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RE: A Randomized Trial of Closed Loop Stimulation after Pacemaker Implantation for
Congenital heart Disease
NCT: NCT03361189
Protocol ID: 17-000932
Date: 1/11/2017

Please find attached the protocol.

Sincerely,

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A Randomized Trial of Closed Loop Stimulation after Epicardial Pacemaker Implantation for Congenital Heart Disease

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1.0 Background

Sinus node dysfunction is highly prevalent among patients with congenital heart disease, manifesting as resting bradycardia or chronotropic incompetence. As children and adults with congenital heart disease are now expected to have increasing lifeexpectancy; with well over 1 million adult patients currently living in North America, [1] issues such as mental health, acquired comorbidities and their impact on overall cardiovascular health have assumed increased scrutiny.

It is now understood that objective measures of aerobic capacity, such as peak \/02, peak VENC02, and heart rate reserve predict all-cause mortality for adult patients with congenital heart disease. As the chronotropic response during exercise is a key determinant of aerobic capacity, improvement in sensor-based technology for heart rate support is expected to have a significant impact on functional capacity and longevity in this population. Some forms of congenital heart disease, such as single ventricle physiology after the Fontan population are especially likely to benefit, as cardiac output is determined almost exclusively by heart rate during exertion due to limited ability to augment cardiac stroke volume. [2]

It is also becoming increasingly clear that sedentary behaviors are highly relevant to overall cardiovascular health in the general adult population. Adult patients with congenital heart disease are at especially high risk for sedentary behavior as a result of I) chronic restriction for physical activities based on ill-founded medical advice, 2) chronotropic incompetence resulting from prior surgical palliations and hemodynamic stressors, and 3) overestimation of physical activity.

The closed-loop stimulation (CLS) algorithm developed by Biotronik Inc. is a novel sensor-based technology that relies on the change in myocardial systolic impedance for modulation of the heart rate during physical and emotional stress. [3] The pacing algorithm has been shown to be highly effective for a wide range of clinical scenarios. Despite the fact that congenital heart disease (CHD) patients are likely to derive significant benefit in terms of functional ability and aerobic capacity using this novel technology, the CLS system has not been adequately studied in this population. As many CHD patients also undergo epicardial placement of pacing systems at the time of concomitant cardiac surgery, CLS has been less often utilized in this population given almost no data in the setting of surgical electrode placement. The present study intends to examine the benefits of the Biotronik CLS algorithm in the CHD population, employing the use of epicardial pacemaker systems in the study protocol.

2.0 Rationale and Specific Aims

Improvement in sensor-based rate adaptation for sinus node dysfunction is needed in the CHD population. Emerging data suggest that greater aerobic capacity and heart rate

reserve are independently associated with superior outcomes in this population. Improvements in these parameters can be expected with the use of the Biotronik CLS algorithm and this pacing system may therefore be particularly well-suited to patients with CHD.

The Specific Aims of this protocol are:

Primary Aim: To determine the performance of CLS for CHD patients after both transvenous and epicardial pacemaker implantation

Hypothesis: CLS after either pacemaker implantation strategy will result in equivalent improvements in autonomic control of chronotropic response as compared to standard sensor based rate modulation

Primary outcome: Objective change in autonomic modulation of heart rate while randomized to CLS pacing with mental stress and ANSAR testing

Secondary outcomes: Increase in aerobic capacity, non-sedentary behavior, and quality of life while randomized to CLS pacing

This will be a single-blind (blinded subjects) randomized cross-over study, in which each patient will receive treatment A (CLS-on or CLS-off) for 3 months followed by treatment B (CLS-0ff or CLS-on).

3.0 Previous Human Studies

The Biotronik CLS alrogithm has been studied extensively in the clinical setting. Notable findings include improvements in heart rate response during mental stress[4 5] reliable tracking of the sympathetic tone [6' 7] and excellent performance despite beta-blocker therapy. [8] In addition, most patients prefer CLS pacing as opposed to traditional accelerometer-based pacing in a ratio of 2:1 after sequential randomization to both pacing modes [4] However, there is almost no data supporting the use of this algorithm in the congenital heart disease population. [9] In addition, there is a very limited amount of clinical data (essentially limited to isolated case reports) describing the use of CLS after epicardial pacemaker implantation. [9 10]

4.0 Inclusion/Exclusion Criteria

Inclusion criteria:

- Congenital heart disease
- Simple, moderate, or complex congenital heart disease o Adolescent or adult age group (age >14 and <65 years) o Significant sinus node dysfunction
- Atrial pacing percentage>70%

- Intrinsic dysfunction resulting from congenital lesion or cardiac surgery • Secondary sinus node dysfunction due to antiarrhythmic drug therapy o Existing, fully functional Biotronik pacemaker or ICD with CLS capability o Epicardial or transvenous route of pacemaker implantation

Exclusion criteria:

- Unable to complete cardiopulmonary exercise testing (CPET) o Contraindication to CPET
- Decreased mental capacity or known psychiatric disorder
- Congestive heart failure, NY HA cass IV
- Total atrial tachyarrhythmia burden >20%

5.0 Enrollment]Randomization

Patient Enrollment: The treating physician will identify potential subjects with a previously implanted Biotronik pacemaker and present a brief overview of the study; if the subject is interested, the study will be described in detail. Informed consent will be obtained by the investigator after discussing the study, including the voluntary nature of participation and notification the subject can withdraw at any time. Ample time for questions and answers will be allowed. The investigator will give the subject and his/her legal guardian the opportunity to take the consent home to think about it more, with the option to call or meet with the investigator to ask additional questions. If the subject and/or his/her parent/legal guardian agree to participate, the investigator will ask them to sign a written, informed consent and assent. A copy of the assent and consent will be given to the subject and/or his/her parent/legal guardian.

Randomization Procedure: This will be a single-blind placebo-controlled randomized crossover study with 2 treatments: CLS-on versus CLS-off (accelerometer only). Each enrolled patient will receive both treatments for 3 months. The order of treatments will be randomized 1 :1.

6.0 Study Procedures

All patients enrolled in the study will undergo the following baseline assessment and data collection:

- Demographics (age, gender, race/ethnicity)
- Review of data confirming the presence of sinus node dysfunction with chronotropic incompetence (prior exercise stress test and/or Holter monitor results)
- Review of clinical history, including age at diagnosis, congenital diagnosis, surgical history, and cardiac device implant procedure
- Antiarrhythmic drugs prescribed and the respective dosages
- Prior ECG and echocardiography and advanced imaging reports

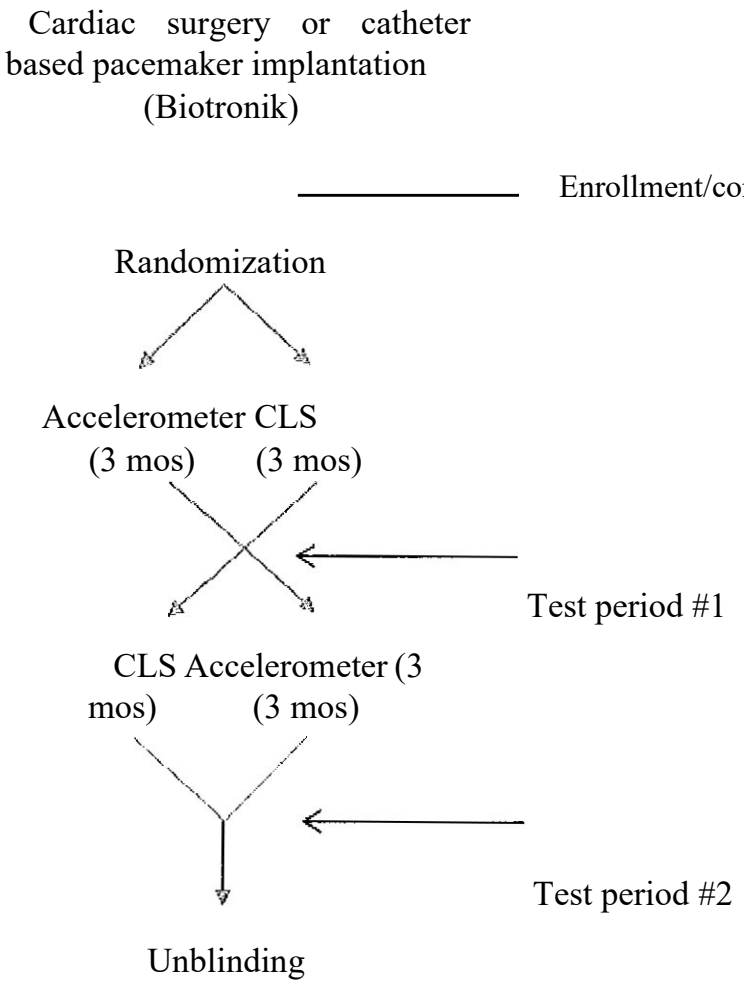
Randomization

There will be a 50:50 randomization, with half the subjects randomized to CLS-on then CLS-off, and half randomized to CLS-off then CLS-on.
Subjects previously receiving rate-responsive pacing with CLS that are randomly selected to CLS-on will continue with the identical programmed parameters. For subjects not previously receiving rate-responsive pacing with CLS that are randomly selected to CLS-on nominal programming will be utilized with a base rate of 60 beats per minute.

Subjects will then initiate treatment A (CLS-on or CLS-off) in a blinded fashion. During the testing period, subjects will be tracked with the implanted device accelerometer to quantify physical activity. At 3 months, all subjects will undergo testing as noted below.

- 24 hour Hotter monitoring with spectral analysis
- Cycle-ergometer stress with cardiopulmonary gas exchange analysis • Free form activities with cardiopulmonary gas exchange analysis (staircase . walking, sweeping, suitcase lifting with right and left arms, etc.)
- ANSAR testing (hand grip, Valsalva, deep breathing, and orthostatic challenge)
- Mental stress test with continuous electrocardiographic recording
- Quality of life questionnaire (SF-36/Somerville index)

After 3 months of treatment A, subjects will be reprogrammed to treatment B. Tracking of physical activity with the device accelerometer will continue during this period. After 3 months of treatment B, repeat testing will be repeated as described above. At the conclusion of the study, patients will be asked which pacing mode is preferred.



Patients will be followed during both treatment phases per usual clinical routine.
Patients who experience significant symptoms (extreme fatigue, debilitating palpitations, or other clinically relevant symptoms) will be evaluated by their treating physician. Subjects that have any adverse events during treatment A will discontinue treatment A and immediately crossover to treatment B. Subjects with events during treatment B will be removed from the study and unblinded. Further treatment will be determined by the treating physician.

7.0 Risks.

All enrolled subjects will have a clinical diagnosis of congenital heart disease with sinus node dysfunction as defined in the inclusion criteria.

Supporting evidence for the clinical diagnosis will be reviewed by the principal investigator prior to enrollment. Patients with sinus node dysfunction are often more s m tomatic and likel to ex erience adverse cardiovascular outcomes b nature of the disease. Those with pacemakers are at risk for lead malfunction and are other forms of pacemaker system malfunction. These risks are inherent to the patient population studied here.

There are risks associated with exercise testing in patients with ACHD, including the risk of provoking both atrial and ventricular arrhythmias. Nevertheless, exercise testing is routinely used to assess clinical status in the adult congenital heart disease population.

There are risks of loss of confidentiality related to the study procedures. Privacy issues are discussed in greater detail in section 1 1 .0.

8.0 Reporting of Adverse Events (AE) or Unanticipated Problems involving Risk to Participants or Others

AES will be reported to the IRB according to the IRB policies and procedures.

9.0 Study Withdrawal/Discontinuation

Subjects may withdraw from the study at any time. Subjects will be unblinded at the time of withdrawal.

10.0 Statistical Considerations

Sample Size Estimation and Power Analysis

The primary endpoint of this randomized controlled 2x2 cross-over trial will be to measure the influence of autonomic function on heart rate response, and to show an equivalent response for both epicardial and transvenous CLS pacemaker systems. The objective of this study is to evaluate changes in heart rate in response to the CLS algorithm versus a standard accelerometer during various tests of autonomic function. Previous studies of adults with chronotropic incompetence using the CLS algorithm have demonstrated a mean increase in heart rate of 16.1 ± 1 .1 beats/minute during mental stress with CLS-on versus 5.8 ± 0.6 beats/minute with standard accelerometer ($p<0.001$).[5]

A further pilot study using ANSAR demonstrated a mean increase in 12.5 beats/minute during isometric hand-grip with CLS-on versus 2.9 beats/min with standard accelerometer (p=0.004), 13.2 beats/minute during deep breathing versus 2.9 beats/minute (p=0.004), 16.0 beats/minute during Valsalva maneuver versus 4.5 beats/minute (p=0.004), and 14.9 beats/minute for postural change versus 6.2 beats/minute ($p=0.039$).[12] The results of the prior pilot study are summarized below.

ANSAR HEART RATE	Baseline	DOD-CLS	DDDR	T test	Wilcoxon test
Resting	55.8	70.0	60.8	<0.001	0.004
Isometric Handgrip	59.4	71.9	62.3	<0.001	0.004
Deep Breathing	58.0	71.2	60.9	<0.001	0.004
Valsalva maneuver	57.1	73.1	61.6	<0.001	0.004
Postural Change	58.1	73.0	64.3	0.015	0.039

From Pavri et al. Circulation 2006;114:II 749. [12]

A two-sided t-test achieves 80% power to infer that the mean difference is not 0 when the total sample size of a cross-over design is 40 (or 81% when n=24 and 96% when n=30) assuming a 5% type I error. The actual difference and the square root of the within mean square error are assumed to be 10. Considering a drop-out rate of 30%, a total of 57 patients will need to be enrolled to achieve the target sample number.

Statistical Analysis Plan

Descriptive statistics, including means, standard deviations, and ranges for continuous variables, as well as percentages and frequencies for categorical variables, will be provided to describe the study sample. Differences between group means for continuous variables will be examined using ANOVA or Kruskal-Wallis Test. Point estimates along with the corresponding p-values and 95% confidence intervals will be reported. The adjusted p-values and the corresponding 95% confidence interval will be reported for multivariate analyses. Statistical analysis will be done with JMP version 12.0 (SAS Corporation, Cary, NC).

11.0 PrivacylConfidentiality Issues

Only individuals directly involved with the study will have access to data. Information is for research purposes only and will be used for publication purposes. All participants will have their names concealed. Access to identified patient information will be limited to the investigators listed within this IRB application. De-identified information with HIPPA identifiers removed will be available to other investigators following appropriate IRB approval. Confidentiality and security will be maintained for the database. The database is stored behind a firewall (in addition to the institutional firewall) with the highest level of protection, i.e. the same level of protection as the on-line hospital information system at UCLA. This means that users must logon to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Only users approved through our institutional review board will be allowed access to patient identifiers. Other levels of authorization may exist for future approved users following IRB approval, e.g. access to de-identified data.

Data is initially collected in the medical record for each individual study participant. The information will be extracted from the patient's medical record and then transferred into the Case Report Form (CRF).
The CRFs will include personal identifiers for participant. However, this data will not be accessible as numbers and initials are assigned for each participant and these will become the identifying information for each study participant. A master list with patient demographics will only be accessible to the principle investigator and his senior coinvestigator. This data will not be available to others.

13.0 Follow-up and Record Retention

The study will continue for 5 years. The data will be maintained for 3 years after completion of the study.

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