The effect of β-adrenergic blockade on T wave alternans in patients with chronic heart failure.

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A. Study Proposal and Rationale

Sudden cardiac death is the most common and often first manifestation of atherosclerotic heart disease and is responsible for approximately 50% of the mortality from cardiovascular disease in the developed world. In the United States, 300,000 to 400,000 deaths annually are attributable to sudden cardiac death.[1] This amounts to an overall incidence in the adult population of .1 - .2 % per year. In patients who have suffered a large myocardial infarction the incidence of sudden cardiac death approaches 30%. Although this population is easy to identify in order to direct, they represent only a small fraction of total sudden cardiac death victims. Currently, patients only present for treatment of ventricular arrythmias after they have experienced a major arrythmic event. Present tests available to screen patients, such as measuring left ventricular ejection fraction[2], ventricular ectopy by Holter monitoring[3], late potentials by signal-averaged electrocardiograms [4-6], heart rate variability[7], and QT dispersion[8], have limited sensitivity and specificity. Thus, in order to make a significant impact on the problem of sudden cardiac death, a means of identifying the larger group of patients who are at high-risk but have not experienced a ventricular arrythmia is desperately needed.

T Wave Alternans is a new and promising technique for the identification of patients at high-risk for sudden cardiac death and ventricular arrythmias. Visual electrical alternans; on the surface electrocardiogram has long been noticed to be associated with ventricular arrythmias and cardiac mortality. However, visually apparent alternans is extremely rare and therefore cannot be used as a sensitive marker of sudden death risk.[9] Recently, techniques have been developed which have made it possible to detect visually inapparent beat-to-beat oscillations of the surface electrocardiogram.[10] In 1994, Rosenbaum et al demonstrated a significant relationship between the presence of microvolt electrical alternans (visually inapparent) measured during atrial pacing with inducibility of ventricular tachycardia and subsequent 20-month arrythmia-free survival.[11] The authors of this study concluded that microvolt T wave alternans may serve as a noninvasive marker of vulnerability to ventricular arrythmias. In 1997, Estes et al. demonstrated that it is feasible to detect T wave alternans with the heart rate elevated by a bicycle exercise protocol rather than atrial or ventricular pacing.[12] This advance has now made it possible to detect T wave alternans in a larger group of patients in order to determine their risk of ventricular arrythmias without the invasive and expensive electrophysiology study.

Thus, T wave alternans appears to be a marker of arrythmia vulnerability. However, what is currently unknown is the underlying electrophysiologic pathology that leads to this finding on the electrocardiogram. In addition, could T wave alternans potentially guide therapy if changes of T wave alternans occurred with therapy and correlated with improved survival? Furthermore, the effect of different autonomic stimuli on T wave alternans is also unknown.

Patients with congestive heart failure and coronary artery disease are at high-risk for sudden cardiac death. Recent controlled clinical trials have shown that P-blockers reduce cardiovascular mortality and sudden cardiac death in this population.[13,14] In a study of 21 patients, Kirk et al. looked at the effect of a short-acting intravenous Pblocker on pacing-induced T wave alternans.[15] In this study, intravenous esmolol showed a 50% reduction in the incidence of T wave alternans in a group of patients with inducible ventricular tachycardia.

This studies aim is to look at the effect of the oral β-blocker Carvedilol on exercise-induced T wave alternans in patients with congestive heart failure secondary to coronary artery disease. This drug has been shown to reduce the incidence of sudden death in large clinical trials and as a consequence we

propose that it will decrease the proportion of patients with T wave alternans and decrease the magnitude of T wave alternans in those who the alternans remains.

B. Study Design and Statistical Analysis

This study will be a single-center prospective trial looking at the effect of chronic oral β-adrenergic blockade on T wave alternans in patients with chronic heart failure.

All patients with chronic heart failure secondary to coronary artery disease who will be referred to the Columbia Presbyterian Congestive Heart Failure center for Carvedilol uptitration will be eligible for the study. Patients will not be on any β-blockers or antiarrythmics at entrance to the study. Consent will be obtained from the patients and we will obtain approval from their cardiologist. Prior to being started on Carvedilol, patients will be brought to the exercise lab where after careful skin preparation high-resolution electrodes (HighRes^{TM}, Cambridge Heart Inc. Bedford MA, USA) will be placed in the standard 12 ECG lead positions and in an orthogonal X, Y, Z configuration. Patients will perform a standardized bicycle exercise protocol while TWA will be measured with the CH2000 system (Cambridge Heart Inc.). TWA will be considered positive if the alternans amplitude is greater than 1.9 uV with the alternans ratio > 3 in the vector magnitude lead, any orthogonal lead, or two consecutive precordial leads.[16] During the exercise protocol, the patients will have continuous electrocardiographic and frequent blood pressure monitoring. The duration of exercise is to be approximately 10 to 15 minutes depending on the patient's endurance.

After the initial T wave alternans measurement, the patients will be started on Carvedilol at the discretion of their attending cardiologist at the Columbia Presbyterian Heart Failure Center. When the patients reach the maximally tolerated dose or 25mg BID, they will be asked to return the exercise lab to have the same exercise protocol performed as described above.

Statistical comparisons will be made between the proportion of patients positive for T wave alternans before and after Carvedilol using χ-square analysis. Power analysis performed with the McNemar test of paired proportions demonstrated that 22 subjects will be required in order to detect a 50% reduction in T wave alternans with a power of 80% and cc of 0.05.

C. Study Procedures

The following table describes the sequence and time requirements for the procedures involved in this protocol:

Test	Description	Time (minutes)
Exercise Test	*Introduction to the laboratory *Placement of the high resolution electrodes *Placement of blood pressure monitor *Graded-intensity bicycle exercise to maximally tolerated heart rate or heart rate of 120 *Time for recovery of vital signs to baseline	60
Total		60

During the exercise period, the patient's blood pressure and electrocardiogram will be monitored as per standard exercise testing protocol. The exercise will be stopped at the request of the patient, if the heart rate reaches 120, if electrocardiographic changes develop suggestive of ischemia, or if the patient develops symptoms.

D. Study Drugs

Carvedilol is a nonselective β-adrenergic blocking agent with cc,-blocking activity. Carvedilol is currently FDA-approved for usage in NYHA class II or III heart failure of ischernic or cardiomyopathic origin, in conjunction with digitalis, diuretics, and an ACE inhibitor. In this study, patients will be started on this drug at the discretion of their attending cardiologist. Initial starting dosage is 3.125mg twice daily for two weeks. If this dose is tolerated, the dosage will be doubled every two weeks until the highest tolerated dose is reached or 25mg twice daily. Common side effects include fatigue, dizziness, and light-headedness. The patient's attending cardiologist will make all dosing decisions.

E. Medical Devices

N/A

F. Study Questionnaires

N/A

G. Study Subjects

All subjects in the study will be ambulatory, aged 18-80, and have NYHA Class I-III heart failure with an ejection fraction of ≤0.40. All patients will be receiving at least two months of treatment with an angiotensin-converting-enzyme inhibitor or angiotensinII receptor blocker and diuretics. All patients will have documented coronary artery disease by electrocardiogram, stress testing, or angiography.

Exclusion Criteria:

- -major cardiovascular event within three months
- -revascularization procedure within three months
- -preexisting therapy with a β-blocker
- -atrial fibrillation
- -treatment with calcium antagonists and inotropic agents except digitalis.
- -treatment with an antiarrythmic drug
- -advanced heart block
- -chronic renal failure
- -prior heart transplant
- -primary valvular disease
- -myocarditis

H. Recruitment of Subjects

Study patients will be recruited from the Columbia Presbyterian Heart Failure Center. The patient's primary cardiologist at the Columbia Presbyterian Medical Center will have to agree to allow the patient into the study.

I. Confidentiality of Study Data

The patient's names will not be used and the record linking the names to a code number will be secure with the principal investigator.

J. Potential Conflict of Interest

None

K. Location of the Study

Columbia Presbyterian Medical Center

L. Potential Risks

The risks of this study are attributable to the risk of exercise testing. These risks include hypo/hypertension, syncope, arrythmias, angina, and in rare cases myocardial infarction or death. However, in this study the patients will be exercised by a similar protocol that is used in stress testing. Stress testing is often used for diagnostic purposes in this population with a low incidence of adverse events. Furthermore, this is a limited exercise protocol, as exercise will be terminated at a heart rate of 120 which is well below the age-adjusted maximal heart rate used in stress testing.

M. Potential Benefits

The patient's physicians will be notified of the results of the T wave alternans test at the end of the study. This knowledge could potentially influence the physician's choice of therapy for the patient in the future.

N. Alternative Therapies

none

O. Compensation to Subjects

none

P. Costs to Subjects

none

Q. Minors as Research Subjects

none

R. Radiation or Radioactive Substances

none

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