Comprehensive Cardiac Structure-Function Analysis in Heart Transplantation

PRINCIPAL INVESTIGATOR: Michael Markl, Ph.D., James Carr, M.D. (Co-PIs)
Associate Professor of Radiology and Biomedical Engineering

Director Cardiovascular MR Research
Northwestern University
737 N. Michigan Avenue Suite 1600
Chicago, Illinois 60611, USA

SUB-INVESTIGATORS: James Carr, MD; Keith Benzuly, MD; Timothy J. Carroll, PhD; Robert Gordon, MD; Gordon Hazen, PhD; Dan Lee, MD; Jon Lomasney, MD; Ed McGee, MD; Ann Ragin, PhD; Vera Rigolin, MD; Clyde Yancy, MD

PARTICIPATING SITES: Northwestern Memorial Hospital
251 East Huron Street
Chicago, IL 60611

FUNDING AGENCY: National Institute of Health (NIH):
Identification Number: 1 R01 HL117888-01A1
## Synopsis

<table>
<thead>
<tr>
<th>Title</th>
<th>Comprehensive Cardiac Structure-Function Analysis in Heart Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Title</td>
<td>Structure-Function CMR</td>
</tr>
<tr>
<td>Protocol Date</td>
<td>08/30/2013</td>
</tr>
<tr>
<td>Study Duration</td>
<td>5 years</td>
</tr>
<tr>
<td>Study Center(s)</td>
<td>Dept. of Radiology, Center for Translational Imaging</td>
</tr>
<tr>
<td>Objectives</td>
<td>To identify the optimal combination of non-invasive multi-modality imaging (structure-function MRI, echo) and invasive procedures (IVUS, EMB, catheter angiography) which provide best outcome (quality adjusted life days) and lowest cost for the individual cardiac transplant patient</td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>190</td>
</tr>
<tr>
<td>Diagnosis and Main Inclusion Criteria</td>
<td>Heart Transplantation</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

*May be revised and numbered as necessary, but should include major sections*

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synopsis</td>
<td>1</td>
</tr>
<tr>
<td>1.0 Introduction</td>
<td>2</td>
</tr>
<tr>
<td>2.0 Study Objectives</td>
<td>3</td>
</tr>
<tr>
<td>3.0 Selection of Subjects</td>
<td>4</td>
</tr>
<tr>
<td>3.1 Inclusion Criteria</td>
<td></td>
</tr>
<tr>
<td>3.2 Exclusion Criteria</td>
<td></td>
</tr>
<tr>
<td>4.0 Subject Registration</td>
<td></td>
</tr>
<tr>
<td>5.0 Study Design &amp; Methods</td>
<td></td>
</tr>
<tr>
<td>6.0 Statistical Plan</td>
<td></td>
</tr>
<tr>
<td>7.0 Data Collection &amp; Record Keeping</td>
<td></td>
</tr>
<tr>
<td>8.0 References</td>
<td></td>
</tr>
<tr>
<td>Appendices</td>
<td></td>
</tr>
</tbody>
</table>
1.0 INTRODUCTION - BACKGROUND AND RATIONALE (include references)

Heart Transplant: Cardiac transplantation (Tx) is the treatment of choice for many patients with end-stage heart failure who remain symptomatic despite optimal medical therapy\(^1\). In the US, approximately 2200 hearts are transplanted every year\(^1-4\). Survival rates have improved dramatically over the last 40 years\(^1,5\). However, during the first 12 months after cardiac transplantation allograft failure and acute, cellular and humoral, cardiac allograft rejection (ACR)\(^6\) and beyond the first year during long-term maintenance cardiac allograft vasculopathy (CAV)\(^7\) remain the most important complications resulting in appreciable mortality\(^1,8\).

Major Complications: Based on data from the 2011 registry of the International Society for Heart and Lung Transplant (ISHLT)\(^1\), the median survival after Tx is 11 years. Allograft failure and ACR account for 40% of the mortality within the first 30 days after Tx and 18% of the mortality for the 2\(^{nd}\) through the 12\(^{th}\) months\(^2\). Beyond the first year, CAV is the single greatest risk factor for 5-year mortality, and together with late graft failure (also related to CAV) accounts for 30% of deaths\(^1\). Due to incomplete reinnervation of the transplanted heart, patients with CAV often lack symptoms\(^1,9\) prior to the onset of adverse events such as progressive heart failure or sudden death\(^10,11\). Therefore, monitoring the patient for post-transplant events is paramount\(^8,12,13\).

Standard of Care, Invasive Techniques and Cost: The current protocol for ACR and CAV monitoring requires invasive endomyocardial biopsy (EMB) and cardiac catheterization at 12-16 monitoring nodes per patient during the first year alone\(^3,14\). However, EMB, which is still the gold standard for the diagnosis of rejection, is limited by sampling error, particularly during early rejection, as cellular infiltrates are known to be highly localized\(^15,16\). Coronary X-ray angiography has limited diagnostic value for CAV\(^9,17,18\). In the United States, the costs and resource utilization associated with this monitoring strategy is staggering. The average number of EMB and catheterizations to monitor for cardiac transplant rejection is approximately 20,000–36,000 per year and the estimated cost ranges from $300,000,000 to $450,000,000 per year\(^19\).

2.0 OBJECTIVES

We have recently developed cardiac MRI techniques for the assessment of myocardial edema (T2-mapping), diffuse fibrosis (pre- and post-contrast T1-mapping), myocardial velocities (tissue phase mapping, TPM), and microvascular quantitative perfusion. We have shown that these techniques can identify distinct regional structural and functional alterations in the heart that correlate with the status of the allograft. A comparative cost-effectiveness analysis using Markov modeling and decision tree analysis has demonstrated that cardiac MR has tremendous potential to reduce monitoring costs by 40-50% during the first year after Tx alone.

We will further develop the MRI techniques to provide a previously unattainable quantitative characterization of myocardial structure-function deficits in Tx patients. The combination into a single acquisition protocol covering both the left (LV) and right (RV) ventricle will permit the comprehensive evaluation of the most important early (ACR) and late (CAV) post-Tx complications by merging markers of regional tissue abnormalities (edema, fibrosis) with segmental RV and LV function (myocardial velocities, dyssynchrony) and quantitative
microvascular perfusion. Integration of MRI with echocardiography and intravascular ultrasound (IVUS) will provide unique multi-modality assessment of the allograft. The application in a longitudinal clinical study coupled with state-of-the-art cost-effectiveness analysis will allow redefining the most effective post-Tx mixed monitoring strategy. The ultimate goal is to identify the optimal combination of non-invasive multi-modality imaging (structure-function MRI, echo) and invasive procedures (IVUS, EMB, catheter angiography) which provide best outcome (quality adjusted life days) and lowest cost for the individual cardiac transplant patient.

Specific Aim 1, Comprehensive LV and RV structure-function MRI in 15 minutes: Our goal is to develop a 15 minute cardiac MRI protocol, integrated into a clinical standard-of-care MRI exam, that provides quantitative information on LV and RV myocardial T2, extracellular volume fraction by T1-mapping, 3-directional myocardial velocities, and microvascular changes as detected by quantitative perfusion MRI.

Specific Aim 2, Multi-Modality Imaging and Longitudinal Study in Tx patients: In two study arms (ACR and CAV), we will investigate the diagnostic value of structure-function cardiac MRI and its optimal combination with echocardiography and IVUS for the early detection of ACR and CAV in 150 Tx patients. Cardiac MRI will be integrated in the standard-of-care monitoring visits of Tx patients during which EMB and catheter angiography are routinely performed which will serve as the reference standards.

ACR: In newly transplanted hearts, structure-function cardiac MRI will be applied during the first year in a follow-up study at 1, 3, 6, and 12 month. We will test the hypothesis that ACR results in altered structure (edema, fibrosis) and function (myocardial velocities) and identify the combination of structure-function parameters and echocardiography results providing the most sensitive marker (risk score) for ACR.

CAV: In patients beyond the first year after Tx we will apply structure-function cardiac MRI at baseline and during 12-months and 24-months follow-up. Our goal is to develop a new non-invasive risk score for CAV by integrating novel information on quantitative perfusion and markers of functional RV and LV deficits with coronary impairment as determined by IVUS (maximal intimal thickness, plaque burden).

Specific Aim 3, Comparative Cost Effectiveness: Based on the longitudinal study data we will conduct a cost-effective analysis comparing non-invasive imaging (structure-function MRI, echo) and invasive techniques (IVUS, EMB, cath) which includes evaluating costs, utility of patient states, and sensitivities and specificities of MRI. We will test the hypothesis that comprehensive cardiac multi-modality imaging can reduce monitoring cost while reducing health care resource utilization and provide similar mortality benefit in identifying ACR and CAV. Furthermore, we will develop a standardized decision model to help clinicians to identify the optimal combination of noninvasive imaging (MRI, echocardiography) with invasive test (IVUS, EMB, and catheter angiography) to manage ACR and CAV in the outpatient clinic setting.

Upon successful completion of the project we will identify the optimal combination of non-invasive (MRI, echo) and invasive (IVUS, EMB, cath) test while reducing the number of costly EMB and catheter angiography.
3.0 SELECTION OF SUBJECTS

This study will be carried out at Northwestern Memorial Hospital (Feinberg Pavilion, 251 East Huron, 4th Floor, Chicago, IL, or the Olson Pavilion, 710 North Fairbanks, Basement, Chicago, IL) or the NMH Outpatient Imaging Facility (676 N. St. Clair Street, 3rd floor, Chicago, IL), and Northwestern University.

210 subjects will be recruited for this study. A total of 150 adult patients after heart transplantation (Tx) will be recruited for cardiac-structure function MRI in a longitudinal clinical study. In addition, 60 healthy volunteers will be recruited to test and optimize the developed cardiac MRI protocol.

The research coordinator will review the MRI schedule in the Department of Radiology weekly to identify eligible patients. Patients scheduled for clinical MRI and meeting study criteria will be contacted by authorized study personnel prior to their scheduled clinical MRI exam. For these patients, the research MR sequences will be added on to their already scheduled standard of care MRI. In patients with cardiovascular disease not scheduled for a clinical MRI, these patients will undergo a research MRI exam. For this group, potential subjects will be identified by the PI or a Co-Investigator. The treating physician will ask potential subjects permission to be contacted by study personnel.

60 Healthy volunteers with no known medical conditions will be recruited for this study from the local populations of Chicago, Illinois by a flyer around Northwestern University’s campus. No subjects under the age of 18 years of age or over the age of 89, or pregnant women will be included. There will be no exclusion of subjects based solely on race or gender. Age-matched volunteers are routinely recruited into imaging studies at Northwestern without difficulty.

The organization, execution, and evaluation of the study will be a joint PhD-MD effort by the PIs in the Department of Radiology (Dr. Markl and Dr. Carr) in close collaboration with the Department of Cardiology and the heart transplant program (Dr. Lee, Dr. Yancy, Dr. Gordon). Subjects will be recruited from Cardiology and Cardiac Surgery. A copy of the signed consent form will be given to subjects. All patients enrolled in this study will be informed and must agree to the use and disclosure of their study information by the institution, clinical trials unit and investigators.

A total of 150 adult patients after heart transplantation (Tx) will be recruited for cardiac-structure function MRI in a longitudinal clinical study. In addition, 60 healthy volunteers will be recruited to test and optimize the developed cardiac MRI protocol.

All cardiac MRI exams will be performed during the regular visits when patients undergo routine monitoring for post-transplant complications. Patients to be included will have routine endomyocardial biopsy (group 1) and catheter angiography (group 2) as their standard-of-care which will serve as the gold standard for ACR and CAV, respectively. In addition all patients will receive echocardiography during each visit (Dr. Rigolin) and intravascular ultrasound at baseline and year one (Dr. Benzuly) as their standard-of-care.
3.1 INCLUSION CRITERIA:
- Male and female subjects 18-89 years of age.
- **Group 1:** To evaluate the cardiac MRI protocol for the detection of acute cardiac rejection (ACR), MRI will be performed in n=75 (n=25/year) newly transplanted patients at baseline (1 months post-Tx) and at follow-up 3, 6 and 12 months later (total of 300 MRI scans).
- **Group 2:** To evaluate the cardiac MRI protocol for the detection of cardiac allograft vasculopathy (CAV), MRI will be performed in n=75 (n=25/year) patients >1 year post Tx at baseline and at 12 and 24 months follow-up (total of 225 MRI scans).
- All subjects must have given signed, informed consent prior to registration on study.

3.2 EXCLUSION CRITERIA
- Contraindication to MRI (i.e., pacemakers, aneurysm clips, or shrapnel fragments).
- Subjects unwilling or unable to give written informed consent.
- Patients with a history of kidney problems (GFR < 30 ml/min) or have had a kidney and/or liver transplant will be excluded from the study or undergo the MRI exam without the use of a contrast agent, per standard MR exclusion criteria.

4.0 SUBJECT REGISTRATION

Studies will be conducted in either the Feinberg Pavilion, 251 East Huron, 4th Floor, Chicago, IL, or the Olson Pavilion, 710 North Fairbanks, Basement, Chicago, IL or the NMH Outpatient Imaging Facility, 676 N. St. Clair Street, 3rd floor, Chicago, IL.

Written, informed consent will be acquired from all human subjects prior to performing the cardiovascular MRI scan. Patients may undergo cardiovascular MRI on a clinical basis at Northwestern for cardiovascular evaluation. However, for patients that do not have a clinical indication for a cardiovascular MRI it will be performed for purposes of this research study. Images will be obtained per Northwestern Memorial Hospital’s standard procedure.

All subjects will be screened for contraindications to MRI (e.g. presence of an implanted cardiac pacemaker) using a standard screening form, similar to that used in the clinical MRI facility. 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 on the same day as the MRI scan either through point of care analysis of a blood sample or direct laboratory analysis. For this study, subjects may receive Magnevist, Multihance, or Ablavar depending on their kidney function and the discretion of the PI. Contrast will be given as follows:

- **For subjects with a GFR > 30 ml/min:**
  A total dose of 0.1 mmol/kg Magnevist or Multihance or a total dose of 0.03 mmol/kg Ablavar will be injected intravenously as the contrast agent.
Subjects with a GFR <30 ml/min will receive no contrast agent and may be excluded from the study.

Prior to scanning, 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) and will change into a hospital gown. The subject will then be brought into the scan room and positioned on the scan table. A receiver coil will be placed on the region of the body to be imaged (e.g. body array coil for cardiac imaging). If contrast is being administered, the intravenous cannula will be connected by extendable tubing to a power injector containing Gadolinium contrast agent. The subject will then be entered into the magnet. All scanning will be carried out on a 1.5T or 3T MRI scanner (Siemens Medical Systems).

Investigational MRI pulse sequences will be developed off-line using software tools provided by the manufacturer and will be tested initially using phantoms and virtual computer systems. Investigational MRI pulse sequences will then be implemented in human subjects. It is envisaged that novel pulse sequences will utilize spin echo, gradient echo or echo planar readout. Scanning parameters (e.g. repetition time, flip angle, etc) may be varied at the time of scanning. Conventional imaging techniques may also be carried out for comparison with investigational sequences. Safety checks in the system protect subjects from excessive radiofrequency power deposition. The system does not allow scanning which exceeds Specific Absorption Rate (SAR) limitations. These are laid down by the FDA and are identical to those present on clinical MRI scanners.

Each MRI study will last between 1-1.5 hours for healthy volunteers and those subjects not scheduled for a clinical MRI. For those subjects scheduled for a standard of care MRI, up to 40 minutes of scan time will be added to their standard of care MRI. Therefore, their total participation for this study will be up to 40 minutes.

Subjects recruited for research MRIs will be reimbursed for their time and receive $50 via check 4-6 weeks after their MRI study in they come in for a research scan and $30 via check 4-6 weeks after their MRI scan if they undergo additional research scanning that has been added to their standard of care MRI scan.

Risks, MRI study: We will exclude patients with pacemakers, metallic implants or pregnant patients. No subjects under 18 years if age will be included. The only potential risk is that of peripheral nerve stimulation. The MRI pulse sequence will ensure all dB/dT limits and Specific Absorption Rate are held within the limits set by the FDA. The MRI research facility is staffed by a registered nurse and certified MRI technologist.

There are few risks to magnetic resonance imaging. Claustrophobia is unusual with adequate patient counseling. All MR scanners are equipped with monitoring methods that allow conversation with the patient and identification. A detailed history for contraindications will be taken (pacemakers, aneurysm clips, etc.). The risks of intravenous injection of paramagnetic contrast for MR imaging are headache, nausea, vomiting, and local irritation at the injection site which occur in 5% of patients. Episodes of mild hypotension occur in 0.1% of patients. More severe anaphylactic reactions have been reported rarely (1 in 400,000). No subjects, patients or asymptomatic volunteers with renal impairment as defined by point-of-care GFR testing
will receive contrast agent in this study.

**Protection against Risk, MRI study:** The CTI facility is fully staffed by a registered nurse and professionally accredited MRI technologist. Patients will be screened for contraindications to MRI at the time of each research scan. Point-of-care GFR testing will be performed in accordance with the rules set forth by our institutional review board. Any subject whose GFR is less than the allowable limits will be prohibited from receiving a contrast agent injection for the purposes of the research scan.

Subjects with metallic hardware, implants, or prostheses will consult with the physician prior to the study. Some subjects may experience claustrophobia inside the scanner. Some portions of the study generate loud noises; earplugs will be provided to prevent discomfort and avoid hearing loss. The placement of the IV used for contrast agent administration may result in a bruise, inflammation of the vein and infection; care will be taken to avoid these complications.

Institutional Review Board and hospital approvals will be obtained prior to accrual of any research subject. The principal investigator will closely monitor each subject that participates in this study for any adverse events, as well as recording number of subjects screened and enrolled, and drop-outs. Unanticipated events involving risks to subjects or others will be reported within 10 days to the IRB.

**5.0 STUDY DESIGN & METHODS**

This proposal addresses methodology to overcome current shortcomings by offering a novel comprehensive structure-function analysis in short time and potentially obviating more invasive diagnostic procedures. Our primary goal is to demonstrate that structure-function MRI combined with echocardiography and IVUS can detect ACR and CAV compared to the gold standard EMB and catheter angiography. In two longitudinal study arms, we will investigate which parameter combination (risk score) will provide the best sensitivity and specificity to detect ACR and CAV.

- For ACR, the focus is on the combination of tissue characterization (edema, fibrosis) and regional ventricular function (myocardial velocities, dyssynchrony) by MRI as well as systolic and diastolic function by echo (E/A, e’, E/e’ and IVRT) as early markers of inflammatory response.
- For CAV, absolute quantification of myocardial perfusion (dMBV, qMBF) will be combined with markers of RV and LV dysfunction (diastolic peak velocities, dyssynchrony) and abnormalities of the coronary arteries (IVUS, intimal thickening, intimal area, plaque burden) to detect microvascular deficits.

The aim is to employ non-invasive multi-modality imaging (cardiac MRI, echo) in conjunction with invasive tests (IVUS, EMB, cath) to analyze in detail the structural and functional abnormalities associated with early (ACR) and long-term (CAV) complications in Tx patients. Test-retest reliability: The cardiac MRI protocol will be applied in 20 healthy volunteers (n=10 extra-cellular, n=10 blood pool agent) twice on different days. Clinical Study: We anticipate enrollment of n=150 Tx patients in years 2-4 in two study arms (Group 1: ACR; Group 2: CAV). Sample sizes of adult Tx patients (>18 years) have been
Follow-Up, ACR study arm (Group 1): The cardiac Tx accumulation rate is 25-30 patients annually. We will recruit 25 newly transplanted patients per year (total in years 2-4 = 75). All Tx patients will be examined at four nodes post-Tx and will have baseline (1 month) and 3, 6, 12 month follow-up cardiac MRI (in total n=300 MRI exams). [Routine transthoracic echocardiography will be employed to assess parameters of systolic and diastolic function within 24 hours of MRI.] As the clinical reference standard, all patients will undergo EMB during each visit.

Follow-Up, CAV study arm (Group 2): A total of about 150 post-transplant patients receive regular follow up care at NMH. From this cohort we will recruit 25 patients per year who are beyond year 1 post-Tx (total in years 2-4 = 75). All Tx patients will be followed at 12 and 24 months (in total n=225 MRI exams). Patients will receive intra-vascular contrast agent for absolute quantification of microvascular blood flow and blood volume. [Intracoronary IVUS is routinely carried out at baseline and year one unless the patient has renal insufficiency or angiographically detectable CAV.] As the clinical reference standard, all patients will undergo catheter angiography during each visit.

6.0 STATISTICAL PLAN

Test-retest reliability: The MRI parameters of interest (table below) will be quantified for each scan session. The test-retest analysis is needed to define parameter variability (mean difference, intra-class correlation, Bland-Altman limits of agreement) for sensitivity analysis during the longitudinal study.

<table>
<thead>
<tr>
<th>Method</th>
<th>parameters for test-retest reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPM</td>
<td>segmental radial, long-axis, rotational peak RV and LV velocities, dyssynchrony</td>
</tr>
<tr>
<td>T2</td>
<td>regional (16+6 segment model) T2-relaxation times</td>
</tr>
<tr>
<td>T1</td>
<td>regional (16+6 segment model) T1-relaxation times and extra-cellular volume fraction</td>
</tr>
<tr>
<td>perfusion</td>
<td>segmental qMBV, qMBF in base, mid, apex</td>
</tr>
</tbody>
</table>

Multi-modality imaging and longitudinal study in Tx patients, ACR study arm (Group 1): This study will determine whether non-invasive MR measurements of function (myocardial velocity) and structure (T1 to quantify fibrosis and T2 to quantify edema) in combination with measures of ventricular function derived from echocardiography can be used to evaluate ACR
within the first year following Tx. MR scans will be conducted in 75 Tx patients at 1 month, 3 months, 6 months and 12 months post-Tx, for a total of 300 scans. Myocardial velocity, T1 and T2 measurements will be determined for 16 segments of the LV and for 6 segments of the RV to correspond to the 16+6 LV & RV model. Per clinical convention, endomyocardial biopsy findings are rated on an ordinal 4 point scale, as follows: 0R (none), 1R (mild), 2R (moderate), 3R (severe). To identify new non-invasive markers for ACR, we will analyze the following imaging biomarkers:

- **TPM**: Radial, long-axis, rotational peak velocities (16+6 segment LV+RV model), dyssynchrony
- **T2-mapping**: regional (16+6 segment LV+RV model) T2-relaxation times
- **T1-mapping**: regional (16+6 segment LV+RV model) T1 times and extra-cellular volume fraction
- **Echocardiography**: E/A, e’, E/e’, IVRT, diastolic function grade (0-3), left ventricular EF

**Pooled analysis of all patients (n=300):** The aim is to assess the diagnostic value of individual imaging biomarkers as well as parameter combinations (echo and MRI) to detect ACR. We will systematically construct different parameter combinations (risk score) to test their diagnostic value to detect ACR compared to the gold standard EMB. The parameter combination with the best prognostic value will be used to test

**Hypothesis 1a:** The new cardiac echo-MRI risk score can detect ACR early and non-invasively with similar sensitivity and specificity compared to the primary outcome measure endomyocardial biopsy.

**Longitudinal follow-up (n=75 patients per node):** The longitudinal data will be used to test

**Hypothesis 1b:** MRI and echo can predict ACR events with improved sensitivity compared to EMB.

**Analysis and statistics ACR study arm (Group 1):** Initially, echo and MR parameters will be analyzed separately at each time point (i.e., 1 month, 3 months, 6 months and 12 months post-Tx). The MRI measurements will be evaluated at different levels of analysis (averaged across 16 LV and 6 RV segments, segmental values). Both echo and MRI data will be compared in the four biopsy ACR groups (i.e., none, mild, moderate and severe) using ANOVA or Kruskal-Wallis test, followed by post-hoc pairwise comparison (with Bonferroni adjustment). To construct risk scores for ACR, logistic regression analysis will be performed using the biopsy measure (EMB result) as the dependent variable, and echo and MR parameters as the independent variables. The area under the ROC (receiver operating characteristic) curve (c-statistic) will be computed to represent the diagnostic accuracy. Multivariable logistic regression models will be constructed to evaluate the diagnostic accuracy to differentiate ACR according to severity, after adjusting for possible confounders (e.g. age of donor heart, donor weight, allograft ischemic time, and recipient age).

**Sample Size ACR study arm (Group 1):** We anticipate that 40% of Tx patients will demonstrate a positive response. A sample size of 75 subjects will conjecture an area under ROC curve of 0.80 within 0.116 as the 95% confidence interval. This sample size will also have 99% power to detect the difference of a 0.80 area under ROC curve from the null hypothesis, a 0.5 area under
ROC curve. In a previous study we found that LV T2-mapping could differentiate between ACR biopsy grades (52.4± 2.9ms for 0R, 53.5 ± 3.3ms for 1R, 60.7 ± 4.1ms for >2R). Based on the small variation in each group with approximately 5% CV (coefficient of variation), a one-way analysis of variance will require only 4-6 (10) subjects in each of the three groups (i.e., 0R, 1R, and 2R & 3R) to achieve a 80% (98%) power to detect the between-group difference at a 0.05 significant level.

Multi-modality imaging and longitudinal study in Tx patients, CAV study arm (Group 2):
Per clinical convention, CAV is diagnosed by cardiac catheterization as present (yes) or absent (no). In this study arm (separate sample) we will determine whether IVUS and quantitative MR measurements of function and perfusion can be used to detect CAV. Cardiac MRI will be performed in n=75 post-Tx patients at study entry (baseline), and at 12 and 24 months follow-up for a total of 225 scans. MRI measures will be combined with data on coronary abnormalities derived from IVUS. We will analyze the following imaging biomarkers:
- Quantitative rest perfusion: qMBV and qMBV (16 segment LV model)
- TPM: Radial, long-axis, rotational peak velocities (16+6 segment LV+RV model), dyssynchrony
- IVUS: Maximal intimal thickness (MIT), EEM area, intimal area, plaque burden

Pooled analysis of all patients (n=225): The aim is to assess the diagnostic value of individual imaging biomarkers as well as parameter combinations to detect deficits in coronary arteries, regional microvascular perfusion and abnormalities in RV and LV function. We will systematically construct different parameter combinations (risk scores) to test their diagnostic value to detect CAV compared to the gold standard catheter angiography. Risk scores will be calculated both including and excluding IVUS since IVUS is invasive. The parameter combination with the best prognostic value will be used to test

Hypothesis 2a: The new risk score can detect CAV early and non-invasively with similar sensitivity and specificity compared to the primary outcome measure – catheter angiography.

Longitudinal follow-up (n=75 patients per node): The longitudinal data will be used to test

Hypothesis 2b: IVUS and MRI can predict CAV with improved sensitivity compared to angiography.

Analysis and statistics CAV study arm Group 2: IVUS and MR parameters will be analyzed separately at each time point (baseline, 12, 24 months). MRI measurements will be evaluated at different levels of analysis (averaged across 16 LV and 6 RV segments, segmental values). Summary values will be compared in the two CAV groups (i.e. yes vs. no) using two-sample t-test or Wilcoxon rank sum test. To construct risk scores for CAV, a logistic regression analysis will be performed using the binary CAV as the dependent variable and IVUS and MRI measures as independent variables. The area under the ROC curve (c-statistic) will be computed to represent diagnostic accuracy. Multivariable logistic regression models will be constructed to evaluate diagnostic accuracy after adjusting for possible confounders (e.g. age).

Sample Size CAV study arm (Group 2): We anticipate that at 12 months, 10% of Tx patients will demonstrate a positive response (i.e., 10% CAV ‘yes’ vs. 90% CAV ‘no’). A sample size of 75 subjects will conjecture an area under ROC curve of 0.80 within 0.21 as the 95% confidence
interval. This sample size will also have 87% power to detect the difference of a 0.80 area under ROC curve from the null hypothesis, a 0.5 area under ROC curve. We anticipate that at 24 months, 15% will demonstrate a positive response. A sample size of 75 subjects will conjecture an area under ROC curve of 0.80 within 0.17 as the 95% confidence interval. This sample size will also have 91% power to detect the difference of a 0.80 area under ROC curve.

**Comparative Cost-Effectiveness**

Comparative cost effectiveness analysis and the development of a decision tree for the optimal mixed monitoring strategy will be conducted in close collaboration with the Department of Industrial Engineering and Management (G. Hazen). Quantification of altered ventricular structure and function in the follow-up study and correlation with standard outcome measures (EMB, catheter angiography) as outlined in Aim 2 will determine the sensitivity and specificity of multi-modality imaging (MRI, echo, IVUS) to detect ACR and CAV. We will base comparative cost-effectiveness analysis on the data from the clinical follow-up study with 150 Tx patients to identify the optimal monitoring strategy to provide the best outcome and lowest cost for the individual patient. Cost-effectiveness analysis (echo and cardiac MRI vs. standard invasive tests vs. mixed monitoring strategies combining MRI, echocardiography, IVUS, EMB and catheter angiography) will be based on Markov modeling and microsimulation to create a complex decision model to provide:

- Risk-based recommendations for clinicians in evaluating post Tx patients in the outpatient setting.
- Cost effectiveness analyses of non-invasive strategies (echo & MRI) and mixed strategies, and the resulting financial implications on health care system by changing to non-invasive strategies.
- Description of quality of life for multi-modality imaging including structure-function cardiac MRI imaging
- Optimal diagnostic strategy to reduce the frequency of invasive procedures (IVUS, echo, cath).

Microsimulation is essential in creating clinical guidelines due to the fact that outcome uncertainty requires not only Markov but also semi-Markov modeling with corresponding incidence and mortality rates depending on elapsed time. We will use advanced decision making tools to evaluate cost effectiveness. The analysis will be carried out using Treeage ProSuite Software (Williamstown, WA) which was developed in an Eclipse an Integrated Development Environment (IDE) with C++ compatibility. Cost data will be prospectively collected and corroborated via retrospective institutional data and by comparing to the Center for Medicare Services (CMS) prospective payment system. Event level microsimulation provides a means to predict intermediate states and their effect on longevity and quality of life. Using our decision model, we will test the

**Primary hypothesis:** Structure-function cardiac MRI in combination with echocardiography and IVUS is effective in terms of improved quality of life, while providing a similar mortality profile as invasive testing over short and long term follow up.

**Secondary hypothesis:** Switching to a partly non-invasive strategy (mixed monitoring including MRI, echo and invasive techniques IVUS, EMB, cath) will decrease health care
resource utilization and cost. We will develop a standardized decision model to help clinicians identify the optimal mixed monitoring strategy, i.e. the optimal combination of non-invasive imaging (MRI, echo) and invasive procedures (IVUS, EMB, catheter angiography) which provide best outcome (quality adjusted life days) and lowest cost for the individual cardiac transplant patient.
7.0 DATA COLLECTION & RECORD KEEPING

Authorization will be obtained from each research subject, i.e. specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI. All data will be strictly confidential. The confidentiality of the subjects' identities shall be well protected consistent with local and national regulations. In cases where study data is published or shared with other institutions, data will be de-identified. No subject will be identified individually in any publication or report. It will never include identifiable information, such as name, social security number, address or medical record number in order to maintain patient’s identity. In addition, in most cases the data will not include identifiers other than age, race, sex, and diagnosis since most reports are only concerned with descriptive summaries and statistical analyses of “grouped” data.

9.0 REFERENCES


