The Feasibility, Tolerability, Safety, and Accuracy of Low-radiation Dynamic Computed Tomography Myocardial Perfusion Imaging With Regadenoson Compared With Single-photon Emission Computed Tomography

van Assen, Marly; Duguay, Taylor M.; Litwin, Sheldon E.; Bayer, Richard R.; Nance, John W.; Suranyi, Pal; De Cecco, Carlo N.; Varga-Szemes, Akos; Jacobs, Brian E.; Johnson, Addison A.

Published in:
Journal of thoracic imaging

DOI:
10.1097/RTI.0000000000000502

The Feasibility, Tolerability, Safety, and Accuracy of Low-radiation Dynamic Computed Tomography Myocardial Perfusion Imaging With Regadenoson Compared With Single-photon Emission Computed Tomography

Marly van Assen, PhD,† Taylor M. Duguay, BS,* Sheldon E. Litwin, MD,*‡ Richard R. Bayer II, MD,*‡ John W. Nance, MD,* Pal Suranyi, MD, PhD,*‡ Carlo N. De Cecco, MD, PhD,* Akos Varga-Szemes, MD, PhD,* Brian E. Jacobs, BS,* Addison A. Johnson, MS,* Christian Tesche, MD,*§ and U. Joseph Schoepf, MD*‡*

Objectives: Computed tomography (CT) myocardial perfusion imaging (CT-MPI) with hyperemia induced by regadenoson was evaluated for the detection of myocardial ischemia, safety, relative radiation exposure, and patient experience compared with single-photon emission computed tomography (SPECT) imaging.

Materials and Methods: Twenty-four patients (66.5 y, 29% male) who had undergone clinically indicated SPECT imaging and provided written informed consent were included in this phase II, IRB-approved, and FDA-approved clinical trial. All patients underwent coronary CT angiography and CT-MPI with hyperemia induced by the intravenous administration of regadenoson (0.4 mg/5 mL). Patient experience and findings on CT-MPI images were compared to SPECT imaging.

Results: Patient experience and safety were similar between CT-MPI and SPECT procedures and no serious adverse events due to the administration of regadenoson occurred. SPECT resulted in a higher number of mild adverse events than CT-MPI. Patient radiation exposure was similar during the combined coronary computed tomography angiography and CT-MPI (4.4 [2.7] mSv) and SPECT imaging (5.6 [1.7] mSv) (*P*-value 0.401) procedures. Using SPECT as the reference standard, CT-MPI analysis showed a sensitivity of 58.3% (95% confidence interval [CI]: 27.7-84.8), a specificity of 100% (95% CI: 73.5-100), and an accuracy of 79.1% (95% CI: 57.9-92.87). Low apparent sensitivity occurred when the SPECT defects were small and highly suspicious for artifacts.

Conclusions: This study demonstrated that CT-MPI is safe, well tolerated, and can be performed with comparable radiation exposure to SPECT. CT-MPI has the benefit of providing both complete anatomic coronary evaluation and assessment of myocardial perfusion.

Key Words: myocardial perfusion imaging, computed tomography, computed tomography angiography, computed tomography myocardial perfusion imaging, patient safety, patient satisfaction

(*J Thorac Imaging* 2021;36:345–352)

Myocardial perfusion imaging (MPI) is an important tool for functional evaluation in patients with known or suspected coronary artery disease (CAD). Single-photon emission computed tomography (SPECT) is the current clinical standard for noninvasive MPI. A combination of anatomic coronary imaging with coronary computed tomography angiography (CCTA) and perfusion imaging with SPECT has theoretical advantages for guiding therapy.[1] However, the need for 2 individual tests, both of which require radiation exposure, presents a limitation of this strategy in clinical practice. Recent technological advances in computed tomography (CT) led to increasing interest in CT for MPI. Combining CCTA and CT-MPI allows for a single-modality approach for the anatomic and functional evaluation of CAD. Dynamic CT-MPI shows similar diagnostic accuracy compared with other techniques, including SPECT, invasive fractional flow reserve (FFR), cardiac magnetic resonance imaging (CMR), and invasive coronary angiography.[2–11] The main advantage of CT-MPI is the ability to absolutely quantify blood flow, in contrast to SPECT and MRI. Whereas (CT-)FFR only yields functional information on a lesion specific level, CT-MPI enables the detection of global perfusion defects caused by microvascular disease, 3-vessel disease or hypertension, and diabetes.

Up to 50% of MPI studies are carried out by pharmacologically inducing stress,[5,12] with adenosine being the most frequently used. Adenosine, an A2A agonist, induces coronary vasodilatation; however, it causes unwanted side effects such as mast cell degranulation and bronchial constriction. The short

From the *Department of Radiology and Radiological Science, Division of Cardiovascular Imaging; ‡Department of Medicine, Medical University of South Carolina, Division of Cardiology, Charleston, SC; †Department of Radiology, Center for Medical Imaging, University Medical Center Groningen, Groningen, The Netherlands; and §Department of Cardiology and Intensive Care Medicine, Heart Center Munich-Bogenhausen, Munich, Germany.

M.v.A. and T.M.D. contributed equally to this work.

The use of Lexiscan (0.4 mg/5 mL regadenoson, Astellas Pharma Global Development, Inc.) during CT myocardial perfusion imaging is not currently approved by the US Food and Drug Administration.

This study was funded by an institutional research grant from Astellas Pharma Global Development Inc.

U.J.S. receives institutional research support from Astellas, Bayer, General Electric, and Siemens Healthineers. U.J.S. has received honoraria for speaking and consulting from Bayer, Elucid, Guerbet, HeartFlow Inc., and Siemens Healthineers. C.N.D.C. is a consultant for/receives institutional research support from Bayer and Siemens. A.V.-S. receives institutional research support from Siemens Healthineers. The remaining authors declare no conflicts of interest.

Correspondence to: U. Joseph Schoepf, MD, Department of Radiology and Radiological Science, Division of Cardiovascular Imaging, Medical University of South Carolina, 25 Courtenay Drive, Charleston, SC 29425 (e-mail: schoepf@musc.edu).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.thoracicimaging.com.

DOI: 10.1097/RTI.0000000000000502

half-life of adenosine requires continuous intravenous administration and weight-based dosing.[12,13] Regadenoson is a selective A2A receptor agonist, approved by the Food and Drug Administration (FDA) for use with SPECT imaging. Regadenoson is administered as a fixed-dose bolus without weight adjustments. Furthermore, there are fewer side effects in patients with reactive airway disease. In addition, regadenoson is less influenced by the consumption of caffeine, an A2A antagonist.[14,15] A single previous multicenter, multivendor study evaluated regadenoson CT-MPI compared with SPECT,[16] which demonstrated the noninferiority of regadenoson CT-MPI to SPECT for the evaluation of myocardial ischemia. However, quantitative information, one of the main advantages of CT-MPI, and the patient experience have not been evaluated.

The aim of the current study was to evaluate regadenoson CT-MPI compared with regadenoson SPECT for the detection or exclusion of myocardial ischemia, safety, and patient experience.

MATERIAL AND METHODS

This prospective study, a phase 2 clinical trial (ClinicalTrials.gov: NCT03103061), was approved by the United States Food and Drug Administration (IND 125,518) and the University's Institutional Review Board. This study received funding and drug support from Astellas Pharma Global Development Inc. Written informed consent was obtained from all study participants before they underwent any study procedure.

Study Population

A total of 27 patients between 18 and 85 years of age with a clinical history and/or symptoms suspicious for cardiac ischemia who recently underwent or were scheduled for SPECT imaging were considered for inclusion in this study. Patients were scheduled for SPECT imaging if they had a clinically indicated CCTA showing moderate to severe coronary stenosis, in accordance with clinical practice at our institution. The exclusion criteria are summarized in Table 1. Covariates, including risk factors, were obtained from patient medical records.

Myocardial Perfusion Imaging

All study participants underwent SPECT and CT-MPI imaging within 60 days of each other. Blood pressure, heart rate, electrocardiogram, and symptoms were monitored before, during, and after each imaging study.

TABLE 1. Exclusion Criteria

Pregnant or nursing	
Respiratory disease	Severe asthma or chronic obstructive pulmonary disease with frequent inhaler use
Previous diagnosis of obstructive CAD	Without revascularization and with interventional (percutaneous balloon angioplasty or stent implantation) or surgical (coronary artery bypass grafting [CABG]) revascularization between the imaging studies.
Implanted cardiac device	Pacemaker or defibrillator
ECG abnormalities	High-grade heart block, a resting heart rate < 45 beats per minute, etc., or ischemic ST segment changes with symptoms
High blood pressure	Systolic blood pressure <90 mm Hg
Caffeine intake	Within the last 12 h
Allergies	To regadenoson or iodinated contrast
Impaired kidney function	Serum creatinine > 1.5 mg/dL

CTA

All patients initially underwent a dedicated contrast-enhanced and prospectively electrocardiogram (ECG)-triggered CCTA using the following parameters: 70 to 130 kV tube potential automatically selected using an automated tube-voltage selection algorithm (CARE kV, Siemens), 200 to 650 mAs tube current-time product, 0.25 s gantry rotation time, and 2×192×0.6 mm detector collimation with a z-flying focal spot. Patients were administered 50 mL of contrast material (Ultravist, 370 mgI/mL iopromide, Bayer, Wayne, NJ) using a biphasic injection protocol at 5 mL/s, followed by a 50 mL saline bolus chaser. There was an adequate time-lapse between the CCTA and perfusion acquisition to eliminate contrast contamination of the perfusion acquisition. If a CTA examination was already performed before the SPECT imaging, the CTA was not repeated during the CT-MPI procedure.

SPECT Imaging

All patients underwent clinically indicated SPECT imaging for symptoms suspicious of cardiac ischemia as determined by their treating physician. All SPECT imaging studies were completed using standard stress/rest protocols. Technetium tetrafosmin (GE Healthcare, Chicago, IL) was used as a radiotracer and dosing was weight based. Patients underwent standard Bruce or modified Bruce treadmill exercise protocols unless they were unable to safely exercise or did not achieve 85% of their predicted maximum heart rate with exercise. In such cases, patients underwent a pharmacological stress protocol using 0.4 mg/5 mL intravenous regadenoson (Lexiscan, Astellas Pharma US Inc.) injection. SPECT images were acquired using a Symbia S (Siemens Healthcare, Hoffman-Estates, IL) dual-head gamma camera.

Analysis of SPECT Images

SPECT examinations were interpreted for perfusion defects by 2 experienced readers (1 nuclear medicine physician and 1 cardiologist) who were blinded to the results of the CT-MPI. Images were analyzed on a dedicated console using commercially available software. When present, the locations of perfusion abnormalities were recorded following the American Heart Association's 17-segment model.[17] Evidence of ischemia was determined by visual comparison of rest and stress SPECT perfusion scans. Perfusion defects were rated as reversible, fixed, or mixed. Both reversible and fixed defects were assessed on the basis of the percentage of left ventricular myocardium affected. Finally, continuous ECG monitoring was performed in all patients irrespective of stress modality. Patient symptoms that developed throughout the SPECT imaging were obtained from the clinical SPECT report.

CT-MPI Imaging

All CT-MPI studies were acquired using a third-generation dual-source CT scanner (Siemens SOMATOM Force, Siemens Healthineers, Forchheim, Germany). If a CTA acquisition was not yet performed, a CTA was performed before the CT-MPI acquisition.

Patients underwent dynamic, first-pass, stress CT-MPI during hyperemia induced with 0.4 mg/5 mL regadenoson. Imaging commenced 90 seconds after the intravenous regadenoson bolus (followed by a 10 mL saline bolus). To achieve the correct timing of the dynamic image acquisition, contrast administration (50 mL Ultravist [370 mg I/mL iopromide, Bayer],

followed by a 50 mL saline chaser at 6 mL/s) began ~80 seconds after the regadenoson administration to allow the contrast material to reach the heart at the time of maximal hyperemia. Data were acquired for 30 seconds with both x-ray tubes set at 80 to 100 kV, a gantry rotation time of 0.28 seconds, a tube current of 300 mAs per rotation, and a temporal resolution of ~75 ms. Patients were instructed to hold their breath for the first 15 seconds of the scan, and then to breath shallowly for the remaining 15 seconds. Perfusion imaging was performed in an ECG-triggered shuttle mode in which the table shifts between 2 z-positions of the heart to cover the left ventricular myocardium. End systolic imaging was used to reduce motion artifacts, image the heart at maximal muscular thickness, and reduce beam-hardening artifacts from contrast in the left ventricular cavity. With a detector width of 38 mm and 10% overlap between the 2 imaging positions, the acquisition z-range was 73 mm. Following institutional protocol, regadenoson was reversed in symptomatic patients with 1 mg/kg of aminophylline if indicated by the supervising cardiologist.

CCTA Reconstruction and Analysis

Filtered back projection image reconstruction was performed in the cardiac phase with the least motion: temporal resolution of 83, 75, or 66 ms, section thickness of 0.75 mm, reconstruction increment of 0.4 or 0.5 mm, and a smooth convolution kernel (B26f). CT coronary angiograms were evaluated by consensus of 2 experienced investigators (C.N.D.C., U.J.S.). The presence of stenosis was assessed in the left anterior descending artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA). The left main coronary artery was included with the LAD. The degree of stenosis was assessed with multiplanar reconstructions and curved multiplanar reconstructions along the vessel centerline (Circulation, Siemens Healthcare). Vessels were visually assessed as to whether they had no stenoses, nonobstructive stenoses ($<50\%$), or obstructive stenoses ($\geq 50\%$).

CT Perfusion Data Reconstruction and Analysis

Dynamic CT-MPI data were reconstructed with a section thickness of 3 mm at a 2 mm increment with a medium smooth convoluted kernel (B30). Data were processed with the volume perfusion CT body application software and workstation (Siemens). After motion correction and 4D noise reduction, a double arterial input function was defined by placing regions of interest in the descending aorta in the cranial and caudal regions of the covered volume. After a volume of interest was manually defined around the left ventricle, the left ventricular myocardium was automatically segmented. A dedicated parametric deconvolution algorithm based on a 2-compartment model of intravascular and extravascular space was used to derive myocardial blood flow (MBF) from the time-attenuation curves for each voxel.[18]

Qualitative and Quantitative Measures of MBF From CT

CT perfusion images were analyzed on a dedicated console using commercially available software (Syngo Volume Perfusion) as previously described.[19] Evidence of ischemia was determined initially by visual inspection of the images by experts blinded to the SPECT results. When present, the locations of perfusion abnormalities were recorded following the American Heart Association's 17-segment model.[17] Evidence of ischemia was determined by detection of hypoperfused areas on the perfusion scans. Quantitative analysis of myocardial perfusion was carried out per segment and the mean MBF in mL/100 mL/min of each myocardial segment (AHA 17 segment model) was recorded. An index-MBF was calculated to account for interpatient differences in MBF. The index-MBF is calculated as a ratio between segment and global MBF. To avoid the effects of beam hardening on the measurements, a region of interest as large as possible was manually placed in each segment with a 1-mm subendocardial zone directly adjacent to the contrast-filled left ventricle and a 1-mm subepicardial zone excluded from analysis.

Analysis of Radiation Dose

Effective radiation dose was calculated using a standard conversion factor of 0.014 for adult chest CT to convert dose-length product into millisieverts.[20] For the SPECT examinations, the effective radiation dose was estimated by multiplying the administered activity of 99mTc-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 were combined to compute the net radiation dose.[21]

Safety and Tolerability Assessment

Patients were monitored for the following events or symptoms for 60 minutes post-CT-MPI: hypotension (systolic blood pressure <90 or >30 mm Hg decrease from baseline), hypertension (systolic blood pressure >180 mm Hg), bronchospasm (requiring inhaler or other medical treatment), allergic reaction (hives, erythema, wheezing), chest pain, nausea, headache, dyspnea, fatigue, or seizures. Once the patient's heart rate had returned to normal, an EKG was obtained and interpreted by a cardiologist. The following abnormalities were recorded: development of a significant new heart block (type II second degree or third degree A-V block) and bradycardia (heart rate <45 beats per minutes, sinus bradycardia, or junctional rhythm). Pre-CT-MPI and post-CT-MPI ECGs were compared with ensure consistency before patient discharge.

After the CT-MPI, all patients were given a participant satisfaction survey to assess their subjective experience with both imaging modalities (CT-MPI and SPECT). Dedicated research personnel administered the survey to ensure question clarity and patient understanding. The 6-question survey assessed the following: (1) patient 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, and (6) willingness to undergo the test again. Each question had a quantitative score of 1 to 4. Further details are provided in Supplemental Material 1 (Supplemental Digital Content 1, http://links.lww.com/JTI/A165). The duration of both the SPECT and the CT-MPI protocol was assessed by recording the time stamps of the first and last image taken. For the CT protocol, this included the CTA and CT-MPI acquisition, whereas the SPECT protocol duration included both the rest and stress acquisition and the waiting time in between.

30-Day Major Adverse Cardiac Event (MACE) Follow-up

Patient phone calls and a review of electronic medical records were used to monitor patients for 30 days post-CT-MPI. The following events were recorded: emergency department visit (relating to a cardiac condition or symptoms), hospitalization (relating to a cardiac condition or symptoms), acute coronary syndrome, myocardial infarction, stroke, revascularization, significant new arrhythmia, and death.

Statistical Analysis

Continuous variables are represented as mean ± SD or medians with interquartile ranges (IQR; Q1 to Q3), depending on their distribution (tested with the Shapiro-Wilk test). Categorical data are shown as absolute frequencies and proportions. Patient experience parameters, adverse events, and radiation dose were compared between CT and SPECT perfusion acquisitions. Diagnostic accuracy parameters such as sensitivity, specificity, and AUCs were constructed for CCTA, CT-MPI, and SPECT. A Wilcoxon signed rank test was used to analyze differences between categorical CT data. SPECT acquisitions and numerical data were compared using a paired *t* test or a Wilcoxon signed rank test depending on the distribution. A *P*-value <0.05 was considered statistically different. Statistical analyses were carried out using SPSS version 23 (IBM, Armonk, NY).

RESULTS

Of the 27 patients considered for inclusion, 24 patients (29% male [n = 7], mean age: 66.5 y) were included and underwent CT-MPI. Two patients who had not yet undergone SPECT imaging were excluded due to a lack of moderate to severe coronary stenosis on CCTA. One patient was excluded due to caffeine intake within 12 hours of the CT-MPI. Comorbid conditions were typical in the population, with hypertension and hyperlipidemia being the most common. Patient demographics are shown in Table 2. The average body mass index was 29.6 ± 4.7 kg/m, indicating that most patients were overweight. Eleven of the 24 patients had undergone pharmacologic stress SPECT imaging, whereas the remaining 13 patients underwent Bruce/modified Bruce exercise protocols.

Patient Experience

Patient experience during CT-MPI and SPECT imaging was similar, except for level of nervousness, which was significantly higher ($P = 0.021$) during SPECT imaging (median: 1, IQR: 1 to 2) than CT-MPI (median: 1, IQR: 1 to 1). Although not statistically significant, patients were more willing to repeat CT-MPI (median: 1, IQR: 1 to 1) compared with the SPECT procedure (median: 2, IQR: 1 to 2) and were more content with the length of the CT-MPI procedure (median: 2, IQR: 1 to 2) compared with SPECT (median: 3, IQR: 3 to 3). The mean duration of the SPECT examination was 134.5 minutes, whereas the mean duration of the total CT examination was 13.5 minutes. A comprehensive overview of the patient experience scores is summarized in Table 3.

Safety

A total of 6 patients reported symptoms or adverse events in the 60-minute period after regadenoson administration during CT-MPI, all of which were considered mild.

TABLE 2. Patient Characteristics

Patient Demographics	
Age (y)	66.5 ± 7.6
Male	7 (28%)
Body mass index, kg/m^2	29.6 ± 4.7
Caucasian ethnicity	19 (76%)
Hypertension	20 (80%)
Hyperlipidemia	22 (88%)
Diabetes	9 (36%)
Smoking	11 (44%)

Data are presented as mean ± SD or n (%).
Smoking indicates both current and former smokers.

TABLE 3. Patient Experience

Satisfaction Parameters	SPECT	CT-MPI	*P*
Level of understanding	1 (1-2)	1 (1-1)	0.174
Willingness to repeat	2 (1-2)	1 (1-1)	0.163
Level of nervousness	1 (1-2)	1 (1-1)	0.021
Difficulty of procedure	2 (2-3)	1.5 (1-2)	0.380
Length of the procedure	3 (3-3)	2 (1-2)	0.448
Level of discomfort	1 (1-2)	1 (1-2)	0.703

Patient experience scores for multiple satisfaction parameters. Where a score of 1 is excellent and 4 is poor.

One patient experienced hypotension and a headache, whereas 5 other patients only experienced a headache. Significantly more patients reported symptoms or adverse events associated with the SPECT acquisitions with a total of 17 (70%), all of which were considered mild. One patient experienced a headache, whereas 9 patients experienced dyspnea and 13 patients felt fatigued.

An overview of all reported adverse events is provided in Table 4.

The radiation dose for the perfusion studies was numerically lower for regadenoson CT-MPI (4.4 ± 2.7 mSv) compared with regadenoson SPECT (5.6 ± 1.7 mSv), but did not reach statistical significance (*P*-value 0.097). The CCTA radiation dose (2.0 ± 0.1 mSv; *P*-value <0.001) was significantly lower compared with the CT-MPI and SPECT studies. A combination of CCTA and CT-MPI had similar radiation dose values (6.6 ± 3.5 mSv) compared with SPECT imaging alone (5.6 ± 1.7 $P = 0.401$).

CCTA, CT-MPI, and SPECT

A total of 12 patients had a perfusion defect on SPECT images (3 reversible defects and 9 fixed defects). CT-MPI diagnosed 7 patients with a perfusion defect, all of which corresponded to a defect found with SPECT imaging. There were 5 patients with a positive SPECT and a negative CT-MPI. Using SPECT as the reference standard, visual analysis of CT-MPI images showed a sensitivity of 58.3% (95% confidence interval [CI]: 27.7-84.8), a specificity of 100% (95% CI: 73.5-100), and an accuracy of 79.1% (95% CI: 57.9-92.87).

TABLE 4. Adverse Events

Adverse Event	CT-MPI, n (%)	SPECT, n (%)
	Number of patients	
Any event	6 (25)	17 (71)
	Number of symptoms	
Hypotension	1 (4)	0
Heart block	0	0
Bradycardia	0	0
Bronchospasm	0	0
Allergic reaction	0	0
Chest pain	0	1 (4)
Nausea	0	0
Headache	6 (25)	0
Dyspnea	0	9 (38)
Fatigue	0	13 (54)
Seizure	0	0

Number of adverse events within 1 hour of regadenoson administration during CT-MPI and post-SPECT.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

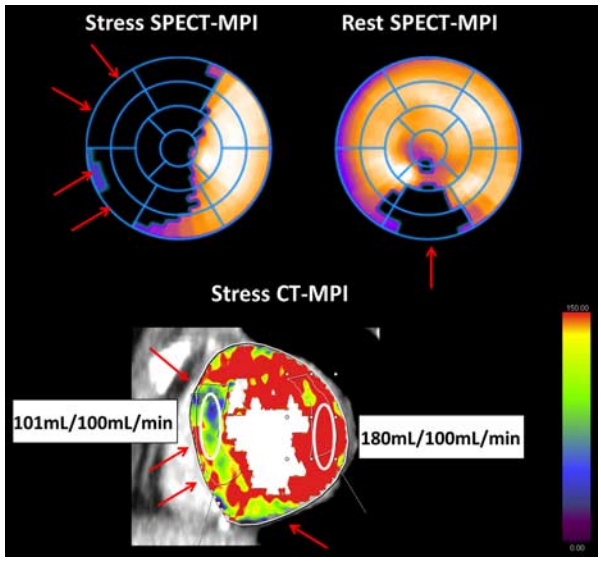

FIGURE 1. Example of concordant findings on CT-MPI and SPECT-MPI. Images of a 56-year-old woman with known CAD. The attenuation-corrected SPECT images show a reversible defect in the anterior and septal walls on the stress SPECT images and a small fixed defect in the inferior wall on the rest SPECT images (red arrows). This reversible defect is reflected by a decreased MBF (red arrows) in the CT-MPI images (101 vs. 180 mL/100mL/min) measured by ROIs (white circles).

See Figures 1 and 2 for representative examples. In this positive SPECT group with negative CT-MPI results (n = 5), 3 SPECT acquisitions showed a perfusion defect that was not observed on CT-MPI, which could possibly be an artifact; one patient showed a very small (~5%) defect on SPECT. Of the 3 patients with perfusion defects on SPECT without corresponding CT-MPI defects, 2 had no coronary stenosis on CCTA and 1 had a nonobstructive stenosis (< 50%) in the vessel supplying the affected territory. This supports the notion that these perfusion defects on SPECT may have been artifactual. An overview of diagnostic accuracy is shown in Table 5.

TABLE 5. Overview of Visual and Quantitative CT-MPI and CCTA Data Compared With SPECT

	SPECT		
CT-MPI Visual	**Negative**	**Positive**	**All (n)**
Negative	12 (true negatives)	5 (false negatives)	17
Positive	0 (false positives)	7 (true positives)	7
All (n)	12	12	24
Sensitivity	58.3% (95% CI: 27.7-84.8)		
Specificity	100% (95% CI: 73.5-100)		
Accuracy	79.1% (95% CI: 57.9-92.87)		
	SPECT		
MBF/MBF-index	**Negative**	**Positive**	**All (n)**
Negative	161 ± 30/ 0.99 ± 0.09	172 ± 19/ 0.89 ± 0.17	17
Positive	—	81 ± 9/0.59 ± 0.13	7
All (n)	12	12	24
	SPECT		
CCTA	**Negative**	**Positive**	**All (n)**
Negative	9 (true negatives)	4 (false negatives)	13
Positive	3 (false positives)	8 (true positives)	11
All (n)	12	12	24
Sensitivity	66.7% (95% CI: 34.9-90.1)		
Specificity	75.0% (95% CI: 42.8-94.5)		
Accuracy	70.83% (95% CI: 48.8-87.4)		
	CT-MPI		
CCTA	**Negative**	**Positive**	**All (n)**
Negative	12 (true negatives)	1 (false negatives)	13
Positive	5 (false positives)	6 (true positives)	11
All (n)	17	7	24
Sensitivity	85.7% (95% CI: 42.1-99.6)		
Specificity	70.6% (95% CI: 44.0-89.7)		
Accuracy	75.0% (95% CI: 53.3-90.2)		

Quantitative analysis of the CT-MPI acquisitions showed a mean global MBF of 155 ± 29 mL/100 mL/min and an overall LAD territory MBF of 159 ± 33 mL/100 mL/min, LCx territory MBF of 165 ± 33 mL/100 mL/min, and

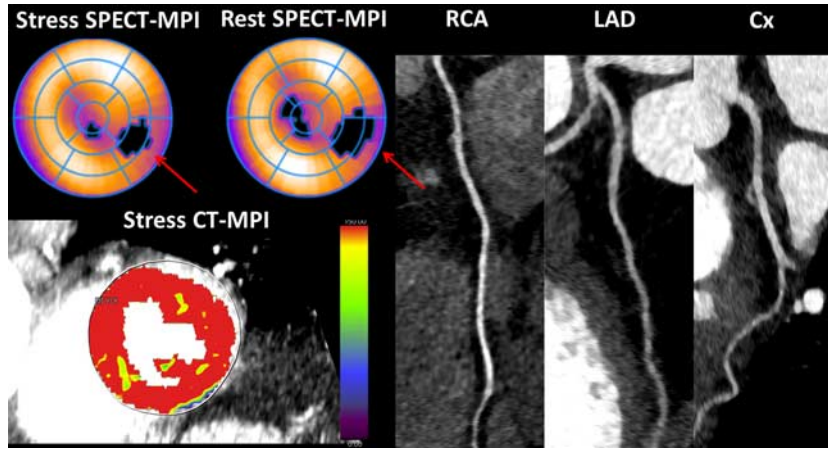

FIGURE 2. Example of discordant findings between CT-MPI and SPECT-MPI. A 68-year-old woman presenting with chest pain. The attenuation-corrected SPECT images show a fixed defect of 10% (red arrows) in the lateral wall supplied by the Cx territory with the suspicion of being an artifact in both rest and stress SPECT-MPI. This defect is not seen on the CT-MPI images and the CCTA images show no calcifications and no stenoses in the RCA, LAD, and Cx.

an RCA territory MBF of 149 ± 27 mL/100 mL/min. The CT-derived MBF in areas of defects) myocardium with perfusion defects (fixed and reversible) as determined by SPECT was significantly lower, with a mean MBF of 110.40 ± 38 mL/100mL/min, compared with global MBF (155 ± 29 mL/100 mL/min, *P*-value = 0.019). After correcting for interpatient variation, the MBF index was also significantly lower in areas of myocardium with perfusion defects, 0.76 ± 0.22, compared with normal myocardium with a mean MBF index of 0.99 ± 0.11 (*P*-value = 0.002). When the patients are divided into a group with fixed or reversible defects based on SPECT, we find that there is no significant difference in absolute MBF values (*P*-value = 0.425), with a mean MBF of 125 ± 52 mL/100ml/min for fixed defects (n = 9) and a mean MBF of 101 ± 38 mL/100 mL/min for reversible defects. The MBF index also shows no difference between reversible and fixed defects (*P*-value = 0.827), with a mean MBF index of 0.76 ± 0.25 for fixed defects and 0.79 ± 0.20 for reversible defects. Using SPECT as a reference, CCTA alone had a sensitivity of 66.7% (95% CI: 34.9-90.1), a specificity of 75.0% (95% CI: 42.8-94.5), and an accuracy of 70.83% (95% CI: 48.8-87.4). Using CT-MPI as a reference standard resulted in slightly higher diagnostic accuracy with a sensitivity, specificity, and accuracy of 85.7% (95% CI: 42.1-99.6), 70.6% (95% CI: 44.0-89.7), and 75.0% (95% CI: 53.3-90.2), respectively (Table 5).

30-Day MACE Follow-up

Eighteen of the 24 patients were contacted via telephone to complete the 30-day MACE follow-up. A review of electronic medical records was used to complete the 30-day MACE follow-up for the remaining 6 patients and to supplement the information acquired from the 18 patients contacted via telephone. One patient was hospitalized and underwent invasive coronary angiography with intervention during the 30-day follow-up period. This procedure was performed on the basis of the abnormal SPECT findings and did not represent an adverse event related to the imaging studies. No other patients experienced any MACE.

DISCUSSION

In this study, we correlated findings on CT-MPI and SPECT examinations and evaluated the safety and patient experience of stress CT-MPI compared with SPECT MPI. This study confirms that the presence of perfusion defects diagnosed with regadenoson CT-MPI and SPECT is similar, and that CT-MPI carries the added value of an anatomic evaluation with concurrent CCTA imaging. Patient experience, radiation exposure, and safety were similar between CT-MPI and SPECT procedures. Neither test resulted in serious adverse events due to the administration of regadenoson. Furthermore, the combination of functional anatomic evaluation using a single modality demonstrated an increased diagnostic accuracy for the detection of myocardial perfusion defects compared with SPECT alone. CT-MPI offers the ability to reduce the number of false-positive examinations, which would be clinically beneficial in reducing unnecessary interventions.

Although used as the reference standard in this study, SPECT is an imperfect "gold standard" for the detection of obstructive CAD as it has well-recognized problems with specificity. Compared with previous studies carried out on the diagnostic accuracy of adenosine CT-MPI with SPECT as a reference standard, our study reported similar specificity (100% vs. 78% to 98%), but lower sensitivity (58.3 vs. 83% to 86%).[6,22–24] The limited sensitivity may be caused by the presence of artifacts found on the SPECT MPI images leading to false positives. CCTA analysis showed that a majority of the patients with abnormal perfusion on SPECT, but not on CT-MPI, had no significant anatomic stenoses in the vessels supplying the territories with perfusion defects on SPECT. Combining CCTA with perfusion images allows for a better differentiation between artifacts and perfusion defects. Taking these artifacts into account, the sensitivity of CT-MPI would be significantly higher and in the range of previously reported studies.[6,22–24]

Cury and colleagues carried out a multicenter, multivendor study on the safety and efficacy of regadenoson CT-MPI compared with SPECT, showing similar results in terms of the diagnostic accuracy.[21] Although they only carried out a visual analysis of CT-MPI images, our study carried out an additional quantitative analysis, showing the true advantage of CT-MPI of SPECT imaging.

Quantitative analysis was carried out and showed that both the absolute and the relative MBF were significantly lower in areas with perfusion defects than in normal myocardium (*P*-values 0.019 and 0.002, respectively). Using a quantitative approach offers the potential to detect subclinical changes in MBF and microvascular disease and potentially yields a better, or less subjective, evaluation of the severity of ischemia.[25] In addition to the visual analysis of CT-MPI images, a quantitative analysis showed that both absolute and relative MBF were significantly lower in areas with perfusion defects than in normal myocardium (*P*-values 0.019 and 0.002, respectively). Using a quantitative approach offers the potential to detect subclinical changes in MBF and microvascular disease.[25] Global ischemia was determined using a relative measure of perfusion limits because there is no normal myocardium present.

CT-MPI demonstrated improved specificity compared with CCTA alone (100% vs. 75%). These findings confirm results from previous studies indicating that regadenoson CT-MPI can provide incremental value to anatomic evaluation alone for the detection of hemodynamically significant stenosis.[24,26] Combined functional and anatomic evaluation using stress CT-MPI and CCTA could be beneficial in patients in whom CCTA has poor diagnostic accuracy, particularly in patients with intermediate stenoses. Moreover, adding CT-MPI to CCTA increased the amount of contrast administered by a factor 2, and the radiation exposure by a factor of 2.15. A study by Coenen and colleagues shows that a stepwise approach using both techniques can also be used in sequence, whereby selective use of CT-MPI improves significant hemodynamic classification, thus increasing the accuracy from 0.74 to 0.85.[27]

One of the major differences between the 2 imaging modalities is the duration of the protocols. CT-MPI has a procedure length that is <10% of the time required for SPECT. This is advantageous for several reasons, including patient comfort and efficiency for the health care system. An inability to lie in a very still position for 2 periods of 15 to 20 minutes each is a significant issue for many patients, including those with congestive heart failure or orthopedic issues. However, it should be noted that our SPECT protocol consisted of a rest and stress acquisition and the waiting time between those acquisitions increased the

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

procedure time significantly. The significantly shorter time of the CT protocol potentially allows for more rapid initiation of treatment in selected cases.

The administration of regadenoson was well tolerated in this study, with most adverse events being mild in nature. Adverse events were consistent with the reported safety and tolerability profile of regadenoson. The SPECT procedure resulted in more reported adverse events than CT-MPI. Specifically, dyspnea and fatigue were frequently reported subsequent to the SPECT procedure, whereas headaches were more common in the CT-MPI procedure. The difference in these events could be explained by the fact that SPECT was performed by exercise in 55% of cases. In addition, the length of the examination and the difference in the contrast agent used could play a role. Headaches are a known side-effect of iodine administration. The radiation doses of CT-MPI alone and combined with CCTA were similar compared with SPECT imaging. Adding CCTA provides additional anatomic information of the coronary arteries and can help differentiate between true perfusion deficits and artifacts. If performed upstream of CT-MPI, the high negative predictive value could decrease the number of patients undergoing subsequent perfusion imaging, thereby reducing both contrast and radiation exposure due to a fixed combined approach. The radiation doses of the CT-MPI examinations in this study are lower than the doses previously reported (17.7 [6.8] mSv) in a similar study utilizing regadenoson CT-MPI.[16] This decrease in radiation dose is most likely due to the advancement in scanner technology and the level of routine use of radiation-reducing protocols (such as lowering of kV and using prospective acquisitions when feasible). Patient experience questionnaires show similar results for the 2 procedures. The only significant difference between the SPECT and CT-MPI procedure was that patients were less nervous for the CT-MPI procedure. However, this difference may be caused by the fact that the SPECT procedure was clinically indicated and performed first, followed by the research CT-MPI procedure.

Several limitations deserve mention. First, this study included a relatively small number of patients from a single center. In addition, the discrepancy in the reported side effects attributed to regadenoson administration may be due to a conditioning phenomenon, as most patients underwent SPECT imaging with regadenoson first, potentially accounting for the lower rate of reported symptoms with CT-MPI. Finally, invasive coronary angiography with FFR measurements, currently considered the gold standard to detect functionally significant coronary artery stenoses, was not performed.

In conclusion, patient experience and safety were similar between CT-MPI and SPECT. This study demonstrates good diagnostic accuracy of CT-MPI for the detection of ischemia compared with SPECT and offers improved diagnostic accuracy compared with CCTA alone. A combined CCTA/CT-MPI examination provides added value with additional anatomic data and can be performed with a similar radiation exposure as SPECT.

REFERENCES

1. Santana CA, Garcia EV, Faber TL, et al. Diagnostic performance of fusion of myocardial perfusion imaging (MPI) and computed tomography coronary angiography. *J Nucl Cardiol*. 2009;16:201–211.
2. Cerqueira MD. Advances in pharmacologic agents in imaging: new A2A receptor agonists. *Curr Cardiol Rep*. 2006;8:119–122.
3. Johnson SG, Peters S. Advances in pharmacologic stress agents: focus on regadenoson. *J Nucl Med Technol*. 2010;38:163–171.
4. Buhr C, Gössl M, Erbel R, et al. Regadenoson in the detection of coronary artery disease. *Vasc Health Risk Manag*. 2008;4:337–340.
5. Al Jaroudi W, Iskandrian AE. Regadenoson: a new myocardial stress agent. *J Am Coll Cardiol*. 2009;54:1123–1130.
6. Wang Y, Qin L, Shi X, et al. Adenosine-stress dynamic myocardial perfusion imaging with second-generation dual-source CT: comparison with conventional catheter coronary angiography and SPECT nuclear myocardial perfusion imaging. *Am J Roentgenol*. 2012;198:521–529.
7. Bastarrika G, Ramos-Duran L, Rosenblum MA, et al. Adenosine-stress dynamic myocardial CT perfusion imaging: initial clinical experience. *Invest Radiol*. 2010;45:306–313.
8. Varga-Szemes A, Meinel FG, De Cecco CN, et al. CT myocardial perfusion imaging. *AJR Am J Roentgenol*. 2015;204:487–497.
9. Rossi A, Uitterdijk A, Dijkshoorn M, et al. Quantification of myocardial blood flow by adenosine-stress CT perfusion imaging in pigs during various degrees of stenosis correlates well with coronary artery blood flow and fractional flow reserve. *Eur Heart J Cardiovasc Imaging*. 2013;14:331–338.
10. Meinel FG, De Cecco CN, Schoepf UJ, et al. 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;270:708–716.
11. Pelgrim GJ, Das M, van Tuijl S, et al. Validation of myocardial perfusion quantification by dynamic CT in an ex-vivo porcine heart model. *Int J Cardiovasc Imaging*. 2017;33:1821–1830.
12. Miyamoto MI, Vernotico SL, Majmundar H, et al. Pharmacologic stress myocardial perfusion imaging: a practical approach. *J Nucl Cardiol*. 2007;14:250–255.
13. Auchampach JA, Bolli R. Adenosine receptor subtypes in the heart: therapeutic opportunities and challenges. *Am J Physiol*. 1999;276(pt 2):H1113–H1116.
14. Kuijpers D, Prakken NH, Vliegenthart R, et al. Caffeine intake inverts the effect of adenosine on myocardial perfusion during stress as measured by T1 mapping. *Int J Cardiovasc Imaging*. 2016;32:1545–1553.
15. van Dijk R, Kuijpers D, Kaandorp TAM, et al. Effects of caffeine intake prior to stress cardiac magnetic resonance perfusion imaging on regadenoson- versus adenosine-induced hyperemia as measured by T1 mapping. *Int J Cardiovasc Imaging*. 2017;33:1753–1759.
16. Cury RC, Kitt TM, Feaheny K, et al. A randomized, multicenter, multivendor study of myocardial perfusion imaging with regadenoson CT perfusion vs single photon emission CT. *J Cardiovasc Comput Tomogr*. 2015;9:103–112.
17. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. *Circulation*. 2002;105:539–542.
18. Bamberg F, Klotz E, Flohr T, et al. Dynamic myocardial stress perfusion imaging using fast dual-source CT with alternating table positions: Initial experience. *Eur Radiol*. 2010;20:1168–1173.
19. Bastarrika G, Ramos-Duran L, Schoepf UJ, et al. 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.
20. Deak PD, Smal Y, Kalender WA. Multisection CT protocols: sex- and age-specific conversion factors used to determine effective dose from dose-length product 1. *Radiol n Radiol*. 2010;257:158–166.
21. ICRP. ICRP 103: The 2007 Recommendations of the International Commission on Radiological Protection. *Ann ICRP*. 2007;37:330.
22. Ho KT, Chua KC, Klotz E, et al. Stress and rest dynamic myocardial perfusion imaging by evaluation of complete time-attenuation curves with dual-source CT. *JACC Cardiovasc Imaging*. 2010;3:811–820.
23. Weininger M, Schoepf UJ, Ramachandra A, et al. Adenosine-stress dynamic real-time myocardial perfusion CT and adenosine-stress first-pass dual-energy myocardial perfusion CT for the assessment of acute chest pain: Initial results. *Eur J Radiol*. 2012;81:3703–3710.

24. Feuchtner GM, Plank F, Pena C, et al. Evaluation of myocardial CT perfusion in patients presenting with acute chest pain to the emergency department: comparison with SPECT-myocardial perfusion imaging. *Heart*. 2012;98:1510–1517.
25. Vliegenthart R, De Cecco CN, Wichmann JL, 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;10:301–308.
26. Rocha-Filho JA, Blankstein R, Shturman LD, et al. Incremental value of adenosine-induced stress myocardial perfusion imaging with dual-source CT at cardiac CT angiography. *Radiology*. 2010; 254:410–419.
27. Coenen A, Rossi A, Lubbers MM, et al. Integrating CT myocardial perfusion and CT-FFR in the work-up of coronary artery disease. *JACC Cardiovasc Imaging*. 2017;10: 760–770.