T-wave alterrians guided prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction.

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A. Study Purpose And Rationale

Sudden cardiac death (SCD) is described as an unexpected natural death from a cardiac cause within one hour of onset of symptoms. It is one of the leading causes of death, especially among those with coronary artery disease (CAD). SCD is often attributed to ventricular tachyaffhythniias (ventricular tachycardia (VT) and ventricular fibrillation (VF)). An implantable cardioverter-defibrillator (ICD) can prevent SCD by terminating the lethal arrhythmias that lead to SCD. However, ICI)s are quite expensive (on the order of $60-70,000) and require a skilled cardiac electrophysiologist for implantation.

A recent study has demonstrated that prophylactic implantation of an ICD can reduce mortality in patients with coronary artery disease and reduced left ventricular ejection fraction without the need of any risk stratification procedure (N Engl J Med 2002;346:877-83.). However, given the large number of patients that would fit this criteria, the application of these results to general clinical practice would create an intolerable financial burden on our healthcare system. Also, from subgroup analysis, it has been suggested that the majority of the benefit of an ICD was driven by the group of "sicker" patients. Therefore, it is essential that a method is developed which would allow the identification of those most likely to benefit from an implantable cardiac defibrillator (ICD) among this group of patients. Thus, one would minimize the cost of implementation of this strategy, while retaining the maximum benefit.

T-wave alternans (TWA), the beat to beat oscillation of the T-wave on an electrocardiogram (ECG), has emerged as a promising screening test for ventricular arrhythmia risk stratification. This test is noninvasive and inexpensive. TWA is derived from the analysis of an ECG, such as those obtained from a cardiac stress test, a cardiac electrophysiological study (EPS), or a 24 hour Holter monitor. It has been shown that the greater the degree of TWA, the higher the risk of SCD. Thus far, studies have highlighted that TWA is a robust marker of future ventricular tachyaffhydiniias. Some studies have also suggested that TWA may be as good as or better than an EPS, the standard of care, in predicting future events. The majority of these studies have been on a small scale, enrolling only about 100 to 200 pts, and have focused on attempting to establish the sensitivity and positive predictive value of TWA. It is believed that the sensitivity of TWA for predicting ftiture ventricular tachyarrhythmias is on the order of 90%, while its positive predictive value is only 30-50%. There have been no studies thus far using TWA to guide therapy.

In this study, we will assess the value of using TWA as a screening test to guide implantation of an ICD.

B. Study Design And Statistical Analysis

Each patient enrolled in the study will undergo a non-invasive 24 hour Holter monitor study. During this time, the subject may carry on their usual daily activities. The ECG obtained from this Holter monitor will be analyzed for TWA. The results of the TWA analysis will be categorized into either positive TWA or negative TWA. Patients with negative TWA will then be randomized to receive either an ICD or no ICD and patients with positive TWA will also then be randomized to receive either an ICD or no ICD. The patients randomized to no ICD will serve as the control arm for the patients randomized to an ICD in their respective groups. The study investigators and the subject's primary physicians will be blinded as to the results of the TWA analysis which will be done by a technician not involved with patient care or data gathering and analysis.

The primary end point under investigation will be total mortality from any cause. The secondary end points will be incidence of ventricular tachyaffhythn-tic events, SCD, cardiac arrest and cardiac related hospitalizations. Analysis will be performed according to the intention to treat principle and the results will be analyzed using the Chi square analysis of proportions.

It is expected that approximately 40-50% of patients enrolling in the study will be TWA positive. The estimated mortality in this group of patients is 20% over 2 years. To detect a 33% relative risk reduction in mortality in the ICD recipients with 90% power at the two sided significance level of 0.05 will require approximately a total of 1370 patients in this arm of the study.

In the TWA negative group, a total of 3000 patients will be required in order to detect a similar reduction in mortality in ICD recipients. A larger number of subjects in order to show a similar effect stems from the fact that this group will most likely have a lower mortality rate, on the order of 10% over 2 years,

C. Study Procedure

TWA will be analyzed from the ECG recordings of each subject's 24hr Hotter monitor using the modified moving average method of Nearing and Verrier Q AppI Physiol. 2002 Feb;92(2):541-9). In brief, odd and even beats of the ECG will be separated into two groups. An average QRS complex will be created for every 15 seconds of data in each group. These average QRS complex will then be compared between the two groups in the region between the J point and the end of the T-wave. The greatest difference between the complexes inside this specified area will be called the TWA value.

The TWA value at the maximal heart rate in lead V5 will be used. A subject with a TWA value of greater than 50 microVolts will be placed in the positive TWA group and subjects below this cutoff into the negative TWA group. Subjects will then be randomized to receive an ICD or no ICD.

All ICI)s will be implanted in clinical electrophysiology device laboratories with the patient under conscious sedation. A small incision will be made in the pectoral region and the device will be placed subcutaneously. The leads will be directed to the heart into the right ventricle via the venous system. The subject will then be tested for defibrillation threshold and the device will be set to at least IOJ above that level.

Subjects will have follow up at least every 6 months with their primary physician and will also follow up with an ICD clinic annually to ensure proper functioning of the ICD. All subjects will be followed for at least one year, but this study will likely need to continue for 4 to 5 years in order to accumulate enough occurrences of the primary end point.

D. Study Drugs

Not applicable

E. Medical Device

ICDs are devices which continuously analyze a patient's heart rhythm looking for sustained ventlicular tachycardia or ventricular fibrillation, the common causes of sudden cardiac death. Upon detection of such a rhythm, the device will deliver an intracardiac electrical shock in the hopes of terminating the dysrhythmia and preventing death. The discharge of an ICD can be uncomfortable, but often the patient will lose consciousness before the device discharges.

ICDs are commercially available from several biotechnology manufacturers and have been FDA approved for several decades. Their implantation is minimally invasive and is a routine procedure for most electrophysiologists. ICDs have very low risk of adverse events and the vast majority of adverse events are non-fatal, involving usually infection or lead problems. The typical indications for an ICD placement are patient history of ventricular tachycardia, ventricular fibrillation, cardiac arrest, or inducibility of ventricular dysrhythmia during an EPS.

F. Study Questionnaires

Not applicable.

G. Study Subjects

a. Inclusion criteria

Patient of either sex over age 21 were eligible for the study if they suffered a myocardial infarction greater than one month prior to study entry and had a left ventricular ejection fraction equal to or less than 30%. Prior myocardial infarction was determined by either 1) elevated cardiac enzymes during hospitalization for suspected myocardial infarction, 2) pathologic Q waves on ECG, 3) a fixed perfusion defect on radionuclide scanning, or 4) localized akinesis on ventriculography or echocardiography. The ejection fraction will be documented using echocardiography, radionuclide scanning, or ventriculography within 3 months of study entry.

b. Exclusion criteria

Patients were excluded for study entry if, at the time of enrollment, they had any FDA approved indication for ICD implantation, had a myocardial infarction within one month, underwent coronary revascularization (angioplasty or coronary bypass surgery) within 3 months, or were taking antiarrhythinic agents. Patients were also excluded if they had any other serious, non-cardiac comorbidity with an extremely poor prognosis with death likely during the trial.

H. Recruitment Of Subjects

Primary care physicians and cardiologists at the 30 clinical centers will be requested to identify patient in their practice who meet the inclusion/exclusion criteria. These physicians will then approach the patient to determine their willingness to participate in this trial. The patient will then meet with a study investigator or his/her representative to explain the study and obtain informed consent.

I. Confidentiality Of Study Data

All study subjects will have a unique trial code to keep track of their data. Thus, no personal identifiers will be stored in the database.

J. Potential Conflict Of Interest

No conflict of interest to declare.

K. Location Of The Study

24hr Holter monitors will be done at the subjects home. TWA analysis will be done in the research laboratory. ICD implantation will be done in the clinical devices laboratory at each clinical center. Due to the large number of subjects required, this study will need to be conducted simultaneously at 30 clinical centers.

L. Potential Risks

The major risks associated with ICD implantation include 1) risk of conscious sedation during implantation procedure, 2) inappropriate discharges of the ICD, 3) infection stemming from ICD placement, and 4) lead problems requiring lead extraction and replacement. Another potential risk will be the subject's ineligibility for magnetic resonance imaging (MRI) secondary to device placement.

M. Potential Benefits

The main benefit subjects from this trial will derive is the implantation of a free ICD. Other benefits include relatively close medical follow up and continuous encouragement of their primary physician to maximize the subject's medical therapy.

N. Alternative Therapies

The study subjects will continue to be aggressively medically managed regardless of ICD implantation.

O. Compensation To Subjects

Subjects will not be monetarily compensated

P. Costs To Subjects

There will be no cost to the study participants.

Q. Minors As Research Subjects

No minors will be allowed to participate in the study

R. Radiation Or Radioactive Substances

Not applicable