Selection of Cardiac Resynchronization Therapy Pacing Modalities in Patients supported by LVADs.

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Table of Contents:

1.0 Background

Heart failure patients with reduced left ventricular systolic function and worsening clinical status are frequently treated with mechanical devices. Cardiac resynchronization therapy (CRT) and left ventricular assist devices (LVAD) are mainstays of advanced heart failure treatment and have independently been demonstrated to decrease mortality. However, minimal research documents the utility of these two modalities in unison. There have been recent investigations comparing Biventricular (BiV) versus right ventricular (RV) pacing suggesting better exercise performance and decreased left ventricular (LV) volumes with RV pacing [1]. This discovery contrasts with prior meta-analysis that reports no difference between LVAD patients with and without CRT including mortality and hospitalizations [2]. We aim to compare BiV pacing and RV pacing in LVAD patients with CRT on patient's exercise tolerance and frequency of tachyarrhythmias. Additionally, research is required to form a conclusion on the role of CRT in LVAD patients.

2.0 Rationale and Specific Aims

The study is a randomized single-blind crossover prospective study in which we will determine the clinical outcomes of CRT pacing modalities in LVAD patients. Only patients are blinded. This is a small-scale study from which future larger scale randomized controls can be performed. The primary endpoint will be the effect of BiV and RV pacing setting on the 6-minute walk test. Secondary outcomes include:

1. To assess effect of BiV and RV pacing settings on serum NT-Pro-BNP (N-terminal pro-brain naturetic peptide)
2. To assess effect of BiV and RV pacing settings on quality-of-life as measured by the EQ-5D-3L Quality of life questionnaire.

Tertiary endpoints for the study are listed below.

1. To assess effect of BiV and RV pacing settings on QRS width.
2. To assess effect of BiV and RV pacing settings on frequency of tachyarrhythmias.

3.0 Inclusion/Exclusion Criteria

Patients will be included if they meet the following parameters:

1. Patients with both an LVAD and CRT device with functional leads.
2. Age 18 years and older.
3. Ability to walk.
4. Ability to sign consent

Patients will be excluded if they meet the following parameters:

1. Patients with permanent Atrial Fibrillation
2. Patients who are pacemaker dependent
3. Patients with sustained ventricular tachycardia

4.0 Enrollment

We plan to have an open enrollment that will last for four months in order to discuss the study with all advanced heart failure patients at their routine quarterly appointment. There are approximately 60 patients we expect to meet criteria from IU Health Methodist Hospital, and we predict a minimum of 28 patients will participate. Informed consent will be obtained from patients using Appendix A (Informed Consent Statement). Patients will act as their own control in this crossover study spending three months in each of the different pacing modalities. Patients will be randomly placed into BiV or RV pacing setting upon enrollment. We will use a randomized cross-over design to assign patients as discussed below in statistical considerations. We will use Heart Failure Clinic routine follow-up visits which occur every three months as crossover points between the different pacing methods. All patients will be blinded to their pacing settings. The assessors will not be blinded to the pacing settings.

5.0 Study Procedures

Upon enrollment, we will collect patient characteristic at including 6-minute walk test, EKG, quality of life questionnaire, and NT-pro-BNP lab draw. In addition to this the CRT device will be interrogated and reprogrammed to a randomly assigned to BiV or RV pacing modality. They will be scheduled for a clinic visit in 3 months. During their return visit, they will undergo a 6-minute walk test, EKG, quality of life questionnaire (EQ-5D-3L Quality of life questionnaire), NT-pro-BNP lab draw, and device interrogation evaluating atrial arrhythmias and ventricular arrhythmias burden. Following completion of these tasks their CRT device will then be reprogrammed to the remaining pacing modality. This process will be repeated at 6-month appointment to complete a total of 3 months in each pacing modality.

The 6-minute walk test has been demonstrated to be an indicator of postoperative mortality in LVAD patients [3]. NT-pro-BNP can be a prognostic predictor of mortality in advanced heart failure. Device interrogation will be performed to evaluate lead impedance, determine quantity of tachyarrhythmias during testing period, and reprogram to next desired pacing modality.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Prior research has shown no difference between LVAD patients with and without CRT regarding mortality and hospitalizations [2]. There is no known significant risk above the inherent baseline risks of having a left ventricular device. Generally, CRT settings are maintained on BiV pacing though the pacing modality can be changed or turned off by the provider. However, recent research suggests that RV pacing may be beneficial to patients with improved functional status and quality of life [1]. While the exact mechanism for this benefit is unclear, we hope to mirror this result with BiV and RV pacing. The LVAD is controlling hemodynamic function and is not being altered for purposes of this study. There is no clear

indication that pacing modalities affects tachyarrhythmia rates; however, the information is easily gathered during device interrogation and will provide additional safety checks during the study. There is a theoretical risk of decreased functional status, which will be minimized with as each patient will spend only a brief 3 months in each modality and patient will be assessed at 3 months interval by their cardiologist. Advance heart failure patients with LVADs have routine 3-month appointments with laboratory tests with their primary cardiologist. All clinic visits and laboratory tests will be as clinically indicated and not explicitly for research purposes. Adverse events will be monitored throughout the study. Adverse events that meet IU HRPP Reportable Events criteria will be promptly reported to the IU IRB with 5 business days.

7.0 Statistical Considerations

Our primary endpoint is differences in 6-minute walk test between two pacing approaches. A sample size of a total n=24 subjects will allow us to detect an effect size 0.6 in a comparison of the two pacing methods with statistical power of 80% at the two-sided significance level of 0.05. We will randomize enrolled patients to either BiV or RV, and once they complete the 3 months of one modality, they will be switched to the other modality. To account for a patient attrition rate of 15%, we will randomize at least 28 patients.

For all subjects, we will assign study ids 1 to 28 to them in a sequential order based on time of enrollment (1 first, 28 last), such that each patient will undergo the pacing methods as ordered in the table below, where A stands BiV and B for RV. If more than 28 participants enroll, they will be assigned ids using consecutive integers from 29 and the statistician will create additional randomization assignments. The sequence (in terms of the order of pacing methods) will be as follows:

Pacing sequence AB: patients 2 6 7 8 11 13 15 16 17 20 22 24 25 27
Pacing sequence BA: patients 1 3 4 5 9 10 12 14 18 19 21 23 26 28

If patients elects to drop-out they will have the option to return to pre-study BiV pacing or to proceed to the next planned pacing assignment.

Analytical Plan: Briefly, descriptive data will be presented as mean ± standard deviation (SD) and median and IQR as appropriate for continuous variables, or frequency and percentages for categorical variables. Statistical significance is set at 5% and nominal p-values are reported without multiple comparison adjustment. Regression analyses using linear mixed models or generalized estimating equations as appropriate for the outcome variable of interest will be used to assess the differences in pacing methods on each outcome variable while accounting for repeated measure correlations within each patient. Models will include subject (as a random effect), pacing method, period, sequence and residual treatment effect (carryover effects). The least square means as well as their confidence intervals for pacing method will be produced with and without carryover effects. Missing data are naturally handled by mixed effect models when data are missing at random. If GEE is used, multiple imputations will be employed before analysis.

8.0 Privacy/Confidentiality Issues

No personal information will be published. Primary data will be collected via patient interview and stored electronically in REDCap. The storage location will be backed up automatically every day. Other data sources include lab data and device interrogations are automatically stored in patient's electronic medical records and will be merged with the primary data as needed. Quality assurance steps will include: testing of database by study team prior to moving to production mode. The following quality control methods will be used: single entry with random checks of accuracy and 2) extraction and cleaning of data that will be used for analysis every 6 months. Once patient data is initially collected, it will be de-identified before analysis.

9.0 Follow-up and Record Retention

Patients will spend approximately 3 months in each of the pacing settings. Follow up will be scheduled to match their routine outpatient clinic follow appointments which occur every three months. At their routine clinical follow-up appointments, we will collect data at the 3- and 6-month marks following enrollment. At these visits, they will undergo 6-minute walk tests, device interrogation, NT-pro-BNP lab draw (N-terminal (NT)-pro hormone B-type natriuretic peptide), EKG, and quality of life screening questionnaire. Then the pacemaker device will be reprogrammed to the next pacing modality. Data will be kept in an encrypted Excel worksheet until the data is analyzed for publications.

10.0 Appendix

A: Informed Consent

B: EQ-5D-3L Quality of life questionnaire

References:

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2. Voruganti DC, Briasoulis A, Chaudhry M, Alvarez P, Cotarlan V, Bhama JK, Giudici M. Cardiac Resynchronization Therapy and Outcomes in Patients with Left Ventricular Assist Devices: A Systematic Review and Meta-Analysis. Heart Failure Reviews, vol. 24, no. 2, 24 Mar. 2019, pp. 229–236.

3. Tomashitis B, Baicu CF, Butschek RA, Jackson GR, Winterfield J, Tedford RJ, Zile MR, Gold MR, Houston BA. Acute Hemodynamic Effects of Cardiac Resynchronization Therapy versus Alternative Pacing Strategies in Patients with Left Ventricular Assist Devices. Journal of the American Heart Association, U.S. National Library of Medicine, 5 Mar. 2021, https://pubmed.ncbi.nlm.nih.gov/33663225/.