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ORIGINAL PAPER

Anatomical versus functional assessment of coronary artery disease: direct comparison of computed tomography coronary angiography and magnetic resonance myocardial perfusion imaging in patients with intermediate pre-test probability

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Abstract Computed tomography coronary angiography (CTA) and cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI) are state-of-the-art tools for noninvasive assessment of coronary artery disease (CAD). We aimed to compare the diagnostic accuracy of CTA and CMR-MPI for the detection of functionally relevant CAD, using invasive coronary angiography (XA) with fractional flow reserve (FFR) as a reference standard, and to evaluate the best protocol integrating these techniques for assessment of patients with suspected CAD. 95 patients (68 % men; 62 ± 8.1 years) with intermediate pre-test probability (PTP) of CAD underwent a sequential protocol of CTA, CMR-MPI and XA. Significant CAD was defined as >90 % coronary stenosis, 40–90 % stenosis with FFR ≤ 0.80 or left main stenosis ≥50 %. Prevalence of significant CAD was 43 %. CTA was more sensitive (100 %) but less specific (59 %) than CMR-MPI (88 and 89 %, respectively) for detection of significant CAD, with a strong trend for higher global diagnostic accuracy of CMR-MPI (88 vs. 77 %, $p = 0.05$). An integrated approach based on an initial CTA and subsequent referral to CMR-MPI of positive/inconclusive results had the best diagnostic performance (AUC 0.91). The direct referral to XA of patients with positive/inconclusive CTA performed worse than a selective approach based on CMR-MPI results (AUC 0.80 vs. 0.91, $p = 0.005$). In this intermediate PTP population, CMR-MPI showed a strong trend toward better performance compared to CTA for the assessment of functionally significant CAD. A combined protocol integrating coronary anatomy and function seems to be a very effective approach in the accurate diagnosis of CAD.

Keywords Computed tomography coronary angiography · Magnetic resonance imaging · Myocardial perfusion · Fractional flow reserve · Coronary artery disease

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Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. Its clinical suspicion frequently leads to referral of patients to cardiology consultation. The most recent guidelines on the management of stable CAD recommend that patients with intermediate pre-test probability (PTP) (15–85 %) should undergo non-invasive testing for the diagnosis of significant CAD [1]. This can be accomplished by anatomical methods detecting the presence of coronary atherosclerosis, even in subclinical phases, or functional tests identifying myocardial ischemia in flow-limiting stenoses. Computed tomography coronary angiography (CTA) is the established non-invasive reference standard for assessment of coronary anatomy [2] and is particularly useful for exclusion of CAD in patients with intermediate to low PTP (15–50 %),

due to its high negative predictive value (NPV) [1, 3, 4]. However, it cannot provide information on the hemodynamic significance of a detected lesion and comparative studies between CTA and functional tests have revealed a substantial discrepancy between the presence of stenoses and myocardial ischemia [5]. In contrast, adenosine stress-rest cardiac magnetic resonance myocardial perfusion imaging (CMR-MPI) detects myocardial perfusion defects and is particularly useful in the assessment of the functional significance of a specific stenosis and therapy guidance [6, 7]. It has been favorably compared with other established methods [8–11] and proved an excellent accuracy when compared to fractional flow reserve (FFR) [12, 13].

Only a few studies compared CTA and CMR-MPI for the assessment of CAD. The vast majority of these studies were performed taking a morphological test as the reference standard [14, 15], which underestimates the diagnostic performance of CMR-MPI and overestimates that of CTA [2]. In a recent study, the combined use of these techniques had a superior diagnostic accuracy than either modality alone for the detection of functionally significant CAD, as evaluated using FFR [16]. However, a direct comparison against this functional invasive standard is still missing.

The main purpose of this study was to compare the diagnostic accuracy of CTA and CMR-MPI for detection of functionally relevant CAD, using invasive coronary angiography (XA) with FFR as the reference standard, in symptomatic patients with intermediate PTP of CAD. Secondly, we aimed to define the best protocol using these two techniques for the non-invasive diagnosis of significant CAD.

Methods

Population and study design

From February 2010 to November 2011, we prospectively screened 176 consecutive patients referred to our hospital outpatient cardiology clinic due to clinical suspicion of CAD. Study inclusion criteria were >40 years of age, symptoms compatible with CAD and at least one cardiovascular risk factor or a positive/inconclusive treadmill test. Exclusion criteria included known CAD, low (<15 %) or high (>85 %) PTP [17], unstable clinical status, valvular heart disease, atrial fibrillation, pregnancy, creatinine clearance ≤60 ml/min and standard contraindications to CMR-MPI and iodinated contrast media. A flow chart of the study population is presented in Fig. 1.

The PTP of obstructive CAD was estimated using a recently published tool for estimation of CAD prevalence [17], recommended by the most recent guidelines for the management of stable CAD [1]. Only patients with intermediate PTP of CAD (values ranging between 15 and 85 %) were included. For subsequent analysis, patients were divided in two groups: intermediate-low PTP (15–50 %) and intermediate-high PTP of CAD (51–85 %).

All patients underwent a sequential protocol of CTA, adenosine stress CMR-MPI and XA within a period of 4 weeks. Readers were blinded to the clinical information and other tests results. Participants provided written informed consent and the study protocol was approved by the local ethics committee.

Computed tomography protocol

All scans were performed using a Somaton Sensation-64 scanner (Siemens Medical Solutions, Forchheim, Germany) as part of a comprehensive stress-rest protocol previously described [18, 19]. For the purpose of current analysis, two CTA acquisitions were used: one retrospectively gated, under adenosine infusion and one prospectively triggered performed after a minimum break of 10 min and heart-rate optimization with fractionated boluses of intravenous metoprolol (5–20 mg). Despite the integration on a stress-rest MDCT perfusion protocol, only coronary angiography data (from both acquisitions) were analyzed for the purpose of this study. One multiphasic and one single-phase (65 %) reconstructions were obtained from the stress and rest scans, respectively, using standard medium-soft frequency cardiac filter (Siemens B25f), and sent to a postprocessing workstation (Aquarius WorkStation, Tera-Recon Inc, San Mateo, CA). Scans were anonymized and analyzed by two blinded readers, using the 17-segment modified American Heart Association classification [20]. Each segment was graded as normal, non-significant stenosis (<50 %), 50–70 % stenosis, ≥70 % stenosis/occlusion or uninterpretable (significant stenoses impossible to exclude but not definitely present). CTA scans were dichotomically classified as positive for CAD if ≥50 % stenosis or inconclusive segments were present and negative if no stenoses ≥50 % were found. Inter-observer disagreements were resolved by consensus.

Cardiac magnetic resonance (CMR) protocol

Cardiac magnetic resonance was performed on a 1.5 T scanner (Symphony, Siemens, Erlangen, Germany) using a 12-channel receiver coil, according to established protocols [21]. CMR-MPI scans were performed during the first pass of a gadolinium bolus (0.07 mmol/kg) at maximal hyperaemia induced by adenosine (140 μg/kg/min) and at rest. Late gadolinium enhancement imaging (LGE) was performed ≥10 min after the last contrast injection.

Two experienced blinded readers analyzed all images. In cases of disagreement, a third blinded reader adjudicated.

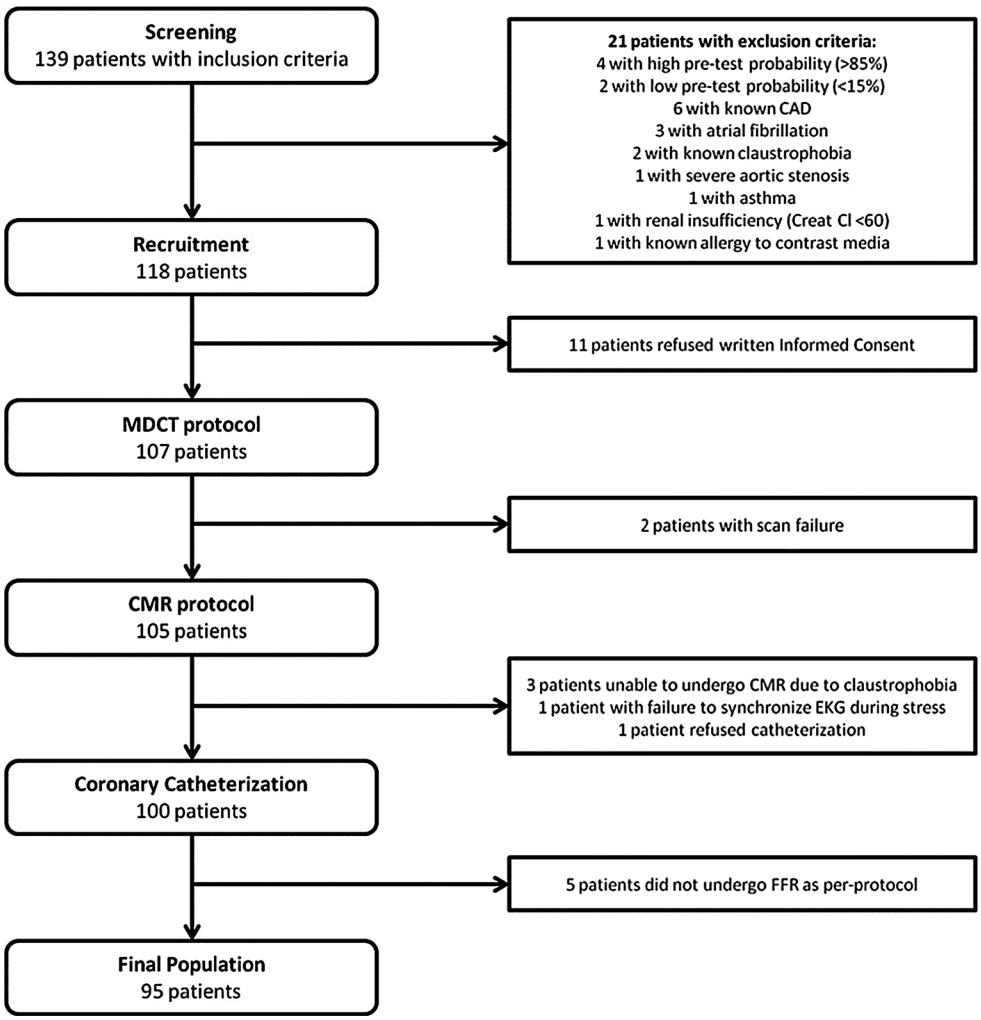

Fig. 1 Study flow-chart and reasons for exclusions

The stress and rest perfusion scans were viewed simultaneously, and areas of hypoperfusion were assigned to the ventricular segments, using the standard ACC/AHA 17-segment model, excluding the apex. Each of the 16 segments was classified based on the presence and transmurality of perfusion defects using a 4-point scoring system (from normal/no defect to transmural defect) and integration with LGE was used to differentiate areas of myocardial scar from induced ischemia. However, a positive CMR scan was only considered when inducible ischemia (not only isolated scar) was present.

X-ray coronary angiography and FFR assessment

XA was performed according to standard techniques by experienced cardiologists unaware of CTA and CMR-MPI results. The operators were asked to analyze all coronary segments and to visually quantify perceived stenoses. In case of intermediate lesions (40–90 %), a pressure wire (Pressure Wire Certus, St Jude Medical, St Paul, MN, USA) was used to determine vessel FFR under steady-state hyperemia induced by intravenous adenosine infusion (140 μg/kg/min over 3–6 min) and recorded on RadiAnalyzer (St Jude Medical, St Paul, MN, USA). Arteries were recorded as having significant flow-limiting disease if they had stenosis $\geq$90 %, 40–90 % stenosis with an FFR value $\leq$ 0.80 or left main stenosis $\geq$50 %.

Statistical analysis

The diagnostic performances of CTA and CMR-MPI for the detection of functionally significant CAD were compared using XA + FFR as the reference standard. For this purpose, inconclusive CTA were considered positive for significant CAD, since both inconclusive and positive scans would imply further testing. Sensitivity, specificity, positive predictive value (PPV), NPV and accuracy were calculated for both tests and diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis. Areas under the ROC curves (AUC or

C-statistics) were reported with 95 % confidence intervals (CI). Multiple hypothetical protocols integrating the imaging studies were tested, according to CTA results and to patient PTP, and compared using ROC curves (Table 1). The McNemar test was used to calculate differences between proportions (e.g. sensitivity, specificity) obtained from paired observations. AUCs were compared using the method of DeLong et al. (1988). A p value < 0.05 was considered significant. Data analysis was performed using SPSS analysis software (Release 19, SPSS Inc, Chicago, Illinois) and MedCalc analysis software (Version 12.3.0, MedCalc Software, Belgium).

Results

The final study population consisted of 95 patients (62 ± 8.1 years, 68 % males) with suspected CAD. Baseline patient characteristics are shown in Table 2. Fourty-nine patients (52 %) had intermediate-low PTP (15–50 %) and 46 patients (48 %) had intermediate-high probabilities (51–85 %). The prevalence of protocol-defined significant CAD was 43 % (39 % in intermediate-low and 48 % in intermediate-high PTP groups).

Imaging results are presented in Table 3. Diagnostic patient-based performances of CTA and CMR-MPI using FFR as reference standard are summarized in Table 4.

CTA performance

All patients with negative CTA (n = 32) had no significant CAD on XA + FFR. When non-evaluable segments were considered to represent significant disease, 63 patients were categorized as positive by CTA, of which 41 (65 %) had functionally significant CAD on reference standard (22 false-positives). Concerning the entire population (n = 95) and considering inconclusive scans as positive (as these results would imply further testing), CTA had an excellent sensitivity (100 %) and NPV (100 %) for detection of functionally significant CAD (Table 2). However, specificity and PPV were low (59 and 65 %, respectively), due to a high rate of false-positive results (23 %). Global diagnostic accuracy was 77 % with an AUC of 0.80 (95 % CI 0.70–0.87).

Thirty-one patients (33 %) had an inconclusive CTA, which resulted mainly from an excessive coronary calcification, preventing accurate quantification of coronary lesions. Analyzing only the patients with fully interpretable arterial tree (n = 64) (excluding inconclusive scans), CTA had a global accuracy of 88 %, with excellent sensitivity (100 %) and moderate specificity (80 %). Accordingly, diagnostic performance was superior in the subgroup of patients with calcium score (CaSc) < 400 compared to patients with CaSc ≥ 400 (AUC 0.85 vs. 0.64, $p = 0.004$). CTA also performed better in patients ≤60 years (AUC 0.87 vs. 0.74 in patients >60 years, $p = 0.05$), due to a trend to higher rate of false positives. The diagnostic accuracy was not significantly different in the groups with intermediate-low and intermediate-high PTP of CAD (AUC 0.82 vs. 0.77, $p = 0.50$).

CMR-MPI performance

Cardiac magnetic resonance myocardial perfusion imaging was positive for ischemia in 36 of the 41 patients with significant CAD (sensitivity of 88 %) and was negative for ischemia in 48 of the 54 patients without disease (specificity of 89 %). Overall diagnostic accuracy was 88 %, with an AUC of 0.88 (95 % CI 0.81–0.96). Performance was not significantly different between intermediate-low PTP (AUC 0.92) and intermediate-high PTP (AUC 0.85) groups ($p = 0.25$).

Comparison of CTA and CMR-MPI performance

Cardiac magnetic resonance myocardial perfusion imaging had a trend to outperform CTA (accuracy of 88 vs. 77 %, $p = 0.05$; AUC 0.88 vs. 0.80, $p = 0.06$) for the diagnosis of functionally significant CAD. CMR-MPI had better specificity (89 vs. 59 %, $p = 0.001$) and PPV (86 vs. 65 %, $p = 0.002$), while CTA had non-significantly better sensitivity (100 vs. 88 %) and NPV (100 vs. 91 %). This global trend was found in patients with intermediate-low PTP of CAD (AUC 0.92 for CMR-MPI vs. 0.82 for CTA, $p = 0.07$), but in patients with intermediate-high PTP the performance of both methods was similar (AUC 0.85 vs. AUC 0.77, $p = 0.29$).

A direct referral to XA (irrespective of non-invasive tests results or patient PTP) would have lower diagnostic accuracy (protocol 3—Table 1, accuracy 43 %) than selecting patients for invasive stratification based on CTA results (protocol 4, accuracy 77 %, $p < 0.0001$) or CMR-MPI findings (protocol 1, accuracy 88 %, $p < 0.0001$).

Anatomy and function integration

In our population, the best performing diagnostic strategy was the integration of CTA and CMR-MPI results according to protocol 2 (AUC 0.91): patients with positive/inconclusive CTA are referred for CMR-MPI and then selected for invasive stratification based on CMR-MPI results; patients with negative CTA are excluded for significant CAD with no further testing. This was the best approach in both the intermediate-high (AUC 0.87) and intermediate-low (AUC 0.96) PTP groups.

Of the 32 patients with a clearly positive CTA (≥50 % stenosis), 8 patients (25 %) had no significant CAD on the

Table 1 Hypothetical tested protocols according to CTA final report and according to PTP of CAD

CTA		Tested protocols													
		1		2		3		4		5		6		7	
Positive		CMR-MPI		CMR-MPI		XA		XA		XA		XA		XA	
Inconclusive		CMR-MPI		CMR-MPI		XA		XA		XA		CMR-MPI		CMR-MPI	
Negative		CMR-MPI		STOP		XA		STOP		CMR-MPI		CMR-MPI		STOP	
AUC (95 % CI)															
All patients (n = 95)		0.88 (0.81–0.96)		**0.91** (0.84–0.98)		0.50 (0.38–0.62)		0.80 (0.71–0.89)		0.78 (0.69–0.87)		0.83 (0.75–0.92)		0.86 (0.78–0.94)	
CAD prevalence = 43.2 %															
TP	TN	36	48	36	51	41	0	41	32	41	30	38	40	38	43
FN	FP	5	6	5	3	0	54	0	22	0	24	3	14	3	11
Sensitivity	Specificity	88	89	88	94	100	–	100	59	100	56	93	74	93	80
PPV	NPV	86	91	92	91	43	–	65	100	63	100	73	93	78	94
Accuracy		88		**92**		43		77		75		82		85	
Intermediate-high PTP (n = 46)		0.85 (0.73–0.97)		**0.87** (0.75–0.98)		0.50 (0.33–0.67)		0.77 (0.63–0.91)		0.77 (0.63–0.91)		0.81 (0.68–0.94)		0.83 (0.70–0.96)	
CAD prevalence = 47.8 %															
TP	TN	18	21	18	22	22	0	22	13	22	13	20	17	20	18
FN	FP	4	3	4	2	0	24	0	11	2	11	2	7	2	6
Intermediate-low PTP (n = 49)		0.92 (0.84–1.00)		**0.96** (0.89–1.00)		0.50 (0.33–0.67)		0.82 (0.73–0.92)		0.78 (0.66–0.91)		0.86 (0.75–0.97)		0.89 (0.80–0.99)	
CAD prevalence = 38.8 %															
TP	TN	18	27	18	29	19	0	19	19	19	17	18	23	18	25
FN	FP	1	3	1	1	0	30	0	11	0	13	1	7	1	5

The values shown in bold font highlight the protocols with better diagnostic performance (higher AUC values)

XA—direct referral to invasive coronary angiography

CMR-MPI—all patients referred to CMR-MPI would undergo further investigation according to results: in case of positive CMR-MPI, patients would undergo invasive coronary angiography; patients with negative CMR-MPI would stop investigation

STOP—no further diagnostic investigation

In protocol 1, all patients perform CMR-MPI after CTA and proceed investigation in accordance with CMR-MPI results. In protocol 2, patients with negative CTA do not undergo further testing (exclusion of significant CAD) and those with positive or inconclusive CTA proceed investigation according to CMR-MPI results. In protocol 3, after CTA all patients are directly referred to invasive coronary angiography. In protocol 4, patients with positive and inconclusive CTA are directly referred to invasive angiography and those with negative CTA stop investigation. In protocol 5, patients with positive and inconclusive CTA are directly referred to invasive angiography and those with negative CTA stop undergo CMR-MPI. In protocol 6, patients with positive CTA undergo invasive coronary angiography and those with inconclusive or negative results are referred for CMR-MPI. In protocol 7, patients with positive CTA are directly referred to invasive coronary angiography, those with inconclusive CTA proceed investigation according to CMR-MPI and in patients with negative CTA significant CAD is excluded with no further testing

TP true positive, *FP* false positive, *TN* true negative, *FN* false negative

Table 2 Clinical characteristics of the study population

	Total population	Intermediate-low PTP (15–50 %)	Intermediate-high PTP (51–85 %)
Patients	95	49 (52)	46 (48)
Male	65 (68)	27 (55)	38 (83)
Age (years)	62 ± 8.1 (41–79)	59 ± 8.2 (44–78)	64 ± 7.3 (41–79)
Risk factors for CAD			
Diabetes	37 (39)	18 (37)	19 (41)
Hypertension	71 (75)	35 (71)	36 (78)
Hypercholesterolemia	76 (80)	39 (80)	37 (80)
Current smoking	14 (15)	7 (14)	7 (15)
Obesity (BMI $\geq$ 30 kg/m^2)	29 (31)	15 (31)	14 (30)
Family history of premature CAD	20 (21)	12 (24)	8 (17)
$\geq$2 cardiovascular risk factors	81 (85)	39 (80)	42 (91)
Clinical presentation			
Typical angina	21 (22)	0 (0)	21 (46)
Atypical angina	49 (52)	30 (61)	19 (41)
Chest pain	20 (21)	16 (33)	4 (9)
Dyspnea on exertion/fatigue	5 (5)	3 (6)	2 (4)

Values are n (%) or mean ± SD, unless otherwise stated

BMI body mass index

Table 3 Imaging results

	Total population	Intermediate-low PTP (15–50 %)	Intermediate-high PTP (51–85 %)
Agatston score			
CaSc $\leq$ 100	36 (38)	25 (51)	11 (24)
CaSc 101–400	17 (18)	5 (10)	12 (26)
CaSc > 400	42 (44)	19 (39)	23 (50)
CTA			
No CAD	9 (9)	6 (12)	3 (6)
Non-obstructive CAD	23 (24)	13 (26)	10 (22)
Obstructive CAD	32 (34)	16 (33)	16 (35)
Inconclusive CTA	31 (33)	14 (29)	17 (37)
Effective radiation dose, total, mSv	4.99 ± 0.97	5.12 ± 0.98	4.85 ± 0.94
Effective radiation stress, mSv	3.31 ± 0.48	3.36 ± 0.47	3.27 ± 0.51
Effective radiation rest, mSv	0.99 ± 0.75	1.06 ± 0.79	0.92 ± 0.70
Effective radiation CaSc, mSv	0.51 ± 0.25	0.52 ± 0.27	0.51 ± 0.23
Total volume of contrast used, ml	164 ± 14.5	165 ± 11.7	163 ± 17.1
Mean heart rate, rest scan, beat/min	63 ± 6.9	63 ± 7.0	63 ± 7.0
CMR			
Myocardial ischemia	42 (44)	21 (43)	21 (46)
One-vessel territory	25 (26)	12 (24)	13 (28)
Two-vessel territories	10 (11)	6 (12)	4 (9)
Three-vessel territories	7 (7)	3 (6)	4 (9)
LGE (ischemic pattern)	16 (17)	8 (16)	8 (17)
Significant CAD on XA (FFR $\leq$ 0.80)	41 (43)	19 (39)	22 (48)
Single-vessel disease	23 (24)	12 (24)	11 (24)
Double-vessel disease	11 (12)	5 (10)	6 (13)
Triple-vessel disease	7 (7)	2 (4)	5 (11)

Values are n (%) or mean ± SD

LGE late gadolinium enhancement

Table 4 Patient-based analysis of CTA and CMR-MPI in predicting functionally significant CAD (FFR $\leq$ 0.80)

	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall population					
CTA	100 (91–100)	59 (45–72)	65 (52–77)	100 (89–100)	77 (69–77)
CMR-MPI	88 (74–96)	89 (77–96)	86 (72–95)	91 (79–97)	88 (79–94)
Intermediate-low PTP (15–50 %)					
CTA	100 (82–100)	63 (44–80)	63 (44–80)	100 (82–100)	78 (64–78)
CMR-MPI	95 (74–100)	90 (74–98)	86 (64–97)	96 (82–100)	92 (79–96)
Intermediate-high PTP (51–85 %)					
CTA	100 (85–100)	54 (33–75)	67 (48–82)	100 (75–100)	76 (62–76)
CMR-MPI	82 (60–95)	88 (68–97)	86 (64–97)	84 (64–96)	85 (69–94)

Values are presented in % (95 % confidence interval)

reference standard and CMR-MPI correctly excluded disease in all of them. Of the 31 patients with inconclusive CTA, 14 (45 %) had no significant CAD on XA and CMR-MPI excluded ischemia in 11 (79 %) of them. Consequently, a strategy of direct referral to XA of all patients with positive or inconclusive CTA (protocol 4) performed worse than referring these patients to CMR-MPI prior to XA (protocol 2) [AUC 0.80 vs. 0.91, $p = 0.005$], with 22 false-positive results. A protocol of direct referral to XA of patients with positive CTA, referral of patients with inconclusive CTA for CMR-MPI and exclusion of significant CAD in patients with negative CTA (protocol 7) had a diagnostic performance not significantly different from that of protocol 2 (AUC 0.86 vs. 0.91, $p = 0.09$), but with a cost of 8 additional false-positives.

Sensitivity, specificity and accuracy of CTA, CMR-MPI and the best protocol integrating anatomy and function were compared and are represented in Fig. 2.

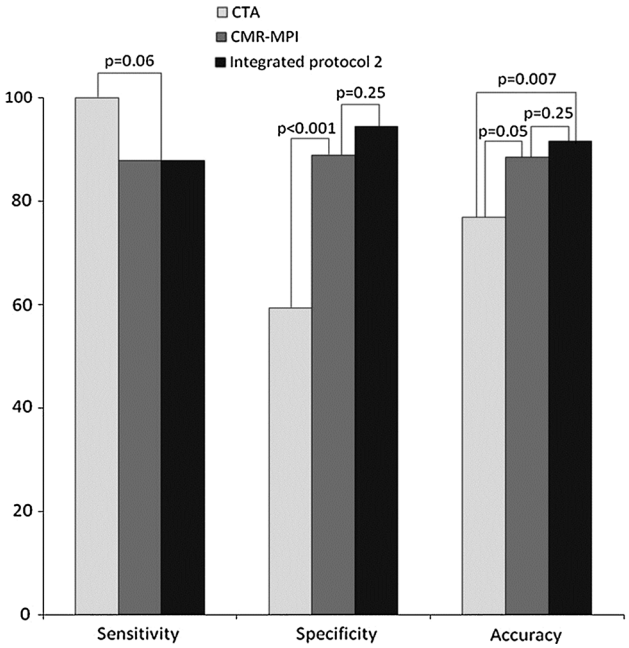

Fig. 2 Comparison of sensitivity, specificity and accuracy of CTA, CMR-MPI and the integrated protocol with great diagnostic performance (protocol 2)

Discussion

This is the first study that directly compares CTA against CMR-MPI using FFR as reference standard. Our main findings are: (1) CMR-MPI shows a strong trend for better diagnostic accuracy compared to CTA (88 vs. 77 %, $p = 0.05$) in this population of symptomatic patients with intermediate PTP; (2) CTA has an excellent performance in the exclusion of significant CAD, with sensitivity and NPV of 100 %, but poor specificity (59 %) for the detection of hemodynamically significant coronary lesions; (3) integration of anatomical and functional information using CTA and CMR-MPI allows an accurate non-invasive diagnosis of obstructive CAD as assessed by FFR: CTA may confidently exclude significant coronary stenoses and CMR-MPI may further evaluate the functional significance of lesions detected on CTA.

The vast majority of published studies testing CTA and CMR-MPI accuracy, including the few ones directly comparing CTA and CMR-MPI for the diagnosis of CAD, used quantitative XA (QCA) or visual assessment of the degree of stenosis as the gold-standard. In such studies, CTA outperformed CMR for detection of stenosis $\geq$50 % and that was interpreted as a superior diagnostic accuracy [14, 15]. However, it is known that anatomical CAD as assessed by conventional angiography does not always correlate with the functional severity of the disease [22], and current recommendations state that revascularization should be guided by the physiological importance of a stenosis as determined by the invasive reference standard FFR in detriment of anatomical evaluations [23–25]. In fact, we have previously reported that integration of anatomy and function with CT perfusion may further improve MDCT accuracy using this standard [19]. However, in clinical practice, 64-slices CT are limited to CTA acquisitions and functional analysis is usually performed using

perfusion techniques, namely nuclear imaging or CMR. In this context, a direct comparison of CTA with CMR-MPI and the potential value of integration of both techniques was lacking.

In our study, CMR-MPI had very good sensitivity (88 %) and specificity (89 %) for the diagnosis of obstructive CAD in a group of patients with intermediate PTP. These results are in line with previous published studies [7, 12]. CTA is considered the non-invasive reference standard for assessment of coronary anatomy and has largely demonstrated high diagnostic performance as compared with quantitative XA. However, this technique tends to overestimate CAD severity and its comparison with functional tests has revealed a substantial discrepancy between the stenosis grade and presence of ischemia [5]. Only a few recent studies evaluated the diagnostic accuracy of CTA using FFR as reference and the results are very disappointing, with specificity values ranging between 25 and 48 % [26–28]. In our study, although the accuracy of CTA was superior to these studies, we also had a low specificity (59 %) and high rate of false-positives. The sensitivity and NPV of 100 % make CTA a valuable and safe first-line tool to exclude significant CAD, but the poor correlation of positive CTA with FFR suggests that further functional lesion evaluation is mandatory.

According to our results, the anatomical method seems to be an effective rule-out test for significant CAD and those patients with no or minimal coronary atherosclerosis on CTA do not need further investigation. Nevertheless, patients with stenosis $\geq$50 % or inconclusive results may best be investigated using a combined approach with a subsequent functional test for confirmation of the hemodynamic significance of the disease. A comprehensive anatomical and functional imaging strategy may correctly identify CAD and discriminate those patients who are likely to benefit from XA and coronary revascularization (coronary atherosclerosis with ischemia) from those who benefit from secondary preventive measures and medical therapy (coronary atherosclerosis without ischemia) [28].

Groothuis et al. [16] also tested an integrated anatomical and functional diagnostic work-up and shown that the combined use of CTA and CMR significantly improved specificity and overall accuracy for the detection of functionally significant CAD in comparison with either modality alone. However, in this study, XA was only performed in patients with positive CTA and/or CMR-MPI, which could have biased the results. Additionally, FFR was not obtained in stenoses >70 % and in almost one-fourth of the stenoses ranging from 30 to 70 %.

In the most recent guidelines on the management of stable CAD [1], it is recommended that patients with suspected CAD and intermediate PTP (15–85 %) should undergo non-invasive stress testing for diagnosis. For this purpose, functional evaluation of CAD with stress imaging is recommended as the method of choice if local expertise and availability permit. However, in patients with intermediate-low PTP (15–50 %) anatomical evaluation by CTA is considered an alternative to stress imaging techniques. In case of unclear result of CTA, a stress imaging test should be performed. Our results seem to support the global preference for functional imaging in patients with intermediate PTP and initial anatomic testing using CTA with further functional testing in case of positive/inconclusive findings. However, it is interesting to note that, in our study, CTA performance was not substantially different in patients with intermediate-low versus intermediate-high PTP and that, even in patients with a PTP $<$ 50 %, only 39 % of patients would be exempted from further testing due to exclusion of CAD using CTA. Therefore, using this pathway, the majority of patients would undergo two tests instead of one. This has to be tempered with the potential advantages of availability and other disadvantages like radiation and contrast-media exposure.

Limitations

In this single-centre study only symptomatic patients without known CAD and with intermediate PTP of CAD were included. A small percentage of patients with contraindications, like renal dysfunction or arrhythmias were excluded. As so, our results may not be applicable to all patients with chest pain and suspicion of CAD. Furthermore, in our study CTA scans were obtained as part of a stress-rest protocol. As a consequence, despite CTA results being in line with other studies using FFR and optimized protocols for CTA [26, 27], it is reasonable to admit that CTA results could be improved if a different scan protocol (including the use of oral instead of intravenous pre-test beta-blockage) would be used. In addition, the relatively high mean age of this cohort may have conditioned a lower specificity of CTA. Nevertheless, image quality was considered to be appropriate in the vast majority of CTA scans and the rate of inconclusive segments due to heavily calcified areas is in line with previous studies [29].

Fractional flow reserve was only measured in vessels with intermediate stenoses on visual assessment. Stenoses $<$40 % were assumed as irrelevant and stenoses $\geq$90 % were considered functionally significant. While this was performed to minimize potential iatrogenic complications, and reflects current clinical practice in many centers, an eventual residual bias may still exist.

Finally, CT was performed on a single-source 64-MDCT. Recent technologies already under clinical use could overcome some of the technical limitations inherent to this scanner.

Conflict of interest None declared.

References

1. Montalescot G, Sechtem U, Achenbach S et al (2013) 2013 ESC guidelines on the management of stable coronary artery disease. The task force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34:2949–3003
2. Bettencourt N, Nagel E (2013) Comparison of MR and CT for the assessment of the significance of coronary artery disease: a review. Curr Cardiovasc Imaging Rep 6:102–106
3. Budoff MJ, Dowe D, Jollis JG et al (2008) Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 52:1724–1732
4. Abdulla J, Abildstrom SZ, Gotzsche O et al (2007) 64-multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis. Eur Heart J 28:3042–3050
5. Schuijf JD, Wijns W, Jukema JW et al (2006) Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol 48:2508–2514
6. Morton G, Schuster A, Perera D et al (2010) Cardiac magnetic resonance imaging to guide complex revascularization in stable coronary artery disease. Eur Heart J 31:2209–2215
7. Rieber J, Huber A, Erhard I et al (2006) Cardiac magnetic resonance perfusion imaging for the functional assessment of coronary artery disease: a comparison with coronary angiography and fractional flow reserve. Eur Heart J 27:1465–1471
8. Greenwood JP, Maredia N, Younger JF et al (2012) Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 379:453–460
9. Schwitter J, Wacker CM, van Rossum AC et al (2008) MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicenter, multivendor, randomized trial. Eur Heart J 29:480–489
10. Schwitter J, Wacker CM, Wilke N et al (2013) 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 multicenter, multivendor trial. Eur Heart J 34:775–781
11. Morton G, Chiribiri A, Ishida M et al (2012) Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. J Am Coll Cardiol 60:1546–1555
12. Watkins S, McGeoch R, Lyne J et al (2009) Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. Circulation 120:2207–2213
13. Bettencourt N, Chiribiri A, Schuster A et al (2013) Cardiac magnetic resonance myocardial perfusion imaging for detection of functionally significant obstructive coronary artery disease: a prospective study. Int J Cardiol 168:765–773
14. Schuijf JD, Bax JJ, Shaw LJ et al (2006) Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. Am Heart J 151:404–411
15. Scheffel H, Stolzmann P, Alkadhi H et al (2010) Low-dose CT and cardiac MR for the diagnosis of coronary artery disease: accuracy of single and combined approaches. Int J Cardiovasc Imaging 26:579–590
16. Groothuis JGJ, Beek AM, Brinckman SL et al (2013) Combined non-invasive functional and anatomical diagnostic work-up in clinical practice: the magnetic resonance and computed tomography in suspected coronary disease (MARCC) study. Eur Heart J 34:1990–1998
17. Genders TS, Steyerberg EW, Alkadhi H et al (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 32:1316–1330
18. Bettencourt N, Rocha J, Ferreira N et al (2011) Incremental value of an integrated adenosine stress-rest MDCT perfusion protocol for detection of obstructive coronary artery disease. J Cardiovasc Comput Tomogr 5:392–405
19. Bettencourt N, Chiribiri A, Schuster A et al (2013) Direct comparison of cardiac magnetic resonance and multidetector computed tomography stress-rest perfusion imaging for detection of coronary artery disease. J Am Coll Cardiol 61:1099–1107
20. Austen WG, Edwards JE, Frye RL et al (1975) 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 51:5–40
21. Kramer CM, Barkhausen J, Flamm SD et al (2013) Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 15:91
22. Gould KL, Johnson NP, Bateman TM et al (2013) Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol 62:1639–1653
23. Pijls NH, van Schaardenburgh P, Manoharan G et al (2007) Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 49:2105–2111
24. Tonino PA, De Bruyne B, Pijls NH et al (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 360:213–224
25. De Bruyne B, Pijls NH, Kalesan B et al (2012) Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 367:991–1001
26. Koo BK, Erglis A, Doh JH et al (2011) Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 58:1989–1997
27. Min JK, Leipsic J, Pencina MJ et al (2012) Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 308:1237–1245
28. Meijboom WB, Van Mieghem CA, van Pelt N et al (2008) 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 52:636–643
29. Bettencourt N, Rocha J, Carvalho M et al (2009) Multislice computed tomography in the exclusion of coronary artery disease in patients with presurgical valve disease. Circ Cardiovasc Imaging 2:306–313