Title: **A**daptive **CRT** effect on **EL**ectrical dys**SYNC**hrony (aCRT ELSYNC)

Clinical Investigation Plan

1st year

Version 6

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Abbreviations

aCRT – adaptive cardiac resynchronization therapy

CRT-D – CRT with defibrillation therapy

CRT-P – CRT with pacemaker only therapy

cCT – Computed Tomography

ECG – electrocardiogram

ECGi – electrocardiographic imaging

EDI – electrical dyssynchrony index

EGM – electrogram

ICD – implantable cardioverter defibrillator

LV/RV – left ventricle/right ventricle

LBBB – left bundle branch block

NYHA Classification – New York Heart Association heart failure classification

SAI QRST – sum absolute QRST integral

Introduction

Study Purpose

This is an investigator-initiated prospective, single-center, randomized, double-blind paralleled controlled clinical trial comparing adaptive cardiac resynchronization therapy (aCRT)[1] to a standard CRT in patients with currently approved (class I-II) indications for CRT[2]. The purpose of this study is two-fold: First, to determine if aCRT is superior as compared to standard CRT, as evidenced by a superior degree of reduction of electrical dyssynchrony index 6-month post-CRT. An Intra-LV electrical dyssynchrony index will be computed from the electrocardiographic imaging (ECGi) LV epicardial activation maps; Second, to determine if a surface ECG metric sum absolute QRST integral (SAI QRST) is a superior estimate of an intra-LV dyssynchrony, as compared to an averaged across 12-lead QRS duration.

All study participants will receive the commercially available Viva™ XT CRT-D Model DTBA1D4, DTBA1D1, Viva™ Quad XT CRT-D Model DTBA1Q1, DTBA1QQ, Viva™ Quad S CRT-D Model DTBB1Q1, DTBB1QQ, Viva™ S CRT-D Model DTBB1D1, DTBB1D4 or Viva™ XT CRT-P Model C6TR01. All the above models with the exception of the Viva™ Quad S and Viva™ S CRT devices have aCRT available[27-31]. All CRT-D devices (Models DTBA1D4, DTBA1D1, DTBA1Q1, DTBA1QQ, DTBB1D1, and DTBB1D4, DTBB1Q1, DTBB1QQ) detect ventricular tachyarrhythmias and can provide treatment in order to resynchronize the pacing of the left and right ventricles and can provide full defibrillation in the case of ventricular fibrillation. These models have the same indications and contraindications. The CRT-P device (Model C6TR01) similarly detects ventricular tachyarrhythmias, but only responds with resynchronization pacing therapy, not defibrillation. CRT-D and CRT-P models are both indicated in patients with heart failure according to the inclusion and exclusion criteria set forth by this protocol. Choice of model is made on a case-by-case basis depending on patient symptoms that would increase likelihood of need for defibrillation. The model and lead type used will be at the discretion of the physician implanting the device. All patients will be randomized to one of two pacing therapy arms, aCRT ON or aCRT OFF.

The outcome of this study is expected to support use of SAI QRST as an estimate of an intra-LV electrical dyssynchrony, and to improve our understanding of the mechanisms behind aCRT effect.

Hypothesis

We **hypothesize** that (1) aCRT is superior as compared to standard CRT, as evidenced by a superior degree of reduction of electrical dyssynchrony index 6-month post-CRT; and (2) a surface ECG metric SAI QRST[3-5] is a superior estimate of an intra-LV dyssynchrony, as compared to an averaged across 12-lead QRS duration.

Study Scope

Study will be conducted at the Oregon Health & Science University. It is a prospective, single-center, randomized, double-blind paralleled controlled clinical trial. As estimated, 32 participants will be enrolled. All study participants will get commercially available Viva™ XT CRT-D device. Participants will be randomized 1:1 to one of two pacing therapy arms, aCRT ON or aCRT OFF (traditional BiV CRT). Patients who are receiving CRT device without available adaptive CRT feature (i.e. it is impossible to program adaptive software feature ON or OFF) per their clinical team (post-screening) will be placed into a third, non-randomized, non-blinded CRT registry arm. Study participants will undergo cardiac MRI and ECGi before device implantation. A second ECGi will be performed within two weeks hours after CRT implantation. Duration of assigned intervention is 6 months. At least 6-month post CRT (within 30-day interval) participants will undergo a 3rd ECGi and echocardiogram. There are ***2 primary outcomes*** in this study: (1) regression slope of Electrical Dyssynchrony Index values measured by ECGi 6 months post-CRT, regressed against Electrical Dyssynchrony Index values measured by ECGi prior CRT; (2) difference in regression slopes of SAI QRST against Electrical Dyssynchrony Index values measured by ECGi vs. QRS duration against Electrical Dyssynchrony Index (EDI) values measured by ECGi.

Background and Justification

Cardiac resynchronization therapy prolongs life and decreases risk of heart failure exacerbation in patients with low ejection fraction (EF) and wide QRS.[6-9] Aging population with high prevalence of obesity, diabetes and hypertension, along with advancements in the treatment of acute cardiovascular diseases resulted in an increase in the incidence and prevalence of the heart failure (HF) over the past decades. Studies estimate that about 2-3% of the population suffer from HF. Despite advances in therapy and management, HF carries substantial morbidity and mortality, and high rates of hospitalizations and hospital readmissions represent large burden to the health-care system. CRT is an effective treatment for patients with HF, wide QRS, and reduced EF. However, about 30% of CRT recipients do not demonstrate mechanical response on CRT.

QRS duration and LBBB serve as criteria for favorable response to CRT. QRS duration served as a main ECG criterion for assessment of electrical dyssynchrony. However, QRS duration has limitations and better measure of electrical dyssynchrony is needed. Approach to patients with QRS 120-150 ms is unclear. We recently showed in blinded analysis of SMART AV study (Tereshchenko et al, abstract presented at HRS 2014) that a novel measure of electrical dyssynchrony, sum absolute QRST integral (SAI), better predicts CRT response than QRS duration alone. Patients with the high mean SAI (3rd tertile) have 2.5 times greater odds of response than those with low mean SAI (1st tertile), and 2.0 times greater than the lower two tertiles combined. Trend towards the interaction between SAI and left BBB was observed (P=0.08). The effect size was stronger in the non-LBBB patients. Thus, high SAI QRST was strongly independently (beyond QRS duration) associated with CRT response in the SMART-AV study. However, association of SAI QRST with a gold standard of LV electrical dydssynchrony (ECGi EDI) has not been tested in a prospective study, and SAI QRST was not compared with QRS duration.

Adaptive CRT is a device-based algorithm that regularly measures the intrinsic conduction intervals that result in continuous optimization of AV and VV delays, and promote synchronized LV pacing[1, 10]. Synchronized LV pacing is a CRT pacing configuration that times the LV pacing with intrinsic RV conduction[11, 12]. It is known that the RV pacing, alone or during BiV pacing, in patients with LV systolic dysfunction worsens LV and RV performance[13]. As was previously reported in GREATER-EARTH study, there was 17% improvement of CRT response by switching from BiV pacing non-responders to LV pacing[14]. Randomized aCRT clinical trial showed that aCRT improves the LV performance and clinical CRT response, and demonstrated superiority of aCRT as compared to echo-optimized BiV pacing[1]. Subsequent analysis of aCRT trial showed that a higher percentage of synchronized LV pacing in the aCRT trial was associated with a decreased risk of mortality and HF hospitalizations[12], with Kaplan-Meier curves starting separation after first 6 months of CRT.

However, mechanistic differences in aCRT effect are incompletely understood, and the population of patients, who would benefit from aCRT the most, is not very well defined. The following knowledge gaps remain and will be addressed in the proposed study.

1. Post-hoc analysis of aCRT trial[12] showed superiority of aCRT in a subgroup of patients with normal intrinsic AV interval at randomization, defined by the device as the interval from the right atrial (RA) activation to the right ventricular (RV) intrinsic activation ≤ 200ms if in sinus rhythm or ≤ 250 ms if in atrial pacing. However, this finding was not replicated in a prospective study, and mechanisms are not completely understood. Currently the best correlate to RA-RV activation time on surface ECG is unknown. It is unknown if PR interval on the surface ECG (or another surface ECG parameter) could predict the response to aCRT, as compared to response on traditional BiV CRT. At the same time, presence of an interaction between PR interval and CRT was shown by several other studies. Recent post-hoc analysis of MADIT-CRT[15] showed that patients with a long PR interval (and non-LBBB) obtained the largest benefit from BiV CRT, whereas patients with normal PR interval (and non-LBBB) did not respond on BiV CRT. This data confirms presence of an interaction of CRT with PR interval. Mechanisms behind such an interaction are not entirely clear, and will be addressed by the proposed study.
2. Few conducted observational ECGi studies[16, 17] showed presence of significant variations in electrical dyssynchrony substrate. Proposed study is the first randomized clinical trial with ECGi-measured electrical dyssynchrony index as an outcome. Proposed study will help to explain results of previously conducted CRT trials and will demonstrate effect of aCRT on electrical dyssynchrony substrate, characterized by ECGi.
3. aCRT trial was conducted in patients who underwent echo-optimization of AV delay. However, echo-optimization of AV delay is not routinely used in clinical practice[18]. SMART-AV study[19] did not show difference in outcomes of echo-optimized and fixed AV delay (120 ms). Proposed study will compare nominal programming without AV optimization to aCRT.

Study Objectives

Primary Objective(s)

1. To determine if aCRT is superior to standard CRT, as evidenced by a superior degree of reduction of electrical dyssynchrony index 6-month post-CRT. An Intra-LV electrical dyssynchrony index will be computed from the electrocardiographic imaging (ECGi) LV epicardial activation maps as the difference & standard deviation of activation times at 352/700 sites on the LV epicardium, including the epicardial aspect of the septum. **Outcome measured**: Change in EDI from baseline to 6-mo post CRT.
2. To determine if a surface ECG metric sum absolute QRST integral (SAI QRST) is a superior estimate of an intra-LV dyssynchrony, as compared to QRS duration. **Outcome measured**: Regression slope of SAI QRST against EDI value and regression slope of QRS duration against EDI value

Secondary Objective(s)

1. To determine if the interval between the end of P-wave and the onset of QRS complex in lead V1 (PeR_{V1}) is associated with intracardiac RA-RV activation time. **Outcome measured:** AVinterval from EGM and PR interval in ECG
2. To determine if aCRT is associated with the development of reverse electrical remodeling (defined as shrinking of non-paced QRS duration above or equal 10 ms at least 6-months post-CRT), and development of mechanical response, defined as a decrease in left ventricular end-systolic volume ≥ 15mls after 6 months of CRT. **Outcome measured:** non-paced QRS duration from ECG and left ventricular end-systolic volume from echo.
3. To determine if aCRT is associated with improvement of the quality of life and adverse events, and other clinically important outcomes. **Outcome measured:** questionnaire scores, hospitalizations, death, device removal/complications, NYHA classification, and 6 minute walk scores.
4. To determine if spatial QRS-T angle and QRS & T loops derived from intracardiac EGMs, correlate with spatial QRS-T angle and QRS & T loops derived from orthogonal ECG (transformed from recorded 12-lead ECG). **Outcome measured:** QRS-T angle and loop values from ECG and EGM.

Device and intended use:

All study participants will receive the commercially available Medtronic Viva™ XT CRT-D Model DTBA1D4, DTBA1D1, Viva™ Quad XT CRT-D Model DTBA1Q1, DTBA1QQ, Viva™ Quad S CRT-D Model DTBB1Q1, DTBB1QQ, Viva™ S CRT-D Model DTBB1D1, DTBB1D4 or Viva™ XT CRT-P Model C6TR01 and three leads (one right atrial, one right ventricular, and one left ventricular lead), implanted as clinically indicated, as part of routine medical care.

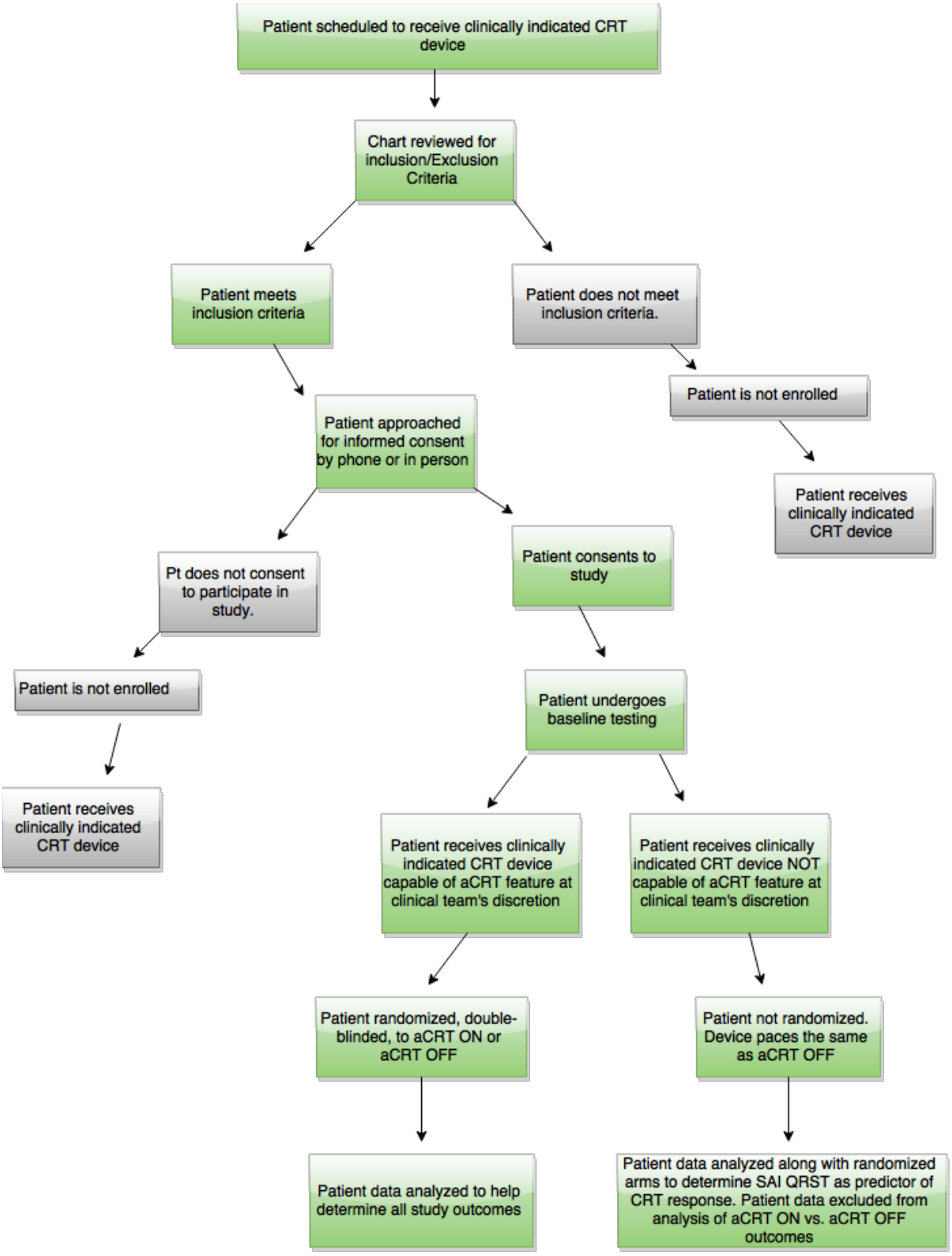
Methodology

Study Design

We will conduct an investigator-initiated prospective, single-center, randomized, double-blind paralleled controlled clinical trial comparing adaptive cardiac resynchronization therapy (aCRT)[1] to standard CRT in patients with currently approved (class I-II) indications for CRT[2]. Following verification that inclusion/exclusion criteria are met, all patients will undergo baseline evaluation/testing. All study participants will receive the commercially available Medtronic Viva™ XT CRT-D Model DTBA1D4, DTBA1D1, Viva™ Quad XT CRT-D Model DTBA1Q1, DTBA1QQ, Viva™ Quad S CRT-D Model DTBB1Q1, DTBB1QQ, Viva™ S CRT-D Model DTBB1D1, DTBB1D4 or Viva™ XT CRT-P Model C6TR01. These devices are already used in standard-of-care for patients receiving CRT implantations. No co-investigators will be paid by Medtronic funding for use of these devices. Following successful implantation, ECG/EGM recording and device programming will be performed according to the protocol and participants will be randomized to either the aCRT ON or the aCRT OFF pacing arm. Should implantation or randomization not be successful, patients will be followed as defined in further sections. Protocol-required 6-month follow-up visit will occur at least 6 months post randomization (within 30-days window). Patients will remain randomized in the assigned therapy arm until 6-month follow-up visit. After that, no study visits is planned. Follow-up will continue during next 5 years remotely (via phone, remote follow-up, RedCap surveys).

Study Schema

Subject Selection



Number of patients: The study will require up to 16 patients randomized to one of two pacing therapy arms (up to 32 patients enrolled).

Patients of both genders with mild to moderate heart failure who meet all inclusion/exclusion criteria are eligible for this study. Listed below are the specific inclusion and exclusion criteria:

Inclusion criteria:

- Patient has a standard class I or class II indications for CRT-P or CRT-D implantation in accordance with ACC/AHA/HRS guidelines (2012 ACCF/AHA/HRS Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities)[2].At least 18 years of age at the time of consent
- Is willing and able to comply with the protocol

Exclusion criteria:

- Chronic atrial arrhythmias defined as: “Atrial fibrillation is permanent when it has resisted all attempts to restore sinus rhythm or when the physician and patient decide that no such attempt should be made.”
- Patient has ever had a previous or has an existing CRT system, ICD, or pacemaker that has PACED the patient the majority of the time.
- GFR <30ml/min
- Patient has had unstable angina, acute myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty within 30 days prior to study enrollment
- Patient has primary valvular disease and is indicated for valve repair or replacement
- Patient is enrolled in ≥1 concurrent studies that would confound the study results (any other interventional trial)
- Patient is pregnant or of childbearing potential and not on a reliable form of birth control. All women of child-bearing potential must undergo a pregnancy test.
- Patient status post heart transplant
- Patient has been classified as NYHA functional class IV within 3 months prior to study enrollment
- Concomitant conditions other than cardiac diseases that were associated with a higher likelihood of death during 1 year after enrollment
- Patient, legal guardian or authorized representative is unable or unwilling to cooperate or give written informed consent

System Description

All study participants will receive the commercially available, clinically indicated (no study expense) Medtronic Viva™ XT CRT-D Model DTBA1D4, DTBA1D1, Viva™ Quad XT CRT-D Model DTBA1Q1, DTBA1QQ, Viva™ Quad S CRT-D Model DTBB1Q1,

DTBB1QQ, Viva™ S CRT-D Model DTBB1D1, DTBB1D4 or Viva™ XT CRT-P Model C6TR01.

Study Procedures

Informed Consent Process

Study protocol will be reviewed and approved by the OHSU IRB before the beginning of the enrollment in the study. All study participants will sign consent form before entering the study. We will request IRB to give us permission (via a Prep to Research form) to review medical records of study candidates for inclusion/exclusion criteria. This information will not be recorded. The research study coordinator will screen the OHSU Arrhythmia and Heart Rhythm Clinic schedule through Epic for patients who may be candidates for CRT and will contact the care provider to discuss if patient is a candidate. Patients, who have approved class I-II indications for CRT-D or CRT-P according to current guidelines, who are scheduled for Medtronic CRT-D or CRT-P device implantation will be approached in the clinic at the time of scheduling for CRT implantation. At this point the study and informed consent form will be explained to the patients. These patients who are willing and able to sign the consent form will be invited to participate in the study and a baseline enrollment visit will be scheduled. Final determination of eligibility will be made during the initial visit and scheduled baseline study visit. After signing consent form eligible study candidate will become study participant.

Randomization

Assignment of patients into aCRT on or off will occur through the randomization module in REDCap. Only the study coordinator and primary investigator will have access to view patient treatment assignments on the REDCap database. The following information outlines the randomization module implemented via REDCap.

The unit of randomization: a person (study participant).
The type of randomization: random stratified block
Assignment ratio: 1:1
Assignment strata: (1) gender (male vs female); (2) cardiomyopathy type (ischemic vs. non-ischemic).
Block size: random (2, 4, or 6) with allocation proportional to the elements of Pascal's triangle.
Random seed used and the randomization list were created using the –ralloc- program in Stata version 13.1

Randomization will be enacted via an envelope-based system, via sealed envelopes containing randomization assignments. Random treatment assignments will be placed in advance in a set of sealed envelopes. Each envelope will be numbered (#1-32),

opaque, and otherwise tamperproof. When a participant is randomized, **his/her name and the number of the next unopened envelope are first recorded in the presence of a second staff member and both sign the envelope**. Then the envelope is opened, and the treatment group contained therein assigned to the participant and recorded on a log.

Study participants who, because of clinical reasons per clinical team decision, will receive a CRT device without the adaptive software feature enabled will NOT be randomized, but instead, will be included in the study registry arm.

Blinding, or Masking

In order to minimize the introduction of bias, this study will be double-blinded (double-mask). Patients will not have access to their randomization assignment. To obtain non-biased information and perform non-biased assessments, physicians and their staff who will evaluate NYHA classification and heart failure stage, and administer the Minnesota Living with Heart Failure Questionnaire, and Patient Global Assessment tools will be masked to the patient's assignment and device programming. Un-masked physicians and staff will be responsible for randomization, programming the system, monitoring the system performance, and collecting system data for this study. Study personnel will be trained to take special care to ensure that patients do not inadvertently learn of their assignment as a result of communication with their care provider. A log will be maintained to identify staff that will remain blinded to the randomization assignment and programming.

Data Collection

For patients that meet all inclusion/exclusion criteria, are enrolled in the study, clinical data will be collected for patient history, implant, pre- and post-implant baseline evaluation/testing, randomization, protocol-required scheduled follow-up visit, remote follow-up visits, system modification and study exit (including death) until study closure (5 years). Hospitalizations and adverse events (including adverse event-related emergency department and urgent care visits) will be reported until the patient exits the study or study closure.

All data will be entered in the digital secure web-based database (REDCap Consortium partner http://www.project-redcap.org/).

Data collection requirements are summarized in Table 1.

Subject Follow-Up Schedule

During the first year of the study, first follow-up visit will be made at least 6 months after CRT-D implantation (within 30-day range). After the six-month follow-up visit, follow-up via phone call, REDCap surveys, or data collection from routine clinic visits will be scheduled at 12 months, 24-, 36-, 48-, 60-months post-CRT implantation. Follow-up after six months will be optional based on patient availability.

Table 1. ***Overview of Data Collection for the aCRT ELSYNC Study***

Study procedure	Before device implantation	During first two weeks after device implantation	Study F/U Visit #1 – 6-month post-CRT	Remote F/U via phone call/ ReDCap survey/ remote device F/U/ medical chart review once a year up to 5 years post-implant
Enrollment	X			
Randomization	X			
Medical History	X			
Cardiovascular medications recorded	X	x	X	X
Lead position imaging		X		
NYHA functional classification recorded	X		X	X
MLHFQ and SF-36	X		X	X
Venipuncture	X		X	
Cardiac MRI or cCT	X			
Body surface mapping (ECGi)	X	X	X	
Kinect-sensors ECG leads position registration/placement	X	X	X	
Digital intracardiac EGMs and ECG recording ON RVP, LVP, BiVP		X	X	
Digital intracardiac EGMs and ECG recording in sinus rhythm (OFF pacing)	X	X	X	
Echocardiogram			X	
Digital resting 12-lead ECG (10-sec)	X	X	X	
Holter ECG during 6-min walk	X		X	
Central venous pressure (CVP) non-invasively by Mespere Venis 1000	X	X	X	
Hospitalizations, death, adverse events or updates		X	X	X

Cardiovascular medications will be collected at patient history and required scheduled follow-up visits. Current cardiovascular medications and dosages must be reported at each required scheduled follow-up visit. The dose reported should reflect the dosage that the patient is on at the end of the visit. If a medication is not given daily, the average daily dose over a seven-day period should be calculated and recorded.

Lead position imaging. After CRT implantation, biplane fluoroscopy in orthogonal views (left anterior oblique [LAO] 60° and right anterior oblique [RAO] 30°) will be performed, as well as traditional AP and lateral views.

The Minnesota Living with Heart Failure Questionnaire and SF-36 Questionnaire will be completed. Every effort should be made to have the patient complete the questionnaire himself or herself. However, blinded study personnel may administer the questionnaire if necessary. The name(s) of blinded personnel administering/overseeing completion of this form must be documented in the patient's medical record.

cCT data acquisition and analysis
Patients with a contraindication to MRI due to personal preference (i.e. severe claustrophobia), body size too large for the MRI bore or medical reasons such as presence of a medical device (pacemaker or ICD not pacing the patient the majority of the time) will undergo a prospective cardiac computed tomography (cCT) scan rather than MRI. cCT will be performed at OHSU.

CMR data acquisition and analysis by tissue tracking

Cardiac research MRI will be performed at OHSU.

Enrolled participants will undergo CMR using 1.5T whole body MRI scanners (Avanto; Siemens Medical Systems, Erlangen, Germany) on the same day as the ECG and ECGi recordings.

Clinical echocardiography laboratory at OHSU will analyze the echo images obtained. A handbook detailing instructions for imaging and data acquisition will be provided to the echocardiographers performing the examinations. Traditional assessment of LV structure and function will be performed.
Echocardiogram performed for clinical indications before CRT-D implantation will serve as baseline echocardiogram.

Cardiovascular medications currently being taken by each subject will be recorded at the baseline visit. Changes in medications will be recorded over the course of the study.

NYHA Classification will be evaluated as part of standard of care by the care provider. This will be recorded at baseline, 6-month follow-up, and subsequent follow-up dates.

The study participant will have Holter ECG monitoring that will record for 30 minutes. 6 Minute Walk Test: The 6MWT will be performed in the hospital where

emergency equipment and personnel are readily available. An indoor walking course of 150 feet in length has been identified A starting line, designating the beginning and end will be marked. The test will be stopped for severe dyspnea, staggering, ashen appearance, or significant chest discomfort. The patient will be instructed on the performance of the test according to the ATS statement: Guidelines for the Six-Minute Walk Test. At the beginning of the test, vital signs will be recorded. The 10-point Borg rating of perceived exertion will also be recorded to measure the individual's baseline dyspnea, and overall fatigue will also be recorded [0=nothing at all; 10=Very, very severe (maximal)]. A timer for 6 minutes will be set. The subject will walk as far as possible for six minutes, back and forth along the 150- foot hallway. The subject will be told every minute how much time remains. Following 6 minutes, vital signs and the post-walk Borg dyspnea and fatigue levels will be assessed. The distance covered in meters/feet will be recorded. Blood pressure and heart rate will be measured after lying supine for 10 minutes, then after 2 minutes after standing up.

Pregnancy test
If a woman is of childbearing age, urine HCG will be sent to obtain pregnancy status before MRI is performed. MRI with contrast will not be performed on a pregnant woman.

ECG: Standard 12 Lead ECG, Signal Average ECG, and Vectocardiogram. Body surface mapping. High resolution (1000 Hz) 12-lead ECG will be recorded during 10 min at rest (via Mortara Holter recorder) in the supine position and in standing the position, and during 6-min walk test.

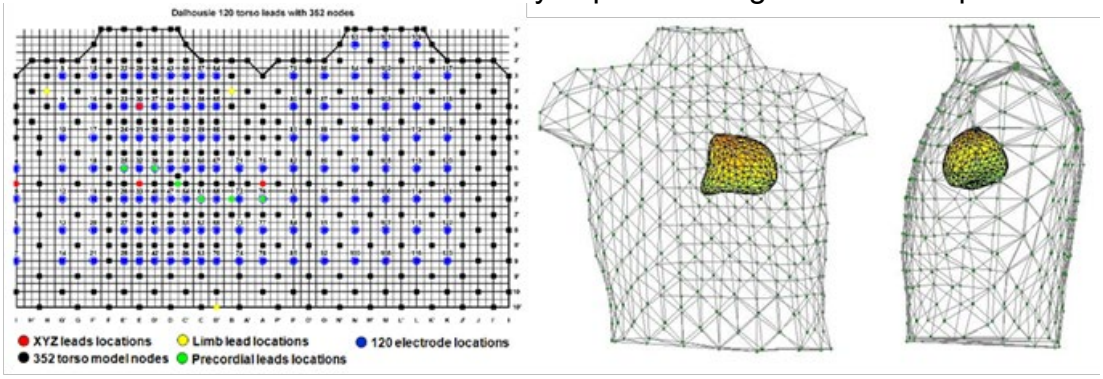
Kinect-sensors ECG leads position registration/placement will be used in order to ensure placement of body surface ECG electrodes at the same location at 6 month post-CRT visit, as it was at the baseline. We will collaborate with Peter van Dam (*Peacs (Arnhem, the Netherlands) and will use his Kinect software. He* developed 3D Kinect Camera software integrated into CIPS that localizes the ECG electrodes. He recently demonstrated the reproducibility of the registration of the 3D image with the MRI derived torso models, by using his custom software. The CIPS software that integrates and registers the 3D camera image of the electrodes to the MRI derived torso model is reproducible. The 3D camera is critical for quantitative localization of electrode positions for CIPS to accurately localize the position of the electrodes to the cardiac anatomy as imaged with a 3D camera. We will use subcontract with Dr. van Dam for the use of his software and training. We will use this approach for recording of ECGi data within two weeks after CRT implantation (to test accuracy of leads placement at the time when heart has not been remodeled yet post-CRT). We will repeat the same procedure at 6-month post-CRT.

Simultaneous Recording of intracardiac EGMs and 12-lead surface ECG will be performed within two weeks after device implantation, before discharge, and at 6-month follow-up visit.

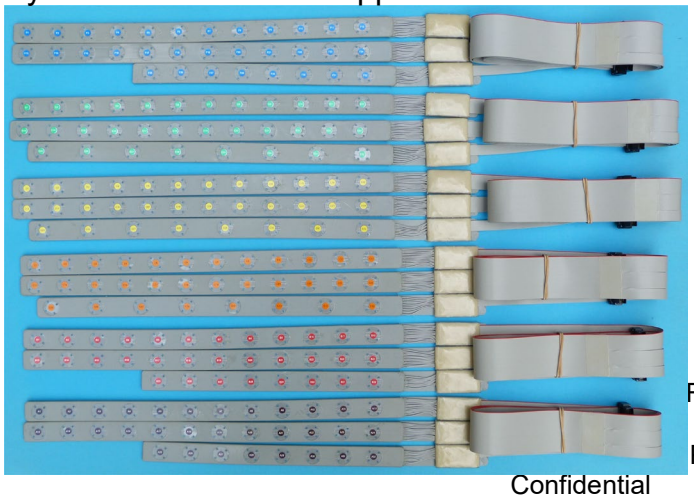
Intracardiac digital EGMs will be recorded via programmer and NI digitizer (NI USB-9215A portable data acquisition [DAQ] system).
EGMs will be recorded according to the following protocol:
Intrinsic rhythm (pacing OFF)
RV pacing
LV pacing
BiV pacing
All available configurations of electrograms will be recorded.

During the follow-up, CRT-D device will be interrogated, and all events with stored EGMs will be saved to disk, and then translated with translational utility and further analyzed.

Electrocardiographic imaging (ECGi) is a novel non-invasive advanced technique, characterizing activation and recovery of electrical activity on the epicardial surface of the heart. A patient-specific heart-torso model derived from cardiac CT or MRI with 291 heart-surface nodes will be used to perform ECGI inverse solution. Figure below illustrates ECGI procedure. Recoding of ECGI essentially does not differ from recording of routine surface electrocardiogram. Surface ECG is recorded in multiple points (133) on the torso. ECG body surface mapping will be performed immediately before cardiac MRI so that attached electrodes will stay in place during MRI data acquisition..

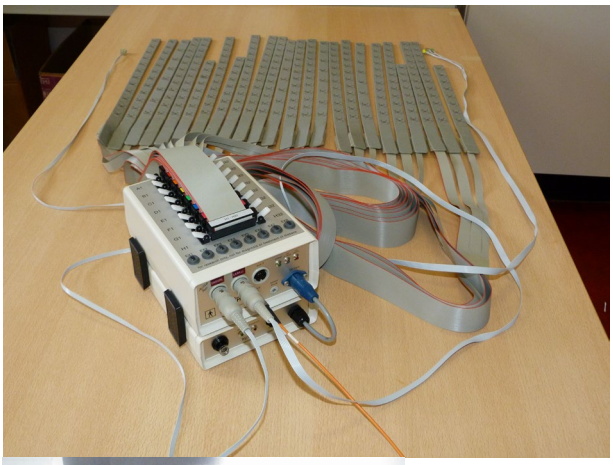


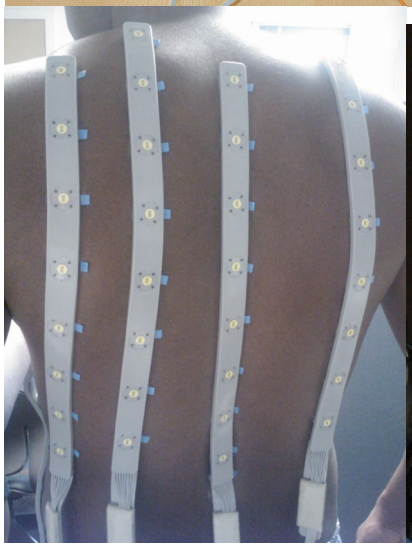
Tereshchenko laboratory recently purchased new Active Two Biosemi ECGI system. System and electrodes application is illustrated by the figures below.

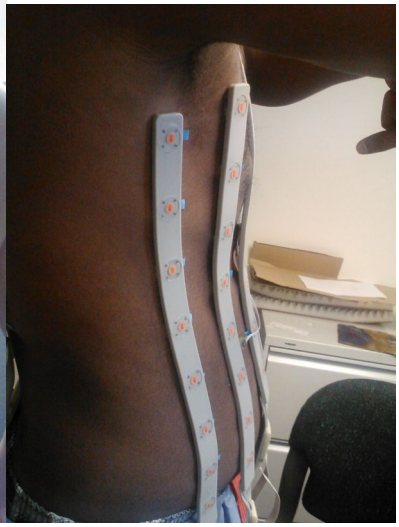


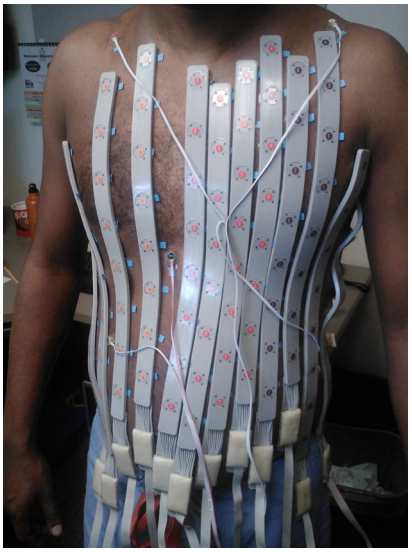
RT effect (ELDYSME aCRT)

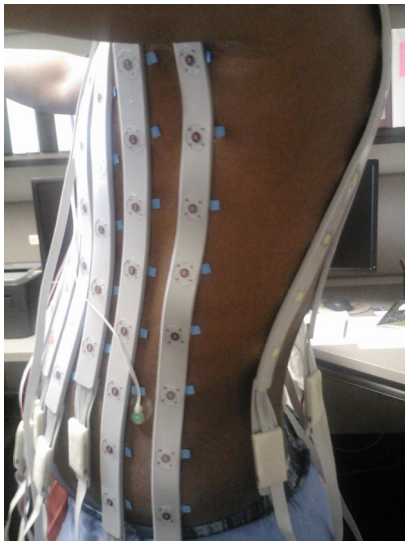
Plan











Postdoctoral fellow of PI (Dr. Muammar Kabir, BME PhD) recently completed 2-week Image-based modeling course at the University of Utah. http://ibbm.sci.utah.edu/
The electrical dyssynchrony index (EDI) is computed as the standard deviation of activation times at 350/700 sites on the LV epicardium.

ECGI will be performed 3 times: first before CRT implantation. Second time – within two weeks post-CRT implantation. Third time – 6 months post-CRT. ECGi will be will be recorded according the following protocol:

- Pacing OFF, in intrinsic rhythm
- During BiV pacing
- During RV pacing
- During LV pacing

At the end of the study de-identified digital data (intracardiac EGMs, ECGI and imaging data) will be provided to Medtronic.

Questionnaires (SF-36 and MLHFQ). Patients will be asked to fill 2 questionnaires: SF-36 and Minnesota Living with Heart Failure Questionnaire (MLHFQ) for assessment of quality of life.

Follow-up

Follow-up in office visit at 6 months of CRT – for assessment of reverse mechanical and electrical remodeling. Follow-up visit will be scheduled as special study visit, additional and separate from routine clinical follow-up visit. Study follow-up visit will be scheduled at 6 months of CRT. Intracardiac digital EGMs will be recorded via programmer and NI digitizer (NI USB-9215A portable data acquisition [DAQ] system) at rest simultaneously

with 12-leads and orthogonal ECG during bi-ventricular pacing ON (5 min) and OFF (during 10 min). CRT-D device will be interrogated, and all events with stored EGMs will be then translated with translational utility and further analyzed. Echocardiogram will be performed and fully analyzed to assess mechanical response to CRT after 6 months of CRT.

After that, at 12-month post CRT, and then during 5 years once a year – phone call F/U (collection of the history of hospitalizations, ICD shocks, death), RedCap surveys, remote device follow-up

Study Exit/Withdrawal

Terms under which subjects can/will be exited

- Subject death
- Subject lost to follow-up
- Subject no longer able to perform study follow-up procedures, or unwilling to continue follow-up and withdraw study consent.
- Subject becomes pregnant before cardiac MRI procedure.

Statistical Methods and Data Analysis

Primary Outcome: There are ***2 primary outcomes*** in this study: (1) regression slope of Electrical Dyssynchrony Index values measured by ECGi 6 months post-CRT, regressed against Electrical Dyssynchrony Index values measured by ECGi prior CRT; Only randomized patients (treatment arm adaptive CRT, and control arm regular CRT) will be included in this analysis. (2) difference in regression slopes of SAI QRST against Electrical Dyssynchrony Index values measured by ECGi vs. QRS duration against Electrical Dyssynchrony Index (EDI) values measured by ECGi. All study participants (randomized two arms, and non-randomized registry arm) will be included in this analysis.

Main analysis: linear regression

Predictors:
Electrical Dyssynchrony Index The electrical dyssynchrony index (EDI) is computed as the standard deviation of activation times at 350/700 sites on the LV epicardium.
SAI QRST
QRS duration

The proposed predictors as variables of interest will be measured as continuous variables and could be dichotomized or divided by quartiles. The distribution of variables of interest will be defined, and Log transformation (or other transformation, if required, depending on the particular case) will be performed for any variable that displays non-normal distribution, with subsequent verification of an achieved normal distribution. Simple and multiple linear regression models will be explored to determine factors that may play the role of predictors of our tested marker of interest, presented as a normally distributed continuous variable. For such linear regression models, the tested marker will be an outcome variable.

Results will be presented as mean ± standard deviation (SD) for normally distributed variables, and as median and inter-quartile range for non-normally distributed variables. Continuous variables will be compared using the independent samples *t* test if normally distributed and the Wilcoxon rank sum test if skewed. The Pearson chi-square test will be used to compare categorical variables. A *p*-value of <0.05 will be considered significant.

Justification for Sample Size

We are planning a study with 15 experimental subjects and 15 controls in which we will regress values of Electrical Dyssynchrony Index values measured by ECGI 6 months post-CRT against Electrical Dyssynchrony Index values measured by ECGI prior CRT within each treatment group. Prior data[17] (Ghosh et al, 2911) indicate that the standard deviation of Electrical Dyssynchrony Index is 3.9 and 2.3 in the responders and non-responders, respectively. We conservatively assumed that the standard deviation of the

regression errors will be 0.08. If the true difference in the slopes of these 2 regression lines is 0.05, we will be able to reject the null hypothesis that these slopes are equal with probability (power) 0.954. The Type I error probability associated with this test of this null hypothesis is 0.05. Figure 1 below illustrates the difference in statistical power as a function of sample size and the difference in regression slopes (λ2 –λ1) that we wish to detect. Therefore, estimated sample size is 30 study participants (15 in experimental aCRT arm, and 15 in control arm). After adjustment of the sample size for a loss of follow-up (+ 6%) estimated sample size is 32 participants (16 in in experimental aCRT arm, and 15 in control arm).

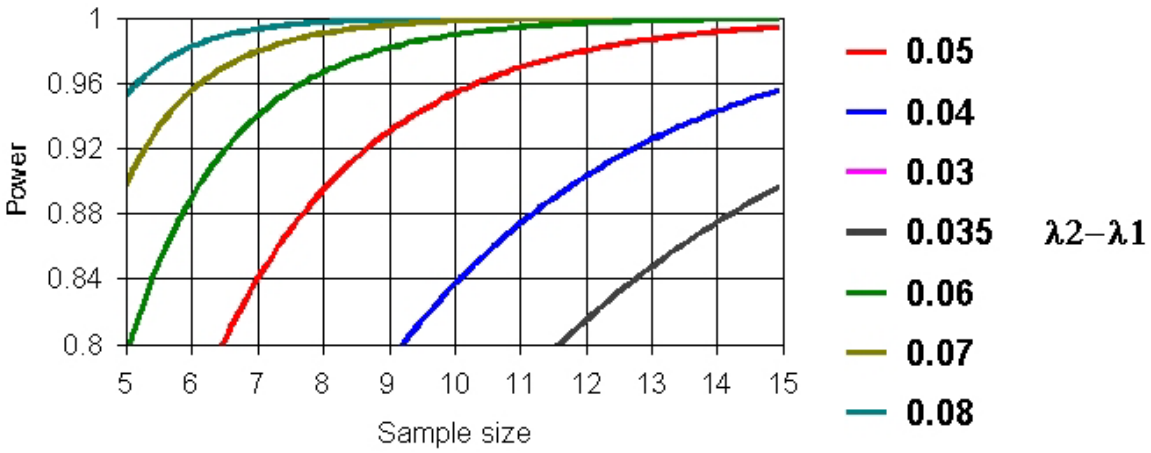


Figure 1. Statistical power estimation as a function of sample size of aCRT arm for a range of the differences in the slopes of the regression lines for the experimental and control groups that we wish to detect (shown by different colors).

Risk Analysis

Potential Risks

This is a randomized clinical trial of 2 FDA-approved CRT strategies. Patients will receive commercially available FDA-approved device. There is no incremental risk of health for study participants.

Very low risk of confidentiality loss always exists in any clinical research. All efforts will be made to keep confidentiality. Patient will be notified immediately if any unforeseen breach in confidentiality occurs (e.g. stolen computer). Safeguards will be in place to protect the identity of the patients and their private health information. Study ID will be assigned by the study coordinator, and all following collected data will be connected with this study ID, but not with the name of the patient. Private health information connected with patient's name will be locked in a secure location in the office, and limited number of people will have access to it (PI and study coordinator).

MRI with IV Contrast: The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. Patients will not be allowed to participate if they have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. Gadolinium contrast will be administered, which is FDA-approved and used routinely for MRI exams. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly. There is a small risk of an allergic reaction to gadolinium; however, severe allergic reaction occurs in less than one in 300,000 people. Pregnant women have higher risk of complications with MRI and will be excluded from this study.
Insertion of the needle to give gadolinium may cause minor pain, bruising and/or infection at the injection site. People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). Patients with severe kidney failure that receive gadolinium have a risk of developing NSF/NFD of 1-5 %. Patients with severe kidney disease, measured by GFR <30ml/min will not be allowed to participate.
Patients with a prior history of being a machinist, welder, metal worker, or similar activity that poses the potential risk of metal exposure to the eyes, will be asked to undergo screening orbit x-rays to rule out the presence of metal fragments. The amount of radiation exposure from the required series of skull x-rays is approximately 0.01 rems.
Six Minute Walk Test: Six-minute walk tests pose no more risk than a subject would experience walking down the street. Should there be any cardiac symptoms while walking, the test will be stopped, and the participant allowed to rest.
ECG/ECGi: There is a low risk that mild skin irritation may occur from the electrode patches used to obtain an electrocardiogram (ECG body surface mapping).

CT Scan: Although the amount of radiation the patients will be exposed to is higher than from a typical x-ray, the risk of harmful effects from a single exam is very small.
Intravenous Radiocontrast Agent Omnipaque 350 and Oral Beta Blocker*:* Most people do not experience side effects or complications; however, out of more than 73,000 patient studied[25], Mild to moderate reactions - defined as reactions that either require no therapy or if therapy is given and patient is sent home from the radiology department - occur in 0.2% of cases. Severe reactions that necessitate intravascular epinephrine use in the emergency room or urgent therapy and follow up in the ER or hospital admission occur in 0.016% of cases. The risk of death is 1/100,000 patients[25]. Potential side effects of non-ionic Iodinated contrast that can cause adverse reactions include: Death (1/100,000 persons), sneezing and nasal congestion, hives, itching, rash, and swelling; laryngeal (oral) edema; bronchospasm; and anaphylaxis, rigors (shaking, chills, fever); seizure; numbness; malaise and achiness; pulmonary edema; chest pain; and hypertension[25].

The radiocontrast agent given along with saline intravenously during cardiac CT will be Omnipaque 350 iodinated contrast unless the decision is made by radiology staff to substitute a different FDA-approved iodinated contrast agent.

A Beta blocker, Metoprolol, is often given before undergoing CT scans. The patient's clinical staff providing care and/or the radiologist at the diagnostic imaging department at the time of the scan will determine whether administration of a beta blocker is necessary before CT scan and will not be administered to a patient if a contraindication exists.

Needle Insertion

Insertion of the needle to administer contrast may cause minor pain, bruising and/or infection at the injection site.

Risk Minimization

All efforts will be made to keep confidentiality. Safeguards will be in place to protect the identity of the patients and their private health information. Study ID will be assigned by the study coordinator, and all following collected data will be connected with this study ID, but not with the name of the patient. Private health information connected with patient's name will be locked in a secure location in the office, and limited number of people will have access to it (PI and study coordinator).

IVs and or blood draws will be performed by trained research coordinators using good clinical practice and standard aseptic technique.

Gadolinium administration:

Patients with renal insufficiency with GFR <30ml/min and pregnant women will be excluded to minimize any risks associated with gadolinium administration for the contrast-enhanced MRI. A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

MRI examination:

No one will be allowed to enter the magnet room when a patient is in the magnet room unless they are involved in the study. No one will be allowed to bring magnetic metal objects near the magnet when other persons are in or near the magnet. The magnet room will be kept closed during the study, and will be opened only by the technologist at the end of the study. Individuals with metal implants and fillings are excluded from the study as described in the exclusion criteria. Patients will be asked to leave magnetic metal objects outside the magnet room, and patients will be required to fill out a questionnaire regarding MR safety and the presence of metal objects in their bodies. Care will be taken to limit the RF power deposition and gradient rise times to well within FDA guidelines. The MRI scanner's software contains safeguards to prevent both excessive RF power and above-threshold gradient changes. The operating technologist will be in voice contact with the patient, and the patient will be told that he/she can contact the operator at any time with a request to be taken out of the magnet. All subjects will be carefully screened for the presence of any contraindications prior to them signing the consent form.

Six Minute Walk Test:

CPR certified personnel will accompany the participant and access to emergency equipment will be available. The participants' vital signs will be monitored before and after the six minute test.

Psychological risk:

The psychological risk of participating in the study may be a transient increase in worry about potential disease. Subjects will be given the opportunity to ask questions of study personnel on this topic. The study coordinators and investigators have extensive experience working with patients with these diseases.

Pregnant women:

Most women included in this study will not be of child-bearing potential (post-menopausal). Women of child-bearing potential who are not on reliable birth control (as assessed by physician) will have a urine HCG test done to obtain pregnancy status before MRI is performed. MRI with contrast will not be performed on a pregnant woman. If participants become pregnant over the course of the study, they will be asked to notify their physician immediately. If patients who become pregnant have already completed the cardiac MRI, they will be maintained as study participants, otherwise they will be excluded. There is no additional risk of CRT to pregnant women.

cCT examination:

Cardiac CT will be acquired using a prospective scan. Total effective dose is 3-4mSv, the equivalent of 7.5-10 mammograms.[26] Patients will complete both the "Cardiac CT Screening Form" and "Patient Contrast Questionnaire and Procedure Record" prior to undergoing scanning. These two forms are standard procedure in the OHSU diagnostic radiology department prior to CT scanning with contrast. The OHSU diagnostic radiology department will review both forms before scanning.

IVs and or Blood Draws

All IVs and/or Blood Draws will be performed by trained research coordinators or clinical staff using standard OHSU clinical practice and standard aseptic technique.

CT Contrast administration - GFR:

Patients with renal insufficiency with GFR <30ml/min and pregnant women will be excluded to minimize any risks associated with contrast administration for the contrast-enhanced CT. A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the contrast should be stopped.

A GFR test will be ordered and paid for by the study team in the event of any of the qualifying criteria below exist in an enrolled subject. The patient will complete the test according to the following timeline per criteria based off Policy # 300.02 in the OHSU Diagnostic Radiology manual.

1)Creatinine/eGFR required within 30 days of CT scan:
Patients >60 years of age
Patients with a history of hypertension requiring medication
Patients with diabetes mellitus

Patients with kidney disease: kidney transplant, single kidney, kidney cancer, kidney surgery

2) Creatinine/eGFR required within 24 hours of CT scan:
Patients whose most recent eGFR<60 and >30
Any patient whose most recent eGFR <30 will be excluded from the study

Plan for reporting unanticipated problems or study deviations.
Data Safety Monitoring Board is monitoring safety of participants and study conduct.
Serious adverse advents will be reported to the IRB

Potential Benefits

There is potential for benefit to the patient since this is the patients' last opportunity to get quality imaging of their heart before CRT implantation. All patients are about to receive a CRT device. CRT devices create immense amounts of artifact on both MRI and CT. Images will be made available to the patients' treating physicians.
This study will advance our understanding of the mechanisms of reverse electrical and mechanical remodeling with aCRT, and will help in identifying appropriate candidates for aCRT.

Appendix: Bibliography

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