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Coronary calcification compromises myocardial perfusion irrespective of luminal stenosis

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ABSTRACT

Aim: The aim of this study was to evaluate the relationship between coronary artery calcification (CAC) assessed by multi-detector computed tomography (MDCT) and myocardial perfusion assessed by cardiac magnetic resonance imaging (CMR) in a group of symptomatic patients.
Method: Retrospective analysis of 120 patients (age 65.1 ± 8.9 years, 88 males) who presented with atypical chest pain to Bethanien Hospital, Frankfurt, Germany, between 2007 and 2010 and who underwent CAC scoring using MDCT, CMR, and conventional coronary angiography. Patients were divided into those with high-grade (HG) stenosis (n = 67, age 65.1 ± 9.4 years) and those with no-HG stenosis (n = 53, age 65.1 ± 8.6 years).
Results: There were more males with HG stenosis (82.1% vs. 62.3%, $p = 0.015$), in whom the percentage and number of abnormal perfusion segments were higher at rest (37.3% vs. 17%, $p = 0.014$) but not different with stress ($p = 0.83$) from those with no-HG stenosis. Thirty-four patients had myocardial perfusion abnormalities at rest and 26 patients developed perfusion defects with stress. Stress-induced myocardial perfusion defects were 22.4% sensitive and 79.2% specific for detecting HG stenosis. The CAC score was lower in patients with no-HG stenosis compared to those with HG stenosis ($p < 0.0001$). On the ROC curve, a CAC score of 293 had a sensitivity of 71.6% and specificity of 83% in predicting HG stenosis [(AUC 0.80 ($p < 0.0001$)]. A CAC score of 293 or the presence of at least 1 segment myocardial perfusion abnormality was 74.6% sensitive and 71.7% specific in detecting HG stenosis, the respective values for the 2 abnormalities combined being 19.4% and 90.6%. The severity of CAC correlated with the extent of myocardial perfusion in the patient group as a whole with stress ($r = 0.22$, $p = 0.015$), particularly in those with no-HG stenosis ($r = 0.31$, $p = 0.022$). A CAC score of 293 was 31.6% sensitive and 87.3% specific in detecting myocardial perfusion abnormalities.
Conclusion: In a group of patients with exertional angina, coronary calcification is more accurate in detecting high-grade luminal stenosis than myocardial perfusion defects. In addition, in patients with no stenosis, the incremental relationship between coronary calcium score and the extent of myocardial perfusion suggests coronary wall hardening as an additional mechanism for stress-induced angina other than luminal narrowing. These preliminary findings might have a clinical impact on management strategies of these patients other than conventional therapy.

1. Introduction

Cardiac magnetic resonance imaging (CMR) myocardial perfusion has high diagnostic accuracy for coronary artery disease (CAD), even superior to single-photon emission computed tomography [1]; however, it is known for its limitations. Coronary artery calcium (CAC) score assessed by multi-detector computed tomography (MDCT) has also been shown to have high specificity in excluding obstructive CAD [2]. The diagnosis of CAD by the two techniques is based on different concepts; while CMR assesses myocardial perfusion as a consequence of coronary disease, MDCT analyzes the arterial disease morphology and allows for quantification of coronary wall calcification. In addition, MDCT non-invasive coronary angiography has shown higher accuracy than CMR in determining coronary stenosis [3].

Coronary calcification itself generally reflects atherosclerosis and its extent correlates with the overall plaque burden, in the form of luminal stenosis [4]. However, many symptomatic patients might present with coronary calcification in the absence of significant luminal stenosis, suggesting that arterial wall hardening could be associated with ischemic and compromised myocardial blood supply as a cause of symptoms. The aim of this study was to evaluate the potential relationship between CAC assessed by MDCT and myocardial perfusion assessed by CMR in a group of symptomatic patients, irrespective of the presence of luminal stenosis.

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2. Methods

This is a retrospective analysis of 120 patients (mean age 65.1 ± 8.9 years, 88 males) who presented with atypical chest pain, defined as inconsistent exertional chest discomfort, to Bethanien Hospital, Frankfurt, Germany, between 2007 and 2010 and who underwent CAC scoring using MDCT and myocardial perfusion scanning using CMR. All patients subsequently underwent conventional coronary angiography, which was performed not more than 1 month after the MDCT and CMR perfusion scans. None of the patients had acute coronary syndrome, heart failure, valvular heart disease, thyroid and parathyroid diseases, inflammatory disease, or chronic kidney disease (creatinine > 130 mmol/L). Significant obstructive coronary disease was considered present when there was clear evidence for at least one high-grade (HG) stenosis with ≥50% lumen narrowing on the conventional angiogram.

According to the coronary angiography results, patients were divided into two groups: HG stenosis group (n = 67, mean age 65.1 ± 9.4 years) and no-HG stenosis group (n = 53, mean age 65.1 ± 8.6 years). Being a retrospective comparison of imaging methods which had been ordered due to clinical indications by the cardiologists responsible for the patients' management. Therefore, an ethical vote did not appear to be necessary, according to the hospital policy.

2.1. CMR perfusion scan

CMR studies were performed using a 1.5-Tesla MRI system (Magnetom Sonata Maestro Class, Siemens AG, Erlangen, Germany), with the patient in the supine position, and additional ECG electrodes connected with external system (Magnitude 3150, InVivo Research Inc., Orlando, FL, USA) for continuous heart rate monitoring [5]. Blood pressure was also monitored. Both a six-channel body phased-array coil and a two-channel spine phased-array coil were used. Sequences acquired during breath-hold were performed during quiet expiration.

After localizers and anatomical images, perfusion imaging was performed. Typically, 3 short-axis slices, each with 10 mm slice thickness, were acquired at the basal, mid papillary, and apical levels of the left ventricle. Patients were stressed using conventional adenosine protocol. Adenosine stimulates A2 receptors in the microvasculature, leading to relaxation of the arterioles. In normal myocardium, this leads to increased perfusion without changes in blood volume [6]. With coronary stenosis, the magnitude of the increased perfusion during vasodilation is compromised [6]. The pressure drop results in capillary closure, reduced perfusion, and reduced blood volume, which is demonstrated as slower arrival and lower contrast agent concentration in the ischemic segment [6].

A single shot prospectively gated balanced Turbo Field Echo (TFE) sequence with a typical in-plane resolution of 2.5 × 2.5 mm was used. Patients were then allowed to rest until the hemodynamic effects of the adenosine had subsided (typically 5 min). The location and distribution of myocardial perfusion defects in the left ventricle were described using the American Heart Association 16-segment model [7].

For the stress study, intravenous adenosine was started 3 min before contrast injection. Twenty short-axis images were taken at every level of myocardium before, during, and after contrast injection. Myocardial perfusion was measured during adenosine infusion using high dose of Gadolinium-DTPA (0.06 mmol/kg). Adenosine was injected at a rate of 0.14 mg/kg/min, for 3–6 min for a total dose of 0.48–0.84 mg/kg. To avoid risk of large bolus drug, adenosine and contrast were administered through separate IVs [8].

Acquired images were subsequently transferred to a dedicated computer for analyzing changes in the myocardial signal intensity [9]. Two experienced observers, blinded to the MDCT results, decided by visual assessment on the myocardial perfusion and the blood supply of the 6 conventionally studied segments.

Rest and adenosine stress scans were magnified and displayed at the same time for visual assessment [10]. In normal scans, the first pass into the myocardium changed its colour uniformly from black to gray. A slowly changing colour to gray suggested impaired perfusion and hence was considered as a perfusion defect either at rest or induced, if it occurred at peak stress. The CMR system employed quantitative parametric tissue analysis [5].

2.2. Coronary artery calcium (CAC) score

CAC was measured using 64 MDCT (Somatom Sensation Cardiac 64; Siemens Medical Solutions, Forchheim, Germany) with a gantry rotation time of 330 ms (collimation 64 × 0.6 mm, reconstruction increment 0.3 mm). Images were acquired with the patient in quiet expiratory pause. Oral beta-blockers (bisoprolol 5 mg or metoprolol 50 mg) were given 1 h before the scan if the resting heart rate was >60 beats/min. Calcification was described as the presence of >2 contiguous pixels with >130 Hounsfield Units. The workstation software automatically detected calcified areas and marked it in colour. The individual lesion scores were automatically summed to calculate the total Agatston score for each of the epicardial coronary artery territories as well as for the total coronary tree [4].

2.3. Coronary angiography

The Judkin's technique was used with at least four views of the left system and two views of the right system. Angiography was performed within 1 month after the CT scan in all patients. Analysis of the coronary angiograms was performed by an independent experienced observer. Significant stenosis was defined as ≥50% lumen narrowing of any epicardial coronary artery.

2.4. Statistical analysis

A standard statistical software package (SPSS 20, IBM, Armonk, NY, USA) was used for the statistical analyses. Categorical variables were expressed as absolute number and percentage (%). Normally distributed continuous data were expressed as mean ± standard deviation. The comparison between the HG stenosis and the no-HG stenosis groups was analyzed using chi-squared test. Spearman rank correlation was used to define the correlation between different CAC levels and myocardial perfusion on CMR. The null hypothesis was rejected on p values <0.05.

3. Results

Coronary risk factor distribution in the total study population and subgroups are listed in Table 1. The cardiovascular risk factors did not differ between the two groups, except for a higher proportion of males in the HG lesions group ($p = 0.015$).

Table 1
Risk factor distribution in the total study population divided into those with HG stenosis and no-HG stenosis

Risk factors	Total n = 120	HG stenosis n = 67	no-HG stenosis n = 53	p value
Males, n(%)	88 (73.3)	55 (82.1)	33 (62.3)	0.015
Age group (over 60 y) n(%)	86 (71)	49 (73.1)	37 (69.8)	0.421
Hypertension, n(%)	45 (37.5)	24 (35.8)	21 (39.6)	0.669
Smoking, n(%)	18 (15.0)	11 (16.4)	7 (13.2)	0.625
Diabetes, n(%)	14(11.7)	8(11.9)	6(11.3)	0.916
Obesity, n(%)	3(2.5)	1(1.5)	2(3.8)	0.427
Family history of CVD, n(%)	20(16.7)	11(16.4)	9(17.0)	0.934
Prior MI, n(%)	34 (28.3)	25 (37.3)	9 (17)	0.014