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ORIGINAL PAPER

Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease?

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Abstract To investigate prospectively, in patients with suspicion of coronary artery disease (CAD), the added value of coronary calcium scoring (CS) as adjunct to cardiac magnetic resonance (CMR) for the diagnosis of morphological coronary stenosis in comparison to catheter angiography (CA). Sixty consecutive patients (8 women; 64 ± 10 years) referred to CA underwent CMR (1.5 T) including perfusion and late gadolinium-enhancement imaging as well as CS with computed tomography. Diagnostic performance was evaluated for CMR and CS separately, and for both methods combined, with CA as reference standard. Best CS threshold combined with a specificity >90% to predict significant stenosis in patients without abnormalities on CMR was determined from receiver operator characteristics (ROC) analysis. Abnormal CMR results were considered to indicate significant stenosis regardless of CS; CS above threshold reclassified patients to have CAD regardless of CMR. CA identified 104/960 (11%) coronary segments with coronary artery stenosis >50% in 36/60 (60%) patients. ROC revealed an area-under-the-curve of 0.83 (95%CI: 0.68-0.99) with the best CS threshold of 495 Agatston score (sensitivity 50%). CMR depicted 128/960 (13%) myocardial segments with abnormalities in 31/60 (52%) patients. Sensitivity, specificity, negative (NPV) and positive predictive value (PPV) of CMR were 78, 88, 72 and 90%. When adding CS to CMR, sensitivity and NPV increased to 89 and 83%, while specificity and PPV slightly decreased to 83 and 89%. Accuracy of the combined approach (87%) was significantly ($P < 0.05$) higher than that of CMR (82%) alone. Adding CS to CMR improves the accuracy for the detection of morphological CAD.

Keywords Coronary artery disease · Calcium scoring · Cardiac magnetic resonance imaging · Coronary catheterization

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Introduction

Myocardial perfusion imaging using cardiac magnetic resonance (CMR) represents a non-invasive alternative imaging modality to catheter angiography (CA) for the diagnostic and prognostic evaluation of patients with suspected coronary artery disease (CAD) [1, 2]. CMR is characterized by a good diagnostic performance for the detection of CAD as determined by CA [2, 3]. Myocardial perfusion deficits however are not necessarily caused by luminal stenosis only but microvascular obstruction [4]. On the other hand, patients with epicardial stenosis—in particular those with three-vessel disease and balanced ischemia-may not be detected by using CMR alone [5].

Recently, computed tomography (CT) has become a valuable tool for assessing the morphology of coronary arteries in patients with suspected CAD. In addition, CT can also quantify the extent of coronary calcifications by calcium scoring (CS) which is performed without the administration of contrast media and by using low radiation dose techniques. CS allows for the diagnosis of early subclinical atherosclerosis and improves risk stratification in asymptomatic individuals [6, 7]. Recent data position CS with CT as valuable test for improving the risk stratification in patients having an intermediate risk for CAD [4, 6, 7]. Although being characteristic in CAD, arterial wall calcifications are not considered an adequate hallmark for the identification of coronary artery stenosis, different studies reported that low CS thresholds are sensitive but not specific for predicting coronary stenoses [8–10].

The aim of this study was to investigate prospectively, in patients with suspicion of CAD, the added value of CS as an adjunct to CMR for the diagnosis of coronary atherosclerosis and particularly epicardial coronary stenoses as determined by CA as the standard of reference.

Methods

Study population

The study protocol was approved by the local institutional review board; all patients gave written informed consent before study enrollment.

The initial study group consisted of 65 consecutive patients referred to CA who all had an intermediate risk of having CAD based on the Diamond and Forrester criteria [11]. Medical history including cardiovascular risk factors, height, weight, blood pressure, lipid profile, and a 12-lead electrocardiogram (ECG) was obtained from all patients.

Patients were excluded if they had contraindications for adenosine (second or third AV-block, sick sinus syndrome, symptomatic bradycardia, severe asthma or obstructive pulmonary disease; $n = 4$), or to magnetic resonance imaging (implanted electronic devices, metallic foreign bodies in the eye, severe claustrophobia, and others according to local regulations and manufacturer's recommendations; $n = 1$).

Finally, a total of 60 patients (52 male, 8 female, mean age 64 ± 10 years) were examined in this study. The characteristics of the study population are summarized in Table 1.

CMR and CS were performed on the same day. The mean time interval between CA and CT/CMR was 8 ± 3 days (range 1–13 days). The CMR and CS results were not communicated to the interventional cardiologist.

Catheter coronary angiography

Angiograms were obtained in at least two orthogonal projections according to standard techniques. Coronary angiograms of the target vessels were evaluated

Table 1 Patient demographics ($n = 60$)

Male patients	52 (87%)
Female patients	8 (13%)
Age (years)	64 ± 10 (41–85)
Body mass index (kg/m^2)	27.4 ± 4.3
Obesity[a]	17 (28%)
Cardiovascular risk factors	
Hypertension	46 (77%)
Nicotine abuse	20 (33%)
Hyperlipidemia	43 (72%)
Family history	11 (18%)
Diabetes	9 (15%)
Symptoms	
Non-anginal pain or no chest pain	21 (35%)
Atypical angina	13 (22%)
Typical angina	26 (43%)

[a] Defined as a body mass index $\geq$30 kg/m^2

by consensus of two readers (with 6 and 8 years of experience) who were blinded to CMR and CS results but aware of the clinical history. Both examined each catheter angiogram using computerized quantitative coronary angiography (QCA) analysis software (Xcelera, Philips Medical Systems, The Netherlands). Coronary arteries were subdivided into 15 segments, according to the scheme of the American Heart Association (AHA) [12]. After averaging results from two orthogonal projections, narrowing greater than 50% of the luminal diameter in relation to the reference diameters was defined as morphological stenosis.

CMR

All CMR studies were performed on a 1.5-T clinical magnetic resonance system (Achieva, Philips Medical Systems, Best, The Netherlands) using standardized protocols [13]. 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 long-axis scout images. Three representative short-axis sections were obtained, one each in the basal, mid-ventricular, and apical region of the left ventricle according to the standardized 17-segment model of the AHA [14]. Pharmacological stress using adenosine (Krenosin, sanofi-aventis, Switzerland) was applied at 140 μg per minute and kilogram of body weight over 3.0 min under ECG, oxygen-saturation and blood pressure monitoring. Injection of gadobutrolum (Gadovist 1.0; Bayer Schering Pharma, Berlin, Germany) was started at 2.5 min after the beginning of pharmological stress with the acquisition of perfusion-CMR images. Contrast media was administered at 0.1 mmol per kg of body weight using a power injector (MR Spectris; Medrad, Pittsburgh, Pa) at an injection rate of 5.0 ml/s, followed by a 40-mL saline flush. Ten minutes after stress perfusion imaging, a second bolus of 0.1 mmol per kg of body weight followed by saline flush was injected and rest perfusion images were obtained with the same orientation and position as in stress imaging. Prior-knowledge driven k–t sensitivity encoding perfusion-CMR imaging was used in combination with a saturation recovery gradient-echo pulse sequence (repetition time/echo time 3.1/1.1 ms; flip angle 20°; saturation pre-pulse delay 110 ms; partial Fourier sampling; acquisition window 120 ms; section thickness 10 mm; k-t factor of five with 11 k-t interleaved training profiles; effective acceleration 3.7; three sections acquired sequentially during a single R–R interval), as previously shown [15]. High-spatial resolution perfusion-CMR was acquired with an in-plane resolution of 2.0 × 2.0 mm and reconstructed with an in-plane resolution of 1.25 × 1.25 mm. Ten minutes after rest perfusion, late gadolinium enhancement (LGE) images were acquired in 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 optimized individually to null the signal from normal myocardium.

All CMR images were evaluated visually on the commercially available ViewForum (Philips, Best, The Netherlands) by two experienced observers (with 4 and 8 years of experience in cardiovascular radiology) fully blinded to the clinical history, results of CA, and additional test results including CS. The myocardium of the apical section was divided into four equiangular segments, and the equatorial and basal sections were divided into six segments according to the guidelines provided by the AHA and the American College of Cardiology [14]. CMR images were visually compared. Segmental perfusion and LGE was scored with a 4-point scale (0 = definitely normal, 1 = probably normal, 2 = probably pathological, 3 = definitely pathological), as previously shown [3, 15, 16]. A score of 2 and 3 was considered abnormal in order to attain binominal scoring. A segment was considered pathological if either reduced peak signal intensity or delayed wash-in compared to remote segments was shown at stress but not at rest-perfusion or if LGE was present [17]. In case of disagreement between the readers, a consensus reading was appended after 2 weeks.

CT calcium scoring

All CT examinations were performed on a dual-source CT scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany). A non-contrast enhanced scan was performed for CS. The scan was

performed in a cranio-caudal direction from the level of the carina to the diaphragm. Data was acquired using prospective ECG-triggering. Sequential scanning was performed using the following 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; tube current time product, 100 mA s/rotation; and tube potential, 120 kV. Data acquisition was performed at 70% of the R–R interval to reduce radiation exposure [18]. This CS protocol resulted in an estimated effective radiation dose of 1.1 ± 0.3 mSv. Image reconstruction was performed using a mono-segment mode, with a non-overlapping effective slice thickness of 3 mm and a medium-soft-tissue convolution kernel (B35f). Images were transferred to an external workstation (Multi-Modality Workplace, Siemens) for further analysis.

Calcifications were semi-automatically quantified with scoring software (Syngo CaScore, Siemens) by a single blinded experienced investigator using the Agatston method [19]. On the basis of the total Agatston score, patients were classified into five categories, as previously reported [10]: CS $\leq$ 10 (no or minimal), 10 $<$ CS $\leq$ 100 (mild), 100 $<$ CS $\leq$ 400 (moderate), 400 $<$ CS $\leq$ 1,000 (severe), CS $>$ 1,000 (extensive). The CS-related risk of each patient was stratified using age- and gender-related percentiles [20]: patients with a CS $\leq$ 25th percentile; 25th $<$ CS $\leq$ 50th percentile; 50th $<$ CS $\leq$ 75th percentile; 75th $<$ CS $\leq$ 90th percentile; CS $>$ 90th percentile.

Patients with a CS >75th percentile were classified to be at high risk [20].

Statistics

Statistical analysis was performed with a commercially available software package (SPSS release 17.0, SSPS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± 1SD, and categorical data as frequencies and percentages.

Differences regarding demographic data (i.e., gender) between patients with and without coronary artery stenosis were calculated using the Fisher exact test and the Mann–Whitney *U* test for quantitative variables (i.e., age, BMI), respectively. Cohen's kappa statistics were calculated for inter-observer agreements with respect to CMR read-out.

Diagnostic accuracy and 95% confidence intervals (CI) were calculated from contingency tables with CA as the standard of reference. Statistics for diagnostic accuracy of CMR, CS, and the combined approach of CMR and CS were calculated on a per-patient basis.

To investigate whether a high CS could be used to detect morphological epicardial coronary artery stenosis in the absence of perfusion deficits as determined by CMR, receivers operating characteristic (ROC) curves along with the area under the curve (AUC) were calculated. The best CS threshold was determined as the cutoff point, which on ROC analysis resulted in the best sensitivity for the detection of stenosis with an associated specificity of at least 90%.

This threshold was used to evaluate the diagnostic accuracy of CMR alone and the combined approach using the following rules (Fig. 1)

- Abnormal CMR results were considered as indicating hemodynamically significant.
- In patients with normal CMR results, the CS was taken into account. If the CS score in those patients was above the cutoff defined by ROC

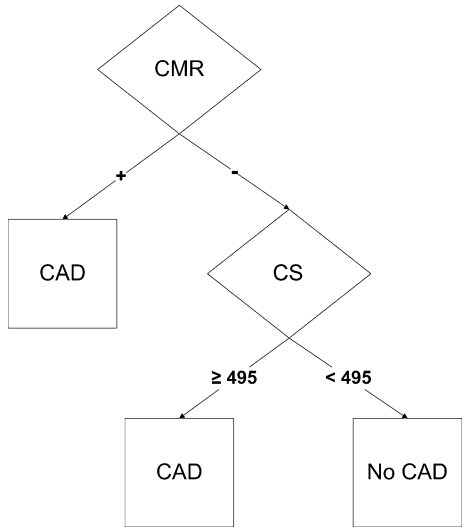

Fig. 1 Algorithm to evaluate diagnostic accuracy of CMR alone and of the combined approach with CMR and CS. In case of a perfusion defect in perfusion-CMR (CMR+), the patient was rated as positive for CAD. In patients with normal CMR (CMR−), CS was evaluated. If patients presented with a CS score ≥ 495, they were reclassified as positive for CAD; otherwise they were rated as having no CAD

analyses, patients were classified and considered to have morphological coronary artery stenosis.

Difference in diagnostic accuracy for both approaches (i.e. CMR alone and CMR combined with CS) was tested for significance by using the Wilcoxon signed rank test.

A P value of less than 0.05 (2-sided) was considered statistically significant for all tests.

Results

There were no significant differences regarding patient age ($P = 0.37$), gender ($P = 0.55$), and BMI ($P = 0.92$) between patients with and without coronary artery stenosis as determined by CA.

Catheter coronary angiography

QCA revealed 104/960 coronary segments (10.8%) with stenosis in 36/60 patients (60%). Eighty-three of the 180 vessels (46%) had at least one significant coronary stenosis. The distributions of single-vessel, 2-vessel, and 3-vessel disease were 9 (25%), 7 (19%), and 20 patients (56%), respectively. Left main stenosis was not found in any patient.

CMR

Concerning all 960 myocardial segments, inter-observer agreements for the assessment of perfusion abnormalities were high for stress (kappa = 0.73) and rest perfusion images (kappa = 0.82) as well as for LGE (kappa = 0.84).

In CMR images, 128/960 myocardial segments (13.3%) were categorized as abnormal in 31/60 patients (52%). All myocardial segments with LGE (17/960; 1.8%) in 3/60 (1.7%) patients showed corresponding perfusion-deficits. Visual analysis revealed pathologic segments in 64/180 vessel territories (35.6%). Of the 64 defects, 25 (39%) were allocated to the territory of the left anterior descending artery, 18 (28%) were allocated to the left circumflex artery, and 21 (33%) were allocated to the right coronary artery territory, respectively. Twenty-nine (48%) patients showed no abnormalities on CMR.

On a patient-based analysis, overall sensitivity of CMR was 78%, specificity was 88%, PPV was 90%, and NPV was 72% (Table 2).

CT calcium scoring

The heart rate during CT was 63 ± 9 beats per minute. The CS could be determined in all 60 patients (100%). The CS was 780 (range 0–4,433).

Ten of the 60 patients (17%) had no or minimal CS, 6 (10%) had mild CS, 10 (17%) had moderate CS, 15 (25%) had severe CS, and 19 (31%) had extensive CS. Figure 2 demonstrates the percentage of patients in each CS group together with coronary stenoses as confirmed by CA (Fig. 2). Calcium scoring-related percentiles stratified 31/60 (52%) patients as having a CS beyond the 75th percentile. Of the 29 patients without ischemia as determined by CMR, 10/29 patients (34%) ranked above the 75th percentile and were classified to be at high risk.

Using CS to identify epicardial stenosis as shown by CA only, a CS of 495 yielded a sensitivity of 50% and a specificity of 90% (AUC = 0.84; 95% CI: 0.70–0.99, Fig. 3).

Diagnostic accuracy of combined CS and CMR

A CS of ≥495 was determined as the best cutoff for the detection of patients with epicardial coronary stenosis but normal CMR. When this threshold was used, the combination of data from CS and CMR resulted in the reclassification of 4 of 8 patients (50%) with negative CMR results (Fig. 4). CMR and CS combined had a sensitivity of 89% and a specificity of

Table 2 Accuracy of CMR and the combination of CMR and CS for the detection of morphological coronary artery stenosis as determined by quantitative coronary angiography

	Sensitivity (CI; *n*)%	Specificity (CI; *n*)%	PPV (CI; *n*)%	NPV (CI; *n*)%	Accuracy (CI; *n*)%
Perfusion CMR	78 (63–93; 28/36)	88 (72–100; 21/24)	90 (78–100; 28/31)	72 (54–90; 21/29)	82 (71–92; 49/60)
CMR and CS	89 (77–97; 32/36)	83 (66–100; 20/24)	89 (77–100; 32/36)	83 (66–100; 20/24)	87 (77–96; 52/60)

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

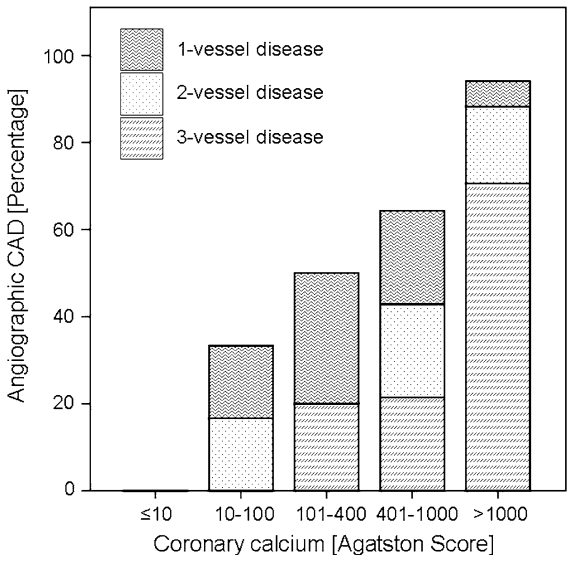

Fig. 2 Relationship between coronary artery calcification and coronary artery disease. *Bar* chart demonstrating the relationship between the extent of coronary artery calcification and both the prevalence and severity of coronary artery disease (CAD) as determined by quantitative coronary angiography

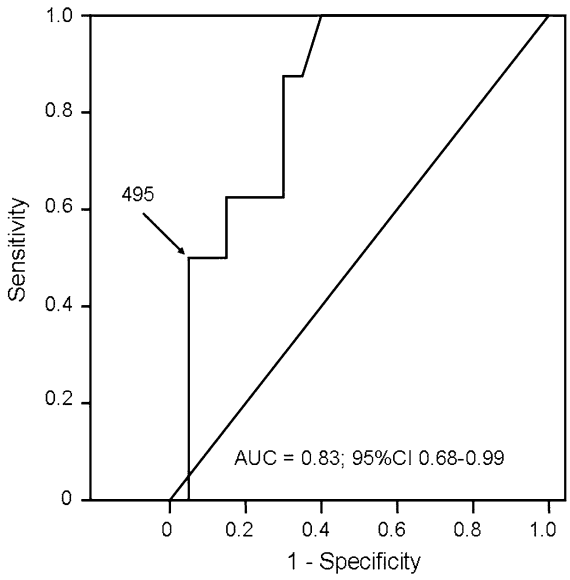

Fig. 3 ROC curve for the detection of morphological coronary stenosis by calcium score. ROC curve adjusted for the coronary artery calcium score for the detection of coronary stenosis (>50%) in patients with normal perfusion CMR results ($n = 29$). An Agatston score ≥495 was defined as the best threshold for detecting patients with coronary stenosis in the absence of perfusion-deficits on CMR. *AUC* area under the curve; *CI* confidence interval

83% for the detection of patients with epicardial stenosis. Adding CS to CMR improved the sensitivity of CMR from 78 to 89% (+11%) with a slight decrease in specificity (from 88 to 83%; −5%). The NPV increased from 72 to 83% (+11%) and the PPV slightly decreased from 90 to 89% (−1%) for the combined approach (Table 2). Diagnostic accuracy of the combined approach (87%) for the detection of morphological coronary stenoses was significantly ($P < 0.05$) higher than that of CMR alone (82%).

Discussion

Morphologic information obtained from CS as well as functional information obtained from CMR provides complementary information on CAD as both modalities investigate different pathophysiologic aspects of CAD. We found that a CS of 495 represents the best cutoff for detecting patients with morphological coronary stenosis in the absence of functional CMR-deficits. When using this CS threshold, the combination of CS and CMR outperformed CMR alone in terms of sensitivity, NPV, and accuracy in detecting patients with morphological coronary stenosis as determined by CA.

Our per-patient based results for CMR (sensitivity/specificity 78/88%) are in the range of data from a recently published meta-analysis with sensitivities of 57–97% and specificities of 68–94% [2]. These performance characteristics indicate that normal perfusion on CMR does not exclude morphological epicardial coronary stenosis as defined by CA.

CS reliably indicates coronary atherosclerosis and reflects the total plaque burden [9] with a strong predictive value for future cardiac events [6] prompting aggressive risk factor modification [6, 21]. In our patient cohort 34% of patients without ischemia on CMR were above the 75th percentile and therefore at high risk for subsequent cardiac events [22]. This information is important as previously published reports have shown that CS data adds incremental prognostic information and can subsequently refine cardiac risk estimates within defined risk categories [23, 24]. Hence, CS provides additional information that cannot be obtained from functional testing alone (*27*).

Combining both CS and CMR led to the reclassification of 50% of the patients as having

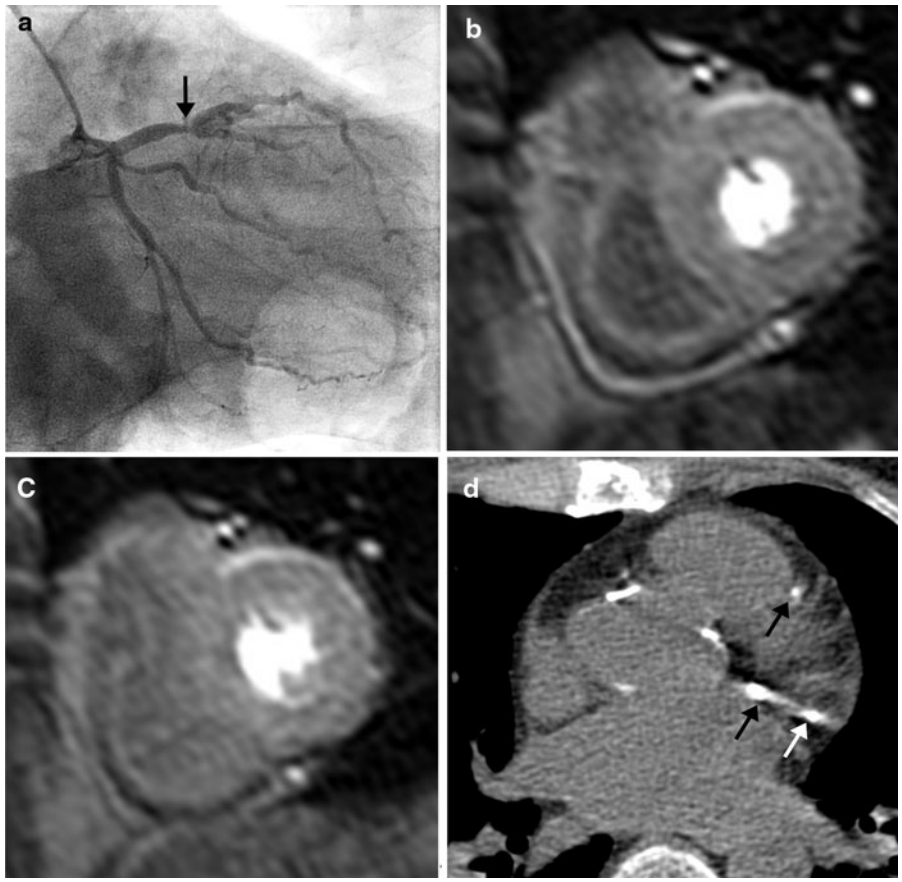

Fig. 4 71-year-old male patient with epicardial stenosis of the proximal left anterior descending artery (*arrow*) in CA (**a**). Perfusion-CMR during adenosine stress (**b**) as well as during rest (**c**) demonstrates normal myocardium without the evidence of perfusion deficits; however, CS (**d**) classified this patient having morpholocial coronary stenosis due calcifications (*arrows*) resulting in an Agatston score of 709

morphological epicardial stenoses despite normal CMR results. Sensitivity, NPV, and accuracy increased by 11, 11 and 5%, whereas specificity and PPV slightly decreased by 5 and 1%. Hence, the combination of both CMR and CS offers incremental diagnostic information over perfusion CMR alone for identifying patients with CAD. These results are in line with recent studies employing CS together with single photon emission CT [25], positron emission tomography [26], and dobutamine stress CMR imaging [27]. In these studies, CS contributed to the identification of patients with CAD that were missed by functional imaging alone. This fact might especially be pronounced in patients with three-vessel disease and balanced ischemia. Secondly, we may think that CS potentially adds in the differentiation of real perfusion deficits when image artifacts are present.

Generally, the *a priori* goal of noninvasive testing for CAD is to refine prognostic assessment [6]. Adenosine stress perfusion predicts a 3-year event-free survival of 99.2% for patients without perfusion abnormalities [28]. Similarly to perfusion-CMR, CS is substantially correlated with patient prognosis [6]. Elevated CS predicted an annual "hard CAD" event rate of 2.8% [7], whereas the absence of coronary calcium is associated with a very low risk of developing future cardiovascular events [29]. Thus, CS may also refine prognosis of patients with an intermediate risk of CAD.

Although we believe adding CS to CMR improves the diagnosis of morphological coronary stenosis and prompts aggressive risk factor modification, we would like to clarify that coronary stenosis should only be treated when functional tests provide evidence for hemodynamical significance [30].

Radiation risk is a major factor that should be considered in selecting the optimal diagnostic test for a patient with suspected CAD. Thus, combined evaluation by CS and CMR is advantageous for the patients by delivering only very low radiation doses in the range 1 mSv [6].

Study limitations

We used CA to determine if CAD was present in the patient population, as did investigators in most previous CMR studies [3, 15–17, 31]. If not combined by functional measures such as the evaluation of fractional flow reserve, CA does not represent an ideal reference standard as it yields only an indirect estimate of the flow limitation caused by coronary stenosis. However, it is the most important clinical reference examination, and the results of CA are often the sole basis for further patient management. A further limitation was the extraction of the best CS threshold for detection of morphological epicardial CAD from the same study population that was subsequently analyzed. We did not incorporate quantitative CMR evaluation in our evaluation protocol. However, most studies evaluating diagnostic accuracy of CMR in the detection of CAD are performed using purely visual evaluation of CMR [3, 16]. CS is prone to test-to-test variability and depends on scanning parameters potentially limiting the transferability of our threshold. Finally, presented findings have to be confirmed in larger scale study populations.

Conclusions

Adding CS to CMR in the non-invasive work-up of patients with suspicious CAD improves the diagnosis of morphological coronary stenosis. CS may also prompt aggressive risk factor modification and thus contribute to the patient management.

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