COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
CAMPUS BOX F-490 TELEPHONE: 303-724-1055 Fax: 303-724-0990

Protocol #: 17-1042
Project Title: Randomized interventiOn of Biventricular pacemaker function on ventricular function among patients with mechaNical circulatory support devices: "ROBIN"
Principal Investigator: William K. Cornwell III, MD
Version Date: 4/24/2019

I. Hypotheses and Specific Aims:

Specific Aim 1: **Determine how cardiac-resynchronization therapy (CRT) influences ventricular performance at rest and during activity/exercise in patients with CF-LVADs.** Hypothesis 1: Cardiac output (Qc) and functional capacity are higher with CRT-pacing enabled, as opposed to conventional treatment with CRT-pacing disabled.

Specific Aim 2: Determine how the right ventricle (RV) functions at rest and during exercise among patients with CF-LVADs. Hypothesis 2A: During resting conditions, adjustments of the CF-LVAD pump speed will alter venous return of blood to the heart, causing RV workload to increase and decrease in response to increases and decreases in pump speed, respectively. **Hypothesis 2B**: During exercise, progressive increases in venous return will increase RV workload and limit the patient's ability to exercise.

II. Background and Significance:

Heart failure (HF) is a devastating disease that affects 6 million people in the United States alone.[1] Overall 5-year survival of patients with HF is only 50%[1-3] and there are significant reductions in quality of life (QOL).[4] While beta-blockers and angiotensin-converting-enzyme inhibitors (medications considered "standard of care") have led to improvements in outcomes[5-12], many patients progress to end-stage, advanced HF, which has an even higher 5-year mortality rate of 80%.[13] While heart transplantation is considered the gold-standard treatment for advanced HF, only ~2,000 donor organs are available per year.[14] As such, demand for a definitive treatment of advanced HF far outweighs supply of available donor organs.[15] To remedy this disparity, continuous-flow (CF) left ventricular assist devices (LVADs), so called "mechanical hearts", have emerged as an attractive alternative.[4] Over 10,000 devices have been implanted over the past decade since CF-LVADs were incorporated into clinical practice, and almost 2,500 implanted in 2013 alone.[16] CF-LVADs restore cardiac output (Qc) to normal levels through a rotating impellar that propels blood from the left ventricle into the ascending aorta. Total Qc therefore is determined by: 1) the CF-LVAD, which provides the bulk of flow to the body, at least during resting conditions; and 2) the heart, which can still provide small amounts of flow to the body by the expulsion of blood through the aortic valve as the heart contracts

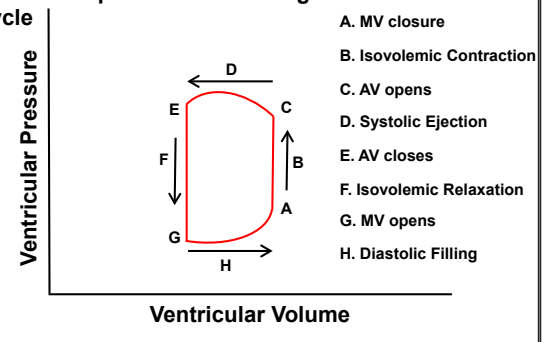
Unfortunately, HF-related symptoms and functional impairments persist after insertion of a CF-LVAD. While survival and QOL generally improve following CF-LVAD implantation[17,18], functional limitations and impairments in exercise capacity persist despite the return of resting Qc to normal levels.[19] Device-related complications are a major source of morbidity[16]. However, post-implantation HF is common, with almost half of patients reporting significant limitations in function 6-12 months after device insertion.[19-21] The average six-minute hall walk score (6MHW, ~350m)[19] and peak oxygen uptake (VO2, 12ml/kg/min)[22] remain low 6-12 months following device implantation compared to normal levels in healthy individuals (normal 6MHW ~600±90m[23], average age-matched peak VO2 ~25-30ml/kg/min[24]). Importantly, cardiovascular-related mortality rises exponentially for patients with 6MHW less than 345m[25] and VO2 less than 14ml/kg/min[26]. Finally, despite a 1-year post-implantation survival rate of ~80%, survival at four years remains low at less than 50%.[16] Thus, despite the assistance to the heart that the device provides, relief from HF-related symptoms is incomplete, which increases the risk of morbidity and mortality over time and is a major limitation of these devices.[27]

RV performance during exercise, even among healthy individuals, is incompletely understood and poorly described among patients with CF-LVADs. Ventricular function is best characterized by formation of pressure-volume (PV) loops, which characterize ventricular performance during all phases of the cardiac cycle (figure 1).[28] Based on animal models, the RV has been found to be a highly compliant, low-pressure chamber (especially compared to the muscular left ventricle (LV).[28-31] In humans, *noninvasive methods* (e.g. echo) have been used to *estimate* how the RV responds to increases in venous return among healthy individuals that occur with exercise.[32] Using high-fidelity conductance (Millar) catheters, it has been shown that diastolic stiffness increases among patients with coronary artery disease and/or hypertension), possibly as a result of ischemia or pericardial constraint.[33] However, RV performance – throughout the *entirety* of the cardiac cycle, during exercise *among healthy individuals* – has not been fully characterized. However, this information can be obtained through use of these high-fidelity conductance catheters (Millar). Thus, there is a need (and the ability) for further investigation of the body's response to changes in loading conditions (such as occurs during exercise), in this population. This information is useful to further understand how the body responds to the hemodynamic demands of exercise, and also will serve as a platform for future investigations to define "normal" responses that diseased populations can be compared to.

CF-LVAD implantation may compromise RV function. The LVAD functions by continuous rotation of a rotor, which creates a suction effect and pulls oxygenated blood into the device, which is then propelled forward to the body.[18] However, this suction also pulls the interventricular septum away from the RV, which increases the diameter of the RV and increases RV wall stress according to the Law of Laplace (wall stress is proportional to the radius of the ventricle).[30,34] With the onset of activity, there is increased venous return of blood to the RV, and a compromised RV may be unable to accommodate this increase in bloodflow. As such, RV function may impair exercise capacity. It is unclear why VO2 and 6MWD scores (as detailed above) remain so low, and the primary determinants of exercise capacity among CF-LVAD patients are not clearly defined.

Following CF-LVAD implantation, there is little data available to guide clinicians with respect to cardiac resynchronization therapy pacemaker-defibrillator (CRT-D) settings. In the setting of advanced HF, CRT-D devices are implanted into individuals with underlying left bundle branch block (LBBB) conduction abnormalities.[4] A LBBB causes "dyssynchrony" between the right (RV) and left ventricles (LV), meaning that they no longer contract at the same time. A CRT-D device is implanted in these patients and includes a coronary sinus (CS) lead on the left side of the heart, in addition to standard pacing/defibrillator leads, which are positioned on the right side of the heart. With pacing leads positioned on both sides of the heart, the CRT-D can pace both ventricles simultaneously, effectively resolving the LBBB conduction abnormality. However, following CF-LVAD implantation, the CRT-D device is left in place, but optimal device settings are unknown – specifically, it is unclear whether the CS lead should remain activated or deactivated. In the absence of definitive data, conventional management is to deactivate the CS-lead. This strategy theoretically allows the interventricular septum to contribute to RV function at the expense of the LV (ie, the septum contributes more to RV function and less to LV function; since the LV is supported by the LVAD, this strategy theoretically should not compromise systemic perfusion). *However, my preliminary data suggest the opposite – namely, that cardiac output (Qc), improves with the CS-lead enabled*. Confirmation of these findings, along with a comprehensive analysis of the impact of CRT pacing on ventricular function and cardiac performance at rest and activity/exercise, will fill current gaps in knowledge about the interaction between

Figure 1: Pressure-Volume loop describes ventricular performance throughout the cardiac cycle



AV: aortic valve; MV: mitral valve

CF-LVADs and CRT-D devices and provide the community with information about best-practices to optimize cardiovascular function and improve exercise capacity in these patients.

III. **Preliminary Studies/Progress Report:**
This protocol is designed to test hypotheses that are based on the following observations:

1. Concerning CRT-D pacing strategies: because there is uncertainty about optimal CRT-D pacemaker settings (ie, whether the CS-lead should be ON or OFF in CF-LVAD patients), CRT-D pacemaker settings were adjusted as part of routine clinical care in two CF-LVAD patients with CRT-D devices and Qc was found to increase by 0.6L/min with the CS-lead ON, v. compared to CS-lead pacing OFF (ie, pacing both ventricles, compared to only pacing the RV). The hypothesis for this study (that enabling the CS-lead leads to an increase in Qc with subsequent increase in exercise capacity) is based off these clinical observations.
2. Regarding RV function in the setting of CF-LVAD support: CF-LVAD patients frequently undergo exercise testing as part of routine clinical care if they have unexplained shortness-of-breath or fatigue with activity. Based on these clinical observations, we have observed that right sided filling pressures may appear normal at rest, but increase dramatically with exercise (e.g. one patient had a right atrial pressure of 4mmHg at rest, but increased to 19mmHg at a workload of 50 Watts on a stationary bicycle). This supports the hypothesis that the LVAD may be compromising RV function by pulling the septum away from the RV and increasing RV wall stress, which makes it difficult for the RV to accommodate the increase in venous return that occurs with onset of exercise.

IV. Research Methods:

A. Outcome Measure(s):

For specific Aim 1: The primary outcome will be the difference in Qc (inert rebreathing) and peak VO2 between CS-lead ON v. OFF. Secondary measures include vital signs including HR and BP, as well as 6-minute hall walk test, 10 minute gait speed test, and quality of life measures (Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure Questionnaire), all compared between CS-lead ON v. OFF.
For Specific Aim 2: The primary outcome will be the pressure-volume (PV) area as measured by Millar catheterization – this data variable is a direct marker of "how hard" the RV must work in the face of changes in preload (venous return). Secondary outcomes include: end-systolic pressure volume relationship (ESPVR), which assesses changes in contractility, end-diastolic pressure volume relationship (EDPVR), which assesses ventricular compliance during the diastolic portion of the cardiac cycle, dp/dt (increase in ventricular pressure during isovolemic contraction period), and tau (measure of isovolemic relaxation of the ventricle). All of these variables will be assessed during changes in LVAD pump speed, and during exercise testing (on visits 1-2, see figure 2 below) with CS-lead ON v. OFF.

B. Description of Population to be Enrolled for completion of specific aims 1-2:

1. **15 patients with advanced HF who have already undergone CF-LVAD implantation**. **Inclusion criteria**: 1) advanced HF patients who have already received CF-LVADs and are clinically stable, ambulatory outpatients and are fully recovered (at least 3 months) from LVAD implantation**Exclusion criteria**: 1) individuals with clinical RV failure under resting conditions, defined as moderate-severely reduced RV systolic function on echocardiography, or clinical evidence of RV failure (elevated jugular venous pressures, 3 or 4+ [significant] peripheral edema); 2) disorders that adversely influence exercise ability (e.g. arthritis, peripheral vascular disease, pulmonary disease)
2. **13 healthy individuals** will serve as a control group to define normal RV function during exercise. Healthy individuals will be defined as persons without a past medical history of cardiovascular disease or related disease (e.g. hypertension, diabetes, peripheral vascular disease, arrhythmias, stroke/transient ischemic attack) and are not taking any cardiac-related medications (e.g. antihypertensive medications). Potential subjects will be recruited by posting flyers at the University of Colorado Anschutz Medical Campus. Individuals requiring systemic anticoagulation with vitamin-K antagonists or new/direct oral anticoagulants ("NOAC"/"DOAC") will not be considered for study. **Exclusion criteria** for this control group includes: 1) individuals requiring systemic anticoagulation with

vitamin-K antagonists or new/direct oral anticoagulants (“NOAC”/”DOAC”); 2) disorders that adversely influence exercise ability (e.g. arthritis, peripheral vascular disease).

Power Analysis:
For specific aim 1-2, based on pilot data, assuming an increase in resting Qc of 0.6Lmin following activation of CRT (coronary-sinus [CS] lead enabled [CS-ON], with a standard deviation of 0.2L/min, a sample size of 15 patients will provide greater than 90% power to detect a difference in Qc using an alpha of 0.05. Assuming an increase in right atrial pressure of ~15mmHg from rest to peak exercise (based on pilot data), a sample size of 15 patients will provide greater than 90% power to detect a difference in right sided pressures from rest to peak exercise, using an alpha =0.05.

For healthy controls, based on available data previously described in the literature[33], assuming a reduction in RV relaxation time by 50msec from rest to exercise, a sample size of 10 patients will provide greater than 90% power to detect a difference in ventricular performance from rest to peak exercise, assuming a standard deviation of ~20msec and an alpha = 0.05.

Study Design and Research Methods

An overview of the study protocol is displayed in figure 2. For completion of aim 1 (testing the effect of the coronary sinus [CS] lead on functional capacity, CF-LVAD patients who have a CRT-D device will complete visits 1-2 as detailed in figure 2 and in the protocol description below. For completion of aim 2, CF-LVAD patients who do not have a CRT-D will complete visit 1 only. For CF-LVAD patients with CRT-D, the study protocol will involve a double-blinded randomized crossover design. Immediately following enrollment, CF-LVAD subjects will be randomized in a double-blind, 1:1 fashion to cardiac pacing with the coronary sinus (CS) lead enabled or disabled (CS-ON v. CS-OFF). The pacing mode will be either VVI-R or DDD-R with a backup pacing rate set at 60bpm. After four weeks, patients will return for visit 1 testing. On completion of testing, cardiac pacing will be switched (CS-ON to CS-OFF, or vice-versa) for four weeks, following which patients will return for visit 2 testing, which is identical to visit 1 testing. In this manner, all subjects will complete testing with the CS-lead ON and the CS-lead OFF; subjects will serve as their own controls to determine the impact that CRT-D pacing has on cardiovascular function and exercise performance. Following completion of visit 2 testing, the study will be completed and original CRT-D device settings returned to baseline. Computerized randomization will be performed in a 1:1 ratio to a CS-lead ON v. OFF pacing strategy – this process will be completed and recorded by a study coordinator who does not have access to the data recorded throughout the study; neither the patient nor the PI will be aware of randomization status during testing. Pacemaker settings will be adjusted by an electrophysiologist who is part of the study group but does not have access to data being collected (to ensure that blinding is maintained).

Visits 1-2 will involve a baseline assessment of hemodynamics using a Swan-Ganz catheter, followed by invasive exercise testing with Millar catheters to provide a detailed analysis of ventricular function during exercise. The **Swan-Ganz catheter** is a 7-French flexible catheter that is routinely used for hemodynamic assessment for clinical and research purposes (we are currently using this catheter for COMIRB #16-1635). The purpose of this catheter is to determine baseline hemodynamic parameters (in “layman’s terms”, to describe pressures in the right and left sides of the heart, as well as the lungs), including cardiac output and pulmonary arterial saturation, which provides an assessment of the integrity of the cardiopulmonary system under resting conditions prior to exercise. The inclusion of Swan-Ganz catheter to determine resting hemodynamics will extend the protocol by only 5 minutes. NOTE: the Swan-Ganz catheter is quickly inserted and removed after pressures, cardiac output and pulmonary arterial saturation are obtained. The **Millar catheter** is a high fidelity, pigtail-shaped central-lumen, 7-French flexible catheter with pressure and conductance electrodes; the insertion technique is the same as that used for a standard right heart catheterization (for example, the same procedure used for IRB study #16-1635). These catheters allow for generation of pressure-volume (PV) loops, as well as several additional measures of ventricular function, including: 1) dp/dt (increase in ventricular pressure during isovolemic contraction period); 2) tau (measure of isovolemic relaxation of the ventricle); 3)end-systolic pressure volume relationship (ESPVR), which represents contractile function of the ventricle; 4) end-diastolic pressure volume relationship (EDPVR), which represents ventricular compliance; and 5) pressure-volume area, which represents the amount of mechanical energy generated from contraction of the ventricle. As such, these catheters provide several parameters that are

essential to understand how CF-LVADs impact RV function, and also determine how RV function influences exercise capacity in these patients.

The testing protocol for visits 1-2 will involve two parts: Part A, and Part B, which will be completed following right heart catheterization. Part A involves LVAD pump speed adjustments at rest in the supine position. Part B involves submaximal and symptom-limited (maximal) exercise. Exercise will be performed using a stationary cycle ergometer. For Part A, measurements will include the following: HR, BP by arterial line, LVAD parameters (from LVAD monitor), pressure-volume loops from the Millar catheter and Qc (inert rebreathing). Echocardiography will be used during pump speed adjustments to assess parameters such as LV and RV systolic and end-diastolic volumes, septal position, and mitral/tricuspid regurgitant flow. For Part B, measurements obtained will include the following: HR, BP by arterial line, respiratory rate, Qc (inert rebreathing), LVAD parameters (flow, rotor speed, pulsatility index and power), echocardiography may be used to estimate flow through the LVAD and left ventricular outflow tract of the native heart), VO2, VCO2 by gas exchange, RPE and measurements outlined above from the Millar catheter (e.g. dp/dt, tau, ESPVR, EDPVR and pressure-volume area). A complete blood count (CBC) will be obtained at rest, prior to initiation of exercise. A CBC is necessary to obtain hemoglobin/hematocrit levels, which are used to further assess VO2 and other cardiac parameters (e.g. cardiac output). Notably, this blood sample will be obtained from the catheter that is placed for invasive hemodynamic monitoring – no additional catheters or peripheral IV's are required. Blood (venous and/or arterial) oxygen saturation levels will be drawn at rest and during each stage of exercise by removing a small amount of blood (approximately 1-2cc) from the catheters (arterial catheter will be used to check arterial oxygen saturation; Millar catheter will be used to check venous oxygen saturation level). Blood oxygen levels are necessary to determine oxygen consumption by exercising muscle. Cerebral and peripheral (musculoskeletal) oxygen uptake may be monitored noninvasively by NIRS. End-tidal carbon dioxide will be monitored by nasal capnography. Brain blood flow may be measured by transcranial Doppler ultrasonography.

On visits 1-2, additional testing will include: 1) echocardiography to measure parameters such as LV end-diastolic and systolic volumes, mitral regurgitation severity, and RV strain; 2) 6-minute hall walk and 10-meter walk test; 3) Kansas City Cardiomyopathy Questionnaire KCCQ) and Minnesota Living with Heart Failure Questionnaire (MLHFQ); 4) CRT-D device interrogation to assess for percentage of time that patients are paced by the CS lead, for ventricular and/or supraventricular arrhythmias, and any "therapies" delivered by the device, such as anti-tachycardia pacing or shocks for treatment of ventricular arrhythmias: and 5) a comprehensive medical history and physical exam.

Note that patients with CF-LVADs will complete two visits (visits 1-2); healthy controls will only complete one day of testing (visit 1) to define normal responses – healthy subjects will only complete part B (exercise testing); part A (pump speed adjustments) is not applicable to healthy controls, who do not have an LVAD.

The following methods will be utilized for completion of visits 1-2:

- Medical History and Physical Exam
- Exercise on stationary bicycle or arm ergometry
- Right heart catheterization
- Arterial line insertion
- Assessment of oxygen consumption (VO2) and carbon dioxide production (VCO2) via metabolic cart
- Assessment of vital signs: heart rate, blood pressure, SpO2, end-tidal carbon dioxide (ETCO2)
- Lactate measurement
- Echocardiography
- 6-minute hall walk
- 10 meter gait speed
- KCCQ and MLHFQ (for LVAD cohort only)
- CRT-D device interrogation (for subjects that have an LVAD and a CRT-D device)

Procedures that will occur in the catheterization lab or the inpatient CTRC for visits 1-2:

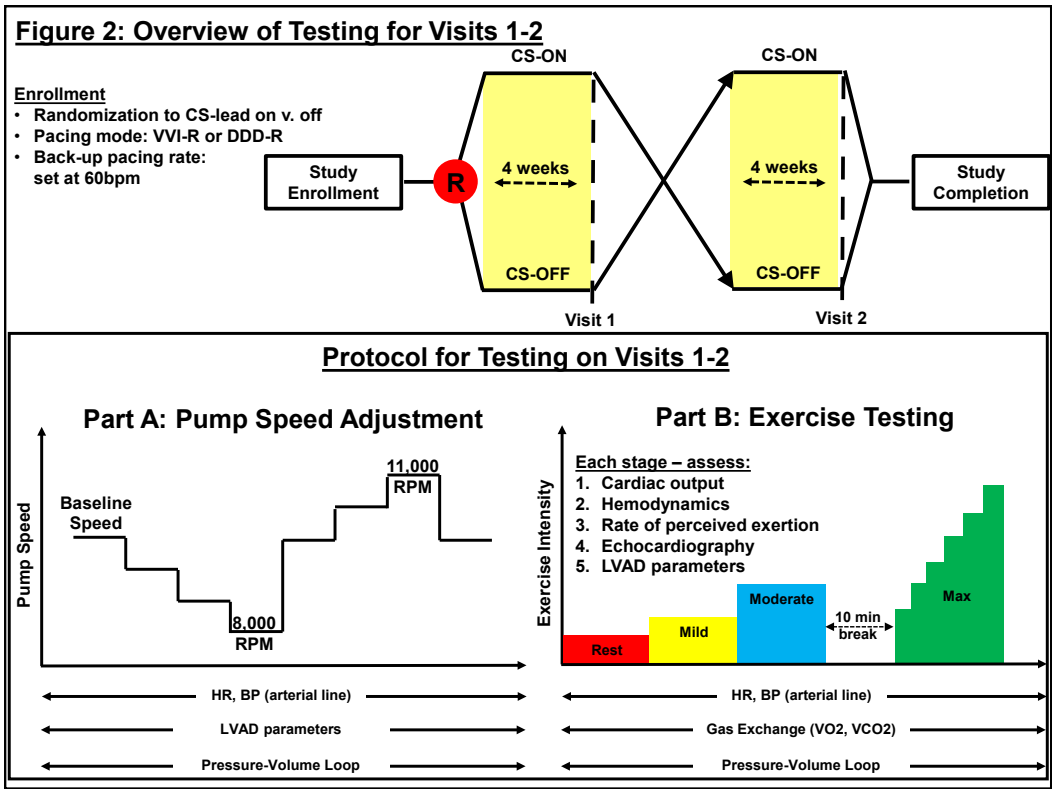
- Right heart catheterization: insertion of a Millar catheter under fluoroscopic guidance
- Arterial line insertion

Procedures that may occur in *either* the catheterization lab or the inpatient unit of the CCTSI (12th floor of the inpatient hospital):

- LVAD pump speed adjustments: pump speed adjustments will be completed after the Millar catheter and arterial line are inserted and will be completed before patients exercise on the stationary ergometer. The location of testing (catheterization laboratory or CCTSI) will be determined based on schedule availability. If testing is completed in the CCTSI, patients will be transported from the catheterization laboratory by the study PI (Dr. Cornwell), a CCTSI nurse, a cath lab staff member and with telemetry monitoring (same as already being done for IRB study #16-1635).
- Exercise testing: following placement of the Millar catheter and arterial line, exercise testing will either be completed in the catheterization laboratory, or the patient may be transported to the inpatient CTRC unit to complete testing. Following completion of the study, the Millar catheter will be removed under fluoroscopic guidance: if testing is completed in the cath lab, the catheter will be removed there, once testing is completed. If testing is completed in the CTRC, the patient will be brought back to the catheterization laboratory for removal of the catheter.
- Echocardiography
- 6-minute hall walk
- 10 meter gait speed
- KCCQ and MLHFQ
- CRT-D device interrogation (for subjects that have an LVAD and a CRT-D device)

Team members that will be present at all times during the study: regardless of the location of the testing (CCTSI v. cardiac catheterization laboratory), the following team members will be present for testing:

- Dr. Cornwell (study PI)
- Study coordinator
- Cath lab staff member
- RN from the CCTSI



Short-Term Effects of CS-lead ON v. OFF pacing mode – Sub-Study

The protocol listed above is intended to determine longterm effects of CS-lead ON v. OFF pacing. However, there is a lack of information regarding the short-term effects – specifically, the possible hemodynamic benefits in an acute, or short-term setting. For example, in one of our patients with advanced heart failure with reduced ejection fraction (HFrEF), mean pulmonary arterial pressure was reduced by 6mmHg (from 31 to 25mmHg) and cardiac output improved by 1L (from 4.8 to 5.7L/min) when the CS-lead was turned from OFF to ON (this was done under close hemodynamic monitoring for clinical purposes). However, these acute improvements in hemodynamics observed in a HFrEF patient, suggest that similar improvements may be observed among HFrEF patients with CF-LVADs. To formally investigate, CF-LVAD patients who have completed the study protocol above, will be invited to complete a **non-invasive**, **short-term** (approximately 2 hour) **substudy** during routine clinical outpatient appointments. The *primary objective of this short-term substudy is to determine whether there are acute improvements in functional capacity with CS-lead ON v. OFF CRT-D pacing.*

Recruitment: patients who have completed the study protocol above will be invited to participate in this substudy. Subjects will be recruited either by telephone or during routine clinic appointments. The rationale and description of the substudy will be described. After subjects have had ample time to review the substudy, and all questions are answered, they will be formally enrolled.

Outcomes of interest:

1. Six-minute hall-walk distance
2. Cardiac output – measured noninvasively by Innocor using inert rebreathing technique
3. Echo parameters: left and right ventricular strain-rate imaging; pulse-wave Doppler of the left ventricular and right ventricular outflow tract as well as the LVAD inflow cannula, to document changes in relative flow through the LVAD v. aorta; M-mode of the aortic valve to assess for aortic valve opening
4. LVAD parameters: flow, speed, pulsatility index and power

Protocol: The standard CRT-D pacing mode is CS-lead OFF, so these patients will begin the substudy with their pacemakers in the CS-lead OFF mode. Following enrollment, patients will undergo a six-minute hall-walk as part of the research substudy. Cardiac output will be assessed noninvasively using the Innocor inert rebreathing technique. Thereafter, a transthoracic echo (TTE) will be completed *as part of standard-of-care* (these patients undergo routine echos during clinic appointments). The above-listed parameters will be recorded. Following completion of the echo, LVAD parameters will be recorded and then the pacemaker will be adjusted to the CS-lead ON setting. Then, patients will complete their routine clinic visit, which typically lasts ~60 minutes. Once completed, the patient will repeat the six-minute hall-walk, as well as cardiac output by inert rebreathing technique, and the same echo images will be repeated. LVAD parameters will be recorded. Once completed, the pacemaker will be returned to original settings, with CS-lead OFF. The procedure will be completed and the patient discharged from clinic.

Compensation: patients will not be provided any further compensation for this substudy.

Data Analysis: all outcomes of interest will be compared by paired t-test to determine differences between CS-lead ON v. OFF. LI statistical analyses will be paerformed using a computer-based analysis system (SAS V9.4, Cary NC, USA). A P value of <0.05 will be considered statistically significant.

Commented [1]: New figure

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Right heart catheterization: risks involve pain/bleeding at site of catheter insertion, infection, pneumothorax, arrhythmias, and chest discomfort. Radiation exposure: there is a very small amount of radiation exposure that will be experienced during insertion of the catheter. The typical amount of radiation exposure is <7mSv. For comparison, the average amount of radiation exposure per year that results from standing outside is around 3-4mSv. These risks will be minimized by applying topical lidocaine cream (numbing medication) and injecting lidocaine over the sight of catheter insertion. All procedures will be performed using sterile technique. Procedures will be performed with use of an ultrasound machine and fluoroscopy – in this manner, all needles, guidewires and catheters will be monitored per standard guidelines and practice patterns. There are no additional risks associated with insertion/removal of a Swan-Ganz catheter prior to insertion of the Millar catheter. Incorporation of the Swan-Ganz catheter will prolong the current study by an estimated 5 minutes.

Arterial line insertion: risks involve pain/bleeding at site of catheter insertion, infection

Exercise testing: exercise testing carries a finite risk of adverse cardiovascular events with less than 1/100,000 in healthy individuals, and approximately 1/10,000 in patients with cardiovascular disease.

Arrhythmias during exercise: during exercise testing, there is a potential for advanced HF patients to develop arrhythmias.

Fatigue: during exercise testing, subjects will eventually develop fatigue, as they are encouraged to exercise at submaximal and peak workloads.

Pump speed adjustments: as the pump speed is increased or decreased, subjects may theoretically feel lightheaded or become short of breath.

Pacemaker setting adjustments (turning the CS-lead ON and OFF): while it is not anticipated that individuals will have any ventricular arrhythmias that result from enabling or disabling the CS-lead of the CRT-D, this is theoretically possible during any adjustment to a pacemaker-defibrillator. This study does not involve adjustment of any "therapies" delivered by the CRT-D, meaning that in the event of an arrhythmia, the CRT-D would provide anti-tachycardia pacing or shocks as necessary by following standard analysis algorithms that are programmed into the device.

Echo/ultrasound: there are no significant risks associated with echo or ultrasound. It is possible that patients may feel slight discomfort from a probe sitting over the skin.

Loss of confidentiality: there is a potential risk of loss of confidentiality any time information is collected. Every effort will be made to keep participant information confidential.

Risks to an embryo, fetus or breast-fed infant: this is not anticipated, since advanced HF patients are highly discouraged from bearing children, particularly when they are scheduled to undergo CF-LVAD implantation. However, any woman of child-bearing age will undergo a pregnancy test prior to being studied. If a female participant becomes pregnant during they study, she will tell the PI immediately and she will be removed from the study.

E. Potential Scientific Problems:

1)Recruitment of subjects for testing: The University of Colorado has an active heart failure and LVAD program, with approximately 50 CF-LVADs inserted in 2015 and over 70 patients followed in the advanced heart failure center. There are currently 37 CF-LVAD patients with CRT-D devices that are being followed clinically by the advanced heart failure and electrophysiology programs here at the University of Colorado. Thus, we do not anticipate any difficulty recruiting subjects for this proposal. Healthy volunteers will be recruited by posting flyers around the University of Colorado Anschutz Medical Campus. We will plan to enroll 30 participants with the anticipation that there will be a few dropouts (no more than 5 anticipated).

F. Safety Oversight:

The independent Data Safety Monitoring Board (DSMB) that oversees IR study #16-1635 will also oversee all operations of this study, from initiation of the study through completion. The principal investigator (Dr. Cornwell) will regularly report to the DSMB, which will be comprised of the following members (who are not affiliated with the study):

CHAIR and Statistician: Alex Kaiser, PhD Assistant Professor
Department of Biostatistics and Informatics
University of Colorado Anschutz Medical Campus

Andreas Brieke, MD
Associate Professor of Medicine-Cardiology
Section of Advanced Heart Failure, LVAD and Cardiac Transplant, Division of Cardiology, Department of Medicine
University of Colorado Anschutz Medical Campus

Prateeti Khazanie, MD, MPH
Assistant Professor of Medicine-Cardiology
Section of Advanced Heart Failure, LVAD and Cardiac Transplant, Division of Cardiology, Department of Medicine
University of Colorado Anschutz Medical Campus

Safety Measures: The following safety measures will be in place during the study:

- Consent: the primary investigator (Dr. Cornwell) will carefully review study objectives, procedures involved, and the risks and benefits of the study with the individual being considered for inclusion. Consent will be obtained from a study coordinator only after the individual being considered has had ample time to carefully review the consent form, the coordinator has personally reviewed the consent

form with the individual, and all questions have been answered to the individual's satisfaction. The coordinator will be responsible for finalizing consent (obtaining signatures), but the primary investigator will be available at any time during the consent process to ensure that the individual makes a fully informed decision about whether or not to participate.

- INR goal: Patients with CF-LVADs are managed with blood-thinners (ie, vitamin-K antagonists [coumadin]), with drug dosages adjusted to an INR goal of 2.0-3.0. For the purposes of this study, all blood-thinners prescribed as part of routine care, will be continued. However, recognizing that there are bleeding risks associated with procedures (right heart catheterization) on patients who are anticoagulated, a right heart catheterization will not be performed on individuals who have an INR > 2.5 less than one week prior to the time of procedure. In the event that the INR is > 2.5, the visit will be rescheduled for another time.
- Participant stopping rules:
    - Hemodynamic monitoring: individuals' vital signs will be monitored continuously during all visits of the study. In the event that an individual becomes hemodynamically unstable during exercise, the study will be discontinued. "Hemodynamic instability" includes, but is not limited to: an unexpected reduction in blood pressure; transition from normal to an abnormal rhythm (e.g. sustained ventricular tachycardia or recurrent nonsustained ventricular tachycardia) at any point in time; clinical instability as determined by Dr. Cornwell (an advanced heart failure cardiologist experienced in conducting studies on these types of patients) or any other team member.
    - Patient comfort: an individual being tested may voluntarily withdraw from the study at any point in time, should he/she become uncomfortable or symptomatic (e.g. excessive dyspnea, lightheadedness) at any point in time during exercise. The primary investigator of the study (Dr. Cornwell) recognizes that patient comfort/discomfort may not be reflected by an individual's vital signs – therefore, the study will be discontinued at any point in time at the patient's request, should the individual become symptomatic despite vital signs being normal).
- A member of the cath lab staff will be present at all times during testing, when a test subject has a heart catheter in place. The cath lab staff member will accompany the patient from the cath lab to the CTRC and remain there until testing is completed. This individual will be responsible for monitoring and serve as an "extra set of eyes", to monitor the well-being of the test subject, while the catheter is in place. In addition, Dr. Cornwell, the primary investigator for the study, will be present at all times, including the duration of time when a test subject has a catheter in place. To further safety oversight, a CTRC nurse will be present throughout the procedure whether testing is completed in the cath lab or the CTRC.
- The study PI (Dr. Cornwell) recognizes that there inherent risks involved with invasive procedures and exercise testing. Therefore, the PI will have authority to withhold enrollment of any individual into the study if there are concerns about patient safety or comfort, even if that individual meets all other inclusion/exclusion criteria.
- During CRT-D interrogations on visits 1-2, if arrhythmias are detected, this information will be communicated to the patient and to the patient's managing cardiologist.

This study will be registered on clinicaltrials.gov prior to study initiation. This study is similar in design to IRB #16-1635, which is funded in part, through the PI's NIH/NHLBI K23 award. However, this study (IRB #17-1042) is not a written part of the K23 award that was awarded by the NIH/NHLBI. As such, while this study seeks to address similar objectives (ie, to determine limitations in functional capacity of patients with advanced heart failure with CF-LVADs), this is an independent study with its own protocol and consent forms.

G. Data Analysis Plan:

For specific aim 1, data across conditions among CF-LVAD patients (ie, CS-lead ON v. OFF) will be compared using repeated measures analysis of variance (ANOVA) with Bonferroni *post-hoc* tests for multiple comparisons. Linear mixed modeling with random effects will be used to account for the variability in hemodynamics (e.g. heart rate, blood pressure, cardiac output) that occur during pump speed adjustments and during progressive stages of exercise (rest, mild, moderate and peak exercise). Comparisons between healthy controls and CF-LVAD patients will be compared using the Mann Whitney U test. All statistical analyses will be

performed using a computer-based analysis system (SAS, V9.4, Cary NC, USA). A P value < 0.05 will be considered statistically significant.

For specific aim 2, data across conditions among CF-LVAD patients (CS-lead ON v. OFF) will be compared using a two-way repeated measures ANOVA, to determine the impact of CS-lead pacing and LVAD pump speed on RV performance, and the impact of CS-lead and exercise on RV performance, with Bonferroni *post-hoc* tests for multiple comparisons. Linear mixed modeling with random effects will be used to account for the variability in parameters of RV function (dp/dt, tau, ESPVR, EDPVR, and PV area). Comparisons between healthy controls and CF-LVAD patients will be compared using the Mann Whitney U test. All statistical analyses will be performed using a computer-based analysis system (SAS, V9.4, Cary NC, USA). A P value < 0.05 will be considered statistically significant.

H. Summarize Knowledge to be Gained:

This proposal will be the first to provide a comprehensive assessment of the impact CRT-D pacing strategies on cardiac function for heart failure patients with CF-LVADs. Currently, there is a lack of knowledge about best-practices for management of CRT-D in patients with CF-LVADs. In the absence of data, practitioners frequently deactivate the CS-lead in an effort to conserve CRT-D battery life and also to allow the interventricular septum to contribute to RV contractility. However, my preliminary data suggest that this strategy is not ideal, and that cardiac function (specifically, Qc) improves with the CS-lead activated.

This proposal will be the first to provide a detailed analysis (using high-fidelity Millar catheters) of CF-LVAD therapy on RV performance at rest and with activity/exercise. It is likely that a CF-LVAD compromises RV function by "pulling" the interventricular septum away from the RV (the septum is "pulled" away from the RV by the suction effect created from the LVAD), which increases RV diameter and limits the ability of the septum to contribute to RV contractility.

This study will define short-term benefits as it pertains to functional capacity (as determined by six-minute hallwalk), as well as hemodynamic parameters (as measured by cardiac output) that result from enabling the CS-lead. Further, acute improvements in cardiovascular performance (determined noninvasively by echocardiogram) will be characterized as well.

Findings from these studies will inform clinicians on best-practices regarding CRT-D programming to optimize cardiac function and exercise capacity, will characterize how CF-LVAD technology influences RV function and also define the extent to which RV function/dysfunction limits exercise capacity in these patients.

REFERENCES:

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* Jan 3 2012;125(1):188-197.

2. Mosterd A, Cost B, Hoes AW, et al. The prognosis of heart failure in the general population: The Rotterdam Study. *European heart journal.* Aug 2001;22(15):1318-1327.

3. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *Journal of the American College of Cardiology.* 1993;22(4 Suppl A):6A-13A.

4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;128:e240-e327.

5. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *The Lancet.* 2001;357(9266):1385-1390.

6. Packer M, Bristow MR, Cohn JN, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. *New England Journal of Medicine.* 1996;334:1349-1355.

7. MERIT-HF Study Group. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001-2007.

8. Cohn JN, Archibald DG, S. Z, et al. Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure: Results of a Veterans Administration Cooperative Study. *New England Journal of Medicine.* 1986;314(24):1547-1552.

9. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *The Lancet.* 2003;362(9377):7-13.

10. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *New England Journal of Medicine.* Swedberg, K.;316(23):1429-1435.

11. Cohn JN, Johnson G, Ziesche S, et al. A Comparison of Enalapril with Hydralazine-Isosorbide Dinitrate in teh Treatment of Chronic Congestive Heart Failure. *New England Journal of Medicine.* 1991;325(5):303-310.

12. Yusuf S. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. The SOLVD Investigators. *New England Journal of Medicine.* 1991;325(5):293-302.

13. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation.* Mar 27 2007;115(12):1563-1570.

14. Everly MJ. Cardiac transplantation in the United States: an analysis of the UNOS registry. *Clinical Transplants.* 2008:35-43.

15. Frazier OH. Mechanical Cardiac Assistance: Historical Perspectives. *Seminars in thoracic and cardiovascular surgery.* 2000;12(3):207-219.

16. Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* Jun 2014;33(6):555-564.

17. Miller LW, Pagani FD, Russell SD, et al. Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation. *New England Journal of Medicine.* 2007(357):885-896.

18. Slaughter M, Rogers J, Milano C, et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. *New England Journal of Medicine.* 2009;361:2241-2251.

19. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *Journal of the American College of Cardiology.* Apr 27 2010;55(17):1826-1834.

20. Slaughter MS, Pagani FD, Rogers JG, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* Apr 2010;29(4 Suppl):S1-39.

21. Burke MA, Givertz MM. Assessment and management of heart failure after left ventricular assist device implantation. *Circulation.* Mar 11 2014;129(10):1161-1166.

22. Leibner ES, Cysyk J, Eleuteri K, El-Banayosy A, Boehmer JP, Pae WE. Changes in the functional status measures of heart failure patients with mechanical assist devices. *ASAIO journal.* Mar-Apr 2013;59(2):117-122.

23. Casanova C, Celli BR, Barria P, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. *The European respiratory journal.* Jan 2011;37(1):150-156.

24. *Advanced Fitness Assessment and Exercise Prescription.* 3rd ed1998.

25. Ingle L, Rigby AS, Carroll S, et al. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. *European heart journal.* Mar 2007;28(5):560-568.

26. Mancini D, Eisen H, Kussmaul W, Mull R, Edmunds LHJ, Wilson JR. Value of Peak Exercise Oxygen Consumption for Optimal Timing of Cardiac Transplantation in Ambulatory Patients With Heart Failure. *Circulation.* 1991;83(3):778-786.

27. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* Apr 2015;34(4):489-496.

28. Tabima D, Hacker T, CHesler N. Measuring right ventricular function in the normal and hypertensive mouse hearts using admittance-derived pressure-volume loops. *American Journal of Physiology Heart and Circulatory Physiology.* 2010;299(6):H2069-2075.

29. Bellofiore A, Chesler NC. Methods for measuring right ventricular function and hemodynamic coupling with the pulmonary vasculature. *Ann Biomed Eng.* Jul 2013;41(7):1384-1398.

30. Matthews JC, McLaughlin VV. Acute Right Ventricular Failure in the Setting of Acute Pulmonary Embolism or Chronic Pulmonary Hypertension- A Detailed Review of the Pathophysiology, Diagnosis, and Management. *Current Cardiology Reviews* 2008;4:49-59.

31. Durando M.M., Reef VB, Birks K. Right ventricular pressure dynamics during exercise- relationship to stress echocardiography. *Equine Exercise Physiology.* 2002;34:472-477.

32. Armstrong D, Matangi M. Estimated right ventricular systolic pressure during exercise stress echocardiography in patients with suspected coronary artery disease. *Canadian Journal of Cardiology* 2010;26(2):e45-e49.

33. Heywood J, Grimm J, Hess O, Jakob M, Krayenbuhl H. Right Ventricular Diastolic Function During Exercise: Effect of Ischemia. *Journal of the American College of Cardiology.* 1990;16(3):611-622.

34. Neragi-Miandoab S, Goldstein DJ, Bello R, Michler R, D'Alessandro D. Right ventricular dysfunction following continuous flow left ventriccular assist device placement in 51 patients- predicators and outcomes. *Journal of cardiothoracic surgery.* 2012;7(60):1-4.