Evaluating the utility of cardiac magnetic resonance imaging in detecting cardiac transplant rejection
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Clinical Research Protocol

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Principal Investigator: James Carr, MD
737 N. Michigan Ave., Suite 1600
Chicago, IL 60611

Project Sites: Northwestern Memorial Hospital
Northwestern University

Co-Investigators: Debiao Li, PhD; William G. Cotts, MD; Kirsi Taimen, MD; Kansal, Priya, MD

Background

Cardiac transplantation is the treatment of choice for many patients with end-stage heart failure who remain symptomatic despite optimal medical therapy. The 2007 report from the Registry of the International Society for Heart and Lung Transplantation (ISHLT) estimated that 5000 – 7000 heart transplants are performed annually worldwide. In the US, approximately 2,200 hearts are transplanted every year and there is constant demand for more donor hearts.

After transplantation there is appreciable mortality in the first twelve months mostly due to acute allograft rejection and infections. Later on, cardiac allograft vasculopathy (CAV) - a form of chronic rejection - is the principal factor limiting long-term survival. CAV is a chronic immune-activated disease which causes diffuse thickening and narrowing of allograft arteries. According to the American Heart Association’s data from year 2008, 1-year survival is 86% and 5-year survival is 70%.

Customarily patients are unaware of signs of rejection so it’s necessary to monitor patients. Most of the techniques used for monitoring are invasive and possess a small risk for life-threatening complications. During the first year, numerous endomyocardial biopsies (EMB) are taken to evaluate for possible rejection (1). Additionally, coronary artery angiography and intravascular coronary artery ultrasound (IVUS) are being used to
screen for the presence of CAV. IVUS is considered to be the most accurate method for diagnosing CAV since traditional coronary artery angiography underestimates the severity of CAV (2). Unfortunately, IVUS is a time consuming and expensive study which seldom is covered by third parties. Treatments are started or intensified if a criterion of rejection is met. Untreated rejection usually causes persistent rejection leading to loss of graft function and death.

Since the 1980’s, cardiac magnetic resonance imaging (CMR) has been studied as a possibility to detect signs of post-transplant cardiac pathology. The main advantage of CMR is to obtain data non-invasively and acquire accurate and reproducible information of both cardiac morphology and function. Several CMR variables have shown good correlation to biopsy proven heart transplant rejection, the strongest of which is quantitative T2 assessment (2, 3, 4). Early enhancement may also prove useful in diagnosing transplant rejection just as it has in the diagnosis of myocarditis (5). Other promising CMR correlates of rejection with scientific proof in literature include late gadolinium enhancement (6), diastolic dysfunction (7) and in animal models paramagnetic iron oxide contrast agents (8, 9). These studies imply that CMR might be a useful tool in the follow-up of cardiac transplant patients providing additional information to current study methods.

Hypothesis/ Research Objectives

The objective of this study is to evaluate the utility of CMR to detect acute and long-term cardiac complications in post- heart transplant patient population. We aim to study if CMR will be comparable to or superior to currently used methods to survey signs of cardiac rejection. Results from CMR scanning will be compared to those acquired from the standard surveillance protocol (EMB, IVUS, echocardiogram, coronary angiography). The long term goal of this study is to improve the sensitivity in detecting heart transplant rejection and possibly reduce the need for endomyocardial biopsy and coronary angiography.

Research Methods

This study will be carried out in collaboration with Northwestern Memorial Hospital’s Bluhm Cardiovascular Institute. 400 post-cardiac transplant patients will be enrolled in this project. This number includes two cohorts (cohort 1: 200 subjects receiving a contrast enhanced MRI and cohort 2: 200 subjects receiving a non-contrast MRI). The patients will continue their regular post transplant follow-up visits to the transplant cardiologist as recommended. According to the Northwestern Memorial Hospital’s schedule, in the first year patients will undergo multiple right heart catheterizations with EMBs, one time IVUS and coronary angiography. Echocardiograms are performed together with right heart catheterizations. From the first year on, the biopsies are taken biannually and coronary angiography with IVUS are performed annually.

In our study, CMR scanning will be carried out within one week of the annual visit which includes IVUS, angiography, EMB and echocardiogram. Written, informed consent will
be acquired from all patients prior to performing the research MRI scan. All subjects will be screened for contraindications to MRI using a standard screening form. If MRI contrast agent is being administered, the subject will be asked about previous exposure to contrast agent and will be fully informed about side effects. All subjects receiving Gadolinium contrast agent will have renal function checked on the same day as the MRI scan. GFR will be tested either through point of care analysis of a blood sample or direct laboratory analysis.

For this study, subjects will receive either Magnevist or Multihance depending on their kidney function. Contrast will be given as follows:

- **For subjects with a GFR > 60 ml/min:**
  A total dose of 0.2mmol/kg Magnevist will be injected intravenously as the contrast agent.

- **For subject with a GFR 30-60 ml/min:**
  A total dose of 0.1mmol/kg Magnevist or Multihance (as determined by the Principal Investigator) will be injected intravenously as the contrast agent.

- **Subjects with a GFR <30 ml/min will not be given any contrast agent.**

All studies will be supervised by a certified MRI technologist and an ACLS certified fully registered nurse. Prior to scanning, if a contrast agent is being administered, an intravenous cannula will be placed in an antecubital vein using sterile technique. All subjects will be instructed to remove any metal objects (e.g. watches, pens, etc) prior to their scan.

All scanning will be carried out on a 1.5T or 3T MRI scanner (Siemens Medical Systems).

Patients will be positioned supine on the scan table and a receiver coil will be placed over the patients chest. All patients will be scanned using a combination of multiplanar cine TrueFISP, dark blood vessel wall imaging, whole heart coronary MRA, T2 mapping, phase contrast MRI, first pass imaging and delayed enhanced imaging.

Patients may receive one dose of sublingual nitroglycerin (0.4mg/mL) 5 minutes before initiation of scanning to achieve maximal dilatation of coronary arteries. If the systolic blood pressure is less than 100 mmHg, nitroglycerin will not be administered.

Patients with heart rates more than 70 beats/min will be given an intravenous beta-blocker called metoprolol in 5 mg dose increments up to a maximum of 15 mg, in order to achieve a target heart rate less than 70 beats/min.
Possible Risks:

Nitroglycerin: the most common side effects include burning or tingling under the tongue, headache (20%), dizziness, or flushing (feeling of warmth). Headache is often a sign the medication is working and can be treated with aspirin or non-aspirin pain reliever as recommended by the study investigator. Symptoms of a serious allergic reaction include: rash, itching, swelling, severe dizziness, or trouble breathing. This drug should not be used with the following medications because very serious (possibly fatal) interactions may occur: drugs to treat impotence (e.g., sildenafil, vardenafil, tadalafil).

Metoprolol: (for subjects given the beta-blocker): For people who take these medications regularly, the most common side-effects are tiredness and dizziness (10%), rash and diarrhea (5%), shortness of breath and slow heart beat (3%). Less common side-effects are low blood pressure, wheezing and coldness in arms and legs (1%). There have been reports of people experiencing a headache, mental confusion and short-term memory loss. More serious or life-threatening allergic reactions are rare. Beta-blockers are traditionally used to lower high blood pressure, relieve angina (chest pain), correct arrhythmias (irregular heartbeats), reduce the risk of dying after a heart attack, and treat heart failure.

Magnevist and Multihance: The use of gadolinium-based contrast agents in patients who already have serious kidney problems or who have had a liver transplant may lead to a possibly fatal disease involving the skin, muscle and internal organs. This possibly fatal disease is called nephrogenic systemic fibrosis (NSF) where patients developed large areas of hardened skin with slightly raised plaques, papules, or confluent papules.

Before we give you a gadolinium-based contrast agent, we will ask you about any history of kidney problems or liver transplant, and will test the health of your kidneys by laboratory tests. If you have known risk factors for developing this disease, you will not be eligible for this study or will be given another contrast agent.

Data Analysis

Investigator faculty will ensure proper labeling of all images acquired. All images will be de-identified prior to analysis. Images will undergo both quantitative and qualitative analysis. Cardiac function and anatomical measurements will be calculated using established clinical protocols. Vessel wall thickness will be measured manually with an interactive visualization and analysis tool by drawing regions of interest around the endoluminal and adventitial surface of each coronary vessel. Total wall thickness will be calculated for each patient.

T2 relaxation times will be measured directly by placing regions of interest on each segment of the left ventricular myocardium based on the 16 segment AHA classification of the left ventricle.
Peak velocity and flow will be measured in each of the three main coronary vessels. The delayed enhanced images will be analyzed using a semi-automated scar analysis tool. The results will be compared to results from EMB, IVUS, conventional coronary angiography and echocardiogram. The medical record will also be reviewed and compared to specific antigen and antibody results.

Statistical methods including student’s T test, linear regression analysis, etc. Sensitivity, specificity, accuracy and ROC analysis will be carried out for each of the CMR techniques. Investigators have access to a faculty Northwestern University statistician for assistance with data analysis.

**Anticipated results**

Compared to the published results in the literature, the study will demonstrate comparable or superior sensitivity, specificity and accuracy of CMR to detect rejection after cardiac transplantation. With acute rejection, EMB will be the gold standard. With CAV, conventional coronary angiography will be used as the gold standard, but the results will also be compared to IVUS which is considered more accurate in many studies.

The Long term goal is to improve performance of CMR to detect heart transplant rejection and possibly reduce the need for invasive methods of endomyocardial biopsy and coronary angiography. CMR potentially offers an alternative non-invasive study with no ionizing radiation or iodinated contrast agent and reduces costs to both patients and hospital by obviating need for multiple diagnostic tests.

**References:**

1) NMH protocol for surveillance for acute rejection and vasculopathy
10) Quin Ye et al. Longitudinal tracking of recipient macrophages in a rat chronic cardiac allograft rejection model with noninvasive magnetic resonance imaging using micrometer-sized paramagnetic iron oxide particles. Circulation 2008; 118