Characterization of Changes in Ventricular Mechanics in Response to Lexiscan™ Stress Using Tagged Cine Cardiac Magnetic Resonance Imaging

A Research Proposal submitted to the Astellas – U.S. Investigator Initiated Program

Revised February 27, 2017

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INTRODUCTION

Vasodilators, including regadenoson, are well established in SPECT and PET myocardial perfusion imaging (MPI) to visualize blood flow during both rest and stress (1-3). In addition, there appears to be evidence that vasodilator induced wall motion abnormalities and changes in left ventricular ejection fraction (LVEF) may provide additional prognostic information (4). Changes in LVEF between rest and stress have been observed during radionuclide ventriculography, stress echocardiography, SPECT and PET MPI (5). In particular, Rubidium-82 PET permits true measurements at rest and peak stress and has demonstrated that patients with significant ischemia experience either a drop or a failure to increase LVEF during stress (6). Despite evidence that vasodilator induced WMA and change in EF represents increased patient risk, current models for the physiological development of these changes is limited.

The potential for pharmacologically-induced stress to produce observable wall abnormalities (WMA) is well documented in the echocardiography literature (4, 7-9). The mechanism for inotropic agents (dobutamine) to induce wall motion abnormalities is to increase oxygen demand by increasing heart rate and the force of contraction (10). In contrast, dipyridamole and other vasodilators effectively reduce the supply of oxygen available to myocardial segments served by diseased coronaries, with the sub-endocardium being particularly vulnerable (11). A limitation of dipyridamole echocardiography is that the recommended dosages are considerably higher than for nuclear myocardial perfusion scintigraphy (0.84 mg/kg over 10 minutes vs. 0.56 mg/kg over 4 minutes respectively (12). In a study of 10,451 patients (10% with documented or suspected coronary disease), 1.2% of patients had a major adverse reaction (13) and 67% reported minor side effects (headache, flushing, gastrointestinal, 14). Further, dipyridamole stress alone is often insufficient and necessarily supplemented with atropine to improve test sensitivity.

Regadenoson functional imaging potentially offers a significant improvement in the side effect profile over high dosage dipyridamole without sacrificing sensitivity. Porter et.al (7) reported similar sensitivity to WMAs in the presence of CAD (61%) to dipyridamole (66% without atropine administration, 15) with no reported major side effects. Despite the comparable sensitivity, the absolute sensitivity is significantly less than perfusion based techniques.

Cardiac magnetic resonance (CMR) imaging is increasingly being used in the assessment of regional and global left ventricular function at rest and during vasodilator stress (16-18). CMR has many important technical advantages including a higher spatial resolution than PET or SPECT, improved tissue characterization (both with and without contrast), and superior repeatability and endocardial definition (including functional assessment) over echocardiography. Its power of tissue characterization is particularly highlighted with the use of late gadolinium enhancement (LGE) and its excellent spatial correlation with infarction, necrosis, and fibrosis (19). With respect to wall motion, myocardial strain imaging with CMR uses magnetic saturation "tag" lines (figure 1) to aid in qualifying and quantifying wall motion, is superior to echo-based strain techniques, and has been demonstrated to correlate well with LVEF (20-23).

At this time, there is ample evidence that vasodilator stress induces functional changes (4-7,9,11,12); however, without an understanding of the etiology of this process, its value in patient management is limited. In order to use functional changes induced by vasodilator stress, it is necessary to first understand the relationship between functional and perfusion abnormalities, local strain and fibrotic burden.

It is the intent of this research to quantify the effects of regadenoson on myocardial function and contraction in the presence of CAD. We are proposing a CMR protocol to evaluate myocardial viability and function, with CMR tagging, on a segment-based approach. We plan to evaluate correlations in wall motion changes (ie. - myocardial radial strain (ΔR) and/or displacement ($\Delta\theta$)) during regadenoson stress and correlate with areas of myocardial infarction (late gadolinium enhancement on CMR), areas with identified perfusion defect (on PET), and a change in LVEF magnitude (on both PET and CMR).

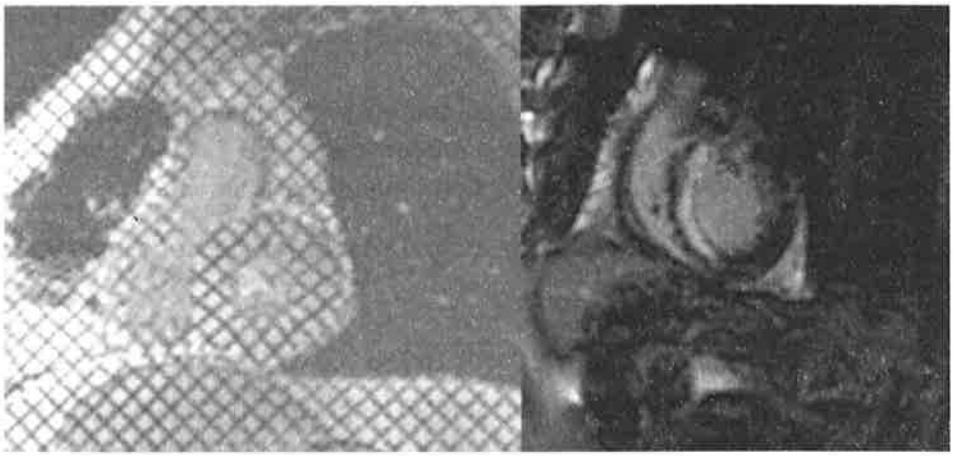

Figure 1: Tagged short axis cine view of the left ventricle (left panel) and late gadolinium enhancement image (right panel) showing a near transmural infarction of the septal wall.

HYPOTHESIS

The hypothesis of this study is that in a population with a demonstrated perfusion defect and WMA (measured by Rb-82 PET), regadenoson stimulates changes in ventricular mechanics (radial strain and rotational displacement) and LVEF associated with the degree of ischemic or fibrotic burden. Additionally, these changes may be different for normal, ischemic, and infarcted myocardium and will be compared between a high-risk population and a cohort of low-likelihood normals.

PRIMARY END-POINTS

For each patient group, every segment of the myocardium will be classified as normal, reversible, or non-reversible based on the PET perfusion data. Then for each segment category the radial strain (ΔR) and rotational displacement ($\Delta\theta$) will be calculated using an industry

standard CMR software package (current plans are to use HARP®, Diagnosoft, Morrisville, NC, though another package may be used). These values will be determined from tagged cine images obtained in three short axis (apical, mid, and basal) views of the left ventricle obtained during regadenoson induced stress and at rest (or difference in stress values).

1. Primary End-Point 1 of this study is to determine if there is a measurable difference in the strain (ΔR) and/or displacement ($\Delta\theta$) of normal and abnormal segments between the defined ischemic and normal patient groups.

2. Primary End-Point 2 of this study is to determine if there are measurable differences in the strain (ΔR) and/or displacement ($\Delta\theta$) between segment classifications (normal, reversible, and non-reversible perfusion defects).

SECONDARY END-POINTS

Secondary end-points will be determined from tagged cine images obtained in three short axes (apical, mid, and basal) views of the left ventricle obtained during regadenoson induced stress and at rest (or difference in stress values).

1. Secondary End-Point 1 of this study is to determine the strain (ΔR) and/or displacement ($\Delta\theta$) scores correlate with flow reserve as measured by PET and/or transmural extent of infarction (TEI) indicated by Late Gadolinium Enhancement (LGE).

2. Secondary End-Point 2 of this study is to track any adverse events as a result of participation in this study.

STUDY DESIGN

Subjects who have had a clinically indicated, ECG-gated, Rb-82 myocardial perfusion PET study will be recruited for participation. Specific inclusion/exclusion criteria are:

Inclusion Criteria

1. Myocardial rest/regadenoson stress perfusion PET study within 60 days
2. Rest LVEF (greater than or equal to 35%)
3. No change in symptoms or treatment between the PET and the MRI study
4. Willing to consent to the study
5. Male or female who is either post-menopausal, surgically sterile, or if has a childbearing potential, a negative pregnancy test within 2 days prior to the MRI study.
6. An estimated glomerular filtration rate completed within 6 months of participation.

Exclusion Criteria

1. Metallic implants, pacemaker, blood vessel clip (contra-indicated for MRI)
2. Patient size exceeds MRI bore/table limits: (Max body diameter > 70 cm, weight > 136 kg)
3. Second or third degree AV block
4. Sinus node dysfunction
5. Acute myocardial infarction (past 3 months)

6. Actively wheezing or with acute asthma or bronchospastic attacks requiring changes in therapy within the past 30 days
7. Patients that have experienced a previous hypersensitivity reaction thought to be related to regadenoson
8. Pregnant Women

STUDY PROCEDURES

Study staff will provide each subject with full and adequate verbal and written information using an IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent will be obtained prior to performing any study-related procedures. If consent is gained, a copy of the executed consent form will be provided to the subject.

Following consent execution and prior to the MRI, the following screening measures will be performed and documented:

- Medical history, including surgeries and procedures;
- Medications, including herbal supplements and vitamins, will be reviewed;
- A MRI Patient Safety Screening questionnaire completed;
- Vital signs will be taken, to include heart rate, breathing rate, and blood pressure will be collected;
- An electrocardiogram will be performed;
- An intravenous catheter will be placed into the subject's arm;
- Females of child-bearing potential* will undergo a serum pregnancy test;
- If a creatinine blood test has not been done clinically in the last six months, one will be performed; and
- The qualifying, clinically-indicated cardiac PET procedure records will be collected.

** Females of childbearing potential are defined as not postmenopausal or surgically sterilized.*

Consented subjects will be asked to undergo a rest/Lexiscan® (Regadenoson) stress cardiac MRI examination. For patients who do not have an estimated glomerular filtration rate on record within 6 months of participation, a creatinine will be drawn as part of the screening procedures. Patients with renal dysfunction (defined as an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 within 6 months of participation) or a history of gadolinium contrast allergy or intolerance will participate in an abridged non-contrast protocol consisting of the localizer, functional and stress imaging sequences only, and no contrast will be administered.

There will be 40 subjects recruited into this study. 15 subjects will be recruited who had normal perfusion, normal LVEF and no WMA on a clinically indicated cardiac PET study. 25 subjects will be recruited into the ischemic cohort. Consented study participants will receive one dose of Lexiscan® (Regadenoson) while taking part in this protocol.

Ischemic Patient Population

The abnormal population will be selected from a group of patients with a clinically indicated myocardial perfusion PET study demonstrating reversible ischemic perfusion defect, a rest LVEF of ≥ 35%, and demonstrated WMA by quantitation, utilizing QPET's QGS analysis program

(Cedars Sinai Health System, Los Angeles, CA). A WMA will be defined as having a drop in LVEF from rest to stress and/or an extent of greater than or equal to 10% thickening and/or motion.

Myocardial perfusion rest/Regadenoson PET protocol

All PET studies will have been clinically indicated and performed prior to study participation. These studies will have been performed on a Biograph™-16 or Biograph™-64 PET/CT or Siemens ACCEL Dedicated PET system (Siemens Medical Solutions, Erlangen, Germany).

Biograph™-16 or Biograph™-64 PET/CT System

A low-dose CT image acquisition will have been acquired for attenuation correction. The resting perfusion images will have been acquired using 20-40 mCi of Rubidium-82, infused over 35 seconds. The ECG gated, list mode acquisition will have started prior to the start of the rubidium-82 infusion and continued for 7 minutes.

With the subject in the same position, a single 0.4 mg dose of regadenoson in 5 mL saline will have been administered as a bolus over 10 seconds and immediately followed by a 5 mL saline flush. Following a 30 second delay, the stress images will have been acquired using 20-40 mCi of Rubidium-82 in ≤ 50 ml saline infused over <35 seconds. An ECG gated, list mode acquisition will have been started prior to the start of the Rb-82 infusion and continued for 7 minutes. A second low dose CT scan will have then been acquired for attenuation correction of the stress study.

Siemens ACCEL Dedicated PET

An infusion of 50 mCi of Rubidium-82 will be delivered 10 seconds after the beginning of the dynamic acquisition. First, a 150 second 2D dynamic acquisition will be acquired and followed by a 300 second 3D gated acquisition. Transition between 2D dynamic and the 3D gated acquisition was approximately 120 seconds.

With the subject in the same position, a single 0.4 mg dose of regadenoson in 5 mL saline will have been administered as a bolus over 10 seconds and immediately followed by a 5 mL saline flush. Following a 30 second delay, the stress images will have been acquired using 50 mCi of Rubidium-82 in ≤ 50 ml saline infused over <35 seconds. The 2D dynamic acquisition will have been followed by a 3D stress ECG gated acquisition.

Patients that meet these inclusion criteria will be discovered using a review of the St. Luke's nuclear database.

Cardiac MRI examination

All MRI studies will be conducted on either a 1.5-Tesla or 3.0 Tesla magnet. When subjects arrive, they will be consented and prepared for MRI scanning. The scanning technician will prepare the subject (screening, change of clothes, placement of positioning pillows, placement of hearing protection, vectorcardiogram leads, and an IV). Subjects will lie supine on the MRI table and then be advanced into the magnet bore. Of the subjects meeting inclusion/exclusion

criteria, those with a GFR < 60 mL/min/1.73m^2 or a history of gadolinium contrast allergy or intolerance will only perform the non-contrast portion of the following protocol, all others will follow the full protocol (Figure 2):

Non-Contrast CMR examination (Tagging at Rest, Stress)

- Localizers
- Pre-Contrast Rest Tagging Images:
  - Short Axis Cine (apex, mid, base)
  - Long Axis Cine (horizontal, vertical)
- Inject Regadenoson
- Pre-Contrast Stress Tagged:
  - Short Axis Cine (apex, mid, base)
  - Long Axis Cine (horizontal, vertical)
- Reverse Patient with aminophylline (if necessary)

**Late Gadolinium Enhancement to assess infarcted and fibrotic tissue:*

- Injection of gadolinium contrast agent
- Delay of at least 8-15 minutes from injection
- Cine IR TI Scout
- LGE Short Axis(apex, mid, and base)
- LGE Long Axis(horizontal and vertical)

**ONLY FOR PATIENTS WITH A DOCUMENTED GFR > 60 mL/min/1.73m^2 WITHIN 6 MONTHS OF PARTICIPATION*

Figure 2: CMR Protocol

The Lexiscan® (Regadenoson) will be administered by a clinical team of physicians, nurses, and clinical physiologists with extensive and daily experience with pharmacologic stress testing. The recommended intravenous dose of 5mL (0.4 mg regadenoson) will be administered as a rapid (approximately 10 seconds) injection into a peripheral vein immediately followed by a 5 mL saline flush. Subjects will be reversed using aminophylline if necessary, in the event of one or more of the following:

a. ECG changes of ST depression >2mm or any significant ST elevation
b. Onset of sustained second or third degree AV block
c. Decreased systolic BP of >20mmHg on two (2) consecutive readings or BP > 240/110

d. Wheezing
e. Severe chest pain associated with ST depression of 2mm or greater.
f. Signs of poor perfusion (pallor, cyanosis, and cold skin).
g. Technical problems with monitoring equipment.
h. Patient's request that on-going symptoms are severe.
i. As deemed necessary by personnel administering the Lexiscan® (Regadenoson) stress test.

Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow intravenous injection (50 mg to 100 mg over 30-60 seconds) to attenuate severe and/or persistent adverse reactions to Lexiscan® (Regadenoson).

The contrast agent, MultiHance (gadobenate dimeglumine) will be administered by a clinical team of physicians, nurses and technologists with extensive and daily experience with contrast MRI. The recommended intravenous dose, 0.1 mmol/kg (0.2 mL/kg), of MultiHance will be administered as a rapid injection immediately followed by a 15 mL saline flush. Subjects with a calculated GFR < 60 mL/min/1.73m^2 within 6 months of participation or have a history of gadolinium contrast allergy or intolerance will not receive contrast.

DATA ANALYSIS

The measurement of PET function LVEF will be performed using the industry standard QPET analysis program (Cedars Sinai Health System, Los Angeles, CA). Absolute myocardial perfusion and flow will be measured using the ImagenQ quantitation package (CVIT, Kansas City MO).

Volumetric data and late gadolinium enhancement post-processing will be performed on an AW workstation using ReportCard v4 software (General Electric). Tagged images will be post-processed for strain and displacement (ΔR and $\Delta\theta$) measurements using the HARP® tagging analysis software package (Diagnosoft) or a similar industry standard software package.

Primary End-Point Analysis:

For each patient group, every segment of the myocardium will be classified as normal, reversible, or non-reversible based on the PET perfusion data. Then for each segment category the radial strain (ΔR) and rotational displacement ($\Delta\theta$) will be calculated using the HARP® software package (Diagnosoft). These values will be determined from tagged cine images obtained in three short axis (apical, mid, and basal) views of the left ventricle obtained during regadenoson induced stress and rest (or difference in stress values). Comparisons will be made using ANOVA and standard t-test methods.

1. For Primary End-Point 1 we will compare the radial strain (ΔR) and rotational displacement ($\Delta\theta$) of normal and abnormal segments *between the defined ischemic and normal patient groups*.

2. For Primary End-Point 2 we will compare radial strain (ΔR) and rotational displacement ($\Delta\theta$) at rest and stress *between abnormal and normal segment classifications*.

Secondary End-Point 1

The secondary end-points of this study will be analyzed using regression analysis to determine the relationships between radial strain (ΔR), rotational displacement ($\Delta\theta$), regional flow reserve, and the degree of transmurality (TEI) as defined by the presence of delayed gadolinium enhancement.

Secondary End-Point 2

Adverse events will be recorded on an Adverse Event log. This log will track:

1. Description of event
2. Start and stop time of event
3. Severity of event
4. Likelihood that the event is related to the study drug
5. Relationship of event to other test procedures
6. Any treatment actions taken
7. The final outcome

Although serious adverse events are not expected, serious adverse events will be reported to the IRB.

Powering Calculation

The patient to patient variability of normal resting LVEF is 5.3% (3). For the normal patients, there is an expected increase in ejection fraction of 8% (3). For ischemic patients, we have defined a change in ejection fraction of 2% as being significant. The net change would be a 10% change in difference in ejection fraction between the control (normal) and the ischemic groups.

If we assume cylindrical geometry, this would imply a roughly 5.6% change in the radius of the myocardium would result in a change in ejection fraction of 10% (assuming a resting LVEF of 55). Based on (3), this would give a Cohen's d of 1.06 and a total of 16 patients per group. However, given the need to explore the abnormal arm of the study, can obtain a similar power of 0.8 using an unequal population sizes of 13 (normal) and 22 (abnormal). We anticipate approximately 15% of patients that may not achieve sufficient quality of data would yield population of 15 normal subjects and 25 ischemic subjects to achieve the 0.8 power.

RESEARCH ENVIRONMENT

ASPIRE Foundation

Study funding will be provided by Astellas to the sponsor, the ASPIRE Foundation. The ASPIRE Foundation is a not-for-profit, non-invasive, imaging-based foundation dedicated to furthering knowledge about the role of imaging in improving patient outcomes. The ASPIRE Foundation is a joint venture between Saint Luke's Cardiovascular Consultants, the Mid America Heart Institute, and Cardiovascular Imaging Technologies. The ASPIRE Foundation will sub-contract with Cardiovascular Imaging Technologies for staff to conduct its trials. Only CVIT study-

specific staff (Co-PIs: Drs. Joseph Soltys and Timothy Bateman; Sub-PIs: Drs. Ibrahim Saeed and James Case; and Study Coordinators: Staci Courter and Jessica Jensen) will have access to patient data.

Saint-Luke's Cardiovascular Consultants

Saint-Luke's Cardiovascular Consultants is a large (48 physician) single-specialty cardiology practice dedicated entirely to the Saint Luke's Health System. The SLHS has 3 state of the art Biograph PET/CT scanners. The nuclear cardiology department includes five Level 3 trained subspecialized cardiologists with 10 – 30 years of nuclear cardiology experience. All studies are interpreted using the standard 17-segment 5-point scoring system as per ASNC Guidelines (14, 24). The team has extensive experience with regadenoson SPECT and PET MPI. Approximately 350 variables including scan interpretations are entered into a searchable computerized database that will serve as the main method of eligible patient identification.

Saint Luke's Hospital

Saint-Luke's Plaza campus currently has multiple MRI scanners specially equipped for cardiac imaging capabilities. These scanners include standard and high field magnets capable of high-performance cardiac imaging [1.5-Tesla Signa, 1.5-Telsa Optima, and 3.0-Tesla Discovery 750 (General Electric, Milwaukee, WI)]. St. Luke's cardiac MRI program is under the direction of Dr. Ibrahim M. Saeed, a level 3 certified cardiologist (Society of Cardiovascular Magnetic Resonance) with more than five years of experience interpreting CMR images.

Study Oversight

The Co-Principal Investigators on this project will be Joseph Soltys Ph.D. and Timothy M. Bateman, MD.

Drs. Bateman and Ibrahim M. Saeed will be responsible for medical oversight of the study. There are no additional risks to human subjects beyond those associated with a standard of care imaging study. Subject data will be regularly reviewed by Drs. Bateman and Saeed.

Drs. Case and Bateman will assist in the scientific and medical conduct of this study. Kevin Kennedy will provide biostatistical support in the design and powering of the study. Staci Courter (Senior Clinical Research Coordinator) will provide needed administrative support (e.g., IRB approvals, patient recruitment, consenting).

Technical analysis will be provided Drs. Joseph Soltys and James Case. They will provide needed analytic, image analysis and quantitative processing support.

Institutional Review Board

The study protocol, informed consent document and relevant supporting information will be submitted to the IRB for review and approval before the study is initiated. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study will be conducted in accordance with the regulations of the United States

Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

Confidentiality

All data obtained in this study will be kept confidential. In any publication or presentation of research results, protected health information will be kept private; however, the records directly pertaining to the study, which identify subjects, could be inspected by authorized individuals of the Study Sponsor, IRB and/or FDA.

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