Clinical Study Protocol

Dotarem® for Myocardial Perfusion Cardiovascular Magnetic Resonance

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Dotarem® Evaluation for Myocardial Perfusion Cardiovascular Magnetic Resonance

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A. SPECIFIC AIMS

The overall goal of this study is to investigate the signal intensity and relaxation rate characteristics of gadoterate meglumine (Dotarem, Guerbet, USA) enhanced myocardium during rest and stress perfusion cardiovascular magnetic resonance (CMR) compared to gadobutrol (Gadavsit) to prove that Dotarem provides constantly high myocardial relaxation necessary for accurate quantitative perfusion evaluation. Within this overall goal, the following specific aims will be pursued:

- **Aim 1:** To test the hypothesis that the signal intensity enhancement during Dotarem myocardial stress/rest perfusion is relatively constant, providing linear and stable enhancement in the myocardium, and is not inferior compared to gadobutrol (Gadavist).
- **Aim 2:** To test the hypothesis that the relaxation rate enhancement during Dotarem myocardial rest perfusion is uniform in the myocardium.

B. BACKGROUND AND SIGNIFICANCE

Stress perfusion imaging is indicated in symptomatic patients suspected of coronary artery disease (CAD) with low or intermediate cardiovascular risk and typical/atypical chest pain or angina-equivalent symptoms, as well as in asymptomatic patients with high cardiovascular risk profiles, such as diabetics, or in patients with known CAD during follow-up.[1] Myocardial perfusion by CMR was introduced approximately two decades ago.[2] Compared with SPECT, which uses a radioisotope that is actively taken up by the myocytes to depict myocardial perfusion, CMR evaluates the first pass of an extracellular contrast agent (CA) within the myocardium. Whereas the stress protocol used for both methods is similar, CMR offers the benefit of superior spatial and temporal resolution, and SPECT is associated with the negative effects of exposure to ionizing radiation.[3, 4] Although, several studies proved that stress perfusion CMR outperforms stress perfusion SPECT[5-7], the quantitative evaluation of myocardial blood flow by CMR is still a challenging topic due to, for example, the non-linear signal intensity changes and the different relaxation rate enhancements caused by the various gadolinium-based CAs[8-10], representing a major limitation to the widespread use of the technique in clinical practice.

Dotarem, a macrocyclic agent with fast clearance kinetics, has the highest thermodynamic stability among the currently approved clinical contrast agents.[11] This high stability is due to its molecular structure, which provides a significantly reduced dissociation rate (i.e. Release of free gadolinium ions) compared to other agents.[11] While the *in vitro* relaxivity (3.4 $mm^{-1}s^{-1}$)[12] of Dotarem is comparable to other agents, we suggest that its high stability and extremely low dissociation rate provide constant signal intensity and relaxation rate enhancement during myocardial perfusion CMR, improving the accuracy and reliability of quantitative perfusion analysis.

The efficacy of Dotarem enhanced late gadolinium enhancement (LGE) imaging has been investigated and compared to gadobutrol (Gadavist, Bayer, Germany) to visualize and quantify myocardial scar.[13] However, a similar comparison for the assessment of myocardial ischemia by CMR myocardial perfusion – an even more crucial step in a clinical CMR protocol – would further strengthen the value of Dotarem in cardiovascular imaging. While LGE is able to visualize irreversible myocardial injury, myocardial perfusion imaging has the ability to depict reversible ischemia that can potentially be treated by coronary intervention.

C. PRELIMINARY STUDIES

Our research group consists of clinical and research faculty who have extensive experience and a substantial publication record related to contrast enhanced cardiac MRI and contrast agent characterization.[14-18] In a previous research project, our team developed an image analysis technique (detailed in Section D) that we will use in Aim 2 to investigate the relaxation profile of Dotarem.[16]

D. RESEARCH DESIGN AND METHODS (INCLUDING DATA ANALYSIS)

D.1 IMAGE ACQUISITION

This prospective study will include a total of 90 patients (Aim 1 + Aim 2) who present to the MUSC Radiology Department for a clinically indicated cardiac MRI scan over a 2-year period. Patients will be imaged using a state of the art 1.5T scanner (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany) system.

Aim 1: In this specific aim, a total of **60 patients** referred for a clinically indicated stress myocardial perfusion MRI scan out of concern of suspected myocardial ischemia will be included. Patients will be scanned using a **standard clinical contrast-enhanced stress perfusion protocol** (regadenoson 0.4mg bolus) detailed in Figure 1. Patients will be randomized into two groups prior to patient consenting: **Group 1 (n=30)** will receive the **clinically approved gadoterate meglumine** (Dotarem, 0.1mmol/kg) as contrast agent for their clinical perfusion study, while **Group 2 (n=30)** will receive the **clinically approved gadobutrol** (Gadavist, 0.1mmol/kg) as contrast agent. The contrast agents will be administered at a flow rate of 5.0 ml/s for both groups. In this study aim, all imaging protocols will comply with standard of care and only the perfusion data will be post-processed and analyzed.

Aim 2: In this specific aim, a total of **30 patients** referred for a clinically indicated contrast enhanced cardiac MRI will be included. These patients will undergo a **clinical viability cardiac MRI protocol** with the administration of **gadoterate meglumine** (Dotarem, 0.1mmol/kg), except that a **prototype MRI T1 mapping pulse sequence** will be used to acquire equilibrium T1 maps during the first pass of the contrast agent. This first pass perfusion step will be performed in rest, no stress agent will be administered. The rest perfusion acquisition is part of the standard protocol, however, we will use this prototype pulse sequence for research purposes.

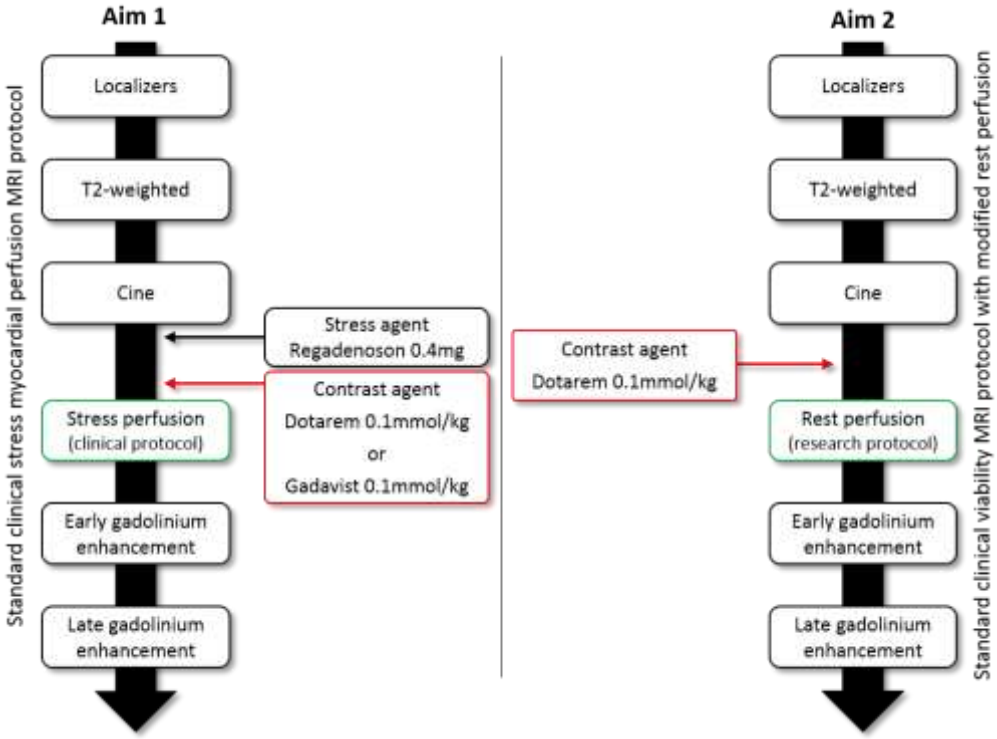

Figure 1 – MRI protocols

D.2 IMAGE ANALYSIS

In Aim 1, we will generate signal intensity-time curves from the perfusion data and evaluate the characteristics of signal intensity changes and absolute myocardial blood flow using the MASS Research Software (LUMC, Leiden, Netherlands). The signal characteristics will be compared between the two contrast groups. Image quality will also be subjectively rated by multiple independent observers.

In Aim 2, we will generate equilibrium T1 maps based on the pre-contrast T1 and repeated inversion recovery images during the perfusion of the CA. This technique allows the calculation of the post-contrast T1 at every phase during the first-pass perfusion of the CA. The uniformity of T1 and R1 (inverse T1) will be evaluated using the MASS Research Software.

D.3 STATISTICAL METHODS / SAMPLE SIZE JUSTIFICATION

All analyses and graphs will be performed by using commercially available software (MedCalc version 12.7.2; SPSS version 21). Descriptive statistics will be provided as mean ± standard deviation (SD) for continuous variables and absolute and relative frequencies for categorical variables. Normal data distribution will be assessed with a Kolmogorov-Smirnov test. For each group, comparisons of patient characteristics will be performed by using the χ^2 test for categorical variables and t-test or Mann-Whitney-U-test for continuous variables as appropriate. Subjective image quality scores will be compared using the χ^2 test with the Yates continuity correction for categorical variables and inter-observer agreement for image quality will be calculated using Cohen kappa statistics and interpreted as follows: ≤0.20 slight or poor agreement, 0.20–0.40 fair agreement, 0.40–0.80 moderate agreement, ≥0.80 excellent agreement.

E. PROTECTION OF HUMAN SUBJECTS

E.1 RISK TO THE SUBJECTS

E.1.a Human Subject Involvement and Characteristics

Aim 1

Inclusion criteria:

To be eligible for the study: (All answers must be **"YES"** for subject to be eligible.)

1. Subject must be referred for a clinically indicated contrast-enhanced stress myocardial perfusion MRI scan out of concern of suspected myocardial ischemia.
2. Subject must be older than 18 years of age.
3. Subject must provide written informed consent prior to any study-related procedures being performed.
4. Subject must be willing to comply with all clinical study procedures.

Exclusion Criteria:

The presence of the following excludes subjects from the study: (All answers must be **"NO"** for subject to be eligible.)

1. Subject is a pregnant or nursing female. Exclude the possibility of pregnancy:
   - By testing (serum or urine beta HCG) within 24 hours before study date, or
   - By surgical sterilization, or
   - Post-menopausal, with minimum one (1) year history without menses.
2. Subject has an implanted cardiac pacemaker or implantable defibrillator.
3. Subject has a ferromagnetic vascular clip.
4. Subject has a neurostimulation system (e.g. TENS-Unit).

5. Subject has any type of cochlear implant.
6. Subject has ocular foreign body (e.g. metal shavings).
7. Subject carries any implanted device (e.g. insulin pump, drug infusion device).
8. Subject has shrapnel, bullet, or other type of metal fragments within the body.
9. Subject has an acute psychiatric disorder or is cognitively impaired.
10. Subject is using or is dependent on substances of abuse.
11. Subject is unwilling to comply with the requirements of the protocol.
12. Subject is in acute unstable condition.
13. Subject has an allergy against gadolinium based contrast agents or pharmaceutical stressors used in this study.
14. Subject has impaired renal function (creatinine > 1.5 mg/dl).
15. Subject presenting with acute coronary syndrome.
16. Positive cardiac enzymes positive troponin, CK-MB, or myosin
17. ST-elevations, new transient ST changes greater than 0.05mV or T- wave inversions with symptoms

Aim 2

Inclusion criteria:

To be eligible for the study: (All answers must be **"YES"** for subject to be eligible.)

1. Subject must be referred for a clinically indicated contrast-enhanced stress myocardial perfusion MRI scan out of concern of suspected myocardial ischemia.
2. Subject must be older than 18 years of age.
3. Subject must provide written informed consent prior to any study-related procedures being performed.
4. Subject must be willing to comply with all clinical study procedures.

Exclusion Criteria:

The presence of the following excludes subjects from the study: (All answers must be **"NO"** for subject to be eligible.)

1. Subject is a pregnant or nursing female. Exclude the possibility of pregnancy:
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11. Subject is unwilling to comply with the requirements of the protocol.
12. Subject is in acute unstable condition.
13. Subject has an allergy against gadolinium based contrast agents used in this study.
14. Subject has impaired renal function (creatinine > 1.5 mg/dl).

There will not be any eligibility criteria for any subpopulations. In addition, there will not be any targeted involvement of special classes of subjects, such as fetuses, neonates, pregnant women,

children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. All race and ethnicities and both genders will be considered for inclusion into the study. Subjects under the age of 18 will not be considered for inclusion into this study.

Targeted/Planned Enrollment Table

Total Planned Enrollment: 90 (Aims 1 and 2 combined)

Table 1: Targeted/planned enrollment *(number of subjects)*.			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	3	3	6
Not Hispanic or Latino	42	42	90
Ethnic Category: Total of All Subjects	90		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	12	12	24
White	32	32	64
Racial Categories: Total of All Subjects	45	45	90

E.1.b Sources of Materials

The research materials that will be obtained from living human subjects are: the MR images, report, injection report, progress notes, medication records, vital signs, medical history and demographics, and all other applicable clinical information.

The Principal Investigator, Sub-Investigator(s) and the Study Coordinator(s) will be the only personnel who will have access to subject identities, with the exception of any regulatory personnel (MUSC IRB auditors, etc.). All subject identities will be removed prior to publication.

Contrast and Drug Management

Contrast agents (Dotarem and Gadavist) and stress agent (Regadenoson) will be ordered and dispensed from the MUSC inpatient pharmacy per clinical protocol.

E.1.c Potential Risks

Vein puncture

Patients could experience bruising, pain, and rare incidence of infection at the vein puncture site. This is like a blood test. This puncture is used to inject the contrast agents. Care will be taken to avoid these possible risks. Skin or vein irritation, fainting, blood clot formation, bleeding at the injection site, or an infection could also occur.

Adverse reactions caused by gadolinium contrast agent

Gadolinium contrast agent will be administered as part of the clinical protocol, independently from the research component of the study. The research protocol will not increase the risk of contrast related adverse reactions in any of the research aims. Despite excluding patients with known history of allergy

to gadolinium-based contrast material, there is a small risk that a patient will have an allergic reaction to contrast medium. In this event, the attending physician supervising the MRI acquisition in the study will administer appropriate care. In patients with pre-existing renal dysfunction, gadolinium-based contrast material may cause further deterioration in renal function. Therefore, patients with decreased renal function (more than 1.50 mg/dL serum creatinine) will be excluded from this study.

Risks from Contrast Agent Extravasation
Although extremely rare, it is possible that an IV needle is not properly located within the vein or becomes dislodged when the patient lies down on the examination table. When contrast material is injected, it may then leak into the surrounding tissue. This can be painful and in very few instances has been reported to cause pressure on underlying nerves or vessels that needs to be surgically relieved. Usually, however, a contrast media extravasation is noticed early on by the personnel monitoring the procedure. However, even if a full dose of contrast material is injected in the tissue surrounding a vein, permanent damage is extremely unlikely. Usually the contrast material is fully absorbed by the body within a day without any harmful effect. In addition, in our department we use the latest automated contrast media injector generation, which also comprises of an automated extravasation detection device attached to the arm of the patient. Since the implementation of this device we have not experienced any major extravasation of contrast material.

Adverse reactions caused by stress agent administration
The following reactions are listed as warnings and precautions when using regadenoson (Lexiscan): Myocardial ischemia, sinoatrial and atrioventricular nodal block, hypotension, bronchoconstriction. The following adverse reactions associated with regadenoson are considered transient and are listed in the package insert: dyspnea or urge to breathe deeply, headache, flushing, chest discomfort, angina pectoris or ST segment depression, lightheadedness/dizziness, chest pain, nausea, abdominal discomfort, impaired taste, feeling hot. In addition, dyspnea can occur during stress myocardial perfusion imaging with associated arrhythmias such as hypoxia induced bundle branch block. The first signs of these rare side effects will cause the termination of the examination. Note, that stress agent will not be administered for research purposes.

Risk of metal objects in the body
Patients may suffer bodily harm in the course of the MRA examination from having metal objects in their clothing, from metal implants (e.g. pacemaker, implanted defibrillator, cochlear implants, cerebral aneurysm clips), or any other metal within the body (shrapnel, bullet or metal fragments). Before patients undergo the procedure, they will be prompted to take out any metal objects. Patients will be asked a series of detailed questions about any metal that they may have their body.

Acquisition of patient information
The risks associated with gathering this information are believed to be very low. This information will be stored on a password-protected computer and network server and in a locked office (ART Cardiac Imaging Research Office). The data from this study will be accessible only to the team of researchers from this application.

E.2 ADEQUACY OF PROTECTION AGAINST RISKS

E.2.a Recruitment and Informed Consent

Patients who have been referred for a stress myocardial perfusion MRI (Aim 1) or myocardial viability MRI (Aim 2) as part of a standard clinical evaluation determined by the treating physician(s) will be eligible for the study and recruited from the MUSC MRI schedule. The MRI technologist or member of the nursing staff will speak with potential subjects to ensure their willingness to be approached by a member of the research team. Willing patients will be approached and will undergo the informed

consent process. Consented subjects will undergo their clinically indicated MRI using the standard stress protocol (Aim 1) or the modified viability protocol (Aim 2).

Patients will be screened by approved study personnel from the MUSC MRI schedule under a HIPAA waiver. Study eligibility determination and study enrollment will be assessed and performed by and investigator in concert with a study coordinator delegated by the PI and approved by the IRB as being authorized to obtain informed consent.

The PI, Sub-I(s) or the Study Coordinator(s) will obtain informed consent prior to enrollment into the study. The subject will be taken to a quiet/private area (which may include the scanning room, the patient bays or other private areas) and the study purpose, procedures, duration, risks/discomforts, benefits, alternatives, new information procedures and privacy statements will be explained to the subject.

The subject will be asked to verbally repeat pertinent study information to ensure subject understands the nature of the research. Subjects will be provided the opportunity to ask any questions they may have. Consent will be documented in the currently IRB approved version of the informed consent and will be signed and dated by the person obtaining informed consent and the subject.

E.2.b Protection against Risk

To minimize the risk of post-contrast nephropathy, patients with decreased renal function (creatinine >1.5 mg/dL) will not be eligible for this study. To minimize the risk of allergic reactions to gadolinium contrast material, patients with a history of allergic reactions to gadolinium contrast material will also be excluded.

All subjects' medical records will be confined in the usual medical health information office according to their policies and procedures. Each staff member that has approved access to electronic medical records will be given their own password and will be instructed not to reveal that password to anyone else. In addition, those copies of subject information utilized for the research protocol will be kept locked in the Radiology Research suite (ART 2244) in a research specific folder that will identify the subject on the outside of the folder only by initials, subject code (subsequent subject identifiers, i.e. 001, 002, 003, etc., this number will not be able to identify the subject), protocol name, and IRB study number (Pro #). Any data that are used in publication, analyses, etc. will not identify the subject by name, etc. Subjects will be monitored in clinic as per clinical standard practice for any possible side effects and treated as indicated.

E.3 POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The subjects whose data, documents, and records will be reviewed are not likely to receive any benefit from the proposed research. However, the quantitative and qualitative evaluation of myocardial perfusion has an important role in patient diagnosis, therapy and prognosis. The improved and more reliable detection of myocardial perfusion defects may provide faster diagnosis and better patient management, as well as avoid unnecessary tests (including invasive procedures and radiation exposure). As of today, Dotarem is the only gadolinium-based contrast agent without any reported nephrogenic systemic fibrosis case. Broadening the clinical use of Dotarem towards the cardiac MRI field would provide substantial benefit to patients, especially those who suffer from pre-existing renal disease.

E. 4 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Clinical stress myocardial perfusion MRI is a contrast enhanced acquisition that requires the administration of gadolinium-based contrast agent. Currently, there is no FDA label exist for such

applications, thus all the clinical contrast-enhanced cardiac MRI scans are performed off-label. This study will further strengthen the evidence that such clinical indication is warranted and will also demonstrate that Dotarem is a suitable agent to provide diagnostics perfusion data.

E.5 SUBJECT SAFETY AND MINIMIZING RISKS (DATA AND SAFETY MONITORING PLAN)

Eligibility in each case will be confirmed by a named investigator. The source data will be collected by an independent technician and/or study coordinator, maintained securely by the PI and checked by the named investigators. Clinical data will be recorded on a Case Report Form (CRF). However, formal monitoring of site records will not be completed as part of the general conduct of the study. Data collected will be authentic, accurate and complete and the study will be conducted in accordance with the currently approved protocol (and any future approved amendments), Good Clinical Practiced (GCP) and all applicable regulatory requirements.

Any event meeting the criteria of an unanticipated problem involving risks to subjects or others will be reported to the MUSC IRB, as required by HRPP 4.7- Unanticipated Problems and Adverse Events Policy and Procedures. Clinical data will not be monitored by a 3rd party (i.e. Contract Research Organization) or sponsor but the results of the study will be written as a paper and may be submitted as abstracts to various conferences. Every effort will be made to ensure patient safety and confidentiality.

F. FACILITIES AVAILABLE

The Radiology department on the 2nd floor of the Ashley River Tower houses the MAGNETOM™ Avanto on which the MRI will occur. Nursing and physician preparation and monitoring of the patient, including the serum creatinine test, will occur in the patient bays of the Radiology department.

G. REFERENCES

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