**A study of correlation between differences in ventricular activation and degree of response to left bundle branch area pacing and biventricular pacing cardiac resynchronization therapy**

**Short title: Cardiac mapping in super- and non-responders to CRT**

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**Study Personnel:**

Data Custodian: Dr. Rajeev Pathak

Data collection: Dr. Jenish Shroff

Statistician: Abhinav Mehta

**Publication and dissemination of results:**

Prof Rajeev Pathak (Lead)

Dr. Jenish Shroff (Joint lead)

**Institution(s) responsible for running the study:**

Canberra Heart Rhythm

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1. **Synopsis**

Heart failure (HF) is associated with significant morbidity and mortality. Cardiac Resynchronization Therapy (CRT) is important therapy along with optimal medical treatment in management of heart failure. Traditional biventricular (BiV) pacing is gold standard which includes right ventricular endocardial pacing and left ventricular epicardial pacing. However, ~30% do not respond to BiV-CRT (1). Conduction System Pacing (CSP) has rapidly emerged as an alternative for CRT and aims to pace His bundle or left bundle branch (LBB) to achieve physiologic ventricular activation. Amongst them, His bundle pacing (HBP) is challenging due to difficult lead placement and often failure to capture His bundle at low threshold while LBB pacing has showed promising results in several studies.

Pacing lead in left bundle branch area may capture left bundle, its fascicles or left ventricular septum which is collectively referred to as ‘left bundle branch area pacing’ (LBBAP). Degree of response to LBBAP CRT is variable in heart failure patients with homogenous baseline characteristics. Whether LV activation pattern is different in patients with varying response to BiV or LBBAP CRT is unknown.

1. **Abbreviations and Acronyms**

|  |  |
| --- | --- |
| BiV | Biventricular |
| CSP | Conduction System Pacing |
| CRT | Cardiac Resynchronization Therapy |
| HBP | His Bundle Pacing |
| HF | Heart Failure |
| LBBAP | Left Bundle Branch Area Pacing |
| LV | Left Ventricle |
| RV | Right Ventricle |

1. **Introduction**

CRT is an important modality in management of heart failure with prolonged QRS (primarily LBBB). In appropriately selected individuals, CRT reduces morbidity and mortality (2).Optimal lead placement for BiV pacing, one on right ventricular septum and another in coronary sinus at site of latest LV activation, allows simultaneous or near simultaneous activation of both ventricles and improves inter and intraventricular dyssynchrony. However, approximately 30%-40% patients do not benefit from BiV-CRT because of challenging venous anatomy, presence of myocardial scar or phrenic nerve capture at optimal pacing location (1).

Conduction system pacing (CSP) has emerged as an alternative pacing therapy which induces ventricular activation in a physiologic manner through His-Purkinje system. CSP with His bundle or left bundle pacing can recruit natural conduction system and provide an ideal resynchronisation option. HBP is often challenging due to difficult lead placement, high capture threshold and low sensed ‘R’ wave (3). Meanwhile, left bundle branch pacing has been evaluated for CRT and shown to be safe and effective in multiple clinical studies (4-6). LBBAP refers to the capture of left bundle branch or left ventricular septum by pacing lead. Response to LBBAP appears to be variable and ranges from no response to super-response. Whether differences in LV activation is responsible for this variable response is unclear. In this study, we aim to evaluate ventricular activation in patients with super-response and non-response to LBBAP and BiV-CRT.

1. **Objectives**

* To assess LV activation pattern in heart failure patients with LBBB before and after CRT
* To evaluate differences in LV activation pattern in super responders and non-responders

1. **Hypothesis**

We hypothesised that super-responders and non-responders may have significantly different LV activation with CRT.

1. **Study methodology**

**Study Design:** This is a prospective study. Super-responders and non-responders will be identified from the Canberra Heart Rhythm CRT database. The response to CRT will be defined as follows.

**Super-responders:** Those who responded with ≥20% improvement in LVEF at 12 months

**Non-responders:** Those who responded with ≤10% improvement in LVEF at 12 months

10 patients representing each category will be selected from LBBAP-CRT database.

5 patients representing each category will be selected from BiV-CRT database.

Non-invasive epicardial mapping of cardiac activation pattern will be done for all patients with Medtronic’s Cardioinsight. Cardiac activation will be assessed with CRT turned off to demonstrate baseline ventricular activation pattern. A second activation map will be created with CRT turned on to demonstrate LV activation after pacing. In patients with LBBAP, activation maps will be created with higher and lower pacing outputs to demonstrate differences in ventricular activation secondary to differences in captured tissue at various outputs. Endocardial mapping using Octaray catheter will be done when patients have significant arrhythmia such as frequent non-sustained ventricular tachycardia or high burden paroxysmal ventricular contractions (PVCs).

**Primary endpoint:**

* eDYS – time difference between the earliest and latest activation site

**Secondary endpoints:**

* Global right/left ventricular electrical synchrony: the difference between mean RV and LV activation times at baseline and after CRT
* Global biventricular total activation time
* Global LV activation time

1. **Study population**

**Inclusion criteria:**

1. Patients with LBBB, QRS ≥130 ms and HF who had LVEF ≤35% at baseline.
2. Received either BiV or LBBAP CRT.
3. Super-responders: Those who demonstrated ≥20% improvement in LVEF at 12 months post-procedure.
4. Non-responders: Those who demonstrated <10% in LVEF at 12 months post-procedure.

**Exclusion criteria:**

1. Patients with dyssynchrony other than LBBB and/or QRS <130 ms at baseline
2. Patients with LVEF >35% at baseline
3. Patients with intermediate (10-19%) improvement in LVEF at 12 months post-procedure.
4. Contraindication to CT scan.
5. Refuse to/unable to give consent.
6. **Study procedure**

**Data Collection:**

Patients meeting inclusion criteria will be offered enrolment. Non-invasive cardiac mapping will be done on site at Canberra Heart Rhythm. LV activation map will be created at baseline with CRT off and then with CRT on.

The demographic and clinical variables that will be collected are name, age, gender, baseline and post-CRT QRS duration, baseline and 12-month post-procedure LVEF, history of severe coronary artery disease/ myocardial infarction (MI). Baseline ventricular activation pattern and post-CRT activation pattern and measures as described above will be recorded and compared between super- and non-responders.

**Study timeline:**

**Non-invasive mapping:** Will be done at Canberra Heart Rhythm, CT scan facility available in the same complex. Mapping for up to 5 patients will be done per day.

**Invasive mapping:** Will be done at National Capital Private Hospital, ACT. Patients will be admitted on the day of proposed mapping. Patient will be brought in electrophysiology laboratory and endocardial activation map will be created using Octaray catheter on CartoTM system.

**Data analysis:** 1 week

**Conference Publication**: 1 month

**Journal publication:** 3 months

**Ethics:** An application has been submitted to ACT human research ethics committee for approval.

1. **Patient consent**

Informed consent will be taken from all the patients after explaining the nature of the study. A patient information sheet will be handed over for them to understand the scope of research and procedure involved. Patients will have a week’s time before they provide their informed consent.

1. **Data management**

All the clinical, demographic and mapping related data of each patient will be stored in a Microsoft Excel data sheet on a secured server at Canberra Heart Rhythm with password protection. The document will be accessible to Prof. Rajeev Pathak, Dr. Jenish Shroff and Data and Safety Monitoring Board who will be responsible for the confidentiality of the stored data. The data custodian will be Prof. Rajeev Pathak.

1. **Adverse event reporting**

Adverse event committee will be chaired by Dr. Girish Palnitkar. Any adverse event as a direct result of conduction of the study will be reported to committee who will investigate the occurrence of the adverse event. However, patients will be undergoing non-invasive cardiac mapping in this study which carries minimum risk. Device procedures have already occurred and procedure related adverse events, if any, were communicated to patient and their family as per standard care. Cardiac CT is a relatively safe investigation which does not pose any excessive risk. Patients who have contraindication to ionizing radiation will not be included in the study. Invasive endocardial mapping include the risks such as vascular/cardiac injury, injury to conduction system, access site hematoma, cardiac perforation, pericardial effusion and rarely death. However, a standard consent entailing all the risks for such procedure will be obtained from patients.

1. **Statistical analysis**

Biostatistician at Australian National University, Abhinav Mehta, will be responsible for data analysis. Nominal data will be presented as frequencies and percentages and will be compared by the Chi-square test. Continuous data will be presented as the mean ± standard deviation and compared with independent Student T-tests. Statistical analyses will be performed using SPSS (version 29.0, SPSS Inc, Chicago, IL). P value of less than 0.05 will be considered significant.

1. **Quality assurance, monitoring & safety**

Study will be conducted under direct supervision of PI. Medtronic will provide CIT vests and technical assistance necessary for non-invasive epicardial mapping with Cardioinsight. Pacemaker will be restored to optimal settings if changes are made during mapping procedure. Endocardial mapping will be done by PI Prof Rajeev Pathak in fully equipped cardiac electrophysiology laboratory.

1. **Data and safety monitoring board (DSMB)**

DSMB is chaired by Dr. Derek Potgeiter. DSMB has reviewed the protocol, safety and scientific validity of the trial. DSMB may periodically review and evaluate the accumulated study data for participant safety, study conduct, progress, and, when appropriate, efficacy. Also, DSMB may make recommendations concerning the modification of the trial.

1. **Ethical considerations**

The data shall be collected, maintained, analyzed and interpreted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (GCP). Data will be deidentified upon collection and stored on the secure server at Canberra Heart Rhythm. Investigators Prof Rajeev Pathak and others have evidence of certificates of GCP training. Major ethical issues are unlikely to occur as CRT procedure has already occurred for all patients and study only involves cardiac mapping which will not affect their standard medical care in any way. Patients will be given enough information related to study prior to consent.

1. **Finance and resources**

Medtronic has provided funding in the form of donation of 30 CIT vests and technical assistance in non-invasive epicardial mapping to undertake this study.

1. **Dissemination of results and publication policy**

The results of the data analysis will be published in conference and journal. The data custodian shall be Dr Rajeev Pathak at Canberra Heart Rhythm. Prof Rajeev Pathak and Dr Jenish Shroff shall oversee, review and critically analyse the data and take joint lead in publication of the same. Funding from Medtronic will be acknowledged appropriately in the publications resulting from the study. The statistician and the support staff shall be acknowledged appropriately in all the publications.

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