Principal Investigator (PI):	Barry London, MD
Title of Study:	Right Ventricular Septal Pacing in Patients with Right Bundle Branch Block and Heart Failure, a Pilot Clinical Trial
Study Center:	University of Iowa
Estimated number of subjects:	40 adults over the age of 18

I. Introduction

Heart failure is the fastest growing cardiovascular diagnosis in the United States, with a prevalence of approximately2.5% in adults. The direct and indirect costs of heart failure exceed $33 billion per year.

Heart failure condition is commonly associated with abnormalities in the heart electrical conduction system that leads to losing the ability to achieve strong synchronized contractions.

During last decade, Cardiac Resynchronization therapy (CRT) has evolved as one of the standard therapies in heart failure field to target this issue; many large randomized controlled trials showed that this therapy significantly improves symptoms, heart function, rate of hospitalization, and overall mortality.

CRT requires pacemaker implantation in the cardiac catheterization laboratory. Implanted pacemaker activates or pace the heart in a synchronized fashion to minimize the deleterious consequences of the electrical abnormalities that are usually associated with heart failure.

It is well known now that patients with a specific conduction disease called left bundle branch block (LBBB) represent the heart failure group that benefit the most from this therapy, while heart failure patients with right bundle branch block(RBBB), another conduction disease, who represent around 10% to 15% of heart failure patients do not benefits as much.

CRT activates the areas of the heart that is affected mainly by LBBB not RBBB, it requires the addition of an extra leader wire to the regular defibrillator device that heart failure patients usually have, this procedure is usually done in the cardiac catheterization lab and considered as an invasive procedure.

As most patients with moderate to severe heart failure including who have RBBB meet current guidelines recommendations for defibrillator placement to prevent sudden cardiac death, most of them have already a defibrillator that is capable of pacing too and is placed routinely in the area of the heart that can normalize the RBBB associated electrical abnormalities if it would be paced by an appropriately programmed device.

In our proposed clinical trial, we are planning to recruit heart failure patients with only right bundle branch block who have already defibrillator or pacemaker, and after obtaining an informative consent, we will program their pacemaker/defibrillator to provide a novel form of CRT that target RBBB as we mentioned earlier without any need for an invasive procedure.

Our study's design is a randomized controlled single blinded cross-over study. Overall designs will include two 12 weeks treatment periods separated by 8 weeks washout periods.

One group will have pacing-washout-placebo sequence while the other will have placebo-washout-pacing sequence. Subjects will be randomized to either pacing (intervention) ornon-pacing (placebo) with 1:1 ratio at the initial visit. each subject will undergo heart ultrasound (echocardiogram), symptoms/quality of life assessment, and 6 minute walking distance assessment at initial, 12, 20, 32 weeks visits. This type of clinical trial design will have an advantage of blinding the intervention to the subject which will minimize bias and would create a control group. Indeed, will allow still to use relatively small number of subjects with enough power to test outcomes comparable to single arm prospective trial design, while parallel randomized controlled studies design would require higher subjects numbers for reaching an adequate power to test outcomes of interest due to lack of self control.

This study will allow us to evaluate the effect of this intervention on heart failure symptoms, heart size and function as well as quality of life in this specific group of heart failure patients.

II. Background

Several randomized trials and meta-analyses (1,2,3,9,10) conducted within the last decade showed that bi-ventricular cardiac resynchronization therapy (BIV-CRT) is an effective therapy for heart failure (HF) patients with LVEF=<35%and NYHA class III and IV symptoms who are on optimal medical therapy and have left bundle branch block (LBBB)with or without ICD. Most recently, some studies have shown that BIV-CRT benefits extend to HF patients that are less symptomatic [NYHA class I and II symptoms].(8,9) BIV-CRT significantly decreases all-cause mortality and cardiovascular morbidity including a reduction in heart failure hospitalizations, and it is associated with remarkable symptomatic improvement in HF patients at short term. Reverse positive remodeling represented by the decrease in left ventricular (LV) size, improvement of intra- and inter-ventricular synchrony and eventually improvement in LV function is the main mechanism of action of this therapy.

Many studies showed that the presence of right bundle branch block (RBBB) in patients with cardiovascular disease is associated with worse cardiovascular outcomes (4). Overall, RBBB prevalence in HF population according to previous studies ranges from 10-15% (3,9).

It is well known from previously conducted studies that BIV-CRT is most effective in patients with LBBB and that non-LBBB patients including RBBB patients tend to be overall non-responders with similar outcomes profile of the patients who underwent only ICD implantation(3,5,11). Studies have linked the response to CRT to the presence of the left intra-ventricular and/or inter-ventricular desynchrony which are common in LBBB patients(2,14). Indeed, patients who did show some response to BIV-CRT in the RBBB group were more likely to have left-sided dyssynchrony (6), left sided conduction disease (15), non-LAFB conduction pattern (5) or prolonged PR interval >230 ms (7). In the last scenario, the response was likely due to the correction of atrio-ventricular dysynchrony.

RBBB is associated with wide QRS and often with wall motion abnormalities and inter-ventricular dyssynchrony. Right sided intra-ventricular dyssynchrony or conduction delay is common and significant which can be accompanied sometimes by also left sided dyssynchrony(6,14). If those abnormalities can be minimized by a specific right sided pacing therapy, it may potentially result in reverse right ventricular remodeling and secondary left ventricular remodeling interventricular interdependence phenomenon which may lead to an improvement in cardiac output and hemodynamics as BIV-CRT does in LBBB situation.

RBBB patients have an intact conduction through the left bundle branch, thus pacing only the right ventricle targeting just the diseased right bundle branch and utilizing the normal conduction through left system may work better than pacing both ventricles together or only Left ventricle (14). By optimizing atrio-ventricular delay interval setting when programming the pacemaker/ICD, we can achieve a narrow fused ventricular activation wave (QRS complex) in RBBB patients that results from fusion of both the pacemaker wave and the normally conducted intrinsic wave through the intact left bundle branch. This may restore the normal ventricular activation sequence and hence we may achieve the wished effects described above.

Placement of the right ventricular (RV) lead tip varies in location between the RV apex and the mid portion of the septum. We do expect that mid septal location of RV lead (or sometimes called right ventricular outflow "RVOT" lead)would result in better fusion of ventricular activation waves (13)and thus will be likely more effective in restoration of the electrical and mechanical synchrony than apical RV leads. Apical lead not uncommonly creates iatrogenic LBBB that can be sometimes of deleterious effect on HF patients. Current practice has shifted toward septal lead placement, but apical leads are still common. Our study will include both types of RV lead location and will hopefully add some insight into this.

We are currently publishing interesting data which shows that right ventricular pacing in RBBB patients by mid septal leads can significantly reduce QRS duration and achieve narrow fused QRS waves(12). Also, we are working on case series to report the effect of this pacing intervention on normalizing wall motion abnormalities associated with RBBB by echocardiogram.

We believe that this is an attractive pacing therapy for heart failure that is worthy of further study; we hypothesize that Cat by only a single RV lead in HF patients with RBBB and has LVEF=<35% would improve heart failure symptoms by inducing reverse remodeling process and likely have a significant impact on cardiovascular outcomes, hopefully similar to those seen with BIV-CRT in HF patients with LBBB.

Our proposed study will be the first on this topic, as no published clinical trials can be found in the literature using this technique of CRT therapy. We expect that if we can prove that such intervention leads to positive remodeling and HF symptom improvement that would create interest in proceeding with a large multi-center randomized clinical trial to test this therapy's effect on major cardiovascular outcomes which may lead to major changes in the current guidelines of the pacing therapies in heart failure.

Tens to hundreds of thousands of heart failure patients in the United States who are not candidates for current conventional BIV-CRT due to the presence of RBBB, already have a right ventricular lead as part of their defibrillator implanted for sudden cardiac death prevention and may benefit from such intervention if we find it is effective. Our proposed intervention requires only a simple re-programming of their device' in other means we would provide potentially an added therapy to be delivered by devices that have already been implanted for another indications. Known current BIV-CRT therapy is associated with significant survival gain. Later studies have quantified this gain by analyzing multiple landmark CRT trials; Finegold JA el et as an example found that the number needs to treat (NNT) to save one life is 15 at 3 years in RAFT trial, which represents a breakthrough in medicine. This huge survival benefit that requires only low number of patients to be treated to save lives makes us excited to proceed with our proposed trial.

III. Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection and Good Clinical Practice training.

IV. IRB Oversight

Human Subjects Office / IRB
J. Andrew Bertolatus, MD
Hardin Library, Office 105
600 Newton Rd
Iowa City, IA 52242
FWA#: FWA00003007
Voice: 319-335-6564
Fax: 319-335-7310
Email: irb@uiowa.edu

V. Location of Study Procedures

University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242

VI. Main Hypothesis

To determine whether cardiac resynchronization therapy by single right ventricular lead in heart failure patient with RBBB will be associated with positive reverse left ventricular remodeling and improvement in heart failure symptoms and quality of life.

Primary endpoint Positive reverse left ventricular remodeling, defined as increase in LV Ejection Fraction >15% from baseline at 6 months.

VII. Inclusion Criteria

Our subject population is one group of patients who has the diagnosis of systolic heart failure.

Inclusion criteria:

Cardiomyopathy, ischemic or non-ischemic on optimal medical therapy per current heart failure treatment guidelines for at least 3 months.

LVEF <=35% by echocardiogram

Prior implantation of pacemaker/defibrillator with at least atrial and RV mid septal leads. Atrial lead can be waived if RV lead has atrial sensing capabilities.

Presence of right bundle branch block (RBBB), with QRS duration =>120 msec

Normal sinus rhythm

PR interval <250 msec on surface EKG

-Note: Subjects with Biventricular pacemaker/ICD will be enrolled if their LV lead has been deactivated by the their primary cardiologist prior to study enrollment for at least 3 months (this could be due to lead malfunction or the decision to deactivate the biventricular pacing therapy for any reason per primary cardiologist discretion)

Exclusion Criteria

Age younger than 18 years old

Any other known conditions other than heart failure that could limit survival to < 6 months.

Acute Myocardial infarction within 6 months of entry into the study

Pregnancy

Inotrope dependent heart failure condition

Left ventricular assist device (LVAD) or heart transplantation

Atrial fibrillation or flutter burden >10% within the last 6 months

Atrioventricular node block disease requires ventricular pacemaker support >10% of the time.

VIII. Study Procedures

After informative consent signed by potential subject and at the same visit (initial visit), every subject will undergo pacemaker/defibrillator screening check, transthoracic echocardiogram if no echocardiogram available within 6 months preceding the initial visit, and pregnancy test for females whose age 18-50 year-old, if subject is deemed still eligible based on the results of this initial visit screening tests, he/she will be randomized to one of the study's arm and undergo the following baseline tests/procedures.

Initial visit baseline tests/procedures:

A- 6-minute walking test if subject has not had one within 3 months prior to enrollment.
B- Subject will be requested to fill two questionnaires:
1- "Minnesota living with heart failure" questionnaire to assess your quality of life
2- "Self-assigned New York Heart Association survey (SA-NYHA)" to evaluate the severity of your heart failure symptoms.
C- Medications review, vital signs (heart rate, blood pressure measurement, and weight)
D Baseline pre- and post-programming 12 leads EKG
E- Pacemaker/defibrillator programming session will be performed on all subjects. Patient assigned to the arm that start with pacing initial treatment period, their devices will be programmed according to our study protocol for RBBB pacing therapy.

After the initial visit, subject will be scheduled for follow up visits. Each visit will last approximately (60-120 minutes) and will be located at University of Iowa Heart and Vascular center –adult outpatient facilities where each subject will have the following tests performed:

A-Follow up trans-thoracic echocardiogram
B-Follow up 6-minute walking test
C-Subject will be requested to fill the two-questionnaire mentioned above again for follow up purposes.
D-Medications review, follow up vital signs (heart rate, blood pressure measurement, and weight)
E-Subject will be asked whether has been hospitalized, has had any medication changes, or has suffered any acute myocardial infarction or stroke/TIA for the preceding 3 months.
F- Blood draw for laboratory tests (Sodium, BUN, Cr, and NT-proBNP)
G-Baseline pre- and post-programming 12 leads EKG
H-Follow up pacemaker/defibrillator check

IX. Adverse Event Reporting:

The University of Iowa requires Investigators to collect and report to the University of Iowa IRB if any of the following occur:

- An unanticipated problem involving risks to subjects or others is any event or problem that:
  1) was unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied AND
  2) suggests that the research places subjects or others (those not directly involved in the research such as research staff or family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized AND
  3) is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research).
  4) Serious adverse drug event (either expected or unexpected) occurring in a UI subject
  5) If a subject is enrolled by U/VAHCS investigators, the investigator must report to the UI IRB either serious adverse drug events or unexpected adverse drug events. By definition, these events must be associated with the use of the drug.
  6) An unexpected adverse drug event is any adverse drug experience (associated with the use of the drug), the frequency, specificity, or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to the subjects and the IRB
- A serious adverse drug event is any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes:
  1) Death

2) Life-threatening adverse drug experience

3) Inpatient hospitalization or prolongation of existing hospitalization

4) A persistent or significant disability/incapacity

5) A congenital anomaly/birth defect

6) Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

- Receipt of new information
  During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

- Noncompliance
  Noncompliance is a failure to follow the federal regulations with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

Once per year, the IRB is required to review and approve all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

Adverse Event Collection:

The clinical research team is responsible for collecting and recording the research data. As the results are collected, all adverse events will be identified after an informed consent is signed by the subject.

Throughout the study, during all follow-up visits, in addition to the medical chart review, adverse events are to be elicited by the investigator (or designate) by asking the subject

non-leading questions. All AEs and SAEs will be reported to the principal investigator (PI) and the PI will determine the final relationship of the event to the investigational product.

X. Data Management

The following people/agencies may have access to subject data/records:

- Study team
- Federal government regulatory agencies
- Auditing departments of the University of Iowa
- The National Institute of Health

To protect confidentiality, we will assign each subject a study ID. All records will be in a locked cabinet in a locked office or password protected computer system. Data and records will be managed as follows:

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Whenever possible, subject identifying information will be blacked out on all paper or hard copy records and replaced with the subject's unique study identifier. Paper records will be stored in a locked file cabinet in the study team's locked office.
- Electronic records (computer files, electronic databases, etc.) – All electronic data bases will only be accessed by the study team and available only with a username and password assigned to study team by the PI.

XI. Subject Safety

- To minimize risks all subjects are carefully pre-screened and screened trying to identify any factors that could contribute to increased risk.
- All testing is completed at University of Iowa Hospitals and Clinics by a very experienced and well-trained staff and monitored by the Principal Investigator.
- All confidential information is kept in locked offices and password protected computers only available to study team members.
- The participant has contact information and study team members available 24/7.

XII. References

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