Research Protocol – 2020_0465

ECG Belt to Assess Electrical Synchronization in Patients with Left bundle branch Area Pacing and His-Purkinje Conduction System Optimized Cardiac Resynchronization Therapy (ECG Belt)

Version: 1.0 27 August 2019
2.0 7 October 2020

Principal Investigator: **Pugazhendhi Vijayaraman, MD**
Regional Director, Cardiac Electrophysiology, Geisinger Northeast
Program Director, Geisinger Clinical Cardiac Electrophysiology Fellowship Program

Geisinger Clinic
1000 E. Mountain Blvd
Wilkes-Barre, PA 18711
570-808-6020
pvijayaraman1@geisinger.edu

Funding Source: Funding for the conduct of this investigator-initiated trial was provided by Medtronic's External Research Program (ERP).

Prepared with assistance from Geisinger Clinical Research

PROTOCOL SIGNATURE PAGE

All necessary sponsor personnel and/or designees have reviewed and approved *the ECG Belt to Assess Electrical Synchronization in Patients with Left bundle branch Area Pacing and His-Purkinje Conduction System Optimized Cardiac Resynchronization Therapy (**ECG Belt**)* protocol.

The sponsor hereby gives approval to Dr. Pugazhendhi Vijayaraman and Geisinger Clinic to proceed with this study as outlined in the above-mentioned protocol.

Authorized Sponsor Signature

The signature below indicates that you have the authority from the sponsor to approve this protocol.

_____ _____

Signature of Authorized Signer Date

_____

Printed Name of Signer

_____

Title of Signer

Primary Investigator Signature

The signature below indicates that you, as Primary Investigator, approve this protocol.

_____ _____

Signature of Primary Investigator Date

Pugazhendhi Vijayaraman, MD

Printed Name of Primary Investigator

Regional Director, Cardiac Electrophysiology, Geisinger Northeast

Title of Primary Investigator

TABLE OF CONTENTS

1 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
ACE	Angiostatin-converting enzymes
AE	Adverse Event
ARB	Angiotensin Resistant II Blockers
CFR	Code of Federal Regulation
CRT	Cardiac Resynchronization Therapy
EHR	Electronic Health Record
GCP	Good Clinical Practice
GIRB	Geisinger Institutional Review Board
HBP	His-Bundle Pacing
HIPAA	Health Insurance Portability and Accountability Act
HOT-CRT	His-Optimized Cardiac Resynchronization Therapy
IRB	Institutional Review Board
LBB	Left Bundle Branch
LBBP	Left Bundle Branch Area Pacing
LV	Left Ventricular Pacing
NYHA	New York Heart Association
PHI	Personal Health Information
RVP	Right Ventricular Pacing
SAE	Serious Adverse Event
WHO	World Health Organization

2 BACKGROUND AND SIGNIFICANCE

Physiologic pacing has become rapidly accepted into clinical practice. His bundle pacing (HBP) has recently been incorporated into Guideline document for bradycardia pacing.[1] Advances have been made in physiologic pacing in the form of left bundle branch area pacing (LBBAP). Recent report by Huang et al[2] described a novel approach to implanting the Medtronic 3830 lead in the Left bundle branch area via right ventricular, deep septal approach. Early experience suggests that LBB pacing can result in significant improvement in LV function in patients with LBBB and heart failure. The potential advantage of this method is several fold:[3] 1. Bypass the site of conduction block in patients with LBBB (even in patients where His bundle pacing fails to correct the LBBB) 2. Achieve low capture threshold with excellent sensing 3. Obtain LV

endocardial pacing in addition to conduction system pacing without a lead in the LV endocardial cavity.

The electrophysiological and ECG characteristics of LBB Pacing has not been well described. The ECG Belt can help assess the difference between baseline, RV pacing, LBBAP and His (or LBBAP) Optimized CRT (HOT-CRT) and understand the electrical synchrony and characteristics of physiologic pacing.

3 OBJECTIVES

3.1 General Objective

The objective of the study is to assess the utility of ECG Belt to understand the conduction and ECG characteristics of LBBAP and HOT-CRT and compare with preexisting data in traditional CRT and RVP.

3.2 Specific Objective

- To demonstrate and establish electrical resynchronization using ECG Belt Research System in LBBP and HOT-CRT.
- To assess ECG Belt derived native conduction parameters and compare them to LBBAP and HOT-CRT.
- To compare with historic ECG belt parameters obtained for right ventricular pacing/ Biventricular pacing in prior studies (Bank et al)[4]

4 STUDY DESIGN

4.1 Description

The ECG Belt study is a prospective, single-center, investigational, pre-market research study. The study team will identify all patients who satisfy the inclusion and exclusion criteria. The study team will evaluate the ECG Belt Research System to assess the electrical characteristics of conduction system pacing in patients with preexisting LBBAP or HOT-CRT.

Eligible patients would have successfully undergone LBBAP using Medtronic 3830 lead and C315His sheath. LBBAP will be confirmed at implant using left bundle potentials recorded from the lead, ECG morphology during unipolar and bipolar pacing, peak LV activation time and lead depth in the LV septum by contrast at implant and 2D echo post-implant.

ECG belt would be used to record ECG during baseline rhythm, LBBAP in unipolar and bipolar configurations and / or during HOT-CRT using HBP or LBBAP. These ECG belt characteristics would then be compared with baseline and existing data on RV pacing and traditional Biventricular pacing.

4.2 Study Population

4.2.1 Approximate Number of Subjects

Approximately 20 patients will participate in the ECG Belt study to be conducted at Geisinger Heart Institute.

All patients will share the same recruitment process, inclusion and exclusion criteria and same procedures.

4.2.2 Inclusion Criteria

The following is the inclusion criteria for the ECG Belt study:

1. Patients > 18 years of age
2. Patient has a previously implanted LBBAP lead for bradycardia indication or heart failure indication with one of the following at Geisinger within the last 5 years:
    - LBBAP
    - LBBAP+LV lead
    - HBP+LV
3. Patient is willing to comply with all study procedures and be available for the duration of the study.

4.2.3 Exclusion Criteria

The following patients or situations are excluded in the ECG Belt study:

1. Inability to provide informed consent
2. Pregnant
3. Enrolled in a concurrent study that may confound the results of this study.

4.3 Recruitment

Potential participants will be identified by clinician referrals, or by review of the electronic health record (EHR) of patients. Research staff will contact potential subjects and invite them to participate.

4.4 Study Duration

4.4.1 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 1 week (+/- 5 days). This includes a monitoring (follow up) period which starts immediately after signing the Informed Consent and completing the baseline visit (visit 1).

4.4.2 Approximate Duration of Study

This study will be completed in approximately 12-15 months duration. The end of the ECG Belt study is the completion of data entry and statistical analysis.

This study duration approximation is composed of the following stages:

- Screening and Enrollment Stage – enrollment of 20 patients from Geisinger Heart Institute is expected to take 10-12 months based on enrollment rate of 1 to 2 subjects per month.
- Monitoring Stage – based on the planned 1 week monitoring period for each patient, last patient completed is expected 10-12 months from the study beginning.

- Data Collection Stage – data entry and management are ongoing leveraging the electronic data capture system and secured database.
- Statistical Processing and Data Analysis – is expected to take 1-3 months from the data entry of the last patient visit or the last patient enrolled.

4.5 Procedures

The ECG Belt study methodology is composed of:

- 1 scheduled clinic visits (baseline)
- 1-week follow-up monitoring period for adverse events (phone call).

Visit 1 – Baseline

The following activities will be completed at Visit 1 (Baseline):

- Subjects will be screened to ensure they meet ALL the inclusion criteria and NONE of the exclusion criteria.
- Subjects will sign an Informed Consent form before any of the study related procedures are performed.
- Sequentially ordered subject identification number will be assigned for the specific site.
- Demographic
- Medical history
- Concomitant medication specifically ACE/ARB, beta blockers, diuretics, and anti-arrhythmics use
- Relevant co-morbidities will be recorded
- NYHA Functional Classification
- Collection of device characteristics and implanted system description.
- ECG Belt Research System Procedure*
    - LBBP

        - Native conduction
        - RV pacing if available
        - Bipolar LBBAP
        - Unipolar LBBAP – nonselective and selective (different outputs)
        - Fusion pacing with native conduction at different AV delays

    - HOT-CRT
        - Native conduction
        - HBP / LBBAP
        - HOT-CRT
        - AV delay optimization.

    - Medtronic Device (pacemaker/ICD) based Holter recording during the ECG belt recording**

- 12-lead ECG (Rhythm Strips)
- Adverse Events related to ECG Belt

*The use of the ECG Belt Research System may add approximately 40 minutes of time to follow-up visits for testing parameters, plus 10 minutes for the application of the ECG Belt and System set-up.

The DR220 Digital Recorder (NorthEast Monitoring, Inc, MA, USA) is a Holter monitor that is designed to facilitate the ambulatory cardiac monitoring and is intended for use with Medtronic System-B compatible implantable pulse generators, implantable cardiac defibrillators, and cardiac resynchronization therapy devices and implantable cardiac monitors. The Holter monitor will be used in accordance with its labeling. Only trained study personnel should apply the monitors. The data obtained by monitoring is not analyzed at the time of the recording. After the recording is complete, the data must later be returned and analyzed at Medtronic. **No personal information will be entered and collected by DR220 recorder.

For the purposes of this study, the Holter will be used during the in-office monitoring and will be removed at the conclusion of the monitoring. Each patient will have one DR220 Holter monitors collected during the study.

The Holter Recorder has application for any subject with a Medtronic IPG. For the purposes of this study, the intended use of the Holter Recorder is to acutely uplink continuous EGM signals that will be collected by the IPG in Holter mode.

Monitoring (Scheduled Follow-up)

Total period of 1 week (+/- 5 days) starting after baseline visit, during which the subject will be contacted by phone to assess any adverse events related to the ECG Belt. Patients will be followed in the device clinic as per standard of care.

Study Exit

Once the 1-week follow-up is completed, the subject is considered exited from the study, unless there is unresolved system related AEs with further actions or treatments planned.

4.5.1 Schedule of Events

	Clinic	**Phone**	**Clinic**
Visit	**Visit 1 – Baseline[a]**	**Week 1 F/U**	**Unscheduled [d]**
Visit Window	**Day 0**	**(+/-5 days)**	
Medical Records Review	**X**		
Informed Consent	**X**		
Inclusion/Exclusion	**X**		
Medical History	**X**		
Demographics	**X**		
Concomitant Medication [e]	**X**		
NYHA Functional Classification	**X**		
Device interrogation	**X**		
ECG Belt System procedure [c]	**X**		
ECG 12 Lead	**X**		
Adverse Events/ SAE [b]		**X**	**X**

a- Potential patients will be identified by clinician referrals. All patients will share same recruitment process and procedures
b- Only adverse event related to the use of the ECG Belt and/or device malfunctions
c- The use of the ECG Belt Research System might add approx. 40 minutes of time to f/u visits for testing parameters, plus 10 min for system set up.
d- When 1-week f/u is completed, subject is considered exited from the study unless unresolved system related AEs occur. An unscheduled follow-up visit may be required.
e- Special attention to: ACE/ARB, beta blockers, diuretics, and anti-arrhythmic use

4.6 Primary Endpoints

The primary endpoints will be

- ECG Belt analysis of Standard Deviation of Activation Times (SDAT) of LBBAP compared to native conduction
- ECG belt analysis of Left Ventricular activations times (LVAT) of LBBAP compared to baseline
- ECG belt analysis of SDAT and LVAT of HOT-CRT compared to baseline
- ECG belt analysis of QRS duration at baseline compared to various LBBAP options
- Comparison of above parameters of LBBP to historic biventricular or RV pacing

4.7 Secondary Endpoints

There are no secondary endpoints.

4.8 Statistics

Summary tables of descriptive statistics will be provided for all variables. Continuous variables will be summarized using means and standard deviations or median and interquartile ranges (IQR), depending on distributional assumptions. Categorical variables will be summarized using percentage and frequency counts. The descriptive statistics will be reported for Baseline and follow-up (adverse events only will be collected).

Analysis of the following objectives will be accomplished using the Chi-square or Fisher's exact tests, and T-tests or non-parametric test (Median test, Wilcoxon rank sum test, etc.), as appropriate.

- To assess ECG Belt derived native conduction parameters and compare them to LBBAP and HOT-CRT.
    - ECG Belt analysis of Standard Deviation of Activation Times (SDAT) of LBBAP compared to native conduction
    - ECG belt analysis of Left Ventricular activations times (LVAT) of LBBAP compared to baseline
    - ECG belt analysis of SDAT and LVAT of HOT-CRT compared to baseline
- These ECG belt characteristics will be compared with historic ECG belt parameters obtained for right ventricular pacing/ Biventricular pacing in prior studies

This study is information gathering and not designed to perform any hypothesis testing. Therefore, any results of statistical tests performed are not conclusive but used to design a larger prospective study.

4.9 Data Management

4.9.1 Data Collection and Storage

Data will be collected by research team members, and the resulting analytic file will be stored in a password-protected database on Geisinger's secure network. Only research team members can access the data file. The research team members will review the charts and gather all the needed information. The research team plans to perform manual chart reviews to access any required data elements.

The following data, including relevant dates, will be collected:

- Medical record number
- Date of birth/date of death
- Information relevant to all encounters, admissions/discharges, clinical procedures, medications administered, problem list entries, and lab values
- Baseline demographic variables of patients (age, sex, ethnicity, tobacco use, comorbidities)
- Clinical outcomes and procedural related complications

All identifiable date will be stored on a secure server in password protected files. Any hard copy data will be secured in a locked (area/suite/drawer/cabinet), if applicable. Only aggregate data (i.e., no PHI) will be shared with the Sponsor.

4.9.2 Records Retention

Records of data generated during the study shall be retained for at least 6 years and could be used for future research studies submitted and approved by the IRB.

5 SAFETY MONITORING

The non-invasive ECG Belt Research System is investigational but has been qualified for human use and tested for safety similar to standard ECG recording systems. There may be skin redness or irritation from the additional ECG Belt electrodes, minor pain or discomfort while attaching and detaching multiple electrodes to the skin, and discomfort due to lying on the ECG Belt. Since a larger surface is covered by the ECG Belt, the area of skin redness or irritation may be larger than with standard ECG electrode systems. There may be additional risks related to use of the ECG Belt Research System that are unknown at this time.

Lastly, we expect patient condition to vary over time. Changes in the patient medical condition in the context of this study is not an adverse event unless directly related to the use of the ECG Belt.

5.1 Adverse Event Reporting

Patients will be asked about adverse events related to the use of the ECG Belt. These data will not be monitored in real time and patients will be educated on the need to contact their physician directly should they have any medical concern.

Only ECG Belt related SAE/AE's will be collected and reported and then assessed if it is device related.

5.2 Other Reportable Information.

Geisinger will notify Medtronic and regulatory authorities as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of the investigational device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- An adverse event that led to death.
- An adverse event that led to a serious deterioration in the state of heath that either resulted in:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

6 PROTECTION OF HUMAN SUBJECTS

6.1 Informed Consent and HIPAA Authorization

This clinical study will comply with HIPAA. Specifically, the electronic database that will be utilized for the collection of the clinical data that is mandated by this protocol (including personal identifiable information and protected health information) will be HIPPA compliant.

The informed consent will be approved by the IRB and will include the appropriate language that will obtain research participants' authorization for use/disclosure of the information for research purposes (per 45 CFR 164.512(i)(1)(i) (HIPAA)) including the right of the subjects to revoke

their consent/authorization as well as disclose his/her right to access the research information (per 45 CFR 164.508 (b) (5) and 164.528).

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent/authorization form will be submitted to the IRB for review and approval.

Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

6.2 Protection of Human Subjects Against Risks

All electronic study data will be kept in password-protected computer files, and hard copy data will be stored in a locked environment that is only accessible only to the study team members. Data will be coded by assigning a unique study identification number to subjects' medical record numbers. Analysis will be performed using the coded data. Only aggregate data without personal identifiers will be included when presenting results or submitting manuscripts for publication.

7 PUBLICATION PLAN

We plan to submit a scientific abstract to upcoming meetings and to publish the data as a manuscript in a peer-reviewed journal.

8 REFERENCES

[1] Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;0:CIR.0000000000000628.

[2] Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. A Novel Pacing Strategy With Low and Stable Output: Pacing the Left Bundle Branch Immediately Beyond the Conduction Block. Can J Cardiol. 2017 Dec;33(12):1736.e1-1736.e3. doi: 10.1016/j.cjca.2017.09.013.

[3] Vijayaraman P, Huang W: Atrioventricular Block at the Distal His Bundle: Electrophysiological Insights from Left Bundle Branch Pacing. Heart Rhythm Case Reports 2019. https://doi.org/10.1016/j.hrcr.2019.01.006

[4] Gage, RM,.Curtin,AE, Burns,KV, et al. Changes in electrical dyssynchrony by body surface mapping predict left ventricular remodeling in patients with cardiac resynchronization therapy. Heart Rhythm 2017;14:392–399.