Journal of the American College of Cardiology Vol. 61, No. 10, 2013

Published by Elsevier Inc.

ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.12.020

Direct Comparison of Cardiac Magnetic Resonance and Multidetector Computed Tomography Stress-Rest Perfusion Imaging for Detection of Coronary Artery Disease

Nuno Bettencourt, MD,*†‡ Amedeo Chiribiri, MD, PhD,† Andreas Schuster, MD, PhD,†§ Nuno Ferreira, MD,* Francisco Sampaio, MD,*‡ Gustavo Pires-Morais, MD,* Lino Santos, MD* Bruno Melica, MD,* Alberto Rodrigues, MD,* Pedro Braga, MD,* Luís Azevedo, MD,‡ Madalena Teixeira, MD,* Adelino Leite-Moreira, MD, PhD,‡ José Silva-Cardoso, MD, PhD,‡ Eike Nagel, MD, PhD,† Vasco Gama, MD*

Vila Nova de Gaia and Porto, Portugal; London, United Kingdom; and Göttingen, Germany

Objectives This study sought to compare the diagnostic performance of a multidetector computed tomography (MDCT) integrated protocol (IP) including coronary angiography (CTA) and stress-rest perfusion (CTP) with cardiac magnetic resonance myocardial perfusion imaging (CMR-Perf) for detection of functionally significant coronary artery disease (CAD).

Background MDCT stress-rest perfusion methods were recently described as adjunctive tools to improve CTA accuracy for detection of functionally significant CAD. However, only a few studies compared these MDCT-IP with other clinically validated perfusion techniques like CMR-Perf. Furthermore, CTP has never been validated against the invasive reference standard, fractional flow reserve (FFR), in patients with suspected CAD.

Methods 101 symptomatic patients with suspected CAD (62 ± 8.0 years, 67% males) and intermediate/high pre-test probability underwent MDCT, CMR and invasive coronary angiography. Functionally significant CAD was defined by the presence of occlusive/subocclusive stenoses or FFR measurements ≤0.80 in vessels >2mm.

Results On a patient-based model, the MDCT-IP had a sensitivity, specificity, positive and negative predictive values of 89%, 83%, 80% and 90%, respectively (global accuracy 85%). These results were closely related with those achieved by CMR-Perf: 89%, 88%, 85% and 91%, respectively (global accuracy 88%). When comparing test accuracies using non-inferiority analysis, differences greater than 11% in favour of CMR-Perf can be confidently excluded.

Conclusions MDCT protocols integrating CTA and stress-rest perfusion detect functionally significant CAD with similar accuracy as CMR-Perf. Both approaches yield a very good accuracy. Integration of CTP and CTA improves MDCT performance for the detection of relevant CAD in intermediate to high pre-test probability populations. (J Am Coll Cardiol 2013;61:1099–107) © 2013 by the American College of Cardiology Foundation

Multidetector computed tomography (MDCT) is the established noninvasive reference standard for the assessment of coronary artery anatomy. It is particularly useful for the exclusion of coronary artery disease (CAD) in patients with intermediate-to-low pre-test probability, largely because of its high negative predictive value (NPV) (1,2). However, a major limitation of this technique is its low specificity and positive predictive value (PPV) (3). Decision on the signif-

From the *Cardiology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; †Kings College London, London, England; ‡Faculty of Medicine, University of Porto, Porto, Portugal; and the §Department of Cardiology and Pulmonology, George-August-University and German Center for Cardiovascular Research (DZHK, Partner Site), Göttingen, Germany. This study was supported by the Department of Health via a National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St. Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. Dr. Bettencourt was funded by Fundação para a Ciência e Tecnologia, Portugal, under grant SFRH/BD/45989/2008 and received grant support from the Portuguese Society of Cardiology and the European Society of Cardiology. Dr. Chiribiri was funded by Wellcome Trust and Engineering and Physical Sciences Research Council grant WT 088641/Z/09/Z. Dr. Schuster was a British Heart Foundation (BHF) clinical research fellow (FS/10/029/28253) and received support from the BHF (grant RE/08/003) and Biomedical Research Centre (grant BRC-CTF 196). All other authors have reported that they have no relationships relevant to this paper to disclose.

Manuscript received October 31, 2012; revised manuscript received December 4, 2012, accepted December, 26 2012.

Abbreviations and Acronyms

CAD = coronary artery disease
CMR = cardiac magnetic resonance
CTA = computed tomography angiography
CTP = computed tomography perfusion
FFR = fractional flow reserve
IP = integrated protocol
MDCT = multidetector computed tomography
Perf = myocardial perfusion imaging
NPV = negative predictive value
PPV = positive predictive value
xA = x-ray coronary angiography

icance of MDCT-findings generally involves additional studies, as the degree of stenosis is often overestimated and the physiologic significance of many lesions remains uncertain (4,5). Furthermore, its diagnostic accuracy is severely limited by calcification, reducing the value in patients with higher pre-test probability. In those cases, it is generally preferable to use functional tests, capable of detecting myocardial ischemia (6).

MDCT perfusion (CTP) has been recently described as a potential tool for ischemia detection and preliminary studies proved the incremental value of integrating CTP and CTA for the detection of obstructive CAD as assessed by invasive x-ray coronary angiography (xA) in high-risk populations (7,8). However, a comparison of these MDCT integrated protocols (MDCT-IP) with established stress perfusion techniques like cardiovascular magnetic resonance (CMR) myocardial perfusion imaging (Perf) (9–11) and fractional flow reserve (FFR), considered the invasive standard for assessing the functional significance of CAD (12) is missing.

The aim of this study was to compare the diagnostic accuracy of a MDCT-IP (including CTA and stress-rest myocardial CTP) with CMR-Perf for the detection of functionally significant CAD, using FFR as the reference standard.

Methods

Population. One-hundred-seventy-six consecutive patients referred to the cardiology outpatient clinic for assessment of CAD were prospectively screened from January 2010 to November 2011. Inclusion criteria were: age >40 years, symptoms compatible with CAD and ≥2 risk-factors or a positive/inconclusive treadmill-test. Exclusion criteria included clinical instability, known CAD, valvular heart disease, atrial fibrillation, creatinine clearance ≤60 ml/min and standard contraindications to CMR, contrast media and adenosine. A total of 139 eligible patients were tested for exclusion criteria. Figure 1 summarizes the study flow and reasons for exclusions. The final population consisted of 101 individuals with an intermediate or high pre-test probability (Table 1) (13). The local research ethics committee approved the study protocol and written informed consent was obtained from all participants.

Study design. Patients were scheduled for CMR and MDCT scans in the week before xA and were instructed to refrain from smoking, coffee, tea, aminophylline, beta-blockers, calcium antagonists and nitrates for 24-h before the tests. At the time of xA, FFR was measured in all major patent coronary arteries with >40% diameter stenosis. CMR and MDCT results were fully blinded.

CMR protocol. CMR-Perf was performed using established protocols on a 1.5-T Siemens Symphony (Siemens, Erlangen, Germany) using a 12-channel receiver coil (14). Three short-axis slices (basal, mid-ventricular, apical) per heartbeat were imaged at apnoea during the first pass of a gadolinium bolus (0.07 mmol/kg) using a gradient-echo sequence during maximal hyperemia (intravenous adenosine 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and at rest. Long- and short-axis cinematic images were obtained using a steady-state free-precession breath-hold sequence for volumetric and functional analyses. Late-gadolinium-enhancement imaging (LGE) using a 2D phase-sensitive inversion-recovery breath-hold sequence was performed ≥10 min after the last administration of contrast (11).

MDCT scan protocol. The MDCT stress-rest protocol was performed as previously described, using a Somatom Sensation 64 scanner (Siemens Medical Solutions, Forchheim, Germany) (15). No pre-test medication was administered.

After calcium-scoring, a retrospectively gated scan during the first-passage of contrast medium (iopromide, 80 ml, at 4.5 ml/s) during adenosine infusion (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 to 6 min) was obtained (tube voltage: 100 kV; tube current modulation with full tube current [600 mAs] applied at 60% to 65% of the RR interval; collimation, 64 × 0.6 mm) using a bolus-tracking technique in the ascending aorta (threshold: 150 HU; delay, 4 s). Adenosine infusion was discontinued immediately after stress acquisition.

If the heart rate exceeded 65 beats/min at 3 min after suspension of adenosine (n = 44), fractionated boluses of intravenous metoprolol (5 to 20 mg) were administered targeting a heart rate ≤60 beats/min. All patients received 0.05 mg of sublingual nitroglycerine 5 min prior to the rest scan. This scan was acquired 10 min after the stress scan, using prospective triggering (65% of cardiac cycle interval; 100 kV; 110 mAs). Timing and contrast injection were similar to the stress scan, using a test-bolus technique.

CMR analysis. Two blinded independent readers analysed all CMR images. In cases of disagreement, a third reader adjudicated. Perfusion defects were defined as subendocardial or transmural dark areas compared to remote healthy myocardium, persisting for at least 10 frames. Stress and rest scans were viewed simultaneously, and areas of hypoperfusion were assigned to the ventricular segments, using the standard 17-segment model, excluding the apex (16). LGE was analysed simultaneously and used to differentiate areas of scar from induced ischemia. Regional wall motion or scar alone was not regarded as a sign of ischemia/CAD. Only areas with ischemia on perfusion imaging were regarded as positive; patients with scar but no additional ischemia were classified as negatives. Image quality and degree of confidence were classified using four-class scales: from poor to

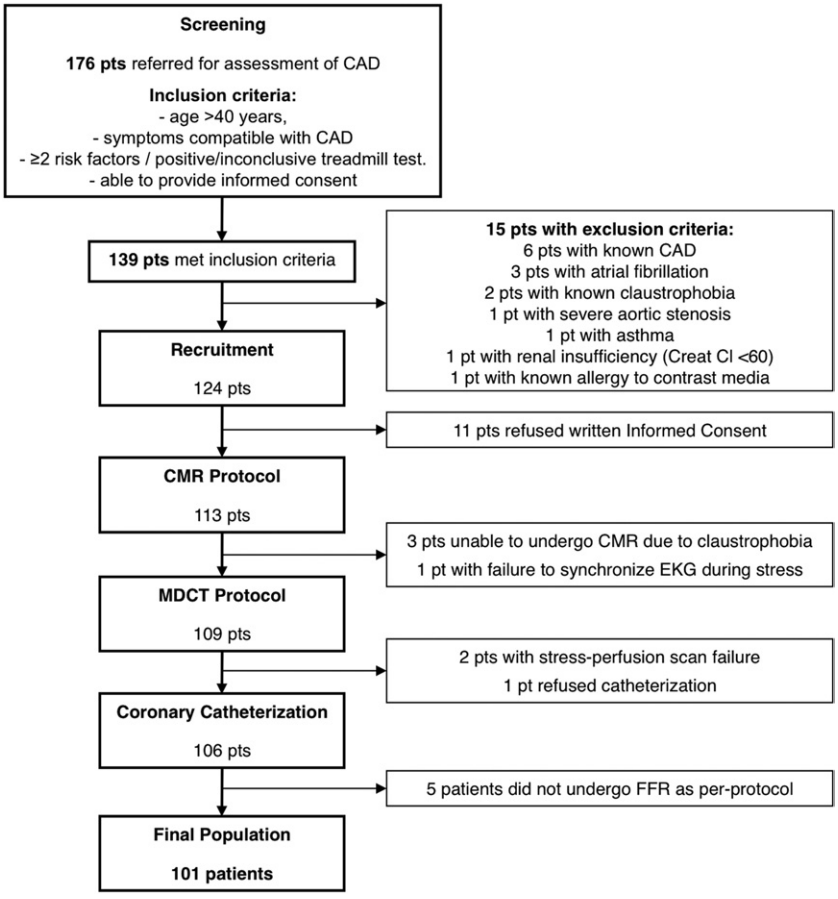

Figure 1 **Study Flow Chart and Reasons for Exclusions**

Of the 176 screened patients, 139 met inclusion criteria; of those, 15 had exclusion criteria and 11 refused written informed consent. Twelve patients were excluded for not completing the protocol as planned. The 101 patients composing the final population underwent cardiac magnetic resonance (CMR), multidetector computed tomography (MDCT), and coronary catheterization with no adverse events. CAD = coronary artery disease; EKG = electrocardiogram; FFR = fractional flow reserve.

excellent and from very unconfident to very confident, respectively.

MDCT analysis. For CTA analysis both stress and rest acquisitions were used. From the stress acquisition, a set of 10 (5% to 95%) plus 1 (60%) phases was reconstructed using a standard soft frequency cardiac filter (Siemens-B25f), with a slice-thickness of 0.6mm. From rest, a single-phase (65%) reconstruction was obtained using the same slice thickness and filter. Resulting datasets were anonymized, sent to a post-processing workstation (Aquarius; TeraRecon Inc., San Mateo, California) and analyzed by two blinded readers using the 17-segment modified AHA classification (17). Each segment was graded according to stenoses: 1 = normal; 2 = <50%; 3 = 50% to 70%; 4 = ≥70%/occlusion; 5 = uninterpretable.

For myocardial CTP analysis, similar reconstructions were obtained using the same parameters but with a very smooth frequency filter (Siemens-B10f). The same blinded readers performed a visual analysis of these images at a different time point of the study, according to the standard 17-segment model (16) using standard 10-mm-thick multiplanar reformat planes (short-axis, 2, 3, and 4 chambers). This analysis was typically initiated using average intensity projections and set to narrow window (W) and level (L) settings (W300/L150), but the reading physician was allowed to adjust settings and projections, as needed. Stress images were typically analyzed as cinematic images, taking advantage of the multiphasic reconstruction and integrating perfusion with regional wall motion analysis. This approach helped in the differentiation of perfusion defects from artifacts, which tend to change position from systole to diastole. A side-by-side comparison of stress and rest images was also used to differentiate inducible ischemia from artifacts or scar. The same criteria used for defining functionally significant CAD in CMR-Perf analysis were applied for CTP. Image quality and degree of confidence were classified as described for CMR. Interobserver disagreements were resolved by consensus.

MDCT radiation exposure estimation. Effective radiation dose exposure was calculated by the method of the Euro-

JACC Vol. 61, No. 10, 2013
March 12, 2013:1099–107

Table 1 Population Characteristics (N = 101)

Males (% of total)	68 (67%)
Age (yrs)	62 ± 8.0 (41–79)
Body mass index (kg/m^2)	28.0 ± 4.45 (19.9–45.2)
Symptoms	101 (100%)
Typical angina	25 (25%)
Atypical angina	49 (49%)
Chest pain	22 (22%)
Dyspnea on exertion/fatigue	5 (5%)
Hypercholesterolemia	80 (79%)
Hypertension	73 (72%)
Diabetes mellitus	39 (39%)
Positive smoking history	34 (34%)
Current smoker	14 (14%)
Ex-smoker	20 (20%)
Family history of premature CAD	21 (21%)
≥2 CRF	85 (84%)
Systolic blood pressure (mm Hg)	147 ± 21.9 (99–184)
Diastolic blood pressure (mm Hg)	78 ± 10.8 (57–102)
Abdominal circumference (cm)	98 ± 10.3 (76–126)
Modified Diamond-Forrester score	14.2 ± 2.7 (9–20)
On regular medication	90 (89%)
Aspirin or clopidogrel	54 (53%)
Statin	66 (65%)
ACEi or A2 receptor blockers	52 (51%)
Beta-blocker	68 (67%)
Agatston score (median-min-max)	291 (0–5,879)
CAC ≤ 10	19 (19%)
CAC 11–100	20 (20%)
CAC 101–400	17 (17%)
CAC 401–1,000	26 (26%)
CAC >1,000	19 (19%)
Any stenosis >40%	54 (53%)
Any significant stenosis (FFR ≤0.80)	44 (44%)
Single-vessel disease	24 (24%)
Double-vessel disease	12 (12%)
Triple-vessel disease	8 (8%)
Left main disease	5 (5%)

Values are n (%) or mean ± SD (range).
ACEi = angiotensin-converting enzyme inhibitor; A2 = angiotensin 2.

pean working group: product of the chest coefficient (0.014) and the dose-length product (DLP) obtained during each scan (18).

X-ray coronary angiography and FFR assessment. xA was performed according to standard techniques. When arteries with stenosis >40% were visually perceived, pressure wire (Certus, St. Jude Medical, St. Paul, Minnesota) was used to determine vessel FFR by using RadiAnalyzer (St. Jude Medical, St. Paul, Minnesota) under steady-state hyperemia (intravenous adenosine, 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 3 to 6 min). Arteries were recorded as having significant CAD if they had a FFR ≤0.80, if they were occluded/subtotally occluded, or if there was severe left main (LM) disease (>50%). This functionally significant CAD was defined as the reference standard against which MDCT and CMR-Perf were compared.

Assignment of perfusion segments to the corresponding vascular territory. For vessel-based analysis, areas of perfusion defects in CTP and CMR were identified using the 16 myocardial segments. Each segment was assigned to one of the 3 "main vessels": right coronary artery (RCA), left anterior descending (LAD), and circumflex (LCX). To ensure correct association of the 16 myocardial segments with the correct vascular territory, xA visualization of vessel dominance was used to decide if the inferior and inferoseptal territories were supplied by the RCA or the LCX. For the distal segment of the inferior wall, an eventual LAD supply was also considered. Additionally, the basal and mid anterolateral segments were assigned to the LCX or LAD vessel depending on whether obtuse marginal or diagonal branches were responsible for the blood supply of those territories (16).

Statistical analysis. The diagnostic performances of MDCT (CTA alone, CTP alone, MDCT-IP) and CMR for the detection of functionally significant CAD were compared against FFR as the reference standard. The "unevaluable" segments/arteries in CTA were coded as being positive for CAD when CTA alone was considered; in the MDCT-IP, they were classified as negative or positive, according to the CTP results of their territory (Fig. 2). CTP performance in detecting reversible myocardial ischemia was also evaluated having CMR-Perf as the reference standard.

All continuous variables were expressed as mean ± SD, whereas categorical variables were expressed as percentages. The McNemar test was used to calculate differences between proportions (sensitivity, specificity and accuracy) obtained from paired observations. Cohen's kappa statistic was used to assess intermodality and intra/interobserver agreements. The area under the receiver-operator characteristic curve (AUC = C-statistic) was calculated and compared for all diagnostic-testing strategies taking FFR as gold-standard. Specific methods to test noninferiority for paired binary data (19) and ROC curves (20) were used to calculate the minimal noninferiority margin that we are able to detect with the present sample size and to perform a formal power analysis. Statistical analyses were performed using MedCalc for Windows, version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium). A p value <0.05 was considered statistically significant.

Results

All patients completed the study protocol without adverse effects. CMR and MDCT scans were performed within 9 ± 8.2 days before xA.

CMR scans. Image quality was classified as poor in 2 patients, moderate in 20, good in 57, and excellent in 22. Readers felt unconfident in the diagnosis of 8 patients, confident in 60 and very confident in 33. Forty-six patients and 70 of the 303 vascular territories had perfusion defects suggestive of ischemia during stress (Fig. 3); 30 were in the

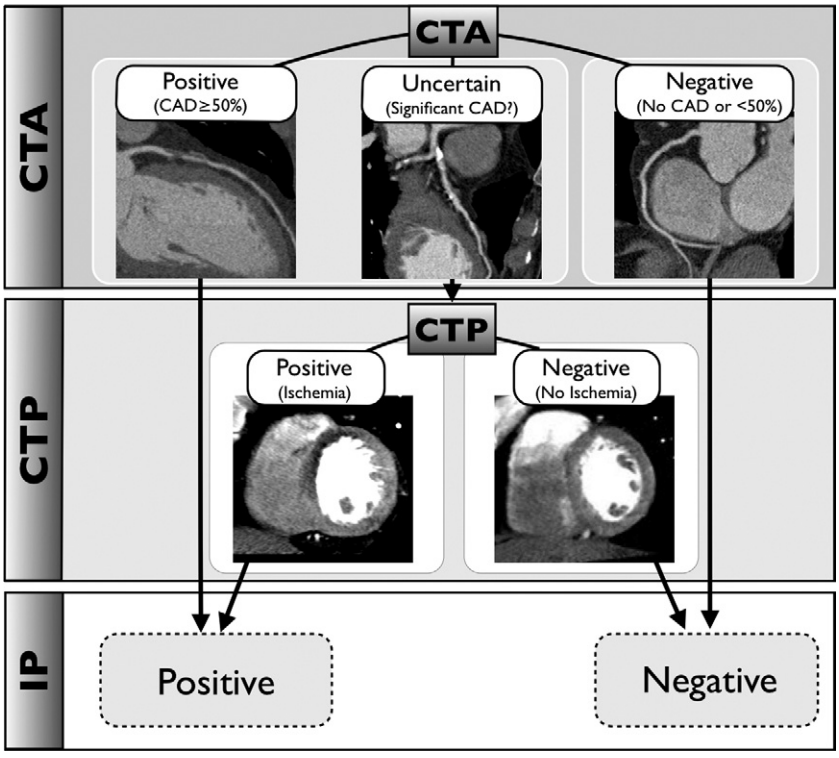

Figure 2 **MDCT Integrated Protocol Interpretative Algorithm**

The MDCT integrated protocol (IP) was classified positive if a definitive luminal obstruction (≥50%) was detected on computed tomography coronary angiography (CTA) or if a perfusion defect was detected on computed tomography coronary perfusion (CTP) in a territory corresponding to a lesion of uncertain significance on CTA. The IP was deemed negative if no stenosis>50% were detected on CTA or if no perfusion defects were found in areas supplied by vessels with uncertain findings on CTA. CAD = coronary artery disease. MDCT = multidetector computed tomography.

LAD territory, 15 in the LCX territory, and 25 in the RCA territory. Sixteen patients had an ischemic pattern of LGE. Intraobserver and interobserver agreements for CMR-Perf in per-patient analysis produced a kappa of 0.71 and 0.57, respectively (substantial agreement).

MDCT scans. Image quality was classified as poor in 9 patients, moderate in 39, good in 52 and excellent in 1. Readers felt unconfident in 49 cases, confident in 47 and very confident in 5. Mean radiation exposure of the entire MDCT protocol was 5.0 ± 0.96 (3.7 to 8.9) mSv. Thirty-three (33%) patients had at least 1 unevaluable segment – usually because of the presence of extensive calcification. Among the patients who had fully interpretable scans, 10 had no atherosclerotic disease, 25 had mild disease (<50% stenosis), and 33 had stenosis ≥50%. When the unevaluable segments were considered to represent significant disease, 65 patients were categorized as having significant CAD. CTP inducible defects were identified in 34 patients and in 46 (15%) of the vascular territories; 190 segments had adenosine-induced subendocardial (88%) or transmural (12%) perfusion defects. CTP had good intraobserver (kappa = 0.66) and interobserver agreement (kappa = 0.44) in per-patient analysis.

FFR results. Fifty-four patients with visually perceived diameter stenosis >40% were considered for FFR assessment. Arteries without any identifiable plaque (n = 179) or with mild (≤40%) disease (n = 29) had no FFR measurements. Vessels with a luminal diameter <2 mm (n = 10) were also excluded. There were 19 completely occluded arteries and 11 subtotally occluded arteries in which FFR could not be measured but regarded as positive. Additionally, in 9 vessels with long sections of severe disease and heavily calcified lesions associated with tortuous anatomy and/or low TIMI-flow after intracoronary nitrates, FFR assessment was considered an unacceptable risk and was not performed. Furthermore, in 5 patients with LM disease FFR was not performed in any vessel of the left coronary. Lesions in which FFR could not be measured because of anatomy or disease complexity were considered positive for the purpose of the comparison with CMR-Perf and CTP. A total of 36 diseased, unoccluded vessels (n = 27) were evaluated using FFR assessment. Using this approach, 72 arteries were classified as positives. Single-vessel disease was seen in 24 patients; 12 had double-vessel disease and 8 had triple-vessel disease.

JACC Vol. 61, No. 10, 2013
March 12, 2013:1099–107

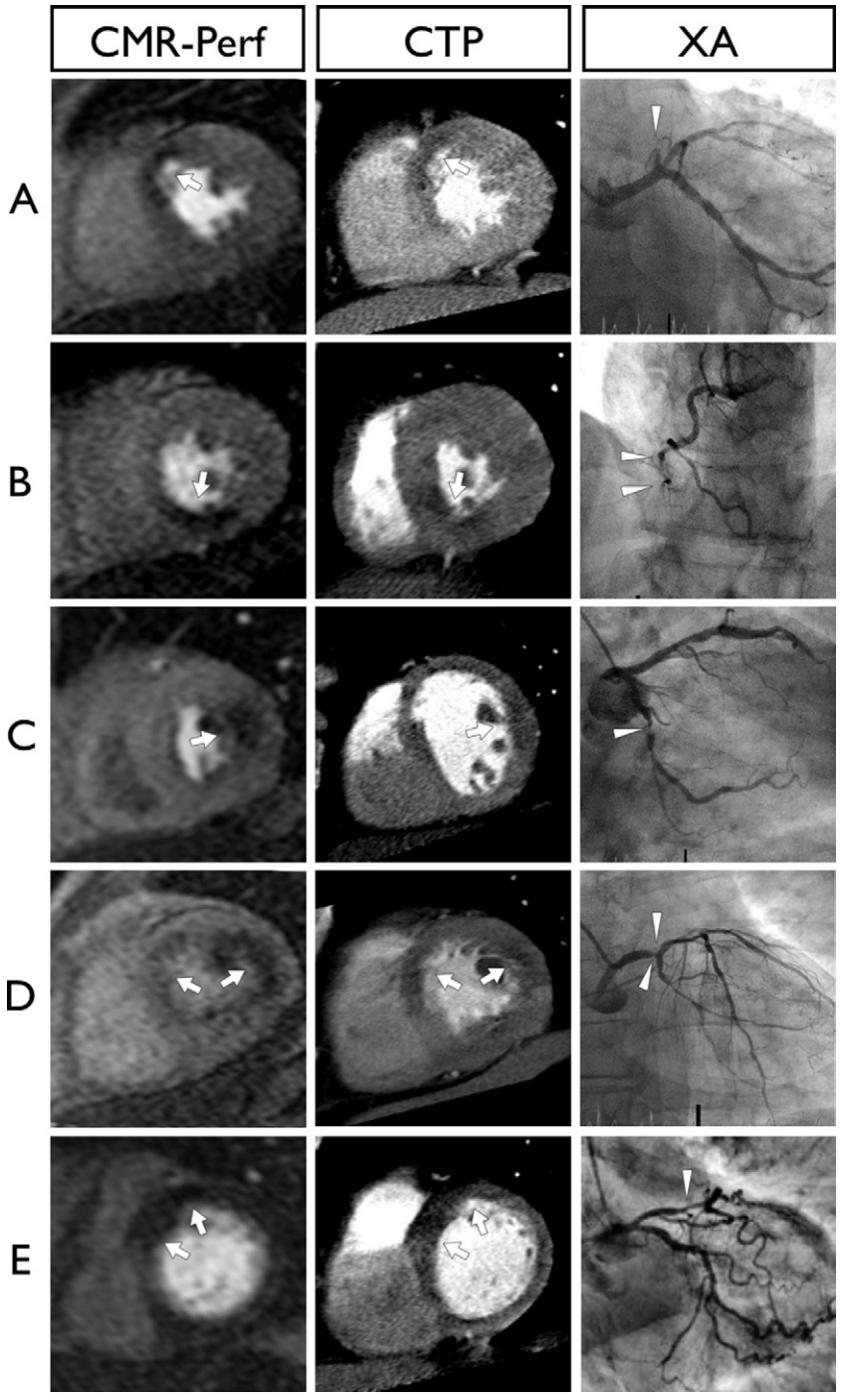

Figure 3 **Five Cases Illustrating CMR-Perf, CTP, and Angiographic Findings in Patients With CAD**

(A) Stress cardiac magnetic resonance perfusion (CMR-Perf) shows inducible ischemia in the septum and anterior wall (**arrow** shows dark area of hypoperfusion). Computed tomography coronary perfusion (CTP) is concordant and x-ray invasive coronary angiography (xA) confirms a stenosis **(arrowhead)** in the LAD. **(B)** Both CMR-Perf and CTP show a dark area of fixed hypoperfusion **(arrows)** in the inferior and inferoseptal wall, corresponding to an occluded right coronary artery as seen on xA. **(C)** Both CMR-Perf and CTP were able to identify the reversible hypoperfusion **(arrow)** caused by a significant stenosis on the left circumflex artery. **(D)** Significant left main disease as seen on xA **(arrowhead)** causing hypoperfusion on both left anterior descendent and left circumflex territories **(arrows)** on CMR-Perf and CTP. **(E)** Intermediate (70%) stenosis in the mid left anterior descendent artery **(arrowhead)** causing functional ischemia detected by CMR-Perf and CTP **(arrows)** and confirmed using fractional flow reserve (FFR = 0.76).

Table 2 Comparison of Diagnostic Protocols in Predicting Functionally Significant CAD (FFR ≤0.80)

	CAD (%)	n	TP	TN	FP	FN	k	% Sensit. (95% CI)	% Specif. (95% CI)	% PPV (95% CI)	% NPV (95% CI)	+LR	−LR	% Accu. (95% CI)
Patient-based														
CTA alone	43.6	101	44	35	22	0	0.58	100 (92–100)	61 (55–61)	67 (61–67)	100 (89–100)	2.59	0.00	78 (71–78)
CTP alone	43.6	101	30	53	4	14	0.62	68 (58–74)	93 (85–98)	88 (75–96)	79 (72–83)	9.72	0.34	82 (73–87)
MDCT Int to Prot	43.6	101	39	47	10	5	0.70	89 (78–95)	83 (74–88)	80 (70–86)	90 (82–96)	5.05	0.14	85 (76–91)
CMR-Perf	43.6	101	39	50	7	5	0.76	89 (79–95)	88 (80–93)	85 (75–91)	91 (83–96)	7.22	0.13	88 (79–94)
Vessel-based														
CTA alone	24.1	303	69	155	75	4	0.47	95 (87–98)	67 (65–69)	48 (44–50)	97 (94–99)	2.90	0.08	74 (70–76)
CTP alone	24.1	303	40	219	11	33	0.56	55 (46–61)	95 (93–97)	78 (66–88)	87 (84–89)	11.46	0.47	85 (81–89)
MDCT Int-Prot	24.1	303	52	206	24	21	0.60	71 (62–79)	90 (87–92)	68 (59–76)	91 (88–93)	6.83	0.32	85 (81–89)
CMR-Perf	24.1	303	58	215	15	15	0.73	79 (71–86)	93 (91–96)	79 (71–86)	93 (91–96)	12.18	0.22	90 (86–93)

Values for sensitivity, specificity, PPV, and NPV and accuracy are presented with 95% CI.

Accu. = accuracy; CAD = coronary artery disease; CTA = computed tomography angiography; CTP = computed tomography perfusion; CMR = cardiac magnetic resonance; FN = false-negative; FP = false-positive; Int-Prot = integrated protocol; k = kappa value; MDCT = multidetector computed tomography; Perf = myocardial perfusion imaging; PPV = positive predictive value; NPV = negative predictive value; Sensit. = sensitivity; Specif. = specificity; TN = true negative; TP = true positive; +LR = positive likelihood ratio; −LR = negative likelihood ratio.

Patient-based analysis. Patient and vessel-based performances are summarized in Table 2. Of the 46 patients with a positive CMR-Perf scan, 39 had functionally significant CAD in at least 1 vessel. Of the 55 patients with normal CMR-Perf scans, 50 were true-negatives. CMR-Perf had very good sensitivity (89%) and specificity (88%). PPV and NPV were 85%, and 91%, respectively.

Isolated CTA analysis had an excellent sensitivity and NPV (100%) for detection of functionally significant CAD. However, specificity and PPV were low (61% and 67%, respectively). CTP, conversely, had higher specificity (93%) with lower sensitivity (68%; $p < 0.001$ for both). The integrated MDCT protocol that results from integration of functional data from CTP with the anatomic data from CTA when the later is not sufficient for a confident diagnosis (Fig. 2) had a sensitivity of 89%, and specificity of 83%. This represents a significant increase of specificity ($p = 0.005$) with a nonsignificant decreased sensitivity ($p = 0.06$). The overall accuracy for functional significant CAD detection was 78% for CTA, 82% for CTP and 85% for the MDCT integrated protocol.

C-statistics for detection of functionally significant CAD were similar for CMR-Perf (AUC = 0.88, 95% CI: 0.81 to 0.96) and MDCT-IP (AUC = 0.86, 95% CI: 0.77 to 0.93; $p = 0.52$). They had the same sensitivity (89%) and nonsignificant differences in specificity (88% vs. 83%, $p = 0.61$). Isolated CTP (AUC = 0.81, 95% CI: 0.71 to 0.90) tends to perform worse than CMR-Perf ($p = 0.06$), having similar specificity (93% vs. 88%, $p = 0.51$) but significantly inferior sensitivity (68% vs. 89%, $p < 0.005$). CMR-Perf had the best performance in discriminating functional relevance of CAD in patients with stenosis >40% (AUC = 0.84, 95% CI: 0.72 to 0.93). Its performance in this subgroup of 54 patients was superior to CTA (AUC = 0.60, 95% CI: 0.46 to 0.73; $p = 0.03$), but nonsignificantly superior to CTP (AUC = 0.79, 95% CI: 0.66 to 0.89; $p = 0.34$). CTP was clearly superior to CTA in this setting ($p = 0.02$). When only the 67 patients with intermediate pre-test probability were analysed similar results were found: integration of CTP with CTA significantly increased MDCT specificity from 63 to 85% ($p = 0.004$) and accuracy was similar for MDCT-IP and CMR-Perf (87% vs. 88%, $p = 1.0$).

Vessel-based analysis. A total of 303 vessels (n = 101) were analyzed. CMR-Perf had the best performance for functionally significant CAD detection (AUC = 0.87, 95% CI: 0.82 to 0.90), clearly outperforming CTP (AUC = 0.75, 95% CI: 0.70 to 0.85; $p = 0.0003$) but not CTA (AUC = 0.81, 95% CI: 0.75 to 0.85) or MDCT-IP (AUC = 0.80, 95% CI: 0.75 to 0.85), despite the tendency found ($p = 0.08$ for both). Furthermore, the MDCT-IP ($p = 0.05$) but not isolated CTA ($p = 0.09$) performed significantly better than isolated CTP. When only vessels that effectively received FFR assessment were considered for analysis, a nonsignificant tendency favouring CMR-Perf over the MDCT-IP was seen (AUC = 0.75 vs. 0.58, respectively, $p = 0.06$). In this particular case, CTP and CTA performances did not differ significantly (AUC = 0.65 for both, $p = 0.99$) with a clear advantage of CTA in terms of sensitivity (95% vs. 42%, $p = 0.002$) and of CTP in terms of specificity (88% vs. 35%, $p = 0.004$).

CTP using CMR-Perfusion as a reference standard. CTP performance in detecting reversible myocardial ischemia having CMR-Perf as reference standard is presented in Table 3. In per-patient analysis, isolated CTP had good overall accuracy (82%) in identifying inducible perfusion defects visualized on CMR-Perf, with a sensitivity of 67% and specificity of 95%. PPV was 91% and NPV 78%.

Noninferiority analysis. Using either the C-statistic or the accuracy analysis results for the noninferiority analysis, an 11% noninferiority limit would be needed to conclude for the noninferiority of MDCT-IP in comparison with CMR-Perf. For the present sample size, and for a nominal significance level of 0.05, the 11% noninferiority limit was estimated with a power of 81.8%. Thus, based on our

Table 3 Analysis of CTP in Predicting Reversible Perfusion Defects as Assessed by CMR-Perf

	CAD (%)	n	TP	TN	FP	FN	k	% Sensit. (95% CI)	% Specif. (95% CI)	% PPV (95% CI)	% NPV (95% CI)	+LR	−LR	% Accu. (95% CI)
Patient-based	45.5	101	31	52	3	15	**0.82**	67 (58–72)	95 (86–99)	91 (78–98)	78 (71–81)	**12.36**	**0.34**	82 (73–87)
Vessel-based	24.1	303	40	219	11	33	**0.56**	55 (46–61)	95 (93–97)	78 (66–88)	87 (84–89)	**11.46**	**0.47**	85 (81–89)

Values for sensitivity, specificity, PPV, and NPV and accuracy are presented with 95% CI.
Abbreviations are as in Table 2.

results, a difference >11% in favour of CMR-Perf compared to MDCT-IP can be confidently excluded.

Discussion

This is the first study to directly compare CTP against CMR-Perf using FFR as reference standard. Our main findings are: 1) both CMR-Perf and MDCT-IP have an excellent sensitivity and very good specificity for the detection of functionally significant CAD and their overall performances are similar; 2) isolated CTP is globally inferior to CMR-Perf for diagnosis of CAD but is very specific; and 3) addition of CTP to CTA increases MDCT global accuracy for functionally significant CAD detection in patients with intermediate to high pre-test probability, mainly because of a significant increase in specificity. Thus, a 64-MDCT morphologic and functional integrated protocol using standard available hardware and software may be as effective as CMR-Perf standard protocols for detection of functionally significant CAD.

Previous smaller studies compared CTP with SPECT or CMR using QCA or visual estimation of stenosis severity as the gold standard (21–23). Only one study compared CTP against FFR in patients with known CAD (24). Evidence shows that patients should be guided by the physiological importance of a stenosis rather than luminal assessment and FFR has emerged as the reference invasive tool to provide this information (12).

Of note, in our study, both MDCT and CMR results were obtained using standard acquisition protocols available in current clinical MDCT and MR scanners. Tube voltage limitation to a maximum of 100 kV, strict tube current modulation in the stress scans and the use of prospective scanning at rest resulted in a low radiation exposure (lower than in previous 64-MDCT studies) (7,8,25). Based on our results, low-dose perfusion protocols might be ready for routine use in clinical practice, without a significant increase of radiation exposure, using standard 64-MDCT scanners: the entire MDCT protocol, including Calcium-scoring, CTA and CTP is completed with an effective radiation exposure that represents less than one half of the exposure usually reported for SPECT (21).

CMR-Perf results are in line with published studies and the excellent accuracy of the method in symptomatic intermediate-to-high risk patients is confirmed. Stress and rest perfusion were simultaneously visualized with LGE images resulting in very good accuracy for ischemia detection. Interestingly, integration of isolated ischemic scar detection as a marker of CAD in the CMR-Perf interpretation algorithm did not improve overall performance for functionally significant CAD detection (data not shown). CMR has several advantages over MDCT for the detection of myocardial ischemia: it does not expose patients to ionizing radiation and provides dynamic real-time imaging of myocardial perfusion over the first-passage of contrast (26). MDCT perfusion is limited to the "one-shot" opportunity to visualize differences of x-ray attenuation between the ischemic and remote myocardium. However, a previous study evaluating myocardial blood flow quantification showed that the difference in upslope between ischemic and normal myocardium remains relatively constant for several seconds during the entire arterial phase, after a minimum delay of 12 s (27). Our imaging time point was chosen to be within this constant wash-in phase. A potential advantage of CTP over CMR is the ability to acquire high-resolution isotropic 3D "whole heart" datasets that allow for simultaneous coronary anatomy and myocardial perfusion analysis. This may be of particular interest for decision and management of revascularization.

Isolated CTP results are also in line with previous studies. However, a slightly lower sensitivity is noticed in our study. This could be justified by scanner limitations in this low-radiation 64-MDCT protocol. Simultaneously, a lower rate of false positives is noticed, resulting in higher specificity. CTP performed equally well in patients with or without ischemic scar revealing that it is capable of detecting perfusion defects that represent true ischemia and not only scar (data not shown). Furthermore, CTP performance in discriminating functionally relevant CAD in patients with stenosis >40% as assessed by xA was clearly superior to CTA. We have recently shown that the addition of CTP to CTA improves diagnostic accuracy of MDCT as assessed by invasive QCA, mainly because of an increased specificity in heavily calcified coronary arteries (15). Not surprisingly, the use of a functional standard in current study confirms this finding and highlights the advantage of functional and anatomic integration.

CTP intra- and interobserver agreement was only moderate and self-reported confidence was lower compared with CMR. This is an expected finding, as CMR-Perf is a well-validated, clinically implemented and better-established technique. The use of a new technique, despite the similarities, involves a certain degree of uncertainty and a learning curve that may explain the results.

Study limitations. Several limitations may decrease generalizability of findings: single-center study, exclusion of patients with known CAD or low pre-test probability and of

patients with contraindications, such as renal dysfunction or atrial fibrillation. The latter may be present in a significant proportion of patients with suspected CAD (20% of study exclusions) and is unclear which test is more susceptible to this arrhythmia. The studied population may not be reflective of the usual population sent for CTA or stress testing as only symptomatic intermediate/high pre-test probability patients were recruited, including high-risk patients that are not usually referred for stress-testing but rather directly to xA. To address this issue, a subanalysis exclusively including patients with intermediate pre-test probability was performed.

FFR was only measured in vessels with intermediate stenoses and a significant proportion of diseased vessels had to be excluded from this evaluation. While this was performed to avoid potential iatrogenic complications, an eventual bias may exist. To minimize this limitation, a subanalysis of vessels with an effective FFR assessment was performed.

The MDCT protocol was based on a single-source 64-MDCT scanner with its known technical limitations, such as low temporal resolution and misalignment artifacts, which may be overcome with more advanced technology. However, it is important to note that low dose CTP imaging is available today and yields important information missed by CTA alone.

Reprint requests and correspondence: Dr. Nuno Bettencourt, Cardiology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE, Rua Conceição Fernandes, 4434-502 Vila Nova de Gaia, Portugal. E-mail: bettencourt.n@gmail.com.

REFERENCES

1. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.
2. Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2663–99.
3. Tamarappoo B, Hachamovitch R. Myocardial perfusion imaging versus ct coronary angiography: when to use which? J Nucl Med 2011;52:1079–86.
4. Schuijf JD, Wijns W, Jukema JW, et al. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol 2006;48:2508–14.
5. Gaemperli O, Schepis T, Valenta I, et al. Functionally relevant coronary artery disease: comparison of 64-section CT angiography with myocardial perfusion SPECT. Radiology 2008;248:414–23.
6. Meijboom WB, Van Mieghem CAG, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.
7. Kurata A, Mochizuki T, Koyama Y, et al. Myocardial perfusion imaging using adenosine triphosphate stress multi-slice spiral computed tomography: alternative to stress myocardial perfusion scintigraphy. Circ J 2005;69:550–7.
8. George RT, Silva C, Cordeiro MAS, et al. Multidetector computed tomography myocardial perfusion imaging during adenosine stress. J Am Coll Cardiol 2006;48:153–60.
9. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 2012;379:453–60.
10. Schwitter J, Wacker CM, Wilke N, et al. MR-IMPACT II: magnetic resonance imaging for myocardial perfusion assessment in coronary artery disease trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. Eur Heart J [serial on the Internet]. Available at: http://eurheartj.oxfordjournals.org/content/early/2012/03/04/eurheartj.ehs022.abstract.
11. Bettencourt N, Chiribiri A, Schuster A, et al. Cardiac magnetic resonance myocardial perfusion imaging for detection of functionally significant obstructive coronary artery disease: A prospective study. Int J Cardiol [serial on the Internet]. 2012: Available from: http://linkinghub.elsevier.com/retrieve/pii/S016752731201354X?showall=true.
12. Tonino PAL, de Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
13. Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med 1997;102:350–6.
14. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Protocols SfCMRBoTTFoS. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 2008;10:35.
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. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of the American Heart Association. Circulation 2002;105:539–42.
17. 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.
18. Bongartz G, Golding SJ, Jurik AG, et al. European guidelines for multislice computed tomography. funded by the european commission. contract number FIGM-CT2000-20078-CT-TIP. March 2004. Available at: www.msct.eu.
19. Liu J-p, Hsueh H-m, Hsieh E, Chen JJ. Tests for equivalence or non-inferiority for paired binary data. Stat Med 2002;21:231–45.
20. Jin H, Lu Y. A non-inferiority test of areas under two parametric ROC curves. Contemp Clin Trials 2009;30:375–9.
21. 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.
22. Okada DR, Ghoshhajra BB, Blankstein R, et al. Direct comparison of rest and adenosine stress myocardial perfusion CT with rest and stress SPECT. J Nucl Cardiol 2010;17:27–37.
23. 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 Imaging 2011;4:540–9.
24. 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.
25. Blankstein R, Okada D, Rocha-Filho J, Rybicki F, Brady T, Cury R. Cardiac myocardial perfusion imaging using dual source computed tomography. Int J Cardiovasc Imaging 2009;25:209–16.
26. Hautvast GLTF, Chiribiri A, Lockie T, Breeuwer M, Nagel E, Plein S. Quantitative analysis of transmural gradients in myocardial perfusion magnetic resonance images. Magn Reson Med 2011;66:1477–87.
27. 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.

Key Words: coronary artery disease ■ fractional flow reserve ■ magnetic resonance ■ multidetector computed tomography ■ myocardial perfusion.