T-Wave Alternans in patients with dual chamber or biventricular pacemakers

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A. Study Purpose and Rationale

Ventricular tachyarrythmias are a serious problem causing approximately 300,000 to 400,000 deaths per year in the United States (1). In fact, half of the patients with congestive heart failure die suddenly from malignant rhythm, (2). In recent years, the advent of the implantable cardiac defibrillator (ICD) I as provided a highly effective mode of preventive therapy for sudden cardiac death (3-6).

However, inserting an ICD is both costly and invassive; it should be targeted toward those at high risk. Traditionally, this has consisted of survivors of sudden cardiac death and patients resuscitated from ventricular arrhythmias. Unfortunately, this cohort represents only 2-3% of people who eventually succumb to sudden cardiac death (7). More recently, indication for insertion of ICD has extended to primary prophalaxis for certain well-defined groups of patients. For example, the Madit 11 trial demonstrated that insertion of ICI)s reduced relative all-cause mortality by approximately 30% compared to conventional medical therapy in patients who are status-post myocardial infarction with an LVEF less than or equal to 30% (8). Insertion of an ICD for every patient meeting the above criteria would incur an enormous economic burden to society, since the cost of the device alone is about $40, 000, not to mention physicians' fees and the resources it takes to expand facilities for defibrillator implantation and maintenance. If it were possible to further risk-stratify the patients meeting the MADIT II criteria, one would be able to avoid unnecessary cost and performance of an invasive procedure (9).

On a surface EKG, the period of cardiac repolarization is represented by the T wave. Microvolt T wave alternans (TWA) is a fluctuation in the morphology of the T wave on an electrocardiogram which occurs with every other beat; these differences occur on the order of microvolts and are not visible by visual inspection. Recent advances in signal processing, i.e. Fourier spectral decomposition (10), h td made it possible to detect TWA in a reliable and non-invasive manner. Studies have shown that the presence of TWA bears a strong relationship with the risk for the development of ventricular tachyarrythmias, although the physiologic reasoning behind this association is not well understood. In 1994, Rosenbaum et al followed 83 patients for 20 months after their electrophysiologic studies for 20 months and found that 81% of those who tested positive for TWA had an arrythmic event compared to only 69,') of those who tested negative (10). A number of other prospective studies further confirmed the value of TWA in predicting ventricular arrythmias in different patient groups- including those with congestive heart failure (11-13), prior myocardial infarction (14,15), long QT (16), or hypertrophic cardiornyopathy (17). In a recent article in Lancet by Hohnloser et al (18), data from two prospective trials studying the T-wave alternans test (11,14) were pooled into a post-hoc analysis of 129 patients meeting the MADIT II criterion. With an average of 16 months of follow up, those who tested positive or indeterminate for the test have a 15.6% event rate for sudden cardiac death (SCD) or cardiac arrest, while those who tested negative has had no SCD ($p<0.02$). This argues T-wave alternans test may be an useful non-invasive tool to separate those at high vs. low risk for the development of malignant ventricular tachyarrythmias. It is important to note that to date no prospective TWA-based treatment studies have been reported; however, such investigations are currently underway (19). One group of patients that have been consistently excluded from TWA studies is those with permanent pacemakers; investigators eliminate this subset due to concern that secondary T wave changes occurring after prolonged period of ventricular pacing may confound the interpretation the TWA test (10). However, approximately 1 million people in the United States have permanent pacemakers (20,21). The prevalence of ventricular arrythinias in the group above is probably significant, especially since most have underlying cardiac pathology. Hence, it is important to be able to extend use of the TWA test to risk stratify these patients and guide

therapy. The presence of TWA correlates tightly with hear rate-the current definition of a negative study requires demonstration of no significant TWA at a HR of 105 or greater. To date, most clinical studies have achieved the HR elevation required for TWA assessment through atrial pacing (10) or exercise (22). The only exception is in a small pilot study done by Smith et al in 1988 where a high heart rate was achieved by pacing at the RV apex. However, the results of this study are difficult to generalize because it was not interpreted using the standard protocol for analyzing TWA (23). Our project is a pilot study that aims to compare measurements of TWA during short term atrial and ventricular pacing- similar to the amount time needed to perform an actual TWA tests on patients with dual chamber pacemakers.. Since TWA measures the intrinsic likelihood that the heart will develop ventricular arrythmias, our hypothesis is that the TWA test result obtained during atrial and ventricular pacing will be the same.

B. Study Design and Statistical Procedures

a. Study Design

T wave alternans will be measured during atrial pacing (with intrinsic ventricular conduction) at the following rate: 100, 105, or 110 each for five minutes. The subjects will then rest until their heart rate and f blood pressure return to baseline. T wave alternans test will again be measured during AV sequential pacing with RV pacing (using the longest PR interval to assure consistent ventricular capture) at the same heart rate and time course as listed above. TWA will be measured using a spatial method outlined in Rosenbaum et al (10). The result of the test would be interpreted with the standard definition outlined by Bloomfield et al (24). The heart rate at which sustained alternans is first present, otherwise known as onset heart rate, will be noted even if it is above 105bpm. We will also monitor all patients in the study for the frequency of appropriately administered ICD shocks for the next x months or attempt to correlate the result of the TWA test obtained through different method of pacing with the frequency of 1CD shocks.

b. Statistical Analysis

Previous studies demonstrated an agreement between atrial pacing and bicycle exercise of 0.85 (22), between bicycle exercise and treadmill testing of 0.81 (25). Atrial pacing and bicycle exercise testing have been validated on subsequent prospective studies to correlate with the risk of development of ventricular arrythmias (10, 11). In this study, we will employ a one group chi square test of proportions, aiming to demonstrate correlation of 0.8, assuming an actual correlation of 0 9. This assumption is reasonable since pacing (whether atrial or ventricular) results in less background noise than exercise testing, hence, the agreement between the two pacing methods should be higher. Allowing for power of 0.8, this study will plan to recruit 109 patients.

C. Study Drug or Devices

This study will use a permanent pacemaker/ICD implanted in the patient to treat previously present clinical conditions. No patient will receive new implantation of a pacemaker or other device for the purpose of participating in this study, This study does not require the administration of any drugs, and will not affect whether a patient receives any drugs.

D. Study Questionnaires

This study will not involve the use of questionnaires.

E. Study Subjects

This study will recruit patients receiving care at 6 e New York Presbyterian Hospital.

a. Inclusion criteria are as follows:

1) Patients with dual chamber ICDs or biventricular pacemaker/ICDs
2) Patients with intrinsic AV-conduction intact, able to be paced AA1 at with 1: 1 AV conduction at 110bpm.
3) Patients who at baseline are ventricular paced less than 10% of the time

b. Exclusion criterion:

1) Patients with atrial flutter/atrial fibrillation
2) Patients with frequent atrial or ventricular ectopy (more than 25% of all complexes)
3) Patients with the Wolf-Parkinson-White syndrome

F. Recruitment

Residents, clinical fellows, and attending physicians will identify potential subjects among their patients. It is anticipated that the rnajority of the patients will be recruited from the ICD clinic at CPMC. Investigators will request permission from the candidate's attending physician prior to discussion of the study with the candidate. Subjects will receive $25 incentive to participate as well as reimbursement for reasonable costs of transportation to and from the studies.

G. Confidentiality of Study Data

The data obtained from this study will track each subject by a unique, confidential numeric identification code; investigators will remove all other patient identifying information from all records maintained for the purpose of this study. Access to the key to the numeric identification code will be permitted only under exceptional circumstances, and only to personnel who require patient identifying information. The study involves the collection of information contained in a subject's medical record. Study investigators and their designees will have access to pertinent medical records to gather pertinent information for the study on a strictly need-to-know basis. People in this group includes: The investigator, study staff and other health professionals (if applicable) who may be evaluating the study; Authorized representatives of the sponsor of this research (if applicable); - Columbia University (are they involved?); - New York Presbyterian Hospital; - Authorized representatives of the National Institutes of Health ("NIH"), Food and Drug Administration ("FDA"), the Office of Human Research Protection ("OHRP") or other government regulatory agencies (if applicable); and - Applicable Institutional Review Boards ("IRB") that independently review the study to assure adequate protection of research participants, as required by federal regulations.

The investigators, regulatory authorities, IRB and study sponsor may keep the research records indefinitely. If the results of the study are published or presented at a medical or scientific meeting, the patients will n)t be identified.

H. Potential Risks

This study performs 3 interventions on the subject's atrial pacing, ventricular pacing, and the TWA test. Performing the TWA test poses minimal risks for the subject. While subjects are paced at a higher than normal I ieart rate, those with coronary artery disease have a small chance of suffering from cardiac ischemia due to increased myocardial demand. Pacing will be increased only during the testing period under the supervision of an experienced physician who will terminate the study if they suspect there are any problems, i.e. any symptoms of chest pain, nausea/vomiting, diaphoresis, or hypotension. Should the ICD fire for any reason during the study, the study will be terminated. After the TWA tests are performed, patients will be discharged with their initial pacemaker parameter.

Should patients experience any injury or illness due to their involvement in the study, they should contact the Dr. Anthony Magnano, the principle investigator, at 212-3057934. If medical treatment is necessary, Columbia University hospital will assist patients in obtaining treatment, including first aid emergency treatment and *follow* up care as needed. In the event of an emergency 1 1 which patients are unable to contact investigator or staff, they should seek treatment immediately.

The cost of such treatment will be billed in an ordinary manner to patients or their insurance company. The patients are responsible for the cost if it is beyond the amount covered by the patients' insurance plan. No other *form* of compensation for an injury or an illness will be provided. For example, compensation for lost wages, transportation, co-pays, deductibles or indirect loses due to the injury/illness is not available.

I. Potential Benefits

This study will offer a free evaluation that would risk stratify the participant's chance of developing ventricular arrythmias and the likelihood of experiencing ICD shocks. This information could be released to those caring for the patient to guide further treatment. Since all patients in this study will already have ICD's, there will be no need to refer patients with positive TWA for electrophysiologic study or ICD implantation.

J. Alternatives:

The alternative to participating in this study would be to not participate. Patients would have read the consent form and understand the nature and purpose of the study. They would have the fully discuss the study with 1 he investigator or study staff, having the chance to ask questions and had received satisfactory answers. They will be told the possible risks and benefits of participating in the study and the alternatives to participation. They are free to withdraw at any point of the investigation. The patient's refusal participate or withdraw will not affect their future care or their relationship with the investigators.

K. References:

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