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Comparing Rate Response With CLS Versus Accelerometer ICD Settings in Heart Failure Patients With BIOTRONIK CRT-Ds

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9. RESEARCH DESIGN AND METHODS

Study Design

This study is a prospective, randomized, single-blind crossover study intended to enroll patients who are implanted or are scheduled to be implanted with a Biotronik CLS and accelerometer capable CRT-D device. Patients will serve as their own control group with regard to modes of rate-adaptive pacing. Patients with a previously implanted Biotronik CRT-D device with CLS-capability will be recruited from health care institutions in San Diego and all dedicated functional testing will be performed at the University of California, San Diego (UCSD). The goal enrollment target for analysis will be 15 patients, with up to 20 patients enrolled to allow for withdrawals.

Patients with suspected CI would include those with a blunted atrial sensing histogram that would justify to a treating clinician enabling a rate response feature, or objective evidence of chronotropic incompetence (e.g., low average heart rate during telemetry monitoring, or <85% MPHR on exercise treadmill testing) before or after CRT-D implantation. Patients who have or are scheduled for implantation of a Biotronik CLS-capable device will be enrolled. Then each patient will complete an initial run-in period of one week whereby no rate response is programmed into the CRT-D device. One week later, patients will then be randomized to either CLS or an accelerometer mode. CPET and 6-minute walk testing scheduled one week after the initial mode is set (CLS or accelerometer). At the conclusion of the initial CPET and 6-minute walk assessments, the initial device setting (CLS or accelerometer) will be programmed to the opposite setting for a period of one week, at which point repeat CPET and 6-minute walk tests will be conducted. Results will be collected and compared. Patient preferences regarding quality of life and symptoms in each mode will be assessed immediately after study completion. Quality of life information will be gathered by a RAND-36 questionnaire at the baseline visit and at each setting change. At the final encounter, the patient will be asked to pick which setting of the 2 they felt improved their overall well-being and exercise performance during testing.. This is a proof of concept design, with cross-sectional analysis, purposefully designed to reduce costs of prolonged follow-up, but also answer the appropriate clinical question.

Study Overview

This study is designed to evaluate patients who have been implanted with a cardiac resynchronization therapy with defibrillator (CRT-D) therapy capable of closed loop stimulation (CLS) as a comparator to an accelerometer setting. Patients with CRT-D and CI will undergo cardiopulmonary exercise stress testing (CPET) and six-minute walk assessments in a randomized crossover study design to evaluate patient performance and preference regarding CLS compared to use of an activated accelerometer. Numerous studies have described the utility of CPET in patients with congestive heart failure and chronotropic incompetence.[4,5,6,7.]

CI as seen on remote or in-person monitoring would be defined as a blunted atrial sensing histogram that would prompt the treating physician to utilize the rate response feature. Patients with CI would then serve as their own controls and undergo testing with CPET and six-minute walk assessments with activation of accelerometer for rate response and again with CLS driven rate response as a comparative arm. Randomization will be performed to determine the order of accelerometer versus CLS driven rate response. Randomization will be performed in computer generated blocks of 5, with sealed envelopes revealing the order of testing. Patients will be blinded to randomization, until study completion at which point unmasking to the patient will occur, and the patient will be set to the patient preferred setting for rate responsive pacing.

Patients would serve as their own controls to increase the study power as an effort to examine whether CLS improves exercise performance and patient satisfaction as compared to use of an accelerometer.

CPET Testing
CPET testing will be performed by trained health professionals proficient in CPET testing. Those individuals performing CPET testing and reporting information will be blinded to rate responsive pacing settings, so as not to introduce bias into interpretation

All patients will undergo CPET testing at the dedicated stress lab or clinical research institute at the University of California, San Diego. Patients will be scheduled after their initial clinic visit when device interrogation and programming is made. Upon presentation to the stress lab, patients will be asked to perform a progressive test (16.7 W/min) on an electrically braked cycle ergometer (or treadmill) until subjective exhaustion, plateauing of oxygen intake, or if any clinical contraindication precludes continuing. All testing will be supervised.

The modified Naughton protocol will be used for treadmill exercise testing in patients. This protocol is designed to increase the workload by approximately 1 metabolic equivalent (MET) (3.5 mL O_2/kg/min) for each two-minute stage. Patients will have continuous electrocardiogram monitoring and frequent blood pressure measurements during exercise testing. The ventilator threshold (VAT) or the Vo_2 at the onset of anaerobic metabolism is visually identified as the onset of a disproportionate rise in VE/Vo_2 relative to VE/Vco_2.

An objective grading system that is based upon values of Vo_2max and the anaerobic threshold will be used to evaluate each patient's functional capacity:

Class A: None to mild; VO2 max >20 mL/kg/min
Class B: Mild to Moderate; VO2 max 16-20 mL/kg/min
Class C: Moderate to Severe; VO2 max 10-15 mL/kg/min
Class D: Severe; VO2 max 6-9 mL/kg/min
Class E: Very severe; VO2 max < 6 mL/kg/min

During CPET testing, data collected will include minimum, maximum, average heart rate, peak VO2 during exercise and associated functional class, and peak and average METs achieved with exercise.

Six-minute Walk Testing
Six-minute walk testing (6MWT) will be performed by trained sub-investigators, including research staff. Those individuals performing six-minute walk testing and reporting information will be blinded to rate responsive pacing settings, so as not to introduce bias into interpretation.

The 6MWT assessment will be performed at the University of California, San Diego at the Thornton Hospital. A practice walk will be performed to orient the patient to the procedure. In addition to total distance walked, the magnitude of desaturation and timing of heart rate recovery will be metrics for clinical outcomes.

Standard protocol will be followed, including: a flat, straight corridor with 100 feet in length; turnaround points demarcated with orange cones; patient rest period of 10 minutes prior to the walk assessment; patients will be instructed to wear comfortable shoes and clothes; Record baseline heart rate and pulse oxygen saturation (SpO_2); monitoring pulse oxygen saturation during test is optional; lap counter will be set to zero and timer to six minutes; patients will be instructed that the object is to walk AS FAR AS POSSIBLE for 6 minutes,

but don't run or jog; at the end of the test, the floor will be marked where the patient stopped; after the test record the Borg dyspnea and fatigue levels will be recorded; the distance walked will be recorded. During 6MWT, average and peak heart rate immediately following exercise will be measured, as well as maximum distance walked.

Quality of Life and Patient Preference Testing

A RAND-36 patient questionnaire will be administered to the patient after both CPET testing and six-minute walk testing have been performed at the end of each of the 2 rate responsive pacing settings.
Patient preference regarding rate response pacing modality (CLS versus accelerometer) will also be collected at the end of the study.

Enrollment
Patients will be recruited from local hospitals in San Diego with all formal testing and data analysis performed at UCSD.

Main Inclusion Criteria
1.) Patients with a Biotronik CRT-D device (capable of both CLS and accelerometer rate responsive pacing).
2.) Patients ≥ 18 years of age
3.) Patients who have plausible symptoms of CI based on previous monitoring and clinical symptoms

Exclusion Criteria
1.) Pregnant patients
2.) Patients who are unwilling or unable to provide informed consent
3.) Patients who are unable to complete study related procedures

Study Procedures

Medical records and device interrogation results of patients who have clinical device interrogations and clinical suspicion of CI will be screened to determine eligibility for the study. Subjects who meet the inclusion/exclusion criteria will be asked to participate in the study and sign the approved informed consent prior to initiating any study related procedures including further patient contact.

As part of the research study, medical history, demographic information (age, race, sex, and date of birth) and baseline information will be obtained from the patient and/or patient chart.

After a minimum of three months post implantation of a Biotronik CLS-capable CRT-D device, patients enrolled will undergo a run-in period with use of no rate response pacing for one week. They will then be randomized to CLS or accelerometer turned on with testing performed after one week in the initial mode set. After CPET and 6-minute walk assessments are performed on the initial device setting (CLS or accelerometer), the device will be programmed to the opposite setting for a period of one week, at which point repeat CPET and 6-minute walk tests will be conducted. Results will be collected and compared. Patient preferences will be assessed immediately after study completion.

The following information will be collected for research purposes:

- Baseline demographic and clinical information
- Any cardiac medication prescription
- Antiarrhythmic drug prescription
- Procedural evaluation (ablation, device implantation, etc.)

Study Duration 24 months

Waiver of consent for recruitment

From clinical data gathered during the main study time period, we will review electronic medical records to collect information the population of patients screened. The study will require a waiver of consent to collect data for patients evaluated The waiver of consent is necessary to meet the specific aims of the trial to ascertain whether patients are reasonable candidates for inclusion in the study.

Data Analysis

All the data for the study will be entered into case report forms and then entered into a database. All variables of interest including subject demographics, baseline characteristics, device information and endpoints will be summarized descriptively. Normally distributed continuous variables will be expressed as means and standard deviations and will compared by unpaired t-tests whereas continuous variables not normally distributed will expressed as medians and interquartile ranges (IQR), and will be compared by the Wilcoxon rank-sum test. Categorical variables will be expressed as percentages and were compared by the χ^2 test. For univariate and multivariable analysis, logistic regression will be used. Analyses will be performed using Stata version 11.0 (StataCorp, College Station, Texas).