Clinical Study Protocol

Use of Lexiscan™ for Myocardial Stress Perfusion Computed Tomography with a 3rd Generation Dual Source CT System

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Table of Contents

A. SPECIFIC AIMS

Primary Study Aim: The purpose of this study is to evaluate the feasibility, tolerability, safety, and image quality of low-radiation, dynamic perfusion CT of the heart in patients with suspected ischemic chest pain and a moderate or severe stenosis seen on coronary CTA.
The main hypothesis is that CTA with stress and rest perfusion imaging using Lexiscan™ as the coronary vasodilator will be safe, well tolerated, have lower radiation dose, acceptable image quality and be much faster than conventional nuclear perfusion imaging.

Secondary Study Aim: The secondary purpose of this study will be to assess the diagnostic accuracy of CT perfusion imaging compared to either SPECT, MRI stress perfusion, or invasive angiography.
Since we expect to be underpowered to prove that CT perfusion is noninferior to SPECT and/or MRI stress perfusion, we will not do any preplanned statistical comparison of the accuracy for diagnosing significant CAD between CT perfusion and SPECT/MRI stress perfusion. Because all patients will not have invasive angiography, we cannot do analysis for sensitivity or specificity for detection of CAD against this gold standard. Furthermore, we believe that SPECT is an imperfect gold standard against which to judge CT (i.e., SPECT has well known problems with specificity and to a lesser extent sensitivity). However, we will present the comparison of findings with each modality on a per-patient and per-segment basis so that they can be used to help plan subsequent larger, head to head studies that are powered to compare the accuracy of each modality.

B. BACKGROUND AND SIGNIFICANCE

Chest pain is one of the most common reasons for emergency department (ED) visits. Rapid and accurate identification of those with acute coronary syndromes allows immediate institution of appropriate treatment and safe discharge of those with non-cardiac causes of chest pain. Current approaches are time consuming, costly, and fraught with errors. A testimony to the problems of our current approach to evaluation of chest pain is the sobering report that more than 50% of patients undergoing invasive coronary angiography in this country are found to have nonobstructive coronary artery disease (CAD).[1] This most likely results from both false positive and false negative results from current noninvasive tests.[2] Several recent randomized trials have shown advantages of coronary CT angiography as the initial diagnostic test for patients presenting with chest pain in the ED setting.[3-5] However, two major concerns about the routine use of coronary CTA in ED patients with suspected cardiac ischemia are: 1) high radiation exposure from the CT scan, and 2) the problem of defining the significance of moderate stenosis identified on CT coronary imaging. The goal of this study is to address both of these issues by: 1) using a novel, 3rd generation CT scanner that is capable of coronary imaging and perfusion assessment at very low radiation doses, and 2) combining coronary (anatomic) imaging with rest and "stress" perfusion (functional) imaging using Lexiscan™ as the coronary vasodilating agent. Addition of perfusion imaging to the anatomic information provided by CTA has the potential to reduce the number of false positive interpretations and thereby improve specificity and positive predictive value.

C. PRELIMINARY STUDIES

Using 1st and 2nd generation dual source CT, we were the first group worldwide able to demonstrate the feasibility and usefulness of the assessment of myocardial perfusion with CT. Our initial findings have been accepted and published in various journals (e.g. Ruzsics Circulation 2008, Eur Radiol 2008,

and Am J Cardiol 2009; Bastarrika, Invest Radiol 2010, J Cardiovasc Comput Tomogr 2010; Meinel 2014, AJR Am J Roentgenol).

The SOMATOM™ Force is a new CT system, and currently no published data involving myocardial perfusion CT are available. However, the vendor has issued estimates on the enhanced performance of this new system that indicate a >20% reduction in radiation dose in all routine scans. Furthermore, cardiac imaging such as CTA and perfusion studies could result in up to a 50% reduction in total radiation dose. Given the technological advances detailed above we have confidence that these data will be realized in practice.

In addition, our research group has a proven track record of conducting CT studies on reductions in radiation dose and contrast material employing the previous generation of CT systems, such as the SOMATOM™ Definition and the SOMATOM™ Definition Flash. We have also conducted pioneering research in the novel applications of dual source CT with a focus on cardiovascular indications. In brief, these studies include the following:

- studies evaluating novel dose-lowering acquisition techniques such as ECG-dependent tube current modulation[8], anatomic tube current modulation[9], prospective ECG-triggering[10] and high-pitch acquisition[11]
- studies on optimizing contrast injection protocols[12-15]
- studies in specific patient populations such as obese patients[11] and pediatric patients[9,12]
- studies using novel reconstruction techniques for dose reduction[18,19]
- studies on specific difficult-to-image clinical scenarios, such as the evaluation of coronary stents[20-21] and heavily calcified coronary vessels[22].

D. RESEARCH DESIGN AND METHODS (INCLUDING DATA ANALYSIS)

D.1 RESEARCH DESIGN

This study will include 100 adults who present to the MUSC ED, hospital, or outpatient clinic with a clinical history and symptoms suspicious for cardiac ischemia and who have undergone or will likely undergo nuclear stress testing (SPECT) or who have undergone MRI stress perfusion imaging.

Patients who have been referred for a coronary CTA performed as part of a standard clinical evaluation determined by the treating physician(s) will be eligible for the study and recruited from the MUSC CT schedule. Before the patient comes in for their clinical coronary CTA, their cardiologist or primary physician will be contacted to ensure patient interest in the study and willingness to be approached. Willing patients will be approached and will undergo the informed consent process. Consented subjects will first undergo their clinically indicated coronary CTA; if there is no moderate or significant stenosis on the CTA following an initial interpretation (i.e., normal or near-normal coronary arteries), the patient will not undergo the stress CT perfusions portion of the study and will have their usual care without further testing for cardiac ischemia. However, these patients will be included in the data analysis, belonging to the negative CT population (see Patient Flow Chart below). Patients with moderate, indeterminate, or significant stenosis of any major or large branch epicardial vessel on the CTA will then undergo the stress CT perfusion study. According to current guidelines, it

is to be expected that this group of patients will also be clinically referred for further ischemia workup with either SPECT or coronary catheter angiography.

Patients who have undergone SPECT *without* referral for cardiac CTA will also be eligible for this study. For these patients, the coronary CT at rest will be performed as a research procedure followed by the stress portion of the CT perfusion study. No interpretation will be performed before the stress portion of the exam so all of these patients will receive the stress portion of the exam. These patients must have the clinically indicated SPECT as well as the research cardiac CTA with CT perfusion study completed within 60 days.

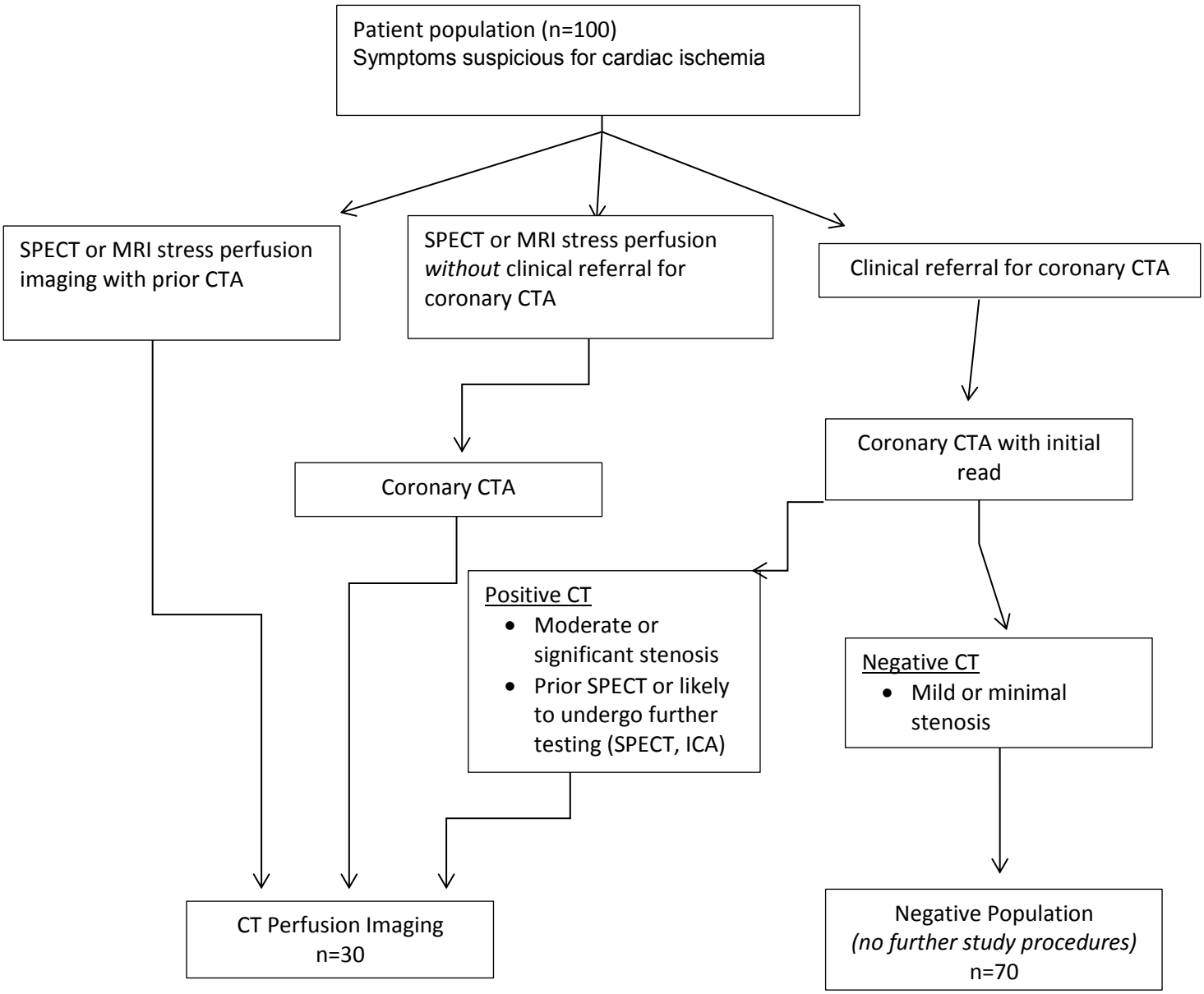
Patients who have undergone SPECT with a prior cardiac CTA will also be eligible for this study. These patients will only undergo the stress portion of CT perfusion study. These patients must have the clinically indicated cardiac CTA and SPECT as well as the research CT perfusion study completed within 60 days.

Patients who have undergone MRI perfusion imaging *without* referral for cardiac CTA will also be eligible for this study. For these patients, the coronary CT at rest will be performed as a research procedure followed by the stress portion of the CT perfusion study. No interpretation will be performed before the stress portion of the exam so all of these patients will receive the stress portion of the exam. These patients must have the clinically indicated MRI stress perfusion imaging as well as the research cardiac CTA with CT perfusion study completed within 60 days.

Patients who have undergone MRI stress perfusion imaging with a prior cardiac CTA will also be eligible for this study. These patients will only undergo the stress portion of CT perfusion study. These patients must have the clinically indicated cardiac CTA and SPECT as well as the research CT perfusion study completed within 60 days.

The CT perfusion scans will be analyzed and read by two highly trained CT readers (cardiologist and radiologist). In addition to assessing the safety and tolerability of the Lexiscan™ perfusion study, the CT perfusion findings will be compared diagnostically to SPECT and/or invasive catheter angiography if this is performed clinically after the research procedure.

Patient Flow Chart



Patients with heart rates > 65 bpm may receive beta-blockers in order to reduce their heart rate to values < 60 bpm. 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 as defined by systolic blood pressure <100 mmHg) are in principle eligible for participation in the study – however, no beta-blockers will be used in such individuals. Patients will receive nitroglycerin based on investigator judgment to better visualize the coronary arteries. Female subjects of childbearing potential will be given a urine pregnancy test prior to study enrollment. Pregnant persons will be excluded. Patients will receive a point-of-care serum creatinine test on the day of their research procedure before any contrast administration and patients with a serum creatinine greater than or equal to 1.5 mg/dL will be excluded from the study.

CT Coronary Angiography Protocol:
Studies will be performed using a 3rd generation, dual source CT scanner capable of coronary imaging at < 1mSv (Siemens, SOMATOM™ Force). The coronary CTA will be performed based on standard clinical indications that conform to published appropriate use criteria. The scan will be done using our usual clinical protocol with administration of 30 – 60 cc of an intravenous contrast agent (Ultravist 370). Acquisition mode (axial, prospective, retrospective or flash) is chosen based on heart rate, rhythm and body size. We will accept patients who have the SPECT study done within 30 days of the scheduled CTA and/or research scan(s).

Pharmaceutical Stress Protocol:
Pharmacological stress testing will be performed with a single injection of 0.4. mg of regadenoson (Lexiscan™) under physician and nursing supervision per MUSC clinical protocol. The cardiologist responsible for clinical stress administration will review a pre-Lexiscan™ EKG and patient medical history to ensure Lexiscan™ can be administered safely. A post-Lexiscan™ EKG will be obtained and read and the cardiologist will determine if and when the patient can be discharged safely.

Analysis of CT Coronary Angiography Images:
CT coronary angiograms will be evaluated by consensus of two experienced investigators. Images will be analyzed using both axial source images and by analyzing dedicated 2D and 3D visualization techniques such as Maximum Intensity Projection (MIP), curved Multiplanar Reconstruction (MPR) and 3D Volume Rendering (VRT).

CT myocardial perfusion protocols:
Patients will undergo dynamic, first pass, stress perfusion imaging during maximal hyperemia induced with Lexiscan™. Imaging will commence approximately 90 seconds after a bolus of Lexiscan™ (0. 4 mg per each 5 mL injection). The Lexiscan™ is followed immediately by a bolus of 10 cc saline. In order to achieve the correct timing of the dynamic image acquisition, contrast administration will begin approximately 80 seconds after the Lexiscan™ bolus to allow the contrast to reach the heart at the moment of maximal hyperemia. Data will be acquired for 30 seconds with both X-ray tubes set at 80 – 100 kV, a gantry rotation time of 0.28 seconds, and a tube current of 300 mAs per rotation. Temporal resolution is approximately 75 ms. Patients will be instructed to hold their breath for the first 15 seconds of the scan, as this is the most important portion of the data acquisition for quantifying myocardial blood flow. They will then be instructed to breath shallowly for the remaining 15 seconds. Perfusion imaging is performed in an ECG-triggered shuttle mode in which the table shifts between two z-positions of the heart to allow coverage of nearly the entire left ventricle. End systolic imaging is used to reduce motion artifacts, to image the heart at its smallest dimensions, and to reduce beam-hardening artifacts from contrast in the LV cavity. The relatively fast rotation time combined with the dual source system gives markedly improved temporal resolution, which helps to reduce motion artifacts associated with the rise in heart rate that frequently occurs after Lexiscan™ administration. With a detector width of 38 mm and 10% overlap between the two imaging positions, the coverage of the acquisition is 73 mm. In some patients, small portions of the base or apex could be cut off. A total of 14 or 15 image volumes during myocardial passage of the contrast bolus will be acquired. CT MPI studies will use 40 – 50 mL of contrast agent (Ultravist 370) administered at a flow rate of 4 – 6 mL/s. Following the perfusion imaging, the Lexiscan™ will be

reversed with 1 mg/kg of aminophylline per standard clinical protocol if indicated by the supervising physician.

CT Perfusion Data Reconstruction and Analysis:
Dynamic CT MPI data are reconstructed with a section thickness of 3 mm and a 2 mm increment with a medium smooth convoluted kernel (B30). The data are processed with the volume perfusion CT body application software and workstation (Siemens). After motion correction and 4D noise reduction, a double arterial input function is defined by placement of ROIs in the descending aorta in the cranial and caudal regions of the covered volume. After a volume of interest is manually defined around the left ventricle, the left ventricular myocardium is automatically segmented. A dedicated parametric deconvolution algorithm based on a two-compartment model of intravascular and extravascular space is used to derive myocardial blood flow and the volume transfer constant (k^{trans}) from the time-attenuation curves for each voxel.[23]

Quantitative Measures of Myocardial Blood Flow from CT:
CT perfusion images will be analyzed on a dedicated console using commercially available software (Syngo Volume Perfusion™) as previously described.[24] Evidence of ischemia will be determined initially by visual comparison of rest and stress CT perfusion scans. Perfusion defects will be visually rated as reversible (only present at stress), fixed (present at both rest and stress) and mixed (more pronounced at stress, partly reversible at rest). Quantitative analysis of myocardial perfusion will be performed and mean blood volume (MBV), mean blood flow (MBF), and mean transit time (MTT) of each myocardial segment will be recorded. Readers will be blinded to the results of SPECT or invasive angiography examinations. The values obtained will be compared to historical published values for each parameter (MBF, MBV, and MTT) obtained using older generation CT perfusion protocols, MRI perfusion, or dynamic perfusion scanning.

Analysis of SPECT images:
SPECT will be used as a comparator for the CT perfusion images. SPECT examinations will be interpreted for perfusion defects by two experienced readers (one nuclear medicine physician and one cardiologist). Images will be analyzed on a dedicated console using commercially available software. Evidence of ischemia will be determined by visual comparison of rest and stress SPECT perfusion scans as well as quantitative analysis available through the commercial analysis program. Perfusion defects will be visually rated as reversible, fixed, or mixed. Readers will be blinded to the results of CT perfusion data and invasive coronary angiography examinations.

Analysis of MRI stress perfusion images:
MRI stress perfusion imaging will be used as a comparator for the CT perfusion images. MRI examinations will be interpreted for perfusion defects by two experienced readers (one radiologist and one cardiologist). Images will be analyzed on a dedicated console using commercially available software. Evidence of ischemia will be determined by visual comparison of rest and stress MRI perfusion scans as well as quantitative analysis available through the commercial analysis program. Perfusion defects will be visually rated as reversible, fixed, or mixed. Readers will be blinded to the results of CT perfusion data and invasive coronary angiography examinations.

Image Quality:
Subjective assessment of image quality, coronary artery visualization, and perfusion images will be performed by two independent observers using a semiquantitative rating scale of 0 – 5. Image quality will be graded on a five-point scoring system: 1 non-diagnostic; 2 limited diagnostic value; 3 adequate (presence of artifacts not limiting detection of luminal stenosis); 4 good; 5 excellent.

All measurements and calculations will be performed by one observer who will be blinded to image acquisition parameters. We will also measure the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) for the coronary CTA and the perfusion images. Circular regions of interest will be placed in the aortic root at the level of the left main coronary artery ostium (size 100 mm^2) as well as in the proximal segments of the left and right coronary arteries and the left lateral ventricular wall (size 1 – 4mm^2). Signal intensity (CT number in HU) and noise (HU standard deviation) will be recorded in each region. All regions-of-interest will be measured three times and mean measurements will be used for statistical analysis. The SNR will be calculated as the mean HU divided by the mean image noise measured in the aorta. The CNR will be calculated by subtracting the mean HU in the left lateral ventricular wall from the mean HU within the lumen of the proximal coronary arteries and dividing this difference by the image noise measured in the aorta.[26] These values (SNR and CNR), although standard measures of image quality in CT research, cannot be compared directly between CT and SPECT. However, they can be used as a quantitative gauge to compare image quality between the 3rd generation CT scanner with low radiation imaging and the older CT perfusion scans that required higher radiation exposure.

Analysis of radiation dose:
The CT dose index and dose-length product will be recorded by the scanner and collected for each image acquisition. Effective radiation dose will be calculated by using a standard conversion factor of 0.0145 for adult chest CT [27]. For SPECT examinations, the effective radiation dose will be estimated by multiplying the administered activity of ^{99m}Tc-tetrofosmin with a tracer-specific conversion factor of 0.008 for rest and 0.0069 for stress acquisition. The effective radiation doses of rest and stress SPECT acquisition with then be combined to computer the net radiation dose[28]. The radiation dose of the CT myocardial perfusion will be compared with the radiation dose obtained with the previous (older) scanner at our institution in order to have a direct comparison of the radiation exposure decrease to the patient. Patients who have MRI stress perfusion imaging as the comparative imaging study will be excluded from the radiation dose analysis.

Safety and Tolerability Assessment:
A checklist will be made and each of the following events will be assessed by an investigator or designated personnel:

1. Hypotension (systolic BP < 90 or > 30 mm Hg decrease from baseline)
2. Hypertension (systolic BP > 200 mmHg)
3. Significant new heart block (type II 2nd degree or 3rd degree A-V block)
4. Bradycardia (heart rate < 45 bpm, sinus bradycardia or junctional rhythm)
5. Bronchospasm (requiring inhaler or other medical treatment)
6. Allergic reaction (hives, erythema, wheezing)

7. Chest pain
8. Nausea
9. Headache
10. Seizures

Additionally, a patient satisfaction questionnaire (detailed below) will be administered to all patients who undergo the CT perfusion scan following the research scan as well as a 30-day event rate (MACE defined by ED visit, hospitalization, ACS/MI, stroke, revascularization, significant new arrhythmia and death) will be assessed by chart review and follow-up phone call one month (+/- 3 days) from the scan.

Patient Satisfaction Survey:

Following the CT perfusion scan, the patient will be given a participant satisfaction survey. The purpose of this survey is to assess the patients' subjective experience with the different imaging modalities (CT vs. SPECT/MRI stress perfusion imaging). The seven question survey will assess: 1) the patient's perception of the overall ease or difficulty of the study, 2) length of the study, 3) perceived discomfort, 4) level of apprehension, 5) understanding of the nature of the test, 6) understanding of the results and 7) willingness to undergo the test again. Each question will have a quantitative score of 1 – 4. Patients who have not yet undergone SPECT imaging at the time will be asked the SPECT specific questions at the time of the 30-day follow-up if they have undergone the SPECT testing at that time. If not, the patient will not be asked the SPECT questionnaire.

D.2 STATISTICAL METHODS / SAMPLE SIZE JUSTIFICATION

This study is intended to primarily demonstrate feasibility, safety, and tolerability of Lexiscan™ for use as a coronary vasodilator during perfusion CT imaging. The study is not powered to prove the diagnostic accuracy of perfusion CT imaging with low radiation compared to SPECT or the current gold standard approach of invasive coronary angiography with invasive fractional flow reserve (FFR) measurement. Nonetheless, we will use the available comparative data for each technique (SPECT, MRI stress perfusion imaging, and invasive angiography) to help design subsequent clinical trials that are adequately powered for an accuracy endpoint. We anticipate that about 15 out of the 30 participants who undergo the CT perfusion portion of the study will have available cath comparisions.

Continuous data are displayed as mean ± SD, if normally distributed, or median and interquartile range if not normally distributed. Binary data are are displayed as proportions. 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.

Subjective image quality scores will be compared using the Chi-squared test with the Yates continuity correction for categorical variables and inter-observer agreement for image quality will be calculated using Cohen kappa (K) 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. For each group, comparisons of patient characteristics will be performed using the Chi-squared test for categorical variables and t-test or Mann-Whitney-U-test for continuous variables as appropriate.

Quantitative data (CNR, radiation dose) will be tested using a non-parametric significance test.

We will present comparisons of normal or abnormal perfusion determined from SPECT/MRI stress perfusion imaging or CT perfusion using the standard 17-segment model. We will also present a comparison of ischemia by CT perfusion (based on vascular territory) compared to anatomic evidence of significant CAD at catheterization. Any segments cut off by the limited z-axis scan range on perfusion CT will be excluded. Given 30 patients, we will have a maximum of 510 regions available to compare CT perfusion and SPECT/MRI stress perfusion. We will first perform a binary analysis where each segment is classified as either normal or abnormal, since the relative severity of perfusion defects has not been defined for CT. If feasible based on the number of patients with SPECT/MRI stress perfusion scans scans, we will compare the number of abnormal segments in each patient by each methodology using a kappa statistic. We will also use standard SPECT/MRI stress perfusion grading of perfusion (1 – 4 scale) and a similar scale for CT perfusion defect severity (also 1 – 4) based on prior measurements of absolute myocardial perfusion (ml/100 ml/min) with each segment graded as 1, 2, 3 or > 4 standard deviations from the norm. We will then perform linear regression (Pearson's correlation) to derive R values for CT perfusion versus SPECT/MRI stress perfusion imaging perfusion grade for each segment.

E. PROTECTION OF HUMAN SUBJECTS

E.1 RISK TO THE SUBJECTS

E.1.a Human Subject Involvement and Characteristics

This study will include 100 adults who present to the MUSC ED, hospital, or outpatient clinic with a clinical history and symptoms suspicious for cardiac ischemia and who have undergone or will likely undergo nuclear stress testing (SPECT).

Patients who have been referred for a coronary CTA performed as part of a standard clinical evaluation determined by the treating physician(s) will be eligible for the study and recruited from the MUSC CT schedule. Before the patient comes in for their clinical coronary CTA, their cardiologist or primary physician will be contacted to ensure patient interest in the study and willingness to be approached. Willing patients will be approached and will undergo the informed consent process. Consented subjects will first undergo their clinically indicated coronary CTA; if there is no moderate or significant stenosis on the CTA following an initial interpretation (i.e., normal or near-normal coronary arteries), the patient will not undergo the stress CT perfusion portion of the study and will have their usual care without further testing for cardiac ischemia. However, these patients will be included in the data analysis, belonging to the negative CT population. Patients with moderate, indeterminate, or significant stenosis of any major or large branch epicardial vessel on the CTA will then undergo the stress CT perfusion study. According to current guidelines, it is to be expected that this group of patients will also be clinically referred for further ischemia workup with either SPECT or coronary catheter angiography.

We will also target patients who have undergone SPECT without referral for cardiac CTA; in this case, the coronary CT at rest will be performed as a research procedure with the stress portion following in all cases. The CT perfusion scans will be analyzed and read by two highly trained CT readers (cardiologist and radiologist). In addition to assessing the safety and tolerability of the Lexiscan™ perfusion study, the CT perfusion findings will be compared diagnostically to SPECT and/or invasive catheter angiography if this is performed clinically after the research procedure. These patients must have the clinically indicated SPECT as well as the research cardiac CTA with CT perfusion study completed within 60 days.

Patients who have undergone SPECT with a prior cardiac CTA will also be eligible for this study. These patients will only undergo the stress portion of CT perfusion study. These patients must have the clinically indicated cardiac CTA and SPECT as well as the research CT perfusion study completed within 60 days.

Patients who have undergone MRI perfusion imaging *without* referral for cardiac CTA will also be eligible for this study. For these patients, the coronary CT at rest will be performed as a research procedure followed by the stress portion of the CT perfusion study. No interpretation will be performed before the stress portion of the exam so all of these patients will receive the stress portion of the exam. These patients must have the clinically indicated MRI stress perfusion imaging as well as the research cardiac CTA with CT perfusion study completed within 60 days.

Patients who have undergone MRI stress perfusion imaging with a prior cardiac CTA will also be eligible for this study. These patients will only undergo the stress portion of CT perfusion study. These patients must have the clinically indicated cardiac CTA and SPECT as well as the research CT perfusion study completed within 60 days.

Only patients with initially negative biomarkers and non-specific-ECG findings will be considered for inclusion in the study in accordance with the Lexiscan package insert. Patients will be screened by approved study personnel from the MUSC SPECT and CT schedules 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 potential use of Lexiscan™ and beta-blockers will be discussed with the responsible physician of record, potential contraindications will be ruled out and permission to approach the patient for possible inclusion will be sought. If the patient is agreeable, they will be approached by one of the licensed physician investigators or designated study coordinators listed on the protocol either prior to or on the day of the CT scan, with a full explanation and request for consent as required by the IRB. MUSC policies regarding patient consent will be followed.

The study will be performed in tight collaboration between the Department of Radiology and the Divisions of Cardiology and Emergency Medicine.

Inclusion criteria:

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

1. Subject must present with symptoms (e.g. chest pain) suspicious for cardiac ischemia as determined by treating physician.
2. Subject must have been referred for cardiac CT angiography OR subject must have undergone clinically indicated SPECT OR subject must have undergone clinically indicated SPECT with prior cardiac CT angiography OR subject must have undergone a clinically indicated MRI stress perfusion imaging.
3. Subject must be 18 – 85 years of age.
4. Subject must provide written informed consent prior to any study-related procedures being performed.
5. 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 agent administration, or
    - By surgical sterilization, or
    - Post menopausal, with minimum one (1) year history without menses.
2. Subject has severe asthma or COPD requiring frequent inhaler use.
3. Subject has prior diagnosis of obstructive CAD that has not been revascularized.
4. Subject with implanted rhythm devices (pacemaker, defibrillator).
5. Subject has significant arrhythmia.
6. Subject has high grade heart block.
7. Subject has resting heart rate < 45 bpm, systolic blood pressure <90 mm Hg, or has consumed caffeine within the last 12 hours.
8. Subject has an acute psychiatric disorder.
9. Subject is unwilling to comply with the requirements of the protocol.
10. Subject has previously entered this study.
11. Subject has an allergy against iodinated contrast agents or pharmaceutical stressors used in this study.
12. Subject suffers from claustrophobia.
13. Subject has impaired renal function (creatinine > 1.5 mg/dl).
14. Subject is in unstable condition.
15. ST-elevations, new transient ST changes greater than 0.05mV or T- wave inversions with symptoms
16. Subject cannot safely be administered Lexiscan™ per prescribing information as determined by investigator
17. Subject has received interventional (PCI, stenting) or surgical (CABG) treatment that may alter the cardiac condition regarding myocardial perfusion status and/or stenosis degree between cardiac CTA, SPECT, MRI, and/or CT stress perfusion studies.

Patients with heart rates >65 bpm may receive beta-blockers in order to lower the heart rate to values <60 bpm. 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 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. This research will only be conducted at the Medical University of South Carolina.

Targeted/Planned Enrollment Table

Total Planned Enrollment: 100

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	0	0	0
Not Hispanic or Latino	50	50	100
Ethnic Category: Total of All Subjects*	100		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	17	17	34
White	33	33	66
Racial Categories: Total of All Subjects*	50	50	100

E.1.b Sources of Materials

The research materials that will be obtained from living human subjects are: the cardiac SPECT, MRI stress perfusion, coronary catheterization, CT, 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 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.

E.1.c Potential Risks

Patient discomfort

The study prolongs the discomfort for the patient of lying supine by approximately 30 minutes for the CT study. Subjects may find it uncomfortable to lie still during the scans. A 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, the physician supervising the scan acquisition in the study will administer appropriate care.

In patients with pre-existing renal dysfunction, iodinated contrast material may cause further deterioration in renal function. Therefore, patients with decreased renal function (more than or equal to 1.50 mg/dl serum creatinine) 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.[24-26]

Radiation exposure
The study-related CTMPI examination exposes the patient to additional ionizing radiation. There is a small stochastic risk of radiation-induced cancer from this additional radiation exposure. The population of patients undergoing cardiac imaging tests at our institution consists primarily of adults >50 years of age that have 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.[29] Since the radiation dose with the new CT system is expected to be substantially lower, 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; this is discussed in more detail in section E of the supporting document attached to this application.

Contrast and Drug Management
The clinical stock of contrast will be used for this study and will be labeled with study specific identifiers tracking the administration and supply. The warmer located in the dual source CT scanner suite will be used to keep the study contrast at required temperature and contrast will not be kept longer than 30 days in the warmer per MUSC policy. The records maintained for the contrast warmer and contrast supply are: temperature, supply of contrast, and contrast bottle used for each patient.

Drugs will be ordered and dispensed from the MUSC inpatient pharmacy per clinical protocol.

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. 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.

Beta Blocker (Lopressor)

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, and tiredness. Rare side effects are: 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 0.4 mg or 0.8 mg for sublingual (under the tongue) administration include 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.

Use of Regadenoson

The following reactions are listed as warnings and precautions when using regadenoson (Lexiscan™, injected as a 0.4 mg bolus): myocardial ischemia, sinoatrial and atrioventricular nodal block, hypotension, and 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, and feeling hot. 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.

CT Examination performed with the new Force scanner

The Siemens SOMATOM™ Force is a new computed Tomography X-ray system, which is substantially equivalent to the previous systems (SOMATOM™ Definition and the SOMATOM™ Definition Flash). The SOMATOM™ Force scanner received 510(k) FDA-approval for clinical use on the 17th April 2014.

The SOMATOM™ Force scanner has been used for two other research studies with excellent results. The risks associated with this CT scanner are comparably low to other CT scanners.

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 coronary CTA performed as part of a standard clinical evaluation determined by the treating physician(s) will be eligible for the study and recruited from the MUSC CT schedule. Before the patient comes in for their clinical coronary CTA, their cardiologist or primary physician will be contacted to ensure patient interest in the study and willingness to be approached. Willing patients will be approached and will undergo the informed consent process. Consented subjects will first undergo their clinically indicated coronary CTA; if there is no moderate or significant stenosis on the CTA following an initial interpretation (i.e., normal or near-normal coronary arteries), the patient will not undergo the stress CT perfusion portion of the study and will have their usual care without further testing for cardiac ischemia. However, these patients will be included in the data analysis, belonging to the negative CT population. Patients with moderate, indeterminate, or significant stenosis of any major or large branch epicardial vessel on the CTA will then undergo the stress CT perfusion study. According to current guidelines, it is to be expected that this group of patients will also be clinically referred for further ischemia workup with either SPECT or coronary catheter angiography.

We will also target patients who have undergone SPECT without referral for cardiac CTA; in this case, the coronary CT at rest will be performed as a research procedure with the stress portion following in all cases. The CT perfusion scans will be analyzed and read by two highly trained CT readers (cardiologist and radiologist). In addition to assessing the safety and tolerability of the Lexiscan™ perfusion study, the CT perfusion findings will be compared diagnostically to SPECT and/or invasive catheter angiography if this is performed clinically after the research procedure. These patients must have the clinically indicated SPECT as well as the research cardiac CTA with CT perfusion study completed within 60 days.

Patients who have undergone SPECT with a prior cardiac CTA will also be eligible for this study. These patients will only undergo the stress portion of CT perfusion study. These patients must have the clinically indicated cardiac CTA and SPECT as well as the research CT perfusion study completed within 60 days.

Patients who have undergone MRI perfusion imaging *without* referral for cardiac CTA will also be eligible for this study. For these patients, the coronary CT at rest will be performed as a research

procedure followed by the stress portion of the CT perfusion study. No interpretation will be performed before the stress portion of the exam so all of these patients will receive the stress portion of the exam. These patients must have the clinically indicated MRI stress perfusion imaging as well as the research cardiac CTA with CT perfusion study completed within 60 days.

Patients who have undergone MRI stress perfusion imaging with a prior cardiac CTA will also be eligible for this study. These patients will only undergo the stress portion of CT perfusion study. These patients must have the clinically indicated cardiac CTA and SPECT as well as the research CT perfusion study completed within 60 days.

Only patients with initially negative biomarkers and non-specific-ECG findings will be considered for inclusion in the study in accordance with the Lexiscan package insert. Patients will be screened by approved study personnel from the MUSC SPECT and CT schedules 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 potential use of Lexiscan™ and beta-blockers will be discussed with the responsible physician of record, potential contraindications will be ruled out and permission to approach the patient for possible inclusion will be sought. If the patient is agreeable, they will be approached by one of the licensed physician investigators or designated study coordinators listed on the protocol either prior to or on the day of the CT scan, with a full explanation and request for consent as required by the IRB. MUSC policies regarding patient consent will be followed.

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 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 iodinated contrast material, patients with a history of allergic reactions to iodinated contrast material will also be excluded.

Clinical procedures involving Lexiscan™ administration in the Radiology department will be followed: Lexiscan™ administration will be supervised by a licensed cardiologist who will review the patient's medication and medical history for contraindications before the scan, read the patient's pre-scan EKG, be present for Lexiscan™ administration, read the patient's post-scan EKG, and approve the

patient's discharge from the Radiology department. Cardiac resuscitation equipment will be available throughout the scan.

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

Since the 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 myocardial perfusion imaging. Substantial reductions in radiation dose are expected with the new CT systems. Considering that ionizing radiation is thought to carry a small stochastic risk of inducing cancer, the dose reduction further reduces this theoretical risk. Furthermore, because of the higher attenuation of iodine at low photon energies, the novel CT system can be expected to substantially decrease the amount of contrast material required for CT cardiac perfusion examinations. The small risk of compromising renal function by administration of iodinated contrast material in patients with preexisting renal disease can thus be further minimized.

E. 4 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Knowledge gained during this study will enable an appreciation of the diagnostic accuracy of Ct cardiac perfusion imaging in comparison SPECT and invasive angiography for diagnosis of acute chest pain and give indications of potential impacts on clinical and diagnostic pathways.

Furthermore, data from this study may potentially allow for substantial reductions in radiation dose and contrast material volume of CT examinations with new CT systems thus further minimizing the small risks of radiation-induced cancer and post-contrast nephropathy. Furthermore, the diagnostic value of 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 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 SOMATOM™ Force on which the myocardial CT perfusion scan will occur. Nursing and physician preparation and monitoring of the patient, including EKG reading and the serum creatinine test, will occur in the patient bays of the Radiology department.

Cardiac catheterization will occur clinically in the Heart and Vascular Center on the 3rd floor of the Ashley River Tower. Clinical SPECT imaging will occur on the 1st floor of the Ashley River Tower. Clinical CTA imaging will occur either in the Radiology department on the 2nd floor of the Ashley River Tower or in the Radiology Department of the MUSC Main Hospital.

G. APPENDIX

The patient satisfaction survey is as follows:

Patient Satisfaction Survey (SPECT/MRI Stress Perfusion)	
How easy or difficult did you find the SPECT or MRI stress perfusion procedure?	**(1)** Very Easy **(2)** Easy **(3)** Difficult **(4)** Very Difficult
How do you feel about the length of the SPECT or MRI stress perfusion procedure?	**(1)** Very Short **(2)** Short **(3)** Long **(4)** Very Long
How much discomfort did you experience during the SPECT or MRI stress perfusion procedure?	**(1)** No Discomfort **(2)** Some Discomfort **(3)** Moderate Discomfort **(4)** A Lot of Discomfort

How nervous were you before and during the SPECT or MRI stress perfusion procedure?	**(1)** Not Nervous **(2)** Somewhat Nervous **(3)** Moderately Nervous **(4)** Very Nervous
How well do you feel that you understand the SPECT or MRI stress perfusion procedure?	**(1)** Very Much Understand **(2)** Moderately Understand **(3)** Somewhat Understand **(4)** Don't Understand
How well do you feel that you understand the results of the procedure?	**(1)** Very Much Understand **(2)** Moderately Understand **(3)** Somewhat Understand **(4)** Don't Understand
How willing would you be to undergo the SPECT or MRI stress perfusion procedure again?	**(1)** Very Willing **(2)** Somewhat Willing **(3)** Somewhat Unwilling **(4)** Not at All Willing

Patient Satisfaction Survey (CT Perfusion Scan)	
How easy or difficult did you find the CT Perfusion Scan procedure?	**(1)** Very Easy **(2)** Easy **(3)** Difficult **(4)** Very Difficult
How do you feel about the length of the CT Perfusion Scan procedure?	**(1)** Very Short **(2)** Short **(3)** Long **(4)** Very Long
How much discomfort did you experience during the CT Perfusion Scan procedure?	**(1)** No Discomfort **(2)** Some Discomfort **(3)** Moderate Discomfort **(4)** A Lot of Discomfort

How nervous were you before and during the CT Perfusion Scan procedure?	**(1)** Not Nervous **(2)** Somewhat Nervous **(3)** Moderately Nervous **(4)** Very Nervous
How well do you feel that you understand the CT Perfusion Scan procedure?	**(1)** Very Much Understand **(2)** Moderately Understand **(3)** Somewhat Understand **(4)** Don't Understand
How well do you feel that you understand the results of the procedure?	**(1)** Very Much Understand **(2)** Moderately Understand **(3)** Somewhat Understand **(4)** Don't Understand
How willing would you be to undergo the CT Perfusion Scan procedure again?	**(1)** Very Willing **(2)** Somewhat Willing **(3)** Somewhat Unwilling **(4)** Not at All Willing

H. REFERENCES

1. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, and Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886-95.
2. Schuifj JD, Wijns W, Jukema JW, Atsma DE, de Roos A, Lamb HJ, Stokkel MP, Dibbets-Schneider P, Decramer I, De Bondt P, van der Wall EE, Vanhoenacker PK and Bax JJ. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. *J AM Coll Cardiol*. 2006;48:2508-14.
3. Nagori M, Narain VS, Saran RK, Dwivedi SK and Sethi R. Efficacy of multi-detector coronary computed tomography angiography in comparison with exercise electrocardiogram in the triage of patients of low risk acute chest pain. *Indian heart journal* 2014;66:435-42.
4. Cury RC, Budoff M and Taylor AJ. Coronary CT angiography versus standard of care for assessment of chest pain in the emergency department. *J Cardiovasc Comput Tomogr*. 2013;7:79-82.
5. Hulten E, Goehler A, Bittencourt MS, Bamberg F, Schlett CL, Truong QA, Nichols J, Nasir K, Rogers IS, Gazelle SG, Nagurney JT, Hoffmann U and Blankstein R. Cost and resource utilization associated with use of computed tomography to evaluate chest pain in the emergency department: the Rule Out Myocardial Infarction using Computer Assisted

Tomography (ROMICAT) study. *Circulation Cardiovascular quality and outcomes*. 2013;6:514-24.
6. Jakobs TF, Becker CR, Ohnesorge B, Flohr T, Suess C, Schoepf UJ, Reiser MF. Multislice helical CT of the heart with retrospective ECG gating: reduction of radiation exposure by ECG-controlled tube current modulation. *Eur Radiol*. 2002;12:1081-1086.
7. Herzog C, Mulvihill DM, Nguyen SA, Savino G, Schmidt B, Costello P, Vogl TJ, Schoepf UJ. Pediatric cardiovascular CT angiography: radiation dose reduction using automatic anatomic tube current modulation. *AJR Am J Roentgenol*. 2008;190:1232-1240.
8. Arnoldi E, Ramos-Duran I, Abro JA, Zwerner PL, Nikolaou K, Reiser MF, Costello P, Schoepf UJ. [Coronary CT angiography using prospective ECG triggering: high diagnostic accuracy with low radiation dose]. *Radiologe*. 2010;50:500-506.
9. Yin WH, Lu B, Hou ZH, Li N, Han L, Wu YJ, Niu HX, Silverman JR, Nicola De Cecco C, Schoepf UJ. Detection of coronary artery stenosis with sub-milliSievert radiation dose by prospectively ECG-triggered high-pitch spiral CT angiography and iterative reconstruction. *Eur Radiol*. 2013;23:2927-2933.
10. Nance JW, Jr., Henzler T, Meyer M, Apfaltrer P, Braunagel M, Krissak R, Schoepf UJ, Schoenberg SO, Fink C. Optimization of contrast material delivery for dual-energy computed tomography pulmonary angiography in patients with suspected pulmonary embolism. *Invest Radiol*. 2012;47:78-84.
11. Weininger M, Barraza JM, Kemper CA, Kalafut JF, Costello P, Schoepf UJ. Cardiothoracic CT angiography: current contrast medium delivery strategies. *AJR Am J Roentgenol*. 2011;196:W260-272.
12. Ramos-Duran LR, Kalafut JF, Hanley M, Schoepf UJ. Current contrast media delivery strategies for cardiac and pulmonary multidetector-row computed tomography angiography. *J Thorac Imaging*. 2010;25:270-277.
13. Kerl JM, Ravenel JG, Nguyen SA, Suranyi P, Thilo C, Costello P, Bautz W, Schoepf UJ. Right heart: split-bolus injection of diluted contrast medium for visualization at coronary CT angiography. *Radiology*. 2008;247:356-364.
14. Wang R, Schoepf UJ, Wu R, Reddy RP, Zhang C, Yu W, Liu Y, Zhang Z. Image quality and radiation dose of low dose coronary CT angiography in obese patients: sinogram affirmed iterative reconstruction versus filtered back projection. *Eur J Radiol*. 2012;81:3141-3145.
15. Tricarico F, Hlavacek AM, Schoepf UJ, Ebersberger U, Nance JW, Jr., Vliegenthart R, Cho YJ, Spears JR, Secchi F, Savino G, Marano R, Schoenberg SO, Bonomo L, Apfaltrer P. Cardiovascular CT angiography in neonates and children: image quality and potential for radiation dose reduction with iterative image reconstruction techniques. *Eur Radiol*. 2013;23:1306-1315.
16. Moscariello A, Takx RA, Schoepf UJ, Renker M, Zwerner PL, O'Brien TX, Allmendinger T, Vogt S, Schmidt B, Savino G, Fink C, Bonomo L, Henzler T. Coronary CT angiography: image quality, diagnostic accuracy, and potential for radiation dose reduction using a novel iterative image reconstruction technique-comparison with traditional filtered back projection. *Eur Radiol*. 2011;21:2130-2138.
17. Wang R, Schoepf UJ, Wu R, Gibbs KP, Yu W, Li M, Zhang Z. CT coronary angiography: image quality with sinogram-affirmed iterative reconstruction compared with filtered back-projection. *Clin Radiol*. 2013;68:272-278.
18. Ebersberger U, Tricarico F, Schoepf UJ, Blanke P, Spears JR, Rowe GW, Halligan WT, Henzler T, Bamberg F, Leber AW, Hoffmann E, Apfaltrer P. CT evaluation of coronary artery stents with iterative image reconstruction: improvements in image quality and potential for radiation dose reduction. *Eur Radiol*. 2013;23:125-132.
19. Kerl JM, Schoepf UJ, Vogl TJ, Ackermann H, Vogt S, Costello P, Herzog C. In vitro evaluation of metallic coronary artery stents with 64-MDCT using an ECG-gated cardiac phantom:

relationship between in-stent visualization, stent type, and heart rate. *AJR Am J Roentgenol*. 2010;194:W256-262.
20. Renker M, Nance JW, Jr., Schoepf UJ, O'Brien TX, Zwerner PL, Meyer M, Kerl JM, Bauer RW, Fink C, Vogl TJ, Henzler T. Evaluation of heavily calcified vessels with coronary CT angiography: comparison of iterative and filtered back projection image reconstruction. *Radiology*. 2011;260:390-399.
21. Bamberg F, Klotz E, Flohr T, Becker A, Becker CR, Schmidt B, Wintersperger BJ, Reiser MF, Nikolaou K. Dynamic myocardial stress perfusion imaging using fast dual-source CT with alternating table positions: initial experience. *Eur Radiol*. 2010;20:1168-1173.
22. http://www.healthcare.siemens.com/computed-tomography/dual-source-ct/somatom-force/technical-specifications, retrieved on Feb 10, 2014.
23. Bamberg F, Klotz E, Flohr T, Becker A, Becker CR, Schmidt B, Wintersperger BJ, Reiser MF and Nikolaou K. Dynamic myocardial stress perfusion imaging using fast dual-source CT with alternating table positions: initial experience. *European radiology*. 2010;20:1168-73.
24. Bastarrika G, Ramos-Duran L, Schoepf UJ, Rosenblum MA, Abro JA, Brothers RL, Zubieta JL, Chiaramida SA, Kang DK. Adenosine-stress dynamic myocardial volume perfusion imaging with second generation dual-source computed tomography: Concepts and first experiences. *J Cardiovasc Comput Tomogr*. 2010;4:127-135.
25. Meinel FG, De Cecco CN, Schoepf UJ, Nance JW, Jr., Silverman JR, Flowers BA, Henzler T. First-Arterial-Pass Dual-Energy CT for Assessment of Myocardial Blood Supply: Do We Need Rest, Stress, and Delayed Acquisition? Comparison with SPECT. *Radiology*. 2013:131183.
26. Hausleiter J, Martinoff S, Hadamitzky M, Martuscelli E, Pschierer I, Feuchtner GM, Catalan-Sanz P, Czermak B, Meyer TS, Hein F, Bischoff B, Kuse M, Schomig A and Achenbach S. Image quality and radiation exposure with a low tube voltage protocol for coronary CT angiography results of the PROTECTION II Trial. *JACC Cardiovasc Imaging*. 2010; 3:1113-23.
27. Deak PD, Smal Y, Kalender WA. Multisection CT protocols: sex- and age-specific conversion factors used to determine effective dose from dose-length product. *Radiology*. 2010;257:158-166.
28. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. *Annals of the ICRP*. 2007;37:1-332.
29. Davenport MS, Khalatbari S, Dillman JR, Cohan RH, Caoili EM, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. *Radiology*. 2013;267:94-105.