IRB Protocol:

Heart rate response to TWA and Exercise Stress Testing

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A. Statement of study rationale and purpose

The current study is a subset of a prospective epidemiologic study investigating T wave alternans (TWA) and risk of new arrhythmic events. There are three major categories of outcome to TWA testing: positive, negative and indeterminate. A large number were classified as indeterminate because they were unable to raise their heart rate (HR) to greater than 105 beats per minute. This study will investigate the relationship between heart rate response to TWA and max heart rate response to exercise stress testing. There are 111 patients from the initial longitudinal cohort who completed both TWA testing and exercise stress testing. The relationships between baseline medication usage, O2 consumption, NYHA class, QRS duration and heart rate response will also be investigated.

B. Background and Hypotheses

Sudden cardiac death accounts for greater than 400,000 deaths each year in the United States and remains a significant health problem. Most sudden cardiac deaths are caused by fatal ventricular arrhythmias (ventricular tachycardia and fibrillation). Identifying patients at risk for these arrhythmias remains a major challenge in preventive medicine/cardiology, as between 2-5% of patients who have a sudden cardiac arrest are resuscitated and survive to hospital discharge. It has been demonstrated that individuals with previous myocardial infarction and congestive heart failure with EF < 30% derive significant mortality benefit from prophylactic AICD implantation (MADIT-II). Further, it has been shown that individuals with ischemic cardiomyopathy and EF < 35% derive significant mortality benefit from prophylactic AICD implantation. However, the cost burden associated with prophylactic AICD implantation may be untenable for the US health care system.

It has been previously demonstrated that T wave alternans may be an efficient and non-invasive method for screening patients who may be at high risk for sudden cardiac death. It has also been shown that TWA has high negative predictive value for identifying those unlikely to benefit from prophylactic AICD. 20-40% of TWA tests are classified as indeterminate. Those with an indeterminate MTWA test may have a risk of arrhythmic events, including death, equal if not greater than that of MTWA positive patients. Approximately 51% of MTWA indeterminate test results are due to the inability to generate HR > 105. Termed “chronotropic incompetence,” poor heart rate response to standardized exercise testing such as the Naughton and Bruce protocols is a known poor prognostic factor for cardiac morbidity and mortality. However, the relationship between HR<105 in response to MTWA testing and max HR response to exercise has not been elucidated. Further, it is not known whether HR<105 to MTWA testing predicts chronotropic incompetence. The relationship between inadequate HR response to MTWA testing and other known prognostic markers in CHF has not been described.

This study will test the following hypotheses:

H1: Participants with MTWA HR < 105 will have a significantly lower max exercise HR than participants with MTWA testing negative, positive or indeterminate results.

H2: MTWA HR<105 will predict chronotropic incompetence, regardless of medication use, oxygen consumption or NYHA CHF class.

H3: There will be no patients with MTWA < 105 and chronotropic incompetence.

H4: MTWA testing may be a proxy for exercise stress testing.

C. Study Design and Analysis

This is a sub-study of 111 patients who participated in a prospective epidemiological study of a total of 410 patients. Patients were recruited from multiple clinical centers around the United States. Patients were followed by telephone or in person one month after the T wave alternans test as well as every four months after the test, until at least 24 months of follow-up was completed.

Using a mathematical approximation to adjust for the difference between the number of patients (MTWA HR < 105) and controls (MTWA +/-/IND), we calculated the difference, or effect, we would be able to show as a proportion of the standard deviation (S.D.) using the formula, assuming equal number of cases and controls:

N = 1 + 16 (S.D./effect) e 2

This calculation demonstrated that we could detect an effect, or difference, of 0.8 x S.D. When using the actual number of cases (N=14) and controls (N=97) in our sample, given the unequal ratio of 7:1 in group 2 (controls) vs group 1 (cases), with the known S.D. of 10 in group 1, a paired t-test with an alpha = 0.05, powered to detect a difference 80% of the time, demonstrate an effect size of 8.1. This validates the equal group size approximation above.

D. Study Procedures

Eligible patients were enrolled by completing standard demographic information consisting of age, gender, race/ethnicity and other background traits and a cardiovascular medical history, including NYHA Functional Class. All patients had a measure of EF at time of enrollment, or one was obtained shortly after enrolling in the study. Participants underwent TWA testing within 4 weeks of enrolling in the study. As per larger study protocol, participants also had 24 hour Holter monitoring at time of enrollment. A standardized exercise protocol (Naughton, Bruce, Treadmill) was performed at time of enrollment.

T Wave Alternans

T wave alternans will be measured during exercise using the spectral method employed by the CH 2000 system (Cambridge Heart Inc., Bedford, MA). The T wave alternans test involves the simultaneous recording of 12-lead ECGs by the CH 2000 Stress Test system using 14 electrodes, 7 standard electrodes and 7 Cambridge Heart Hi-Res ECG Electrodes. The T wave alternans test involves an ECG recording made during supine rest, exercise, and recovery. Following a rest recording, the patient will exercise on a bicycle or treadmill. The T wave alternans exercise protocol is a submaximal exercise protocol, which has an endpoint of 70% of maximal age predicted heart rate or a heart rate of 105 BPM (whichever is greater), or symptoms which limit exercise. No specific exercise protocol is mandated by this protocol. The only requirement is that the exercise protocol results in a gradual increase in heart rate in the range of 90 – 120 bpm. Immediately following the exercise recording, the patient will rest quietly while 4 minutes of recovery ECG data are recorded.

Exercise Stress Testing

Exercise stress testing was completed at time of enrollment by one of four standardized protocols (Naughton, Bruce, Treadmill). These protocols were conducted by the exercise physiology lab at Columbia University Medical Center. Maximum heart rate achieved was recorded by each protocol. Since no difference in prognosis has been shown through the use of different exercise modalities, testing method was determined at the time of enrollment by the exercise physiology lab. Tests may have been terminated early if participants experienced chest pain, dyspnea or other symptoms of cardiac ischemia. All exercise testing was conducted in standardized fashion.

E. Study Drugs

There are no study drugs in this protocol.

F. Medical Devices

The CH 2000 is a computerized platform for TWA testing 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 published by J.M. Smith et al., Circulation 1988; 77:110-21

This testing protocol and materials used therein have been approved by the FDA for clinical use. The CH2000 and the Hi Res ECG Electrode are manufactured by Cambridge Heart, Inc., located in Bedford, Massachusetts.

The exercise testing protocol was determined at the time of testing by the exercise physiologists performing this portion of the protocol.

G. Study Questionnaires

No questionnaires will be used in this protocol

H. Study Subjects

Four hundred and ten adult male and female patients presenting for evaluation of or treatment of left ventricular dysfunction will be recruited from approximately 10 clinical centers within North America. 111 patients participated in this sub-study and completed both TWA testing and exercise stress testing. Listed below is the original inclusion and exclusion criteria used.

Inclusion criteria

- Left ventricular ejection fraction ≤ 0.40
- Age ≥18 years
- Signed IRB approved consent form

Exclusion Criteria

- Unable to give informed consent
- Unstable coronary artery disease
- NYHA Class IV heart failure
- History of syncope of unknown origin
- Persistent atrial fibrillation or flutter
- Planned revascularization
- < 90 days post MI, or < 90 days post-CABG
- Any other significant medical condition that in the opinion of the investigator precludes participation such as: serious ongoing cardiac dysrhythmia, endocarditis, severe aortic or mitral stenosis, severe left ventricular dysfunction, acute pulmonary embolus/infarction, acute or serious non-cardiac disorder or severe physical handicap
- Known history of a prior ventricular tachyarrhythmia requiring therapy (either antiarrhythmic drugs or an ICD).
- Patient receives ventricular pacing
- Participation in another randomized clinical trial and randomized to an arm that includes antiarrhythmic drug therapy

I. Recruitment of Subjects

Full recruitment and enrollment was completed by the time this sub-analysis was completed.

J. Confidentiality of Study Data

The data obtained from this study are considered confidential. Each patient was assigned a unique numeric identifier that was used throughout the study. An off site facility was used to store date. The data storage system was developed by an outside company. However, the data was analyzed at Columbia University. Results of the study were presented to study members at termination of the study protocol. On the basis of the data, manuscripts will be written by the investigators.

K. Potential Conflict of Interest

There are no potential conflicts of interest related to this protocol.

L. Location of the Study

Data analysis, interpretation and manuscript preparation will be completed at Columbia University.

M. Potential Risks

There are no specific risks associated with participating in the study other than the known risks for the specific procedures.

N. Alternatives

The alternative to participating in this protocol would be for patients to continue with their current treatment programs, without having exercise and TWA testing.

O. Compensation to Subjects

There will be no compensation to subjects for participating in this protocol.

P. Costs to Subjects

There will be no additional costs for a subject to participate in this protocol. Patients will be charged for their regularly scheduled clinical care.

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.

S. Highlighted References

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