The Role of Cardiac Magnetic Resonance Imaging in Identifying Acute Cellular Rejection in Heart Transplant Recipients

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A. Study Purpose and Rationale

Following orthotopic heart transplant, transplant recipients are at risk for developing acute cellular rejection. Cellular rejection can occur suddenly days, months, or even years following the transplant. According to the International Society for Heart and Lung Transplantation, 40% of patients are treated for rejection within the first year after transplant [1]. Moreover, rejection represents a major cause of mortality in heart transplant recipients [1]. However, allograft rejection often occurs without symptoms. For this reason, cardiac transplant recipients undergo close monitoring of the allograft. This is done by routine endomyocardial biopsy. In the first month following transplant, the patient undergoes endomyocardial biopsies weekly. Following the first month, the biopsies are slowly decreased in frequency until a year after the transplant at which point the patient continues to have biopsies every 6 to 12 months. However, acute cellular rejection continues to occur even beyond 5 years following transplant. With 1 year survival rates approaching 90%, 5 year survival rates approaching 70%, and 10 year survival rates approaching 50%, the need to detect cellular rejection remains great [1]. Efforts to discover new methods for detect allograft rejection have been largely unsuccessful and patients continue to undergo routine endomyocardial biopsies for the remainder of their lives.

These biopsies are not without risk however. They involve cardiac catheterization and removal of several portions of cardiac muscle from the right ventricle for examination at each routinely scheduled procedure. While the risk of death associated with this procedure is very small, the morbidity associated with the procedure is not. In several reports, the overall rate of complications in right ventricular biopsy ranged from 1 to 1.7 percent and included ventricular perforation, valvular damage, and death [2-4]. In addition, it is possible for an episode of cellular rejection to be missed by the current method of detection because of the sample error involved in taking blind biopsies of the right ventricle.

Cardiac MRI has been proposed as a less invasive method for detecting acute cellular rejection of the cardiac allograft. Several small studies have shown that MRI is able to detect changes in the myocardium of patients with an episode of allograft rejection. Early studies suggested that the T2 signal on the MRI was higher in patients undergoing some grade of rejection when compared to those without any evidence of rejection [5]. Another study showed that the T2 signal was elevated in all biopsies with abnormal results [6]. However, one study revealed that all heart transplant recipients had elevated T2 signals in the immediate post-operative period, lasting up to 25 days. After this time, the T2 signals returned to values comparable to normal volunteers who had not undergone orthotopic heart transplant. More importantly, 14 of 15 patients diagnosed with rejection by biopsy more than 25 days following transplant had a T2 signal that was elevated above the normal value by more than 2 standard deviations [7]. Smart et al. demonstrated a similar correlation between evidence of rejection on biopsy and an increase in T2 signal intensity by more than 14% of the patient's baseline value [8]. A correlation between increase in T2 signal intensity and degree of rejection has also been reported [9]. These studies suggest that cardiac MRI is a powerful tool in the evaluation of acute cellular rejection following heart transplant.

In this study, we seek to further define the role of cardiac MRI in the detection of acute cellular rejection. Specifically, we hypothesize that the negative predictive value of cardiac MRI in detection of allograft rejection is such that it is safe for patients more than 25 days after transplant

surgery to undergo MRI as a means of ruling out rejection. Those patients in whom rejection could not be ruled out would then undergo the biopsy. Such a finding would save many patients the morbidity associated with recurrent routine endomyocardial biopsy.

B. Study Design and Statistical Analysis

The study will be prospective and observational. It will be conducted at a single center. The primary outcome will be a negative result on cardiac MRI so that the negative predictive value of the MRI may be assessed. All patients will undergo endomyocardial biopsy and cardiac MRI on the same days, as dictated by the biopsy schedule pre-determined for the patient by their cardiologist. The pathologist and radiologist reading the biopsy and MRI respectively will be blinded to each other's report. Patient care will be directed only by the results of the biopsy as is currently the standard of care.

The results of the initial MRI will be considered the patient's baseline if the biopsy taken that day shows no evidence of rejection (grade 0). The results of subsequent cardiac MRIs will be considered positive, and representative of possible rejection, if the T2 signal is elevated above the patient's baseline study value by 10% or more. Any result less than a 10% increase will be considered negative, and not representative of rejection. This definition of a positive MRI uses a more conservative value than previous studies have suggested is associated with rejection. This will result in an increase in the negative predictive value of the MRI, yet still allow it to be clinically useful in preventing many patients from having to undergo biopsy. This definition of a negative test was chosen as a result of the potentially life-threatening consequences of a false negative test.

After the results of all studies have been finalized, they will be unblinded and compared. MRI results will be categorized in the following way: true negative (TN) if the biopsy and study are negative, false negative (FN) if the biopsy is positive but the study is negative, or positive. The negative predictive value (NPV) of the MRI will then be calculated using the following formula:

$$NPV=TN / (TN + FN)$$

The exact limits for the 95% confidence interval (CI) of the NPV for rejection will be calculated using the binomial distribution [10]. With estimates that the proposed definition of a negative MRI would result in a NPV of 99% and that 80% of MRIs will be read as negative using this definition, 210 follow up studies would be needed to show a NPV of at least 95%. This value would likely be acceptable to cardiologists and patients alike. Using an estimate that each patient would be willing to undergo an average of 3 cardiac MRIs after their initial study, we will need to enroll 75 patients to have 70 patients that will remain in the study following an initial negative biopsy.

C. Study Procedure

Patients will be enrolled in the study on the day of a scheduled biopsy and will have a cardiac MRI on the same day. Those patients with an initial biopsy showing no evidence of rejection (grade 0) will remain in the study. They will continue to undergo cardiac MRI on the days they return for biopsies, as directed by their cardiologist for routine care for post-transplant patients. They may terminate their enrollment in the study at any time they wish. It is estimated that each patient will be willing to undergo an average of 3 MRIs after their initial study. It is likely that the study will reach the goals for number of studies needed based on the power analysis in 6 months, with the average patient enrollment lasting 18 weeks. Those patients whose initial

biopsy shows evidence of acute rejection will not remain in the study. Subjects will not be required to undergo any more endomyocardial biopsies for the purposes of the study than those that occur as part of routine care after transplant.

Endomyocardial biopsy, which is part of routine medical care for heart transplant recipients involves localization of the internal jugular vein and passage of a small catheter through the vessel and into the right ventricle. Using this catheter, 4-5 samples of right ventricular muscle, usually 0.1-0.3 cm in size are taken. The catheter is then removed. The cardiac MRI, which is not currently part of routine medical care for heart transplant recipients involves obtaining images of the heart using a strong magnetic field. It requires the patient to remain motionless in the imager for 30 to 60 minutes, and some patients experience anxiety related to the inability to move freely during this time. Cardiac MRI involves no radiation, but contrast dye is injected intravenously during the course of the study.

D. Study Subjects

Patients will be eligible for this study if they have undergone orthotopic heart transplant more than 25 days prior to enrollment, are above the age of 18, and are presenting for routine medical follow-up with endomyocardial biopsy.

Patients will be excluded if they are not older than 18 years of age or have undergone orthotopic heart transplant less than 25 days prior to enrollment. Patients presenting with signs or symptoms suggestive of heart failure or arrhythmia including dyspnea or worsening edema will not be enrolled. Pregnant patients and those with renal insufficiency defined as a GFR less than 30ml/min will also be excluded. In addition, patients with a history of inability to undergo MRI will be excluded. Examples include those with claustrophobia or metallic implants such as pacemakers, ICDs, Swan-Ganz catheters, or prostheses.

E. Recruitment of Study Subjects

Patients will be recruited for enrollment by their cardiologist at their routine scheduled biopsy. Because they will be recruited by their own cardiologist, it is assumed that these providers will recruit subjects they feel are suitable for the study.

F. Confidentiality of Study Data

To ensure confidentiality of the study data all patients will be assigned a number at enrollment. All data collected from each patient will be stored with connection only to this number and any possible identifying information will be removed from the study database. The key linking each subject to the assigned study number will be destroyed and the de-identified patient information will be stored electronically in a computer accessible by password only to the study investigators.

G. Potential Conflict of Interest

There are no potential conflicts of interests for the study investigators.

H. Location of Study

The study will be carried out at the New York-Presbyterian Hospital Columbia Campus in New York City. The endomyocardial biopsies will all take place in the designated biopsy suite in the

Presbyterian Hospital building and the MRIs will take place in the research scanner located in the Neurology Institute.

I. Potential Risks

The risks involved in this study are primarily those associated with the magnetic resonance imaging. Since MRI uses a magnetic field for the purpose of imaging, there is no exposure to radiation during it. There are several risks associated with MRI though. These include feelings of discomfort and anxiety during the procedure because of the size of the imager in which the patient must lie without movement for 30 to 60 minutes. In addition, patients with metallic implants are at risk of injury during the MRI because these implants may move within the body. These patients will be excluded from the study. Finally, a rare, potentially fatal disease called nephrogenic systemic fibrosis has been reported in patients with renal failure who received MRI contrast material. For this reason, any patient with renal insufficiency will also be excluded. Since routine endomyocardial biopsy is the standard of care for heart transplant recipients, the patients in the study will not be subjected to any additional risk associated with this procedure.

J. Potential Benefits

The benefits of enrollment in the study include the diagnosis of any other cardiothoracic abnormalities by the MRI. Otherwise, there are no benefits to the study subjects.

K. Compensation to Subjects

Patients who choose to enroll in the study will be compensated with $20 for each completed cardiac MRI, with no limits on the number of MRIs a patient may undergo. Patients who are unable to tolerate the cardiac MRI will be compensated with a portion of that sum based on the fraction of the study they complete.

L. Costs to the Subjects

There will be no additional cost to patients.

M. Minors as Research Subjects

All patients below the age of 18 will be excluded from this study.

N. Radiation

Because MRI uses a magnetic field to obtain images, there is no radiation exposure during this portion of the study. Patients undergoing endomyocardial biopsy are frequently exposed to radiation with fluoroscopy to verify the position of the catheter used to obtain the tissue samples. Such radiation exposure is limited to the amount required for the patient's safety during this procedure. Because endomyocardial biopsy is part of routine medical care in heart transplant recipients and because the study subjects will not be required to undergo additional biopsies for the purpose of the study, there will be no increased radiation exposure to those patients who enroll.

Appendix

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