The Use Of SAECG To Assess The Early Effect Of ACE Inhibition

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A. Study Purpose and Rationale

Throughout the 1980s and 1990s, multiple large clinical studies supported experimental findings that angictensin converting enzyme (ACE) inhibitors improved mortality in patients who were recovering from acute myocardial infarction (AMI). Some of these trials showed that treatment with ACE inhibitors is associated with' a reduced mortality from sudden death which, in most cases, is due to the occurrenceof malignantyentricular arrhythmias. In the past several-years, experimental models have been studiedto determine the potential role of ACE inhibitors in decreasing ischernic and reperfusion affhythmias. Several investigators have hypothesized that ACE inhibitors possess a primary antiarrhythmic; effect which may participate in their cardioprotective action. Some of the proposed mechanisms of protective effect include a direct physiological action, decreased sympathetic tone/vagomimetic action, improved electrolyte homeostasis, protection of ischemic myocardium (decreased effects of angiotensin H, free radical scavenging, inhibition of the breakdown of bradykinin), modulation of electromechanical feedback, and myocardial remodeling.

After a moderate to severe myocardial infarction, remodeling of the left ventricle takes place. The initial stages of this process is described as infarct expansion in which acute dilatation and thinning of the area of infarction occurs and results in a more dilated ventricle with reduced functional capacity. Specific electrical characteristics of this remodeled tissue are closely tied to the expression of ventricular tachycardia (VT) and may explain the ability to use clinical tools in addition to ejection fraction (EF) to predict arrhythinia. Current modalities include electrophysiologic study (EPS) with programmed electrical stimulation, Holter monitoring, measurement of heart rate variability and the signal-averaged electrocardiogram (SAECG). The SAECG was introduced over a decade ago and has been used extensively in clinical investigation and clinical practice to study *non-invasively* the duration of ventricular activation. A major advantage of the SAECG over standard ECG recording is the ability to record cardiac signals in the microvolt range, which allows a more accurate measurement of ventricular activation delay, an unportant determinant of reentrant VT. While the results of large studies have indicated that EPS provides the most unportant information regarding affhythmic; risk stratification, it is also clear that an abnormal SAECG does contribute to risk prediction, especially in concert with other noninvasive modalities (e.g., echocardiogram, 24 hour Holter).

The goal of this study, however, is not to assess the utility of the SAECG in predicting future mortality from fatal malignant affhydunias, but to use the SAECG as a non-invasive, yet sensitive reflection of the abnormal electrophysiology in the acutely post-infarcted heart in order to assess the early effect of ACE inhibition, if any, on the modification of ventricular conduction velocities. A secondary objective then will be to identify which sub-groups, if any (based on EF, successful reperfusion or presence of ventricular ectopy on telemetry), may benefit from early ACE inhibitor therapy.

B. Study Design and Statistical Analysis

This will be a randomized, placebo-controlled double blinded study to assess the shortterm effect of i.v. ACE inhibitor therapy on the signal-averaged electrocardiogram. A minimum of 63 patients will be enrolled into each group for an n of 126; n was calculated based on an alpha of 0.05 and 80% power. SAECGs will be performed on each patient according to the schedule outlined below; QRS duration and the root mean square (RMS) voltage of the terminal 40 ms will beMeasured,.for each patient [see Section C]. Results of the signal averaged ECG in the control and experimental groups will be compared using chi

square analysis. Logistical regression will be applied to determine if certain collections of patients (based, on EF <45%, presence of ventricular ectopy on telemetry, or successful reperfusion) within,both the control and experimental groups are more or less predisposed toaw abnormiat SAECG,and if these groups are -more or less responsive to therapy.

C. Study Procedures

Once study subjects are selected to participate in the study [see Section E below] and informed consent is obtained, patients will be randomized to, receive an iv infusion of either the study drug or placebo. An echocardiogram. and SAECG will be obtained by a designated technician at baseline, at 10 minutes after the first infusion and again 5 days after initiation of therapy. Two conventional time domain indices will be calculated: 1) duration of the total QRS complex in milliseconds, 2) root-mean-square voltage (in microvolts) of the last 40 msec of the QRS complex. Late potentials will be defined as root-mean-square voltage < 20 microvolts or total filtered QRS duration > 114 msec, or both. Blood pressure and heart rate will be monitored routinely and formal measurements for study purposes will be made both before and 20 minutes after each daily infusion. A designated physician will be available throughout the infusion process and for the subsequent hour. All patients will also be monitored on telemetry throughout the 5 day infusion period. Blood chemistries [potassium, magnesium, calcium] and creatinine will be monitored daily. Electrolytes will be repleted as necessary. Patients with either biochemical or physical adverse effects felt to be secondary to study drug therapy will be released from the study protocol.

D. Study Drugs

Patients will be randomized to receive either enalapril 2.5 mg/50cc normal saline iv infusion over 10 minutes or placebo [50 cc NS infused iv over 10 minutes]; each infusion will be given once daily for 5 days.

E. Study Subjects

Patients with known hypersensitivity, dilated carchomyopathy, bundle branch block, long QT syndrome, syncope, current use of antiarrhythmic drugs, known infiltrative or valvular heart disease, history of alcohol or cocaine use, chronic atrial fibrillation, permanent pacemaker stimulation, hypotension in the setting of adequate preload, or impaired renal function will be excluded from the study.

F. Recruitment of Subjects

Potential study subjects will be selected from patients admitted to the CCU at the Columbia-Presbyterian Medical Center with a principal diagnosis of "acute myocardial infarction. " Informed consent will be obtained from those.patients ,satisfying the criteria noted above.

G. Medical Devices

The only medical devices used win be the SAECG machine which will be operated by a designated technician and offers no risk to the subject.

H. Study Questionnaires

Not applicable.

I. Confidentiality of Study Data

All data concerning study subjects will be confidential.

J. Potential Conflict of Interest

Not applicable.

K. Location of the Study

The study will be conducted in the clinical areas of Milstein Hospital Building of the New York Presbyterian Hospital.

L. Potential Risks

The risks involved in this study are related to the inherent susceptibility of this study population to complications and to a lesser degree to the specific drug therapy. However, clearly the use of iv vasodilator therapy in patients already prone to hypotension may increase risks inherent at baseline.

M. Potential Benefits

While the actual participants may or may not derive any symptomatic or mortality benefit at the conclusion of this study, the understanding gained from the results of this study about the possible mechanisms of action of a widely used agent may help to elucidate which patients, if any, may benefit from ACE inhibitor therapy acutely post infarction.

N. Alternative Therapies

All patients, regardless of the group into which they are randomized, will receive what is considered standard therapy for acute post infarction patients. This may include treatment with aspirin, beta-blockers, iv/SL nitroglycerin, and/or morphine. This study examines the acute electrical effects of an *additional* agent, enalapril iv, given within 12-36 hours as compared with placebo. Although there is little disagreement that high-risk AMI patients (elderly, anterior infarction, prior infarction, asymptomatic patients with globally depressed ventricular function) should receive long-term ACE inhibitor therapy, the benefits of early initiation of ACE inhibition post-infarction are less well documented.. For those patients unable to participate in this study, the alternative therapy would be simply to receive no iv ACE inhibitor.

O. Compensation to Subjects

No monetary compensation will be offered to subjects for participation in this study.

P. Costs to Subjects

Subjects will not be responsible for any additional- costs beyond what they would incur from their designated hospitalization for the AMI.

Q. Minors as Research Subjects

Minors will not be eligible for participation in the study.

R. Radiation or Radioactive Substances

No radiation or radioactive substances will be used in this study aside from exposure from routine diagnostic imaging.