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General Study Information

Protocol Title:	Effects of CRT Optimization on LV Mechanical Synchrony, Structure, and Function in CRT Patients as Assessed by Cardiac MR
Short Title:	CRT and MRI
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Overview

Background

Cardiac resynchronization therapy (CRT) has been shown in large multi-center randomized studies to improve symptoms, quality of life, left ventricle (LV) size and function, hospitalization rate, and mortality in selected heart failure (HF) patients with low ejection fraction (EF) and wide QRS. However, ~30% of patients are considered non-responders, and a large but less well-defined number of patients are incomplete-responders. One major reason for non-response is suboptimal CRT programming. There is no well-accepted and proven clinical approach to optimizing CRT programming despite the vast number of publications on this topic. For this reason, the vast majority of CRT patients do not undergo any type of optimization procedure and are left at their standard device settings. We have developed and patented a novel methodology using a multi-lead ECG system for measuring electrical dyssynchrony and generating electrical dyssynchrony maps (EDM) over a wide range of atrio-ventricular (AV) and ventriculo-ventricular (VV) delays. A pilot non-randomized study has shown that CRT optimization using this technology is practical, reproducible, and results in improvements in cardiac function.

The main purpose of the present study is to extend these findings by assessing the acute and chronic effects of CRT optimization on mechanical synchrony, LV regional wall motion and LV structure/function in CRT non-responders or incomplete-responders using cardiac magnetic resonance imaging (CMR). It has previously been challenging to perform CMR in patients with CRT devices due to difficulty with image quality and concern about the effects of CMR on device settings or function. This is no longer the case at Minneapolis Heart Institute (MHI) as a specific protocol has been developed and is in use for assessing cardiac structure, function and dyssynchrony in patients with an implantable CRT device in a safe manner.

CRT non-responders or incomplete-responders will have electrical dyssynchrony maps acquired. They will subsequently have CMR images obtained at 3 different settings to assess the acute effects of CRT: native (CRT off), current baseline CRT setting, and best CRT setting (optimal electrical synchrony). Subjects will be randomized 1:1 to either their baseline setting or the optimized setting. After ~ 6 months subjects will have repeat CMR studies to assess the chronic effects of CRT optimization, and patients randomized to the control arm will crossover and have their device reprogrammed to the optimal. All subjects will follow up ~6 months later with an echocardiogram to further assess chronic effects of CRT optimization. We believe the information gained from this study will help us demonstrate that improvement in LV electrical synchrony using our new methodology translates into improvement in LV mechanical synchrony and LV function both acutely and chronically. This will support the clinical strategy of routine CRT optimization using EDMs for management of this complex and high-risk group of patients.

Primary Objectives

1. Quantify acute differences in LV mechanical synchrony, regional wall motion, and LV function at native (off CRT), baseline, and optimal CRT settings.
2. Determine whether programming at optimal CRT setting results in chronic improvement in LV mechanical synchrony, regional wall motion, and LV structure/function.
3. Correlate changes in electrical synchrony as measured by cardiac resynchronization index (CRI) with changes in LV mechanical synchrony, regional wall motion, and LV function both acutely and chronically.

Secondary Objectives

1. Assess differences in 6 minute hall walk (6MHW) in patients randomized to baseline CRT setting vs optimal CRT setting
2. Assess differences in quality of life (QOL) in patients randomized to baseline CRT setting vs optimal CRT setting

Study Design

This is a prospective, proof-of-concept single-blind pilot study of patients with HF and CRT. Subjects will be recruited for this study from clinics at MHI at United and MHI at Abbott Northwestern. We anticipate enrolling 40 subjects in the present study. Subjects will be blinded to randomization assignment and randomized in 1:1 fashion to experimental and control arms and subsequent control arm cross-over as described below. There will be an interim analysis performed after the first 6 subjects to assess efficacy.

Study Population

Inclusion criteria:

- Currently on standard medical therapy
- CRT device in place for > 4 months
- Non-responder (EF improvement with CRT < 5%) or incomplete responder (EF $\leq$ 40%)
- Suboptimal electrical wavefront fusion at current CRT programming as observed on 12-lead ECG
- LBBB, IVCD, or RV paced underlying QRS complex
- Age $\geq$ 18 years

Exclusion criteria:

- Decompensated heart failure
- RBBB
- Pregnancy or lactation
- History of severe allergic reactions to ECG gels, electrode adhesives, and/or CMR contrast

- Implantation of pacing lead in the his bundle or left bundle branch
- Frequent ventricular ectopy as defined as >10% PVC burden by either device interrogation or Holter monitor, or sustained ventricular tachycardia/ventricular fibrillation
- Uncontrolled atrial fibrillation (HR > 100 bpm)
- Severe kidney disease as defined as glomerular filtration rate (GFR) <30 mL/min
- Patient is enrolled in concurrent research study that would potentially confound the results of this study (noting co-enrollment acceptable if patient is enrolled in registry study)

Study Activities

This study consists of four research visits after subjects provide consent.

Visit 1 – All subjects will undergo baseline assessments, device check, and multi-lead ECG assessment/ generation of EDM(s)

- Medical chart abstraction via CRF includes:
  - Demographics
  - Cardiovascular history
  - CRT device data
  - Imaging (includes values and images from past chest x-rays, cardiac MRI, echocardiograms, fluoroscopic images from CRT implant, CT imaging)
  - Medications
  - Lab values
  - Vital signs
- 6MHW
- QOL will be assessed (KCCQ) and research questionnaire (see Appendix C)
- NYHA classification
- Device Check
- Multi-lead ECG assessment, data collection, and generation of EDM(s)

EDMs will be reviewed by study staff to determine optimal CRT device programming. Randomization of study arm will be determined prior to Visit 2.

Visit 2 – Subjects will return to study site for CMR study and randomization to study arm/ reprogramming of CRT programming. A device nurse will be present to assist in the programming of the device during the CMR study and during the randomization. Subjects will be blinded to device programming throughout duration of the 6 month follow up period. All patients will receive gadolinium contrast during CMR study at Visit 2. Creatinine levels will be drawn prior to admistration of gadolinium contrast to determine renal function and if use of contrast is safe.

- CMR study at the following:
  - Native rhythm (CRT off)
  - Current baseline CRT programming
  - Optimal CRT programming (optimal electrical synchrony)

- Subjects will be randomized 1:1 to either the control arm or experimental arm after completion of CMR study
    - Control arm: Subject randomized to the control arm will remain at their current baseline settings for the next 6 months
    - Experimental arm: Subjects will be programmed to the optimal settings based on the EDM(s) for the next 6 months

Visit 3 – Subjects will return to study site for follow-up CMR study and assessments 6 months after Visit 2. No patients will receive gadolinium contrast during CMR study at Visit 3.

- CMR study at current, randomized programming
- Medical chart abstraction
    - Review chart for interim cardiovascular events and medication changes
    - CRT device data (remote or in-clinic device checks)
    - Imaging (abstraction of interim values and images of chest x-rays, cardiac MRIs, echocardiograms)
- 6MHW
- QOL will be assessed (KCCQ) and research questionnaire (see Appendix C)
- NYHA classification assessment
- Device check and reprogramming: At Visit 3, patients randomized to the control arm will have their device reprogrammed to the optimal programming as determined by the multi-lead ECG assessment at Visit 1. Patients randomized to the experiment arm will remain at the optimal programming implemented at Visit 2.

Both groups will have the optimal programming as determined by the multi-lead ECG assessment at the end of visit 3.

Visit 4 – Subjects will return to study site for an echocardiogram 6 months after Visit 3

- Medical chart abstraction
    - Review chart for interim cardiovascular events and medication changes
    - CRT device data (remote or in-clinic device checks)
    - Imaging (abstraction of interim values and images of chest x-rays, cardiac MRIs, echocardiograms)
- 6MHW
- QOL will be assessed (KCCQ) and research questionnaire (see Appendix C)
- NYHA classification assessment
- Standard of care echocardiogram will be obtained from both study arm subjects to continue to evaluate and monitor chronic response to CRT optimization.
- Standard of care device check (remote or in-clinic)

Subject participation in the study will end after follow-up echocardiogram. CRT programming and management of heart failure will continue under discretion of clinical providers upon completion of the study. Standard 12-lead ECGs will be ordered and collected whenever CRT device programming is altered during the study to ensure most up-to-date ECG is available in the medical record.

Visit Windows:

Visit 2 must be completed within 3 months after Visit 1.

Visit 3 must be completed within 6 months (- 4 weeks/ +12 weeks) after Visit 2.

Visit 4 must be completed within 12 months (- 4 weeks/ +12 weeks) after Visit 3.

Study Duration: The duration of this study for an individual subject can be up to 24 months.

Identification of Potential Participants: Potential participants for this research study will be identified by screening the electronic medical record system (EPIC) from both MHI at United and MHI at Abbott Northwestern to determine eligibility prior to requesting consent and HIPAA authorization from patients. In addition, there are no other practical ways to obtain contact information or appointment schedules in order to reach out to potential subjects or determine when they will be at a study site to approach and gauge interest in this study. Subjects' release of information MRA boxes will be reviewed prior to conducting screening procedures. Subjects who have opted out of this release of information for research or missing MRA will not be screened, and their medical charts will be immediately closed. For this reason, we will be requesting a partial waiver of HIPAA authorization, which will only apply during the screening process. Name, date of birth, MRN, and eligibility criteria will be recorded in a password-protected excel spreadsheet (screening log) housed in the password-protected Allina Health share drive with access granted only to study staff. Patients who are not eligible to participate will remain in the screening list until completion of study, so repeated screening does not occur. Subjects who decline participation will remain in the screening log, and declined participation notes will be added to the screening log and medical record, so these subjects are not contacted or approached again regarding participation in the study. The screening log will be destroyed upon study completion and closure.

Study Recruitment Process: Eligible subjects will be identified by physician referral or screening through the electronic medical record. Qualified study physician will determine whether or not potential subjects satisfy eligibility criteria. Subjects will be contacted either by phone or approached in clinic by study staff to gauge interest in participation. If recruited in one of the enrolling sites' clinics, subjects' privacy will be ensured by having encounters held in a private setting away from non-site staff. If contacted via a telephone encounter (phone interview), the conversation will take place in a room away from non-site staff. A phone script is to be used if patients are contacted by phone. Subjects will be allotted time to ask questions and be given sufficient time to make a decision (up to 30 days) about whether or not they want to participate. Subjects who choose to voluntarily participate in the study will be asked to sign HIPAA authorization and consent prior to the start of any study-related activities. The consent process and subsequent research activities and visits will be documented in the subject's medical chart.

Compensation to Subjects: Subjects will not be paid for their participation.

Electrical Dyssynchrony Mapping

Appendix A provides details of EDM generation and the measurements made from EDMs. Briefly, EDMs are generated using 2 standards, clinical ECG machines with 9 electrodes from

one machine placed anteriorly over the chest and 9 electrodes from another machine placed posteriorly over the upper back. Multiple atrio-ventricular delays (AVD) and ventriculo-ventricular delays (VVD) are tested over the practical range of programmable settings with 20 ms steps between settings. A butterfly plot of the 18 electrograms for a single beat is generated, and the area under the curves (AUC) of multiple pairs of anterior and posterior electrograms is quantified using a proprietary algorithm. Cardiac resynchronization index (CRI) is calculated as the absolute value of the percent change in AUC at any given setting as compared to native. CRI values at each setting are plotted on a color-coded map using Matlab software. An optimal synchrony line (OSL) is generated on the EDM and optimal synchrony is defined as a setting on the OSL.

EDMs will be acquired at current (baseline) device vector. In some subjects, an EDM at a different vector (e.g. pacing from a different quadripolar LV lead) will be obtained, particularly if electrical synchrony using the baseline pacing vector appears suboptimal.

Variables measured from EDM

1. Optimal CRI (overall, during BiV pacing, during LV-only pacing)
2. Timing of native, RV-paced (RVp) pacing and LV-paced (LVp) electrical wavefronts

Cardiac MR

CMR will be performed after measurement of EDMs at Visit 2 and 6 months later at Visit 3. The acute CMR study data will be acquired at three different settings at Visit 2: native (CRT off), current baseline CRT setting, and optimal CRT setting. The three settings will be programmed randomly, and the reader will be blinded to the device settings. At Visit 3, the 6 month CMR study will be acquired at the randomized programmed setting only, and the reader will be blinded to this setting. In the instance of incidental findings, study doctor(s) will relay findings to patient's care team or cardiologist for clinical follow-up if appropriate.

A list of CMR values collected are listed in Appendix B.

NYHA assessment, QOL questionnaires, 6MHW

This data will be acquired at baseline and at 6 months (Visits 1 and 3, respectively). NYHA class will be assessed by study staff blinded to patient randomization. QOL will be measured using Kansas City Cardiomyopathy Questionnaire (KCCQ), and a study-specific questionnaire found in Appendix C. Delegated study staff will perform 6MHWs.

Randomization

All subjects will be randomized 1:1 to experimental and control arms of the study using a computer program to randomly generate assignments. The prepopulated randomization assignment for each enrolled subject will be placed in sealed envelopes and labeled with the corresponding study ID number. These randomization assignment envelopes will be kept in the keypad secured research drug closet at MHI at United and are only accessible by research staff. Randomization envelopes will be opened after generation and review of EDM(s), and

determination of optimal CRT programming after Visit 1 and prior to Visit 2. An excel spreadsheet of all randomization assignments will be kept on the secured Allina Health share drive to confirm correct assignment. This spreadsheet will be password protected and only accessible by the research staff delegated to oversee randomization assignments.

Alternatives to Participation

Alternative to participation, include (but not limited) to the following:

- 12-lead ECG CRT optimization: Patient can alternatively undergo non-research electrocardiography guided CRT optimization at either MHI at United or MHI at Abbott Northwestern. The 12-lead ECG CRT optimization uses fewer electrodes to collect a more limited amount of information about which CRT device settings are more optimal.

This alternative listed above would both involving the changing of CRT device settings during ECG acquisition similar to that of the multi-lead ECG assessment and EDM generation. However, the alternative options do not implement the use of CMR and contrast, mitigating the risks as described below in the protocol under "Risks Associated with Cardiac Magnetic Resonance Imaging" and "Risks and Side Effects from the Required Intravenous Agents: Gadolinium".

Interim Analysis:

After the first six subjects complete the study, an interim analysis will be completed to assess the efficacy of multi-lead ECG assessment and EDM generation in optimizing patients with CRT and deemed non-responders/ incomplete responders to the therapy. Acute and chronic changes to LV mechanical synchrony, regional wall motion, and function will be assessed by CMR imaging and echocardiography in order to measure response to CRT optimization.

Data Safety Monitoring Plan:

Subjects' medical and cardiovascular history will be abstracted at follow up Visit 3 and Visit 4, and abstractions will be reviewed by study doctors alongside the medical imaging collected during the interim and at these study visits. Study doctors will determine if there has been a decline in cardiovascular health related to the interventional component of altering CRT programming during the study and whether it is safe for subjects to continue participation.

If it has been determined by a study doctor that it is no longer safe for a subject to continue participation, a study doctor will contact patient and inform them that it is unsafe for the subject to remain in the interventional portion of the study. A study doctor will consult with electrophysiology provider(s) overseeing the device management of the subject prior to withdrawal. The subject may be asked by a study doctor to return to the study site for a clinical follow-up with the device clinic and/ or office visit with an electrophysiologist provider to assess CRT programming prior to being withdrawn from the study. ***All requested follow-up prior to withdrawal is voluntary, but a subject's decision not to follow up prior to withdrawal from the interventional portion of the study due to safety concerns may pose additional risks that are unknown at this time and may include worsening symptoms of heart failure.*** A study doctor

may ask if the subject wishes to participate in continued follow-up as described in the consent form and may ask if the research team can continue to review and record information from the subject's medical chart as listed in Appendix D for the remaining duration of the study. Verbal permission from the subject for continuing review and recording of information from the subject's medical chart will be documented in their medical chart prior to withdrawal from the interventional component of the study. Patients who are withdrawn from the interventional component of the study and who also decline further review and recording of information from their medical chart will be withdrawn from the study.

Subjects who are withdrawn from the interventional component of altering CRT programming during study will have CRT programming either set back to baseline CRT programming (same programming prior to enrollment) or further changes to CRT device programming will be under the discretion of the subject's device, cardiology, and electrophysiologist providers.

Records and Data Collection Procedures

Data Management

Data Collection: See Appendix D variable lists

Data Storage: Upon completion of data abstraction, data recorded will be split into two files. The first file will be a linking key which will contain identifiable PHI (Name, MRN, DOB, etc.), and the second file will be a limited data set. The linking key will be stored in a folder separate from the limited data set. The data will not be transferred outside of Allina Health.

Data Sharing and Use Agreements: Not required for this study.

Data and Security and Confidentiality: The confidentiality of records identifying the subject will be maintained to the extent permitted by applicable laws and/or regulations. Paper documents will be secured physically in a secure office suite with badge access. Electronic study records will be protected with electronic safeguards, which include computer passwords, access privileges, and firewalls. Confidentiality statements are required of research staff upon hire. Access to study records will be limited to research staff. The site will not use collected information for purposes other than the research purposes for which a waiver of consent and HIPAA Authorization was obtained.

An auditor, IRB, and/or other regulatory authorities as required by law will have access to study-related records. Study-related records identifying the subject will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publically available. If any results of the study are published, the subject's identity will remain confidential

Data Retention & Destruction:

Storage and access: After verifying that the study results have been published, the dataset will be reviewed to ensure de-identification and retained indefinitely. De-identified datasets will be housed in the password-protected Allina Health share drive. The linking key will also be retained electronically on the Allina share drive, will be password protected, stored in a separate location from the de-identified dataset, and will be restricted to key personnel responsible for managing archived study data. The linking key will be retained in order to validate any inquiries regarding study results after publication and closure of the study, as well as if a subject's medical providers has questions regarding participation and continuing cardiovascular care. The screening log will be destroyed upon closure of the study. The destruction of documents containing identifiers after publication and study closure will be conducted as follows:

Paper files will be shredded in a secure bin. Electronic files, which are stored on the Allina server network, will be deleted using Allina's electronic data practices. 14 days after these files and data are deleted, they cannot be recovered and will therefore be destroyed.

De-identified data collected for this study may be used by MHIF for future research purposes and may be shared in de-identified form with outside researchers for their use in other research studies.

Sharing of Results with Subjects:

Study staff or study doctor(s) will discuss these results with participants in clinic or over the phone after the 12 month/ Visit 4 follow-up visit and completion of all study activities. Patients will be un-blinded to randomization assignments after 12 month/ Visit 4 follow-up visit and complete all study activities. Study doctors will be made available if needed. A research or telephone encounter will be created to document the review of the results of the study. Patients will be informed of the detailed information regarding their heart's function when seen in follow-up.

Consent/HIPAA Waiver Criteria

Consent and HIPAA Authorization Details for all Aspects of Study

Written Informed consent
Informed consent and HIPAA authorization will be obtained for the prospective collection of data for patients consenting to participation in the trial.

HIPAA Authorization – Partial Waiver Request and Justification
To identify potential participants for this research study, pre-screening procedures using EPIC need to be performed prior to requesting patients to sign the consent form. It is not practical for the research team to request HIPAA Authorization from every patient who is seen at MHI for CRT, who might be eligible to participate in the study. By approaching all patients, who may be ineligible, eligible patients may be missed and would not have the opportunity to participate in the research study. In addition, requiring HIPAA Authorization for pre-screening procedures would not only be burdensome and challenging for the research team and make the research not practical to carry out, but also patients' total time in hospital would lengthen because more patients presenting for coronary angiography would be approached to provide such authorization, who may be found to not be eligible to participate and such knowledge could have been gained from the information in EPIC, thus lengthening overall standard of care visits for patients who do not otherwise qualify.

Without access to and use of PHI, eligible participants could not be identified for this research study. Therefore, as PHI is required for the identification of eligible participants and manual extraction of data from the EMR and EDW, the research could not practicably be conducted without access to and use of PHI.

Study Risks and Benefits

The benefits associated with participation in the study include, but not limited to, the following:

Subjects may benefit from having CRT device programming optimized which could result in improvements to cardiovascular function and/or improvements in heart failure symptoms. Subjects may also benefit from early discovery of new or worsening cardiovascular issues if present during time of the multi-lead ECG assessment or CMR. In the case that study staff identifies new cardiovascular issues, such issues will be acknowledged and relayed to an appropriate physician for clinical follow-up.

This study may not provide benefit to some subjects but may offer further insights on patients deemed non-responders to cardiac resynchronization therapy as well as future treatment in patients implanted with CRT devices

The risks associated with participation in the study include, but are not limited to, the following:

Risks Associated with Multi-lead ECG Assessment

The multi-lead ECG assessment does not, by design or intention, introduce energy into the subject. The multi-lead ECG assessment captures data similar to a standard 12-lead ECG but has more electrodes. There are risks of irritation or allergic reaction to electrode adhesives and gels; however, severe reactions are rare, and most subjects have had some form of ECG prior with no adverse reactions to the use of electrode adhesives and gels. The research team has utilized the multi-lead ECG in more than 100 subjects in other studies and has reported no injuries or allergic reactions.

The risks of changing CRT device settings during the multi-lead ECG assessment are similar to those associated with changing device settings using standard 12-lead ECGs. A device nurse will be present during the device check and multi-lead ECG assessment. Having a device nurse present will minimize risks by:

- Monitoring heart rhythm
- Reviewing any irregular heart rhythms recorded by a patient's device (arrhythmias)
- Ensuring device settings tested during the data collection are appropriate for the patient based on their underlying conduction
- Setting up and reviewing device monitoring parameters per site's clinical protocols
- Address and forwarding any cardiovascular health concerns to other providers as a component of a patient's clinical care if needed

Risk Associated with Changing Cardiac Device Settings:

Risk of changing device settings from the information obtained from the multi-lead ECG assessment are similar to those associated with changing device settings using information from standard electrocardiography. These risks could include worsening symptoms of heart failure, although instances of worsening heart failure due to changes in cardiac device settings as part of device optimization have been rarely observed in hundreds of previous patients. Some examples of worsening symptoms of heart failure include, but are not limited to, the following:

- Shortness of breath when performing activities
- Buildup of fluid in the legs (edema)
- Tiredness or fatigue
- Impaired thinking or confusion
- Lack of hunger or feeling sick (nausea)
- Persistent coughing or wheezing

Risks Associated with Cardiac Magnetic Resonance Imaging

Magnetic fields and radio waves are not associated with any known risks unless patients have an implanted medical device that is magnetic. The main risks/discomforts associated with CMR are related to lying flat in the scanner and not moving for approximately one hour. These are listed below:

- Claustrophobia (fear of confined spaces) during CMR scan
- Mild diaphoresis (sweating) during and up to 1 hour after CMR scan
- Sensation of bodily warmth during and up to 1 hour after CMR scan
- Hearing Impairment (less than 24 hours)
- Body stiffness related to immobility (less than 48 hours)

Risks and Side Effects from the Required Intravenous Agents: Gadolinium

GADOLINIUM. Patients undergoing a CMR will require an intravenous (IV) dye (contrast) known as gadolinium**.** Gadolinium is a liquid chemical that has useful magnetic properties allowing a high resolution image of the heart muscle and any scar tissue which may be present. Gadolinium is FDA approved and considered quite safe. Potential risks and side effects are listed below:

- **Extravasation**. A rare side effect from any IV contrast injection is extravasation. Extravasation means that the contrast material went outside the blood vessel and has gone into the surrounding tissue. Extravasation may result in moderate local irritation, redness, or swelling at the injection site.

- **Nephrogenic Systemic Fibrosis (NSF).** Nephrogenic systemic fibrosis (NSF) is a fibrosing (scar tissue) disorder seen only in patients with advanced kidney disease. The condition often first appears as swelling or itching of the skin. It can lead to thickening or hardening of the skin and deposits in other parts of the body, such as the lung and muscle.

  Nephrogenic systemic fibrosis has been linked to patients receiving gadolinium contrast agents in the presence of underlying severe kidney disease.

  Over the past several years, no new cases of nephrogenic systemic sclerosis have been reported. This is likely the consequence of the use of less toxic gadolinium agents and limiting the use of gadolinium in patients with severe kidney disease. Newer gadolinium agents are considered much less toxic. The agent patients in this study will receive - Gadavist (gadobutrol) is in this class, and toxicity cases reported.

- **Allergic Reactions.** Patients who have had an allergic reaction to the contrast used in CT, IVP, and angiographic examinations are at increased risk of allergic reactions to other contrast agents, including gadolinium. There is no way to predict who will have an allergic reaction before the contrast (gadolinium) is given. Allergic reactions generally develop within 10 minutes. Minor contrast reactions are the most common but happen in *less than 0.05% of cases.* Symptoms may include headache, sneezing, nausea, vomiting, hives, and swelling and usually, resolve rapidly. Occasionally medications may be required to help treat these symptoms if they persist. Rarely, a severe reaction can happen. This may include a rapid or slow heart rate, low blood pressure, an asthma attack (bronchospasm), or complete circulatory arrest/shock. Such reactions require urgent medical treatment, which our offices are prepared to handle.

- **Gadolinium retention**. Gadolinium may persist for months in some body areas, such as the brain, or in bone. The importance of this is unclear, and no disease process has been

associated. The lowest retention has been shown with the type of agents (macrocyclic) used at all of our clinics.

Statistical Considerations and Data Analysis

AUC and CRI values derived from the multi-lead ECG assessment are exported to de-identified digital spreadsheets. CMR values will be stored on de-identified paper CRFs in the subject binders and then entered into a digital spreadsheet that can be imported into statistical analysis software. Student *t*-tests will be utilized to compare continuous variables. Paired *t*-tests will compare CMR values collected between study visits, while two-sample tests will compare values between experimental and control arms. Fischer's Exact Test will compare categorical variables (i.e. proportional differences) between the groups. An alpha level of 0.05 will be considered significant.

APPENDICES

APPENDIX A: Electrical Dyssynchrony Map

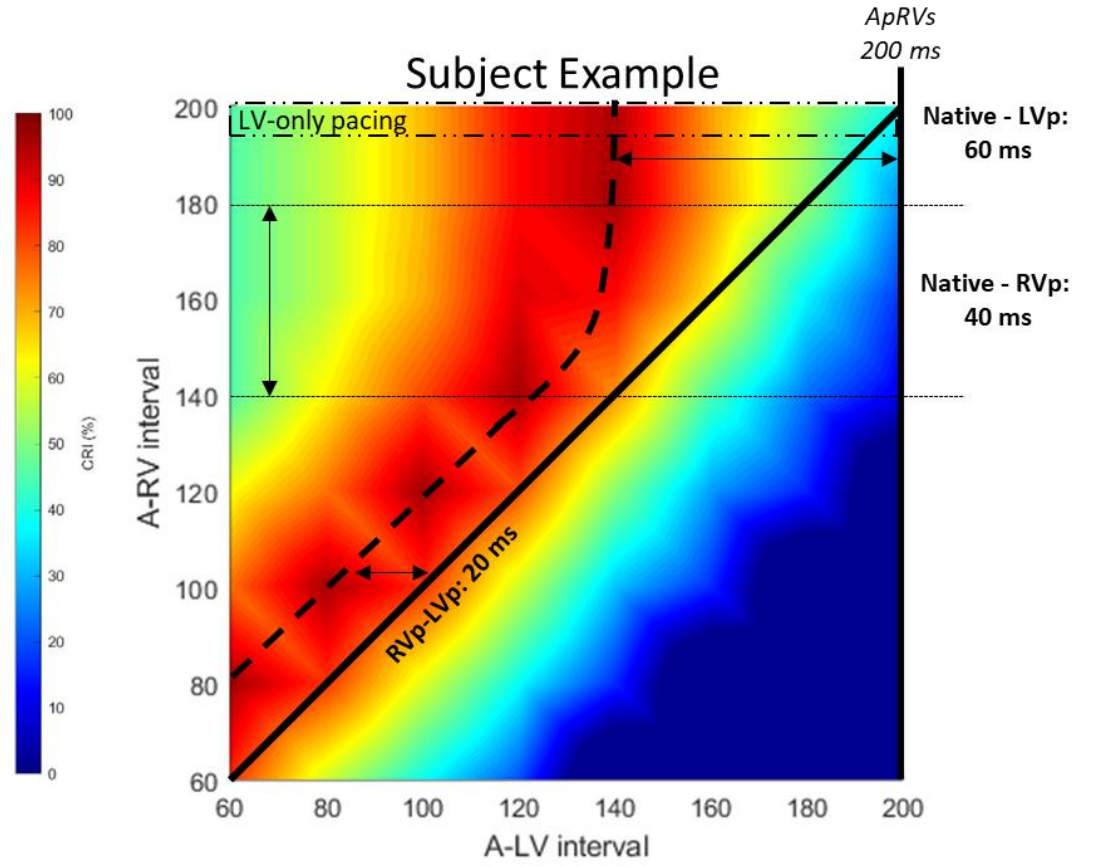
APPENDIX B: CMR variables

APPENDIX C: Research Questionnaire (study-specific)

APPENDIX D: Data Collection

APPENDIX A: Electrical Dyssynchrony Map (EDM)

An EDM from an HF patient with LBBB, QRSd 178 ms, and PR interval 200 ms is shown. Atrial to RV-pace (A-RVp) and atrial to LV-pace (A-LVp) intervals are shown in milliseconds on the "y" and "x" axes, respectively. The AUC from each setting collected during the multi-lead ECG assessment is calculated using the propriety algorithm, and the corresponding CRI value is used to fill each A-RVp and A-LVp location in a grid-like fashion in the EDM. The mesh-grid of CRI values is then interpolated using MatLab software to generate an EDM where high electrical dyssynchrony (low CRI value) is depicted in cool colors, and low electrical dyssynchrony (high CRI value) is depicted in warm colors.



The bold horizontal line traversing from the lower-left corner to the upper right corner of the EDM shows CRI during simultaneous BiV pacing at a range of different AVDs. The dashed box across the top of the EDM depicts electrical synchrony at LV-only pacing since the A-RVp is very long and not contributing to LV depolarization. The optimal synchrony line (OSL) is depicted as a dashed line through the middle of the red area on the graph and allows for calculation of the native, RVp, and LVp electrical wavefronts as well as the optimal CRI overall. The optimal setting during simultaneous BiV pacing is the highest CRI along the bold horizontal line; likewise, the optimal setting during LV-only pacing is the highest CRI in the dashed box.

APPENDIX B: Magnetic Resonance Imaging variables (at each one of the CRT settings).

- Left and Right Ventricular volumes (end-diastolic, end-systolic, stroke volume, forward stroke volume) (ml)
- Left and Right Ventricular mass (g)
- Left and Right Ventricular ejection fraction (%)
- Left and Right Ventricular Global Longitudinal Strain (%), Global Circumferential Strain (%) and Global Radial Strain (%)
- Time difference between the anteroseptal and posterior wall segmental peak strain (msec)
- Left and Right Atrial volume (ml)
- Forward LV and RV stroke volume (ml)
- Mitral regurgitation (reg. volume and reg. fraction)

The following variables will not be modified by the CRT pacer settings and measured only once:

- Native T1 mapping (pre-contrast) (msec)
- Post Contrast T1 mapping (msec)
- Scar Burden (%) - ratio between scar mass/LV mass
- Extracellular volume fraction (%)

APPENDIX C: Research questionnaire (study-specific)

Each subject will be asked at baseline and follow-up visits (Visit 1 and Visit 3, respectively) the following questions regarding CRT implantation and cardiovascular health.

Visit 1: Research Questionnaire

In regards to your cardiovascular health and heart failure symptoms, how have you felt since implantation of your cardiac resynchronization therapy device?

- Worse
- Same
- Mildly Better
- Moderately Better
- Markedly Better

Visit 3: Research Questionnaire

In regards to your cardiovascular health and heart failure symptoms, how have you felt since the beginning of this study?

- Worse
- Same
- Mildly Better
- Moderately Better
- Markedly Better

Visit 4: Research Questionnaire

In regards to your cardiovascular health and heart failure symptoms, how have you felt since the beginning of this study?

- Worse
- Same
- Mildly Better
- Moderately Better
- Markedly Better

APPENDIX D: Data collected from medical chart

Data to be collected on enrolled subjects:

1. Demographics (abstracted from medical chart)
    a. Medical record number (MRN)
    b. Date of birth (DOB)/ age
    c. Gender
    d. Body mass index (height/ weight)
    e. Race/ethnicity
2. Medical and cardiovascular history (abstracted from medical chart)
    a. Cardiovascular history
    b. Respiratory and pulmonary history
    c. Cardiac electrical conduction history
    d. Current cardiac medications
    e. Labs and vitals
3. Imaging (includes imaging prior to CRT implantation)
    a. Echocardiographic values and images
    b. CMR values and images
    c. Chest x-rays images
    d. Fluoroscopic images from CRT implantation
    e. CT images
4. CRT device and device interrogations
    a. Date of implant
    b. Manufacturer of device
    c. Lead positions
    d. Types of leads present
    e. Programming of device
    f. Arrhythmia episodes
    g. Device measurements and values
5. ECGs
    a. Pre-CRT ECGs
    b. Post-CRT ECGs
    c. Interim ECGs
    d. Multi-lead ECG data (collected during study)