Quantitative Cardiac MRI Perfusion for longitudinal Studies

Protocol Summary

IRB Approval Date of Current Version:	6/11/2019
University of Utah IRB #:	IRB_00058133
Sponsor:	NIH NATIONAL HEART LUNG & BLOOD INST
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Background and Introduction

Heart disease is the leading cause of death in the U.S. Detection and characterization of coronary artery disease (CAD) can contribute significantly towards reducing mortality and improving quality of life for large numbers of people. Currently, SPECT and echo imaging are the clinical standards for non-invasive assessment of regional blood flows (perfusion) in the myocardium, but do not provide quantitative estimates of regional myocardial blood flow. While quantitative MRI perfusion, in its current state, is a useful clinical and research tool, improved methods are needed along with better benchmarks of how well the methods quantify perfusion in humans. The techniques proposed here will be advantageous for quantifying myocardial perfusion and are ideally suited for studying patients with atrial fibrillation.

Our initial cardiac MRI work under IRB 8157 and IRB 10342 has shown promising results and this project builds on these past experiences.

This protocol is to support the development and validation of new pulse sequences and automated mathematical modeling approaches to provide practical and accurate methods for assessment of myocardial perfusion and viability.

Purpose and Objectives

This work seeks to develop, evaluate and use new MRI methods for non-invasive quantitative assessment of myocardial perfusion reserve (MPR). The methods will be designed to work robustly for patients with arrhythmias or poor ECG signals. The methods will be applied along with left ventricular (LV) and left atrial (LA) function and LA fibrosis measurements to study changes due to treatment for atrial fibrillation (AF).

Specific aims are (1) To design and test highly-undersampled ungated perfusion acquisitions and reconstructions. (2) To provide robust quantitative perfusion estimates by improved processing and by identifying an accurate arterial input function using methods that are widely applicable across a range of doses and acquisition types. (3) To determine the validity and repeatability of the proposed quantitative methods and the differences in perfusion and MPR measured at systole and diastole, including determining if systole or diastole is most repeatable when quantifying perfusion. (4) To determine the changes over time in perfusion reserve and cardiac function and left atrial fibrosis, after ablative treatment for AF. This will allow for determining the extent of perfusion improvement acutely due to conversion to sinus rhythm and the degree of recovery of perfusion reserve that recovers more slowly over months.

Study Population

Age of Participants: 18-60 +

Sample Size:

At Utah: 140
All Centers: NA

Inclusion Criteria:

All participants will be over the age of 18 and able to provide consent

Control Group A (healthy or non-AF volunteers): Volunteers will be in normal sinus rhythm and available for at least one study visit.

Control Group B (risk based volunteers): Volunteers will consist of both normal sinus rhythm and suspected or confirmed paroxysmal or persistent AF.

Atrial Fibrillation MRI and PET cohort will have suspected or confirmed paroxysmal or persistent AF.

Atrial Fibrillation Blood Flow MRI cohort will be patients with paroxysmal or persistent AF that are scheduled for RF catheter ablation treatment. These subjects will require clinical MRI scans to assess pulmonary vein stenosis and LA fibrosis before ablation, 1-3 days after, and 6 months after ablation. The study visits will be schedule according to the three clinical MRIs. Research scans will not be added in the acute (1-3 days after) MRI studies, but at pre-ablation and at later time points.

Exclusion Criteria:

Exclusion criteria for all cohorts:

Critically ill patients, patients on ventilators, patients with unstable angina or with hypotension, asthmatics, and other patients whose medical care or safety may be at risk from undergoing an MRI examination will be excluded. Patients with claustrophobia will also be excluded from the study if this cannot be controlled with standard methods (valium or benadryl). Patients with contraindication to MRI (pacemaker, metal implants, or certain types of heart valves), pregnant patients, minors, mentally disabled patients and prisoners will be excluded from this study. (All criteria apply to patients and normal volunteers). Gadolinium nephrotoxicity will be addressed by having patients with abnormal kidney function (GFR<30) excluded from the study due to the (very small) risk associated with gadolinium contrast agents. This threshold may be modified, depending on practices determined by the Radiology Department and the IRB. Patients with a known allergy or contraindication to Adenosine and/or Regadenoson will be excluded from stress MRI cohorts.

All participants that will receive a stress agent will refrain from consuming caffeine for at least 12 hours prior to each MRI

Atrial Fibrillation cohorts:

Participants will be selected to have very low pre-test likelihood of coronary artery disease based on being asymptomatic and having none of the following risk factors: diabetes, family history of premature coronary artery disease, hyperlipidemia, hypertension, and smoking.

Volunteers:

No contra-indications in addition to those listed above for all cohorts. Volunteers with a known allergy or contraindication to Adenosine and/or Regadenoson will only be enrolled in scans where no stress agent will be administered.

Design

Prospective Clinical Research

Study Procedures

Recruitment/Participant Identification Process:

Subjects will be recruited from those being treated by colleagues in the Cardiology clinic, that fit the inclusion criteria given above.

We are planning on using clinical schedule review and an opt in recruitment letter for increasing enrollment. We plan on being able to identify potential subject from the information gained from EPIC to meet subjects in the clinic. We will plan on discussing their possibility of being part of the research study with the physician prior to meeting the patient.

Healthy volunteers will be recruited by study coordinators and use of a volunteer information sheet (attached). A participant pool will be used to recruit healthy volunteers. This pool consists of previous study participants that have agreed to be contacted for future research studies.

Volunteers will also be recruited from the University of Utah using flyers (attached) posted on campus.

Participants who are University Staff, Students, and Faculty will be recruited only when there is not the chance of coercion or undue influence to participate in the study. Specifically, anyone who works for the PI or receives a grade from the PI will not be allowed to volunteer.

The volunteer information sheet will be given to people that contact the study staff and show interest in research participation.

The study will be listed online at http://healthcare.utah.edu/clinicaltrials with staff contact information listed for volunteers that would like to participate. We will also list the study in the ResearchMatch database (also known as the National Recruitment Registry Project).

Informed Consent:

Description of location(s) where consent will be obtained:
At the hospital or at INC or at HCH, depending on which imaging study is being performed.

Description of the consent process(es), including the timing of consent:
When possible, consents are emailed to the participants a week ahead. Otherwise, consents are done prior to the imaging procedure when the subjects arrive at the imaging center. Subjects may take as much time as they like to read and ask questions, and to think about whether they want to participate.

Procedures:
STUDY PROCEDURE

As described in the participant characteristics, all subjects will be imaged with MRI, and some also with PET. All subjects enrolled in the AF cohorts will have three study visits or will consist of extra scans added to a clinically scheduled MRI. All subjects enrolled in the healthy volunteer and risk based cohorts will have at least one study MRI and up to three study MRIs depending on the study aim. It will not be a deviation if not all three visits are completed for these cohorts

For the below, LV=left ventricle, LA=left atrium, LGE=late gadolinium enhancement (to see atrial fibrosis), MRA=magnetic resonance angiography

MRI Protocol Each study will first hook up ECG and IV. Then the imaging protocol will include: 1) 0.05 mmol/kg adenosine or regadenoson stress perfusion, with initial 1/10 concentration volume matched dual bolus. For all perfusion sequences, gadolinium is given i.v. with a power injector at 5cc/s, 25 ml saline flush at 5cc/s. 2) LV cine with tags in the same 5 slices imaged with perfusion. 3) LV wall motion cine (without tags), short axis of whole heart. 4) 0.05 mmol/kg rest perfusion, with dual bolus. 5) MRA of the LA (used for guiding the ablation procedure) with 0.1mmol/kg. 6) Finish LV cines and do LA cines - 4 chamber view stack for LA function. 7) High resolution 3D LGE scan of the LA.

We estimate the time in the scanner (after IVs and ECG leads are in place) as 5 min. scouts, 10 min. perfusions, 5 min. MRA, 20 min. tags and cines, 10 min. LGE = ~60 minutes.

For the subjects undergoing repeated MRIs, a second MRI study will also be scheduled up to 10 weeks later to see how repeatable the MRI measurements are. The second MRI study will be identical to the first. A third MRI visit will be optional and offered to the subject at the end of the second MRI.

For the PET or PET/CT scans: a study at rest and at adenosine or regadenoson stress will be performed. For each PET study, you will receive through the IV a small amount of a radioactive tracer. Each scan will last approximately 30 minutes. A transmission scan or a low-dose X-ray CT scan to provide information about your anatomy in order to enhance the PET data will also be performed. (The PET data shows blood flow rather than body structure). This will take approximately 1-15 minutes.

For the subjects undergoing both an MRI and a PET scan, the order of the tests will depend on scheduling issues and may be on the same or different days. For both imaging sessions, you will be asked to not have any caffeine for at least 12 hours before the scan. An IV (Intra-Venous) line will be inserted into a vein in each of your arms, and ECG (electrocardiogram) leads will be placed on your chest or back.

A blood draw has been added to each cohort and for each study visit. A hematocrit will be ordered for the day of the study visit and will be drawn at the time the IV is placed in an attempt to limit patient discomfort. In the event that the lab can not be obtained while the IV is placed the patient will be escorted to the outpatient lab in the hospital after the scan has been completed.

	Study Visit 1	Study Visit 2	Study Visit 3

	Day 1		
Control Group A Non-AF	MRI with contrast Blood Draw	*Optional Scan* MRI with contrast Blood Draw	*Optional Scan* MRI with contrast Blood Draw
	Day 1	within 10 weeks of 1st MRI	within 10 weeks of 2nd MRI
Control Group B with and without AF	MRI with contrast, stress agent and Blood Draw	MRI with contrast, stress agent and Blood Draw	*Optional Scan* MRI with contrast, stress agent and Blood Draw
	Day 1 PET or PET/CT can be done at study visit 1 or 2		within 10 weeks of first MRI
MRI and PET Group AF	MRI with contrast and stress agent Blood Draw	PET or PET/CT with radioactive tracer, stress agent and Blood Draw	MRI with contrast and stress agent Blood Draw
	Day 1 pre-ablation	post ablation	final
Blood Flow MRI AF Clinical Scans	Clinical MRI with research scans, contrast, stress agent, blood draw	Clinical MRI with research scans, contrast, stress agent, blood draw	Clinical MRI with research scans, contrast, stress agent, blood draw

Procedures performed for research purposes only:

All of the procedures described in #6, above, will be done for research purposes only, exce for the subjects that are undergoing clinical MRIs before and after AF ablation treatment (blood flow MRI AF clinical scans). In those subjects, some of the above scans will be performed and billed clinically. That is, the LV wall motion cines, the MRA, and the LGE the LA form a portion of the standard clinical scan.

Statistical Methods, Data Analysis and Interpretation

Analysis The primary hypothesis is that MPR will significantly increase due to ablation therapy. The significance (computed with a t-test) of any changes in perfusion and MPR will take into account the inter-study ability from D.3 by using the procedure by Bland-Altman. Considering 3 independent territories per study, and estimating mean MPR changes of 0.3, the power of a paired t-test to detect significant change is 85% with 20

patients. 30 subjects are planned and it is expected that ~33% of the patients will recur, leaving 20 subjects. Additional analysis of changes in MPR in the patients that recur will also be done, although with reduced power. Results from the gender and age-matched control group of 10 subjects without AF will be used to determine how MPRs before and after ablation compare to normal values.

Further comparisons of perfusion, MPR, function including strain, and LA fibrosis size will be done with t-tests and Bland-Altman methods. ANOVAs will be performed to analyze relations between MPR, function, and fibrosis size. MPR for coronary artery territories as well as smaller regions and division of each region into an endocardium portion and an epicardium portion will be studied with separate analyses. We do not expect MPR to be the best predictor of recurrence, since LA size and function and fibrosis are known to be powerful predictors. We will test if MPR is an independent predictor of recurrence. And a combined best linear predictor for recurrence will be constructed from the LA and LV function and size, along with LA fibrosis and perfusion values. This analysis will add to our understanding and serve as a basis for designing larger trials if there are particularly promising integrated metrics that predict response to therapy.

The longitudinal dataset that will be collected here will be extremely valuable. While the most unique piece with the most unanswered questions is the perfusion data, the inclusion of LA fibrosis which is still relatively new, along with LA and LV function and sizes forms a valuable resource that will be freely shared with the scientific community to allow additional analyses and comparisons. For example the results may shed light on whether MPR changes instigate the remodeling process, or result from the anatomical changes (smaller LA and improved function). If LA first shrinks and then MPR returns to baseline, this implies the latter.

The addition of obtaining labs from each subject at each visit will be to collect a hematocrit level for the day of the scan. The hematocrit can be used along with the T1 maps to calculate extracellular volume (ECV). We want to measure ECV along with perfusion and other parameters within this project.