Device Therapy in Heart Failure Management: A Comparison of Right Ventricular, Left Ventricular, and Biventricular Pacing Strategies

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A. Study Purpose and Rationale

a. Background

Heart failure is a disease of immense burden and cost to individuals and society. It is estimated that over 4.5 million people in the United States currently suffer from heart failure and over 400,000 cases are newly diagnosed each year (1). The prevalence of the disease increases with age such that nearly 10% of the population will be affected in the ninth decade of life (2). Further, heart failure is the leading cause of hospitalizations of individuals over 65 years of age and it is estimated that there will be over one million hospitalizations for heart failure this year with an economic cost of over $40 billion (3). Given the tremendous scope of heart failure, a great deal of research has gone into finding therapies that can reduce its morbidity and mortality.

Numerous trials have resulted in guidelines which currently recommend the use of beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics, aldosterone antagonists, and digoxin for the treatment of heart failure patients at various stages of the disease (4). Despite these advances in the pharmacological management of heart failure patients, it is clear that there still remain a significant number of patients with persistent symptoms while on maximal medical therapy. More importantly, heart failure continues to be one of the most progressive and lethal diseases and still directly and indirectly contributes to 250,000 deaths annually (4). Given the likelihood that the personal, societal, and economic burden of heart failure will only grow as the number of individuals over the age of 65 increases in the next few decades, it is imperative that all varieties of therapies that can potentially reduce morbidity and mortality be fully explored and utilized.

An important characteristic of heart failure is the presence of dysrhythmias and conduction system abnormalities. Some have estimated that up to 53% of heart failure patients have intraventricular conduction delays that can lead to abnormal electrical depolarization and subsequent dyssynchrony between the right ventricle (RV) and left ventricle (LV) (5). While many efforts have focused on other aspects of heart failure such as optimization of preload, afterload, and contractility, recent technological breakthroughs have now made addressing the correction of ventricular dyssynchrony a possibility. This is of significance since the consequences of ventricular dyssynchrony, including abnormal interventricular septal wall motion, reduction in stroke volume, reduction in the rate of rise of left ventricular pressure, diminished diastolic filling times, and prolongation of mitral regurgitation, all contribute, worsening heart failure and can cause symptomatic deterioration (6-8).

To identify patients in whom ventricular dyssyncbrony may be a problem, the presence of a bundle branch block or interventricular conduction delay on a standard electrocardiogram has been used since these findings are the manifestation of ventricular dyssynchrony. In fact, the presence of a wide QRS complex has been shown to be an independent or contributing risk factor in patients with heart failure, presumably because of the dyssynchrony it represents (5, 9-12). While pacemakers were primarily designed to treat atrioventricular (AV) and sinus node conduction defects, numerous pacing strategies were attempted to resynchronize electrical depolarization prior to the development of current biventricular (BV) systems. Attempts to manipulate parameters, such as the AV delay, of traditional pacemakers which have right atrial (RA) and RV leads have yielded inconsistent results and in certain cases have worsened ventricular dyssynchrony (6-8, 13-20).

These results led to investigations of various stimulation sites within the RV, including the apex, septum, and outflow tract, as well as studies looking at LV and BV stimulation using epicardial leads placed through a thoracotomy; results demonstrated that the LV and BV strategies were far superior in achieving a hemodynamic improvement (21-26). Specifically, improved LV contractility, increased pulse pressure, decreased myocardial oxygen utilization, decreased LV end-diastolic and end-systolic volumes, and improved myocardial performance index (MPI) were all seen (23, 25-31). Further, improvement in six-minute walk distances, oxygen uptake at peak exercise, quality of life scores, and NYHA class have all been seen (31-32). Finally, preliminary results from currently ongoing randomized trials have shown that BV resynchronization in heart failure patients significantly improves myocardial performance and numerous clinical parameters (33-35).

An important aspect of recent trials has been the replacement of LV epicardial leads placed via a thoracotomy by coronary venous leads placed percutaneously; initial experience with these leads has been very good in terms of their ftinctioning and in terms of reduced implantation morbidity (36-37). Based on this technological advancement, current investigational systems now incorporate entirely percutaneously placed leads and support various programmable resynchronization therapies.

b. Purpose and Rationale

All of the trials and studies to date have only looked at heart failure patients with intraventricular conduction delays who have no indications for permanent pacing. One reason for excluding patients who need pacemaker support for sinus or AV node disease is that they often dramatically improve from pacing alone; thus, it would have been difficult to determine the true effects of LV or BV pacing in these patients. As well, since the coronary venous lead was only recently introduced, it was previously impossible to blind patients in trials in terms of whether they were given an RV or BV/LV system because of the thoracotomy that was required. Finally, current devices do not allow individual leads to be turned on or off such that a BV pacing device is either on or off and cannot be switched to only LV or RV pacing. Thus, patients who needed pacemaker therapy could not be included in trials because of the inability to switch to traditional RV pacing if BV pacing was not optimal.

However, investigational devices currently being developed will allow the programmable capability to turn on or off specific leads. This, combined w ' ith complete percutaneous placement of leads, now affords the ability to do randomized, blinded trials to look at the effect of BV and LV pacing as compared to RV pacing in heart failure patients. More importantly, it allows for confirmation of the fact that the hemodynamic improvements seen in heart failure patients who do not have indications for pacemaker therapy is preserved in patients who do have sinus or AV node disease. Further, it will help better define how best to optimize a pacing therapy for a given patient and whether or not BV pacing systems should replace dual chamber RV pacing systems in all heart failure patients with ventricular dyssynchrony.

Therefore, the purpose of this study is to compare RV, LV, and BV pacing in heart failure patients with ventricular dyssynchrony specifically referred to have a pacemaker placed because they meet the criteria for pacemaker implantation as outlined by the American College of Cardiology and the American Heart Association (38). The hypothesis being tested is that BV and LV pacing will improve hemodynamic and clinical outcomes more than traditional RV pacing in these patients. These improvements will occur without compromising device treatment of the underlying conduction disease for which the patient was referred. To date, these patients have not been enrolled in trials of BV pacing and thus represent an important group who have yet to be studied.

B. Study Design and Statistical Analysis

a. Design

This trial is designed to ascertain whether BV and LV pacing improve measures of cardiac performance and clinical symptoms when compared to RV pacing in heart failure patients with ventricular dyssynchrony referred for pacemaker implantation. This trial is a double-blind, prospective,

randomized clinical trial. After patients have been screened for certain criteria (see below), the ones who are eligible and choose to enroll will have their pharmacologic therapy optimized, regardless of randomization. They will subsequently be randomized in a 1: 1: 1 fashion to the following arms: RV pacing, LV pacing, or BV pacing. Stratification for use of beta-blockers will be employed so that the distribution of beta-blocker use will be equivalent in all arms at the time of randomization. Only the biostatistician controlling the randomization and the cardiologist implanting the device will not be blinded; the patients will all have the same device implanted and should not be able to determine the mode of pacing to which they were assigned. At the time of device implantation, the cardiologist performing the implantation will ensure that the device is implanted properly, will turn on the device to pace according to the type of pacing that the patient, was randomized to, and will ensure the patient tolerates the therapy in the immediate post-operative period. There is to be no cross-over implemented in this trial.

b. Endpoints

The primary endpoints of the trial are MPI measurements obtained during two-dimensional Doppler echocardiography performed at six week intervals after device implantation. The MPI is a Doppler-derived index assessing both systolic and diastolic performance and has been shown to correlate with simultaneous invasive measures of cardiac function; thus, it has prognostic significance in assessing myocardial performance (39-41). Secondary endpoints include sixminute walk distance, cardiopulmonary exercise testing to measure peak oxygen uptake, quality of life assessment using a standardized tools, and pacemaker interrogation to ensure proper pacemaker function and therapy. Interrogation will be done by the cardiologist responsible for the implant. Endpoint data will be collected at time of pre-implantation/randomization and at six week intervals after implantation to a total of 24 weeks.

c. Statistical analysis

The MPI will be generated using echocardiographic data every six weeks and an MPI difference will be calculated by subtracting the measured MPI from the pre-implant MPI for each patient. The mean and standard deviation for these MPI differences will be calculated for each of the three groups of patients at each six week endpoint and then compared to each other using an unpaired t-test.

Based on data from studies of BV pacing in heart failure patients in which the MPI was also utilized, it is anticipated that the calculated MPI difference for the, RV pacing group will be near zero and for the BV and LV pacing groups will be 0. 15-0.20 with a standard deviation of roughly 0.20 (42). Of note, mean MPI values in these studies have been;t~0.75 prior to implantation; MPI values in normal subjects is 0.37 ± 0.05 (41). Assuming a presumed effect (MR1 difference) of 0.15 and a standard deviation of 0.20, for a power of 80%, testing at p=0.05, each arm of the trial would need roughly 30 people. Thus, a total of 90 patients would need to be randomized.

C. Study Procedures

a. Device implantation

Once informed consent for the implantation of the device is obtained, the patient will be taken to the operating room and given general anesthesia. The coronary sinus is then accessed via the subclavian vein and a coronary venogram is obtained using a balloon catheter placed in the proximal coronary sinus. This allows for visualization of the cardiac veins available for placement of the LV lead. The cardiologist will then test various cardiac veins for signal strength, pacing thresholds, and lead impedance and subsequently place the lead in the vein where he thinks it will perform the best. As there is no way to select the optimum site for maximal hemodynamic benefit, the lead is simply placed in the best site available. Next, the RA and RV leads are placed via the cephalic vein with the RV lead placed in the apex in a place allowing for good separation of the LV and RV signals. A pocket is made in the anterior chest and the pulse generator is placed there after all the leads are connected to it and tested. The overall procedure takes roughly three to four hours to complete. Once out of the operating room, the cardiologist

will make sure the device is mechanically stable and ensure there have been no complications. He will then turn it on to RV, LV, or BV pacing as per the randomization. The patient will only feel a few days of post-operative pain at the sites of venous access and where the generator was placed.

b. Interval measurements

Two dimensional echocardiography, cardiopulmonary testing, and six-minute walk will all be performed at pre-implantation and at six week intervals for 24 weeks. Echocardiography is noninvasive and should last no more than 30 minutes. Cardiopulmonary testing should require less than 3 0 minutes and will require a patient to pedal on a stationary bicycle. The only discomfort from this and the six-minute walk will be when the patient reaches his or her exercise capacity and thus may feel somewhat fatigued.

D. Study Drugs

No study drugs are to be used in this trial.

E. Medical Devices

The heart failure device to be used in this trial is comprised of a programmable pulse generator, a transvenous RA pace/sense lead, an insulated bipolar RV pace/sense lead, and an LV coronary venous pace/sense lead. The RA and RV leads are commercially available and have been used extensively. The LV coronary venous pace/sense lead has been safely used in numerous previous trials in which BV pacing was utilized. All of the leads are placed percutaneously. The pulse generator is currently under development and is soon to be available from Guidant Corporation, St. Paul, MN for investigational use in the United States. It will allow programmability of the RV and LV leads such that either one can be turned on or off individually or simultaneously. This will allow for continuous pacemaker support not only during the trial, but also after it ends. It will also allow for standard RA/RV pacing should LV or BV pacing prove problematic in a given patient. Once the pacing therapy has been assigned during randomization, it is the mode of pacing that will be programmed and will remain on barring any unforeseen complications.

F. Study Questionnaires

The questionnaire to be used is still being developed, but will focus on quality of life issues for heart failure patients and will be based on standardized tools such as the Minnesota Living with Heart Failure questionnaire.

G. Study Subjects

a. Basic inclusion criteria
1 Age: 18 years or older
2. NYHA class: 11 - IV
3. QRS complex duration: >120 milliseconds
4. Ejection fraction: <35%
5. Maximal pharmacologic therapy including diuretics, ACE inhibitors, spironolactone, beta-blockers, and digoxin

b. Basic exclusion criteria
1. Cannot or will not tolerate device implantation or anesthesia
2. Meets indications for an implantable cardioverter defibrillator
3. Life expectancy less than six months due to other medical condition

4. Expected to receive a heart transplant within the next six months

H. Recruitment of Subjects

The patients to be screened for this trial will be heart failure patients referred to the Arrhythmia Center/Electrophysiology Division for pacemaker placement.

I. Confidentiality of Study Data

All patients will be assigned an unique code number at the time of randomization. These numbers will be the only identification used when data is collected on patients. The records of all the data collected will be kept in the Department of Cardiology and will only be accessible to the principal investigator.

J. Potential Conflict of Interest

There is no conflict of interest on the part of any of the investigators or cardiologists involved.

K. Location of the Study

The device implantation will take place in the operating rooms and all follow-up will be done in the cardiology division offices. Measurements will be done in the echocardiography lab and cardiopulmonary testing lab. Interrogation of the pacemaker will be done by the cardiologist who implanted the device in his office or pacemaker clinic.

L. Potential Risks

Transvenous implantation of RV and RA leads has been done for many decades with an extremely low risk of complication while coronary sinus LV lead placement is relatively new; however, its use so far has also only carried a low risk of complications. The entire procedure has the usual risks of a percutaneous procedure/minor surgery with the following potential risks: infection due to the device or implantation procedure, excessive bleeding, pneumothorax, thromboembolism, stroke, myocardial rupture, arrhythmia, myocardial ischernia or infarction, valvular trauma, hemolysis, and/or death. In addition, the long term effects of an LV lead are not yet well defined. The patients will also not be able to have magnetic resonance imaging scans in the future.

M. Potential Benefits

As all of the patients referred to be a part of this study are candidates for a pacemaker, the ability the have a LV lead placed at the same time offers them the ability to not only receive pacemaker support for their sinus or AV node disease, but also potentially improve their myocardial performance and clinical status. This, in turn, may lead to an improved quality of life. Further, if BV or LV pacing becomes the standard of care in the future, they will not need to undergo a second operation to have this lead placed and have their pacemaker changed, but simply will be able to have it turned on at the time of interrogation.

N. Alternative Therapies

The alternative to not participating in this study is to continue with medical management of the patient's heart failure and have a traditional dual chamber pacemaker placed.

O. Compensation to Subjects

Subjects will not receive monetary compensation for participation in this study.

P. Costs to Subjects

The cost of the procedure implantation that the patient and/or their insurance company will be responsible for will be based on the reimbursement for a standard pacemaker; any costs above and beyond that are to be paid for by the maker of the device. As echocardiography and cardiopulmonary testing are often part of the routine care of heart failure patients, the measurements made at pre-implantation and at 24 weeks will be billed to the patient and/or their insurance company. The patients will not be responsible for the costs of the interval follow-up.

Q. Minors as Research Subjects

No minors are to be enrolled in this trial.

R. Radiation or Radioactive Substances

No radiation or radioactive substances are to be used in this trial.

R. References

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