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ORIGINAL PAPER

Usefulness of coronary calcium scoring to myocardial perfusion SPECT in the diagnosis of coronary artery disease in a predominantly high risk population

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Abstract Coronary calcium scoring (CCS) adds to the diagnostic performance of myocardial perfusion single-photon emission computed tomography (SPECT) to assess the presence of significant coronary artery disease (CAD). Patients with a high pre-test likelihood are expected to have a high CCS which potentially could enhance the diagnostic performance of myocardial perfusion SPECT in this specific patient group. We evaluated the added value of CCS to SPECT in the diagnosis of significant CAD in patients with an intermediate to high pre-test likelihood. In total, 129 patients (mean age 62.7 ± 9.7 years, 65 % male) with stable anginal complaints and intermediate to high pre-test likelihood of CAD (median 87 %, range 22–95) were prospectively included in this study. All patients received SPECT and CCS imaging preceding invasive coronary angiography (CA). Fractional flow reserve (FFR) measurements were acquired from patients with angiographically estimated 50–95 % obstructive CAD. For SPECT a SSS > 3 was defined significant CAD. For CCS the optimal cut-off value for significant CAD was determined by ROC curve analysis. The reference standard for significant CAD was a FFR of <0.80 acquired by CA. Significant CAD was demonstrated in 64 patients (49.6 %). Optimal CCS cut-off value for significant CAD was >182.5. ROC curve analysis for prediction of the presence of significant CAD for SPECT, CCS and the combination of CCS and SPECT resulted in an area under the curve (AUC) of 0.88 (95 % CI 81–94), 0.75 (95 % CI 66–83 %) and 0.92 (95 % CI 87–97 %) respectively. The difference of the AUC between SPECT and the combination of CCS and SPECT was 0.05 ($P = 0.12$). The addition of CCS did not significantly improve the diagnostic performance of SPECT in the evaluation of patients with a predominantly high pre-test likelihood of CAD.

Keywords Coronary calcium · Myocardial perfusion SPECT · Coronary artery disease

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Introduction

According to current guidelines invasive coronary angiography (CA) is a suitable diagnostic procedure for patients with a high pre-test likelihood of significant coronary artery disease either with or without troublesome symptoms or clinical findings [1, 2]. In this population the reported diagnostic yield of invasive CA is 44–88 % [3–5]. In real life invasive CA has an even lower diagnostic yield

of obstructive CAD of about 38 % [6]. Non-invasive testing could be of value to defer from invasive diagnostic procedures, even in a subset of patients with an intermediate to high pre-test likelihood of CAD.

Nuclear myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is known for its role in diagnosis, risk stratification and guidance of treatment decision making in the general population [7, 8]. However, diagnostic performance in patients with a high pre-test likelihood of CAD is low with a sensitivity of 56–94 % [3, 9]. Additional anatomical information could be of value to increase diagnostic performance in this subset of patients.

Coronary calcium scoring (CCS) is known for its role in risk prediction for a-symptomatic patients. Patients with CCS <10 are at low risk of major cardiovascular events during follow-up [10, 11]. In symptomatic patients the value of CCS is disputed. Although the prevalence of significant disease is low and the follow-up is favorable in patients with a CCS <10, the prevalence of >50 % stenosis in this category might still be 12–65 % [12–16]. Functional imaging could be of added value to identify these patients.

With the advent of integrated SPECT and Computed Tomography (CT) systems and the use of low dose CCS scans for attenuation correction purposes, high quality anatomical and functional data are readily available [17, 18]. SPECT findings suggestive of myocardial ischemia are associated with high CCS, vice versa it was suggested that low CCS associated with these findings could obviate the need for further invasive testing [19, 20]. On the other hand in patients with normal SPECT findings a high CCS could be suggestive of significant CAD [21–23].

We evaluated the influence of the pre-test likelihood of significant CAD on these findings and hypothesized that in a subset of patients with an intermediate to high pre-test likelihood of CAD there would be added value of CCS to the diagnostic performance of SPECT.

Materials and methods

Study population

Patients with an intermediate to high pre-test likelihood of CAD were prospectively enrolled in this study. Pre-test likelihood was calculated according to Diamond and Forrester criteria [24]. Intermediate pre-test likelihood was defined as 13–87 % and high pre-test likelihood was defined as >87 %, similar to boundaries used in literature [2]. Excluded were patients with a known history of CAD defined as any unstable coronary condition, myocardial infarction, coronary revascularization or diagnostic Q wave on baseline ECG. Also patients with a known history of non-ischemic cardiomyopathy or a cardiac rhythm other than sinus rhythm were excluded. By non-invasive assessment, CAD was defined as a summed stress score (SSS) of >3 on SPECT or the presence of significant coronary calcification defined by a CSS cut-off value of >0 or the cut-off value defined by receiver operating characteristics (ROC) curve analysis. Fractional flow reserve measurements served as the standard of reference, an FFR <0.80 was used for de definition of hemodynamically significant CAD. The study conformed to the principles outlined in the declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients.

Image acquisition

All patients received SPECT and CCS imaging followed by CA, including those patients with normal SPECT and CCS results as part of the prospective study. Gated SPECT and CCS images were acquired from a Hybrid SPECT-CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands) with a 2-day stress/rest MPI protocol. Stress images were considered normal if no perfusion defect was visualized, SSS was <3, no wall motion abnormalities (WMA) or >10 % transient ischemic dilatation (TID) were present and left ventricular ejection fraction (LVEF) was >50 % (male and female). Patients with abnormal stress SPECT findings underwent rest imaging and CA at the second day of imaging. Patients with normal stress SPECT findings only underwent CA at the second day. The second imaging day was scheduled within 14 days of the first. CCS was performed in the stress SPECT imaging session.

Bicycle stress according to a stepwise protocol or pharmacological stress (adenosine at standard rate of 0.14 mg/kg/min over 6 min) was performed for stress image acquisition. In case the target heart rate was not reached at maximum exercise stress, atropine was given at the discretion of the attending physician. For stress and rest SPECT a weight adjusted dose of 400–600 MBq of ^{99m}Tc-sestamibi was used. Attenuation correction was performed for all images using the CT non-enhanced calcium scan. SPECT data were analyzed by two experienced nuclear medicine physicians with regard to the presence of reversible and/or fixed perfusion defects on short axis and vertical and horizontal long axis slices. Semiquantitive perfusion data and gated data with respect to WMA, TID and LVEF were included in the analysis using the QGS/QPS software package (Cedars-Sinai Medical Center, Los Angeles, Ca, USA).

A nonenhanced scan to calculate the total CCS was performed with the following scanning parameters: prospective ECG triggering, at inspiration, 2.5 mm slice thickness, 120 kV tube voltage, 55 mAs tube current.

Agatston scores were computed using the Extended Brilliance Workspace software (Philips Medical Systems, Best, The Netherlands).

As part of the prospective study, CA was performed in all patients, including those with normal non-invasive test results. CA was acquired on Allura (Philips Medical Systems, Best, The Netherlands) catheterization equipment via femoral or radial artery access. From all patients biplane views were acquired from all major coronary arteries. Additional views were obtained at the discretion of the performing operator. FFR measurements were obtained from patients with angiographically estimated 50–95 % obstructive disease. During FFR measurement distal coronary pressure was measured with a pressure guidewire (Certus Wire, Radi Medical Systems, Uppsala, Sweden) during maximal hyperemia induced by adenosine intravenously at 0.14 mg/kg/min, with simultaneous measurement of aortic pressure through the catheter. FFR was calculated as the ratio between mean distal pressure and mean aortic pressure [25]. The angiograms were visually evaluated for lesion severity according to 5 categories of luminal loss: no CAD (0 % luminal loss), mild lesion severity (luminal loss 0–50 %), intermediate lesion severity (luminal loss 50–70 %), severe lesions (luminal loss 70–99 %) and total occlusion. Interpretation was performed on a consensus basis by two experienced cardiologists. Occluded vessels were considered severely stenotic with an FFR of 0.50. Vessels with angiographically >95 % obstructive disease were considered severely stenotic with an FFR <0.80. Normal vessels (<10 % luminal loss) were considered not severely stenotic; FFR >0.80. As a result, FFR measurements were available from 47 of the patients with angiographically estimated 50–95 % obstructive disease (84 %). Significant disease was defined as an FFR <0.80.

All imaging modalities were interpreted blinded for clinical data and the respective other modalities.

Statistical analysis

Statistical analyses were performed with SPSS software (version 18.0, IBM Corporation, Somers, New York, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median and range (if distribution was skewed), and categorical variables as numbers and percentages. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) with corresponding 95 % confidence intervals (CI) were calculated. ROC curve analysis was performed to calculate the optimal cutoff value for the detection of significant CAD by CCS. As a measure of discrimination we calculated the area under the ROC curve (AUC) with 95 % confidence intervals for CCS and SPECT for the detection of significant CAD. Also binary logistic regression analysis was used to construct the formula for the combination of SPECT and CCS in the evaluation of the presence of significant CAD. A P value of <0.05 was considered statistically significant.

Results

Study population

In total, 129 patients (mean age 62.7 ± 9.7 years, 65 % male) with stable anginal complaints and a predominantly high pre-test likelihood of CAD (median pre-test probability 87 % (range 22–95)), were included in the study. Sixty-nine patients (53.5 %) had more than three cardiovascular risk factors. Complete characteristics of the study population are presented in Table 1.

Coronary angiography

CA showed significant CAD in 64 patients (49.6 %). The distribution of vessel involvement is presented in Table 2. From the 64 patients with significant CAD, 28 (43.8 %) patients underwent CABG, 26 (40.6 %) patients underwent percutaneous coronary intervention (PCI) and 10 (15.6 %) patients were treated conservatively because of peripheral or very diffuse disease. From the 66 patients without significant CAD, 1 patient (1.5 %) underwent PCI, the remainder was treated conservatively.

Myocardial perfusion SPECT

Exercise stress prior to image acquisition was performed in 103 patients (79.8 %), the remainder 26 (20.2 %) patients underwent adenosine stress. 33 (32.0 %) patients required atropine infusion to reach the target heart rate during exercise stress. Mean LVEF after stress was 61.5 ± 9.0 %, and at rest 64.9 ± 10.1 %. Mean transient ischemic dilatation was 8.2 ± 16.5 ml (median 6.0 ml, range −35 to 55). During stress testing, 32 (31.1 %) patients showed ECG changes suggestive of myocardial ischemia (at least 2 mm ST-segment depression), 52 (50.5 %) patients had a negative stress test and 19 (18.4 %) had either uninterpretable or equivocal stress ECG results. During adenosine stress 3 (11.5 %) patients had positive ECG findings. From the 57 patients with a SSS >3, 51 had significant CAD. From the 13 patients with a false negative SPECT eight had a pre-test likelihood ranging between 52 and 86 %. The remaining five patients had a high pre-test likelihood, >90 %. Data regarding the SPECT characteristics are presented in Table 2. Diagnostic performance of SPECT is presented in Table 3 and Fig. 1.

Table 1 Characteristics of the patients included in the analysis

Age (years)[a]	62.7 ± 9.7	
Men	84	65.1 %
Women	45	34.9 %
Cardiac History		
Paroxysmal atrial fibrillation	6	4.7 %
Pacemaker implantation	1	0.8 %
Risk factors		
Smoking		
Current	29	22.5 %
History	24	18.6 %
Hypertension	84	65.1 %
Diabetes mellitus	16	12.4 %
Dyslipidaemia	70	68.0 %
Family history	79	61.2 %
Risk factors ≥ 3	69	53.5 %
Angina pectoris		
Non-anginal	1	0.8 %
Atypical	40	31.0 %
Typical	88	68.2 %
CCS Angina class		
Class I	8	6.2 %
Class II	111	86.0 %
Class III	10	7.8 %
Class IV	0	0.0 %
Systolic blood pressure (mmHg)[a]	135 ± 21	
Diastolic blood pressure (mmHg)[a]	78 ± 15	
Body mass index (kg/m^2)[a]	27.0 ± 4.0	
Cockroft creatinin clearance (ml/min)[a]	93.4 ± 26.5	
Pre-test likelihood[b]	0.87 (0.22–0.95)	
Low	0	0.0 %
Intermediate	56	43.4 %
High	65	50.4 %
Unknown	8	6.2 %

Values are shown as number and percentage unless otherwise noted

CCS Canadian cardiovascular society

[a] Values expressed as mean ± standard deviation

[b] Values expressed as median (range)

Coronary calcium scoring

The median CCS of the study population was 145 (range 0–4142). For patients with significant CAD the median CCS was 363 (range 0–4142), for patients without significant CAD the median CCS was 28 (range 0–2891, P value < 0.001). From the 97 patients with a CCS >0, 56 (58 %) had significant CAD. From the 32 patients with a CCS of 0, eight (25 %) patients had significant CAD. These patients had a pre-test likelihood of disease ranging from 73 to 93 %. The distribution of CCS is presented in Table 2. ROC curve analysis for the detection of significant CAD using CCS in high pre-test likelihood patients gave an optimal cutoff value of 182.5 for significant CAD, yielding an area under the curve (AUC) of 0.75(95 % CI 0.66–0.83). (Figure 1) The sensitivity, specificity, NPV, PPV and accuracy values of CCS are presented in Table 3.

Combined SPECT and CCS

Using a CCS cutoff value of >0 added to a SSS >3 on SPECT led to the diagnosis of significant CAD in 104 patients, 61 (58.6 %) of these had significant CAD according to the reference standard. Despite a CCS of 0 and a SSS <3 on SPECT, 3 patients of a total of 22 (12 %) had significant CAD. By introducing the CCS cutoff value of 182.5 added to a SSS >3 on SPECT, the number of false positive results decreased without adding to the number of false negatives (Table 3).

CCS added to the diagnostic accuracy of SPECT in 10 patients. Eight patients with a normal SPECT had a CCS >1000. Two patients with a negative SPECT had a CCS of respectively 245 and 369; they had an intermediate pre-test likelihood of CAD. SPECT added to the diagnostic accuracy of CCS in 5 patients. Three patients with significant CAD and a CCS of 0 and a negative SPECT had an intermediate pre-test likelihood of CAD (Table 4).

ROC curve analysis for CCS, SPECT and the combination of SPECT and CCS resulted in an AUC of 0.75, 0.88 and 0.92 respectively. Both SPECT and the combination of SPECT and CCS performed significantly better in the evaluation of the presence of significant CAD than CCS, $P = 0.0093$ and $P < 0.0001$ respectively. However the combination of SPECT and CCS performed comparable to standalone SPECT, difference in AUC 0.05, $P = 0.12$ (Fig. 1).

Discussion

Our study shows no significant added value of CCS on top of SPECT in a population with a predominantly high pre-test likelihood of CAD. SPECT alone has a reasonable performance with an NPV of 82 % and an AUC of 0.88 as determined by ROC curve analysis. By adding CCS information the NPV increased to 94 %, but at the cost of a substantial number of false positives. As such the increased AUC of 0.92 did not differ significantly from SPECT as standalone procedure. Moreover, it failed to identify three patients with significant CAD, a CCS of 0 and a negative SPECT result.

In the overall patient population with anginal complaints SPECT has a good diagnostic performance. Well-designed studies have shown sensitivities ranging from 85 to 90 %. If ECG gated information and attenuation correction

Table 2 Results of coronary calcium scoring, myocardial perfusion SPECT and invasive coronary angiography

Coronary calcium scoring		
0	32	24.8 %
1–10	8	6.2 %
11–100	17	13.2 %
101–400	27	20.9 %
401–800	15	11.6 %
>800	30	23.3 %
Myocardial perfusion SPECT		
Exercise stress	103	79.8 %
Adenosine stress	26	20.2 %
Summed stress score 0	53	41.1 %
Summed stress score 1–3	19	14.7 %
Summed stress score > 3	57	44.2 %
Stress SPECT, n = 129		
Left ventricle end diastolic volume, ml[a]	107.1 ± 44.7	
Left ventricle end systolic volume, ml[a]	44.8 ± 30.8	
Left ventricle ejection fraction, %[a]	61.5 ± 9.0	
Rest SPECT, n = 87		
Left ventricle end diastolic volume, ml[a]	107.2 ± 46.3	
Left ventricle end systolic volume, ml[a]	41.4 ± 34.1	
Left ventricle ejection fraction, %[a]	64.9 ± 10.1	
Invasive coronary angiogram		
Extent of significant CAD[b]		
No significant CAD	65	50.4 %
1-vessel disease	22	17.1 %
2-vessel disease	23	17.8 %
3-vessel disease or left main stenosis	19	14.7 %

Values are shown as number and percentage unless otherwise noted

SPECT single photon emission computed tomography, *CAD* coronary artery disease

[a] Values expressed as mean ± standard deviation

[b] A fractional flow reserve of <0.80 was defined significant CAD

Table 3 Diagnostic performance of SPECT, CCS and the combination of SPECT and CCS

	Sensitivity	Specificity	PPV	NPV	TP/FP/TN/FN	Accuracy
CCS >0	88	37	58	75	56/41/24/8	62
CCS >182.5	66	71	69	68	42/19/46/22	68
SSS >3	80	91	90	82	51/6/59/13	85
CCS >0 or SSS >3	95	34	59	88	61/43/22/3	64
CCS >182.5 or SSS >3	95	66	74	94	61/22/43/3	81

Diagnostic performance of single photon emission computed tomography (SPECT), coronary calcium scoring (CCS) or combinations for the detection of significant coronary artery disease (CAD). A fractional flow reserve of <0.80 was defined significant CAD

PPP positive predictive value, *NPV* negative predictive value, *TP* true positive, *FP* false positive, *TN* true negative, *FN* false negative

algorithms are used specificity values range between 80 and 90 % [7, 8]. In 123 patients with a high pre-test likelihood of disease Groutars et al. demonstrated a sensitivity of 97 % and a specificity of 59 % for the detection of >70 % lesions on CA [3]. More recently, Hamirani et al. demonstrated a lower diagnostic performance of SPECT in a high pre-test likelihood population of 122 patients with sensitivity and specificity values of 58 and 43 %, respectively [9]. Both groups used a 1 day dual isotope imaging protocol with ^{201}Tl rest imaging and ^{99m}Tc stress imaging. The former population was truly high risk with a mean pre-test likelihood of 92 ± 20 % and a prevalence of >70 % stenosis in 80 % of the patients. The latter was retrospectively constituted of patients who underwent SPECT, CT coronary angiography and CA. The prevalence of >70 % stenosis was 64 %, suggestive of a high risk population. In our hands SPECT had a reasonable performance with sensitivity and specificity values of 80 and 91 % respectively and an AUC of 0.88 for the detection of significant CAD in a high pre-test likelihood population.

Coronary calcium scoring is known for risk prediction, but it is unable to depict the coronary lumen and therefore

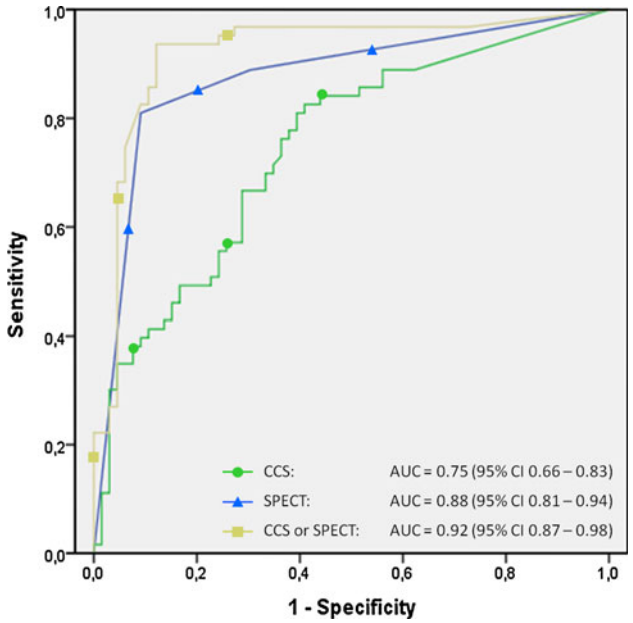

Fig. 1 ROC curve analysis for the detection of significant coronary artery disease (CAD) by the use of coronary calcium scoring (CCS), Single Photon Emission Tomography (SPECT) and the combination of CCS and SPECT. A fractional flow reserve of <0.80 was defined significant CAD. A CCS of 182.5 was optimal cutoff for the detection of significant CAD. Area under the curve 0.75. The difference of the AUC between SPECT and the combination of CCS and SPECT was 0.05 ($P = 0.12$)

not suitable for the diagnosis or exclusion of flow limiting CAD. In a population of patients referred for CA, the incidence of significant CAD in patients with a CCS of zero is 15–19 %. In a large symptomatic population (N = 291) with a predominantly intermediate pre-test likelihood of CAD, Gottlieb et al. found that among 72 patients with a CCS of zero, 15 % had a stenosis >70 % on CA [12]. In our population 25 % of the patients with a CCS of zero had significant CAD. This resulted in a sensitivity of 88 % using a CCS greater than zero as a diagnostic tool for significant CAD. Conversely the specificity was just 37 % using this cut-off value. The optimal CCS cut-off value in our population for the detection of significant CAD was 182.5 as calculated by ROC curve analysis. In light of the inability of CCS to depict the coronary lumen, let alone the functional consequences, this value remains artificial. Which is demonstrated by an AUC of 0.75 as determined by ROC curve analysis.

A false-negative SPECT in patients with balanced ischemia is a well-known pitfall for clinicians. Several authors have noted that a high CCS may have diagnostic value in this patient category [17, 22]. Schepis et al. showed that in patients with an intermediate risk of CAD a CCS >709 is predictive for significant CAD (>50 % stenosis) in patients with a normal SPECT. When CCS at this cut-off value was added to SPECT, the sensitivity

Table 4 Distribution of coronary calcium scores and summed stress scores for patients with significant coronary artery disease and either CCS = 0 (N = 8) or SSS < 3 (N = 13)

	SPECT SSS = 0	SPECT SSS = 1–3	SPECT SSS > 3
CCS = 0	2	1	5
CCS = 1–10			
CCS = 11–100			
CCS = 101–400	1	1	
CCS = 401–1000			
CCS > 1000	4	4	

SPECT single photon emission computed tomography, *CCS* coronary calcium score, *SSS* summed stress score

increased from 76 to 86 % and specificity remained similar (91 and 86 %, respectively) when compared to SPECT alone [17]. In a selected population of 50 patients with a normal SPECT and a CCS >1000, Ghadri et al. found a 74 % prevalence of stenosis >50 % [22]. Our data showed that out of the 13 patients with a false-negative SPECT, 8 had a CCS >1000. And although median CCS in patients without significant CAD was 29, still 5 % of patients with a true negative SPECT had a CCS >1000. If we used CCS >0 as a cut-off value for CAD we observed a NPV of 88 % for the exclusion of significant CAD when added to SPECT, although at the cost of a high number of false positives, PPV 59 %. Adding the optimal CCS cut-off value of 182.5 to SPECT, the number of false positive results decreased. The PPV improved from 59 to 74 %, the NPV of 88 % increased to 92 %. However, AUC as determined by ROC curve analysis did not differ significantly between the combination of CCS and SPECT and standalone SPECT. This shows that in a group of patients with high risk of CAD, excluding the presence of coronary calcifications in patients with a normal SPECT makes the exclusion of significant CAD reliable. However, a relatively low or zero CCS does not completely rule out significant CAD in these patients. One of the three patients with a CCS of zero and a negative SPECT result had a significant left main stenosis. When the presence of calcifications is proven in patients with a negative SPECT result, however, the significance of CAD is not.

Several limitations of our study need to be taken into account when interpreting the results. First, our study population was at predominantly high-risk of CAD. Patients with an intermediate to high pre-test likelihood were allowed to be included and over 50 % of patients had a high pre-test likelihood. Thus, this study is not exemplary for the general clinical population referred for SPECT. The majority of patients with false negative results had a high pre-test likelihood of disease. Second, for each patient we

chose the optimal stress protocol, either adenosine or exercise. However, adenosine stress has a known limited diagnostic performance compared to exercise stress. The reason for not being able to reach an adequate heart rate response during exercise, not only could be the reason to switch to adenosine stress; this could also be the confounding factor for the increased presence of significant CAD (f.i. peripheral atherosclerotic disease or chronic obstructive pulmonary disease). As a result of the higher prevalence of significant CAD, negative predictive value of adenosine stress SPECT could be hampered. Despite the fact that almost a quarter of the patients received adenosine stress, the diagnostic performance of SPECT alone in this population is reasonable. FFR measurements were available from 84 % of patients with angiographically 50–95 % obstructive disease. According to available literature it is safe to assume that lesions with <50 % stenosis have no hemodynamic significance [26]. Nine patients with angiographically 70–95 % obstructive disease did not receive FFR measurements, mainly for practical reasons on a busy catherization laboratory. The impact of the possible error by the assumption that these lesions were indeed hemodynamically significant is limited [26].

Conclusion

When using coronary calcification as additional information to myocardial perfusion SPECT, physicians should be aware that in a population with a predominantly high pretest likelihood of CAD, the presence of coronary calcifications does not reliably discriminate between the presence and absence of significant CAD. Indeed a high CCS, >1000 in literature and >182,5 in our population, can identify patients with significant CAD and a normal SPECT. However, even in patients with significant CAD and a normal SPECT result, the calcium score may be as low as zero.

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Conflicts of interest None.

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