 30 days after surgery

COLLECTION OF LONGITUDINAL DATA

Patients will be followed for 1 year after surgery. All LVAD patients’ standard of care includes three planned follow-up assessments at 30 days (+/- 5 days), 6 months and 1 year after surgery. At each visit, the detailed medical history and clinical examination (including weight, height, blood pressure, heart rate, ECG, TTE, and blood draw) are performed. Relevant data will be collected from the medical record

and transferred to case report forms. Additional research blood draws will be done at the follow-up appointments.

SURGICAL TECHNIQUE

After standard cardiac anesthesia, surgical access to the heart for LVAD implantation will be gained through a median sternotomy in all of the patients. Scavenged blood from the operative filed will be collected in a cell saver and transfused back to the patient after washing for recovery of red blood cells in all patients. Intra-operative trans-thoracic ultrasound (TEE) will be used on all patients to evaluate for associated pathologies that will require surgical management at the time of LVAD implantation and thereby contraindicate an off-pump approach. All of these procedures (median sternotomy, cell saver and TEE) are standard procedures used in cardiac surgery.

The decision to implant an LVAD on-CPB or off-pump will be made intraoperatively at this point by the surgeon. The surgeon's decision is based upon their test of the hemodynamic stability of the patient by positioning maneuver of the heart. Only patients who will be hemodynamically stable during the positioning of the heart will be included in the study and will be randomized. If the surgeon declares the patient is eligible for an off-pump procedure, a prepackaged envelope will be opened that indicates whether the procedure is to proceed off-pump or if an on-pump procedure will be used. (A pre-specified envelope will be created prior to each surgery with the assistance of REDCap).

To implant the device off-CPB, the patient will be heparinized at a dosage of 1mg/kg. The CPB will be left on standby should the patient's medical condition at any moment during the surgery necessitate the use of CPB. The pericardium will be opened to expose the heart and major vessels, and the aortic cannulation sutures will be placed. The Estech (AtriCure Inc; West Chester, OH) pyramid positioner will be applied to the apex of the heart, and the heart will be manually elevated upward with care to maintain the hemodynamic stability of the patient. This maneuver exposes the diaphragmatic surface of the LV and eliminates the presence of an extra hand in the operative field. The inflow cannula placement location and placement of the sewing ring will be done with pledged sutures as previously described (7). The LV diaphragmatic site coring will be completed, and immediate LV digital exploration will be accomplished, which also allows for control of bleeding and palpation of potential muscular inflow obstruction. After ending digital exploration of LV, the pump inflow canula is quickly inserted through the sewing ring into the LV cavity. Upon completing proper pump inflow cannula placement into the LV and securing it in position, the heart will be dropped into the pericardial cavity with the

outflow graft elevated at for pump and outflow graft de-airing and to prevent potential later air embolization. Following complete de-airing and verification with intraoperative TEE, the graft is clamped and a partial occlusion clamp is placed on the ascending aorta (39). Appropriately trimmed outflow graft will be sewn to the aorta using a 5/0 prolene suture in a continuous running suture fashion. appropriately trimmed outflow graft will be sewn to the aorta using a 5/0 prolene suture in a continuous running fashion. The percutaneous driveline will be tunneled to the left upper abdominal quadrant 3 cm below the costal margin, in the midclavicular line. Heparin will be reversed with protamine, and the pump speed will be optimized under TEE guidance.

LVAD Implantation with CPB: In conventional LVAD implantation with CPB, normothermia is maintained and the heart continues to beat while a cylindrical blade excises a core of myocardium from the apex. This is readily accomplished in the decompressed, bypassed heart. The LVAD sewing ring is then sutured to the margins of the apical hole. The LVAD is inserted into the LV cavity through the sewing ring. During these maneuvers, neither hemostasis nor hemodynamic stability is difficult to maintain, due to maintenance of CPB and to the availability of a cardiotomy sucker. Only when the LVAD is secured in position is the ventricle pressurized. The patient is then weaned from CPB and decanulated (40).

Conversions from the assigned technique (crossover) will be recorded. The reason for the conversion (ischemia, anastomotic leak, etc.) and the time of conversion (during manipulation of the heart, during LVAD implantation, etc.) will allow us to better understand the respective benefits of each technique and to enable secondary analysis.

PERIOPERATIVE MANAGEMENT PROTOCOLS

Intensive insulin and glycemic control

Inadequately controlled blood sugar levels can result in increased morbidity and mortality in all patients whether diabetic or not. Hyperglycemia is associated with increased inflammation, infectious complications, ventilator dependence, length of hospital stay and mortality. Hypoglycemia is equally dangerous, it adversely affects the circulatory and both the autonomic and central nervous system. Therefore, tight glycemic control protocol will be used while the patient will be in the ICU (41); an insulin infusion will be started if the blood glucose level will exceed 110 mg per deciliter, and the infusion will be adjusted to maintain normoglycemia (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]). The maximal dose of insulin should not exceed 50 IU per hour. When the patient will be discharged from the

ICU, a conventional glycemic approach will be adopted (maintenance of blood glucose at a level between 180 and 200 mg per deciliter).

Adjustments of the insulin dose will be based on measurements of whole-blood glucose in undiluted arterial blood, performed at one to four hour intervals with the use of a glucose analyzer. The dose will be adjusted according to a strict algorithm by a team of intensive care nurses, assisted by an attending physician who will not be aware of study group assignment.

Antithrombotic therapy

To evaluate the role of CPB on hemostatic and fibrinolytic parameters, we will make sure that the perioperative level of heparinization will be comparable between groups.

All patients will be postoperatively treated with 81mg aspirin daily and coumadin with a target international normalized ratio range of 2.0–2.5. Data on the use of antithrombotic therapy will be recorded at baseline and at each follow-up appointment. Time-in-Therapeutic Range (TTR) will be calculated using the Rosendaal method as a measure of quality of anticoagulation dose management (42).

Use of tranexamic acid

Tranexamic acid is a well-documented fibrinolytic inhibitor. The medical team will be advised to use always the same dose of tranexamic acid (if the patient's condition will allow it) in the perioperative period as it has an effect on overall fibrinolytic potential.

SELECTION OF SURGEONS

All surgical procedures will be performed by an "experienced" cardiac surgeon with more than 5 years of practice in cardiac surgery after residency training and has performed more than 100 LVAD implantations. Primary surgeons have experience with both techniques (on-pump and off-pump LVAD implantation). All procedures will be done under the supervision of an "expert" cardiac surgeon (IDG/PI of this protocol) who has more than 30 years of experience in advanced and complex cases of cardiac surgery, has performed more than 500 LVAD implantations, and is very experienced with both techniques (on-pump and off-pump LVAD implantation). Residents and fellows will not be eligible to participate as primary surgeons in the trial.

BLOOD COLLECTION AND PREPARATION

For research purposes, two additional vials of blood will be collected at the same time that standard of care blood draws are done. The timepoints for the research blood draws will be at baseline (within 48 hours of surgery), within 24-48 hours post-operation (but before discharge), 30 days, 6 months and 1 year. For the follow-up blood draws (+/- 5 days is acceptable).

For the preparation of plasma, we will use vacutainer tubes with K2 EDTA. Each tube will be pre-labeled with patient's unique identifying number, patient's first and last name (two person-specific identifiers on the patient label) and date of blood draw from the subject. The collection tubes will be filled as defined by the manufacturer's package insert. Blood from tubes with reduced volume will not be processed. Immediately after filling each tube, the tube will be inverted 10 times gently (inversion can be performed while subsequent tubes are being filled). Blood tubes will stand at room temperature for approximately 30 minutes prior to centrifugation. Specimens will be processed and frozen within 2 hours of blood draw. Vacutainer tubes will be stored at 4-25°C (39-77°F) until processing. The study coordinator or other CAHF research staff will process the blood samples. Blood will spin in the centrifuge two times. First centrifugation will be used to separate plasma from white and red blood cells (RBCs). Whole blood will be centrifuged in the collection tubes for 12 minutes at 1500 x g, the temperature will be set to 4°C/39°F. The tubes will be removed from the centrifuge. If any of the Vacutainer tubes demonstrate gross hemolysis (bright red plasma), the tube will be discarded. After the first centrifugation, the buffy coat (containing leucocytes and platelets) will be visible as a very small whitish band above the RBCs. Using a disposable bulb pipette, plasma will be transferred from each collection tube to a 15 mL centrifuge tube. Centrifuge tubes will be placed in a centrifuge for a second time to remove any remaining cell debris that might contaminate the plasma sample. Plasma will be centrifuged for 12 minutes at 1500 x g. Using a clean disposable bulb pipette, plasma will be transferred from each centrifuge tube to a 15 mL pooling tube. A residual amount of plasma (≥0.5 mL; 12 mm or 1/2” in height) in the bottom of the centrifuge tube will be left in the centrifuge tube to avoid contamination with the pelleted cells. We expect to gain ~ 4 mL of plasma per Vacutainer tube. Plasma will be decanted into 1ml and 200ul aliquots in Eppendorf tubes. Plasma will be frozen in the pooling tubes upright in–80°C freezer until use. All used blood collection and processing tubes and pipettes will be discarded as biohazardous waste.

Preparation of buffy coat: Buffy coat will be removed after the first spinning of the centrifuge and decanted into Eppendorf tubes. The remaining packed RBCs in tubes will be stored for later (storage at -80°C).

DETERMINATION OF ALLOANTIBODIES

The measurement and assessment of alloantibodies is now a standard of care test performed on patients scheduled for LVAD surgery. A single-bead antigen assay on the Luminex platform (One Lambda Inc., Canoga Park, CA) is used at the institution. Mean fluorescence intensity (MFI) >4,000 is considered the threshold of clinical significance. Whenever the alloantibodies and panel reactive antibody status (PRAs) are measured, the data will be transferred from the medical record to the case report forms.

Calculated PRA (cPRA) values will be obtained using the United Network of Organ Sharing cPRA calculator. Sensitization will be defined as cPRA >10%. LVAD-associated sensitization will be defined as cPRA >10% documented after LVAD implantation in patients with cPRA <10% before LVAD implantation.

STATISTICAL METHODS

We calculated a sample size of 140 patients (70 in each arm), which will provide 80% power to detect a 30% relative risk reduction for the composite primary outcome at 30 days. The intention-to-treat principle, in which all participants will be included in their assigned treatment groups regardless of actual surgical procedure performed, will guide all analyses.

Data will be represented as frequency distributions and percentages. Values of continuous variables will be expressed as mean ± standard deviation and median with interquartile range, as necessary. Continuous variables will be compared using independent samples t-tests or Wilcoxon rank-sum tests, where appropriate. Categorical variables will be compared by means of $\chi 2$ tests or Fischer's exact test, where appropriate. Hemodynamic variables between ON-pump and OFF-pump procedures will be compared with Kruskal-Wallis tests. To analyze changes in echocardiographic and hemodynamic parameters and laboratory values, McNemar matched-pairs tests will be used to compare preoperative values to postoperative values after matching individual patient data. For all analyses, a $p < 0.05$ will be considered statistically significant. Kaplan-Meier analysis will be used to calculate survival along with a log-rank p value when comparing ON-pump and OFF-pump groups. Actuarial survival at 30-days, 6-months and 1-year post-implantation will be calculated by constructing life tables. All data will be analyzed using STATA 15 software (STATA, 2017, College Station, TX).

EXPECTED RESULTS AND IMPORTANCE OF THE STUDY

As LVADs become a more widely used and accepted treatment option for patients with refractory, end-stage heart failure, it will be necessary to further optimize outcomes and reduce the incidence of postoperative complications. We believe that using off-pump LVAD implantation will significantly reduce transfusion requirements, right ventricular dysfunction and alloantibody formation. We expect that in the off-pump group, there will be less exposure to blood products, which will lead to reduced immunosenzitization. If this research finds that off-pump use can decrease the morbidity and mortality in this patient population, it will greatly influence the manner in which these patients are managed. This would reduce hospitalizations and delays in subsequent transplant planning. This would not only be of great benefit to the patient but would significantly decrease health-care costs.

RISK AND BENEFITS

As this study used two approved methods, it is a comparative effectiveness model. The risk to the patient is no more than that of any patient undergoing LVAD implantation. As the decision for eligibility for an off-pump is made based upon data and clinical evaluation, the risk of having to convert the procedure to on-pump is very small (less than 6 % of cases). The conversion is done to eliminate the risk of patients that are not able to tolerate the off-pump surgery. In our experience the off-pump insertion of the LVAD has been safe. Patients choosing to enroll in this trial are not an any additional risk as compared to that of having the procedure done outside of this trial. The benefit of participating in this trial is the contribution of novel data that is collected in a randomized fashion and will enable future cases to be decided upon quality evidence bases.

STUDY DATA COLLECTION AND STORAGE

Study data will be collected and managed using the REDCap electronic data capture tool (36). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data will be stored on the password-protected computers. Only the principal investigator and co-investigators will have access to source documents, which will be password protected. All analysis will be completed on de-identified datasets.

DATA AND SAFETY MONITORING

The research team will follow the international, national, and institutional regulations and standards:

- Any patient that chooses to leave the study will be removed and their data up until that point will be retained in an de-identified fashion.
- Safety monitoring is accomplished through periodic review by the Primary Investigator, who will consult with the a Research Review team which will consist of a cardiac surgeon, a cardiovascular disease specialist, a biostatistician, and a pathologist. None of the Committee members will be directly involved in the study and will not work at our department.
- Further, this protocol will undergo continuing review by the Insitutional Review Board at UTHealth.
- All necessary steps will be taken to maintain the confidentiality of the data. Access to the data will be restricted to the study investigators and study coordinators. No subject identifiers will be released to any persons or outside agency.
- A linking log will be used to assign a unique study code to each subject enrolled. We will use the patient's medical record number (MRN) to link the patient to a study code.
- The following protected health information will be accessed and retained: MRN, name, date of birth, dates of service/treatment.

PUBLICATION PLAN

We plan to present data at invited lectures, poster presentations and oral presentations at various international and national scientific meetings. We are anticipating that we will publish at least two manuscripts in journals with impact factors >5.0.

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