PARTNERS HUMAN RESEARCH COMMITTEE

DETAILED PROTOCOL

Percutaneous RVAD to Preemptively Treat Right Heart Failure Post-LVAD

Protocol 2020P000422 / NCT04458103

MASSACHUSETTS GENERAL HOSPITAL

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I. TABLE OF CHANGES

VERSION / DATE	SUBSECTION	CHANGE/RATIONALE
2 / July 14, 2020	Title	Remove "preoperative" from title to reflect protocol changes allowing for concomitant RVAD placement to LVAD implantation.
2 / July 14, 2020	Background and Significance; Specific Aims; Subject Selection; Subject Enrollment; Study Procedures; Biostatistical Analysis; Potential Benefits	Timing of percutaneous RVAD placement changed to allow for intraoperative placement in addition to pre-operative placement.
3 / March 5, 2021	Cover Page	Add IRB protocol number and NCT number to protocol cover page.
3 / March 5, 2021	Table of Changes	Add table of changes to reflect amendments to protocol.
3 / March 5, 2021	Subject Selection	Remove "severe tricuspid regurgitation in a patient where a valve intervention is expected" and "known or expected PFO closure" from exclusion criteria based on amended protocol allowing for concomitant percutaneous RVAD placement, therefore allowing valve intervention or PFO closure to occur prior to RVAD placement, no longer impeding safe placement of the device.
3 / March 5, 2021	Data Collection Schedule	Update data collection schedule to reflect that RVAD placement can occur concomitantly to LVAD implantation

II. ABBREVIATIONS, ACRONYMS, DEFINITIONS

AKI – Acute Kidney Injury

ALT- Alanine Aminotransferase

AST – Aspartate Aminotransferase

CBC – Complete Blood Count

CI – Cardiac Index

CMP – Comprehensive Metabolic Panel

CVP – Central Venous Pressure

EDC – Electronic Data Collection

EKG – Electrocardiogram

ICU – Intensive Care Unit

INR – International Normalized Ratio

IRB – Institutional Review Board

IVC- Inferior Vena Cava

LOS – Length of Stay

LVAD- Left Ventricular Assist Device

MGH – Massachusetts General Hospital

PA - Pulmonary Artery

PI – Principal Investigator

RIJ – Right Internal Jugular

RVAD – Right Ventricular Assist Device

RVF – Right Ventricular Failure

SAE – Serious Adverse Event

sCr – Serum Creatinine

VIS – Vasoactive Inotrope Score

II. BACKGROUND AND SIGNIFICANCE

Prior studies have shown that left ventricular assist device (LVAD) implantation commonly results in right ventricular failure (RVF) due to changes in septal positioning and the left heart cardiac output returning to normal, causing acute right ventricular overload. Right ventricular dysfunction and failure after LVAD implantation is known to increase morbidity and mortality and contribute to longer post-implant hospital length of stay. More severe right ventricular failure is highly correlated with poor prognosis and death post-LVAD implantation (Kang).

In current practice, patients who receive LVADs require right heart support, provided in the form of inotropes. Additionally, the operational speed of the newly implanted LVAD is typically purposely low for the first 24 – 48 hours to reduce the negative impact on RV geometry and function. Vasoactive inotrope score (VIS) is a measure that quantifies the amount of right heart support required post-operatively, including dopamine, dobutamine, milrinone, epinephrine, norepinephrine, and vasopressin. It has been used in other studies as a surrogate marker for hemodynamic cardiovascular derangement (Han). The use of 2 or more inotropic agents has been found to be correlated with a higher right atrial to pulmonary capillary wedge pressure ratio and a lower pulmonary artery pulsatility index when compared with 0-1 agents. This means that a higher VIS is correlated with right heart dysfunction (Morine). The use of two or more vasopressors or inotropes is also correlated with worsening of biomarkers such as higher creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) (Morine). Therefore, greater use of vasopressors and inotropes could be associated with end organ dysfunction. Higher VIS is also associated with increased hospital mortality (Na).

In some cases, right ventricular failure post-LVAD also requires mechanical circulatory support during the perioperative period. When used, these devices allow for rapid down titration of inotropic support and an increase in LVAD operation speed and therefore systemic perfusion. Newer generation, percutaneous assist devices are now available and can be positioned in the right ventricle providing up to 4.5 L/min of support. Several attempts have been made to create calculations to predict RVF in LVAD patients, with little success (Salna). Since RVF is difficult to predict and can have harmful effects such as increased ICU stay, adverse outcomes, and mortality (Anderson), it could be beneficial to preemptively treat patients through preoperative or intraoperative percutaneous right ventricular assist device (RVAD) placement to prevent RVF. The purpose of this study is to test the hypothesis that preemptive use of percutaneous RVADs will mitigate the need for inotropic support in LVAD patients, reducing associated adverse outcomes.

There are two types of percutaneous RVADs that will be used in the study: the Impella RP and the ProtekDuo. These devices allow for early intervention in RVF without the need for invasive surgical procedures requiring placement of durable RVADs via thoracotomy or sternotomy. Unplanned reoperation and implantation of surgical RVADs is associated with higher morbidity and poor outcomes (Salna). The use of percutaneous RVADs to prevent RVF requiring reoperation and durable RVADs therefore may be a safer alternative that yields better outcomes. The objective of this prospective study is to assess whether RVAD placement in patients prior to or during LVAD implantation leads to a mitigated need for vasoactive inotropic support and improved end organ function compared with standard of care LVAD implantation in the absence of percutaneous RVAD placement.

The Impella RP, manufactured by Abiomed, is a heart pump that delivers blood from the inferior vena cava (IVC) to the pulmonary artery (PA). Its insertion is done percutaneously via catheterization through the femoral vein. The use of the Impella RP device is often used for the management of RVF post-LVAD placement. In these patients, hemodynamics have been shown to improve immediately after Impella RP initiation. This includes an increase in cardiac index

(CI), which results in the improvement of systemic and end-organ perfusion, as well as the reversal of cardiogenic shock. Impella RP placement has also been shown to decrease central venous pressure (CVP) (Anderson). This improvement in hemodynamics facilitates the weaning of inotrope and vasopressor support. LVAD flow has also been shown to improve after Impella RP support is initiated (Anderson).

ProtekDuo, manufactured by TandemLife, is another device placed percutaneously for right heart support via the right internal jugular (RIJ) vein. Like the Impella RP, use of the ProtekDuo is associated with improved hemodynamics in patients with right ventricular failure. Studies looking at concomitant insertion of the ProtekDuo and LVAD to preempt RVF in patients with impaired RV function have shown advantageous effects on patient outcomes compared to insertion post-LVAD (Schmack). It is expected that preemptive placement of RVADs prior to or during LVAD implantation to preemptively treat RVF will similarly result in improved patient outcomes.

III. SPECIFIC AIMS

The purpose of this study is to compare clinical outcomes of standard of care treatment versus preemptive percutaneous right ventricular assist device (RVAD) placement surrounding left ventricular assist device (LVAD) implantation. We hypothesize that the use of the RVAD will mitigate need for inotropic support, reducing the vasoactive-inotrope score (VIS) by 50%, and will improve end organ function in patients compared to standard of care.

IV. SUBJECT SELECTION

This trial will include both a prospective interventional cohort and a retrospective control cohort. The prospective interventional cohort will consist of patients undergoing LVAD implantation at Massachusetts General Hospital. These patients will receive an RVAD (either the ProtekDuo or Impella RP) prior to or during LVAD implantation. The historical control cohort will consist of retrospective data collection on patients who have undergone LVAD implantation in the past. This group will be age and sex matched with the enrolled prospective interventional patients.

INCLUSION:

- Ages 18-75
- Accepted for LVAD implantation by MGH multidisciplinary team

EXCLUSION:

- Disorders of the pulmonary artery wall that would preclude placement or correct positioning of RVAD
- Presence of mechanical valves
- Mural thrombosis of the right atrium or vena cava
- Anatomic conditions precluding insertion of the RVAD
- Complicated venous access precluding or complicating device placement (i.e. femoral and jugular thrombosis)
- No evidence of right ventricular dysfunction by echocardiogram

V. SUBJECT ENROLLMENT

Potential study subjects will be identified only after they have been deemed eligible and appropriate for LVAD implantation.

The primary specialist/healthcare provider who is known to the potential subject and has firsthand knowledge of the patient's medical history will give approval for his/her patient to be contacted for research purposes. The primary specialist/healthcare provider will introduce the study and obtain the patient's/family's permission to be contacted by study staff verbally. Potential participants may be identified from among the PI's, or Co-Investigators' direct patient populations. It will be made clear to the subject that participation in the study is entirely voluntary and that their decision will not affect their care now or in the future.

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

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

Phone consent will be considered if a subject wishes to participate but does not want to wait until their next regularly scheduled appointment to sign consent. The Investigator will assure that the subject has a copy of the consent form during the phone discussion. The consent will have been given in person at a prior visit or in the event the subject has misplaced the consent, will be sent via mail, fax or email. Emails sent outside Partners will be sent securely by encryption per Partners policy, unless the subject agrees to allow non-secure email transmission. The phone consent discussion will reflect the same process if conducted in person. If the subject agrees, he/she will sign the consent form and return it to the research nurse. Upon receipt, the consent form will be signed by the Investigator who spoke with the subject by phone and a copy of the consent form (with both signatures) will be returned to the subject (with the original consent containing both signatures retained in the research file). A note will be entered in the research file inclusive of the following: consent method (i.e. by phone), who obtained consent, notation that all questions/concerns were answered, and the date/time consent was obtained.

If it is determined that a potential subject is not capable to give consent or in the event of patient incapacity by sedation/intubation/clinical acuity, the PHRC preferred order of surrogates will be followed and the Investigator will document the relationship of the surrogate to the subject in the research record:

a. Court appointed guardian with specific authority to consent to participation in research or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research;
b. Health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research; or
c. Spouse, adult child, or other close family member who knows the subject well and has been involved in their care.

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

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

After consent is signed, subjects in the prospective interventional cohort will be assigned to receive either the Impella RP or ProtekDuo, as indicated by the treating physician. The RVAD will be placed within 48 hours preoperatively of the LVAD implantation, at the time of LVAD implant, or immediately following the implant. The RVAD will be left for up to 72 hours. RVAD management will be performed according to MGH standard of care by the medical staff.

There will be no consent process for the historical control cohort as there are no interventions for this group. The clinical data required for this study is already collected in a secure database per standard of care.

VI. STUDY PROCEDURES

All LVAD candidates at Massachusetts General Hospital (MGH) will be screened for trial eligibility. Every eligible candidate will be asked to participate. Subjects who consent to the study will undergo pre-operative or intra-operative placement of an RVAD, which will be left in up to 72 hours postoperatively. If it is determined that a subject requires support for longer than 72 hours, the treating physician will consider utilizing a more durable form of right ventricular support (CentriMag paracorporeal RVAD requiring direct cannulation), as is standard practice. The type of RVAD (Impella RP or ProtekDuo) inserted will be determined by patient needs and venous access and will be up to the discretion of the treating physician. The use of the ProtekDuo will be prioritized due to the benefit of the jugular approach in device placement, which does not limit patient mobility. If there is no jugular access, the Impella RP, which is placed through a femoral approach, will be used. We aim to enroll 25 subjects in the prospective interventional cohort, and compare to 25 subjects in the matched retrospective control cohort.

All enrolled patients in the prospective interventional cohort will undergo surgical placement of a percutaneous RVAD within 48 hours preoperatively to LVAD implantation, at the time of LVAD implant, or immediately following the implant. After removal of the RVAD, subjects will receive standard treatment according to MGH's standard of care. Data will be obtained for subjects in both cohorts from the electronic medical record in EPIC at MGH and will be reviewed throughout the study through the 1-year follow-up period. Other standard of care tests are administered regularly at LVAD follow-up visits, including: the KCCQ-12 and EQ-5D surveys, a neurocognitive trailmaking test, and a six-minute walk and gait speed test. These are collected per standard of care at the following timepoints: pre-implant, 3 month (+/- 30 days), 6 month (+/- 60 days), and 1 year (+/- 60 days). These results will also be collected and entered to the study database.

Clinical data will be collected and entered into the secure database by study coordinators. All subjects will be followed through 12-month post-LVAD implantation with data collection occurring at the following timepoints: pre-implant, time of implant, discharge, 1 week (+/- 3 days), 1 month (+/- 7 days), 3 month (+/- 30 days), 6 month (+/- 60 days), and 1 year (+/- 60 days), all of which will align with routine clinical standard of care visits. Subjects will not be asked to come for additional visits separate from their usual standard of care visits. All follow-up tests and procedures will also be done per standard of care.

VII. DATA COLLECTION SCHEDULE

DATA COLLECTION SCHEDULE									
ASSESSMENT	Pre-LVAD Implant	RVAD Placement	LVAD Implant	1 Week Follow-up	Implant Discharge	1 Month Follow-up	3 Month Follow-up	6 Month Follow-up	1 Year Follow-up
Screening	X								
Demographics	X								
Medical History	X								
RVAD Placement Details		X	X						
LVAD Implant Details			X						
Discharge Details					X				
Status	X			X		X	X	X	X
Right Heart Failure Assessment				X		X	X	X	X
Hemodynamics	X			X		X	X	X	X
Medications	X			X	X	X	X	X	X
Laboratory	X			X		X	X	X	X
Device Details							X	X	X
Exercise/Trailmaking	X						X	X	X
Quality of Life	X						X	X	X
Adverse Events		X	X	X		X	X	X	X

VIII. BIOSTATISTICAL ANALYSIS

STUDY VARIABLES

Eligibility Data

Potential study participants who have left-heart failure and are planned to undergo LVAD placement will be approached by the study staff. The study will be explained, and these potential participants will be provided with study information and consent forms. Potential participants who meet study criteria will be assigned a unique identifier at this time (regardless if they are enrolled, which will ensure accurate recording of number of screened vs. enrolled patients). Enrolled subjects in the prospective arm will be matched to historical controls, which will consist of patients who underwent LVAD implantation in the past in the absence of pre-operative or concurrent percutaneous RVAD placement.

Demographics – collected at outpatient visit when patient is being considered for LVAD placement
Demographic data assessed and recorded at the initial screening visit will include date of birth, gender, race, and ethnicity.

Comorbidities
Past medical history will be assessed at the time of screening and documented at the time of enrollment. Data collected will relate to underlying cardiovascular pathology and to associated pathology of the pulmonary, renal, hepatic, endocrine, hematologic, or neurologic systems.

Medications
Data on both active and past medications will be collected at the time of initial screening. If the patient is admitted at the time of screening, both current inpatient medications and home medications will be recorded. If the patient is outpatient at the time of screening, home medications will be recorded. Record of active medications will also be collected at each timepoint throughout the study.

Laboratory Data
Pre- and post-operative lab data including but not limited to CBC, CMP, INR, NT-pro-BNP will be collected at various timepoints during the study, including at time of enrollment.

EKG, ECHO, and Cardiac Catheterization assessment
EKG, ECHO, and Cardiac Catheterization results will be collected at several points during the study.

Inpatient Events/Procedures
Data on events and procedures that occur while patients are admitted will be collected on an ongoing basis while study participants are admitted to the hospital. Where complications occur, adverse event forms will be completed and principal investigators will be notified.

PRIMARY ENDPOINT

The primary outcome of the study will the vasoactive inotropic score (VIS). Both the average/mean VIS and the cumulative VIS over the first 24 hours post-LVAD implantation of the experimental cohort (those enrolled in the prospective study who undergo pre-emptive RVAD placement) will be compared to a historical cohort of patients who received the current standard of care. The VIS will be calculated for each patient in both arms of the study. Both the maximum score and the cumulative sum achieved in the first 24 hours after LVAD implantation will be recorded (maximal 24-hour VIS and cumulative 24-hour VIS).

The primary analysis will be performed in an intention-to-treat fashion using a two-sided T-test (alpha level=0.05). The null hypothesis is that the mean maximal 24-hour VIS will not differ between intervention and historical groups. The alternate hypothesis is that compared to standard of care (historical cohort), placement of an RVAD within 48 hours before or during LVAD implantation will decrease the mean maximal 24-hour VIS score by 50%. Analysis assumptions will include independence of study groups and lognormal (or normal) distribution of data in each group.

SECONDARY OUTCOMES

Secondary end points will include:

- Total VIS (throughout hospitalization)
- ICU length of stay (LOS)
- Total post-operative LOS after LVAD implantation
- Survival at discharge after LVAD placement
- Survival at 1 year after LVAD placement or heart transplant
- End organ dysfunction including
    - Development of acute kidney injury (AKI) – defined as increase in serum creatinine (sCr) to 4mg/dl or greater, a 150% or greater increase in sCr over the baseline preoperative value, or a new requirement for renal replacement therapy
    - Liver dysfunction
- LVAD device speed

Cox proportional hazard models (one sided, 0.05 significance level) will be used to compare rates of secondary outcomes between intervention and historical arms. Event rates and relative risks will also be estimated for each of these outcomes.

POWER ANALYSIS

Sample size calculations are estimated based on expected effect size, which was determined based on expert consensus (reduction in the mean maximal 24-hour VIS score by 50% in the intervention arm compared to the historical controls). 80% power will be generated with 2-tailed confidence interval of 0.05 from a sample size of 34 patients (17 per group). Estimating a

standard deviation of 0.5 of the outcome in the population and 20% attrition and/or cross-over, investigators anticipate that 20 patients will be needed to test this hypothesis. This power estimation assumes a lognormal distribution of the data. We plan to allow for 25 patients to participate in the prospective arm of the study to allow for incorrect assumptions.

IX. RISKS AND DISCOMFORTS

There is a risk of complications associated with the surgical procedure of Impella RP or ProtekDuo placement, which may include arrhythmia, atrial fibrillation, bleeding, cardiac tamponade, cardiogenic shock, death, device malfunction, hemolysis, hepatic failure, insertion site infection, perforation, deep venous thrombosis, pulmonary valve insufficiency, respiratory dysfunction, sepsis, thrombocytopenia, thrombotic vascular complication, tricuspid valve injury, vascular injury, venous thrombosis, ventricular fibrillation and/or tachycardia.

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

X. POTENTIAL BENEFITS

Previous studies have shown that RVAD placement post-LVAD implantation improved hemodynamics, including an increase in cardiac index and decrease in central venous pressure. These patients also experienced reversal of shock, favorable survival, and improved LVAD flow. RVADs also mitigate the need for inotropes, and thereby lessen inotrope-related adverse outcomes such as worsening biomarkers of end organ function. We hypothesize that preemptive RVAD placement could lead to a lower vasoactive inotrope score, better clinical outcomes, shortened hospital length of stay, and improved end-organ function in patients with LVADs. Therefore, subjects may receive direct benefits from their participation in this study. This study may also benefit future LVAD patients by potentially improving standard of care procedures surrounding LVAD management.

XI. MONITORING AND QUALITY ASSURANCE

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

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

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

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

We will perform an interim safety/outcomes analysis after the first 10 subjects have been enrolled to ensure that the anticipated risk/benefit assessment remains unchanged. The report will be made available to the IRB in a timely manner. If this analysis shows that 10 subjects provide enough data to draw significant conclusions, enrollment will be stopped and the study will be concluded. If other assumptions prove to be wrong and additional patients will be needed, this will be carefully considered and communicated to the IRB prior to proceeding.

XII. REFERENCES

1. Anderson, M., Morris, D. L., et. Al. (2018). Outcomes of patients with right ventricular failure with the Impella RP device. *The Journal of Heart and Lung Transplantation, 37*(12), 1448-1458. doi: 10.1016/j.healun.2018.08.

2. Han, J., Pinsino, A., et. Al. (2019). Prognostic value of vasoactive-inotrope score following continuous flow left ventricular assist device implantation. *The Journal of Heart and Lung Transplantation, 38*(9), 930-938. doi: 10.1016/j.healun.2019.05.007

3. Kang, G., Ha, R., & Banerjee, D. (2016). Pulmonary artery pulsatility index predicts right ventricular failure after left ventricular assist device implantation. *The Journal of Heart and Lung Transplantation, 35*(1), 67-73. doi: 10.1016/j.healun.2015.06.009

4. Morine, K., Esposito, M., et. Al. (2018). CRT-100.09 Vasoactive Agent Use Prior to Acute Mechanical Circulatory Support for Cardiogenic Shock Is Associated with End Organ Dysfunction and Mortality. *JACC: Cardiovascular Interventions, 11*(4). doi: 10.1016/j.jcin.2018.01.020

5. Na, S. J., Chung, C. R., et. Al. (2018). Vasoactive Inotropic Score As A Predictor Of Mortality In Adult Patients With Cardiogenic Shock. *Journal of the American College of Cardiology, 71*(11). doi: 10.1016/s0735-1097(18)31355-x

6. Salna, M., Garan, A., et. Al. (2020). Novel percutaneous dual-lumen cannula-based right ventricular assist device provides effective support for refractory right ventricular failure after left ventricular assist device implantation. *Interactive CardioVascular and Thoracis Surgery*. doi: 10.1093/icvts/ivz322

7. Schmack, B., Weymann, A., Popov, A.-F., Patil, N. P., et. Al. (2016). Concurrent Left Ventricular Assist Device (LVAD) Implantation and Percutaneous Temporary RVAD Support via CardiacAssist Protek-Duo TandemHeart to Preempt Right Heart Failure. *Medical Science Monitor Basic Research, 22,* 53-57. doi: 10.12659/msmbr.898897