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Date: November 15, 2024

To: Whom it may Concern

Re: Project # 130663
NCT02154750
Evaluation of AV Delay Optimization vs. Intrinsic Conduction in Patients with Long PR Intervals Receiving Dual Chamber Pacemakers for Symptomatic Bradycardia.

Please note that date referred to in your comments section is the date of the IRB form version, not the protocol date. The protocol date which is entered is correct.

If there are any questions or concerns regarding this submission, please contact Benyraemon Batenga, Research Coordinator, at 858-246-2405. Thank you for your consideration in this matter.

Sincerely,

Gregory Feld, MD /bb
Professor of Medicine
Director Cardiac Electrophysiology Program
University of California, San Diego

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

These are instructions are for completing the Research Plan are available from the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response in for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 10/29/2010

1. PROJECT TITLE

Evaluation of AV delay optimization vs. intrinsic conduction in patients with long PR intervals receiving dual chamber pacemakers for symptomatic bradycardia.

2. PRINCIPAL INVESTIGATOR

Dr. Navinder Sawhney, M.D.

3. FACILITIES

UCSD Medical Center including Encinitas Clinical and Echocardiography Facilities

4. ESTIMATED DURATION OF THE STUDY

24 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS

Short and long term effects of different pacemaker settings on hemodynamics such as cardiac output and on right ventricular remodeling and other chamber dimensions, in patients with dual chamber pacemakers for symptomatic bradycardia with long PR intervals.

6. SPECIFIC AIMS

To evaluate the acute effects on cardiac output with a long AV delay allowing for intrinsic conduction as compared to an echocardiographically optimized AV delay during dual chamber pacing, and then to follow the patients to see if there are any remodeling changes related to a high degree of RV pacing.

7. BACKGROUND AND SIGNIFICANCE

Cardiac pacing is the only effective treatment for symptomatic sinus node dysfunction. Most patients with preserved left ventricular function receive dual chamber pacemakers; however, right ventricular apical pacing can have detrimental effects on left ventricular function due to the abnormal electrical and mechanical activation pattern of the ventricles.

Many patients receiving dual chamber pacemakers for symptomatic bradycardia have prolonged intrinsic AV conduction (first degree AV block), and as a result, will receive a significant amount of ventricular pacing if programmed at physiologic AV intervals. As an alternative, many pacemakers can be programmed to minimize ventricular pacing at the expense of allowing longer AV delays; however, these long AV delays are also not physiologic and may also lead to reduced cardiac output.

The main scientific questions being addressed in this study are to evaluate the acute effects on cardiac output with a long AV delay allowing for intrinsic conduction as compared to an echocardiographically optimized AV delay during dual chamber pacing, and then to follow the patients to see if there are any remodeling changes related to a high degree of RV pacing.

8. PRELIMINARY STUDIES/PROGRESS REPORT

There is a paucity of data in the type of patients being enrolled in this study. There is only one small study (reference 3) which did show a benefit to AV delay optimization with dual chamber pacing. However, this study was done before the new pacing modalities with MVP and the like that allow for longer AV intervals, and also before the data with regard to the potential detrimental effects of RV pacing. As such, this prior study (reference 3) had no follow up data on what would happen with the increased pacing over time, and is also

outdated as there are newer pacemaker programming options that were not in existence at the time of that investigation.

9. RESEARCH DESIGN AND METHODS

Study Design:

This will be a randomized, prospective clinical trial. All patients enrolled will undergo echocardiographic evaluation with AV delay optimization which will be compared to intrinsic conduction, and thus patients will serve as their own controls with respect to the acute hemodynamic data.

After observing the acute hemodynamic effects of AV delay optimization vs. intrinsic conduction, patients will be randomized in a 1:1 ratio by order of enrollment to either the echocardiographically optimized AV delay vs. with a long fixed AV delay allowing for intrinsic conduction. All patients will then get follow up echocardiograms at 6 months after randomization to assess if there are any remodeling changes associated with a higher burden of RV pacing. Patients will be monitored for any adverse events with routine clinic visits one-two weeks after implantation and programming and at 3 month intervals or as needed as per standard of clinical care.

Methods:
Patients who have AV conduction with long PR intervals (>230 msec) with preserved LV function who are receiving dual chamber pacemakers for symptomatic bradycardia will be evaluated by echocardiography evaluating baseline systolic and diastolic function as well as for mechanical dyssynchrony. Baseline aortic TVI, as a surrogate of cardiac output, will be measured and will be compared with aortic TVI with AAI pacing at 70 bpm and 90 bpm and with DDD pacing 70 bpm and 90 bpm at the optimal AV delay achieved with atrio-ventricular pacing at each heart rate.

To determine the optimal AV delay, the bradycardia device will be programmed to the DDD mode, and all patients will undergo echocardiographic analysis at varying AV delays. Measurement of continuous-wave aortic Doppler flow velocities in the apical five chamber view at baseline and at eight AV intervals: 220, 200, 180, 160, 140, 120, 100, 80 ms. will be done. After 20 cardiac cycles at each AV delay, measurements will be made on the final three to four cardiac cycles and averaged. The optimal AV delay will be defined as the AV delay associated with the largest average aortic Doppler VTI.

Measurements of diastolic dysfunction and dyssynchrony will also be re-evaluated with AAI pacing and with DDD pacing at optimized AV delays to evaluate the effects of pacing on these parameters as well.

Patients will then be randomized in a 1:1 ratio by order of enrollment to either the echocardiographically optimized AV interval or to a long-fixed AV delay that will allow for intrinsic conduction. Patients will have routine clinical follow up at 3 month intervals in the pacemaker clinic as per our usual standard of care, and then will have a comprehensive follow up 2D echo at 6 months after randomization to assess for any potential changes related to RV pacing including, RV function, LV function, LV end-systolic volume, LV end-diastolic volumes, wall thickness, and dyssynchrony as assessed by tissue Doppler imaging.

10. HUMAN SUBJECTS

A total of 40 patients will be recruited from the Cardiology Electrophysiology clinics of either gender for Echocardiography and AV delay optimization.

Inclusion Criteria: (all must be met)

1. Must have Symptomatic bradycardia requiring dual chamber pacemaker

2. PR interval of > 230 msec
3. Must give written informed consent
4. Must be at least 18 years old

Exclusion Criteria: (presence of any one or more)

1. Complete or high grade AV block
2. Persistent Atrial Fibrillation
3. EF < 45%
4. Patient's refusal to participate in the study

11. RECRUITMENT

Patients will be recruited from the Cardiology Electrophysiology clinic. Dr. Sawhney will review the potential patients' eligibility and if eligible, he or she will be consented in the clinic and will follow up as per protocol.

12. INFORMED CONSENT

Only the principal investigator or designee will obtain informed consent, after complete explanation of the nature and purpose of this study.

13. ALTERNATIVES TO STUDY PARTICIPATION

Participation in the study is voluntary, and patients may choose to not participate in this study. These patients will continue to get routine follow up as indicated for their medical condition.

14. POTENTIAL RISKS

The published literature indicates that there are no known immediate or delayed or long-term risks from ultrasound imaging using the ultrasound output levels and techniques for routine ultrasound exams.

The AV optimization involves temporary programming changes, and an electrophysiologist will be present throughout the programming. In the unlikely event that a patient does not tolerate a change in pacemaker mode, the pacemaker will be reset to its initial mode and that patient's study will be terminated.

After final programming, patients will be followed and pacemaker adjustments made as per routine clinical care. Follow up echocardiograms will be obtained to ensure there are no significant changes in cardiac function with pacing. If any changes are noted, the pacemakers will be adjusted as per routine clinical practice.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Patients will be monitored for any adverse events with routine clinic visits 1-2 weeks after initial implantation of the pacemaker and at 3 month intervals or as needed as per standard of clinical care. Patients will also be enrolled and followed by home remote monitoring if possible (weather or not this is possible depends on the brand of pacemaker implanted, and if they have a home telephone line).

The arrhythmia clinic is staffed by two nurse practitioners and a dedicated technician for pacemaker interrogations and related issues. We currently follow over 1,000 patients with implanted intracardiac devices. The clinic number (619) 543-5428 is answered daily from 8 AM to 5 PM, and the nurse practioners are always available during this time period. The nurse practioners discuss all phone calls with the primary electrophysiologist and make notes into the EPIC electronic medical record.

After business hours, the answering machine provides the number for the electrophysiology fellow and attending on call, whom are available 24 hours daily for urgent issues.

There are also two research assistants in the electrophysiology division who can assist with the reporting of any adverse events to the Human Studies Committee.

The study will be funded by existing funds provided by Dr. Ajit Raisinghani for the purpose of performing echocardiograms.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

To maintain patient confidentiality, patient names and medical record numbers will be used only to retrieve (1) the final interpretation reports of the pre-pacing and post-pacing echocardiographic examinations and (2) demographic data, as described above. We will strictly maintain patient confidentiality and destroy patient identifying data immediately after data collection. Data collection forms will include only identifying research numbers—patient names, birthdates, and medical record numbers will not be used. Further, PHI will not be re-used of disclosed for other purposes. All data will be kept in a locked cabinet accessible only by the principal investigator. Any data kept on a computer will be encrypted and password protected.

Patients who may have any questions or concerns can contact the principal investigator at 619 543-5428 or the HRPP

17. POTENTIAL BENEFITS

It is possible that AV delay optimization guided by echocardiography will improve cardiac output which may lead to improvement in energy levels, and quality of life.

18. RISK/BENEFIT RATIO

It is possible that AV delay optimization will improve hemodynamics with regard to cardiac output which may improve energy levels and quality of life. There is very little risk to echocardiographically optimizing the AV delay. Patients will be followed closely after pacemaker placement and programming at 2 weeks after implantation and programming and at 3 month intervals as is routine standard of clinical care. If there are any changes in clinical functional status, patients will be assessed as needed by echocardiography and any clinically indicated device programming changes will be made.

19. EXPENSE TO PARTICIPANT

There will be no added expense to enrolled subjects.

20. COMPENSATION FOR PARTICIPATION

There is no payment for participation in this study.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Only physicians, registered diagnostic cardiac ultrasonographers, and registered nurses will perform this study. All procedures will take place at UCSD Medical Center or UCSD Encinitas Echocardiography Lab.

1. Dr. Navinder Sawhney, M.D.: Faculty, licensed in California with full Attending privileges at UCSD. Implements the protocol as well as performs data analysis and reviews images.

2. Dr. Ajit Raisinghani, M.D.: Faculty, licensed in California with full Attending privileges at UCSD. Implements the protocol as well as performs data analysis and reviews images.
3. Dr. Unnati Sampat, M.D.: Fellow, Cardiac Imaging at UCSD, licensed in California. Implements the protocol as well as performs data analysis.
4. Karen McClure, RDCS: Staff sonographer licensed in California, performs echocardigograms.

22. BIBLIOGRAPHY

1. Sawhney NS, Waggoner AD, Garhwal S, et.al. Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. (Heart Rhythm 2004;1:562–567).

2. Tops LF, Schalji MJ, Bax JJ. The Effects of Right Ventricular Apical Pacing on Ventricular Function and Dyssynchrony. J Am Coll Cardiol 2009;54:764–76

3. Iliev II, Yamachika S, Muta K, et al. Preserving normal ventricular activation versus atrioventricular delay optimization during pacing: the role of intrinsic atrioventricular conduction and pacing rate. Pacing Clin Electrophysiol. 2000 Jan;23(1):74-83.

4. Sweeney MO, Ellenbogen KA, Tang AS, et al. Atrial pacing or ventricular backup–only pacing in implantable cardioverter-defibrillator patients Heart Rhythm2010;7:1552-60.

23. FUNDING SUPPORT FOR THIS STUDY

There are no outside sources of funding. The study will be funded by existing funds provided by Dr. Ajit Raisinghani for the purpose of performing echocardiograms.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable.

26. IMPACT ON STAFF

All research activities will be done in the echocardiography lab by the investigators. Pacemaker management and follow up will be done as per routine standard of care.

27. CONFLICT OF INTEREST

Not applicable.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not needed at this time.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not needed at this time.