Research Protocol – 2022-0917

Intra-procedural Transthoracic EChocardiogram to facilitate LBBAP (EC-LBBAP study)

Version: 1.1 11 April 2023

Version: 2.0 6 March 2024

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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 Resources

PROTOCOL SIGNATURE PAGE

All necessary sponsor personnel and/or designees have reviewed and approved the **Intra-procedural Transthoracic Echocardiogram to facilitate LBBAP** (EC-LBBAP) study 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

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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

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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] and others[3-7] 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.[8] Additionally, LBBAP has been shown to be safe, feasible and effective in patients with AV block and superior to right ventricular pacing in observational case-controlled studies.[7] The potential advantage of this method is several fold:[3] 1. Bypass the

site of conduction block in patients with infranodal AV block and 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 success of LBBAP has been variable between 80-90% based on several observational studies and Geisinger experience. The procedural duration and fluoroscopy duration for LBBAP is somewhat longer than traditional right ventricular pacing. Left bundle branch area pacing (LBBAP) can be challenging in patients where the sheath cannot be oriented perpendicularly to the septum. In some patients, the lead may advance deep into the septum in a tangential fashion. Existing methods have limitations in assessing the exact depth of the lead in the septum and proximity to the LV endocardial surface. We hypothesize based on our early experience that transthoracic echocardiogram including hand-held echo can be helpful in most of the above scenario to both facilitate successful implantation and assessment of the lead location during the implantation and possibly reduce the fluoroscopy duration.

3 OBJECTIVES

3.1 General Objective

The objective of the study is to assess the utility of intraprocedural transthoracic echocardiogram to facilitate successful LBBAP.

3.2 Specific Objective

- To assess the success rate of intraprocedural transthoracic echocardiogram guided LBBAP lead implantation.
- To develop a work-flow and define echocardiography windows to achieve successful LBBAP
- To demonstrate reduction in fluoroscopy and procedural duration for LBBAP.
- To assess the success rates of using hand-held echo probe to achieve LBBAP

4 STUDY DESIGN

4.1 Description

The EC-LBBAP study is a prospective, single-center, observational research study. The study team will identify all patients who satisfy the inclusion and exclusion criteria. The study team will evaluate the feasibility and success rates of echocardiogram guided LBBAP lead implantation.

Eligible patients would undergo 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 2D transthoracic echo at implant.

During implant procedure, transthoracic echo windows will be identified and documented: Parasternal short and long axis, apical 2 and 4 chamber views and subcostal views to visualize the proximal interventricular septum. Following venous access using cephalic vein cut-down or ultrasound guided axillary vein access, the lead implantation in the left bundle branch region will be guided by echocardiography.

Retrospectively, the study team will identify 30 consecutive previous patients who satisfy inclusion and exclusion criteria (control patients). The study team will compare the difference in procedural success between Case and Control patients.

4.2 Study Population

4.2.1 Approximate Number of Subjects

Approximately 30 patients will participate in the EC-LBBAP study to be conducted at Geisinger Heart Institute.

All patients will share the same recruitment process, inclusion and exclusion criteria and same surgical procedure. Twenty patients will undergo intraprocedural transthoracic echocardiogram via standard practices. An additional 10 patients will undergo intraprocedural transthoracic echocardiogram using a hand-held ultrasound device.

4.2.2 Inclusion Criteria

The following is the inclusion criteria for the EC-LBBAP study:

1. Patients > 18 years of age
2. Patient with an indication for permanent pacemaker or ICD utilizing conduction system pacing lead for bradycardia or cardiac resynchronization therapy
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 EC-LBBAP 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. 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 3 months (+/- 1 week). 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 18 to 24 months duration. The end of the EC-LBBAP 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 30 patients from Geisinger Heart Institute is expected to take 15-18 months based on enrollment rate of 1 to 3 subjects per month.
- Monitoring Stage – based on the planned 3 month 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 EC-LBBAP study methodology is composed of:

- 1 scheduled clinic visits (baseline)
- 2-week follow-up monitoring period for device evaluation and adverse events (device clinic visit).
- 3-Month follow-up/exit visit for device evaluation and adverse events (device clinic visit).

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.
- 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.
- EC-LBBAP research procedure *

  Intraprocedural transthoracic echocardiogram*

  Fluoroscopy duration for LBBAP lead implantation

  Procedural duration for LBBAP lead implantation

  Total fluoroscopy duration

  Total procedural duration

  Success of LBBAP
- 12-lead ECG (Rhythm Strips)
- Adverse Events related to echocardiogram

*The use of the EC-LBBAP may add approximately 15 minutes of time for total procedure but may lower the fluoroscopy and procedure duration for LBBAP lead implantation. Additionally, this may improve the safety and success of the procedure.

Monitoring (Scheduled Follow-up - Visit 2)

Total period of 2 week (+/- 1 week) starting after baseline visit, during which the subject will be seen in device clinic for routine follow-up to assess device function and to assess any adverse

events related to the study. Patients will subsequently be followed in the device clinic as per standard of care.

Study Exit (Visit 3)

Once the 3-month 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.

4.6 Primary Endpoints

The primary endpoints will be

- Success rate of LBBAP utilizing intraprocedural transthoracic echocardiogram
- Reduction in fluoroscopy/procedure duration for LBBAP lead implantation compared to historic data from prior Geisinger studies utilizing LBBAP
- Identification of work-flow and echocardiographic windows to facilitate LBBAP

4.7 Secondary Endpoints

The secondary outcomes will be as follows:

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 above endpoints 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.

This study is information gathering and designing workflow. 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

Echocardiogram is routinely used in clinical practice and is associated with minimal adverse events related to ultrasound gel use on the skin. Rare skin irritation or erythema may be noted. No significant adverse events are anticipated as several thousand ultrasound-based procedures are performed each year in the Geisinger Health System.

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 intraprocedural echocardiogram.

5.1 Adverse Event Reporting

Patients will be asked about adverse events related to the use of the echocardiography. 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 echocardiogram related adverse event will be collected and reported and then assessed if it is procedure related.

5.2 Other Reportable Information.

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

- 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

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area pacing compared to right ventricular pacing: Results from the Geisinger-Rush Conduction System Pacing Registry. Heart Rhythm. 2021 Sep 3:S1547-5271(21)02102-0. doi: 10.1016/j.hrthm.2021.08.033. Epub ahead of print. PMID: 34481985.

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