TITLE:
Left Bundle Area Versus Selective His Bundle Pacing (LEFTBASH): Single Center, Open Label, Randomized Pilot Study to Evaluate Capture Thresholds and Acute Echocardiographic Hemodynamic Characteristics

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Study Protocol and Statistical Analysis Plan

Left Bundle Area Versus Selective His Bundle Pacing (LEFTBASH): Single Center, Open Label, Randomized Pilot Study to Evaluate Capture Thresholds and Acute Echocardiographic Hemodynamic Characteristics

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Background

Symptomatic bradyarrhythmias are effectively treated with cardiac pacing. Ventricular pacing burden at traditional sites such as the right ventricular apex and septum have been associated with increased rates of atrial fibrillation, heart failure, and mortality (Lamas et al., 2002) (Sweeney Michael et al., 2003; Wilkoff et al., 2002). Traditional pacing sites result in cardiac electromechanical dysychrony, for which alternate pacing sites to minimize these untoward effects have been sought. One promising strategy has been his bundle pacing, which utilizes a patient's native conduction, and has demonstrated improved electrical synchrony and left ventricular function when compared to traditional pacing (Vijayaraman, Naperkowski, et al., 2018). Barriers to wide spread application to this technique include the His bundle anatomic location and its attendant difficulties associated with implant, as well as higher capture thresholds leading to decreased battery duration.

An alternative to His bundle pacing is placing the lead distal to the His bundle and to actively fixate the lead into the interventricular septum. This strategy has been referred to as Left bundle Pacing, as it may electrically capture the left bundle to simulate a patient's native conduction. Published reports have described similar maneuvers which pace the left bundle branch (LBB) region to restore LV function and correct a left bundle branch block (LBBB) (Huang et al., 2017) (Chan, Huang, & Yan, 2018; Chen, Wu, Su, Su, & Huang). (Vijayaraman P & Mascarenhas V, 2019
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For patients who require dual chamber pacing, patients will be randomized to His bundle versus left bundle area pacing for active fixation. We will evaluate the acute and follow-up capture threshold of His bundle versus left bundle pacing.

Objectives

Primary Objective

To compare 3 month follow up complete ventricular capture thresholds of His bundle pacing versus left bundle area pacing lead placement. Complete loss of capture will be measured with a width of 1.0 ms and during unipolar or bipolar output, whichever value is lower.

Secondary Objectives

To compare changes in left ventricular performance and mechanical synchrony, selective or non selective-His Pacing, left bundle area pacing, in patients who require ventricular pacing at 3 months.

The endpoints collected will be:

1. Ejection Fraction
2. Stroke volume
3. Mechanical dyssynchrony, characterized by the time to peak systolic velocity of the Left Ventricle (LV) myocardial walls, elicited by tissue Doppler:
    a. Anterior
    b. Posterior
    c. Anterior-Septal
    d. Anterior-Lateral
    e. Lateral
    f. Inferior-lateral
4. QRS duration

Other secondary endpoints collected will be:

1. 6 month complete loss of capture threshold as defined in the primary endpoint.
2. 12 month complete loss of capture threshold as defined in the primary endpoint

Methods

Design

Single center, open label, randomized pilot study to evaluate the complete ventricular capture thresholds of His Bundle versus left bundle area pacing.

Secondary analysis will focus on echocardiographic hemodynamic parameters of HIS pacing, versus left bundle branch pacing.

Based on previous studies (Vijayaraman, Naperkowski, et al., 2018) and our experience with non-selective and left bundle area pacing, a difference of 0.5 V at 1.0 ms in capture threshold at 3 month follow-up between His and left bundle area pacing sites, is to be expected. With a standard deviation of 0.5 V, This would require an enrollment of 20 patients to obtain a power of 0.8 to demonstrate

statistical significance. Thus we anticipate enrollment of 26 patients to evaluate differences in capture threshold between the studied pacing sites, and an expected 20% patient drop out.

Enrollment

Investigators providing care will be tasked with patient screening. This will be performed at both the inpatient and outpatient arenas, and can occur within any timeframe prior to the pacemaker implant. During the screening process, patients will be given consent forms to be reviewed collectively with an investigator.

Statistical Analysis

Continuous variables will be reported as mean +/- standard deviation. Categorical variables will be expressed as percentages. Paired comparisons will be made using a Student t-test if the data is normally distributed, and with the Wilcoxon signed-rank test for nonparametric data. Paired categorical data will be compared using the Wilcoxon test. P-value ≤ 0.05 was considered significant.

Randomization

Randomization will be in a 1:1 assignment. Twenty-six envelopes with random assignments to one of the two treatment arms will be created. As patients are enrolled, they will be assigned to an envelope. Each envelope number will be correlated with patient information, as well as date of procedure, and assigned ID number.

Randomization will occur after the patient demonstrates acceptable selective or non-selective HIS bundle pacing prior to active fixation.

If the patient is identified at the Beaumont Troy site, the above shall still continue to apply. The key personnel will bring the randomization card to the site on the day of the procedure.

Study Population

Inclusion Criteria

Prospective enrollment of patients:

1. Over 18 years old
2. Signed consent
3. Pacemaker indication according to 2018 ACC/ AHA HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay with one or more of the following
    a. Symptomatic sinus node dysfunction.
    b. Symptomatic Atrioventricular (AV) block or high degree AV block.
    c. Tachy-Brady syndrome

Exclusion Criteria

Patients with any condition of the following will be excluded:

1. Previously implanted cardiac pacing devices except transvenous temporary pacemaker.
2. Patients who are eligible for appropriate cardiac resynchronization therapy(CRT) or implantable cardiovert defibrillator (ICD) implantation
3. Patients with prior septal myectomy
4. Patients with prior surgical or transcatheter aortic valve replacement
5. Anatomy precluding implant evaluated during the screening or identified during the procedure.
6. Those without ability to achieve selective His bundle pacing evaluated during the screening or identified during the procedure
7. Pregnant women

Pre-Operative Characterization

After enrollment, patients will be evaluated in the Heart Rhythm Center Holding Center, prior to pacemaker implant.

A baseline 12 lead EKG will be obtained prior to or at the onset of the procedure, and the following will be collected.

1. QRS duration
2. QRS morphology

Patients will then be randomized, after the selective or non-selective HIS bundle pacing can be achieved, to either selective His bundle, or left bundle pacing site for active fixation of the ventricular lead.

The following baseline characteristics will be collected:

1. Age
2. Sex
3. QRS
4. Known Coronary artery Disease
5. Previous Atrial Fibrillation
6. Hypertension
7. Diabetes
8. Peripheral Vascular Disease
9. Renal Failure
10. Systolic blood pressure
11. Diastolic blood pressure
12. Pulse pressure
13. New York Heart Association (NYHA) class
14. Left ventricular Ejection fraction (LVEF)

15. Pacing indications
16. Etiology of cardiomyopathy (if applicable)

Procedural Protocol

Patients will be prepped and draped in the usual sterile fashion. The 12 lead surface electrodes will be covered with sterile towels. Incision and subcutaneous pocket in the deltopectoral region will be created using standard technique.

Venous accesses are to be obtained by axillary vein or cephalic cut-down access utilizing modified Seldinger technique. Sheaths are to be placed into the venous system.

His Bundle Pacing is now included in the ACC/AHA guidelines for pacemaker implants. For those operators who chose to implant a pacemaker lead at the His bundle, the Medtronic 3830 lead is the standard of care. The region just distal to the His bundle is now being recognized as the Left bundle area pacing. Given both the His bundle and the right ventricle pacing, including the left bundle area, are standard of care with the 3830Medtronic Lead, there is no increased risk to the device use in this study. Additionally, the Medtronic 3830 lead has been FDA approved since July 12, 2018 for implantation of His bundle pacing and has an excellent safety and performance record.

For the ventricular lead placement, it is to be performed using the Select Secure (3830, 69 cm, Medtronic Inc.) pacing lead delivered through a fixed-curve (C315 HIS, Medtronic Inc.) or a deflectable catheter delivery system (Attain, Medtronic Inc.). The sheath is to be advanced, over the wire to the right ventricle. The 3830 leads will be inserted through the selected sheath and the tip of lead will be exposed from the sheath. The lead will be connected to the electrophysiological recording system on the atrial channel, with gain setting of 0.05 mV/mm, and a sweep speed of 50 mm/sec.

The lead and sheath will be withdrawn to the tricuspid valve annulus. A unipolar intracardiac electrogram will be recorded from the lead tip using electrophysiological recording system in order to identify a selective His bundle electrogram. Once a discrete His bundle electrogram is identified, unipolar pacing, at a pulse duration of 1.0 ms, will be initiated to elicit selective or non-selective HIS Bundle pacing based on criteria outlined by prior authors (Vijayaraman, Chung, et al., 2018). Effort will be made to achieve selective His bundle pacing, but if non-selective His bundle pacing can be elicited, this is acceptable.

Once selective or non-selective His bundle capture is demonstrated, the patient is randomized to His or left bundle area pacing for active fixation.

If the patient does not have the anatomy suitable for identifiable selective or non-selective HIS bundle capture, they will be removed from the study. Instead, they will undergo active fixation of the lead to the RV apex, septum, or left bundle area. This will be at the discretion of the operator.

If the patient is randomized, active fixation of the lead will be performed based on randomization to either His bundle or left bundle area pacing site.

If the left bundle area location is selected, the sheath and lead tip will be advanced to the anterior lower site of His bundle position, and then rotated in a counterclockwise fashion to place the lead tip in a perpendicular orientation to the IVS. To signify the site of left bundle area pacing, the following parameters should be sought; (1)A typical "W" with a notch at the nadir of the QRS complex in lead V1, or qR paced morphology in surface lead V1, (2) A shorter pacing-to–QRS interval than the initial His-bundle pacing–to–QRS interval, (3) and no His potential identified during intrinsic rhythm. Unipolar pacing will be performed at a pulse duration of 1.0 ms, and an output which allows for the narrowest complex QRS. The lead will then be screwed into the IVS by performing 4-5 initial clockwise revolutions of the fixation screw. To avoid penetration into the left ventricular cavity, intermittent observation of the impedance values, and anatomic septal penetrance by surface echo evaluation will be performed. An additional 4-5 clockwise revolutions will be performed, until impedance values start to drop, and the fixation screw has penetrated to the left septum on surface echo. Published expected impedance values and depth of penetrance have recently been published to be used as a template (Vijayaraman P & Mascarenhas V, 2019

) Afterwards, a small (<5 mL) contrast injection will be delivered through the sheath to verify septal penetration of the lead. Left bundle capture will be accepted if there is narrowing of the QRS when compared to pre-fixation QRS width at the proposed left bundle area site, or narrowing if the QRS complex at higher outputs indicating conduction system capture. A RBBB is expected, but not required for capture of the left bundle branch.

If the selective His site is to be used for active fixation, the lead will be placed with at least 5 revolutions of the screw into the myocardium.

The atrial lead will be inserted and actively fixed.

Device

The leads will be connected to Medtronic dual chamber pacemaker generator. The device will be placed in the pocket and the pocket will be closed with sutures in a standard manner as per the operator.

Echocardiographic Evaluation Protocol

A standard of care echo done within 3 months of the procedure will be used as the baseline echo. Data acquired from the echo will be and assessed by a single, non-blinded Cardiac Echocardiographer. Tissue doppler if not performed during the echo, post processing will be utilized if possible.

To evaluate the hemodynamic properties of the pacing site, echocardiography will be utilized.

Hemodynamic assessment will be obtained by collecting stroke volume at each site, utilizing the velocity time integral. The VTI will be obtained in the apical long axis view.

Left ventricular ejection fraction will also be assessed at each pacing site utilizing the biplane method of disks.

Tissue Doppler imaging will be used to assess longitudinal LV dyssynchrony. Myocardial velocity curves are to be obtained from the apical 2 and 3 chamber views. These views are selected to assess the anterior, inferior, lateral anterior-septal, inferior-septal, and inferior lateral left ventricular walls. The peak sustained myocardial systolic velocity (during the ejection phase) for each of the 4-LV segments is to be identified. The time to peak systolic velocity will be measured with reference to the onset of QRS complex.

The following data will be collected:

1. Left ventricular Ejection Fraction
2. Stroke volume (by VTI)
3. The peak sustained myocardial systolic velocity (during the ejection phase) for each of the 4-LV segments is to be identified:
    a. Anterior
    b. Anterior-Septal
    c. Inferior-Septal
    d. Inferior
    e. Inferior-lateral
    f. Lateral

Electrocardiographic evaluation

During the procedure, a 12-lead electrocardiogram will be available, and recorded while atrio-ventricular paced. The following will be collected:

1. The stimulation-to-QRS
2. QRS duration
3. QRS morphology
4. Pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6

The following will be collected after active fixation, during the most narrow QRS morphology obtained:

1. The stimulation-to-QRS
2. QRS duration
3. QRS morphology
4. Pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6

Procedural Data

Data collected will be:

1. Fluoroscopic time
2. Amount of contrast administered
3. Procedural time

Device Evaluation

Intra procedural data will be collected. After active fixation of the lead, the capture threshold will be collected. A pulse width of 1.0 ms will be used in all patients. Selective Left bundle branch (LBB) pacing (S-LBBP) is defined as only capturing the LBB without myocardial capture, with a discrete isoelectric component between the pacing stimulus and the onset of QRS complex in the electrocardiogram (ECG) and electrogram(EGM)s recorded by the EP system and the programmer. Nonselective LBB pacing (NS-LBBP) captured both the LBB and the local myocardium around the lead without the discrete isoelectric component. Selective HIS bundle (HB) pacing (S-HBP) is defined as only capturing the HB without myocardial capture, with a discrete isoelectric component between the pacing stimulus and the onset of QRS complex in the electrocardiogram (ECG) and electrogram (EGM)s recorded by the EP system and the programmer. Nonselective HB pacing (NS-HBP) captured both the HB and the local myocardium around the lead without the discrete isoelectric component. We will measure the pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6 defined as the stimulus to the peak of the R wave and the paced QRS morphology.

Data Collected:

Unipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Bipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Post-Procedure Data

The following day, patient will receive a PA and lateral chest X-Ray.

A 12-lead electrocardiogram will be obtained while the patient is set to a parameter that ensures selective His ventricular pacing or the narrowest QRS achievable with left bundle area pacing, depending on the randomization group.

The following will be collected during pacing which yields the most narrow QRS:

1. The stimulation-to-QRS
2. QRS duration
3. QRS morphology
4. Pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6

The device will be interrogated to obtain the following:

Unipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Bipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Follow-up

Patients will be assessed in the outpatient area at 3 (± 1 month), and 6 months (±1 month), and 12-month (± 1 month) post implant. A 12-lead electrocardiogram will be obtained while the patient is set to a parameter that ensures selective His ventricular pacing or the narrowest QRS achievable with left bundle area pacing, depending on the randomization group.

1. The following will be collected at 3 months during pacing which yields the most narrow QRS, at 1.0 ms pulse duration: The stimulation-to-QRS
2. QRS duration
3. QRS morphology
4. Pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6
5. Pacing burden

The device will be interrogated to obtain the following at 3month

Unipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Bipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

The device will be interrogated to obtain the following at 6 months during pacing which yields the most narrow QRS, at 1.0 ms pulse duration::

1. stimulation-to-QRS
2. QRS duration
3. QRS morphology
4. Pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6
5. Pacing burden

Unipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Bipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

The following will be collected at 12 months, during pacing which yields the most narrow QRS, at 1.0 ms pulse duration:

1. The stimulation-to-QRS
2. QRS duration
3. QRS morphology
4. Pacing stimulus to left ventricular activation time (LVAT) in unipolar lateral precordial leads V4-V6
5. Pacing burden

The device will be interrogated to obtain the following at 12 months:

Unipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

Bipolar

1. Selective Capture
2. Non-selective
3. Complete loss of capture
4. Impedance values at the site of active fixation will be collected
5. Sensed R wave amplitudes

At 3 months the patient will have a limited echocardiogram while the patient is set to parameter that ensures AV synchronous, selective HIS pacing or the narrowest QRS achievable with left bundle area pacing, depending on the randomization group. The echo will be performed by sonographer and included in the budget. The following echo data will be collected at 3 months:

1. Left ventricular Ejection Fraction
2. Stroke volume (by VTI)
3. The peak sustained myocardial systolic velocity (during the ejection phase) for each of the 4-LV segments is to be identified:
    a. Anterior
    b. Anterior-Septal
    c. Inferior-septal
    d. Inferior
    e. Inferior-Lateral
    f. Lateral

4. The distance from the septal leaflet of the tricuspid valve to the entry point in the RV septum was measured from a standard 4- chamber view.
5. The length on penetration of the RV His or left bundle area lead into the myocardium
6. The degree of tricuspid regurgitation (TR)

Potential Risks

Adverse outcomes will be collected, and compared between the His bundle, and left bundle area pacing cohorts. These will include:

1. Lead pacing exit block
2. Threshold increase (defined as an increase in chronic pacing threshold >1 V at 1.0 ms)
3. Lead dislodgment
4. Need for lead revision.

Complications associated with device implantation will be recorded. Potential risks of any pacemaker implant, which may require additional reparative operations include

1. Excessive bleeding and pocket hematoma, requiring evacuation or transfusion)
2. Infection
3. Pneumothorax
4. Vascular injury
5. Cardiac perforation and tamponade
6. Lead dislodgement requiring revision
7. Radiation exposure
8. Pain at the incision site

Potential risks to the patient beyond those attributable to routine pacemaker implant are:

1. Additional contrast exposure
2. A theoretical interventricular septal puncture into the left ventricle with the active fixation of the screw if using the left bundle area location.

Interventricular septal puncture has been reported at a rate of 3 % in prior literature, which was corrected without any long term complication (Vijayaraman P & Mascarenhas V, 2019

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Potential Benefits

Potential benefits are derived from recent studies (Vijayaraman, Naperkowski, et al., 2018), which include:

1. Decreased rate of hospitalization for heart failure
2. Increased LVEF
3. Improved capture threshold and battery longevity

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