JACC: CARDIOVASCULAR IMAGING
VOL. 12, NO. 2, 2019

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Incremental Diagnostic Value of Stress Computed Tomography Myocardial Perfusion With Whole-Heart Coverage CT Scanner in Intermediate- to High-Risk Symptomatic Patients Suspected of Coronary Artery Disease

Gianluca Pontone, MD, PhD,[a] Daniele Andreini, MD, PhD,[a,b] Andrea I. Guaricci, MD,[c,d] Andrea Baggiano, MD,[a] Fabio Fazzari, MD,[e] Marco Guglielmo, MD,[a] Giuseppe Muscogiuri, MD,[a] Claudio Maria Berzovini, MD,[f] Annalisa Pasquini, MD,[g] Saima Mushtaq, MD,[a] Edoardo Conte, MD,[a] Giuseppe Calligaris, MD,[a] Stefano De Martini, MD,[a] Cristina Ferrari, MD,[a] Stefano Galli, MD,[a] Luca Grancini, MD,[a] Paolo Ravagnani, MD,[a] Giovanni Teruzzi, MD,[a] Daniela Trabattoni, MD,[a] Franco Fabbiocchi, MD,[a] Alessandro Lualdi, MD,[a] Piero Montorsi, MD,[a,b] Mark G. Rabbat, MD,[h,i] Antonio L. Bartorelli, MD,[a,j] Mauro Pepi, MD[a]

ABSTRACT

OBJECTIVES The goal of this study was to evaluate the diagnostic accuracy of stress computed tomography myocardial perfusion (CTP) for the detection of functionally significant coronary artery disease (CAD) by using invasive coronary angiography (ICA) plus invasive fractional flow reserve (FFR) as the reference standard in consecutive intermediate- to high-risk symptomatic patients.

BACKGROUND Stress CTP recently emerged as a potential strategy to combine the anatomic and functional evaluation of CAD in a single scan.

METHODS A total of 100 consecutive symptomatic patients scheduled for ICA were prospectively enrolled. All patients underwent rest coronary computed tomography angiography (CTA) followed by stress static CTP with a whole-heart coverage CT scanner (Revolution CT, GE Healthcare, Milwaukee, Wisconsin). Diagnostic accuracy and overall effective dose were assessed and compared versus those of ICA and invasive FFR.

RESULTS The prevalence of obstructive CAD and functionally significant CAD were 69% and 44%, respectively. Coronary CTA alone demonstrated a per-vessel and per-patient sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 98%, 76%, 99%, 63%, and 83% and of 98%, 54%, 96%, 68%, and 76%, respectively. Combining coronary CTA with stress CTP, per-vessel and per-patient sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were 91%, 94%, 96%, 86%, and 93% and 98%, 83%, 98%, 86%, and 91%, with a significant improvement in specificity, positive predictive value, and accuracy in both models. The mean effective dose for coronary CTA and stress CTP were 2.8 ± 1.4 mSv and 2.5 ± 1.1 mSv.

CONCLUSIONS The inclusion of stress CTP for the evaluation of patients with an intermediate to high risk for CAD is feasible and improved the diagnostic performance of coronary CTA for detecting functionally significant CAD. (J Am Coll Cardiol Img 2019;12:338–49) © 2019 by the American College of Cardiology Foundation.

From the [a]Centro Cardiologico Monzino, IRCCS, Milan, Italy; [b]Department of Cardiovascular Sciences and Community Health, University of Milan, Milan, Italy; [c]Institute of Cardiovascular Disease, Department of Emergency and Organ Transplantation, University Hospital "Policlinico" of Bari, Bari, Italy; [d]Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; [e]Department of Cardiology, University Hospital P. Giaccone, Palermo, Italy; [f]Radiology Institute, Department of Surgical Sciences, University of Turin, Turin, Italy; [g]Department of Cardiology, Policlinico Umberto I,"Sapienza" University of Rome, Rome, Italy; [h]Loyola University of Chicago, Chicago, Illinois; [i]Edward Hines Jr. VA Hospital, Hines, Illinois; and the [j]Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan, Milan, Italy. Dr. Pontone has received institutional fees

ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2017.10.025

Coronary computed tomography angiography (CTA) has been introduced as an excellent alternative imaging modality to rule out coronary artery disease (CAD) with low radiation exposure (1) and strong prognostic ability (2). However, the data are conflicting regarding the optimal diagnostic strategy when comparing anatomy alone using coronary CTA versus functional testing (3) due to a lack of functional information resulting in increased resources or revascularization (4,5). Therefore, coronary CTA is recommended only in the subset of patients with a <50% pre-test likelihood of CAD; patients with intermediate to high risk for CAD should undergo a stress imaging-based strategy.

In this regard, stress computed tomography myocardial perfusion (CTP) recently emerged as a potential strategy to combine anatomic and functional evaluation in a single scan (6). Preliminary single-center and multicenter trials (7–30) illustrated the promising diagnostic accuracy of this approach. However, in most cases, these trials were performed with previous-generation scanners, did not include patients at intermediate to high risk for CAD, and typically compared coronary CTA versus invasive coronary angiography (ICA) alone or versus the combination of ICA plus noninvasive stress testing.

Recently, a newer coronary CTA technology was introduced featuring 16-cm wide coverage, 0.23 mm of spatial resolution, faster gantry rotation time with an intracycle motion-correction algorithm, and the latest generation iterative reconstruction. However, to date, no study validated its performance in stress CTP. The aim of the present study therefore was to evaluate the diagnostic accuracy of stress CTP to detect functionally significant CAD in consecutive intermediate- to high-risk symptomatic patients using ICA plus invasive fractional flow reserve (FFR) as the reference standard.

SEE PAGE 350

METHODS

The institutional ethics committee approved the study protocol, and all patients signed informed consent.

SCREENING PROCEDURE AND ENROLLMENT. In this single-center study, a total of 846 consecutive patients with chest pain symptoms who were scheduled for ICA were prospectively screened. The exclusion criteria are listed in **Figure 1**. Patients meeting all selection criteria were asked to sign an informed consent form before undergoing any study-specific evaluation. A structured interview was performed to collect clinical history and cardiac risk factors. The final patient population consisted of 100 patients.

PATIENT PREPARATION. Patients were asked to refrain from smoking and caffeine for 24 h and to observe a fast for 6 h before the scan. In patients with a resting heart rate (HR) >65 beats/min before the scan, metoprolol was administered intravenously with a titration dose up to 15 mg to achieve a target HR ≤65 beats/min. Before the rest scan, all patients received sublingual nitroglycerin (2 puffs of 300 μg each one).

REST CORONARY CTA. We performed rest coronary CTA with a Revolution CT scanner (GE Healthcare, Milwaukee, Wisconsin) according to the recommendations of the Society of Cardiovascular Computed Tomography (SCCT) (3). The following parameters were used: slice configuration 256 × 0.625 mm with scintillator detector; gantry rotation time 280 ms; tube voltage 120 KVp and 100 KVp in patients with body mass index >30 kg/m^2 and ≤30 kg/m^2, respectively; and an effective tube current of 500 mA. One-beat axial scan was used in all patients with a variable padding ranging from 70% to 80% and 40% to 80% of the cardiac cycle in patients with HR ≤65 beats/min and >65 beats/min. All patients received a 70-ml bolus of iodixanol 320 (Visipaque 320 mg/ml, GE Healthcare, Oslo, Norway) at an infusion rate of 6.2 ml/s followed by 50 ml of saline solution at the same rate of infusion. The scan was performed by using visual assessments to determine timing of image acquisition. An adaptive statistical iterative reconstruction algorithm was used instead of the standard filtered back-projection algorithm. Datasets of each coronary CTA examination were transferred to an image-processing workstation and analyzed according to the SCCT guidelines for reporting (18) by 2 cardiac radiologists (G.P. and D.A.) who had ≥8 years of experience and who were blinded to the clinical history and ICA findings of the patients.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CTA = computed tomography angiography

CTP = computed tomography myocardial perfusion

ED = effective radiation dose

FFR = fractional flow reserve

HR = heart rate

ICA = invasive coronary angiography

ICD = implantable cardioverter defibrillator

PM = pacemaker

SCCT = Society of Cardiovascular Computed Tomography

as a speaker and clinical research grants from GE and Bracco; institutional fees as a speaker from Medtronic and Bayer; and an institutional research grant from HeartFlow. Dr. Andreini has received institutional fees as a speaker and clinical research grants from GE, Bracco, and Heartflow. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 19, 2017; revised manuscript received October 18, 2017, accepted October 19, 2017.

FIGURE 1 Flowchart of the Study Population

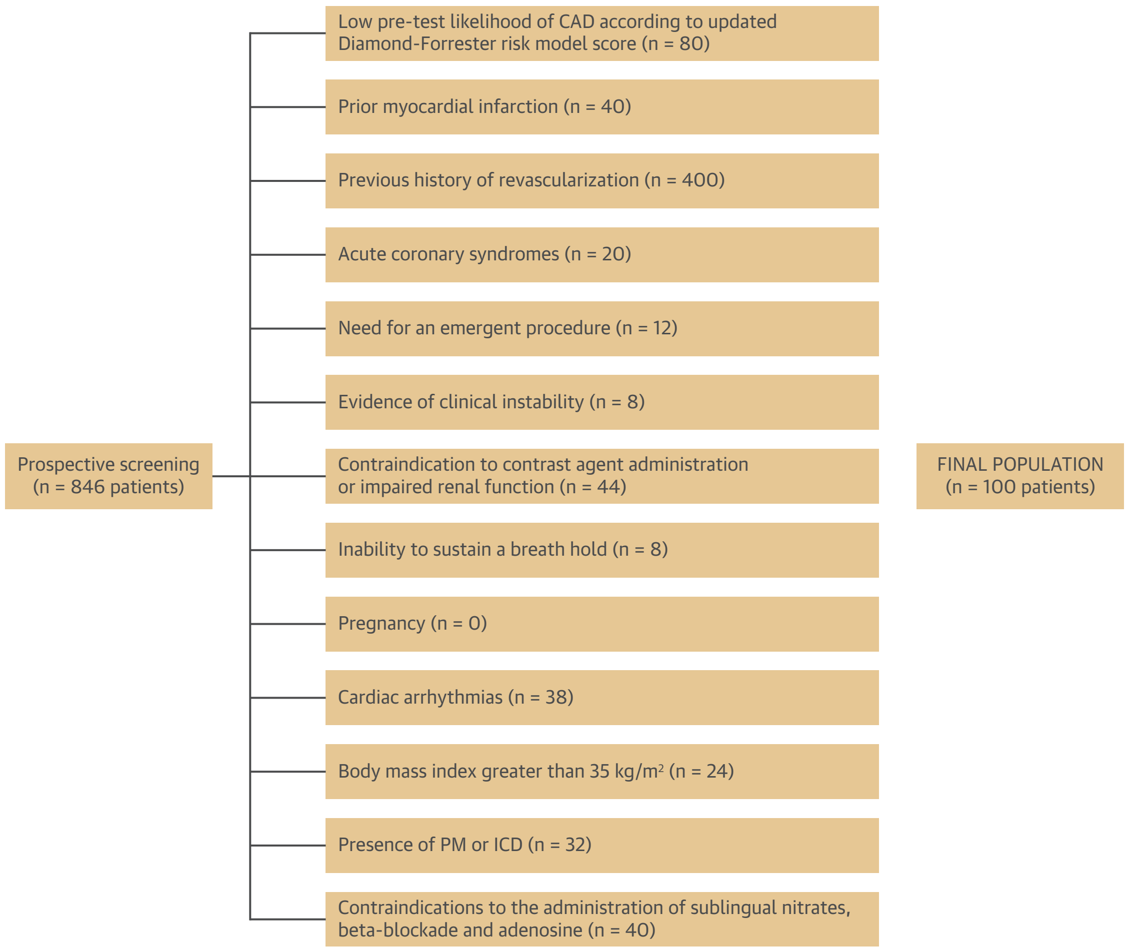


Diagram showing the screening and selection process of subjects. CAD = coronary artery disease; ICD = implantable cardioverter defibrillator; PM = pacemaker.

For analysis of the coronary CTA, coronary arteries were segmented as suggested by the American Heart Association (31). Impaired image quality was classified as blooming artifacts, motion artifacts, or impaired signal-to-noise ratio. Accordingly, the Likert score was used to estimate image quality as follows: score 1—nondiagnostic, impaired image quality precluding appropriate evaluation of the coronary arteries because of severe artifacts; score 2—adequate, reduced image quality because of artifacts but sufficient to rule out obstructive CAD; score 3—good, presence of artifacts but fully preserved ability to assess the presence of luminal stenosis; and score 4—excellent, complete absence of artifacts.

In each coronary artery, coronary atherosclerosis was defined as the presence of any tissue structure >1 mm^2 either within the coronary artery lumen or adjacent to it that could be discriminated from the surrounding pericardial tissue, epicardial fat, or vessel lumen itself. The severity of the coronary lesions was quantified in multiplanar curved reformatted images by measuring the minimum diameter and reference diameter for all stenoses and categorized according to SCCT guidelines for reporting (32). All nonevaluable coronary artery segments were censored as positive. Obstructive CAD was defined as the presence of stenosis $>50\%$. A third cardiac radiologist (A.I.G.) with ≥ 8 years of experience in coronary CTA adjudicated the scores in cases of disagreement.

STRESS CTP. Figure 2 illustrates the study protocol. Vasodilatation was induced with an intravenous adenosine injection (0.14 mg/kg/min over 4 min). At

FIGURE 2 **Study Protocol**

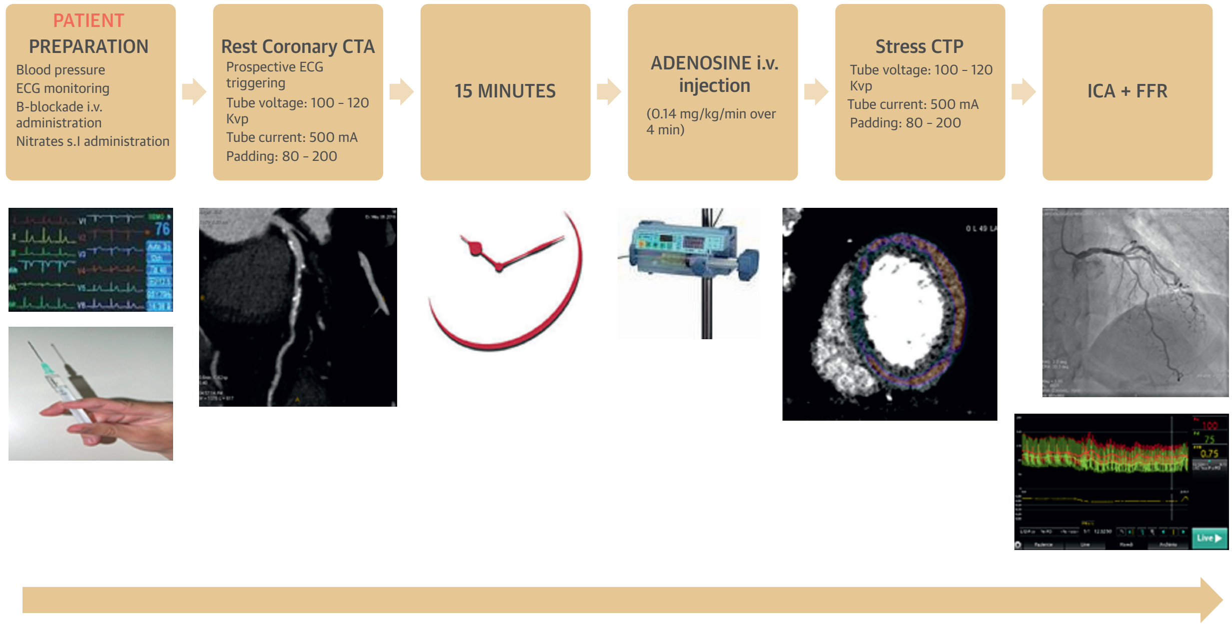


Diagram showing the acquisition protocol. CTA = computed tomography angiography; CTP = computed tomography perfusion; ECG = electrocardiogram; FFR = invasive fractional flow reserve; ICA = invasive coronary angiography; i.v. = intravenously.

the end of the third minute of the adenosine infusion, a single data sample during first-pass enhancement of coronary CTA was acquired with the same protocol described for rest coronary CTA. All datasets of stress CTP were transferred to an image processing workstation (Advantage Workstation Version 4.7, GE Healthcare) and evaluated by 2 cardiac radiologists (A.B and M.G.) who had ≥8 years of clinical experience in cardiac CT performance and analysis and who were blinded to the clinical history, coronary CTA, and ICA findings of the patients. A third cardiac radiologist (S.M.) adjudicated the scores in cases of disagreement.

Myocardial segments were evaluated on short-axis (apical, mid, and basal slices) and long-axis (2-, 3-, and 4-chamber projections) views with 4- to 8-mm average multiplanar reformatted images. Narrow window width and level (350 W and 150 L, respectively) were used for perfusion defect evaluation. A 4-point image quality score was then recorded for each myocardial segment as follows: 1 = very uncertain (poor confidence, could be an artifact or poor image quality); 2 = uncertain (moderate confidence, probably an artifact and less likely a perfusion defect); 3 = rather certain (good confidence, probably a defect, good image quality/no or minor artifacts); and 4 = very certain (excellent image quality/no artifacts) (17). True perfusion defects were defined as subendocardial hypoenhancements encompassing ≥25% transmural myocardial thickness within a specific coronary territory that was not present in the rest dataset.

ADJUDICATION SELECTION ALGORITHM TO MATCH CORONARY ARTERIES WITH MYOCARDIAL TERRITORY. Blinded adjudication was performed to meticulously verify co-registration of CTP-defined perfusion defects with culprit vessels as defined by coronary CTA, previously described by Cerci et al. (33) for the CORE320 (Coronary Artery Evaluation Using 320-Row Multidetector CT Angiography) multicenter study. Briefly, the entry criterion for the algorithm was the presence of both at least 1 coronary arterial lesion of ≥50% diameter stenosis and at least 1 myocardial perfusion defect. For each vessel, the following territories were identified: 1) primary territory—myocardial territories in which blood flow is supplied by the coronary vessel in the most common right dominant anatomic coronary pattern; 2) secondary territories—myocardial territories for which blood flow may be supplied by the coronary vessel under some normal anatomic variations that need confirmation; and 3) tertiary territories—myocardial territories where blood flow is usually not supplied by the coronary vessel. The adjudication process was applied each time there was a coronary arterial lesion of ≥50% diameter

TABLE 1 Characteristics of the Study Population (N = 100)

Baseline characteristics	
Age, yrs	66 ± 9
Male	69 (69)
BMI, kg/m^2	26.8 ± 4
Risk factors	
Hypertension	78 (78)
Smoker	28 (28)
Hyperlipidemia	74 (74)
Diabetes	18 (18)
Family history of CAD	59 (59)
Symptoms	
Typical angina	60 (60)
Atypical angina	40 (40)
Pre-test likelihood of CAD	67.6 ± 10.6
Reasons for invasive coronary angiography	
Symptoms	32 (32)
Positive ex-ECG	35 (35)
Positive stress echocardiography	5 (5)
Positive single-photon emission tomography	25 (25)
Positive stress cardiac magnetic resonance	3 (3)
MDCT scan protocol, rest	
HR before scanning, beats/min	68.3 ± 11.3
β-blocker	51 (51)
β-blocker dosage, mg	5.4 ± 6.5
HR during scanning, beats/min	62.7 ± 9
Dose length product, mGy · cm	203.5 ± 102.9
Effective dose, mSv	2.8 ± 1.4
MDCT scan protocol, stress	
HR during scanning, beats/min	76.1 ± 14
Dose length product, mGy · cm	182.7 ± 75.3
Effective dose, mSv	2.5 ± 1.1
Prevalence of obstructive CAD (≥50%) at ICA	
No disease	31 (31)
1-vessel disease	38 (38)
2-vessel disease	14 (14)
3-vessel disease	17 (17)
Prevalence of functionally significant CAD*	44 (44)

Values are mean ± SD or n (%). *Stenosis >80% or fractional flow reserve <0.8 in intermediate stenosis 30% to 80%.

BMI = body mass index; CAD = coronary artery disease; ex-ECG = exercise electrocardiogram stress test; HR = heart rate; ICA = invasive coronary angiography; MDCT = multidetector computed tomography.

stenosis and at least 1 myocardial perfusion defect in the secondary territories.

EVALUATION OF CORONARY CTA COMBINED WITH STRESS CTP. All coronary artery imaging datasets were combined with stress CTP according to the following interpretation: 1) nonobstructive CAD with negative matched CTP was considered negative; 2) obstructive CAD with negative stress CTP was considered negative; and 3) obstructive CAD with positive matched stress CTP was deemed positive.

ICA AND INVASIVE FFR. In all patients, a certified interventional cardiologist performed diagnostic ICA. The coronary arteries were reported using the American Heart Association classification system. Coronary angiograms were analyzed with quantitative coronary angiography (QantCor QCA, Pie Medical Imaging, Maastricht, the Netherlands) by an interventional cardiologist who had >20 years of experience and analysis and who was blinded to the clinical history of patients and to the coronary CTA and CTP findings. The severity of coronary stenoses was assessed in 2 orthogonal planes by measuring the minimum diameter and reference diameter for all index vessels, and the percent narrowing was derived accordingly. All stenoses ranging between 30% and 80% were evaluated by using invasive FFR according to standard clinical practice (34). For FFR, the pressure wire (Certus Pressure Wire, St. Jude Medical Systems, St. Paul, Minnesota) was calibrated and electronically equalized with the aortic pressure before being placed distal to the stenosis in the distal third of the coronary artery being interrogated. Glyceryl trinitrate (100 mg) was given by intracoronary injection to prevent vasospasm. Intravenous adenosine was administered (140 mg/kg/min) through an intravenous line in the antecubital fossa.

At steady-state hyperemia, FFR was assessed by using the RadiAnalyzer Xpress (Radi Medical Systems, Uppsala, Sweden) and calculated by dividing the mean coronary pressure, measured with the pressure sensor placed distal to the stenosis, by the mean aortic pressure measured through the guide catheter. All intermediate stenoses with invasive FFR ≤0.8 or stenoses >80% diameter reduction or total occlusions were considered functionally significant.

RADIATION EXPOSURE. The effective radiation dose (ED) was calculated as the product between dose-length product and a conversion coefficient for the chest (K = 0.014 mSv/mGy · cm) (35). For ICA, ED was calculated by multiplying the dose area product by a conversion factor (K = 0.21 mSv/mGy · cm^2) for lateral and posteroanterior radiation exposure in the chest.

STATISTICAL ANALYSIS. Statistical analysis was performed with dedicated software SPSS version 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York). Continuous variables are expressed as mean ± SD, and discrete variables are expressed as absolute numbers and percentages. The diagnostic performance of rest coronary CTA alone and the combination of rest coronary CTA plus stress CTP were measured. In detail, the overall evaluability, sensitivity, specificity, negative predictive value, and positive predictive value were calculated and compared with ICA and invasive FFR, as previously described. The nonevaluable coronary and

TABLE 2 Image Quality and Overall Evaluability of Rest Coronary CTA in a Segment-Based Model

	N	Overall Artifacts	Breath Artifacts	Blooming Effects	Motion Artifacts	Impaired Signal-to-Noise Ratio	Likert Score	Nonevaluable Segments
Rest coronary CTA								
LM	99	31	0	26	0	0	3.6 ± 0.7	1
Proximal LAD	100	58	1	46	1	0	3.1 ± 0.9	2
Mid LAD	100	51	1	35	2	0	3.2 ± 0.9	4
Distal LAD	100	33	0	15	4	2	3.4 ± 0.9	4
D1	100	41	0	28	1	1	3.2 ± 0.9	5
D2	73	20	0	7	1	1	3.4 ± 1.0	1
Proximal LCX	100	45	0	34	2	0	3.3 ± 0.9	2
Mid LCX	100	37	0	14	2	1	3.3 ± 0.9	3
Distal LCX	100	17	1	5	1	1	3.6 ± 0.8	2
M1	98	36	1	16	1	3	3.3 ± 1.1	2
M2	56	21	1	9	0	1	3.3 ± 0.9	1
Proximal RCA	100	43	2	29	1	0	3.3 ± 0.9	5
Mid RCA	100	44	3	24	2	2	3.3 ± 0.9	3
Distal RCA	100	32	1	22	0	1	3.5 ± 0.8	2
PLA	100	14	0	4	0	1	3.7 ± 0.7	0
PDA	100	26	1	13	1	1	3.5 ± 0.9	2
All segments	1,526	373 (24)	12 (1)	327 (21)	19 (1)	15 (1)	3.4 ± 0.9	39 (2)

Values are n, mean ± SD, or n (%).

CTA = computed tomography angiography; D1 = first diagonal branch; D2 = second diagonal branch; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; M1 = first marginal branch; M2 = second marginal branch; PDA = posterior descending coronary artery; PLA = posterolateral coronary artery; RCA = right coronary artery.

myocardial segments for coronary CTA and stress CTP were coded as positive for each modality. For the combined protocol of rest coronary CTA plus stress CTP, nonevaluable coronary and myocardial segments were classified according to the combination of both findings. To account for repeated and potentially correlated measurements in multiple perfusion territories in a patient, generalized estimating equations were used with an exchangeable working correlation matrix for comparisons of positive and negative outcomes. The intraclass correlation coefficient was used to determine the intraobserver and interobserver variability in combined rest coronary CTA plus stress CTP interpretation compared with the reference standard. The McNemar test was used to calculate differences in diagnostic performance.

TABLE 3 Image Quality of Stress CPT in a Segment-Based Model

	N	Score 1	Score 2	Score 3	Score 4	Score
Stress CTP						
1. Basal anterior	98	2	17	29	50	3.30
2. Basal anteroseptal	98	0	21	25	52	3.32
3. Basal inferoseptal	98	1	16	31	50	3.33
4. Basal inferior	98	3	19	31	45	3.20
5. Basal inferolateral	98	0	18	32	48	3.31
6. Basal anterolateral	98	1	14	31	52	3.37
7. Mid anterior	98	1	7	19	71	3.63
8. Mid anteroseptal	98	0	8	23	67	3.6
9. Mid inferoseptal	98	0	6	22	70	3.65
10. Mid inferior	98	0	13	19	66	3.54
11. Mid inferolateral	98	0	7	23	68	3.62
12. Mid anterolateral	98	1	4	22	71	3.66
13. Apex	98	0	3	19	76	3.74
All myocardial segments	1,274	9 (0.7)	153 (12)	326 (26)	786 (62)	3.48 ± 0.18

Values are n, n (%), or mean ± SD.

CTP = computed tomography myocardial perfusion; Score 1 = very uncertain; Score 2 = uncertain; Score 3 = rather certain; Score 4 = very certain.

TABLE 4 Diagnostic Accuracy in a Vessel-Based and Patient-Based Model Between Rest Coronary CTA and Rest Coronary CTA Plus Stress CTP Compared With Functionally Significant CAD

	Rest Coronary CTA	Rest Coronary CTA + Stress CTP	p Value
Vessel-based analysis			
True positive	86	80	–
True negative	162	193	–
False positive	50	13	–
False negative	2	8	–
Sensitivity	98 (95-100)	91 (85-97)	0.06
Specificity	76 (71-82)	94 (90-97)	<0.001
Negative predictive value	99 (97-100)	96 (93-99)	0.11
Positive predictive value	63 (55-71)	86 (79-93)	<0.001
Accuracy	83 (78-87)	93 (90-96)	0.002
Patient-based analysis			
True positive	49	49	–
True negative	27	40	–
False positive	23	8	–
False negative	1	1	–
Sensitivity	98 (94-100)	98 (94-100)	1
Specificity	54 (40-68)	83 (73-94)	<0.001
Negative predictive value	96 (90-100)	98 (93-100)	0.7
Positive predictive value	68 (57-79)	86 (77-95)	0.02
Accuracy	76 (68-84)	91 (85-97)	0.004

Values are n or % (95% CI). Functionally significant CAD was defined as stenosis >80% or fractional flow reserve <0.8 in intermediate stenosis 30% to 80%.

CI = confidence interval; other abbreviations as in Tables 1 to 3.

RESULTS

STUDY POPULATION. Table 1 summarizes the patient clinical characteristics. The mean age was 66 ± 9 years, and 69% were male. All patients underwent ICA, and invasive FFR was measured in 87 of 100 patients. The prevalence of obstructive CAD and functionally significant CAD was 69% and 44%, respectively.

IMAGE QUALITY AND OVERALL EVALUABILITY OF REST CORONARY CTA AND STRESS CTP. The rest coronary CTA was successfully performed in all patients. Fifty-one (51%) patients received metoprolol before the scan, with an average dose of 5.4 ± 6.5 mg, and reached a HR during the scan of 62.7 ± 9.0 beats/min (Table 1). Table 2 shows image quality and overall evaluability of coronary artery imaging in a segment-based model. The mean Likert score was 3.4 ± 0.9. Overall evaluability of native coronary arteries was 98% (1,495 of 1,526 coronary artery segments).

Stress CTP was successfully performed in 98 of 100 patients with a mean HR during the scan of 76.1 ± 14.0 beats/min (Table 1). In 2 patients, the stress phase was interrupted due to the onset of dyspnea during the stressor infusion. Table 3 displays the quality of myocardial perfusion imaging in a myocardial segment-based model showing that <1% was classified as very uncertain. The mean image quality score for myocardial perfusion was 3.48 ± 0.18.

DIAGNOSTIC ACCURACY OF REST CORONARY CTA AND COMBINED REST CORONARY CTA PLUS STRESS CTP. The diagnostic performance of rest coronary CTA is presented in Table 4. Coronary CTA alone demonstrated a per-vessel and per-patient sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 98%, 76%, 99%, 63%, and 83%, and 98%, 54%, 96%, 68%, and 76%, respectively. In a vessel-based model, the addition of stress CTP to coronary CTA yielded an improvement of specificity (94%; $p < 0.001$), positive predictive value (86%; $p < 0.001$), and accuracy (93%; $p = 0.002$). Similarly, in a patient-based model, improvements in specificity (83%; $p < 0.001$), positive predictive value (86%; $p = 0.02$), and accuracy (91%; $p = 0.004$) were also observed when stress CTP was combined with coronary CTA.

To further investigate the potential influence of β-blockade use before the scan, we measured and compared the diagnostic accuracy of coronary CTA plus stress CTP in a vessel and a patient-based model between patients who did not receive pre-treatment before the scan (92% [95% confidence interval (CI): 88% to 97%] and 92% [95% CI: 84% to 99%], respectively) versus patients who did receive it (94% [95% CI: 90% to 98%] and 90% [95% CI: 82% to 98%]), and we found no difference. The intraobserver and interobserver agreement for combined rest coronary CTA plus stress CTP interpretation was good, with intraclass correlation coefficients of 0.81 and 0.74. It is noteworthy that stress CTP correctly reclassified 18 of 23 patients with coronary CTA false-positive findings, suggesting a potential reduction of 78% of unnecessary invasive evaluation among patients with positive coronary CTA.

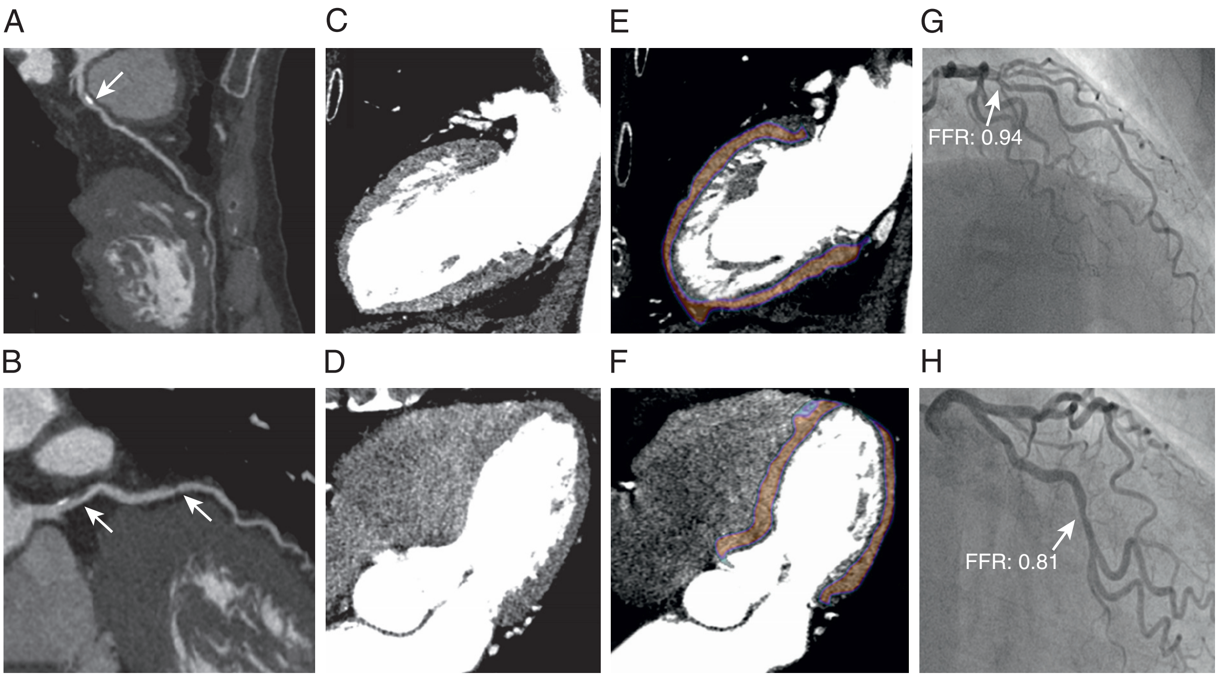
Representative case examples are illustrated in Figures 3 and 4.

EFFECTIVE RADIATION EXPOSURE. The mean dose-length product and ED for coronary CTA and stress CTP were 203.5 ± 102.9 mGy · cm and 2.8 ± 1.4 mSv and 182.7 ± 75.3 mGy · cm and 2.5 ± 1.1 mSv, respectively, for a cumulative mean ED of 5.3 mSv. The average ED of ICA was 10.3 ± 2.5 mSv.

DISCUSSION

To the best of our knowledge, this study is the first that prospectively evaluated the incremental value of

FIGURE 3 **Case Example of CTP Adding Value Over Coronary CTA Alone to Rule Out Hemodynamic Significant Stenosis**



A 76-year-old male patient with angina. **(A)** Rest coronary CTA shows calcified obstructive plaques of the proximal left anterior descending coronary artery. **(B)** Rest coronary CTA shows mixed obstructive plaque of the proximal and mid left circumflex coronary artery. **(C to F)** Stress CTP during adenosine infusion shows normal myocardial perfusion as indicated by the homogeneous **gray** color **(C and D)** and **orange** color code **(E and F)** in 2-chamber and 4-chamber views of the left ventricle. **(G)** ICA shows mild left anterior descending coronary artery stenosis with normal FFR (0.94). **(H)** ICA confirms left circumflex coronary artery stenosis (50%) but with normal FFR (0.81). Abbreviations as in Figure 2.

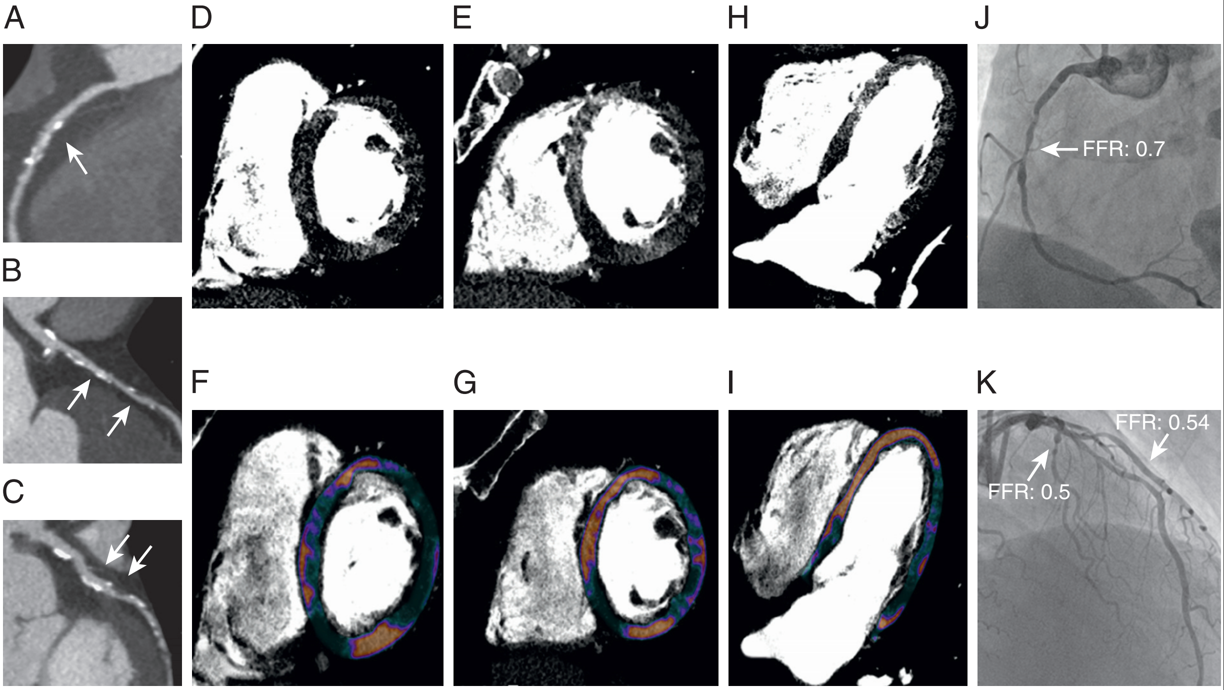
a combined protocol of coronary CTA plus stress CTP using the latest generation whole-heart coverage CT scanner and ICA plus invasive FFR as the reference standard in consecutive patients at intermediate to high risk for CAD. Our main finding is that the addition of stress CTP to coronary CTA significantly increased overall specificity, positive predictive value, and accuracy to detect functionally significant CAD with a cumulative ED of approximately 5 mSv.

A high pre-test likelihood of CAD is associated with increased coronary calcium burden that impairs the ability of coronary CTA to correctly rule out CAD (4) and, in real-world clinical practice, uninterpretable segments found on coronary CTA are often considered as a positive result. In this regard, combined evaluation of coronary artery stenosis and myocardial perfusion during a single examination seems desirable. More recent studies assessed the diagnostic accuracy of a combined protocol of coronary CTA plus stress CTP (7-30). However, in most cases, the study design was retrospective (30), the prevalence of obstructive CAD was low to intermediate (8,15,20,21,23) or was not reported (7,14,17,26-30), the sample size was smaller compared with our study population (7-9,17,25,26,30), the stress CTP protocol was based on dynamic acquisition (14,27) with a stress-rest approach (9,15-17,19,20,28,30), the reference standard was not the combination of ICA and invasive FFR (9,15-17,20,21,25,28,29), and the ED was higher, approximately ≥10 mSv (7,8,9,10,14,21,22,25,26,28,30), or was not reported (16,27,29).

One of the critical steps when assessing the diagnostic accuracy of a combined anatomic and functional evaluation is the appropriate choice of the reference standard technique. In the present study, we chose the combination of ICA plus invasive FFR because it is vessel specific and able to guide revascularization and improve clinical outcomes (34).

Similar to our study, previous prospective studies tested the diagnostic performance of a rest-stress CTP protocol versus a combination of ICA plus invasive FFR by using static (23,26) or dynamic (14,22,27) techniques. In a study by Bettencourt et al. (23), a total of 101 symptomatic patients with suspected CAD underwent an integrated protocol of

FIGURE 4 Case Example of Perfusion Defects Correlating With Pathological Invasive FFR Measurements in Multivessel Disease



A 73-year-old male patient with typical chest pain. Rest coronary CTA showing severe proximal stenoses of the **(A)** right coronary artery, **(B)** left anterior descending coronary artery, and **(C)** obtuse marginal. Stress CTP in **(D to G)** short axis and **(H and I)** 4-chamber long-axis view showing multiple transmural perfusion defects in the anterior, lateral, and inferoseptal walls due to the presence of low attenuation myocardial segments as indicated by **(D, E, and H)** the **black area** and **(F, G, and I)** the **purple area in the colored map**. ICA confirmed severe stenoses of the **(J)** proximal right coronary artery, left anterior descending coronary artery **(K)**, and obtuse marginal **(K)**. FFR values are shown. Abbreviations as in Figure 2.

coronary CTA plus static stress CTP and demonstrated a per-vessel and per-patient diagnostic accuracy of 85% and 88%, respectively, with a mean ED of 5 mSv. However, the study population exhibited a lower prevalence of per-patient obstructive CAD (53% including all stenoses >40%) and a lower per-vessel positive predictive value (only 68%). Moreover, the investigators used a 64-slice scanner. These scanners are limited by a longitudinal axis coverage of 4 cm; the perfusion assessment of the entire heart therefore requires multiple gantry rotations involving 5 to 8 heartbeats, and this approach could affect the performance of the test. Similarly, Wong et al. (26) tested a rest-stress static CTP using more recent 320-slice scanner technology and reported a per-vessel sensitivity, specificity, negative predictive value, and positive predictive value of 76%, 89%, 88%, and 78%, respectively. However, the sample size was smaller, the prevalence of functionally significant CAD was lower, and the ED was twice as much (9.8 mSv) compared with that of the present study. Our findings are in agreement with a recent meta-analysis on myocardial perfusion (36) in which the authors found an area under the curve of 0.91 and 0.93 for the vessel- and patient-based analyses, which are very similar to our results.

Several factors may explain the higher specificity and positive predictive value and the lower ED observed with our study protocol compared with those reported by the previous 2 studies (26,36). First, the single beat acquisition allows a more precise timing of scan when the maximum contrast resolution is reached (27). Second, the high spatial and contrast resolution of the technology used is probably more sensitive to detect the difference in Hounsfield units between normal and hypoperfused myocardium that is only in a range of 50 Hounsfield units (37). Third, the high temporal resolution of the scanner used in this study, has the capability of reducing motion artifacts due to the increased HR usually associated with adenosine injection that may cause false-positive perfusion defects. Fourth, compared with previous-generation scanners, whole-heart CT scanner technology is wide enough to cover the entire left ventricular myocardium within 1 gantry rotation and in a single heartbeat, leading to a more homogeneous attenuation of the myocardium. Finally, the latest generation iterative reconstruction algorithms may further optimize the contrast-to-noise ratio that is crucial to improving sensitivity.

In addition to the aforementioned technical innovations, our protocol involved rest coronary CTA followed by stress CTP. This approach highlights the potential role of combining an anatomic and a functional strategy. Indeed, despite this protocol having the limitation of potential cross-contamination of contrast in the stress phase and potential reduction of sensitivity due to the use of nitrates and beta-blockers in the rest phase, the diagnostic accuracy reported in our study is very robust. This outcome allows the option to skip the stress phase when obstructive CAD is not found at rest acquisition.

Nevertheless, despite all the advantages of the static rest-stress CTP protocol over dynamic scanning, including lower radiation dose and shorter scan time, some drawbacks should be taken into account. Indeed, static CTP is highly dependent on cardiac output and contrast injection protocols. More importantly, static CTP cannot quantitatively assess myocardial blood flow, unlike dynamic CTP. Finally, in the era of CT-derived FFR, there is great interest in the comparison between this technique versus stress CTP. In this regard, in the PERFECTION (Comparison Between Stress Cardiac Computed Tomography Perfusion Versus Fractional Flow Reserve Measured by Computed Tomography Angiography in the Evaluation of Suspected Coronary Artery Disease) study, an intrapatient head-to-head comparison of per-vessel diagnostic accuracy of FFR_{CT} versus stress CTP will be performed (38).

STUDY LIMITATIONS. First, invasive FFR was not performed in all vessels but in intermediate lesions only. However, this method is in agreement with generally accepted clinical standards. Second, the combination of coronary CTA and invasive FFR can only detect ischemia due to epicardial coronary lesions. Third, the cumulative ED was not negligible even though it was significantly lower than that reported by previous studies. Moreover, our study protocol was not focused on radiation exposure reduction, and a further decrease of ED can be achieved by using a single cardiac phase acquisition rather than a multiphase acquisition during stress. Finally, we included patients at intermediate to high risk for CAD, and our results are therefore limited to populations with the same prevalence of disease.

CONCLUSIONS

Our results suggest that use of stress CTP in patients at intermediate to high risk for CAD is a feasible and effective strategy for improving the diagnostic accuracy of coronary CTA. Therefore, if obstructive CAD is not detected by coronary CTA, stress CTP is not needed. However, if an obstructive or nonevaluable coronary artery segment is detected, stress myocardial CTP may be considered as a useful tool to improve diagnostic accuracy. Further studies are warranted to evaluate the prognostic value and cost-effectiveness of the promising technique used in the present study.

ADDRESS FOR CORRESPONDENCE: Dr. Gianluca Pontone, Centro Cardiologico Monzino, IRCCS, Via C. Parea 4, 20138 Milan, Italy. E-mail: gianluca.pontone@ccfm.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The guidelines recommend coronary CTA only in the subset of patients with low to intermediate risk of CAD due to its limited positive predictive value and lack of functional information resulting in a lower cost-effectiveness, and they state that patients with intermediate to high risk should undergo a stress imaging–based strategy. In this regard, new coronary CTA techniques such as stress CTP recently emerged as potential strategies to combine anatomic and functional evaluation in a single scan. In this study, we showed in consecutive patients at intermediate to high risk for CAD that the addition of stress CTP to coronary CTA with a novel generation of a whole-heart coverage CT scanner significantly increased overall specificity, positive predictive value, and accuracy in vessel-based and patient-based models with a cumulative ED 50% less than the combination of ICA plus invasive FFR.

TRANSLATIONAL OUTLOOK: The use of stress CTP in patients at intermediate to high risk for CAD is a feasible and effective strategy for improving the diagnostic accuracy of coronary CTA. If obstructive CAD is not detected by coronary CTA, stress CTP is not needed. However, if an obstructive or nonevaluable coronary artery segment is detected, stress myocardial CTP may be considered as a useful tool to improve diagnostic accuracy. Further studies are warranted to evaluate the prognostic value and cost-effectiveness of the promising technique used in our study.

REFERENCES

1. Pontone G, Andreini D, Bartorelli AL, et al. Diagnostic accuracy of coronary computed tomography angiography: a comparison between prospective and retrospective electrocardiogram triggering. J Am Coll Cardiol 2009;54:346–55.

2. Pontone G, Andreini D, Bartorelli AL, et al. A long-term prognostic value of CT angiography and exercise ECG in patients with suspected CAD. J Am Coll Cardiol Img 2013;6:641–50.

3. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

4. Pontone G, Bertella E, Mushtaq S, et al. Coronary artery disease: diagnostic accuracy of CT coronary angiography—a comparison of high and standard spatial resolution scanning. Radiology 2014;271:688–94.

5. Pontone G, Andreini D, Guaricci AI, et al. The STRATEGY study (Stress Cardiac Magnetic Resonance Versus Computed Tomography Coronary Angiography for the Management of Symptomatic Revascularized Patients): resources and outcomes impact. Circ Cardiovasc Imaging 2016;9:e005171.

6. Rossi A, Merkus D, Klotz E, et al. Stress myocardial perfusion: imaging with multidetector CT. Radiology 2014;270(1):25–46.

7. George RT, Arbab-Zadeh A, Miller JM, et al. Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. Circ Cardiovasc Imaging 2009;2:174–82.

8. Blankstein R, Shturman LD, Rogers IS, et al. Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. J Am Coll Cardiol 2009;54:1072–84.

9. 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;254:410–9.

10. Cury R, Magalhães TA, Borges AC, et al. Dipyridamole stress and rest myocardial perfusion by 64-detector row computed tomography in patients with suspected coronary artery disease. Am J Cardiol 2010;106:310–5.

11. Ho KT, Chua KC, Klotz E, Panknin C. Stress and rest dynamic myocardial perfusion imaging by evaluation of complete time-attenuation curves with dual-source CT. J Am Coll Cardiol Img 2010;3:811–20.

12. Tamarappoo BK, Dey D, Nakazato R, et al. Comparison of the extent and severity of myocardial perfusion defects measured by CT coronary angiography and SPECT myocardial perfusion imaging. J Am Coll Cardiol Img 2010;3:1010–9.

13. Ho KT, Panknin C. CT myocardial perfusion imaging of myocardial blood flow reserve before and after coronary artery stenting. J Cardiovasc Comput Tomogr 2011;5:125–6.

14. Bamberg F, Becker A, Schwarz F, et al. Detection of hemodynamically significant coronary artery stenosis: incremental diagnostic value of dynamic CT-based myocardial perfusion imaging. Radiology 2011;260:689–98.

15. Bettencourt N, Rocha J, Ferreira N, et al. Incremental value of an integrated adenosine stress-rest MDCT perfusion protocol for detection of obstructive coronary artery disease. J Cardiovasc Comput Tomogr 2011;5:392–405.

16. Cury RC, Magalhães TA, Paladino AT, et al. Dipyridamole stress and rest transmural myocardial perfusion ratio evaluation by 64 detector-row computed tomography. J Cardiovasc Comput Tomogr 2011;5:443–8.

17. Feuchtner G, Goetti R, Plass A, et al. Adenosine stress high-pitch 128-slice dual-source myocardial computed tomography perfusion for imaging of reversible myocardial ischemia: comparison with magnetic resonance imaging. Circ Cardiovasc Imaging 2011;4:540–9.

18. Ko BS, Cameron JD, Leung M, et al. Combined CT coronary angiography and stress myocardial perfusion imaging for hemodynamically significant stenoses in patients with suspected coronary artery disease: a comparison with fractional flow reserve. J Am Coll Cardiol Img 2012;5:1097–111.

19. Ko BS, Cameron JD, Meredith IT, et al. Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: a comparison with fractional flow reserve. Eur Heart J 2012;33:67–77.

20. 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. AJR Am J Roentgenol 2012;198:521–9.

21. Nasis A, Ko BS, Leung MC, et al. Diagnostic accuracy of combined coronary angiography and adenosine stress myocardial perfusion imaging using 320-detector computed tomography: pilot study. Eur Radiol 2013;23:1812–21.

22. Huber AM, Leber V, Gramer BM, et al. Myocardium: dynamic versus single-shot CT perfusion imaging. Radiology 2013;269:378–86.

23. Bettencourt N, Ferreira ND, Leite D, et al. CAD detection in patients with intermediate-high pre-test probability: low-dose CT delayed enhancement detects ischemic myocardial scar with moderate accuracy but does not improve performance of a stress-rest CT perfusion protocol. J Am Coll Cardiol Img 2013;6:1062–71.

24. Rochitte CE, George RT, Chen MY, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. Eur Heart J 2014;35:1120–30.

25. Bamberg F, Marcus RP, Becker A, et al. Dynamic myocardial CT perfusion imaging for evaluation of myocardial ischemia as determined by MR imaging. J Am Coll Cardiol Img 2014;7:267–77.

26. Wong DT, Ko BS, Cameron JD, et al. Comparison of diagnostic accuracy of combined assessment using adenosine stress computed tomography perfusion + computed tomography angiography with transluminal attenuation gradient + computed tomography angiography against invasive fractional flow reserve. J Am Coll Cardiol 2014;63:1904–12.

27. Rossi A, Dharampal A, Wragg A, et al. Diagnostic performance of hyperaemic myocardial blood flow index obtained by dynamic computed tomography: does it predict functionally significant coronary lesions? Eur Heart J Cardiovasc Imaging 2014;15:85–94.

28. 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;9:103–12.

29. Magalhães TA, Kishi S, George RT, et al. Combined coronary angiography and myocardial perfusion by computed tomography in the identification of flow-limiting stenosis—the CORE320 study: an integrated analysis of CT coronary angiography and myocardial perfusion. J Cardiovasc Comput Tomogr 2015;9:438–45.

30. Yang DH, Kim YH, Roh JH, et al. Diagnostic performance of on-site CT-derived fractional flow reserve versus CT perfusion. Eur Heart J Cardiovasc Imaging 2017;18:432–40.

31. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51:5–40.

32. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342–58.

33. Cerci RJ, Arbab-Zadeh A, George RT, et al. Aligning coronary anatomy and myocardial perfusion territories: an algorithm for the CORE320 multicenter study. Circ Cardiovasc Imaging 2012;5:587–95.

34. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

35. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. Circulation 2007;116:1290–305.

36. Takx RA, Blomberg BA, El Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. Circ Cardiovasc Imaging 2015;8. pii:e002666.

37. George RT, Jerosch-Herold M, Silva C, et al. Quantification of myocardial perfusion using dynamic 64-detector computed tomography. Invest Radiol 2007;42:815–22.

38. Pontone G, Andreini D, Guaricci AI, et al. Rationale and design of the PERFECTION (Comparison Between Stress Cardiac Computed Tomography Perfusion Versus Fractional Flow Reserve Measured by Computed Tomography Angiography in the Evaluation of Suspected Coronary Artery Disease) prospective study. J Cardiovasc Comput Tomogr 2016;10:330–4.

KEY WORDS accuracy, computed tomography, coronary artery disease, myocardial perfusion