

A Study to Determine if T Wave Alternans is a Marker of Therapeutic Efficacy in the Long QT Syndrome

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A. Statement of study rationale and purpose

T wave alternans (TWA), an alteration of the amplitude and morphology of the T wave that occurs every-other-beat, is emerging as an important new marker for identifying patients at risk of developing malignant ventricular arrhythmias. {Rosenbaum, Jackson, et. Al 1994} It is undergoing intense investigation in a number of areas where patients are thought to be at higher risk for Sudden Cardiac Death including heart failure, and hypertrophic cardiomyopathy. However, patients with congenital Long QT have yet to be evaluated. In addition, there appears to be no definitive way to evaluate the efficacy of treatment of the Long QT Syndrome. Finally, the role that the sympathetic nervous system plays in the Long QT Syndrome is not well understood and still controversial. The primary purpose of this study is to evaluate the presence of TWA in patients with Long QT Syndrome, and to assess whether TWA is a predictor of efficacy of treatment. Another purpose of this study is to understand the role of the sympathetic nervous system in the Long QT Syndrome.

B. Background

Sudden cardiac death affects approximately 400,000 people per year in the United States alone. {Gillum 1989} Most of these deaths are due to malignant ventricular tachyarrhythmias (VT). Patients with the Long QT syndrome have an increased incidence of these arrhythmias. Identifying which patients are still at increased risk for sudden cardiac death even after treatment of the Long QT Syndrome would be beneficial to this population of patients.

T wave alternans is a new noninvasive marker of risk for sudden cardiac death. T wave alternans (TWA) is a fluctuation in the morphology or amplitude of the T wave that occurs every-other-beat. Initially, it was noted on an anecdotal basis that the development of macroscopic TWA, i.e., TWA visible to the naked eye on an EKG, was a harbinger of the development of malignant ventricular tachyarrhythmias in a number of disease states: {Raeder, Rosenbaum, et al. 1992} acute myocardial infarction, Prinzmetal's angina, long QT syndrome, acute myocardial ischemia during coronary angioplasty, and various electrolyte abnormalities. Later, however, Richard Cohen, et al at MIT, developed a technique for measuring microvolt TWA, TWA not otherwise visible to the naked eye, in dogs during atrial pacing {Smith, Clancy, et al.} This technique involves the identification of points on the T wave by time-aligning EKG complexes and plotting the fluctuation in the amplitude of these points over time. A spectral analysis of this fluctuation is then performed, which generates a power spectrum. The power spectrum represents the various frequencies at which the points on the T wave oscillate. Therefore, for example, a peak on the power spectrum occurring at 0.1 cycles/beat represents a change in the amplitude of the T wave that occurs once every tenth beat. TWA, on the other hand, would be represented by a peak on the power spectrum that occurs at 0.5 cycles/beat, or once every-other-beat.

The prognostic significance of microvolt TWA was confirmed initially in dogs, on which numerous experiments with myocardial ischemia and hypothermia established the relationship between the development of TWA and subsequent onset of ventricular tachycardia and ventricular fibrillation {Smith, Clancy, et al} Additionally, the magnitude of the alternans (i.e., the height of the peak at 0.5 cycles/beat on the power spectrum) was found to be inversely proportional to the ventricular fibrillation threshold. It was also discovered that T wave alternans occurred above certain heart rates. Therefore, it was determined that TWA measurements must be made at heart rates between approximately 105 and 110 bpm.

Rosenbaum, et al, published the first prospective human study examining TWA in 1994 (Rosenbaum, Jackson, et. Al 1994). This study examined the ability of TWA to predict inducibility of ventricular arrhythmias during EPS as well as the prognostic value of TWA as compared with electrophysiologic testing in determining arrhythmia-free survival. The study population consisted of 83 patients who were referred for electrophysiologic testing for a variety of different indications. In addition to EPS, all patients underwent measurement of TWA during atrial pacing at 100 bpm. TWA was found to be a statistically significant predictor of inducibility during EPS, independent of the presence of organic heart disease. It was also found to be equivalent to EPS as a predictor of arrhythmia-free survival during the 20-month follow-up period. Thus, a strong association between TWA and the development of malignant ventricular tachyarrhythmias was established.

Patients with the Long QT Syndrome have been known to be predisposed to malignant ventricular arrhythmias. However, no study to date has showed an association between the Long QT Syndrome and microvolt T wave alternans. It is very likely that many of these patients will be TWA positive. In this case, TWA can be further used to assess the risk of sudden cardiac death after treatment. Another more controversial marker for sudden death, QT Dispersion, has been used to show which patients continue to be at risk for sudden death while on a beta blocker. However, QT Dispersion has inherent technical limitations which have continued to make it a less reliable technique. Thus, we propose to use TWA to first establish an association between the Long QT Syndrome and TWA. We then wish to evaluate whether TWA is a useful method to identify efficacy of treatment, by comparing patients successfully treated with a beta blocker to those not successfully treated who then require left stellate ganglionectomy.

C. Study Design and Statistical Analysis

This is a study to demonstrate that patients with Long QT Syndrome have TWA, and that the method of looking for TWA can then be used to evaluate the efficacy of treatment. The study will take place on the 9th floor of Presbyterian Hospital in the Cardiopulmonary Exercise Laboratory. Approximately 50 subjects will be enrolled from the Long QT Syndrome Registry. Another 25 healthy volunteers will serve as control subjects with an age comparable to that of the study population. Patients from the study population will be broken down by group into Long QT Syndrome patients who responded to treatment, and patients after beta blocker therapy who did not respond to treatment and will subsequently undergo left cardiac sympathetic denervation.

All patients will undergo T wave Alternans measurements during bicycle exercise. Those patients who do not respond to treatment and continue to have events such as syncope or cardiac arrest will then undergo cardiac sympathetic denervation as per current guidelines. The patient will then undergo a repeat T wave alternans test to evaluate the efficacy of treatment by denervation.

We expect approximately 70% of patients to respond to beta blocker therapy and have no more events, while the other 30% will continue to have adverse events requiring sympathetic denervation. Statistical analysis will be done comparing proportions in a 2 x 2 table using the chi square test. Although the sensitivity and specificity of the TWA test has been published to be >80%, if we assume a sensitivity and specificity of 70%, the patient number needed in the study calculates to approximately 50.

D. Study Procedures

Prior to testing, a brief clinical history will be obtained. The T wave alternans measurement will be made using the spectral method employed by the Cambridge Heart 2000 system (described previously), using bicycle exercise. The patient will be followed for 1 year. If the patients continues to have events such as syncope or arrest he/she will undergo left cardiac nerve sympathetic denervation as per current guidelines and then be asked to have another TWA test as described above. The entire study protocol will take approximately 3-4 hours to complete per session with a maximum of two sessions. Follow up will be for one year.

a. Exercise Stress Test

The T wave alternans test consists of recording continuous 12-lead and orthogonal ECGs using 7 standard electrodes and 7 Cambridge Heart High Resolution (Hi-Res) electrodes. Prior to placement of the Hi-Res electrodes, small areas of the patient's skin will be shaved, if necessary, cleaned with alcohol, and gently abraded to maximize lead contact. Patients will have their ECG recorded during sitting, exercise, and recovery. The TWA exercise protocol is a submaximal exercise protocol, the endpoint of which is achieving and sustaining a target heart rate of 105 bpm. The exercise test will be performed as part of previous protocols (IRB #7540 and IRB#7813).

b. Beta Blocker

Patients will continue their beta blocker treatment as usual the morning of the test. Only patients who have started therapy within one month's time will be enrolled in the study. The patient's heart rate and rhythm will be monitored by continuous ECG during all stages of the study.

c. Follow Up

Patients will be followed up for a period of one year. Those patients who did not respond to treatment and continue to be symptomatic and have syncope or cardiac arrest will undergo left cardiac sympathetic denervation. These patients will then be asked to return for a repeat TWA exercise test after surgery.

E. Medical Devices

The CH 2000 Stress Test System, i.e., the equipment used to measure and record T wave alternans during exercise, received FDA 510(k) clearance on 2/29/96, #K950018. This system is a computerized platform, which supports a wide range of standard stress test protocols as well as performing T wave alternans computation at rest, during exercise, pacing, or pharmacologic stress. T wave alternans is computed by the spectral method, as discussed above. The CH 2000 meets the standards for diagnostic electrocardiographic devices and for cardiac monitors, heart rate meters, and alarms. The Hi-Res, or high-resolution, ECG electrode is manufactured by Cambridge Heart, Inc. It received FDA 510(k) clearance on 8/29/96, #K962115. The Hi-Res ECG electrode is a pre-gelled, single use, multi-segment, silver/silver chloride electrode for short-term use to measure ECG signals with the Cambridge Heart CH 2000 Stress Test System.

F. Study Questionnaire

The study questionnaire will include questions on onset of symptoms, date of diagnosis, current medications being taken, and family history of disease.

G. Study Subjects

The study will not include "vulnerable" populations, nor will the study be restricted based on gender or race.

Inclusion and Exclusion Criteria: only patients from the National Long QT Registry who have started therapy within one month of the alternans test will be allowed to participate. Any patient with Class IV heart failure, or a history of bronchospasm will be excluded from the study.

H. Recruitment of Subjects

Patients from the Long QT Registry will be asked to participate. Only those patients who have been started on treatment with a beta blocker will be recruited. The patient's primary physician will be approached first concerning the patient's enrollment in the study. If the primary physician agrees that it is

appropriate, he/she will then discuss potential participation in the study with the patient. If the patient is amenable, either the primary investigator or one of his assistants will then approach the patient concerning enrollment in the study. The principal investigator or one of his designated representatives will describe the study, including the procedures and risks, to the patient and review the consent form with the patient. Written consent for the study will be then be obtained.

I. Confidentiality of Study Data

All patients will be assigned a unique study number, and, thus, all study data will be coded. The results of all studies will be stored and analyzed in a computer to which only the primary investigator and his assistants have access.

J. Potential Conflict of Interest

Dr. Bloomfield receives research support from Cambridge Heart Inc., although he has exclusive rights to analyze and publish the data from this study.

K. Location of Study

The study will take place on the 9th floor of Presbyterian Hospital in the Cardiopulmonary Exercise Laboratory.

L. Potential Risks

The patients will be informed that the risks of the study are minimal. The procedures involved are not likely to result in serious discomfort or inconvenience to the patient. During the assessment of T wave alternans using the two aforementioned methods, the patients will experience an increase in heart rate to either 70% of their predicted maximum heart rate, or to a heart rate of 105 bpm, whichever of the two is greater. This level of exercise is moderate and will occur under electrocardiographic and blood pressure monitoring. A cardiologist will be physically present during the exercise and recovery portions of every procedure. Exercise will be terminated in the event that the test precipitates either ischemia or serious rhythm disturbances. There is a small risk that even this moderate increase in heart rate will exacerbate existing conditions such as CHF or asthma, induce an arrhythmia, or cause ischemia, which, in rare circumstances, may lead to cardiac arrest, myocardial infarction, or death. The potential side effects of the gel and adhesive used in the manufacture of the Hi-Res ECG electrodes are the same as those for all electrodes; these include mild irritation, itching, redness of the skin, or, in rare cases, chemical burns leading to scarring.

M. Potential Benefits

The patient may gain benefit from being identified early as potential non responders to beta blocker treatment. The TWA protocol should allow for early detection and risk stratification of those patients at risk for sudden cardiac death.

N. Alternatives

The alternative to this study is for the patient to have their clinically scheduled tests without undergoing the additional testing in this protocol. It will be made clear to the patient that their decision not to participate in this study will in no way effect the quality of their future care.

O. Compensation to Subjects

Patients will receive a stipend of \$75.00 each visit for their participation in the study in order to cover their travel expenses and to compensate them for their inconvenience. The patients will receive compensation within 3 weeks of their participation in the study.

P. Costs to Subjects

Participation will not incur additional medical expense to the patient.

Q. Minors as Research Subjects

This study will not involve the participation of minors.

R. Radiation or Radioactive Substances

This study will not involve the use of radiation or radioactive substances