Heart Rate Response to Regadenoson and Sudden Cardiac Death

Study Protocol & Statistical Analysis Plan

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Fadi G Hage, MD Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

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Objectives:

The main objectives of this proposal are to investigate whether:

1. A blunted heart rate response to regadenoson is an independent predictor of sudden cardiac death.
2. A blunted heart rate response to regadenoson can be used as a predictor of response to implanted cardiac defibrillator (ICD) on top of traditionally used indicators.

Hypotheses:

1. Patients with a blunted heart rate response to regadenoson are at higher risk of sudden cardiac death (death or appropriate cardiac defibrillation). This risk is maintained after controlling for age, gender, left ventricular ejection fraction, heart failure symptoms and medication use.
2. Patients with a normal heart rate response to regadenoson have a low rate of events (death or appropriate cardiac defibrillation) despite meeting current indications for having an ICD.

Background:

In patients with left ventricular systolic dysfunction and in those with a history of sudden cardiac death, an ICD reduces mortality.[1-3] However, not all patients with an ICD receive appropriate therapy from it (In a large study, only one third of patients received appropriate therapy from an ICD over the first 3 years of follow-up)[4], and inappropriate ICD shocks are common and are associated with worse quality of life and increased mortality.[5] Furthermore, ICDs are expensive (the procedure costs ~$35,000) and place a toll on the health care system. Establishing a better predictor of risk of sudden cardiac death and of response to ICD is desirable.

Adenosine and regadenoson are routinely used as pharmacological stress agents to induce coronary hyperemia for myocardial perfusion imaging (MPI) in lieu of exercise. The increase in heart rate seen during adenosine infusion has previously been attributed to its vasodilatory effect on the systemic circulation and has thus generated little interest. Recently, it was recognized that this rise in heart rate is related to a direct stimulation of the sympathetic nervous system by adenosine therefore allowing for a novel simple method for the evaluation of autonomic function.[6] Using data from the ADenoscan Versus RegAdenosoN Comparative Evaluation for Myocardial Perfusion Imaging (ADVANCE MPI 1 and 2) Trials, we demonstrated that patients with diabetes mellitus have a blunted heart rate response to adenosine presumably due to cardiac autonomic dysfunction.[7] Furthermore, the heart rate response associated with multiple risk factors of sudden cardiac death.[7, 8] Since cardiac autonomic dysfunction has been linked to increased

cardiovascular risk,[9] we postulated that the heart rate response may carry useful prognostic information. Recently we showed that a blunted heart rate response to adenosine is associated with increased mortality in the overall population and that it assisted in the risk stratification of patients at high risk (such as those with diabetes mellitus or chronic kidney disease) when added to traditional MPI findings.[10] In a Cox regression model, a blunted heart rate response was the strongest predictor of mortality and provided additional prognostic data to MPI after controlling for age, gender, race, history of myocardial infarction, diabetes mellitus, chronic kidney disease and beta-blocker use. We also demonstrated that a decreasing heart rate response to regadenoson is associated with stepwise increase in mortality.[11] In a Cox proportional model for mortality that adjusted for age, gender, diabetes mellitus, renal disease and MPI findings, heart rate response to regadenoson in the lowest quartile was independently associated with 5-fold increase in mortality compared to the highest quartile. Patients with a normal heart rate response had a relatively low annualized total mortality despite the presence of risk factors.

We propose that patients with a blunted heart rate response to regadenoson have an altered autonomic nervous system (cardiac autonomic neuropathy) that places them at higher risk of sudden cardiac death. Using this novel and easily measured parameter, we will be able to select patients who are high risk and will benefit from an ICD and, at the same time, identify patients who are at low risk of experiencing sudden cardiac death despite satisfying current criteria for having an ICD (mainly a low left ventricular ejection fraction). In this proposal, we will be able to verify this using a highly selected population that is being continuously monitored for the occurrence of ventricular arrhythmias through their implanted devices.

Study Design: Prospective Observational

Population:

A total of 150 patients (18-80 years) with an indication for ICD implantation for primary prevention of sudden cardiac death as defined in the current American College of Cardiology/American Heart Association/Heart Rhythm Society Practice Guidelines.[12] Specifically we will recruit:

1. Patients with left ventricular ejection fraction (LVEF) less than 35% due to prior myocardial infarction who are at least 40 days post--myocardial infarction and are in NYHA functional Class II or III.
2. Patients with nonischemic dilated cardiomyopathy who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III.
3. Patients with LV dysfunction due to prior myocardial infarction who are at least 40 days post--myocardial infarction, have an LVEF less than 30%, and are in NYHA functional Class I.

Protocol

1. Prior to the implantation of a clinically indicated ICD, the heart rate response to regadenoson will be assessed. Regadenoson will be administered intravenously as a fixed intravenous bolus dose of 400 µg followed by a 5 mL saline flush. Medications (including beta-blockers) will be withheld on the morning of the test. The heart rate and blood pressure will be measured at baseline and every minute after regadenoson bolus for at least 5 minutes and until the heart rate and blood pressure are clearly returning towards baseline. The peak heart rate will be defined as the maximum achieved heart rate after regadenoson injection. The peak blood pressure will be defined as the blood pressure when the systolic component is at a minimum during the test. The heart rate and blood pressure response will be calculated for each patient as the maximum percent change from baseline.[7, 8] A heart rate response in the lowest tertile will be defined as blunted. A heart rate response in the highest tertile will be defined as normal. Secondary analyses will be performed with the heart rate response as a continuous variable and using the following cut-offs, <20% (blunted), ≥40% (normal).[10, 11]
2. An ICD will be placed for clinical indications using standard techniques.

Follow-up: 2-years from the time of ICD implantation.

Duration of study: 4 years

Endpoints:

1. Primary Endpoint: Sudden cardiac death
2. Secondary Endpoints
    a. All-cause death
    b. First appropriate ICD therapy
    c. All-cause death or first appropriate ICD therapy
    d. Inappropriate ICD therapy

Patients will be followed up at 6 months intervals with ICD interrogation. ICD therapy (shocks or anti-tachycardia pacing) will be determined as appropriate or inappropriate by an experienced clinical electrophysiologist (H.D.) after review of the intra-cardiac electrograms. If patient fails to show up at their scheduled appointment, patients or their designated relatives will be contacted to verify their status. In case of death, relatives will verify circumstances of death.
SCD will be strictly defined as death within 1 hour of symptom onset, or an unobserved death in which the patient was seen and known to be doing well within 24 hours of death. Survivors of aborted SCD, resuscitated cardiac arrest, and those receiving appropriate ICD therapy will also be considered to have experienced SCD and will be included in the primary end point.[13, 14]

Sample Size:

In a recent study from our group, patients with ICD implanted for primary prevention at our center experienced an event rate of death or first appropriate ICD therapy ~ 20% over first 2 years.[15] In our recent study on the heart rate response to regadenoson, patients in the lowest heart response tertile experienced a 4-fold increased risk of death compared to those in the highest tertile.[11] We believe that is a conservative estimate of risk for this study since the heart rate response should be a better predictor of sudden cardiac death than overall mortality. A sample size of 126 patients will provide a 90% power to detect a 4-fold increase in risk of the primary outcome for patients in the lowest compared to the highest tertile of the heart rate response to regadenoson (40% vs. 10% over 2 years) at a preset P value of 0.05. We plan for a sample size of 150 to account for any dropouts and or loss of follow-up.

Statistical Plan:

All statistical analyses will be carried out using SPSS version 17 for Windows (SPSS Inc., Chicago, Illinois). We will collect data on patient demographics (age, gender, race, education), patient characteristics (height, weight), co-morbidities (history of myocardial infarction, diabetes mellitys, hypertension, dyslipidemia, atrial fibrillation, stroke), prior cardiovascular procedures (percutaneous coronary intervention or coronary artery bypass grafting), habits (tobacco use), symptoms (NYHA classification), medication intake (aspirin, beta-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), aldosterone antagonist, loop diuretic, statin, insulin), electrocardiographic characteristics (left bundle branch block, right bundle branch block, QRS, QT, PR) and laboratory results (serum creatinine, electrolytes, brain natriuretic peptide).

The population will be divided into 3 groups with 50 patients in each group based on tertiles of the heart rate response on regadenoson. Continuous variables will be presented as mean ± SD and discrete variables as frequencies and percentages. The chi-square test or an analysis of variance (ANOVA) will be used for the comparison of categorical variables. Continuous variables will be compared using the unpaired student t test or the Mann-Whitney U test, as appropriate. In order to determine the predictors of the HRR to regadenoson, a linear regression model will be constructed with the HRR as the dependent variable and all the characteristics that are associated with the HRR ($p<0.2$) as dependent variables. An estimation of the effect of each of the variables on the HRR will be determined based on the coefficient of the variable in the regression equation. Follow-up time will be calculated from the time of evaluation to sudden cardiac death or to end of follow-up censored at 2 years from time of evaluation. Event-free survival curves will be constructed using the product-limit method (Kaplan-Meier) and differences among survival curves will be estimated by the log-rank test. Cox proportional hazard analysis will be used to estimate unadjusted and age, gender and LVEF adjusted (multivariate) risks for sudden cardiac death. We will introduce interaction terms to test for interaction between HRR and the different variables in the model. Estimated risks will be reported as hazard ratios (HR) with correspondent 95% confidence intervals (CI). All tests will be 2-tailed, and a p value of <0.05 will be considered statistically significant.

Amendments

During the conduction of the trial, the following amendment were introducted:

1. The original protocol enrolled patients with a clinical indication for an implanted cardiac defibrillator (ICD) for primary prevention of sudden cardiac death. We amended the protocol to enroll patients who are undergoing an ICD implantation or a generator exchange for clinical indications.

2. The original protocol enrolled patients prior to implantation of a clinically indicated ICD. We amended the protocol to include patients with an implanted ICD for primary prevention of sudden cardiac death who are undergoing a clinically indicated regadenoson MPI. We have extensive data from our laboratory showing that the heart rate response to regadenoson at the time of clinically indicated MPI has important prognostic implications.[7, 11, 16-19]

3. Shorten the duration of follow-up and sample size. The original protocol allows for 2 years of follow-up from the time of ICD implantation. We modified this to follow-up from time of regadenoson MPI to end of study.

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