Stress Dual-Energy Computed Tomography-Myocardial Perfusion Imaging to Identify Coronary Artery Stenoses Causing Ischemia: A Direct Comparison between Invasive Coronary Angiography and Cardiac Magnetic Resonance-Myocardial Perfusion Imaging

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Objective: We determined the diagnostic performance of stress dual-energy computed tomography-myocardial perfusion imaging (DECT-MPI) for diagnosing coronary artery stenoses causing ischemia.

Materials and Methods: Institutional review board approval and informed patient consent were obtained before patient enrollment in the study. One hundred ninety-two consecutive patients (135 males, 63.1±8.0 years) underwent coronary computed tomography angiography (CCTA), stress DECT-MPI, and a combined invasive coronary angiography (ICA)/cardiac magnetic resonance-myocardial perfusion imaging (CMR-MPI) for further comparison. Stress DECT-MPI and CMR-MPI were evaluated for perfusion deficits, whereas CCTA and ICA were evaluated for coronary stenosis ≥50%. The primary endpoint was the diagnostic performance of combined CCTA/stress DECT-MPI compared with combined ICA/CMR-MPI at the per-vessel level. Individual direct comparisons of CCTA to ICA and stress DECT-MPI to CMR-MPI were explored.

Results: One hundred forty-four (75%) patients and 257 (45%) vascular territories manifested ischemia-causing coronary stenoses based on combined ICA/CMR-MPI. Per-vessel sensitivity, specificity, positive predictive value, and negative predictive value of combined CCTA/stress DECT-MPI were 88, 82, 79, and 89%, respectively, compared with combined ICA/CMR-MPI. The values for CCTA alone were 95, 45, 63, and 94%, respectively, and the values for stress DECT-MPI alone were 91, 75, 75, and 92%, respectively. The area under the receiver operating characteristics curve for combined CCTA/stress DECT-MPI was higher than that for CCTA alone (0.85 vs. 0.75, p=0.001).

Conclusion: When compared with combined ICA/CMR-MPI, combined CCTA/stress DECT-MPI improved the predictive value for coronary stenoses causing ischemia compared with CCTA, but only mildly improved the diagnostic performance of stress DECT-MPI alone.

Key words Coronary artery disease · Magnetic resonance · Coronary angiography · Dual-energy · Computed tomography · Myocardial perfusion imaging.

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INTRODUCTION

Coronary computed tomography angiography (CCTA) is a noninvasive method for diagnosing high-grade coronary stenosis. However, prior multicenter studies have shown a non-negligible false-positive rate for CCTA-identified coronary stenosis, with diagnostic accuracy limited by severe coronary calcification, intracoronary stents, and coronary motion [1-3]. These limitations are associated with a general overestimation of the degree of coronary stenosis based on CCTA compared with invasive coronary angiography (ICA) [4]. Furthermore, less than half of high-grade stenoses identified using CCTA physiologically cause myocardial ischemia, and concerns have arisen that the use of CCTA-identified coronary artery disease (CAD) may precipitate high rates of unnecessary ICA [5,6]. To address these limitations, pharmacological CT myocardial perfusion imaging (MPI) has emerged as an additional CT method for diagnosing myocardial ischemia and showed satisfactory diagnostic performance compared with single photon emission computed tomography (SPECT)-MPI, fractional flow reserve (FFR), a combination of ICA and SPECT-MPI, and a combination of ICA and cardiac magnetic resonance (CMR)-MPI [7-14]. However, these investigations have been largely limited to the use of single-energy CT, which relies on relative Hounsfield unit density measurements to detect myocardial perfusion deficits.

Dual-energy computed tomography (DECT) has recently emerged as a novel method for assessing myocardial perfusion. Based on the specific absorption characteristics of iodine for different X-ray energies, DECT allows mapping of intra-myocardial iodine extent and distribution, and small sample studies have demonstrated the feasibility of this technique to detect myocardial perfusion deficits [15-17]. However, large-scale studies examining stress DECT-MPI are lacking [18,19]. Furthermore, the diagnostic performance of combined CCTA and stress DECT-MPI compared with CCTA, based on a combined anatomical-physiological reference standard, has not been performed. Thus, in this prospective study, the performance of combined CCTA and stress DECT-MPI to diagnose coronary stenoses that cause ischemia was compared with the combined ICA and CMR-MPI reference standard and evaluated.

MATERIALS AND METHODS

Study population and design

A total of 192 consecutive patients with suspected or known CAD who underwent CCTA and ICA were enrolled from June 2009 to December 2013. Inclusion criteria were age ≥ 40 years, significant coronary stenoses ($\geq 50\%$ reduction of luminal diameter) or nonevaluable coronary arteries based on CCTA, and no intervening cardiac event (coronary revascularization, myo-

cardial infarction, or hospitalization for any cardiac cause) between CCTA and ICA. All participants were considered for non-urgent revascularization. Exclusion criteria included atrial fibrillation, deteriorated renal function (serum creatinine >1.5 mg/dL, estimated glomerular filtration rate <60 mL/min/1.73 m²), contraindication to CMR (incompatible metallic implants or claustrophobia), previous coronary artery bypass graft surgery, unstable clinical status (including critical aortic stenosis and New York Heart Association class IV congestive heart failure), or contraindication to adenosine (e.g., advanced heart blockage, asthma, or systolic blood pressure <90 mm Hg). Fig. 1 summarizes the patient flow chart in this study. Enrolled patients underwent stress DECT-MPI, CMR-MPI, and ICA within 30 days without intervening changes in clinical status or coronary revascularization. This study protocol was approved by the institutional ethics committee, and all patients provided written informed consent before enrollment.

Image acquisition

CCTA

All CT examinations were performed using a Somatom Definition dual-source CT scanner (Siemens Medical Solutions, Forchheim, Germany) and the following scanning parameters: collimation, 32×0.6 mm; slice acquisition, 64×0.6 mm; gantry rotation time, 330 msec; pitch, 0.20–0.43 adapted to heart rate (HR); tube voltage, 100/120 kV; and tube current-time product, 320 mAs per rotation. A non-enhanced electrocardiography-gated CT scan, prospectively triggered at 75% of the R-R interval, was performed before the helical scan to measure the coronary calcium score. Electrocardiography-based tube current modulation was implemented with the “MinDose” protocol to minimize radiation exposure to all patients with mean HR <80 beats per minute (bpm) in normal sinus rhythm. The full dose window of 30–80% of the cardiac cycle was used in patients with HRs of 65–79 bpm, and the full dose window of 60–80% of the cardiac cycle was used in patients with HRs <65 bpm.

Patients with a pre-scan HR >65 bpm were administered 50–100 mg metoprolol orally 1 h prior to CCTA. All patients received 0.6 mg nitroglycerin sublingually immediately prior to CCTA. A Stellant D dual-head power injector (Medrad, Indianapolis, PA, USA) was used for all CT examinations to administer a three-phase bolus at a rate of 4.5 mL/s. First, 70–80 mL of undiluted contrast media (Iopromide, Ultravist 370 mg I/mL; Bayer-Schering Pharma, Berlin, Germany) was administered after optimal timing was determined via a bolus tracking technique. For CCTA, a mixture of 70% contrast and 30% saline (45 mL) was administered with a saline chaser.

Fig. 1. Flow diagram of patients eligible for recruitment and reasons for exclusion. CABG: coronary angiography bypass grafting surgery, CAD: coronary artery disease, CCTA: coronary computed tomography angiography, ICA: invasive coronary angiography, CMR-MPI: cardiac magnetic resonance-myocardial perfusion imaging, DECT-MPI: dual-energy computed tomography-myocardial perfusion imaging.

Stress DECT-MPI

All patients were subsequently scanned by stress-only DECT-MPI on a separate day within 40 days of CCTA. Premedication with beta-blockers or nitroglycerine was not used in order to avoid any impact on myocardial perfusion. Stress DECT-MPI was performed as single-phase acquisition using the following protocol. One X-ray tube was operated with 82 mAs/rotation at 140 kV, and a second tube was operated with 164 mAs/rotation at 80 kV. Intravenous adenosine was infused at 140 μ g/kg/min, including retrospective electrocardiography-gated imaging with tube current modulation and pitch adaptation obtained 4 min after initiation. Full tube current was applied from 60–75% of the cardiac cycle and was reduced to 4% outside the adjusted pulsing window. Image acquisition started 9 sec after the signal density level reached the predefined threshold of 120 Hounsfield unit at the aortic root. Rest-perfusion DECT was not performed because of prior acquisition using single-energy CCTA.

CMR-MPI

CMR-MPI was performed on a Signa HDxt 1.5-T system (GE Medical Systems, Milwaukee, WI, USA) with an eight-ele-

ment phased array surface coil or a Magnetom Skyra 3.0-T system (Siemens, Erlangen, Germany) with a 32-channel body coil within 7 days after stress DECT-MPI. Perfusion data were acquired in three left ventricular short-axis slices (basal, mid-ventricular, and apical) during breath-hold at end-expiration. Adenosine was administered using an identical protocol as for stress DECT-MPI. An intravenous bolus of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Bayer-Schering Pharma AG, Berlin, Germany) or gadoterate meglumine (Dotarem, Guerbet, Roissy CdG Cedex, France) was injected during adenosine infusion. Rest perfusion was performed using a second bolus of 0.1 mmol/kg gadopentetate dimeglumine or gadoterate meglumine 10 min after first-pass MPI. Perfusion data were acquired with the 1.5-T system using a hybrid gradient echo/echo-planar pulse sequence (echo time, 1.2 msec; repetition time, 270 msec; flip angle, 25°; slice thickness, 8 mm; preparation pulse, 90° for each slice; echo train length, 4; field of view, 360×360 mm; matrix, 128×128; pixel size, 2.8×2.8 mm) or with the 3.0-T system using TurboFLASH (echo time, 1.03 msec; repetition time, 156 msec; flip angle, 10°; slice thickness, 8 mm; saturation recovery time, 100 msec; field of view, 360×274

mm; matrix, 192×142; pixel size, 1.9×1.9 mm). Delayed enhancement images were acquired 10 min after the second bolus in 2 long axes and 10 or 11 short axes using a 1.5-T system with a phase-sensitive myocardial delayed enhancement sequence or using a 3.0-T system with a phase-sensitive inversion recovery sequence.

ICA

ICA (Allura Xper FD-10; Philips Medical Systems, Eindhoven, the Netherlands) was performed in direct accordance with societal guidelines and within 7 days after the CMR examination. A minimum of six projections was obtained: four views of the left coronary artery and two of the right coronary artery (RCA).

Image processing and interpretation

CCTA

CCTA images were reconstructed with a slice thickness of 0.75 mm at an increment of 0.4 mm using a medium-soft tissue convolution kernel (B26f). In case of extensively calcified plaques or stents, additional images were reconstructed using a sharp-tissue convolution kernel (B46f). CCTA datasets were evaluated at a cardiac phase with the least amount of motion using a dedicated 3D workstation (Vitrea® 2, Version 4; Vital Images, Plymouth, MN, USA). Coronary artery segments of the three main coronary arteries and their major side branches with a luminal diameter ≥ 1.5 mm were classified based on a modified 16-segment AHA coronary model, as described previously [20]. Lesions with a luminal diameter reduction $\geq 50\%$ were considered high-grade. Coronary segments were considered non-interpretable if any of the following were present: extensively calcified plaque or an obfuscating stent that precluded coronary luminal assessment, significant motion artifact, or inability to determine the degree of stenosis as severe or non-severe. Coronary arteries with coronary stenoses $\geq 50\%$ or with nonevaluable segments were considered “positive” for anatomically obstructive coronary stenosis. Short-axis multiplanar reformatted images were obtained using a 5-mm slice thickness and no intersection gap at a mid-diastolic phase for resting CTP analysis. CCTAs were evaluated by an experienced radiologist blinded to other image data as well as clinical information. Image quality of CT and CMR was determined using a subjective three-point ranking scale (1=excellent, 2=good, 3=poor).

Stress DECT-MPI

Myocardial perfusion datasets were semi-quantitatively evaluated using a 0.75-mm slice thickness and a 0.4-mm slice increment using a dedicated dual-energy convolution kernel (D26f) at the mid-diastolic phase [15]. DECT-based color-

coded iodine distribution maps were superimposed onto grayscale multiplanar reformats of the left ventricular myocardium in the short- and long-axis views (5-mm slice thickness and no intersection gap) using the dual-energy image post-processing software application of the Syngo-Multi-Modality Workplace (syngoDualEnergy; Siemens, Forchheim, Germany). Perfusion defects were defined as contiguous, circumscribed areas of reduced or absent iodine content within the left ventricular myocardium relative to remote normal-appearing myocardium, as described previously [17]. The stress DECT-MPI and resting CTP obtained using CCTA were read side by side in the short-axis view to distinguish stress-induced perfusion defects from artifacts or myocardial infarction. Two independent experienced radiologists, blinded to patient and other imaging data, evaluated the stress DECT iodine maps using an AHA 17-segment model and three vascular territorial distributions (left anterior descending artery (LAD), left circumflex artery (LCX) and RCA [21]. A perfusion defect ≥ 2 segments was considered positive for ischemia on both stress DECT-MPI and CMR-MPI.

CMR-MPI

CMR-MPI was reviewed on a 3D workstation (Advantage Windows; GE Medical Systems or Syngo, Siemens Healthcare). Myocardial perfusion was evaluated using the same procedure as was used for stress DECT-MPI. The presence of hypoenhancement in a coronary artery territory persisting for more than six heartbeats under adenosine stress was considered positive for a perfusion defect [22]. All CMR-MPI images were independently analyzed by 2 experienced radiologists blinded to all patient and other imaging data.

ICA

Quantitative assessment of stenosis severity on ICA was performed using commercially available software in accordance with societal recommendations (CAAS; Pie Medical, Maastricht, the Netherlands). ICAs were interpreted by an experienced interventional cardiologist. Coronary segments were categorized using the same procedure as for CCTA.

Matching of perfusion segments to corresponding vascular territories

CCTA was used to ensure correct association of the 17 myocardial segments with the correct vascular territory for stress DECT-MPI and CMR-MPI, as described previously. Vessel dominance was used to determine the vessel supplying the inferior and inferoseptal territories. Based on whether the obtuse marginal or diagonal branches supplied the anterolateral wall, the LCX or LAD vessel was determined to supply the mid and basal anterolateral wall. The ramus intermedius was designated

as supplying the anterior wall (LAD territory) or anterolateral wall (LCX territory). The distal LAD wrapped around the apex was designated to supply the apical inferior wall. In addition, the large septal perforator of LAD was designated to supply the inferoseptum [8,10].

Hemodynamically significant coronary stenosis and reference standard

An angiographically significant stenotic ($\geq 50\%$ reduction in luminal diameter) or nonevaluable vessel was considered to cause or not cause ischemia if a perfusion defect was observed or not observed, respectively, in the same vascular territory. A perfusion defect in a vascular territory subtended by a coronary vessel with $<50\%$ stenosis was considered a false-positive result. Furthermore, the presence or absence of hemodynamically significant coronary stenosis on a per-patient or per-vascular territory was assessed with the combination of CCTA/stress DECT-MPI and with the combination of ICA/CMR-MPI; the latter was considered the reference standard for a combined assessment of coronary morphology and hemodynamic lesion severity. The vessel-based analysis included the LAD, LCX, and RCA territories in all patients.

Radiation dose

The effective radiation dose for the CCTA and stress DECT-MPI examinations was calculated for all patients. The dose-length product was converted to millisieverts (mSv) by multiplying the dose-length product by a conversion coefficient ($\kappa = 0.014 \text{ mSv} \cdot \text{mGy}^{-1} \cdot \text{cm}^{-1}$) [23].

Statistical analysis

Quantitative variables are expressed as mean $\pm$ standard deviation, and categorical variables are expressed as frequency or percentage. The McNemar test was used to compare paired proportions. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated from 2×2 contingency tables, and their respective 95% confidence intervals (CIs) were calculated from the binomial expression. Receiver operating curve (ROC) analysis and the area under the curve (AUC) were calculated for all diagnostic testing strategies for which a reference standard was available. Kappa (κ) statistic values were used to determine interobserver agreement and intermodality concordance. A p -value < 0.05 was considered statistically significant for all analyses. All statistical analyses were performed using SAS Proprietary Software, version 9.1 (SAS Institute, Cary, NC, USA). In addition, we performed a two ROC curve power analysis to validate the study purpose or hypothesis using PASS 2008 statistical software (NCSS, LLC, Kaysville, UT, USA).

RESULTS

Patient population

A total of 192 patients (average age 63.1 ± 8.0 years; range 40–83 years; 70% male) were enrolled and successfully underwent CCTA, stress DECT-MPI, CMR-MPI, and ICA without serious adverse events. The patient characteristics are provided in Table 1.

Scan protocol findings

CCTA

Mean HR during CCTA was 57 ± 12 bpm, with a mean Likert score of 1.2 ± 0.4 . Mean effective radiation exposure values for

Table 1. Patient clinical characteristics

Characteristics	Total (n=192)
Mean age (years)	63.1 $\pm$ 8.0
Women (%)	57 (30)
Body mass index (kg/m ²)	25.9 $\pm$ 3.5
Risk factors (%)	
Smoking history	85 (44)
Current smoker	46 (24)
Ex-smoker	39 (20)
Hypertension	124 (65)
Diabetes mellitus	60 (31)
Hyperlipidemia	112 (58)
Obesity	17 (9)
Systolic BP (mm Hg)	128 $\pm$ 18 (87–196)
Diastolic BP (mm Hg)	77 $\pm$ 12 (51–125)
Biomarker of lipid level (mg/dL)	
Total cholesterol	179.6 $\pm$ 41.7
HDL cholesterol	44.7 $\pm$ 11.7
LDL cholesterol	142.5 $\pm$ 24.7
Serum triglyceride	164.3 $\pm$ 41.7
Medical history (%)	
Previous angina pectoris	115 (60)
Previous myocardial infarction	29 (15)
Peripheral vascular disease	6 (3)
Prior cerebrovascular accident	12 (6)
Prior coronary revascularization	15 (8)
Baseline medication (%)	
Aspirin	99 (52)
Anti-hypertension	98 (51)
Statin	63 (33)

Values are numbers or means $\pm$ standard deviations (95% confidence intervals). Obesity was defined as a body mass index $\geq 30 \text{ kg/m}^2$. Hyperlipidemia was defined as total cholesterol $> 240 \text{ mg/dL}$, triglycerides $> 200 \text{ mg/dL}$, or treatment for hypercholesterolemia. Hypertension was defined as BP $> 140/90 \text{ mm Hg}$ or treatment for hypertension. BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein

the calcium and CCTA scans were 0.75 ± 0.16 mSv and 5.5 ± 1.7 mSv, respectively. The median Agatston calcium score was 223 (range 0–5029). A total of 203 (6.8%) coronary segments in 59 patients were considered nonevaluable due to extensive calcified plaque ($n=177$), the presence of a stent ($n=24$), or a cardiac motion artifact ($n=2$). When nonevaluable segments were considered as representing significant stenoses, 41 (21%) patients with 58 (10%) arteries were categorized with anatomically obstructive CAD. Accordingly, CCTA revealed 674 (23%) significantly stenotic segments and 389 (68%) vessels in 192 patients.

Stress DECT-MPI

Stress DECT-MPI was completed for all 192 patients within 13 ± 15 days of CCTA at an average HR of 74 ± 16 bpm. Mean image quality was 1.5 ± 0.6 . Forty-nine (1.6%) myocardial segments were nonevaluable due to cardiac motion artifacts ($n=32$) or beam hardening artifacts ($n=17$). Perfusion defects were identified in 172 (90%), 314 (55%), and 1120 (37%) patients, vascular territories, and segments, respectively (Figs. 2 and 3). In patients with perfusion defects, 74 (43%), 54 (31%), and 44 (26%) had a defect involving one-vessel, two-vessel, or three-vessel territories, respectively. Good interobserver agreement

(86%) was calculated to identify perfusion defects (per-segment κ , 0.70). The average effective radiation dose for the stress DECT-MPI was 5.1 ± 1.1 mSv (range, 2.5–7.7 mSv).

CMR-MPI

CMR-MPI was performed in 102 patients using the 1.5-T MR scanner and in 90 patients using the 3.0-T MR scanner. All CMR-MPIs were obtained within 3.3 ± 3.4 days of stress DECT-MPI, with an average Likert score of 1.3 ± 0.4 . Perfusion defects were identified in 150 (78%), 279 (48%), and 1064 (35%) patients, vascular territories, and segments, respectively (Figs. 2 and 3). In patients with perfusion defects on CMR-MPI, 65 (43%) had a defect involving one-vessel territory, 41 (27%) had defects in two-vessel territories, and 44 (29%) had defects in three-vessel territories. Delayed enhancements were identified on delayed contrast-enhanced CMR in 61 (32%), 94 (16%), and 256 (8%) patients, vascular territories, and segments, respectively (Fig. 3). Good interobserver agreement (91%) for detecting perfusion defects per segment was observed with a κ value of 0.81.

Fig. 2. Images of a 58-year-old man with severe chest pain on exercise. (A) Curved multiplanar reformatted coronary computed tomography angiography image shows severe stenosis with noncalcified plaque in the mid-segment of the right coronary artery (RCA, arrow). (B) Invasive coronary angiography confirmed the presence of severe stenosis in the mid RCA (arrow). (C) Resting computed tomography perfusion image does not show any perfusion defects in the left ventricular (LV) myocardium. (D) Dual-energy computed tomography-myocardial perfusion imaging-based iodine map during adenosine infusion reveals blood-pool deficits in the mid inferoseptal and inferior LV myocardium (arrows). (E and F) Cardiac magnetic resonance images acquired at rest (E) and stress (F) show completely reversible subendocardial perfusion defects in the mid inferior and inferoseptal LV myocardium (arrows).

Fig. 3. Images of a 69-year-old man with chest pain. (A, B, and C) Curved multiplanar reformatting coronary computed tomography angiography images show significant stenoses in proximal (arrow in A) and middle segments (arrowhead in A) of the right coronary artery (RCA), second diagonal branch (arrow in B), and proximal (arrow in C) and distal left circumflex arteries (LCX, arrowhead in C). (D) Resting computed tomography perfusion image does not show any perfusion defects in the left ventricular (LV) myocardium. (E) Dual-energy computed tomography-myocardial perfusion imaging-based iodine map during adenosine infusion reveals perfusion defects in the mid inferolateral and inferior LV myocardium (arrows) and an artifact in the mid anterior wall LV myocardium (arrowheads). (F and G) Corresponding short-axis views of stress (F) and rest (G) cardiac magnetic resonance perfusion reveal reversible subendocardial perfusion defects in the mid anterior, lateral, inferior, and inferoseptal LV myocardium (arrows). (H, I, and J) Invasive coronary angiography findings confirm the presence of significant stenoses in proximal (arrow in H) and mid RCA (arrowhead in H) and the second diagonal branch (arrow in I) and total occlusion in the distal LCX (arrow in J).

ICA

More than one significantly stenosed coronary artery was noted in 168 (88%) patients; 93 had significant stenoses in RCA territory, 148 in LAD territory, and 98 in LCX territory. Of these 168 patients, 55 (33%) had one-vessel disease, 55 (33%) had two-vessel disease, and 58 (34%) had three-vessel disease.

Diagnostic performance characteristics

CCTA alone and stress DECT-MPI alone

On a per patient basis, $\geq 50\%$ of the stenoses based on CCTA

were identified as one-vessel, two-vessel, and three-vessel CAD for 33, 31, and 36% of the population, respectively. The sensitivity, specificity, PPV, and NPV of CCTA for detecting angiographically obstructed arteries were 93, 69, 81, and 87%, respectively, compared with ICA alone.

In 172 patients, 314 vascular territories, and 1120 segments with perfusion defects based on stress DECT-MPI, 143 (83%) patients, 252 (80%) vascular territories, and 827 (74%) segments were abnormal on CMR-MPI (Figs. 2 and 3). Six patients, 27 vascular territories, and 237 segments with perfusion defects on CMR-MPI were not identified using stress DECT-MPI. Sen-

sitivity, specificity, PPV, NPV, and accuracy of stress DECT-MPI compared with CMR-MPI on a per-segment basis were 78% (95% CI, 75–80%), 85% (95% CI, 83–87%), 74% (95% CI, 71–76%), 88% (95% CI, 86–89%), and 82% (95% CI, 81–84%), respectively; on a per-vessel basis the values were 90% (95% CI, 86–94%), 79% (95% CI, 74–84%), 80% (95% CI, 75–85%), 90% (95% CI, 85–93%), and 85% (95% CI, 81–87%), respectively; on a per-patient basis the values were 95% (95% CI, 91–99%), 33% (95% CI, 19–49%), 83% (95% CI, 77–88%), 70% (95% CI, 46–88%), and 82% (95% CI, 76–87%), respectively. The κ values were higher on a per-vessel basis (0.69; 95% CI, 0.63–0.75) than on a per-patient basis (0.35; 95% CI, 0.19–0.51), with similar relationships for AUCs of 0.85 (95% CI, 0.82–0.88) and 0.64 (95% CI, 0.57–0.71), respectively. CCTA tended to be inferior

to DECT-MPI alone in the ROC analysis for hemodynamically significant CAD detection in both per-vessel (0.75 vs. 0.83, $p=0.001$)- and per-patient-based (0.63 vs. 0.5, $p=0.06$) analyses (Table 2 and 3).

Combined CCTA and stress DECT-MPI

Combined CCTA and stress DECT-MPI identified 139 patients and 226 vessel territories subtended by hemodynamically significant coronary stenosis, which compared favorably to the combined ICA and CMR-MPI reference standard that showed hemodynamically significant stenoses in 144 patients with 257 vessel territories. Of the 58 nonevaluable arteries on CCTA, 38 (66%) were significantly stenosed on ICA, and 27 (47%) were significantly stenosed on combined ICA/CMR-MPI. When

Table 2. Per vessel territory diagnostic accuracy of CCTA, stress DECT-MPI, and combined CCTA/stress DECT-MPI compared with ICA/CMR-MPI

	CCTA $\geq 50\%$	Perfusion defect on stress DECT-MPI	CCTA $\geq 50\%$ and perfusion defect on stress DECT-MPI
True positive (n)	245	235	226
False positive (n)	144	79	59
True negative (n)	175	240	260
False negative (n)	12	22	31
Sensitivity (%)	95 (92–98)	91 (87–95)	88 (83–92)
Specificity (%)	55 (49–60)	75 (70–80)	82 (77–86)
PPV (%)	63 (58–68)	75 (70–80)	79 (74–84)
NPV (%)	94 (89–97)	92 (88–95)	89 (85–93)
Accuracy (%)	73 (69–77)	82 (79–85)	84 (81–87)
Kappa statistic	0.48 (0.42–0.54)	0.65 (0.59–0.71)	0.69 (0.63–0.85)
AUC	0.75 (0.71–0.79)	0.83 (0.80–0.86)	0.85 (0.82–0.88)

Values for sensitivity, specificity, PPV, NPV, accuracy, kappa statistic, and AUC presented with 95% confidence intervals. CCTA: coronary computed tomography angiography, ICA: invasive coronary angiography, DECT-MPI: dual-energy computed tomography-myocardial perfusion imaging, CMR-MPI: cardiac magnetic resonance-myocardial perfusion imaging, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

Table 3. Per patient diagnostic accuracy of CCTA, stress DECT-MPI, and combined CCTA/stress DECT-MPI compared with ICA/CMR-MPI

	CCTA $\geq 50\%$	Perfusion defect on stress DECT-MPI	CCTA $\geq 50\%$ and perfusion defect on stress DECT-MPI
True positive (n)	144	138	139
False positive (n)	48	34	40
True negative (n)		14	8
False negative (n)		6	5
Sensitivity (%)		96 (91–98)	97 (92–99)
Specificity (%)		29 (17–44)	17 (7–30)
PPV (%)	75 (68–81)	80 (73–86)	78 (71–84)
NPV (%)		70 (46–88)	62 (32–86)
Accuracy (%)	75 (68–81)	79 (73–85)	77 (81–87)
Kappa statistic		0.31 (0.16–0.46)	0.17 (0.04–0.31)
AUC	0.50 (0.43–0.57)	0.63 (0.55–0.69)	0.57 (0.49–0.64)

Values for sensitivity, specificity, PPV, NPV, accuracy, kappa statistic, and AUC presented with 95% confidence intervals. CCTA: coronary computed tomography angiography, ICA: invasive coronary angiography, DECT-MPI: dual-energy computed tomography-myocardial perfusion imaging, CMR-MPI: cardiac magnetic resonance-myocardial perfusion imaging, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

stress DECT-MPI was added to CCTA, the number of false-positive vessels based on CCTA decreased from 144 to 59 (Fig. 3), but the number of false-negative vessels based on CCTA increased from 12 to 31. Compared with CCTA alone, combined CCTA and stress DECT-MPI showed significant increase in AUC in a per-vessel-based analysis (0.75 vs. 0.83, $p < 0.001$) but insignificant increase in AUC in a per-patient-based analysis (0.5 vs. 0.57, $p = 0.326$) for hemodynamically significant CAD detection. The AUC for combined CCTA/stress DECT-MPI was not significantly different from the AUC for stress DECT-MPI alone on per vessel-based analysis (0.85 vs. 0.83, $p = 0.263$) and on per patient-based analysis (0.57 vs. 0.63, $p = 0.08$). The present sample size of 576 vessel territories achieved 99% power to detect a difference of 0.1 between CCTA, with an AUC of 0.75 and CCTA/stress DECT-MPI with an AUC of 0.85 using a two-sided z-test at a statistical significance level of 0.05. The per-vessel and per-patient diagnostic performance, agreement, and discrimination of combined CCTA and stress DECT-MPI are listed in Table 2 and 3.

DISCUSSION

Our study represents the largest group of patients assessed using stress DECT-MPI and CMR-MPI to date. We demonstrated that the combination of CCTA and stress DECT-MPI has good diagnostic accuracy for detecting hemodynamically significant coronary artery stenoses causing perfusion defects based on combined ICA/CMR-MPI compared with CCTA alone on per-vascular territory analysis in patients with suspected or known CAD scheduled for ICA. In addition, stress DECT-MPI alone showed similar diagnostic performance for detecting hemodynamically significant stenoses in per-vascular territory and per-patient analyses compared with combined CCTA/stress DECT-MPI.

SPECT-MPI and FFR are established standards for determining the functional significance of coronary stenosis inducing perfusion defects, which is valuable for guiding therapeutic plans and helping with prognostic assessments of patients [24-29]. CMR-MPI is an alternative to SPECT for detecting anatomically significant stenoses with better sensitivity and NPV compared with ICA [30]. In addition, CMR-MPI has excellent diagnostic performance for discriminating hemodynamically significant from insignificant stenoses compared with FFR as the reference standard [31-33]. Accordingly, combined ICA/CMR-MPI is sufficient as a reference standard for collecting anatomical and physiological information regarding coronary stenosis. CTP has been widely investigated using various CT scanners, acquisition protocols, study populations, and reference standards and is considered a promising method for imaging myocardial ischemia, comparable to SPECT and CMR-

MPI [7-14]. Bettencourt et al. [14] demonstrated that CTP is globally inferior to CMR-MPI; however, integrating CTP and CCTA showed similar diagnostic performance to CMR-MPI using FFR as the reference standard for detecting hemodynamically significant CAD. CCTA is not recommended due to its low specificity and PPV for identifying angiographically significant stenoses in patients with suspected or known CAD [34]. Our results showed that severe coronary calcification was the leading cause of nonevaluable coronary segments on CCTA, with a specificity of 69% and a PPV of 81% in the per-vessel analysis compared with ICA for detecting angiographically significant stenoses. Although the capability of resting CCTA for detecting myocardial ischemia remains debatable [35], CCTA does not reliably provide the physiological significance of coronary stenoses [36]. In our series, ICA revealed stenosis $\geq 50\%$ in 168 (88%) and hemodynamically significant stenosis in 144 (75%) patients. The correlation of combined ICA/CMR-MPI with CCTA was moderate and had a specificity of 55%, PPV of 63%, and AUC of 0.75 for CCTA alone for detecting hemodynamically significant CAD. In contrast, stress DECT-MPI showed high diagnostic accuracy for detecting hemodynamically significant coronary stenoses based on combined ICA/CMR-MPI, resulting in significant improvement in specificity (82%), PPV (79%), and AUC (0.85) as well as reclassification of 41 (71%) of 58 nonevaluable arteries on combined CCTA/stress DECT-MPI compared with CCTA alone. The use of CCTA in patients with suspected or known CAD complicated the exclusion of hemodynamically insignificant coronary stenosis. Those patients were considered to have significant stenoses mainly due to an overestimation of coronary stenosis degree and severely calcified nonevaluable lesions based on CCTA [1-4]. Based on the increased diagnostic accuracy of stress DECT-MPI and CCTA for identifying hemodynamically significant CAD, combined CCTA/stress DECT-MPI is a potential alternative to combined ICA/CMR-MPI, SPECT, or FFR in patients with suspected or known CAD as it allows a direct comparison of coronary anatomy and myocardial perfusion [19].

Myocardial perfusion on routine or single-shot CTP is assessed using semi-quantitative metrics such as the transmural perfusion ratio and visual perfusion assessment [7-14]. Mapping the iodine distribution within the left ventricular myocardium is possible with DECT. Accordingly, DECT-based iodine maps highlight areas of decreased iodine in the left ventricular myocardium [15-17]. The present results are in accordance with our previous stress DECT-MPI studies. Even though stress DECT-MPI is potentially superior to routine CTP for detecting perfusion defects, the diagnostic performance and increased value of stress DECT-MPI for detecting perfusion defects are limited and mainly involve only small pilot studies. Compared to the study by Feuchtnner et al. [11], the diagnostic performance of stress

DECT-MPI is similar in the per-segment analysis but lower in the per-vessel analysis compared with routine CTP against CMR-MPI, particularly the lower specificity and PPV. Our results differ from Bettencourt et al. [14], who reported that routine CTP showed 67% sensitivity and 95% specificity at the patient level and 55% sensitivity and 95% specificity at the vessel level compared with CMR-MPI for detecting perfusion defects. The higher sensitivity of stress DECT-MPI on per-vessel (90%) and per-patient (95%) levels may be explained by the iodine distribution map based on DECT-based material decomposition and is better suited than visual assessment of the differences in Hounsfield units between ischemic and normal myocardium. Higher numbers of false-positive vessels and patients were identified on stress DECT-MPI, resulting in lower specificity on per-vessel (79%) and patient (33%) levels. False-positive perfusion defects of stress DECT-MPI may be caused by cardiac motion artifacts due to insufficient temporal resolution (330 msec) of DECT, normal non-uniform distribution of iodine within the myocardium, and the beam-hardening artifact [21]. The combined CCTA/stress DECT-MPI demonstrated no further improvement for detecting hemodynamically significant coronary artery stenoses in per-vessel and per-patient analyses, as shown on combined ICA/CMR-MPI compared with DECT-MPI alone. Based on these results, stress DECT-MPI alone may be sufficient for diagnosing hemodynamically significant stenoses in patients with suspected or known CAD.

Our study had several limitations. First, this was a single-center study. Second, the prevalence of significant CAD based on ICA among the patients was 88%. Our study population was a high risk group with a significantly high prevalence of CAD in whom CCTA or stress testing has only limited clinical value. Selection bias may have affected interpretation of the stress DECT-MPI and CMR-MPI data (optimistic test results), leading to a decrease in the generalizability of the results. However, the patient selection may be reasonable when considering the population scheduled for ICA and the application of stress testing, which assists in management decisions by demonstrating the presence or absence of perfusion defects. Third, the assessments of myocardial perfusion on stress DECT-MPI were based on a visual instead of quantitative analysis, which may provide objective criteria for the reader to consider as perfusion defects. Fourth, we only performed stress-only DECT acquisition and used stress DECT-MPI and resting CTP obtained from CCTA for the direct comparison with CMR-MPI. This protocol design was justified when the reduction of patient exposure to radiation was considered. The mean radiation exposure values for CCTA and SP-DECT were 5.5 ± 1.7 mSv and 5.1 ± 1.1 mSv, respectively. Fifth, our study protocol had separate time points for conducting CCTA and stress DECT-MPI, raising the question of applicability of the results and making it impossible to

simultaneously evaluate anatomical and functional information regarding CAD. Lastly, CMR-MPI was considered as the reference standard for determining the functional significance of CAD, and no FFR measurement was performed in the study. We used only 3 short-axis slices for CMR-MPI at 1.5-T and 3.0-T MR scanners, leading to a potentially heterogeneous reference method with underestimation or no detection of small perfusion defects. In the clinical setting, ICA combined with FFR is a more appropriate anatomical-physiological reference standard aiding final decisions for treatment strategy [24,26].

In conclusion, the combination of CCTA and stress DECT-MPI in patients with suspected or known CAD detected hemodynamically significant coronary stenoses compared with combined ICA/CMR-MPI. Stress DECT-MPI provided clinical benefit to patients with insufficiently evaluated coronary lesions based on CCTA alone. Thus, combined CCTA and stress DECT-MPI allows identification of hemodynamically relevant CAD in clinical practice, because it provides useful information to assess the need for combined CCA/CMR-MPI, SPECT-MPI, or FFR and revascularization procedures.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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