Cardiovascular magnetic resonance imaging and computed tomography in patients with suspected coronary artery disease

Groothuis, J.G.J.

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Chapter 5

Combined non-invasive functional and anatomical diagnostic work-up in clinical practice: the magnetic resonance and computed tomography in suspected coronary artery disease (MARCC) study

Jan G.J. Groothuis, Aernout M. Beek, Stijn L. Brinckman, Martijn R. Meijerink, Mijntje L.P. van den Oever, Mark B.M. Hofman, Cornelis van Kuijk, Albert C. van Rossum

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ABSTRACT

Aims: The combined use of cardiac computed tomography (CT) coronary angiography (CTCA) and myocardial perfusion imaging allows the non-invasive evaluation of coronary morphology and function. Cardiovascular magnetic resonance (CMR) imaging has several advantages: it can simultaneously assess myocardial perfusion, ventricular and valvular function, cardiomyopathy and aortic disease and does not involve any additional ionizing radiation. We investigated the combined use of cardiac CT and CMR for the diagnostic evaluation of patients with suspected coronary artery disease (CAD) in clinical practice.

Methods and results: A total of 192 patients with low or intermediate pre-test probability of CAD underwent CTCA and CMR. All patients with obstructive CAD on CTCA and/or myocardial ischemia on CMR were referred for invasive coronary angiography (ICA). Fractional flow reserve was measured in case of intermediate lesions (30-70% diameter stenosis) on ICA. Additional cardiac and extra-cardiac findings by CTCA and CMR were registered. The combination of CTCA and CMR significantly improved specificity and overall accuracy (94% and 91%) for the detection of significant CAD compared with their use as a single technique (CTCA 39% and 57%, $p<0.0001$; CMR 82% and 83%, $p=0.016$). No events were recorded during follow-up (18 ± 6 months) in 104 patients who did not undergo ICA. Furthermore, the combined strategy provided an alternative diagnosis in 19 patients.

Conclusion: The combined use of CTCA and CMR significantly improved specificity and overall diagnostic accuracy for the detection of significant CAD, and allowed the detection of alternative (extra-) cardiac disease in patients without significant CAD.

INTRODUCTION

The combined use of computed tomography coronary angiography (CTCA) and myocardial perfusion imaging allows the clinician to non-invasively evaluate coronary morphology and function in patients with suspected coronary artery disease (CAD). (1-3) CTCA accurately detects CAD and is particularly useful to exclude obstructive disease in patients with low or intermediate pre-test probability of having CAD. Myocardial perfusion imaging can subsequently be used to assess the hemodynamic significance of CAD and to direct further treatment. The addition of CTCA to myocardial perfusion imaging has been shown to significantly improve specificity and overall diagnostic accuracy for the detection of significant CAD. (3) So far, predominantly nuclear imaging modalities have been used in combination with CTCA.

Several studies have shown that cardiovascular magnetic resonance (CMR) myocardial perfusion imaging can reliably assess the hemodynamic relevance of CAD. (4,5) CMR does not involve ionizing radiation and has a diagnostic accuracy for detection of CAD that is at least equivalent as single photon emission tomography myocardial perfusion imaging. (6-8) Moreover, CMR allows the simultaneous assessment of ventricular and valvular function, cardiomyopathy and aortic disease.(9)

Therefore, the objective of this study was to investigate the usefulness of a combined noninvasive anatomical and functional work-up using CMR imaging and cardiac CT for the diagnostic evaluation of patients with low to intermediate pre-test probability of CAD in clinical practice.

METHODS

Patients and study protocol

Patients were prospectively recruited from the outpatient cardiology clinic in our hospital. Inclusion criteria were chest pain and low or intermediate pre-test probability CAD according to the previously described Diamond/Forrester and CASS scale. (10-12) Exclusion criteria were any prior history of CAD (prior documented myocardial ischemia, myocardial infarction, percutaneous coronary intervention, or cardiac surgery), significant arrhythmia, pregnancy, renal insufficiency (serum creatinine > 110µmol/L), known allergy to iodinated contrast material, any absolute contra-indication for magnetic resonance imaging (e.g. cerebral clips), claustrophobia and asthma. The study population is a shared study population with a previous publication. (13)

All patients underwent CT and CMR within 2 weeks. All patients with at least one atherosclerotic lesion causing > 50% diameter stenosis on CTCA and/or myocardial ischemia on CMR underwent invasive coronary angiography (ICA) within 2 months. Additionally, patients with no or non-obstructive CAD on CTCA and normal myocardial perfusion on CMR could be referred for ICA on the basis of their physician's clinical assessment. In case of intermediate CAD on ICA, additional fractional flow reserve (FFR)

measurements were performed to determine the hemodynamic significance. Patients with no or non-obstructive CAD on CTCA and normal myocardial perfusion on CMR who did not undergo ICA were followed-up by standardized telephone interview after 1 year. After excluding significant CAD as the cause of their complaints, and depending on alternative findings and their cardiovascular risk profile, patients were advised treatment according to current guidelines for primary prevention of cardiovascular disease and/or referred to the appropriate physician for further evaluation. The study protocol was approved by the local ethics committee and written informed consent was obtained in all patients.

Cardiac computed tomography

Computed tomography was performed using a 64-slice CT scanner (Sensation 64, Siemens, Erlangen, Germany). When the resting heart rate was > 65 beats per minute, 50 mg metoprolol was administered orally one hour before the start of computed tomography. All patients received 0.4 mg nitroglycerin sublingual before the start of the scan.

First a non-contrast scan was performed at 150 mAs and 120 kV. Using dedicated software (Syngo Calciumscoring, Siemens, Germany) the Agatston calcium score was calculated semi-automatically by an experienced observer, blinded to CTCA and CMR data. The coronary angiography scan was performed using a scan collimation of 64x0.6 using a flying z-focus at 900mAs and 120 Kv and automated bolus tracking after injection of 100 ml of non-ionic contrast agent (Ultravist300, Bayer, Germany). Using retrospective ECG triggering, data were reconstructed at 65% of the RR interval (slice thickness 0.75 mm, increment 0.4 mm). Two additional axial reconstructions from the same raw dataset were made with full field of view using a lung and a soft tissue reconstruction algorithm (slice thickness 5 mm, increment 5 mm). The radiation exposure was estimated using dedicated software (ImPACT, version 0.99x, St George's Hospital, London, UK).

CTCA data were analysed in consensus by a radiologist and a cardiologist, blinded to the CMR and ICA data. The coronary tree was evaluated according to a 16-segment coronary artery model modified from the American Heart Association. (14) Each segment was graded by visual assessment on a four-point scale: normal (no stenosis); non-obstructive CAD (0-50% diameter stenosis); obstructive CAD (>50% diameter stenosis) and non-diagnostic (severe motion artefacts that impaired adequate image interpretation). Non-diagnostic segments were excluded from the analysis. The additional full field-of-view reconstructions were qualitatively evaluated for extra-cardiac pathology along the entire z-axis of the dataset using lung, mediastinal and bone window settings.

Cardiovascular magnetic resonance imaging

All imaging was performed on a 1.5 Tesla whole-body MRI scanner (Sonata/Avanto, Siemens, Erlangen, Germany). Patients were instructed to refrain from caffeinated drinks and other competitive antagonists of adenosine 24 hours before the examination. Ventricular and valvular function were assessed using retro-triggered, balanced steady-state free precession gradient-echo cine imaging (slice thickness 5 mm, temporal resolution

35-50ms) in 4-, 3- and 2- chamber long axis and short axis orientations. Myocardial perfusion was assessed using a dynamic single shot saturation recovery gradient-echo planar pulse sequence (matrix-size 160 x 144, voxel size 2.5 x 2.5 x 10 mm^3), accelerated by parallel imaging with a factor 2 using TSENSE, during the administration of 0.1 mmol/kg body weight of a gadolinium-based contrast agent (Magnevist, Schering AG, Germany), acquiring 3 short axis slices (basal, mid and apical) per heartbeat during 50 heart beats. Stress images were acquired after 3 minutes of continuous infusion of adenosine (140 µg/kg/min). The rest scan was acquired at least ten minutes after the stress scan, with identical scan parameter setting, contrast dose and slice positions. After the rest perfusion scan late gadolinium enhancement (LGE) images were obtained in identical orientations as the cine images using a 2D segmented inversion recovery gradient echo pulse sequence (slice thickness 5 mm, inversion time 250-300 ms).
CMR data were analysed visually by two cardiologists blinded to the CT and ICA data. Left ventricular volumes and ejection fraction were calculated using Siemens Syngo Argus software. Both stress and rest perfusion images were analysed simultaneously on one workstation using a 16 segment model as described previously. (15) Segments were scored as normal, ischemic or scar. A myocardial perfusion defect was defined as hypo-enhancement lasting more than three consecutive images after the arrival of the contrast agent in the left ventricular cavity. Myocardial ischemia was defined as a stress induced myocardial perfusion defect without hyperenhancement at LGE imaging. Scar was defined as a region of hyperenhancement at LGE imaging. The presence of any hyperenhancement at LGE was scored per segment and subsequently categorized as subendocardial, transmural or non-ischemic (mid-wall) LGE. Subsequently, all segments were allocated to their coronary artery territories according to the 16 segment model. (14) Additionally, all CMR images were evaluated for other significant (extra-) cardiac pathology such as cardiomyopathies, myocarditis, valvular heart disease, aortic disease and other extra-cardiac diseases. They were defined according to established criteria. (8, 16-18)

Invasive coronary angiography

ICA was performed according to standard clinical protocols. During the procedure, the invasive cardiologist performed direct visual assessment of the coronary arteries. In case of intermediate lesions (30-70% visually assessed diameter stenosis), FFR was measured using a 0.014-inch pressure guide wire (Volcano Corporation, USA). The FFR was calculated as the ratio between the mean coronary artery pressure distal to the coronary stenosis measured by the pressure wire and the mean aortic pressure measured through the guiding catheter, recorded simultaneously under conditions of maximal hyperemia induced by intracoronary administration of 30-60 µg adenosine. (19)
An invasive cardiologist blinded to CTCA and CMR data evaluated the angiograms. The coronary arteries were subdivided according to the same model as used in the CTCA images. (14) Significant CAD was defined as diameter stenosis >70% in at least 2

orthogonal directions using visual analysis, or as diameter stenosis 30-70% with FFR ≤ 0.75. When no FFR measurements were available, intermediate lesions (30-70%) were defined as significant when diameter stenosis was >50% in two orthogonal directions using quantitative coronary analysis (QCA; Inturis, CIVP, Philips, the Netherlands).

Follow-up

Patients with normal CTCA and CMR who did not undergo ICA within 2 months were followed-up by standardized telephone interview and review of their medical charts after 1 year. The following points were registered: interval diagnosis of significant stenosis on ICA, major adverse cardiovascular events (acute coronary syndrome, myocardial infarction, stroke, percutaneous or surgical coronary revascularization), cardiovascular and all-cause mortality.

Definitions and statistical analysis

The following parameters for detection of significant CAD were calculated in the group of patients that underwent ICA: receiver operating characteristic (ROC) curves, sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy. First, these parameters were calculated for all imaging modalities separately: CCS0 (coronary calcium scoring (CCS) using a cut-off value of zero), CTCA (CTCA showing obstructive CAD) and CMR (myocardial ischemia on CMR). Second, these parameters were retrospectively calculated for the following combined stepwise strategies: CCS-CMR (additional CMR when CCS > 0) and CTCA-CMR (additional CMR when CTCA shows obstructive CAD). A true positive CCS-CMR strategy was defined as a patient with CCS > 0 and myocardial ischemia on CMR and significant CAD on ICA/FFR. A true positive CTCA-CMR strategy was defined as a patient with obstructive CAD on CTCA with myocardial ischemia in the corresponding vessel territory on CMR and significant CAD on ICA/FFR. Figure 1 shows these two stepwise strategies in detail.

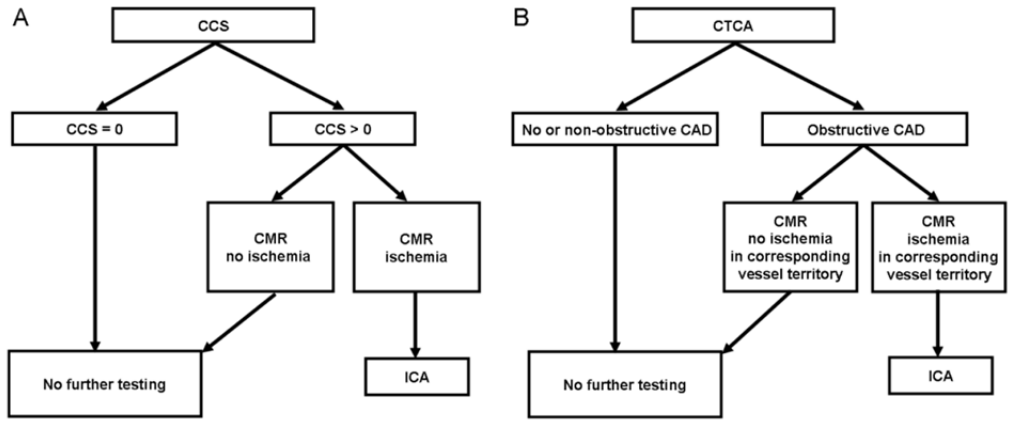

Figure 1. Combined stepwise diagnostic strategies.
Panel A, CCS-CMR: using coronary calcium scoring (CCS) with a cut off value of 0 as initial test. Panel B, CTCA-CMR: using computed tomography coronary angiography (CTCA) as initial test.

All data were presented as mean ± standard deviation for continuous data. Differences between groups were tested by a paired t-test. Diagnostic parameters for the detection of significant CAD were obtained from two-by-two tables. Data were expressed with a 95% confidence interval (CI) calculated from binomial expression using Wilson's approximations. (20) The ROCs were compared using the method of the DeLong et al. (21) The sensitivity, specificity and diagnostic accuracy of the different strategies were compared using the pair wise McNemar test. Positive and negative predictive values of the different algorithms were compared by using the Fisher's exact test. In 50 randomly selected patients intra- and interobserver agreement for CMR perfusion was tested using Cohen's kappa test. Statistical analysis was performed using standard software packages, SPSS version 15.0 (SPSS, Chicago, IL, USA) and SAS version 9.2 (SAS institute, Inc., Cary, NC, USA).

RESULTS

Among the 210 consecutive patients enrolled in the study, 192 patients underwent both CT and CMR successfully. In 10 patients CTCA was not performed because of persistent heart rates > 65 beats per minute after the administration of metoprolol orally and intravenously. In 6 patients the CMR protocol could not be completed: 3 patients had prior unknown claustrophobia, 2 patients had transient adenosine induced third degree atrioventricular-block that disappeared after stopping the adenosine administration and 1 patient had transient supra-ventricular tachycardia. Two patients were excluded on the basis of findings on CTCA: one patient had bilateral pulmonary embolism and another patient had an anomalous origin of the left coronary artery with an interarterial course between the ascending aorta and main pulmonary artery. The flow chart of the remaining 192 patients who were included in the analysis is shown in figure 2.

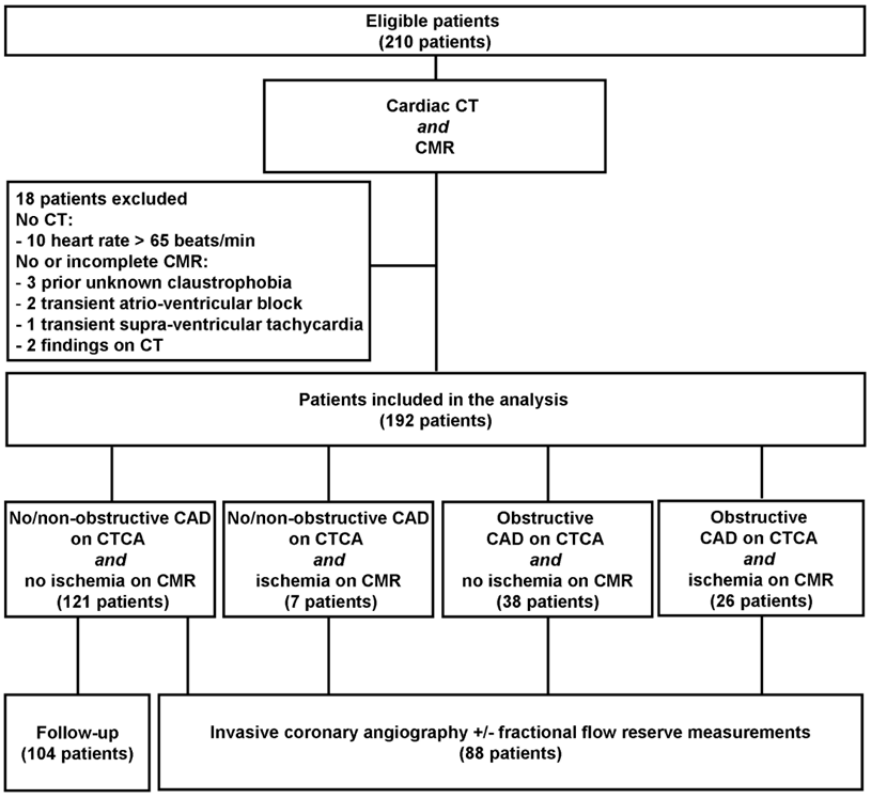

Figure 2. Patient flow chart.

The mean interval time between CT and CMR was 4±3 days (range 0-14 days, median 5 days). The estimated radiation exposure of CTCA was 17.0 mSv. Detailed patient characteristics are listed in table 1. In 71 patients CTCA showed obstructive CAD and/or CMR showed myocardial ischemia. All these patients were referred for ICA. Of 121 patients with no or non-obstructive CAD on CTCA and normal myocardial perfusion on CMR, 17 patients were referred for ICA on the basis of their physician's clinical assessment.

Table 1. Clinical characteristics

Patients	192
Male	96 (49)
Mean age (yrs)*	56±10
Body mass index > 30 kg/m²	39 (20)
Risk factors for CAD	
Diabetes	23 (12)
Hyperlipidaemia	39 (20)
Hypertension	73 (38)
Family history	80 (41)
Current smoking	52 (27)
Symptoms†	
non-anginal chest pain	73 (38)
atypical chest pain	86 (45)
typical chest pain	33 (17)
Pre-test probability of CAD‡	
low-intermediate (<30%)	86 (45)
intermediate (30-70%)	63 (33)
intermediate-high (70-90%)	43 (22)

Note: unless otherwise stated data are expressed as number of patients with percentages within parentheses.
*Mean ± standard deviation. †Typical chest pain 1) Substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or NTG. Atypical chest pain meets 2 of the above characteristics. Nonanginal chest pain meets one or none of the typical anginal characteristics (10). ‡According to the combined Diamond/Forrester and CASS scale (10-12).

Of 88 patients who underwent ICA, 13 (15%) patients had at least one lesion causing >70% diameter stenosis and 37 (42%) had intermediate lesions (30-70% diameter stenosis). FFR was performed in 28 patients with intermediate lesions, 10 of whom had FFR ≤0.75. In 9 patients FFR was not performed due to logistic or technical reasons. Of these, 3 had stenosis > 50% in 2 orthogonal views using QCA. Overall, significant CAD was found in 26 (30%: 26/88) patients. Single vessel disease was detected in 19 patients, two-vessel disease in 5 patients and three-vessel disease in 2 patients. No left main stem disease was found. Prevalence of significant CAD among patients with non-anginal chest pain, atypical and typical chest pain were 7% (5/73), 15% (13/86) and 24% (8/33), respectively. All imaging results are presented in table 2.

Table 2. Imaging findings

Coronary calcium scoring			
	CCS (equivalent Agatston)*		6 (0-136)
	CCS 0		81 (42)
CTCA			
	heart rate (b/min)†		59±6
	non-diagnostic segments‡		40 (1.3)
	no CAD		86 (45)
	non-obstructive CAD		42 (22)
	obstructive CAD		64 (33)
CMR			
	heart rate at rest†		73±14
	heart rate during adenosine†		94±16§
	Left ventricular end-systolic volume (ml/ m^2)†		30±12
	Left ventricular end-diastolic volume (ml/m^2)†		77±17
	Left ventricular ejaction fraction (%)†		61±7
	Myocardial ischemia		33 (17)
	LGE	subendocardial	6 (3)
		transmural	1 (0.5)
		non-ischemic	17 (9)

Note: data are expressed as number of patients with percentages within parentheses unless otherwise stated. *Median and quartiles. † Mean ± standard deviation; ‡ In 23 coronary arteries in 21 patients; § Significantly higher than heart rate at rest ($p<0.05$);

A case example is shown in figure 3. Intra- and interobserver agreement for CMR perfusion results was good : kappa 0.78±0.09 and 0.81±0.09, respectively (both p<0.0001).
During a mean follow-up of 18±6 months, no events were recorded in 104 patients with no or non-obstructive CAD on CTCA and normal CMR. One patient underwent ICA after 1 year, but no significant CAD was found. No patients were lost to follow-up.

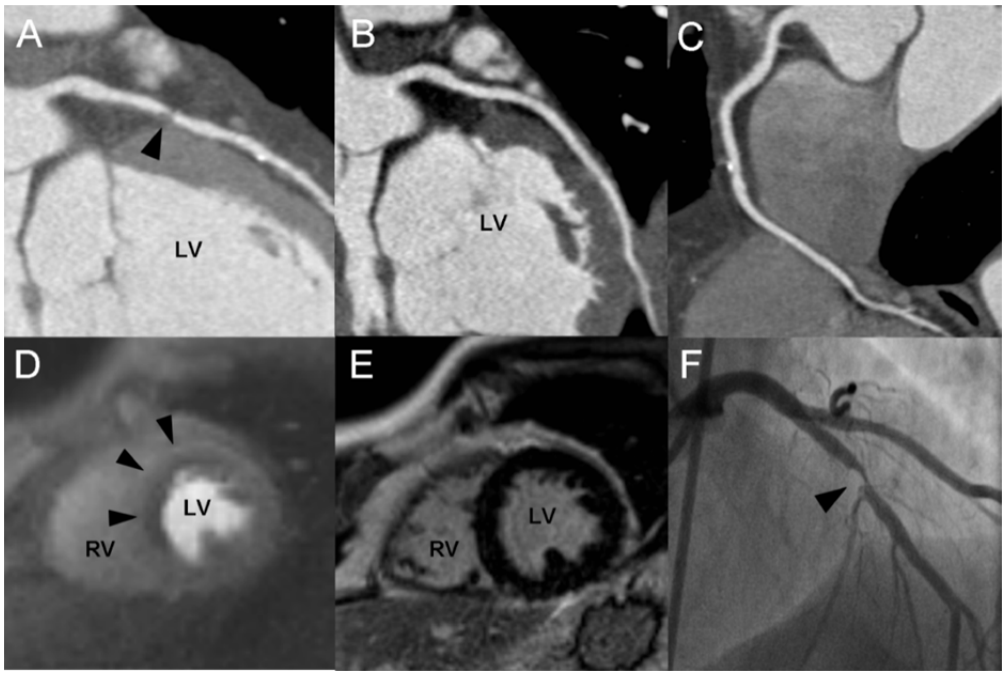

Figure 3. Case example.
A patient with obstructive coronary artery disease (CAD) on computed tomography coronary angiography in the left anterior descending coronary artery (A), normal circumflex coronary artery (B) and non-obstructive CAD in the right coronary artery (C). Cardiovascular magnetic resonance imaging showed an adenosine stress induced perfusion defect in the anterior and anteroseptal myocardial wall (D, mid ventricular short axis orientation) and absence of myocardial fibrosis on gadolinium late enhancement imaging (E). Invasive coronary angiography (F) confirmed significant CAD in left anterior descending coronary artery. LV: left ventricle; RV: right ventricle.

Detection of significant coronary artery disease

Table 3 shows the diagnostic performance for detection of significant CAD of the 5 different imaging strategies in the group of patients that underwent ICA. Owing to its low specificity, the overall accuracy of CCS0 was lowest. The proportions of patients with significant CAD among patients with a CCS of 0, 1-99, 100-399, 400-999 and >999 were 0% (0/8), 20% (7/35), 32% (10/31), 75% (6/8) and 50% (3/6), respectively.

Table 3. Diagnostic accuracy for detection of significant coronary artery disease of different imaging strategies.

strategy	sensitivity %; 95% CI (n)	specificity %; 95% CI (n)	NPV %; 95% CI (n)	PPV %; 95% CI (n)	accuracy %; 95% CI (n)
CCS0	100; 87-100 (26/26)	13; 7-24 (8/62)	100; 68-100 (8/8)	33; 23-43 (26/80)	39; 29-49 (34/88)
CTCA	100; 87-100 (26/26)	39; 28-51 (24/62)	100; 86-100 (24/24)	41; 30-53 (26/64)	57; 46-67 (50/88)
CMR	85; 67-94 (22/26)	82; 71-90 (51/62)	93; 83-97 (51/55)	67; 50-80 (22/33)	83; 74-89 (73/88)
CCS-CMR	85; 67-94 (22/26)	87; 77-93 (54/62)	93; 84-97 (54/58)	73; 56-86 (22/30)	86; 78-92 (76/88)
CTCA-CMR	85; 67-94 (22/26)	94; 85-98 (58/62)	94; 85-98 (58/62)	85; 67-94 (22/26)	91; 83-95 (80/88)

Note: data are expressed as percentages with number of patients within parentheses.
NPV: negative predictive value; PPV: positive predictive value

ICA was performed in 24 patients without obstructive CAD on CTCA. In these patients no significant CAD was found. CTCA was falsely scored as obstructive CAD in 38 patients. Twenty-four of these patients had intermediate lesions, but no significant CAD on ICA/FFR.

Of 55 patients with normal myocardial perfusion on CMR who underwent ICA, 4 (7%) patients were false negative. These 4 patients had single vessel disease on ICA of which 2 had only intermediate lesions with borderline FFR (0.74). Of 33 patients with myocardial ischemia on CMR, 11 patients did not have significant CAD on ICA. Of these patients, 8 had left ventricular hypertrophy, 1 had a dilated cardiomyopathy and 1 patient had multiple risk factors for microvascular dysfunction (diabetes, hypertension and obesity). Of the 9 patients with left ventricular hypertrophy or multiple risk factors, 5 patients had no obstructive CAD on CTCA. The observed perfusion defect in these patients comprised 1 to 3 segments per patient. No specific pattern of the perfusion defect could be detected.

Prevalence of myocardial ischemia among patients with non-anginal chest pain, atypical and typical chest pain were 8% (6/73), 21% (18/86) and 27% (9/33), respectively. A stress induced perfusion defect with hyperenhancement at LGE suggestive of prior myocardial infarction (scar) was found in 7 patients (6 subendocardial and 1 transmural). In 6 of these patients significant CAD was observed on ICA. There were no patients with non-ischemic scar and ischemia.

In 8 patients an irreversible perfusion defect without the presence of hyperenhancement at LGE was found. These defects were scored as normal.

Of 30 patients with CCS>0 and myocardial ischemia, 22 (73%) patients had significant CAD. Of 26 patients with obstructive CAD on CTCA and myocardial ischemia in a corresponding vessel territory, 22 (85%) patients had significant CAD.

ROC analysis showed that the area under the curve (AUC) for detection of significant CAD using the combination of CTCA and CMR was significantly higher than the AUC using CCS, CTCA or CMR alone, see table 4. Furthermore, the combination of CTCA and CMR resulted in a significantly higher specificity than CTCA or CMR alone: 94% versus 39%, $p<0.0001$ or 82%, $p=0.016$, respectively. Moreover, the combination of CTCA and CMR resulted in a significantly higher overall diagnostic accuracy compared with CTCA or CMR alone: 91% versus 57%, $p< 0.0001$ or 83%, $p=0.016$, respectively. CTCA-CMR resulted in a significantly higher positive predictive value than CTCA alone: 85% versus 41%, $p<0.001$, and there was a trend towards a higher positive predictive value of CTCA-CMR than CMR alone (85% versus 67%, $p=0.14$). There was no significant difference in sensitivity between the combined strategies and CTCA or CMR alone: 85% versus 100%, $p=0.13$ or 85%, $p=1.0$, respectively.

The specificity of the combined CCS-CMR strategy was significantly higher than CCS or CTCA alone (87% versus 13% $p<0.0001$, or 29% $p<0.0001$, respectively) but was not significantly different from the specificity of CMR: 87% versus 82%, $p=0.25$.

Similarly, the overall diagnostic accuracy of the combined CCS-CMR strategy was significantly higher than CCS or CTCA alone (86% versus 39% p<0.0001, or 57% p<0.0001, respectively) but it was not significantly different from the diagnostic accuracy of CMR: 86% versus 83%, p=0.25.

Table 4. Diagnostic accuracy for detection of significant coronary artery disease of different imaging strategies using receiver operating characteristic curves (ROC).

strategy	AUC (95% CI)	p-value*
CCS0	0.57±0.06 (0.44-0.69)	p<0.0001
CTCA	0.69±0.06 (0.59-0.80)	p<0.0001
CMR	0.83±0.05 (0.77-0.95)	p=0.005
CCS-CMR	0.86±0.04 (0.77-0.92)	p=0.040
CTCA-CMR	0.89±0.05 (0.80-0.98)	

AUC: area under the curve. *compared to CTCA-CMR

Additional findings by CT and CMR

In 17 patients without significant CAD, the combination of CT and CMR provided an alternative cardiac diagnosis: myocarditis was found in 7 patients, hypertrophic cardiomyopathy in 7 patients, dilated cardiomyopathy in 2 patients and 1 patient had an anomalous coronary artery with a malignant interarterial course. Furthermore, 1 patient was diagnosed with bilateral pulmonary embolism and 1 patient had pneumonia.

Additional clinically relevant cardiac findings were detected in 33 patients.

Twenty patients had left ventricular hypertrophy. Twelve patients had mild but significant valvular heart disease and one had a mildly stenotic bicuspid aortic valve. There were no patients with moderate or severe valvular heart disease. Furthermore, in 14 patients, clinically relevant non-cardiac findings were detected by CMR and CT requiring treatment or follow-up, such as dilated thoracic aorta and emphysema. In table 5, all additional findings are listed.

Table 5. Additional findings detected by cardiac computed tomography and cardiovascular magnetic resonance imaging.

Finding			n
Heart			
	Myocarditis		7
	Hypertrophic cardiomyopathy		7
	Dilated cardiomyopathy		2
	Left ventricular hypertrophy		20
	Valvular heart disease	acquired	12
		congenital	1
	Coronary anomaly	malignant	1
		benign	2
Aorta			
	Aneurysm descending aorta		1
	Dilated ascending aorta		6
Lungs			
	Embolism		1
	Emphysema		2
	Pneumonia		1
	Suspected malignancy		3

Note: data are expressed as number of patients.

DISCUSSION

The present study investigated a combined non-invasive anatomical and functional diagnostic work-up using CT and CMR in a clinical population of patients with suspected CAD. It showed that the combined use of CTCA and CMR significantly improved specificity and overall accuracy for the detection of significant CAD compared with either modality alone.

Our study has some unique characteristics. First, no study has as yet compared the combined use of computed tomography and CMR with invasive coronary angiography with conditional fractional flow reserve measurements. Second, the study population consisted of patients who were referred for non-invasive diagnostic evaluation of suspected CAD that represent the average patient population in an outpatient cardiology clinic. This is in contrast to other studies that primarily focused on patients who were already referred for ICA. (1,3) Furthermore, this study investigated the usefulness of the proposed combination for the detection of both significant CAD and additional (extra-) cardiac diagnoses.

The need for more specific strategies for the non-invasive diagnostic work-up of patients with suspected CAD was demonstrated in a large study comprising 398,978 patients who underwent ICA. (22) Obstructive CAD was found in only 38% of these patients. Recently, the superior diagnostic value for the detection of significant CAD of a combined anatomical and functional strategy was shown using CTCA and nuclear myocardial perfusion imaging modalities.(3,23) Similar to our results, the significantly higher diagnostic accuracy for the combination of CTCA and myocardial perfusion imaging than for either CTCA or myocardial perfusion imaging alone, was primarily a result of an improvement in specificity. This might be explained by the fact that myocardial perfusion imaging could demonstrate the functional (ir)relevance of CAD found on CTCA, and, conversely, that CTCA could exclude CAD in patients with abnormal myocardial perfusion, e.g. due to microvascular dysfunction. Improved specificity will ultimately result in less unnecessary invasive procedures. Furthermore, Pazhenkottil et al (24) recently showed that the combined use of CTCA and SPECT provided added clinical value in the decision making process in patients with suspected CAD.

Hybrid imaging modalities, that combine CTCA with a nuclear perfusion imaging technique in one single scanning session, are increasingly used. Our results show that a stepwise approach improves diagnostic accuracy in a comparable way. In a low to intermediate risk group, exclusion of CAD with the highest degree of confidence should be the first and main priority. Although CMR would be an attractive initial examination because of the lack of radiation, CTCA is the most appropriate choice because of its exceptionally high negative predictive value. In such a strategy, only patients with abnormal CTCA will undergo further perfusion imaging and, thus, a large proportion of patients can be discharged home safely after only one test (67% of all patients did not have obstructive CAD on CTCA in our study). However, in patients with other (higher) risk profiles, other strategies, using CMR as a first-line or even as a stand-alone technique may

be more appropriate, since in these patients, functional severity rather than the presence of CAD is the main question

In the present study, diagnostic performance of CMR and CTCA for the detection of significant CAD was lower than previously reported. (5,25,26) This may be explained by the clinical profile of our study group. In contrast to other studies, patients were at low or intermediate risk of having significant CAD and were not yet referred for ICA. Accordingly, the prevalence of significant CAD and multi-vessel disease in the present study was low and a substantial number of patients had intermediate lesions (37 patients, 42% in ICA group).

Conventional strategies for the diagnostic work-up of patients with low or intermediate risk CAD using exercise electrocardiography and (nuclear) perfusion imaging modalities focus on establishing the absence or presence of significant CAD. However, this may not always explain the etiology of (atypical or non-anginal) chest pain sufficiently. The present study shows how the combined use of computed tomography and CMR broadens the diagnostic scope in patients with chest pain by providing an alternative, clinically relevant diagnosis in a significant number of patients. In addition, it may obviate the need for further tests such as echocardiography and chest X-ray. When using the stepwise approach, significant epicardial CAD is excluded, but additional techniques are generally required to explore the presence of other, non-ischemic, cardiovascular disease. Further research is needed to determine safety and cost efficiency of the combined and stepwise protocols .

Limitations

The objective of our study was to investigate the usefulness of the combined strategy in clinical practice. Therefore, we included patients with low to intermediate likelihood of having significant CAD who were not already referred for ICA. As several studies have shown the excellent negative predictive value of CTCA and CMR, in the view of the authors it was found unethical to perform ICA in patients with no or non-obstructive CAD on CTCA and normal CMR myocardial perfusion. Seventeen of these patients underwent ICA after referral by their own physician on clinical grounds (referred on their physician's clinical assessment) with none having significant CAD, and the remaining patients did not experience any events during a one year follow-up. However, in these patients significant CAD was not definitively excluded and this study was not powered for prognostic endpoints. Therefore, the fact that ICA was not systematically performed in all patients can be regarded as an important limitation and referral bias might have influenced our results. Further research is needed to evaluate the prognostic value of the combined use of CTCA and CMR in these patients. Although we acknowledge that in research QCA may be more appropriate, this clinical practice oriented study was designed using visual analysis to assess stenosis severity. Furthermore, FFR measurements were only performed in lesions of intermediate severity (diameter stenosis 30-70%). Stenoses of higher grade (>70) were classified as hemodynamically significant, in concordance with clinical practice. However,

recent studies have shown that angiographic lesions with 70-91% diameter stenosis are not always functionally significant according to FFR measurement (27). Performing FFR measurement in all vessels might therefore have changed the results of this study. Furthermore, considering current recommendations, radiation dose in our study was quite high. With the use of prospective triggering techniques and newer generation CT-scanners (dual source, 256-320 slice) radiation dosage can be significantly reduced.(28)

Conclusions

The present study showed the advantages of the combination of computed tomography and CMR for the diagnostic evaluation of patients with suspected CAD in clinical practice. The combined work-up significantly improved specificity and overall diagnostic accuracy for the detection of significant CAD, and allowed the detection of alternative (extra-) cardiac disease in patients without significant CAD.

REFERENCES

1. Gaemperli O, Schepis T, Valenta I, Koepfli P, Husmann L, Scheffel H, Leschka S, Eberli FR, Luscher TF, Alkadhi H, Kaufmann PA. Functionally relevant coronary artery disease: comparison of 64-section CT angiography with myocardial perfusion SPECT. Radiology 2008;248:414-23.
2. Schuijf JD, Wijns W, Jukema JW, Atsma DE, de Roos A, Lamb HJ, Stokkel MP, Dibbets-Schneider P, Decramer I, De Bondt P, van der Wall EE, Vanhoenacker PK, Bax JJ. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol 2006;48:2508-14.
3. Kajander S, Joutsiniemi E, Saraste M, Pietila M, Ukkonen H, Saraste A, Sipila HT, Teras M, Maki M, Airaksinen J, Hartiala J, Knuuti J. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. Circulation 2010;122:603-13.
4. Rieber J, Huber A, Erhard I, Mueller S, Schweyer M, Koenig A, Schiele TM, Theisen K, Siebert U, Schoenberg SO, Reiser M, Klauss V. 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. 2006;27:1465-71.
5. Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR, Marincek B, Luscher TF, von Schulthess GK. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. Circulation 2001;103:2230-5.
6. Schwitter J, Wacker CM, van Rossum AC, Lombardi M, Al-Saadi N, Ahlstrom H, Dill T, Larsson HB, Flamm SD, Marquardt M, Johansson L. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. Eur.Heart J. 2008;29:480-9.
7. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, Schönberg SO, Luchner A, Strohm O, Ahlstrom H, Dill T, Hoebel N, Simor T; for the MR-IMPACT Investigators. 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. 2012 Mar 4.
8. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, Bijsterveld P, Ridgway JP, Radjenovic A, Dickinson CJ, Ball SG, Plein S. 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.
9. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, Ho VB, Jerosch-Herold M, Kramer CM, Manning WJ, Patel M, Pohost GM, Stillman AE, White RD, Woodard PK. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J.Am.Coll.Cardiol. 2010;55:2614-62.
10. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Patel,M.; Pohost,G.M.; Stillman,A.E.; White,R.D.; Woodard,P.K. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J.Am.Coll.Cardiol. 1999;33:2092-197.
11. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N.Engl.J.Med. 1979;300:1350-8.

12. Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R, Kennedy JW, Fisher L, Judkins MP, Mock MB, Killip T. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981;64:360-7.
13. Groothuis JG, Beek AM, Brinckman SL, Meijerink MR, Koestner SC, Nijveldt R, Götte MJ, Hofman MB, van Kuijk C, van Rossum AC. Low to intermediate probability of coronary artery disease: comparison of coronary CT angiography with first-pass MR myocardial perfusion imaging. Radiology 2010;254:384-92
14. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. 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.
15. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. 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.
16. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras,A.; Laissy,J.P.; Paterson,I.; Filipchuk,N.G.; Kumar,A.; Pauschinger,M.; Liu,P. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J.Am.Coll.Cardiol. 2009;53:1475-87.
17. Gelfand EV, Hughes S, Hauser TH, Yeon SB, Goepfert L, Kissinger KV, Rofsky NM, Manning WJ. Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. J.Cardiovasc.Magn.Reson. 2006;8:503-7.
18. Rickers C, Wilke NM, Jerosch-Herold M, Casey SA, Panse P, Panse N, Weil J, Zenovich AG, Maron BJ. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation 2005;112:855-61.
19. Pijls NH, De Bruyne B, Peels K, Van D, Bonnier HJ, Bartunek JKJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N.Engl.J.Med. 1996;334:1703-8.
20. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat.Med. 1998;17:857-72.
21. DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-845.
22. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. N.Engl.J.Med. 2010;362:886-95.
23. Gaemperli O, Saraste A, Knuuti J. Cardiac hybrid imaging. Eur Heart J Cardiovasc Imaging 2012;13:51-60. Epub 2011 Nov 17.
24. Pazhenkottil AP, Nkoulou RN, Ghadri JR, Herzog BA, Küest SM, Husmann L, Wolfrum M, Goetti R, Buechel RR, Gaemperli O, Lüscher TF, Kaufmann PA. Impact of cardiac hybrid single-photon emission computed tomography/computed tomography imaging on choice of treatment strategy in coronary artery disease. Eur.Heart.J. 2011;32:2824-9. Epub 2011 Jul 30
25. Donati OF, Scheffel H, Stolzmann P, Baumuller S, Plass A, Leschka S, Alkadhi H. Combined cardiac CT and MRI for the comprehensive workup of hemodynamically relevant coronary stenoses. Am.J.Roentgenol. 2010;194:920-6.
26. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, Van Mieghem CA, Nieman K, van Werkhoven JM, Pundziute G, Weustink AC, de Vos,A.M., Pugliese,F.; Rensing,B., Jukema,J.W., Bax,J.J.; Prokop,M.; Doevendans,P.A.; Hunink,M.G.; Krestin,G.P.; de Feyter,P.J. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J.Am.Coll.Cardiol. 2008;52:2135-44.
27. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH.Angiographic versus functional severity of coronary artery stenoses in the FAME

study fractional flow reserve versus angiography in multivessel evaluation. J.Am.Coll.Cardiol. 2010;55:2816-21.

28. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2009;3:190-204.