

# Cardiac Resynchronization Therapy For Heart Failure With Preserved Ejection Fraction

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## A. Study Purpose and Rationale

Congestive heart failure affects nearly 5 million people in the United States<sup>1</sup>. Approximately half of these patients have heart failure with preserved ejection fraction (HFpEF), commonly referred to as diastolic heart failure. These patients are symptomatic with decreased exercise tolerance, shortness of breath, and fatigue, and are frequently hospitalized. Patients with HFpEF tend to be older and female, and suffer from multiple co-morbid conditions including hypertension, diabetes mellitus, obesity, chronic kidney disease, and anemia. There are currently no FDA approved treatments for HFpEF. In clinical practice, these patients are commonly treated with similar medications as are patients with systolic dysfunction, including beta blockers, ACE inhibitors, and diuretics.

In addition to medical therapy for heart failure, devices have been developed that have led to improvements in symptoms and mortality. Specifically, cardiac resynchronization therapy (CRT) is a pacemaker with an atrial lead, right ventricular lead, and left ventricular lead, that allows for coordinated ventricular contraction. CRT is indicated for heart failure with certain features including New York Heart Association (NYHA) Class III-IV symptoms despite standard medical therapy, QRS duration > 120, and EF < 35%. Major clinical trials (CARE-HF, MIRACLE, COMPANION trials) have showed symptomatic improvement by 1-3 months and survival benefits in selected patients receiving biventricular pacemakers<sup>2,3,4</sup>.

Some studies have shown a correlation between mechanical dyssynchrony of left ventricular systole as defined through several echocardiographic indices, and degree of response to CRT<sup>5,6</sup>. Additionally, recent prospective trials have shown similar symptomatic benefit in patients with narrow QRS intervals and evidence of mechanical dyssynchrony by echocardiographic criteria compared to those with wide QRS intervals<sup>7,8</sup>.

The cardiac cycle is composed of systole and diastole, and their function is closely integrated. Notably, a recent echocardiographic analysis in CRT demonstrated marked improvement in diastolic dysfunction in patients receiving CRT<sup>9</sup>. Furthermore, two recent studies have shown that 33-39% of patients with HFpEF demonstrate evidence of systolic dyssynchrony<sup>10,11</sup>. Given that mechanical dyssynchrony of left ventricular contraction is a powerful predictor of response to CRT, and that many patients with HFpEF demonstrate mechanical dyssynchrony, the current study aims to evaluate CRT in patients with HFpEF who have mechanical dyssynchrony during ventricular contraction. The hypothesis is that patients with HFpEF and mechanical dyssynchrony who receive CRT will demonstrate improvement in exercise tolerance when compared to placebo.

## B. Study Design and Statistical Analysis

Patients at the Columbia University Medical Center heart failure clinics who meet criteria including NYHA Class III-IV heart failure despite optimal medical therapy and

EF > 50%, will be recruited for the study. All subjects will receive baseline evaluation including tissue doppler echocardiography to assess mechanical dyssynchrony, 6 minute walk test (6MWT), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and assessment of New York Heart Association (NYHA) functional class. Only subjects with mechanical dyssynchrony will be included in this study. All subjects will receive a biventricular pacemaker. Subjects will be randomized to having the device programmed to biventricular pacing (CRT) or to back up pacing only. After device implantation at 1, 3, and 6 months the subjects will undergo repeat evaluation including 6MWT, MLHFQ, NYHA functional class, and tissue doppler echocardiography. Subjects and the investigators will be blinded to pacemaker programming. The primary end point is change in 6MWT at 6 months. Secondary end points are changes in the MLHFQ score, NYHA functional class, and dyssynchrony index.

Prior studies in patients with low EF and narrow QRS interval receiving CRT showed that subjects improved on the 6MWT on average 89m +/- 107m<sup>8</sup>. We will aim for a more modest effect size of 70m, generally thought to represent the minimal change in 6MWT that is clinically meaningful<sup>12</sup>. To demonstrate 70m improvement in 6MWT with power 0.80 and  $\alpha = 0.05$ , we calculate that 39 subjects will need to be included in each study arm. Allowing for a 10% unsuccessful rate of pacemaker implantation, 45 will be included in each arm. Approximately 270 patients will need to be screened for mechanical dyssynchrony. Outcomes will be assessed on an intention-to-treat basis. Unpaired Student's t-test will be used to compare change from baseline for all measurements in the two groups. Statistical significance will be set at  $p = 0.05$  for the primary outcome and  $p = 0.01$  for the secondary outcomes.

### **C. Study Procedure**

Standard echocardiography with tissue doppler capabilities will be performed. Briefly, the patient will have limb leads placed for continuous monitoring of the electrocardiogram. Tissue doppler echocardiography will be performed in the apical 4-chamber, 2-chamber, and long-axis views. 3 consecutive beats will be stored and the images will be analyzed off-line. Myocardial velocity curves will be reconstituted for basal and mid-segmental sections of lateral, septal, anteroseptal, inferior, posterior, and anterior walls. Time to maximal systolic velocity (TMSV) referenced to the start of the QRS interval will be determined, and the standard deviation of all 12 segments will be used as the index of mechanical dyssynchrony (TMSV-SD). The normal cut-off value for TMSV-SD is 33msec.

Biventricular pacemakers will be implanted according to standard technique. Briefly, under conscious sedation and local anesthesia, using sterile technique an incision will be made in the left upper chest wall. Under fluoroscopic guidance, pacemaker leads will be placed via the left cephalic vein into the right atrial appendage and right ventricle, and via the left subclavian vein and coronary sinus into the left ventricle. The pacemaker generator will be fixed in the chest wall pocket. The biventricular pacemaker used will be the Medtronic InSync III.

The 6-minute walk test will be performed in a 30-meter hallway, and the patient will be asked to walk for 6 minutes, up and down the hallway. Total distance walked will be recorded. Standardized encouragements will be used.

The Minnesota Living With Heart Failure Questionnaire will be given to the patient, who will be asked to read and respond to all 21 questions. The values corresponding to the patients' responses will be summated.

#### **D. Medical Device**

The biventricular pacemaker used for CRT in this study will be the Medtronic In-Sync III. This device is commercially available, and approximately 19,000 have been implanted since US market release 2/2003. There have been 2 device malfunctions reported. Current indications are for patients with NYHA Class III-IV heart failure on optimal medical therapy with EF < 35% and QRS duration > 120msec. Package insert is available upon request.

#### **E. Study Questionnaire**

Minnesota Living With Heart Failure Questionnaire (available upon request).

#### **F. Study Subjects**

Subjects will be referred by their primary cardiologist in the Columbia University Medical Center heart failure clinics. Inclusion criteria include class III-IV heart failure despite optimal medical management as determined by the patient's cardiologist and ejection fraction > 50%. All subjects will be screened by echocardiography for mechanical dyssynchrony as described above, and only those patients demonstrating mechanical dyssynchrony will be included. Exclusion factors include patients with active ischemia, atrial fibrillation, known hypertrophic obstructive cardiomyopathy or amyloidosis, or inability to provide informed consent.

#### **G. Recruitment of Subjects**

Patients in the adult heart failure clinics at Columbia University Medical Center who have ejection fraction > 50% and NYHA Class III-IV symptoms will be contacted by their primary cardiologist either by phone or in person at routine follow up for referral to the study investigators.

#### **H. Confidentiality of Study Data**

Patient data will be recorded on paper and electronic databases on CD, and echocardiographic data will be recorded on CD that will be stored in secure fashion in the office of the primary investigator. This information is property of Columbia University Medical Center and may be made available to the study investigators, authorized representatives of the National Institutes of Health, Food and Drug Administration, and Institutional Review Board. Patients will not be identified should the data be published or presented in a scientific meeting.

## **I. Location of the Study**

Echocardiography and questionnaires will take place in the echocardiography research laboratory. 6-minute walk test will be performed in a corridor in the Columbia University Medical Center. Biventricular pacemakers will be implanted in the electrophysiology laboratory.

## **J. Potential Risks**

The greatest risk to subjects is implantation of the pacemaker. In approximately 10% of patients, device implantation is unsuccessful due to inability to implant the left ventricular lead. Common complications of biventricular pacemaker implantation include coronary sinus trauma (0.8 to 2.4 percent), lead dislodgment (up to 9%), and diaphragmatic or phrenic nerve stimulation<sup>2,4,13,14</sup>. Patients will receive close routine follow-up after device implantation by the electrophysiologist. Additionally these patients should not have MRI performed in the future. There are minimal risks to echocardiography although some subjects may complain of chest pressure from application of the ultrasound probe, and can ask the echocardiographer to lessen pressure. Subjects may experience shortness of breath or chest pain during the 6MWT, and may stop at any time.

## **K. Potential Benefits**

Subjects may experience improved exercise capacity and decreased heart failure symptoms after device implantation.

## **L. Alternative Therapies**

Subjects may opt to not participate in this study, and will resume their usual care with their primary cardiologist.

## **M. Compensation to Subjects**

Subjects will receive \$25 compensation for each evaluation session.

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<sup>1</sup> American Heart Association, 2005.

<sup>2</sup> Cleland JG. NEJM 352(15): 1539-49, 2005.

<sup>3</sup> Abraham WT. NEJM 346(24 ): 1845-53, 2002.

<sup>4</sup> Bristow, MR. NEJM 350(21): 2140-50, 2004.

<sup>5</sup> Bax JJ. JACC 44(9): 1834-40, 2004.

<sup>6</sup> Penicka M. Circulation 109(8): 978-83, 2004.

<sup>7</sup> Yu C. JACC 48(11): 2251-7, 2006.

<sup>8</sup> Bleeker GB. JACC 48(11): 2243-50, 2006.

<sup>9</sup> Kantharia BK. Congest Heart Fail 12(4): 192-5, 2005.

<sup>10</sup> Wang J. JACC 49(1): 106-8, 2007.

<sup>11</sup> Yu C. JACC 49(1): 88-96, 2007.

<sup>12</sup> American Thoracic Society, 2002.

<sup>13</sup> McAlister FA. Ann Intern Med 141(5): 381-90, 2004.

<sup>14</sup> Leon AR. JACC 46(12):2348-56, 2005.