# Study Protocol

MyocardiAl CT Perfusion and Coronary Flow: a CompreHensive Cardiac CT Myocardial Perfusion Imaging (MPI)/Fractional Flow Reserve (FFR) and PET-CT MPI Evaluation (The MATCH Investigation)

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# Emory University

## Clinical Study Protocol

**M**yocardi**A**l C**T** Perfusion and **C**oronary Flow:
a Compre**H**ensive Cardiac CT Myocardial Perfusion Imaging (MPI)/Fractional Flow Reserve (FFR) and PET-MPI Evaluation
(The **MATCH** Investigation)

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**A. SPECIFIC AIMS**

The overall goal of this project is to compare the absolute quantification of myocardial perfusion done by using CT myocardial perfusion imaging (CT-MPI) and the coronary flow measured by using CT Fractional Flow Reserve analysis (CT-FFR) to the gold standard represented by PET myocardial perfusion imaging (PET-MPI). The overall goal will be achieved through the following specific aims:

**Specific Aim 1:** To compare the absolute quantification of myocardial perfusion between CT-MPI and PET-MPI.

**Specific Aim 2:** To investigate the correlation between myocardial perfusion measured using CT-MPI and PET-CT MPI, and coronary flow measured using CT-FFR.

**Specific Aim 3:** To compare the accuracy of PET-CT MPI and combined CT-MPI / CT-FFR approach in the detection of myocardial perfusion abnormalities and coronary stenosis.

**B. BACKGROUND AND SIGNIFICANCE**

Myocardial perfusion imaging (MPI) is a well-researched technique to evaluate myocardial ischemia. Originally started as a technique limited to nuclear imaging techniques such as Single Photon Emission Computerized Tomography (SPECT) and Positron Emission Tomography (PET), MPI has become available for Computed Tomography (CT) as a result of technological developments. PET-MPI and CT-MPI are the only two techniques that allow for the absolute quantification of myocardial blood flow, directly calculated from the myocardium. Absolute quantification of myocardial perfusion is not only able to quantify lesion specific ischemia but also able to identify global ischemia and microvascular abnormalities, this in contrast to MPI using other modalities (1,2). Some research even implies that subclinical changes, caused for example by diabetes and hypertension, can be detected (2).

The main reason that PET and CT are able to quantify myocardial perfusion is the linear relationship between myocardial blood flow and myocardial tracer/contrast uptake. In figure 3, the relationship between PET and SPECT tracers is shown, where the PET tracers clearly show an superior relationship compared to the SPECT tracers (3). Although both iodine and gadolinium are considered extracellular contrast agents, the advantage of iodine is that the relationship between contrast agent concentration and the change in signal intensity is linear over a wide range and contrast agents concentrations are thus strictly proportional to the signal enhancement, see figure 4 (4). For SPECT tracers as well as gadolinium, used for MRI MPI, the relationship becomes non-linear at higher myocardial blood flows (3,5,6) making absolute quantification impossible.

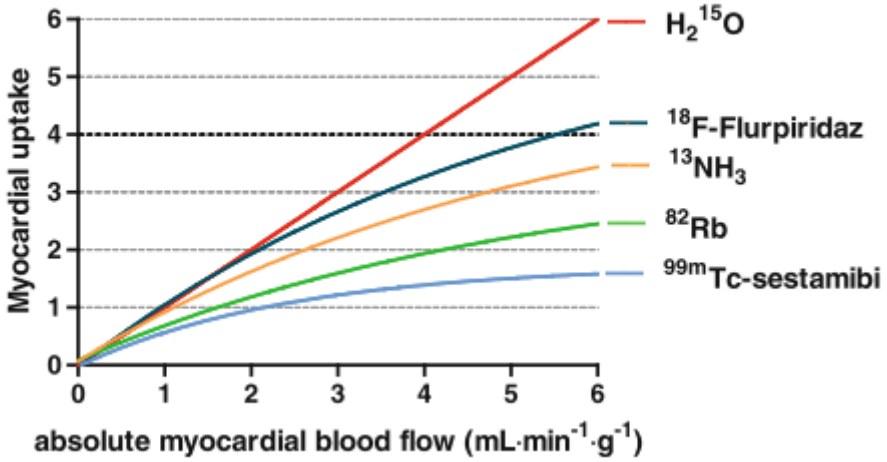


**Figure 3.** Kinetics of MPI perfusion tracers. Graphical presentation of the relationship between absolute Myocardial Blood Flow (MBF) of the several PET radiotracer and actual tracer uptake.

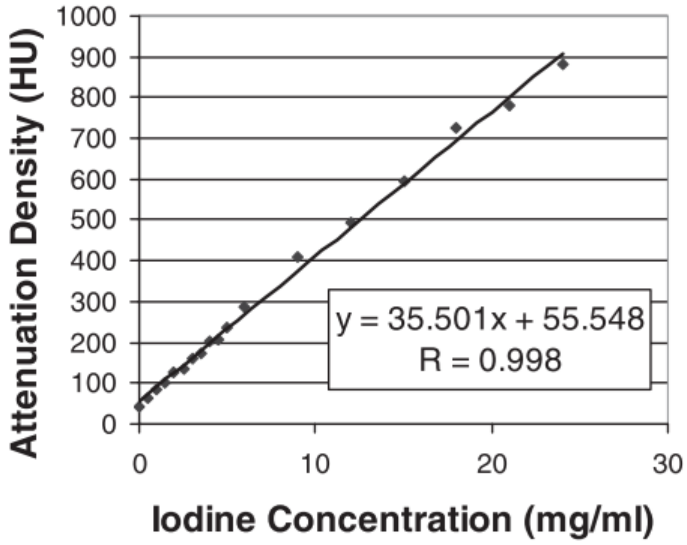


**Figure 4.** Attenuation density versus iodine concentration. Note the linear relationship even at higher concentrations of iodine (HU: Hounsfield units).

CT is the latest modality that's being able to perform MPI. Traditionally, this technique was limited by the low temporal resolution and high radiation dose of CT systems, however, on current high-end

systems CT MPI is now possible at equal or even lower radiation doses then the nuclear equivalent. One of the issues with CT MPI is the wide variety of protocols, systems and models used resulting is a wide variety of absolute myocardial blood flow (MBF) values with corresponding ranges of threshold values (7–9). Another issues encountered when comparing CT-MPI to perfusion imaging with other modalities are the significantly lower MBF values measured with CT-MPI (10). Currently, the mathematical models used to calculate MBF, are directly extracted from MRI perfusion studies and an optimal model for CT-MPI has not been determined. Comparing CT-MPI to PET-MPI would help gain insight in the ability of CT to quantify myocardial blood, what the optimal imaging protocol and tracer kinetic model is and is needed to give CT-MPI the last push into clinical implementation on a wide scale.

Another option to evaluate the functional significance of coronary artery disease is measuring the fractional flow reserve (FFR). Fractional flow reserve has been used to measure the functional consequences of specific lesions by measuring a pressure gradient over this lesion, assuming that a drop in pressure will result in an corresponding drop in coronary blood flow and thereby impairing the blood flow to the myocardium (10). This technique has been hampered by the high cost and invasiveness of the procedure. More recently a new approach to calculate FFR has been developed, CT derived FFR (CT-FFR). With the use of computational fluid dynamic and optionally the use of artificial intelligence, it is now possible to calculate FFR from regular CCTA images and anatomically and functionally evaluate the significance of a lesion (11). Several studies have proved the excellent diagnostic accuracy of CT derived CT-FFR with the use of AI, either compared to invasive FFR or in comparison with computation fluid dynamics derived CT-FFR (12–16).

While both CT-FFR and CT MPI focus on the functional analysis of coronary artery disease (CAD), they visualize different processes. While CT-FFR looks at stenosis specific coronary flow changes, CT-MPI looks at overall changes to the myocardial perfusion. CT-FRR could play a role in indicating which coronary artery and which stenosis should be targeted by therapy while CT-MPI could also detect perfusion defects

as a results of non-stenosis specific causes such as microvascular diseases. To our knowledge no prospective studies comparing CT-MPI and CT-FFR to PET-MPI, the gold standard technique for quantitative MPI analysis, actually exists in literature. Comparing CT-FFR and CT-MPI with PET-MPI could give better insight in the relationship between coronary flow and myocardial perfusion and helping in establishing the diagnostic value of both techniques for the detection of clinically significant CAD.

**C. PRELIMINARY STUDIES**

Our research group has a proven track record of conducting CT-MPI and CT-FFR studies. Our initial findings have been accepted and published in various journals:

1. van Assen, De Cecco et al. Prognostic value of CT myocardial perfusion imaging and CT-derived fractional flow reserve for major adverse cardiac events in patients with coronary artery disease. J Cardiovasc Comput Tomogr 2019;
2. van Assen, De Cecco et al. Iodine quantification based on rest / stress perfusion dual energy CT to differentiate ischemic, infarcted and normal myocardium. Eur J Radiol 2019;
3. van Assen, De Cecco et al. Intermodel disagreement of myocardial blood flow estimation from dynamic CT perfusion imaging. Eur J Radiol 2019;
4. Mastrodicasa, De Cecco et al. Artificial intelligence machine learning-based coronary CT fractional flow reserve (CT-$FFR_{ML}$): Impact of iterative and filtered back projection reconstruction techniques. J Cardiovasc Comput Tomogr 2018;
5. Tesche, De Cecco et al. Coronary CT Angiography-derived Fractional Flow Reserve: Machine Learning Algorithm versus Computational Fluid Dynamics Modeling. Radiology 2018;
6. Tesche, De Cecco et al. Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve for Therapeutic Decision Making. Am J Cardiol 2017;
7. Tesche, De Cecco et al. Coronary CT Angiography-derived Fractional Flow Reserve. Radiology 2017;
8. Duguay, De Cecco et al. Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve Based on Machine Learning for Risk Stratification of Non-Culprit Coronary Narrowing in Patients with Acute Coronary Syndrome. Am J Cardiol 2017;

9. Meinel, De Cecco et al. Prognostic Value of Stress Dynamic Myocardial Perfusion CT in a Multicenter Population with Known or Suspected Coronary Artery Disease. AJR Am J Roentgenol 2017;
10. Meinel, De Cecco et al. Global quantification of left ventricular myocardial perfusion at dynamic CT imaging: Prognostic value. J Cardiovasc Comput Tomogr 2017;
11. Caruso, De Cecco et al. Dynamic CT myocardial perfusion imaging. Eur J Radiol 2016;
12. Vliegenthart, De Cecco et al. Dynamic CT myocardial perfusion imaging identifies early perfusion abnormalities in diabetes and hypertension: Insights from a multicenter registry. J Cardiovasc Comput Tomogr 2016;
13. Wichmann, De Cecco et al. Semiautomated Global Quantification of Left Ventricular Myocardial Perfusion at Stress Dynamic CT: Diagnostic Accuracy for Detection of Territorial Myocardial Perfusion Deficits Compared to Visual Assessment. Acad Radiol 2016;
14. Wichmann, De Cecco et al. Absolute Versus Relative Myocardial Blood Flow by Dynamic CT Myocardial Perfusion Imaging in Patients with Anatomic Coronary Artery Disease. AJR Am J Roentgenol 2015;
15. Meinel, De Cecco et al. Global quantification of left ventricular myocardial perfusion at dynamic CT: feasibility in a multicenter patient population. AJR Am J Roentgenol 2014.

## D. RESEARCH DESIGN AND METHODS (including data analysis)

### D.1 Research Design

We propose enrolling Emory patients with suspected coronary artery disease (CAD) who are referred to undergo a clinically indicated PET-MPI for the analysis of myocardial perfusion. After the PET-MPI patients will be referred to a CT-MPI studies using the CT Force scanner in the Emory Clinic Tower. The CT examinations will be scheduled within 90 days of the PET examination. Patients will be excluded if they underwent prior cardiac interventions such as a PCI or CABG, or if they have any contra-indications for CT imaging. If patients receive a change in treatment such as medical adjustments or interventional treatment of their CAD, they will be excluded. Female subjects of childbearing potential will be given a urine pregnancy test prior to study enrollment. Pregnant persons will be excluded. We intend to use our

clinically established PET-CT and CT-MPI protocols with the administration of iodinated contrast media. The goal is to include 30 patients, of which 15 should have significant CAD.

**PET-MPI Protocol**

Patients with suspected CAD who are referred to a clinical PET-MPI will undergo the standard clinical protocol applied in the Emory Nuclear Medicine department. For technical details, please see the PET protocol form included as additional material in the section F.

**CT-MPI and CT-FFR Protocol**

**Image Acquisition**

The CT protocol will consist of a CT-MPI acquisition followed by a coronary CT angiography (CCTA) acquisition for the FFR assessment, and it will be performed on a 3rd generation dual-source scanner (Siemens Force) located in the Emory Tower. The CT-MPI acquisitions will be performed first to avoid interference of contrast agent contamination. Between the CT-MPI acquisition and the CCTA will be an adequate time interval to allow the outflow of contrast agent and for the patient to return to a full rest state. CT-MPI will be performed under stress, using the same stressor agent used in the PET-MPI examination to ensure optimal comparison conditions.

For the CT-MPI, dynamic volume CT myocardial perfusion applying the “dynamic shuttle” mode will be used to rapidly cover the entire cardiac anatomy during infusion of a contrast medium bolus for monitoring bolus passage through the left ventricular myocardium. The “dynamic shuttle” mode consists of an image acquisition during rapid, yet smooth back-and-forth movement of the CT scanner table, so that contrast media bolus passage can be evaluated within the entire left ventricle in a time-resolved fashion. This scan acquisition will be performed during pharmacologically induced stress and during rest conditions. CT-MPI studies will be contrast medium enhanced by 50-70 ml of iodinated contrast agent,

administered at a flow rate of 5 mL/s. CCTA will be performed for delineation of the coronary arteries, detection of potential coronary stenosis and FFR calculation. CCTA will be performed at rest following administration of intravenous contrast agent (50-70 mL of iodinated contrast material at a flow rate of 4-5 mL/s). A total radiation dose of approximately 8 mSv has expected to be administered with the stress/rest protocol to the patient. The total amount of contrast agent will not exceed 140 ml. Administration of any drugs will be performed by a physician or by a licensed Health Care Professional (nurse practitioner, physician assistant or registered nurse).

**Pharmaceutical stress protocol**

Pharmacological stress testing will be performed with a single injection of 0.4. mg of regadenoson (Lexiscan) *and any other drugs that they may be using to challenge the patients* under physician and nursing supervision. Based on experiences at nuclear myocardial perfusion imaging there is indication that regadenoson may have better patient tolerance, with less of the systemic effects (sensation of heat, flushing, tachycardia) compared to traditional adenosine. The usefulness of this drug over traditional adenosine has not been established for CT perfusion imaging. However, in previous studies we observed better patient tolerance of regadenoson also at CT, so that this will be our preferred drug for inducing pharmacological stress. Any adverse side effect (severe tachycardia, tachyarrhythmia, severe bradycardia, allergic reaction) causes the termination of the injection.

**Image Analysis**

In all patients CT coronary angiograms, acquired at rest, will be evaluated by consensus of two experienced investigators. Images will be analyzed by scrolling through the individual axial source images and by analyzing dedicated 2D and 3D visualization techniques such as Maximum Intensity Projection

(MIP) and 3D Volume Rendering (VRT). The central and peripheral coronary segments will be evaluated using the segmental model as used by the American Heart Association. For each segment the coronary-artery lumen will be classified as having 0% stenosis, <50% stenosis, ≥50% and ≤70% and >70% stenosis, or occluded.

Quantitative analysis of the PET-MPI and CT-MPI acquisition will be performed on per segment (AHA 17 segment model), per territory, per slice and per patient basis. Not only area specific MBF will be calculated but also global perfusion parameters will be taken into account. For the CT-MPI images, MBF will be calculated with different tracer kinetic models and using different temporal sampling rates in order to find the optimal protocol resulting in the highest diagnostic accuracy and lowest radiation dose possible. CT-FFR analysis as well as anatomical evaluation will be performed on all CCTA acquisitions, on per vessel as well as per patient level. Clinical data of the patients will be recorded, such as clinical risk factors, medication use etc. If the patients receive invasive coronary angiography (with or without invasive FFR measurements) or receive treatment after both PET-MPI and CT-MPI were performed, either medicational or interventional, this will be recorded. Readers will be blinded to the results of examinations.

**D.2 Statistical Methods / Sample Size Justification**

Statistical analysis and graphs will be performed with Sigma Stat 3.5, SigmaPlot 8.0, and Sample Power 2.0 (SPSS, Chicago, IL.). Disease information and demographic variables, such as age and sex, will be summarized by means of descriptive statistics. Data will be reported as means ±SD or rates with 95 percent confidence intervals. A difference with P value of 0.05 or less will be considered significant. Sensitivity, specificity, accuracy, negative predictive value and positive predictive value will be estimated by using generalized estimating equations, assuming that all measurements in each individual vessel and for each person will be correlated interchangeably. Accuracy of CT-MPI compared with PET-MPI for

detection and grading (in percent of the myocardial slice or myocardial infarct) of perfusion deficit and reduction in myocardial function will be compared. P values for comparisons of reader specific values will be calculated by means of the McNemar test. Kappa analysis will be used to determine agreement for the detection and grading of myocardial ischemic insult and/or infarction during adenosine-stress. This is a preliminary and pilot study, with a convenience sample of 30 patients, that we deem adequate to demonstrate our hypothesis. The analysis includes patient-based analysis and coronary artery-based analysis.

## E. PROTECTION OF HUMAN SUBJECTS

### E.1 RISK TO THE SUBJECTS

#### E.1.a Human Subject Involvement and Characteristics

We plan to recruit a total of 30 individuals (male, female; age range 18-85 years) referred to undergo a clinically indicated PET-CT examination. Patients will be identified from the Radiology department schedule. Study eligibility determination and study enrollment will be assessed and performed by a physician who is a principle investigator or a sub-investigator, as recorded with the IRB as being authorized to obtain informed consent. In the absence of exclusion criteria the responsible physician of record will be contacted, the study will be discussed and permission (or not) to approach the patient will be sought. At this time the potential use of beta-blockers will be discussed with the responsible physician of record, potential contraindications will be ruled out and permission to approach the patient for beta-blocker administration will be sought. The patient will be approached by IRB-approved study personnel under the direction of one of the licensed physician investigators listed on the study, either prior to or on the day of the planned PET-CT examination, with a full explanation and request for consent as required by the IRB. Emory policies regarding patient consent will be followed. The study design is not randomized.

**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 CT-MPI for CAD assessment.
2. Subject must be 18 – 85 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 ßHCG) within 24 hours before study agent administration, or
    - By surgical sterilization, or
    - Post menopausal, with minimum one (1) year history without menses.
2. Subject is currently taking or has taken within 48 hours the following excluded medications:

    ActoPlus Met (Pioglitazone + metformin)

    Avandamet (Rosiglitazone + metformin)

    Fortamet (metformin)

    Glucovance (Glyburide +metformin)

    Glucophage (metformin)

    Glucophage XR (metformin)

    Glumetza (metformin

    Janumet (Sitagliptin + metformin)

Metformin (metformin)

Metaglip (Glipizide + metformin)

Riomet (metformin)

3. Subject has an acute psychiatric disorder.
4. Subject is unwilling to comply with the requirements of the protocol.
5. Subject has previously entered this study.
6. Subject with known hypersensitivity to iodinated contrast material, beta-blockers, or pharmaceutical stressors used in this study.
7. Subject suffers from claustrophobia.
8. Subject has impaired renal function (GFR < 45 ml/min).
9. Acute hypotension (<100 mm Hg systolic).
10. Subject with 2nd or 3rd degree AV block.

Patients with heart rates >75 bpm will receive ß-blockers in order to level-down the heart rate. Patients with contraindications to the use of beta-blockers (chronic obstructive pulmonary disease, asthma sensitive to beta agonists, second- or third-degree heart block, hypotension (<100 mm Hg systolic) are in principle eligible for participation in the study, however, no beta-blockers will be used in such individuals. There will not be any eligibility criteria for any subpopulations. In addition, there will not be any 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. This research will only be conducted at the Emory University.

### E.1.b Sources of Materials

The research materials that will be obtained from living human subjects are: the cardiac CT-MPI, PET-MPI and all applicable other imaging studies (e.g. echocardiography), progress notes, medication records, vital signs, medical history and demographics and all other applicable clinical information.

The Principle 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 (Emory IRB auditors, etc.). All subject identities will be removed prior to publication.

### E.1.c Potential Risks

**Patient discomfort**

The study prolongs the discomfort for the patient of lying supine by approximately 20 minutes for the CT study. Subjects may find it uncomfortable to lie still during the scans; a cushioned mattress, and study duration of no more than 60 minutes room time will be used to minimize this discomfort.

**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 iodinated contrast media**

Despite excluding patients with known history of allergy to iodinated contrast material, there is a small risk that a patient will have an allergic reaction to contrast medium. In this event appropriate care will be administered by the physician supervising the scan acquisition in the study.

In patients with pre-existing renal dysfunction, iodinated contrast material may cause further deterioration in renal function. Therefore, patients with decreased renal function (GFR < 45 ml/min) will be excluded from this study. Large cohort studies and a recent meta-analysis have consistently demonstrated that there is no significant risk for post-contrast nephropathy from intravenous contrast material in patients with normal renal function (17–19).

**Risks from Contrast Media 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.

**Radiation exposure**

The study-related CT examination exposes the patient to additional ionizing radiation. There is a small stochastical risk of radiation-induced cancer from this additional radiation exposure. The population of patients undergoing cardiac imaging tests at our institution consists primarily in adults >50 years of age with significant cardiovascular risk factors. In this population, the risk of radiation-induced cancer from

cardiac CT has been estimated to be in the order of 1-in-2,000 individuals (20). Since the radiation dose with the state-of-the-art CT system utilized is expected to be substantially lower than standard cardiac CT, the risk is likely to be even smaller. In particular, the novel scanner is equipped with a novel selective photon shield which is expected to decrease radiation dose in particular for perfusion studies. In the majority of patients (those with a relatively regular heart rhythm), a prospectively ECG-triggered acquisition will be performed for the CT angiography, which allows for acquiring coronary CT angiography with a radiation dose of <3mSv and thus less than the radiation an average American receives annually from natural sources.

**Contrast and Drug Management**

The stock of contrast to be used for this study will be labeled with study specific identifiers tracking the administration and supply. Color coded tape and labeling will be placed over each bottle cap to prevent warm supply from being used incorrectly. The warmer located in the CT scanner suite will be used to keep the study contrast at required temperature. The supply of this contrast agent will be kept in a key locked drug cabinet, in a key locked. The records maintained for this contrast warmer are temperature, supply of contrast, and contrast bottle used for each patient.

**Beta Blocker**

Common side effects of the drug Metoprolol (a Beta-Blocker) used to slow down the heart rate are: Depression, diarrhea, dizziness, itching, rash, shortness of breath, slow heartbeat, tiredness. Rare side effects: Blurred vision, cold hands and feet, confusion, congestive heart failure (ineffective pumping of the heart leading to an accumulation of fluid in the lungs), constipation, difficult or labored breath.

**Nitrate (Nitroglycerine)**

Common side effects of the drug, Nitroglycerine (a Nitrate available in .4mg or .8mg for sublingual (under the tongue) administration are headache which may be severe and persistent and may occur immediately after use. Vertigo, dizziness, weakness, palpitation (irregular beatings of the heart), and other symptoms of postural hypotension (low blood pressure) may develop occasionally, particularly in upright, motionless subjects. Fainting, which may lead to falls and injuries has also been reported. Flushing, drug rash, and flaky skin have been reported in subjects receiving nitrate therapy.

**Regadenoson**

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. Regadenoson (Lexiscan) is injected as a 0.4 mg bolus under physician and nursing supervision. 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.

**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 (AT 503 Room). 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**

All subjects scheduled for a clinically indicated PET-MPI will potentially be eligible for inclusion into the study. Potential subjects will be identified via Radiology Department clinical schedules and consultation with PI according to satisfaction of the inclusion and exclusion criteria previously listed will be performed.

The PI, Sub-I(s) or the SC(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, costs, compensation, alternatives, new information procedures and privacy statements will be explained to the subject. The patient will be also asked in private if any coercion or undue inducement to the study exists. In case of positive answer, the patient will be excluded from the study and Emory IRB office will be notified.

The subject will be asked to verbally repeat pertinent study information to ensure subject understands the nature of the research, etc. 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 1) Person obtaining the informed consent, 2) witness 3) participant (subject) and 4) Legal Guardian (if applicable). A copy of the signed informed consent will be given to the subject.

**E.2.b Protection against Risk**

To minimize the risk of post-contrast nephropathy, patients with impaired renal function (estimated glomerular filtration rate <45 mL/min) will not be eligible for this study. To minimize the risk of allergic reactions to iodinated contrast material, patients with a history of allergic reactions to iodinated 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 department suite (Room AT503 ) in a research specific binder that will identify the subject on the outside of the binder 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

Since the CT examinations in this study are performed for research purposes and are not used for diagnostic purposes, there are no direct benefits for study participants. However, the knowledge gained from this study may benefit future patients undergoing CT-MPI and CT-FFR.

**Compensation to Participants**

Participants will be compensated with a $200.00 gift card to cover for parking, travel costs etc.

## E.4 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Knowledge gained during this study will enable an appreciation of the diagnostic accuracy of CT-MPI and CT-FFR in comparison to PET-MPI for diagnosis of coronary artery disease and give indications of potential impacts on clinical and diagnostic pathways. Furthermore, the diagnostic value of cardiac CT imaging in detection coronary stenosis may be improved.

## 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 Emory 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. Clinical Research Associate (CRA)) or sponsor but the results of the study will be written up as a paper and may be submitted as abstracts to various conferences. Every effort will be made to ensure patient safety and confidentiality.

## F. ADDITIONAL MATERIAL

**PET MPI Clinical Protocol**

EMORY
HEALTHCARE

| | |
|---|---|
| **PROCEDURE TITLE:** Rubidium PET Myocardial Perfusion Imaging | |
| **APPLICABLE FACILITIES:** (Check all that apply)<br>☐EUH ☐EUOSH ☐EWWH ☐EUHM ☐EJCH ☐ESJH ☐TEC ☐ESA ☐ERH | |
| **EFFECTIVE DATE:** 1/9/2019 | **ORIGINATION DATE: 1/9/19** |

**SCOPE:**
The myocardial perfusion study demonstrates the distribution of blood flow and perfusion to the myocardium at stress and rest. In addition, the eletrocardiographic gated study provides assessment of left ventricular wall motion and ejection fraction.

**PURPOSE:**
**INDICATIONS:** This protocol is designed for patients with or without prior history of coronary artery disease. To evaluate extent and severity of coronary artery disease, evaluate chest pain syndrome, document myocardial perfusion abnormalities before and after interventional therapy, surgical risk stratification. Rubidium PET should be preferred over SPECT in obese patients (>30 BMI), in patients with known multi-vessel disease, and to evaluate chest pain syndrome in patients admitted to the CDU. Inpatient requiring MPI, will preferably have a cardiac PET

**PROCEDURE:**
**EXAM TIME:** 30 min →Rest study: Rb infusion and image acquisition (7.5 minutes)
→Stress study: Rb infusion and image acquisition (7.5 minutes)

**PATIENT PREPARATION:**
a) The patient should be off:
   1. Beta-blockers up to 24-48 hours.
   2. Long acting nitrates for at least 4 hours, nitroglycerin for at least 1 hour.
   3. Calcium channel blockers 24-48 hours.
   4. Caffeine for 12 hours prior to pharmacologic stress with dipyridamole, adenosine, or regadenoson.
b) The patient will undergo pharm stress with Lexiscan according to the attached protocol.
c) The patient should be **fasting for a minimum 6 hours**.
d) Record the patient's height, weight, and all other clinical information as per database form.
e) Carefully instruct the patient not to move during the acquisition.

**RADIOPHARMACEUTICAL:** 30-60 mCi rest/ 30-60 mCi stress Rb-82 chloride

**TECHNIQUE OF ADMINISTRATION:**
Rest: intravenous infusion.
Stress: intravenous infusion.

**MATERIALS AND EQUIPMENT:**
Siemens Biograph 40 PET/CT camera

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HEALTHCARE

**INSTRUMENTATION & SETUP PARAMETERS:**
3D PET: 350-650 keV window

**PATIENT POSITIONING:** Supine with the arms placed above the patient's head. The patient should not move during acquisition.

**ACQUISITION PROTOCOL**
1. Start IV preferably in right hand.
2. Place 12-lead EKG electrodes for monitoring.
3. Blood pressure cuff should be positioned on the opposite arm from the IV or ankle.
4. Position patient in scanner with arms overhead
5. Start the CT scout, followed by a slow pitch rest CT attenuation scan under shallow breathing.
6. Start the Agatston scoring CT (breath hold, ECG gated)
7. Start the generator for rest Rb-82 infusion IV immediately followed by PET emission acquisition (7.5min) in list mode.
8. Inject Lexiscan 0.4 mg IV bolus over 10s followed by 5 mL saline flush. Immediately thereafter, start the generator for stress Rb-82 infusion IV as well as the PET emission acquisition (7.5 min) in list mode. Blood pressure and EKG should be monitored at one minute intervals.
9. Post-image processing for all cardiac studies is detailed below.

**DATA PROCESSING:**
The PET reconstruction quantitative processing is described below:
1. Calcium scoring CT, slow pitch CT, and reconstructed static rest and stress images are exported to the Leonardo workstation.
2. Technologist analyzes the fused CT and PET images to ensure proper image registration. Manufacturer-provided software will be used to correct for misalignment prior to final reconstruction of images.
3. Static images for tomographic display and gated images are reconstructed after applying a 2 min delay from start of rest and stress acquisitions. Longer delays may be needed in patients with low ejection fraction and increased blood pool activity at the discretion of the cardiac reader. OSEM iterative is used, 4 iterations, 16subsets, Gaussian post-filter 7 mm.
4. Quantitative processing is performed on the Emory Cardiac Toolbox Processing PC by a technologist with appropriate training in the used of the Toolbox. Care should be taken to complete the following sections:
   Parameters, Slices, Polar Maps, and Functional Analysis. Upon completion of processing a review file is automatically transferred to the reading room for physician review.

**OPTIONAL MANEUVERS:**
→"Stress" may be induced pharmacologically with adenosine or dipyridamole if regadenoson is not available.

**RELATED DOCUMENT(S)/LINK(S):**
N/A

**DEFINITIONS:** *(If applicable)*

EMORY HEALTHCARE

N/A

**REFERENCES AND SOURCES OF EVIDENCE:**

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**KEY WORDS: myocardial perfusion imaging, possitrom emission tomography, cardiac pet.**

| **REVIEW/APPROVAL SUMMARY:** Please select all Approving Bodies: | |
|---|---|
| ☐EUH MEC ☐ EUHM MEC ☐ESJH MEC ☐EJCH MEC ☐CNE Council ☐System Operations | |
| ☒Supervisor, Nuclear Medicine Raghuveer K. Halkar, MD; Director, Nuclear Medicine | |
| **REVIEW/REVISION DATES:** 1/9/2019 | **APPROVAL DATE:** 1/9/2019 |

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