

Signal Averaged Electrocardiograms in patients with combined Cardiac Resynchronization/Implantable Cardioverter Defibrillators (CRT-D)

A) Study Purpose and Rationale

Cardiac Resynchronization Therapy (CRT) is a device-based treatment for advanced congestive heart failure (CHF), specifically patients with evidence of electrical dyssynchrony (QRS > 120 ms) where the right atrium (RA), left ventricle (LV) and right ventricle (RV) are sequentially paced, allowing for improved electrical coordination within the failing heart. It has been shown in numerous trials to improve heart failure symptoms as well as mortality. Specifically, the CARE-HF trial showed a 15% reduction in rates of sudden cardiac death or tachyarrhythmias (10% vs 25%) 3 years out from implantation. (1) Results of other trials have shown a mortality benefit of combining CRT with implantable cardioverter defibrillator (ICD, or CRT-D) as well over medical therapy. (2) Although no large-scale study has specifically compared mortality in CRT-D to conventional CRT, it is becoming the standard of care to implant CRT-D devices in all patients due to the high likelihood of these patients requiring an ICD later in life. (3) CRT-D implantation is much more expensive (\$30,699 vs \$12,328) (4) and at least one trial suggests a similar mortality and hospitalization rates in patients with CRT-D vs CRT alone.(2) Therefore the additional ICD component may not be necessary in all patients. We seek to investigate the technique of signal averaged EKG (SAEKG) to stratify CRT patients into those requiring and not requiring ICD functionality. It is a non-invasive study where surface EKG signals are recorded for an extended period of time and averaged to enhance the signal-to-noise ratio. This allows for late potentials to be observed. These high frequency, low amplitude oscillations are thought to be indicators of an arrhythmogenic substrate and increase greatly in the presence of prior ischemia and previous episodes of ventricular tachycardias and fibrillation, regardless of underlying etiology. Their prevalence ranges from 6% in healthy low risk control groups to 92% in patients with documented history of VT and CAD. They have been used in the past experimentally to stratify intermediate-risk patients for ICD therapy.(5) We seek to characterize these electrical phenomena further in the CRT population to see if they could be used to stratify patients into CRT vs CRT-D therapy

B) Study Design and Statistical Analysis

The study is designed as a prospective observational study. Our primary outcome would be rates of ICD firing in patients with normal versus abnormal pre-CRT-D placement. Data from post-MI patients suggests that 33% of patients who have had a distant MI but no history of ventricular arrhythmias will have an abnormal SAEKG, presumably predicting an ICD firing in the future. In the same study a normal SAEKG predicted a 5% likelihood of VT, whereas abnormal SAEKG has a positive predictive value of VT of 30% at 3 years. (6) Extrapolating this to the population to get CRD-devices, assuming an event rate of 30% in the abnormal SAEKG group, 5% in the normal SAEKG group and a group size ratio of 1:2, a total of 89 patients would be required (30 in group 1, 59 in group 2) No randomization would be required. At 3 years, the proportions of ICD firing would be compared in patients who had late potentials before, early and late after CRT-D implantation. Secondary outcomes include rates of abnormal SAEKG at

one month and one year after implantation and the changes compared to pre-implantation. A Chi-squared test would be used to compare rates of late potentials both before and after CRT-D implantation as well as the proportions in patients who had experienced an ICD firing with $\alpha = 0.05$. A post-hoc power analysis would be performed to verify that the study is powered to SCD mortality of at least 80%.

C) Study Procedure

All patients would undergo standard pre-procedural care for CRT-D implantation, including medical optimization of their CHF, 12-lead EKG and transthoracic echo. They would undergo SAEKG one week prior to device implantation. The procedure takes approximately 7-minutes, is non-invasive and involves no discomfort to the patient other than being required to lie still during the procedure. SAEKG would be repeated one month and one year after implantation to look for both short- and long- term effects of CRT-D on late potentials.

D) Study Drugs

No investigational medications would be used in this study. Patients would be expected to receive standard CHF medical optimization in addition to other medications they may be taking.

E) Medical Device

All study patients would be implanted with CRD-D devices. These devices are non-investigational; the ACC/AHA guidelines currently recommend them in patients with the inclusion criteria described in section B above with class Ia evidence(3). SAEKG would be considered investigational; although it is non-invasive and there are no risks to the procedure, it should be noted that the most recent ACC/AHA guidelines do not recommend its use in stratifying post-MI patients for ICD therapy. (3,5)

F) Study Questionnaires

No study questionnaires would be given

G) Study Subjects

Patients with NYHA class III-IV heart failure with LV ejection fraction (LVEF) <35%, LV end diastolic dimension (LVEDD) > 30 mm, QRS > 120 ms, optimized on medical therapy and deemed appropriate for CRT-D by a cardiac electrophysiologist would be enrolled in the study. Men and women over the age of 18 would be eligible Exclusion criteria are a major cardiovascular event including acute coronary syndrome or ventricular tachyarrhythmia in the previous 6 weeks, pre-existing atrial arrhythmias, pre-existing pacemaker or ICD, stage IV CHF requiring continuous IV infusions and CHF due to congenital heart disease.

H) Recruitment of Subjects

Patients would be recruited by cardiac electrophysiologists at New York Presbyterian hospitals after being referred for CRT evaluation. The patients must be agreeable to the study and be

informed that he/she may discuss the study with the research team to answer any questions before the additional procedures are performed.

I) Confidentiality of Subject Data

All patient records, including clinical charts, electrocardiographic and echocardiographic data would be de-identified and assigned a unique code. The data would be stored electronically on encrypted hard drives stored in a secure location.

J) Potential Conflicts of Interest

Study investigators and recruiting physicians would be required to disclose pre-existing conflicts of interest as well as any conflicts that may arise in the procurement of funding for the study.

K) Location of the Study

Recruitment, diagnostic and therapeutic procedures would all be performed at New York Presbyterian (Cornell and Columbia Campuses) as well as any other associated outpatient clinic or procedural center. The trial would be eligible for multi-center enrollment.

L) Potential Risks

The risks of the study include the standard risks associated with CRT-D device implantation, including bleeding during the procedure, post-procedural infection, perforation of vascular or cardiac structures and/or induction of arrhythmias during the procedure. The SAEKG is akin to a standard 12-lead EKG but takes approximately 7 minutes. There have been no identified risks to this procedure and it is noninvasive.

M) Potential Benefits

Potential benefits include an early detection of increased risk of arrhythmias than would be identified if the patient were not enrolled in the study, although they would already be receiving an ICD, which is the current standard of care for patients with high ventricular tachyarrhythmia/SCD risk. The patient may not benefit from participation in this study.

N) Alternative Therapies

Alternative therapies to CRT-D implantation include CRT alone, ICD, left-ventricular assist device (LVAD) or transplantation. All of these have their own risks and benefits as well and are approved for the treatment of advanced CHF.

O) Compensation to Subjects

Subjects will not be paid for the procedure.

P) Cost to Subjects

Subjects will be billed the standard cost of the CRT-D implantation as well as pre-procedural evaluation and post-procedural care. They will not be charged the additional cost of the SAECG, which will be funded by the institution and study funds.

Q) Minors as Research Subjects

No minors will be recruited for this study.

R) Radiation or Radioactive Substances

The CRT-D procedure involves direct fluoroscopic guidance, and thus patients will be exposed to radiation in the procedure. However as stated above, this exposure is non-investigational and is part of a well-established procedure sanctioned by ACC/AHA guidelines.

Sources:

1. Cleland JGF, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *NEJM*. 2005 Apr 14;352:1539-49
2. Bristow MR, Saxon LA Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *NEJM* 2004 May 20;350(21) 2140-50
3. Jessup M, Abraham WT, Casey DE et al. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart failure in Adults. *Circulation* 2009; 119:1977-2016
4. Mattias N, Strooband S, Obyn C et. Al. Cost-effectiveness of cardiac resynchronization therapy for patients with moderate-to-severe Heart Failure: A Markov Model. *BMJ* 2011;1(2) e000276
5. Signal-Averaged Electrocardiography. *J Am Coll Cardiol* 1996; 27:238
6. McGuire M, Kuchar D, Ganis J et al. Natural History of late potentials in the first ten days after acute myocardial infarction and relation to early ventricular arrhythmias. *Am J Coll Cardiol* 1988; 61(15):1187