Randomized Controlled Trial Adaptive CRT effect on ELectrical dysSYNChrony aCRT ELSYNC: study design

Larisa Tereshchenko, MD, PhD, Jason Thomas, BS, Charles Henrikson, MD, MPH
Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR, USA

KNIGHT CARDIOVASCULAR INSTITUTE
Oregon Health & Science University

ABSTRACT

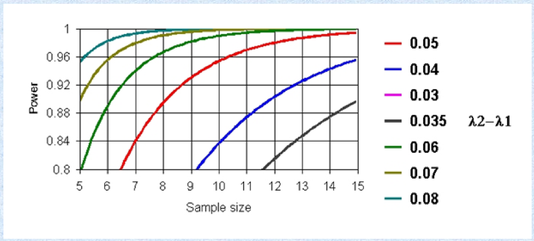
We designed a prospective, randomized, double-blind, parallel-controlled clinical trial comparing adaptive cardiac resynchronization therapy (aCRT) to a standard CRT in patients with currently approved (class I-II) indications for CRT. The goal of this study is two-fold: (1) to determine if aCRT is superior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

All study participants will receive commercially available CRT devices capable of aCRT, and will be randomized 1:1 to one of two pacing therapy arms, aCRT ON or aCRT OFF. Duration of assigned intervention is 6 months.

Primary Outcome Measures: (1) Regression slope of Electrical Dyssynchrony Index (EDI) measured on epicardial activation map 6 months post-CRT, regressed against EDI measured by ECGi prior to CRT; (2) Difference in regression slopes of SAI QRST against EDI vs. QRS duration against EDI prior to CRT and 6 months post-CRT.

Secondary Outcome Measures: (1) Surface ECG and intracardiac spatial QRS-T angle and QRS & T loops morphological characteristics measured 6 months post-CRT regressed against the same measures prior to CRT; (2) Clinical Composite Score. End-point adjudication committee will decide whether patient (a) improved; (b) worsened; (c) not changed, based on: 6-minute walk distance, NYHA class, heart failure hospitalization, death, CRT turned OFF, MLHFQ and SF-36 score, LVEF/LVESV on echocardiogram; (3) Reverse electrical remodeling, defined as shortenedduration of non-paced QRS complex 6 months post-CRT≥10 ms; (4) Regression slope of PeRV1 interval, measured 6 months post-CRT, regressed against PeRV1 interval measured prior CRT.

SATISTICAL POWER



We are planning a study with 15 experimental subjects and 15 controls in which we will regress values of EDI values measured by ECGI 6 months post-CRT against EDI values measured by ECGI prior CRT within each treatment group. Prior data (Ghosh et al, 2911) indicate that the SD of EDI is 3.9 and 2.3 in the responders and non-responders, respectively. We assumed that the SD 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 is 0.05. We added 6% for loss of FU. Planned enrollment N=32

DESIGN

- investigator-initiated
- prospective,
- single-center,
- randomized,
- double-blind
- paralleled
- controlled clinical trial
- comparing adaptive cardiac resynchronization therapy (aCRT) to a standard CRT in patients with currently approved (class I-II) indications for CRT

PRIMARY OBJECTIVES

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 (EDI) 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. **Primary outcome**: 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. **Primary outcome** : Regression slope of SAI QRST against EDI value and regression slope of QRS duration against EDI value

RANDOMIZATION

- 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 created using the –ralloc- program in Stata

INCLUSION CRITERIA

1. 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
3. Is willing and able to comply with the protocol

SECONDARY OBJECTIVES

1. To determine if the interval between the end of P-wave and the onset of QRS complex in lead V1 (PeRV1) is associated with intracardiac RA-RV activation time. **Outcome measured**: AV_interval 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 LV end-systolic volume (LVESV) ≥ 15mls after 6 months of CRT. **Outcome measured**: non-paced QRS duration and LVESV.
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.

EXCLUSION CRITERIA

1. 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."
2. Patient has ever had a previous or has an existing CRT system, ICD, or pacemaker.
3. GFR <30ml/min
4. 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
5. Patient has primary valvular disease and is indicated for valve repair or replacement
6. Patient is enrolled in ≥1 concurrent studies that would confound the study results (any other interventional trial)
7. 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.
8. Patient status post heart transplant
9. Patient has been classified as NYHA functional class IV within 3 months prior to study enrollment
10. Concomitant conditions other than cardiac diseases that were associated with a higher likelihood of death during 1 year after enrollment
11. Patient, legal guardian or authorized representative is unable or unwilling to cooperate or give written informed consent

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