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CARDIAC

Low-dose CT coronary angiography for the prediction of myocardial ischaemia

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Abstract The purpose of this study was to prospectively determine the accuracy of low-dose computed tomography coronary angiography (CTCA) for the diagnosis of functionally relevant coronary artery disease (CAD) using cardiac magnetic resonance (CMR) as a standard of reference. Forty-one consecutive patients (age 64±10 years) underwent *k*-space and time broad-use linear acquisition speed-up technique accelerated CMR (1.5 T) and dual-source CTCA using prospective electrocardiography gating within 1 day. CTCA lesions were analysed and diameter stenoses of more than 50% and more than 75% were compared with CMR findings taken as the reference standard for assessing the functional relevance of CAD. CMR revealed perfusion defects in 21/41 patients (51%). A total of 569 coronary segments were analysed with low-dose CTCA. The image quality of low-dose CTCA was diagnostic in 566/569 segments (99.5%) in 39/41 patients (95%). Low-dose CTCA revealed stenoses of more than 50% in 58/123 coronary arteries (47.2%) in 24/41 patients (59%) and more than 75% stenoses in 46/123 coronary arteries (37.4%) in 23/41 patients (56%). Using a greater than 50% diameter stenosis, low-dose CTCA yielded the following per artery sensitivity, specificity, positive and negative predictive values, and accuracy for the detection of perfusion defects: 89%, 79%, 72%, 92% and 83%, respectively. Low-dose CTCA is reliable for ruling out functionally relevant CAD, but is a poor predictor of myocardial ischaemia.

Keywords Computed tomography · Myocardial perfusion imaging · Magnetic resonance imaging · Coronary artery disease · Myocardial ischaemia · Low dose

Introduction

Myocardial perfusion imaging using either single-photon emission computed tomography (SPECT) or cardiac magnetic resonance (CMR) is an established method for the noninvasive functional assessment of coronary artery disease (CAD). When compared with conventional coronary angiography, recent studies have revealed CMR to have similar [1] or even higher [2–4] diagnostic accuracy compared with that achieved with SPECT [2–4] or gated SPECT [1], with no radiation exposure to the patients. Contrary to the purely anatomical information provided by invasive catheter angiography (ICA) and computed tomography coronary angiography (CTCA), perfusion imaging allows for the evaluation of the functional significance of coronary stenoses and provides prognostic information for risk stratification [5–7].

CTCA has emerged as a robust and accurate tool for the noninvasive evaluation of CAD [8–11]. Because of concerns regarding the radiation exposure of patients undergoing CTCA, a number of dose-reducing methods have been developed [12, 13]. One of the most efficient techniques for radiation dose reduction in CTCA is prospective electrocardiography (ECG) gating [14–16].

With this technique, radiation is only delivered at predefined time points of the cardiac cycle, rather than during the entire cardiac cycle, as with the retrospective ECG gating technique. Initial studies have shown that low-dose CTCA is accurate for diagnosing coronary stenoses in comparison with ICA [17]. Concerning functional information, 64-section CTCA was already evaluated against SPECT and helped in ruling out haemodynamically relevant CAD [18]; however, there are no data on the diagnostic performance of low-dose CTCA for the prediction of ischaemia in comparison to CMR.

Thus, we aimed to prospectively determine the accuracy of low-dose CTCA for the detection of functionally relevant CAD as determined by CMR.

Materials and methods

Study population

The study was conducted prospectively, enrolling 80 consecutive patients who had undergone CTCA because of suspected CAD. The patient demographics are summarised in Table 1. Exclusion criteria for low-dose CTCA were impaired renal function (creatinine level above 120 μmol/L, $n=1$), known hypersensitivity to contrast medium ($n=0$) and absolute arrhythmia ($n=0$). Scanning with prospective ECG triggering was not performed in patients with hearts rates of 70 bpm or higher ($n=4$). These four patients were examined with a retrospectively ECG gated CT protocol but excluded from this study. Patients with previous stent graft placement ($n=14$) or bypass surgery ($n=5$) as well as history of previous myocardial infarction ($n=8$) were excluded from the study. All remaining patients ($n=48$) were asked to participate in this study comparing CTCA with CMR. Patients were excluded from CMR if they presented contraindications to adenosine (second or third AV block, sick sinus syndrome, symptomatic bradycardia, severe asthma or obstructive pulmonary disease; $n=1$), or to MR (implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia, and others according to local regulations and manufacturer's recommendations; $n=6$). Thus, a total of 41 patients could be included in this study (Fig. 1). According to the criteria published by Diamond and Forrester [19], each patient in this population had an intermediate ($n=31$) to high ($n=10$) pretest probability of CAD. This method uses age, sex and symptoms to stratify risk into three categories. Patients with a pretest probability below 13.4% were categorized as low probability and those with a pretest probability above 87.2% were categorized as high probability. Those that fell between these limits would be categorized as intermediate probability (Table 1). All CTCA and CMR examinations were performed within 1 day.

The study protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

Table 1 Patient demographics ($n=42$)

Men	36 (88%)
Women	5 (12%)
Age (years)	64±10 (41–77)
Body mass index (kg/m^2)	28±4
Obesity[a]	10 (24%)
Cardiovascular risk factors	
Hypertension	24 (59%)
Nicotine abuse	12 (29%)
Hyperlipidaemia	13 (32%)
Diabetes	4 (10%)
Family history	6 (15%)
Symptoms	
Nonanginal chest pain	17 (42%)
Atypical angina	11 (27%)
Typical angina	13 (31%)
Pretest probability of CAD	
Intermediate	31 (76%)
High	10 (24%)

CAD coronary artery disease
[a]Defined as a body mass index ≥30 kg/m^2

Low-dose CTCA

All CT examinations were performed on a dual-source CT machine (Somatom Definition, Siemens Healthcare, Forchheim, Germany) using prospective ECG gating. All patients received a single 2.5-mg dose of sublingual isosorbide dinitrate (Isoket, Schwarz Pharma). No beta-blockers were given before CT. Eighty to 100 ml of contrast medium (iopromide, Ultravist 370, Bayer Schering Pharma, Berlin, Germany) was administered at a flow rate of 5–6 ml/s, followed by 50 ml of a 20% contrast agent/80% saline solution mixture. Contrast agent was applied using a dual-head power injector (Stellant, Medrad, Indianola, USA) and was controlled by bolus tracking using a region-of-interest in the ascending aorta (attenuation threshold 120 HU). Data were acquired in the craniocaudal direction during mid-inspiration using the parameters: detector collimation 2×32×0.6 mm, slice acquisition 2×64×0.6 mm by means of a z-flying spot, gantry rotation time 0.33 s. Attenuation-based tube current modulation was used with a reference tube current–time product set at 190 mAs per rotation. The data acquisition window was set at 70% of the R–R interval; the temporal resolution was 83 ms. Patients with a body mass index (BMI) of 25 kg/m^2 ($n=28$) or above were examined with a tube voltage of 120 kV; patients with a BMI below

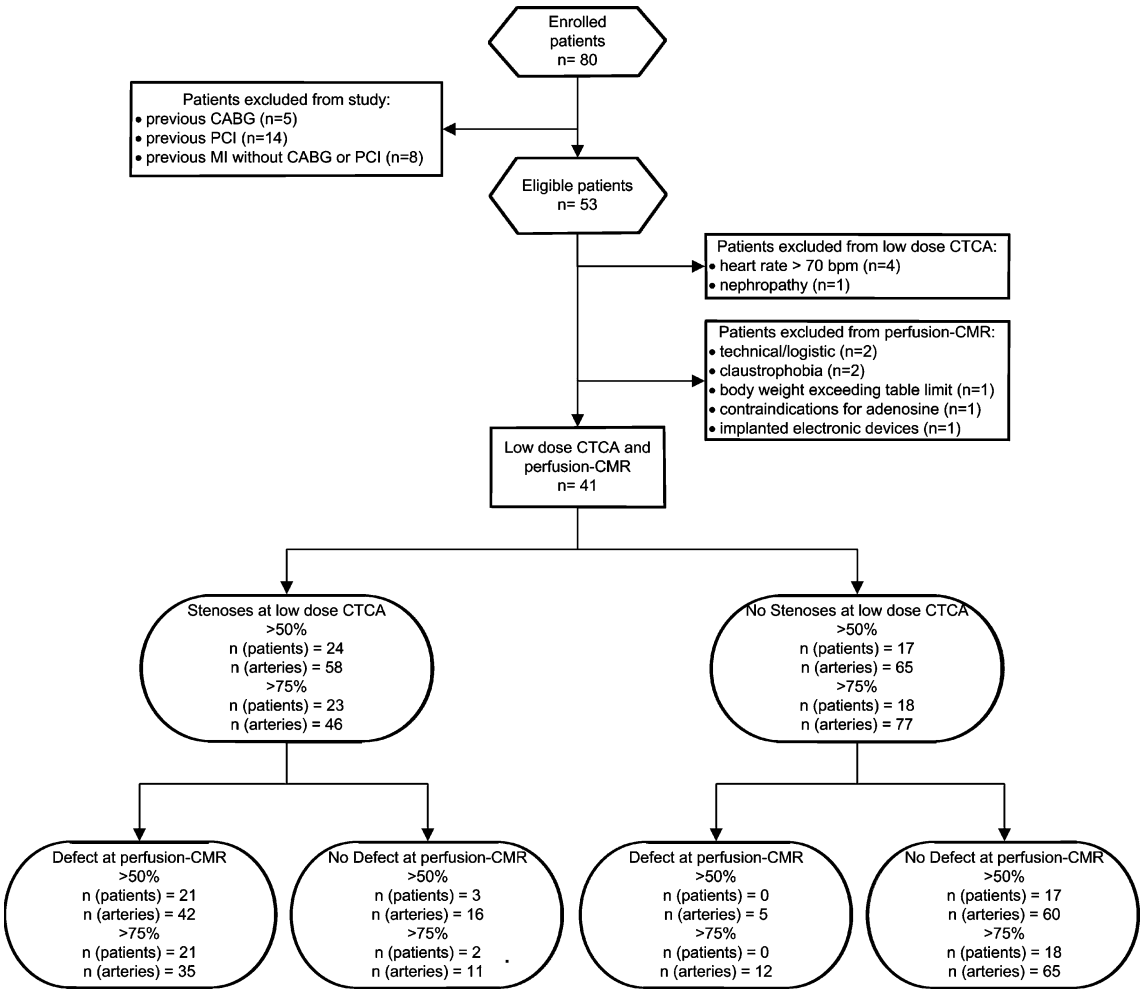

Fig. 1 Flowchart of the study

25 kg/m^2 (n=13) with 100 kV. Low-dose CTCA images were reconstructed in a monosegment mode with a slice thickness of 0.6 mm, using a medium-smooth tissue convolution kernel (B30f). If the vessel segment was calcified, additional reconstructions were performed using a sharp tissue convolution kernel (B45f) to compensate for blooming artefacts. All images were anonymised and transferred to an external workstation (Multi-Modality Workplace, Siemens Healthcare) for analysis.

Low-dose CTCA data analysis

Low-dose CTCA data analysis was performed by two independent radiologists who were both blinded to the clinical history and to the results from any other test (including CMR). All images were evaluated using transverse source images and multiplanar reformations. All segments with a diameter of 1 mm or greater at their origin were included. Vessel segments distal to occlusions were excluded from analysis.

Coronary segments were defined according to a scheme proposed by the American Heart Association [20]. Both the left main stem (segment 5) as well as the intermediate artery (segment 16), if present, were considered to belong to the left anterior descending coronary artery (LAD).

First, both readers independently rated the image quality of each coronary segment as being diagnostic or non-diagnostic. Reasons for nondiagnostic image quality were assigned to motion or stair-step artefacts, image noise, severe vessel wall calcifications or insufficient contrast attenuation.

Then, both readers independently evaluated all coronary segments for the presence or absence of significant stenoses, defined as luminal diameter narrowing of more than 50% and more than 75%, respectively. All diameter measurements were performed with an electronic calliper tool on reconstructions perpendicularly oriented to the vessel's centerline. In the case of disagreement, a consensus reading was appended 1 week after the initial readout.

CMR

All MR studies were performed on a 1.5-T clinical MR system (Achieva, Philips Medical Systems, Best, the Netherlands). Dedicated cardiac phased-array receiver coils were used for signal reception (five elements). All data were acquired during breath hold in end-inspiration. The true short axis of the left ventricle was determined from a series of scout images. Three representative short-axis sections were obtained, one each in the basal, mid-ventricular and apical regions of the left ventricle according to the standardised 17-segment model of the American Heart Association [21]. Pharmacological stress was applied using adenosine, which was administered intravenously at 140 μg per kilogram of body weight over 2.5 min under ECG, oxygen saturation, and blood pressure monitoring. Acquisition of perfusion images was started immediately after the injection of gadoterate meglumine (Gd-DOTA) (Dotarem; Guerbet Research, Aulnay-sous-Bois, France). Contrast medium was dosed at 0.1 mmol per kilogram of body weight using a power injector (MR Spectris; Medrad, Pittsburgh, PA) at an injection rate of 5 ml/s, followed by a 40-ml saline flush. Ten minutes after stress perfusion imaging, a second bolus of 0.1 mmol gadoterate meglumine was injected and rest perfusion images were obtained with the same orientation and position before and after the administration of adenosine. A delay of 10 min after the stress examination allowed residual gadopentetate dimeglumine to be washed out from the myocardium. SENSE (*k-t* sensitivity encoding) imaging was used in combination with a saturation recovery gradient-echo pulse sequence for both of these sequences (repetition time/echo time 3.1/1.1 ms, flip angle 20°, saturation prepulse delay 110 ms, partial Fourier sampling, acquisition window 120 ms, section thickness 10 mm, *k-t* factor of 5 with 11 *k-t* interleaved training profiles, effective acceleration 3.7, three sections acquired sequentially during a single R–R interval), as previously shown [22–24]. High spatial resolution perfusion CMR was performed with an in-plane resolution of 1.25×1.25 mm.

Ten minutes after rest perfusion, late gadolinium enhancement images were acquired in a continuous short-axis view using an inversion-recovery gradient-recalled echo MR sequence with the following parameters: field of view 350–400 mm, repetition time/echo time 7.4/4.3 ms, inversion time 200–350 ms, flip angle 20°, matrix 240×240, slice thickness 10 mm. The inversion time was chosen to minimise the signal from normal myocardium.

CMR data analysis

CMR data analysis was performed by two different, independent radiologists who were both blinded to the clinical history and to the results from any other test (including low-dose CTCA). In the case of disagreement between the readers, a consensus reading was appended within 1 week.

Rest and stress perfusion as well as late gadolinium enhancement MR data were evaluated by visual analysis for each patient according to a 16-segment model (the 17-segment American Heart Association model [21] minus the apical segment).

The following algorithm was used to define myocardial segments presenting a perfusion defect: Segments were considered to have a perfusion defect if (a) late gadolinium enhancement was present and/or (b) a perfusion deficit was found in stress perfusion but not in rest perfusion [25]. In each case of disagreement between the readers, a consensus was obtained, thereby getting dichotomic values for presence of perfusion defects (0 = normal; 1= abnormal). Myocardial territories were assigned to the three major coronary arteries according to standard definitions [21].

Statistical analysis

Quantitative data are expressed as mean ± standard deviation. Qualitative data are given in proportions. As the assignment of single coronary segments on CT to myocardial territories on CMR is not feasible, data analyses were performed on a per artery (left anterior descending coronary artery, LAD; left circumflex artery, LCX; right coronary artery, RCA) and per patient basis, as previously described [26]. Nondiagnostic segments at CTCA were censored as positive findings in the vessel-based and patient-based analyses, reflecting the intention-to-diagnose nature of the study. We also added per patient analysis as this provides the clinically most meaningful information for patient management. Both analyses were separately performed for diameter stenoses of more than 50% and more than 75%.

The unweighted κ statistic with binary data was used to assess inter-reader variability, assessing low-dose CTCA and CMR. κ values less than 0.4 indicated positive but poor agreement, 0.41–0.75 good agreement and above 0.76 excellent agreement.

Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy including 95% confidence intervals were calculated for both lesion degrees as mentioned above from χ^2 tables of contingency with CMR as the standard of reference. Statistical analyses were performed using commercially available software (SPSS, release 15.0, Inc., Chicago, IL).

Results

Low-dose CTCA

Low-dose CTCA examinations were performed successfully in all patients without complications. All patients

were in sinus rhythm, and mean heart rate during CT was 60±7 bpm (range 43–69 bpm). The average effective radiation dose per patient was 3.9±1.4 mSv.

Of the 656 theoretically possible coronary artery segments (16 segments x 41 patients), 81 segments (12.3%) were not present or were less than 1 mm in diameter at their origin; six (0.9%) segments were located distal to coronary artery occlusion. Hence, 569 of the theoretically possible 656 segments (86.7%) were included in the analysis.

Image quality of low-dose CTCA was diagnostic in 566/569 (99.5%) segments in 39/41 (95%) of patients. Three segments (two in segment 2, one in segment 7) were not assessable because of motion artefacts. No stair-step artefacts, image noise, severe vessel wall calcifications or insufficient contrast attenuation rendering image quality nondiagnostic were found.

Low-dose CTCA revealed stenoses of more than 50% in 101/566 segments (17.8%), corresponding to 58/123 coronary arteries (47.2%) in 24/41 patients (59%). Twenty-four of these stenoses were located in the LAD (41.4%), 17 in the LCX (29.3%) and 17 in the RCA (29.3%).

When applying a cutoff of more than 75% for significant stenoses, 68 segments (12.0%) were identified as stenotic by low-dose CTCA, corresponding to 46 coronary arteries (37.4%) in 23 patients (56%). Nineteen stenoses were located in the LAD (41.3%), 13 in the LCX (28.3%) and 14 in the RCA (30.4%).

CMR

CMR was successfully performed in all patients without complications. Image analysis revealed defects in 100/656 (15.2%) myocardial segments in 21/41 (51%) patients. Of the 100 myocardial segments with perfusion defects, 30 (30%) were located in the LAD, 38 (38%) in the LCX and 32 (32%) in the RCA territory. Twenty patients (49%) showed no perfusion abnormalities on CMR. Of the 41 patients, a total of 7 patients (17%) showed LGE. Of the 27 myocardial segments with LGE, 2 (7%) were located in the LAD, 15 (56%) in the LCX and 10 (37%) in the RCA territory.

Inter-reader variability

The κ values for the detection of coronary stenosis of more than 50% and more than 75% with low-dose CTCA were 0.89 and 0.96, respectively, indicating excellent inter-observer agreement.

The κ value for the detection of CAD using CMR was 0.81, indicating excellent inter-reader agreement.

Comparison of low-dose CTCA and CMR

Per artery analysis

Applying a cutoff for stenoses of more than 50%, 42/58 stenotic coronary arteries (72%) were associated with defects in their corresponding territory according to CMR (Fig. 2). Sixteen of 58 stenotic coronary arteries (28%) were not associated with abnormalities on CMR (Fig. 3). Five of 47 myocardial territories with perfusion defects (11%) showed no coronary stenoses in the corresponding arteries on low-dose CTCA when a threshold of more than 50% was applied.

For coronary stenoses of more than 75%, 35/46 stenotic vessels (76%) on low-dose CTCA were associated with defects in the corresponding territory on CMR (Fig. 2). Eleven of 46 stenotic coronary arteries (24%) were not

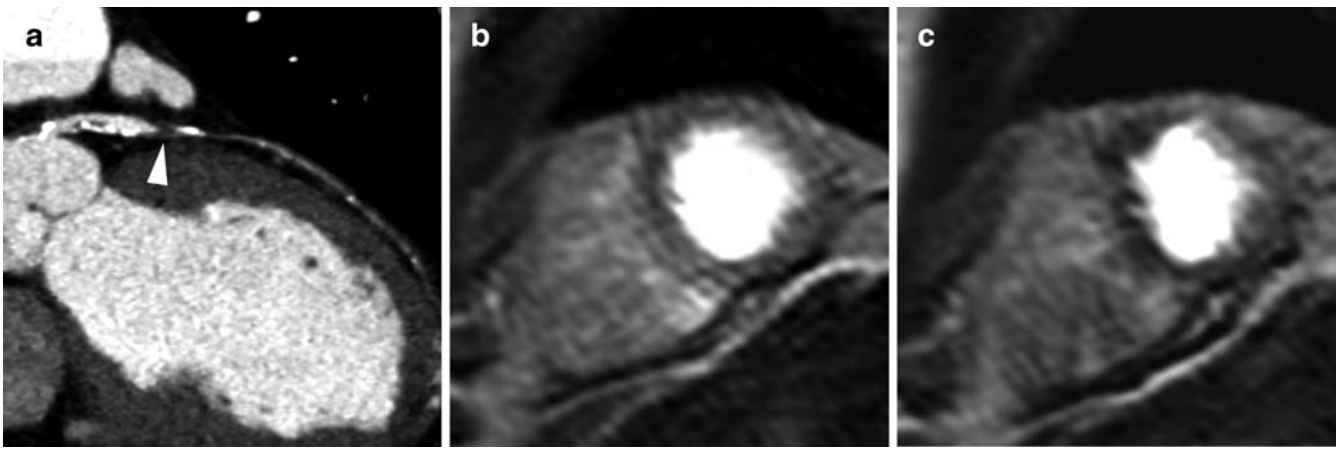

Fig. 2 **a** Low-dose CTCA in a 70-year-old male patient showing a significant stenosis (rated as causing more than 75% luminal diameter narrowing) of the proximal segment of the left anterior descending artery (*arrowhead*). **b** Perfusion CMR during rest demonstrates a normal signal in the myocardium. **c** Perfusion CMR during adenosine-induced stress shows a perfusion deficit in the subendocardium of the mid-ventricular septal wall, indicating myocardial ischaemia

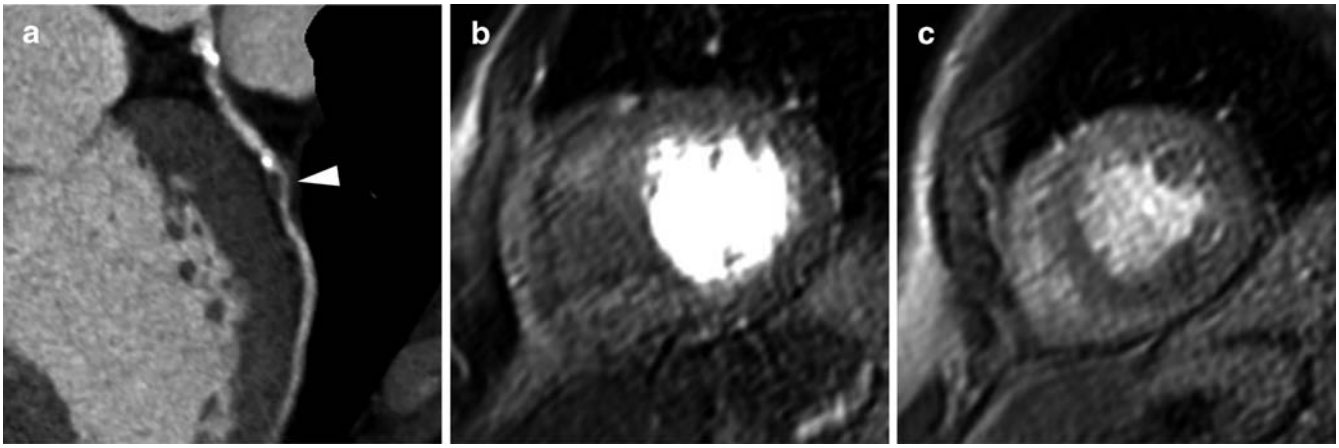

Fig. 3 **a** Low-dose CTCA in a 51-year-old male patient showing a significant stenosis (rated as causing more than 50% luminal diameter narrowing) of the middle segment of the left anterior descending artery (*arrowhead*). Perfusion CMR during rest (**b**) and during adenosine-induced stress (**c**) shows normal myocardial perfusion indicating no ischaemia or scarring

associated with abnormalities on CMR. Twelve of 47 myocardial territories with perfusion defects (26%) showed no coronary stenoses in the corresponding arteries on low-dose CTCA when a threshold of more than 75% was applied.

The sensitivity, specificity, NPV, PPV and accuracy of low-dose CTCA for the detection of any myocardial defects are given in Table 2, for coronary stenoses of more than 50% and more than 75%.

Per patient analysis

For coronary stenoses of more than 50%, 26/30 patients (86.7%) with stenotic coronary arteries on low-dose CTCA had segments with perfusion defects in CMR. Four of the 30 patients (13.3%) showed coronary stenoses without corresponding defects in CMR. Of the 12 patients without significant stenoses on CTCA, 11 (91.7%) did not show any abnormalities on CMR. One patient (8.3%) had perfusion defects in the LAD territory (segments 8, 13 and 14) on CMR without corresponding stenosis in CTCA. This patient had undergone percutaneous coronary intervention (PCI) with stenting of the proximal LAD 1 year before the study.

Applying a cutoff of more than 75%, 25/28 patients (89.3%) with stenotic coronary arteries on low-dose CTCA had segments showing perfusion defects on CMR. Of the remaining 14 patients, 2 (14.3%) had defects on CMR (Table 2).

The sensitivity, specificity, NPV, PPV and accuracy of low-dose CTCA for the detection of any myocardial defects are given in Table 2, for coronary stenoses of more than 50% and more than 75%.

When late gadolinium enhancement imaging was not considered, specificity and PPV decreased by 8% and 9%, respectively, for more than 50% stenosis and by 8% each for more than 75% stenosis, while sensitivity and NPV remained unchanged (100%).

Discussion

This study is the first to demonstrate that low-dose CTCA is excellent for ruling out haemodynamically relevant CAD as compared with CMR. On the other hand, an abnormal

Table 2 Accuracy of low-dose CTCA for the detection of perfusion defects as determined by perfusion CMR

	Sensitivity (CI; *n*)	Specificity (CI; *n*)	PPV (CI; *n*)	NPV (CI; *n*)	Accuracy (CI; *n*)
Per artery analysis					
>50% stenosis	89% (79–99; 42/47)	79% (69–89; 60/76)	72% (60–85; 42/58)	92% (85–100; 60/65)	83% (76–90; 102/123)
>75% stenosis	74% (61–88; 35/47)	86% (77–94; 65/76)	76% (63–90; 35/46)	84% (76–93; 65/77)	81% (73–88; 100/123)
Per patient analysis					
>50% stenosis	100% (98–100; 21/21)	85% (67–100; 17/20)	88% (72–100; 21/24)	100% (97–100; 17/17)	93% (83–100; 38/41)
>75% stenosis	100% (98–100; 21/21)	90% (74–100; 18/20)	91% (78–100; 21/23)	100% (97–100; 18/18)	95% (87–100; 39/41)

NPV negative predictive value, *PPV* positive predictive value, *CI* 95% confidence interval

low-dose CTCA study is a poor predictor of the functional relevance of the disease.

Coronary morphology and myocardial function

Previous reports have demonstrated that the anatomical assessment of a coronary stenosis as determined by ICA correlates only poorly with the haemodynamic significance of the stenosis [27]. Although ICA is the most accurate technique for imaging luminal morphology, it does not reflect the haemodynamic impairment of blood flow to the myocardium, as it does not account for the effects of collateral circulation, the mass of viable myocardium, the shape and length of stenosis, the inflow and outflow configuration and the haemodynamic features of blood flow [28]. In addition, the diffuseness of atherosclerosis, often resulting in disease proximal and distal to the major lesion, may lead to an underestimation of the extent and severity of coronary atherosclerosis. Similar results to those from ICA could also be demonstrated for low-dose CTCA in this study. Being an entirely morphological imaging tool, CTCA insufficiently predicted the haemodynamic significance of a coronary stenosis on myocardial perfusion as demonstrated by the PPV. On the other hand, our study results indicate that, in the same patient cohort, low-dose CTCA is an adequate tool for excluding functionally relevant CAD, as shown by the excellent NPV in this study.

Altogether, this study confirms previous studies employing nuclear tests [18, 26, 29–31] and ICA [28, 32] in comparison with CTCA, while extending the results to the low-dose technique for CTCA and for the first time using CMR as the standard of reference.

An important aspect when correlating coronary obstruction with myocardial perfusion is related to the cutoff value for defining the "significance" of a stenosis. Previous studies used various definitions, such as a 50% *area* stenosis [26], a 50% *diameter* or a 75% *diameter* stenosis [31]. In this study, we used both a 50% and a 75% *diameter* stenosis as cutoff values for defining stenosis at low-dose CTCA.

As expected, shifting the cutoff diameter stenosis from 50% to 75% led to an improvement in the specificity and PPV of low-dose CTCA for predicting myocardial ischaemia through a reduction of "false-positive" stenoses with CTCA: the higher the stenosis, the higher the likelihood of flow disturbances in the corresponding myocardial territory. On the other hand, the sensitivity and NPV decreased because "false-negative" stenoses of between 50 and 75% diameter narrowing leading to perfusion defects were missed.

Clinical implications

Based on our study results and according to the literature [18, 26, 28–31], CTCA appears to be best suited as an effective test for ruling out functionally relevant CAD. Those patients with suspected CAD and no or minimal coronary atherosclerosis on CTCA do not need further investigation, as previously also demonstrated with regard to their midterm outcome [33, 34]. On the other hand, patients with morphologically obstructive CAD on CTCA appear to be best investigated using a combined approach including a functional test such as nuclear stress testing, stress echocardiography or CMR. Considering the radiation dose applied to patients undergoing cardiac SPECT [35], CMR should be considered the preferred imaging investigation.

The advantage of a combined evaluation using low-dose CTCA and CMR lies in the very low radiation exposure to the patients, a total of 1–4 mSv [14, 15, 17]. Reviewing the literature reveals that studies on radiation exposure caused by catheter coronary angiography are conspicuously rare. Depending on the studies, effective doses ranged from 4 to 22 mSv for diagnostic invasive procedures [36]. Previous single-source 64-slice CT coronary angiography studies have reported estimated radiation doses of up to 21 mSv without the use of the ECG pulsing technique [9]. On the other hand, Hausleiter et al. [37] reported a mean effective dose of 15 mSv for single-source 64-slice CT coronary angiography without and 9 mSv with the use of ECG pulsing, the latter being comparable to those of dual-source CTCA employing retrospective ECG gating [13]. All of these radiation dose values are higher when compared with the CTCA approach with prospective ECG triggering.

Study limitations

First, ICA was not available in all patients from this study to verify the findings from low-dose CTCA. On the other hand, the accuracy of low-dose CTCA has been previously documented [17], and the aim of this study was to assess the impact of low-dose CTCA findings on myocardial perfusion. Second, low-dose CTCA is feasible only in patients with regular heart rates, thus limiting the application of the technique to a broader patient population. Third, CMR images were not analysed using quantitative measures. In most studies analysing CMR images, however, evaluation of perfusion defects is done on a purely visual basis [1, 24, 25, 38–41]. Fourth, using strict inclusion criteria, 13% of the consecutive patients had to be excluded due to CMR exclusion criteria. Fifth, no separate comparisons between CT and CMR were performed in respect to coronary morphology as assessed with both methods separately. Similarly, there are no data on perfusion imaging using CT. Sixth, 5/53 patients (9%) were excluded from low-dose CTCA because of high heart rate. This number theoretically could have been lowered by administering beta-blockers prior to CT, because beta-receptor antagonists reduce the average and the variability of heart rate [42]. Seventh, we must state that the pretest

probability was intermediate to high and therefore results may be different in "real-world" patients having lower pretest probability. Additionally, perfusion deficits may also occur in microvascular disease and may alter results of this comparison. Finally, the assessment of coronary stenoses on low-dose CTCA using two cutoff values may have been inaccurate, particularly considering the still limited spatial resolution of CTCA in comparison with ICA.

Conclusion

Low-dose CTCA is a reliable tool for identifying patients with no functionally relevant CAD. On the other hand, an abnormal low-dose CTCA study appears to be a poor predictor of myocardial ischaemia.

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