**Catheter Ablation of Arrhythmias to Improve CRT Response: The ABLATE-CRT Study**

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**1. Protocol Summary:**

Cardiac resynchronization therapy (CRT) is an effective therapy for heart failure patients. Often arrhythmias such as atrial fibrillation/flutter (AF/AFL), supraventricular tachycardia (SVT), premature ventricular contractions (PVC) and ventricular tachycardia (VT) impair synchronization of the atrial and ventricular contractions. These arrhythmias therefore interfere with optimization of heart failure therapy using CRT. This study proposes to evaluate if catheter ablation of cardiac arrhythmias such as AF, AFL, SVT, PVC or VT will result in improved biventricular synchrony and thus improve ejection fraction. This will be a prospective, randomized study with intention to treat. A total of 189 patients will be enrolled for the study, 126 in the catheter ablation arm and 63 in the medical therapy arm. The consented patients will be enrolled into either catheter ablation or medical therapy arms. Patients enrolled to the catheter ablation arm will undergo ablation of the respective arrhythmia and will be followed up for a period of 1 year after procedure. Patients randomized to the medical therapy arm will have their medications titrated/added to improve bi-ventricular optimization. Those patients who do not respond to medication therapy after 3 months have the option to be crossed over to the catheter ablation arm at physician's discretion. Patients who are non-responders to CRT are defined as those with biventricular pacing <94% and ejection fraction improvement less than 5% for at least 3 months post CRT implantation. Patients that continue in the medical management arm will remain in the study for 1 year after they have signed the informed consent. If the patient crosses over to the treatment arm, they will be followed for one year post procedure. Primary and secondary outcomes will be compared between the catheter ablation and medical therapy arm.

**2. Background and Significance**

Heart failure is a chronic condition that is associated with high mortality, morbidity and decreased quality of life. The estimated prevalence of heart failure in the United States is about 2.2% and is estimated in the elderly to approach 8.4% (1). Complications of chronic heart failure also include adverse effects on the conduction pathways of the heart and particularly delays in the onset of ventricular contractions (2). This is evident in nearly 30% of patients with chronic heart failure (3,4). This abnormal conduction may further exacerbate the dyssynchrony between the two ventricles and may lead to further impairment of cardiac output. The conduction abnormalities in heart failure lead to poor quality of life and higher mortality (5-8).

Cardiac resynchronization therapy (CRT) is designed to circumvent the dyssynchronous contraction of the ventricles by simultaneously pacing both the right and left ventricles together. CRT is also referred to as biventricular or "Bi-V" pacing. The depolarization of both ventricles by means of simultaneous pacing results in improvement of global mechanical contractility and decreases mitral regurgitation. Multiple studies have demonstrated the benefit of CRT therapy in

patients with heart failure and widened QRS complex. In patients with a left bundle branch block and heart failure, CRT therapy resulted in improvement of ejection fraction by 11.9 ± 5.1 % (9). In addition, other markers of heart failure such as left ventricular end diastolic volume and left ventricular end systolic volume also showed improvement. There was a 35% decrease in mortality with the use of CRT devices, and patients who were implanted with CRT devices had less severe symptoms and greater quality of life (10).

Cardiac resynchronization therapy is an effective therapy for patients with heart failure and a prolonged QRS complex who remain in sinus rhythm (2,11). Irregular heart rhythms such as AF and PVCs can prevent optimization of the synchrony between the ventricles and undermine the effects of CRT. Atrial arrhythmias prevent optimization of the atrial and ventricular function, and the high ventricular rate prevents optimal biventricular capture by the device (11). Medications to control heart rate and rhythm may impart negative inotropic effects and thereby worsen heart failure. This approach is suitable when the AF burden is low to intermediate (12). Alternatively, for patients with permanent atrial fibrillation, atrio-ventricular (AV) nodal ablation can be done to prevent the supraventricular arrhythmia from disrupting optimal biventricular pacing (12). This approach has been shown to be superior to medical therapy and decreases the overall and cardiovascular mortality compared to medical management of AF (11).

Several studies have evaluated optimal biventricular pacing time and have concluded that mortality was inversely proportional to the time spent in biventricular pacing (13). Patients with AF and biventricular pacing <98.5% of the time had a higher mortality rate compared to those who had biventricular pacing >98.5% of the time (13). Therefore every effort should be made to improve the biventricular pacing to as close to 100% as possible. In fact, when atrio-ventricular nodal ablation was performed in an atrial fibrillation population, the % biventricular pacing was 96 ± 6% which was significantly higher than patients treated with AV nodal blocking medications (87 ± 14 %) (11).

Radiofrequency ablation (RFA) is an effective treatment for atrial fibrillation and is increasingly being used in patients with symptomatic recurrences while on anti-arrhythmic medications. RFA of AF has also been shown to improve left ventricular ejection fraction and heart failure symptoms (14). Furthermore AF ablation has been shown to improve ejection fraction when compared to atrio-ventricular nodal ablation and biventricular pacing in heart failure patients (15). There was greater improvement in ejection fraction, functional capacity and quality of life in the AF ablation group (15). Besides AF, ventricular arrhythmias such as PVCs also decrease optimization of the CRT response (16). Ablation of the PVC foci has been shown to improve CRT response (16). Our group has shown that ablation of the PVC foci increased biventricular

pacing to 98 ± 2% from a baseline 76 ± 12% (16). There was also improvement in left ventricular ejection fraction and other heart failure echocardiographic parameters (16). A previous study of 86 consecutive patients that had either a pacemaker or ICD at the time of RFA for symptomatic AF was both safe and efficacious (17). RFA is routinely done in patients with atrial fibrillation, atrial flutter, ventricular tachycardia, and supraventricular tachycardia and concomitant cardiac implantable electronic devices without any issues. Based on the above studies and evidence, we hypothesize that ablation of atrial and/or ventricular arrhythmias is likely to improve biventricular pacing in patients with suboptimal CRT response, as compared to medication therapy.

**3. Hypothesis and Objectives**

We hypothesize that catheter ablation of atrial and/or ventricular arrhythmias is superior to medical management for optimization of CRT response in CRT non-responders.

**Objectives:**

1. To evaluate if catheter ablation of atrial and/or ventricular arrhythmias will help improve patient's biventricular pacing percentage.
2. To evaluate if catheter ablation of atrial and/or ventricular arrhythmias will result in greater improvement in patients' ejection fraction compared to medical management at 3 months and if the effect will be sustained at 12 months follow-up.
3. To evaluate if quality of life is improved after catheter ablation of atrial and/or ventricular arrhythmias in patients with CRT devices compared to medical management.

**4. Study Population, Study Inclusion & Exclusion Criteria:**

Consecutive patients who have a previously implanted CRT and are non-responders to CRT therapy (as defined by Bi-V pacing less than 94% and one of the following arrhythmias: atrial fibrillation, atrial flutter, supraventricular tachycardia, premature ventricular contractions and/or ventricular tachycardia) presenting to the participating institutions will be screened for the inclusion and exclusion criteria. Those subjects meeting the following criteria will be asked to participate in the study.

*Inclusion Criteria:*

- Between ages 18-80 years old
- Heart failure patients with CRT-D or CRT-P greater than 3 months
- Bi-ventricular pacing less than 94% of the time
- 3 months after CRT-D or CRT-P implantation an EF improvement less than 5%

- Presence of one of the following arrhythmias and eligible for catheter ablation:
    - Atrial fibrillation
    - Atrial flutter
    - Supraventricular tachycardia
    - Premature ventricular contraction burden greater than 10% in a 24-hour period
    - Ventricular tachycardia

*Exclusion Criteria:*

- Estimated survival less than one year
- Patient unable to make scheduled follow up visits at treating center
- Participating in another investigational study

**5. Participating Centers**

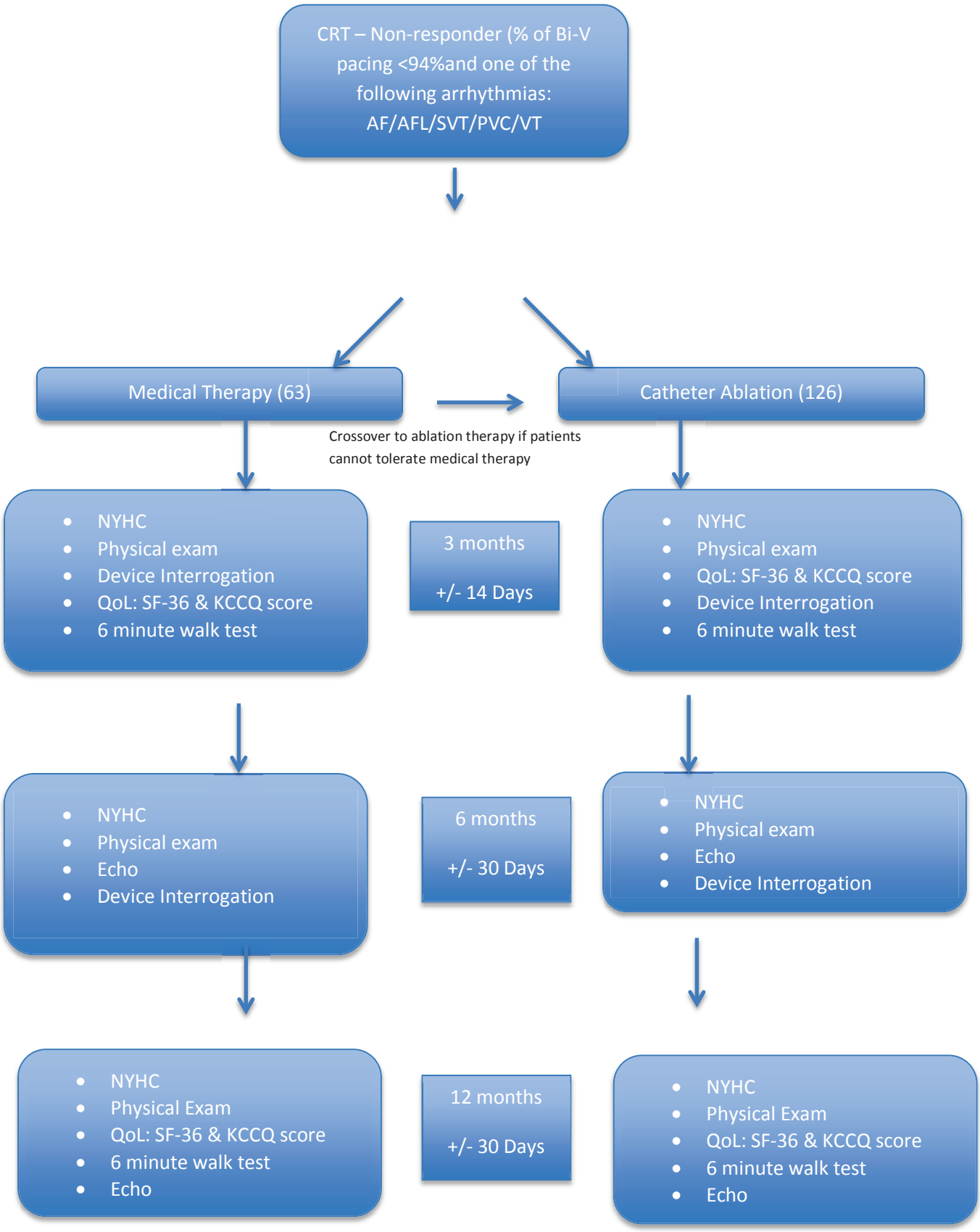
This will be a multicenter open-label randomized control study. The principal coordinating site will be the University of Kansas Hospital, Kansas City, Kansas. The remaining centers include: Massachusetts General Hospital, Boston, Massachusetts, Arizona Heart Rhythm Institute, Phoenix, Arizona, Texas Cardiac Arrhythmia Institute, Austin, Texas, Mayo Clinic, Rochester, Minnesota, The Ohio State University Medical Center, Columbus, Ohio, and Baptist Health Lexington, Lexington, Kentucky.

**6. Study Design and Analysis:**

This will be an open-label randomized control study. Patients will be screened for participation in the study during their visits to the cardiology clinic. Patients who are non-responders to CRT defined as biventricular pacing less than 94% and ejection fraction improvement less than 5% for at least 3 months post CRT implantation will be included in the study if they meet all other inclusion and have no exclusion criteria. The study design is illustrated in Figure 1. Patients will be considered enrolled into the study after they sign the informed consent form. Once patients are enrolled they will be randomized, by sealed envelope, to either continued medical management or ablation. Patients enrolled into the ablation arm will undergo catheter ablation of atrial or ventricular arrhythmia within 3 months of signing the informed consent form. The technique and type of ablation will be at the discretion of the treating electrophysiologists. The medical treatment arm consists of the use of antiarrhythmic drugs that are deemed to be appropriate for the given arrhythmia by the treating physician. All patients will then be followed for a period of 1 year after randomization. Standard of care follow up visits will be conducted at 3, 6 and 12

months post treatment (either ablation or randomization for medical treatment arm). Those patients in the medical therapy arm will be crossed over to the ablation arm if they become severely symptomatic or have worsening cardiovascular function after 3 months of medical management. Patients will be enrolled in a 2:1 ratio to the catheter ablation arm and medical therapy arms respectively.

Figure 1: ABLATE-CRT Study Design



Primary and Secondary Endpoints

Primary Endpoints

- EF improvements greater than 5%
- Bi-ventricular pacing improvement greater than 5%
- Cardiovascular mortality

Secondary Endpoints – the following will be reported as observational endpoints

- All-cause mortality
- Hospital admissions for heart failure exacerbation
- NYHA class change
- 6 minute walk test
- QoL assessment: SF-36 and KCCQ score changes

**7. Data Collection**

The Cardiovascular Research Institute will be the coordinating site for the study. REDCap will be the electronic data capture used for this project. All coordinators will have an account created and forms will be available to them during the study. A project manager (PM) with the help of the PI will create the study worksheets and create the CRFs. The PM will assist the database manager (DM) with updating REDCap and providing computer support for outside centers. All data will be submitted via REDCap including de-identified patient data that is to be used as source.

Participant's data will be de-identified and a code will be assigned. The code will consist of site number, patient number and patient initials. The coordinator at that site will have access to the code, and the linking list will be destroyed at the completion of the project.

The coordinating center will monitor patient records using REDCap. Charts will be reviewed on a regular basis for discrepancies.

The following data points will be collected:

A. Baseline demographics (age, sex, height, weight, BMI, NYHA class).
B. Co-morbidities (including but not limited to HTN, DM, CVA, TIA, HF, CRF, GI bleeding, intracranial bleeding, device implantations, infections, history of other arrhythmias, CAD, h/o of Lariat procedure, CABG, PCI or other procedures).
C. Family history of AF and other arrhythmias will be collected.

D. Medications used in the past and current medications and their adverse effects will be collected.
E. Social and other personal history including but not limited to smoking, alcohol usage, other nonprescription medications and amount of coffee intake will be recorded.
F. Physical examination findings (hepatomegaly, jugular venous pressure, hepatojugular reflux, ascites, heart sounds, murmur, rales, peripheral edema, BP, HR, weight, height, BMI)
G. Laboratory variables including but not limited to sodium (Na), potassium (K), magnesium (Mg), phosphorus, complete blood count (CBC), comprehensive metabolic profile (CMP), lipid profiles, basic natriuretic levels (BNP) and coagulation profile.
H. 6 minute walk test.
I. CRT device interrogation – Percent of bi-ventricular pacing and percent of arrhythmia burden.
J. Kansas City Cardiomyopathy Questionnaire (KCCQ) and SF-36 forms
K. Echocardiogram parameters including the left atrial size, Cardiac CT parameters including the PV anatomy, size of the PV and left atrial appendage size, MRI parameters including the myocardial structure, scar data and other significant imaging that will be helpful to test the hypothesis.
L. Procedural variables for the index ablation (type of ablation, use of general anesthesia, procedure length, fluoroscopy time, radiation time, complications during procedure, ablation time, type of catheters used or other changes on the device/ICD parameters).
M. Adverse events related to the procedure and medical treatment including but not limited to bleeding from the groin site, infections, pericardial effusion, myocardial rupture, mortality and other complications.
N. Length of stay and number of hospitalizations during the study.
O. Cost associated with the procedure.
P. Quality parameters including but not limited to success of ablation procedure, ancillary staff utilization, nursing staff utilization and use of other resources.
Q. Follow up visit history and all changes to the management plan will be recorded.
R. Mortality data will be collected.

**8. Statistical Analysis:**

To observe a minimum 5% difference in the ejection fraction or biventricular pacing, with a two tailed hypothesis and power of 80% and $\alpha$ of 0.05, we need to enroll 48 and 96 patients respectively to the medical and catheter ablation arms respectively. Assuming a dropout rate of

about 10% during the follow up period, the final enrollment should be aimed at 53 and 106 patients in the medical and catheter ablation therapy arms respectively. The total number of subjects analyzed may be 189 subjects. The above estimate is provided assuming an EF of 30 ± 10% in the medical therapy group and post ablation if the EF were to improve to 35 ± 10% in the ablation group (5% improvement in the mean EF).

Standard statistical tools will be utilized. IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp) will be used to analyze the data. Continuous data will be presented as the mean value ± SD, and categorical data will be presented as n (%). The catheter ablation and medical therapy arms will be compared on an intention to treat basis. Categorical variables will be compared using chi square or Fisher's exact test and continuous variables will be compared using t-test or Mann-Whitney U test as and when appropriate. Univariate and multivariate analysis will be performed to detect factors affecting the outcomes between the two groups. A 'p' value <0.05 will be considered statistically significant.

**9. Data Safety Monitoring Board**

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring Board (DSMB) will monitor results during the study. The board consists of 2 general cardiologists and 1 statistician who have no formal involvement or conflict of interest with the subjects or the investigators. Records will be reviewed after the first 30 patients and then routinely after every 30 patients. The study will be stopped if the major complication rates (ie. Stroke, cardiac perforation, cardiac tamponade requiring surgery) exceed 15% at each given time points. All participant sites will have to upload their data in REDCap within 7 days of the time point. All adverse events will have to be reported within 48 hours.

**10. Subject Consent**

Participation of the subjects is voluntary and all participants will sign a written informed consent before participating in the study. The principal investigator or research staff will fully inform the subjects of the risks and benefits of participation in the study and will obtain their consent before enrollment into the study. Patients will be screened for enrollment into the study during standard of care office visits in the cardiology outpatient clinic. Patients will be given all the details of the study and will be asked for their voluntary participation. The patients may provide the consent anytime between their preoperative visit and the day of the procedure before the procedure actually begins in order to participate in the study.

**11. Patient Safety:**

**Risks:** Catheter ablation, standard of care, will be done on patients randomized to this group and also the crossover patients. This is an invasive procedure and the risks from catheter ablation include a small risk for bleeding, hematomas, cardiac perforation, stroke, myocardial infarction and rarely death. These risks are the same for this standard of care procedure. Patients in the medical therapy arm not responding to medical therapy will have the chance to be crossed over to the catheter ablation arm and these patients will have similar risks if they undergo catheter ablation. Patients will sign a separate informed consent form outlining the risks of the procedure.

**Benefits to the subjects:**

Participation of subjects in this study is voluntary and there are no direct benefits to these study subjects. The knowledge gained from this study may help benefit future patients undergoing CRT implantations to help maximize their ejection fraction and decrease morbidity. Additionally it will greatly help the research community at large in understanding the benefits versus risks of catheter ablation of atrial and ventricular arrhythmias in patients with CRT-D devices.

***Records Retention***

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by Biosense Webster, whichever is longer.

If the investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another investigator, another institution, IRB). Notice of such transfer will be given in writing to Biosense Webster.

**12. Funding:**

Funding provided by Biosense Webster.

**Study Assessments and Procedures**
Time and Events Schedule

| **Procedure** | **Baseline** | **Randomization** | **Procedure** | **3 Month** (+/- 14 Days) | **6 Month** (+/- 30 Days) | **12 Month** (+/- 30 Days) |
|---|---|---|---|---|---|---|
| **Eligibility Assessments** | | | | | | |
| Informed Consent | X | | | | | |
| Medical History | X | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | |
| **Study Assessments** | | | | | | |
| New York Heart Class Assessment | X | | X | X | X | X |
| Physical Exam | X | | X | X | X | X |
| Device Interrogation | X | | X | X | X | X |
| SF 36 | X | | | X | X | X |
| KCCQ Score | X | | | X | X | X |
| 6 Minute Walk Test | X | | | X | | X |
| Echocardiogram | X | | | | X | X |
| Procedural Variables | | | X | | | |
| Adverse Events Assessment | | X | X | X | X | X |

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