Effects of exercise on optimization of cardiac resynchronization therapy using echocardiographic assessment and QuickOpt™ Timing Cycle Optimization

Natalie Bello, MD

A. Study Purpose and Rationale

Congestive heart failure (CHF) is a major global cause of morbidity and mortality. In the United States it is estimated that 1-2 million people between the ages of 25 and 74 are affected[1] with mortality rates approaching 20% at 3 months after diagnosis, 33% at 1 year, and 70% at 8 years[2]. As the population continues to age and medical advances enable more people to live with cardiovascular diseases rather than die from it, the prevalence of and mortality due to heart failure will continue to rise. Furthermore, the high cost of treating patients with CHF will place an increasing economic strain on an already taxed healthcare system.

A variety of medications such as ACE inhibitors/ARBs, beta-blockers, and aldosterone inhibitors have been shown to slow the progression of heart failure and are now accepted as standard of care for the treatment of CHF. Despite optimal medical management a significant percentage of heart failure patients remain symptomatic. Recently a subpopulation of these patients has been shown to benefit from biventricular (BiV) pacing with improvements in symptomatology, and decreases in length of hospitalization and risk of death[3, 4].

BiV pacing involves the simultaneous pacing of both ventricles to decrease ventricular dyssynchrony in patients who have intraventricular conduction delay (QRS duration >120ms) and reduced ejection fraction (<35-40%). This therapy is also referred to as cardiac resynchronization therapy (CRT). Despite the implantation of BiV pacers and initiation of CRT a subset of patients do not symptomatically improve. In these cases echocardiogram has been used to adjust the timing of atrioventricular (AV) and interventricular (VV) delay to improve ejection fraction and exercise tolerance, a process known as optimization. Optimization is a lengthy procedure performed by an echocardiographer which to date has only been carried out at rest. Little is known about whether the AV and VV delay settings calculated at rest will be the most advantageous during exertion.

St. Jude has recently developed a software program known as QuickOpt™ for use with their BiV pacemakers and BiV ICDs. QuickOpt™ works by running an automated sequence of intracardiac electrograms and providing the optimal AV and VV delay settings within 90 seconds rather than the 2-3 hours required for traditional echocardiographic assessment. Initial studies have shown a 97-99% correlation between results obtained from QuickOpt™ and echocardiogram[5,6]. It is hoped that this software will increasingly be used to quickly optimize patient's BiV devices- augmenting both the number of patients who are able to be optimized and the frequency of optimization. Perhaps in the future devices will soon be able to continuously self-optimize as required by demand.

The purposes of this study are:

1. To show that the optimal timing of BiV pacing using the QuickOpt™ program is not significantly different than timing values obtained using traditional echocardiographic assessment.
2. To investigate whether optimal timing of BiV pacing during exercise using both echocardigraphic assessment and the QuickOpt™ program is significantly different from optimal timing obtained at rest.
3. To assess changes in quality of life related to CHF symptoms following exercise optimization utilizing the Minnesota Living with Heart Failure questionnaire (MLHF).

B. Study Design and Statistical Analysis:

This study will be conducted as a prospective, randomized, double-blinded trial of patients who have a St. Jude's BiV pacemaker or BiV ICD comparing the use of echocardiographic optimization to QuickOpt™ at rest and during exercise. Because of the inter-subject variability in ejection fraction and hemodynamics the study will utilize a cross-over design with each patient being optimized via echo and QuickOpt™ during exercise on two separate occasions. The order of optimization will be randomly generated by a computer and the subjects and investigators will be blinded to this information.

Using a paired t-test to analyze the continuous variables of AV and VV dyssynchrony obtained via echo and QuickOpt™ 34 subjects must be enrolled in this study to detect a 10% difference in optimization at rest and during exercise based on 80% power with a standard deviation of 0.2 msec and $\alpha = 0.05$.

B. Study Procedure

Participants will have their BiV device optimized by both echo and QuickOpt™ at baseline with the device being set to the echo parameters. Echo Opt is performed using echocardiogram, an ultrasound of the heart, to provide optimal hemodynamics as (measured by ejection fraction and cardiac output) obtained during the implementation of the full range of possible timing delays. This process takes between 2 and 3 hours to perform. The BiV settings are adjusted by placing a programmer wand on the skin over the BiV device thus allowing communication between the BiV device and the programmer. QuickOpt™ is a special algorithm built into the software of the programmer. QuickOpt™ uses intracardiac electrical data collected from the device of each participant to calculate the optimal parameters within 90 seconds.

After the optimization at rest, participants then will be asked to return in 2 weeks to exercise on a reclining stationary bicycle under supervision of medical doctors. Non-invasive blood pressure and heart rate will be monitored according to the standard exercise testing protocol. The speed of the pedal will be slowly increased every two minutes to achieve a goal of 60% of maximal predicted heart rate. The overall exercise workload will be very light. The bicycle can be stopped at any time a participant requests. This entire intervention is expected to last approximately 4 hours with subjects being unlikely to experience any pain, discomfort or inconvenience.

During exercise, Echo Opt and QuickOpt™ will be performed in a randomized order with the final optimization parameters becoming the new set point. Once the exercise finishes, participants will be monitored until their blood pressure and heart rate return to baseline. Participants will be asked to return on a different day 2 weeks later to repeat the entire process in the opposite optimization order and set point. They will again return 2 weeks later at which time the BiV will be reprogrammed to the original setting. The decision to change the BiV parameters to a value obtained from either method is at the discretion of participant's cardiologist.

During each visit and 3, 6 and 12 months following completion of the study the participants will fill out the Minnesota Living with Heart Failure questionnaire (MLHF). This well-validated tool is used to assess the effects of a heart failure treatment on key physical, emotional, social and mental dimensions of quality of life[7-9].

Data to be collected include:

- Demographics: age, sex, ethnicity
- Past medical history: myocardial infarction, dilated cardiomyopathy, hypertension, diabetes, etc.
- Non-invasive hemodynamic data: heart rate and blood pressures at rest and during each stage of exercise.
- Echocardiographic data: stroke volume, dyssynchrony indices, optimal AV and VV delays at rest and during exercise.
- QuickOpt™ calculated optimal AV and VV delays at rest and during exercise.

Analyses will be made on the following:

1. Changes in optimal AV and VV delays during rest and exercise using echocardiographic optimization.
2. Changes in optimal AV and VV delays during rest and exercise using QuickOpt™.
3. Comparison of the optimal AV and VV delays derived from Echo Opt and QuickOpt™ during rest and exercise.
4. The reliability of each method will be assessed by performing the exercise testing on two different days.
5. Changes in symptomatology as measured by the Minnesota Living with Heart Failure questionnaire (MLHF) at baseline and the above specified intervals.

D. Study Drugs

N/A

E. Medical Devices

This study involves the use of a commercially available software program, QuickOpt™, designed by St. Jude Medical for use with their BiV pacemakers and BiV ICDs. QuickOpt™ works by running an automated sequence of intracardiac electrograms and providing the optimal AV and VV delay settings within 90 seconds. QuickOpt™ is FDA

approved for use in United States. The software has been shown to be safe and effective and is easily programmed into pre-existing devices. Non-randomized studies have shown a 97-99% correlation between results obtained from QuickOpt™ and traditional echocardiogram [5,6].

F. Study Questionnaires

The MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE (attached) will be given to the subjects at baseline, prior to each exercise test, 3, 6 and 12 months after completion of the study.

G. Study Subjects

Inclusion Criteria:

- Prior implantation of a St. Jude Medical BiV pacemaker
- NYHA Class II/III heart failure
- QRS duration > 120 msec
- Ejection Fraction <40%

Exclusion Criteria:

- Age <18 years
- Inability to exercise
- Inability to lay supine for 3 hours
- Rhythm other than sinus rhythm
- Technically inadequate echocardiogram.

The study is not restricted by gender, race, ethnicity, language spoken, or age.

H. Recruitment of Subjects

Physicians in the Department of Cardiology at CUMC who implant and/or follow patients with BiV pacemakers have been approached and asked to inform their eligible patients about this research. The primary cardiologist will ask if the patient is willing to discuss the study with the research team. If a patient is agreeable to being contacted by the research team his/her contact information will be forwarded to the research investigators.

I. Confidentiality of Study

Patients will initially be referred to the study by name, medical record number, and date of birth and then once enrolled they will be de-identified with each patient receiving a unique coded identifier. Data will be stored in a secure location and be password protected with access granted only to investigators and study staff. All material containing identifying information will be destroyed after de-identification.

J. Potential Conflict of Interest

The investigators have no proprietary interest in any device or procedure under investigation nor will they benefit financially in any way from the results of this investigation.

K. Location of the Study

The study will be performed within the clinical areas of CUMC.

L. Potential Risks

There are minimal risks associated with exercise testing using a reclining bicycle during this study. The incidence of a serious adverse event such as arrhythmia or death occurring during exercise testing is estimated at less than 1 in 10,000 in the general population, and less than 1 in 1,000 in high risk patients. ACLS trained staff will be present at all sessions involving optimization.

Echocardiogram and BiV programming pose virtually no risk to patients. Some patients may experience discomfort from the pressure of the ultrasound probe on their chest wall.

M. Potential Benefits

Prior studies have shown that optimization of BiV pacemakers at rest can improve cardiac output. It is hypothesized that optimization during low levels of exercise may provide an additional benefit of improved exercise capacity for subjects with symptomatic CHF.

QuickOpt™ Timing Cycle Optimization has the potential to dramatically shorten the time required for optimization of BiV pacemakers thus making it possible for more patients to be optimized and more frequent optimization of the device as clinical conditions change over time.

The subjects may or may not benefit as a result of participation in this study. The results of this study may help to guide patient care in the future and may help to delineate the role of BiV optimization during exercise for patients with CHF and BiV pacemakers.

N. Alternative Therapies

The alternative therapy is for patients to not enroll in this study and have their BiV left in the default setting or optimized at the decision of their primary cardiologist.

O. Compensation to Subjects

Subjects will be compensated in the amount of $30 per visit. The payment will be in the form of a check that will be mailed to the subjects approximately 6 to 8 weeks after each

visit. If the subject does not complete the study there will no pro-rating of the compensation. They will only be compensated for the visits completed.

P. Costs to Subjects

The subjects will not incur any additional costs as a result of participating in the study.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

The study will not expose the participants to any radiation or radioactive substances.

S. References

1. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality of congestive heart failure in the United States. J Am Coll Cardiol 1992;20:301-6.

2. Mortality from congestive heart failure-- United States 1980-1990. MMWR February 11, 1994 / 43(05);77-81

3. Leclercq, C, Hare, JM. Ventricular resynchronization: current state of the art. Circulation 2004; 109:296.

4. Jarcho, JA. Resynchronizing ventricular contraction in heart failure. N Engl J Med 2005; 352:1594.

5. Meine et al. IEGM-based method for estimating optimal VV delay in cardiac resynchronization therapy. Europace Supplements, Vol. 6, June 2004 (#149/2).

6. Porterfield et al. Device based intracardiac delay optimization vs. echo in ICD patients (acute IEGM AV/PV and VV study). Europace Vol 8 Supp 1 July 2006 [abstract #6178].

7. Rector TS, Francis GS, Cohn JN. Patients'self-assessment of their congestive heart failure. Part 1 Patient perceived dysfunction and its poor correlation with maximal exercise tests. Heart Failure 1987;Oct/Nov:192-196.

8. Rector TS, Kubo SH, Cohn JN: Patients'self-assessment of their congestive heart failure. Part 2: Content, reliability and validity of a new measure, the Minnesota Living with Heart Failure questionnaire. Heart Failure 1987;Oct/Nov:198-209.

9. Rector TS. A conceptual model of the quality of life in relation to heart failure. J Cardiac Failure 2005

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little					Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5	
2. making you sit or lie down to rest during the day?		0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?		0	1	2	3	4	5
4. making your working around the house or yard difficult?		0	1	2	3	4	5
5. making your going places away from home difficult?		0	1	2	3	4	5
6. making your sleeping well at night difficult?		0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5	
8. making your working to earn a living difficult?		0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5	
10. making your sexual activities difficult?	0	1	2	3	4	5	
11. making you eat less of the foods you like?		0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5	
13. making you tired, fatigued, or low on energy?		0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5	
15. costing you money for medical care?	0	1	2	3	4	5	
16. giving you side effects from treatments?	0	1	2	3	4	5	
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5	
18. making you feel a loss of self-control in your life?		0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5	
20. making it difficult for you to concentrate or remember things?		0	1	2	3	4	5
21. making you feel depressed?		0	1	2	3	4	5

©1986 Regents of the University of Minnesota, All rights reserved.