

The Impact of End Stage Renal Failure and Hemodialysis on T Wave Alternans

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A. Study Purpose and Rationale

Patients with chronic renal failure frequently suffer from cardiovascular death and sudden cardiac death. Indeed, 50% of patients with end stage renal failure ultimately die from cardiovascular causes. Of these patients, an estimated 10% die from sudden cardiac death likely due to arrhythmias. Many of these patients have cardiac disease because frequent causes of chronic renal failure such as hypertension and diabetes often lead to coronary artery disease and cardiomyopathies. These patients are highly susceptible to ventricular arrhythmias which might lead to sudden death.

Patients on hemodialysis undergo rapid and significant shifts of electrolytes and volume. In particular, hemodialysis affects potassium, calcium, and proton levels in addition to total body volume. Derangements in electrolytes, pH, and hemodynamics are associated with known abnormalities on the resting electrocardiogram as well as arrhythmic events. Multiple studies have examined the association between hemodialysis and abnormalities on the resting EKG as well as Holter monitoring. The results of these studies have conflicted with some suggesting an association between hemodialysis and EKG abnormalities while others finding no relationship between hemodialysis and arrhythmias. As a result, it remains unclear whether patients with end stage renal failure on dialysis constitute a group whose risk of arrhythmic events differs from other patients with cardiomyopathies.

T wave alternans is a new technology which detects repolarization abnormalities at microvolt levels. Several clinical studies have demonstrated an association between a positive T wave alternans result and a propensity toward ventricular arrhythmias. Moreover, a negative T wave alternans result strongly suggests a low likelihood of future arrhythmias.

This study attempts to determine the prevalence of T wave alternans among patients with end stage renal failure and whether hemodialysis affects results on T wave alternans. Specifically, we propose to examine the results of T wave alternans studies for patients with a cardiomyopathy and with advanced renal failure on hemodialysis to see whether these patients are at higher risk than other patients at risk for sudden cardiac death. We also intend to perform T wave alternans tests before and after hemodialysis to assess whether hemodialysis has an effect on the results of T wave alternans. We also seek to measure routine laboratory and hemodynamic values on these patients before and after hemodialysis to see whether alterations in any of these variables affects T wave alternans and the propensity for arrhythmias.

a. Purpose

To study the effects of hemodialysis and rapid metabolic shifts on patients with chronic renal insufficiency and cardiomyopathy on results of T wave alternans.

b. Hypothesis

Patients on hemodialysis suffer from metabolic derangements that will increase the prevalence of T wave alternans. Additionally, hemodialysis itself, through rapid shifts in electrolytes and volume, will affect the results of the T wave alternans test.

B. Study Design and Statistical Analysis

The study will be an observational study of 200 stable outpatients undergoing long-term and routine hemodialysis at New York Presbyterian Hospital with a cardiomyopathy defined as an EF < 40% measured on transthoracic echocardiogram or radionuclide studies. Recruitment will not be based on gender, ethnicity, or socioeconomic status. Subjects will be recruited from the Haven Avenue Hemodialysis center.

a. Data Analysis

The primary analysis will focus on the prevalence of T wave alternans tests among patients with end stage renal failure and heart failure. The prevalence of T wave alternans among this population of patients will be compared to data describing the prevalence of T wave alternans in patients with congestive heart failure using a chisquared test between two groups. Additionally, changes in the result of T wave alternans prior to hemodialysis will be compared to results post-hemodialysis using a chi square test. Routine pre-and-post dialysis laboratory and hemodynamic values will be correlated to the results of T wave alternans using unpaired t-test for continuous variables and chi square t-test for categorical variables. If hemodialysis affects the results of T wave alternans, a logistic regression model will be created to assess whether any variable significantly affects the result of T wave alternans.

b. Power calculation

Previously reported data suggest that the probability of a low-risk T wave alternans is .35. Data among patients with end stage renal failure suggests that 50% of these patients may be at risk of an arrhythmic event, a chi squared test among two groups indicates that 182 patients will be needed in each group to detect a significant difference between the groups.

Among patients with a high risk T wave alternans, there is little data to suggest the likelihood that hemodialysis itself might affect the result. A difference of .01 would be of clinical interest. Using a single group chi square test on proportion and estimating a proportion of .09 before testing and .10 after testing, 6850 patients would be required to detect a difference.

C. Study Procedures

All patients on hemodialysis for greater than six months will be approached for recruitment only after the referring physician has determined that the patient is willing to discuss participation in the study. Patients will be scheduled to undergo a T wave alternans exercise test on the morning of routinely scheduled hemodialysis. Blood samples will be collected before and after hemodialysis using vascular access for hemodialysis. Hemodynamic measurements will be made at hemodialysis. Patients will then be scheduled to undergo a T wave alternans exercise test within 12-24 hours after the completion of hemodialysis.

T wave alternans tests will include exercise test on a treadmill or exercise bike as appropriate. Patients will be asked to exercise so that they achieve a heart rate of at least 105 beats per minutes for at least 10 minutes. High resolution electrodes will be placed in the standard 12 lead positions as well as in positions to permit an orthogonal X,Y,Z configuration of the EKG. Measurements will be made with a CH2000 system device. Using a spectral method of analysis that detects alterans in the microvolt range of amplitude, the T wave alternans test will be interpreted by the Alternans Report Classifier software (Version DIO). High risk and low risk results will be defined according to previously described criteria.

D. Study Drugs

There will be no study drugs in the study.

E. Medical Devices

There will be no medical devices used for treatment in the study.

F. Study Questionnaires

There will be no study questionnaires used in the study.

G. Study Subjects

a. Inclusion Criteria

- Chronic renal insufficiency with hemodialysis at least three times per week. Hemodialysis for greater than six months.
- Age over 21
- Cardiomyopathy defined as an EF < 40%. associated technologies.

H. Location of Study

T wave alternans exercise test will occur at CPMC in the exercise physiology laboratory in Harkness Pavilion. Blood samples for laboratory analysis and hemodynamic measurements will be made at the Haven Avenue Dialysis Center during a regularly scheduled hemodialysis.

I. Potential Risks

Exercise testing to induce T wave alternans may involve discomfort, dyspnea, and fatigue to patients particularly when patients undergo exercise testing after hemodialysis. Inflation of blood pressure cuffs may lead to local discomfort or bruising. Laboratory analysis of blood drawn at hemodialysis should involve no risk because all patients will already have vascular access for hemodialysis.

There is a small risk of a significant adverse clinical event in the course of exercise testing from elevating a patient's heart rate including cardiac ischemia and cardiac arrhythmia.

J. Potential Benefits

Patients who test positive for T wave alternans will benefit from the knowledge that they may be at higher risk for sudden cardiac death and may benefit from further evaluation or intervention. Patients who test negative for T wave alternans will benefit from the knowledge that they may be at lower risk for sudden cardiac death despite their cardiac disease.

K. Compensation and Costs to Subjects

There will be no compensation to nor costs incurred by any subjects.

Lay Summary

The Impact of End Stage Renal Failure and Hemodialysis on T Wave Alternans

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Study Purpose:

50% of patients with end stage renal failure die from cardiovascular causes. A substantial percentage of these patients die from sudden cardiac death which likely is a result of an arrhythmia. While some studies have found that patients with end stage renal disease on hemodialysis have abnormalities in the standing EKG as well as in longer term monitoring with a Holter monitor, others have found no higher incidence of . However, it remains unclear whether patients on hemodialysis from chronic renal disease are at higher risk of an arrhythmic event than other patients with cardiovascular disease.

T wave alternans is a new technology that permits better identification of patients who are at risk of arrhythmic events. This study attempts to determine the incidence of T wave alternans among a patient of populations of end stage renal failure patients on hemodialysis. Furthermore, this study attempts to discern in a small sample of patients whether hemodialysis itself has any effect on T wave alternans.

Study Subjects and Recruitment

100 patients with end stage renal failure will be recruited from the Haven Avenue Hemodialysis Center. Patients will have been on hemodialysis for at least six months and will be clinically stable. -Patients will also have congestive heart failure with an ejection fraction < 40%.

Study Procedures

Patients will be asked to undergo exercise test for T wave alternans on the morning of hemodialysis. After dialysis, patients will undergo a repeat T wave alternans test immediately after hemodialysis or the next morning.

Exercise testing for T wave alternans will involve exertion on a treadmill or stationary bicycle as appropriate. Testing will be done until a heart rate of at least 105 beats per minute is achieved for 10 minutes. After that time, exercise will be terminated.

Blood pressure and heart rate will be measured before and after hemodialysis as well as before both exercise tests for T wave alternans. Bloods will be drawn through the vascular access device before and after hemodialysis to measure electrolytes and other routine clinical laboratory values.

Issues

The study involves minimal risks to the patient. Exercise testing may induce fatigue, shortness of breath, and leg discomfort. More serious clinical events during exercise testing that may occur are cardiac ischemia or a cardiac arrhythmias in which case testing would be terminated and the patient would be given appropriate medical.