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EDITORIAL

Diagnostic pathway of integrated SPECT/CT for coronary artery disease

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Abstract Treatment strategy in patients with suspected coronary artery disease (CAD) is driven by symptomatology in combination with diagnostic evaluation of the extent and/or severity of atherosclerosis in the coronary arteries and ischemia in the myocardium, i.e., the anatomic and functional correlates of CAD. Whereas multislice row computed tomography (MSCT) has the advantage of detecting coronary atherosclerosis at its earliest stages, thereby allowing initiation of appropriate therapeutic measures well before development of obstructive CAD, myocardial perfusion imaging (MPI) SPECT can clarify the hemodynamic consequences of the anatomic findings on MSCT based on a functional assessment of myocardial blood flow. There is a lack of correlation between coronary artery calcium (CAC), coronary artery stenosis, and MPI SPECT. Therefore CAC scoring and stress MPI should be thus considered complementary approaches rather than exclusionary in the evaluation of the patient at risk for CAD. The integration of anatomic and functional information may provide additional information for the clinician by the improved risk stratification and diagnostic accuracy of integrated techniques. The majority of previous studies are based on a sequential flowchart, starting with either SPECT or CAC scoring that finally directs the therapeutic strategy. Patients at low risk for CAD can be selected for primary prevention, and patients at high risk for CAD can be directly selected for coronary angiography (CAG). The remaining group of patients at intermediate risk for CAD can be substratified into lower- and higher-risk categories based on the presence or absence of stress-induced ischemia on MPI SPECT and CAC scoring. An integration of SPECT and CAC as a starting point for CAD detection in symptomatic patients at intermediate risk for CAD may facilitate a tailored diagnostic as well as therapeutic approach. Finally, using SPECT/CT, MPI SPECT, and CAC findings may be completed with CT angiography. The development of SPECT/CT hybrid systems is therefore of important value for the nuclear cardiology armamentarium. This editorial commentary outlines a diagnostic pathway of integrated SPECT/CT for CAD assessment in symptomatic patients at intermediate risk for CAD.

Keywords SPECT/CT · Coronary artery disease · Workflow

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Introduction

Treatment strategy in patients with suspected coronary artery disease (CAD) is driven by symptomatology in combination with diagnostic evaluation of the extent and/or severity of atherosclerosis in the coronary arteries and ischemia in the myocardium, i.e., the anatomic and functional correlates of CAD. Whereas multislice row computed tomography (MSCT) has the advantage of detecting coronary atherosclerosis at its earliest stages, thereby allowing initiation of appropriate therapeutic

measures well before development of obstructive CAD, myocardial perfusion imaging (MPI) SPECT can clarify the hemodynamic consequences of the anatomic findings on MSCT based on a functional assessment of myocardial blood flow. There is a lack of correlation between coronary artery calcium (CAC), coronary artery stenosis, and MPI SPECT [1]. Therefore CAC scoring and stress MPI SPECT should be thus considered complementary approaches rather than exclusionary in the evaluation of the patient at risk for CAD [2]. The integration of anatomic and functional information may provide additional information for the clinician by the improved risk stratification and diagnostic accuracy of integrated techniques. The majority of previous studies are based on a sequential flowchart, starting with either SPECT or CAC scoring that finally directs the therapeutic strategy. Patients at low risk for CAD can be selected for primary prevention, and patients at high risk for CAD can be directly selected for coronary angiography (CAG). The remaining group of patients at intermediate risk for CAD can be substratified into lower- and higher-risk categories based on the presence or absence of stress-induced ischemia on MPI SPECT and CAC scoring. An integration of SPECT and CAC as a starting point for CAD detection in symptomatic patients at intermediate risk for CAD may facilitate a tailored diagnostic as well as therapeutic approach. Finally, using SPECT/CT, MPI SPECT, and CAC findings may be completed with CT angiography. The development of SPECT/CT hybrid systems is therefore of important value for the nuclear cardiology armamentarium. This editorial commentary outlines a diagnostic pathway of integrated SPECT/CT for CAD assessment in symptomatic patients at intermediate risk for CAD.

Background of the diagnostic value of CAC score, CT coronary angiography, and MPI SPECT

Electron beam computed tomography (EBCT) was the first technique that was used on a large scale for quantifying CAC. EBCT can detect and quantify CAC. Recently CAC assessment with MSCT has been shown to yield comparable results [3, 4]. The Agatston score and volume assessment are used for CAC scoring. The extent of CAC using the Agatston score is determined as absolute (<10, 11–100, 101–400, >400) and as relative cutoff values (defined as the 25th, 50th, 75th, and 90th percentiles within age- and gender-specific strata). Several studies found a strong independent association between CAC score and CAD detected with CAG [5–7]. The sensitivity and specificity of CAC score for detection of CAD in symptomatic patients has been described to be as high as 100 and 63%, respectively [8], but may vary considerably depending on patients' age and sex [9, 10]. The negative predictive value of EBCT varies between 95 and 100% [11].

MSCT has also emerged as a tool to visualize the coronary arteries and to detect coronary stenoses. The 64-slice CT generation is a robust technique which allows high-resolution and almost motion-free coronary imaging. A high temporal resolution is mandatory to obtain motion-free image quality. Heart rates above 65 bpm need to be reduced to prolong the relative motion-free mid-diastolic phase, by administration of an oral or intravenous β-blocker prior to the CT investigation. The new generation of CT scanners equipped with dual source 64, 128, or even 256 slices no longer depend on the reduction of bpm. High-density material, such as calcified plaques or stents, can cause imaging artifacts, which may hamper accurate assessment of the integrity of the coronary lumen. Previous studies have demonstrated that noninvasive CAG using CT coronary angiography (CTCA) is good alternative to CAG in the detection of significant obstructive CAD [12]; however, a positive CTCA scan may overestimate the severity of atherosclerotic obstructions [13]. In a patient-based analysis, the sensitivity for detecting patients with significant CAD was 85–99%, specificity was 64–90%, positive predictive value was 86–91%, and negative predictive value was 83–97% [13, 14]. In a segment-based analysis, the sensitivity was 62–88%, specificity was 79–90%, positive predictive value was 36–47%, and negative predictive value was 95–99% [13, 15]. Also the anatomic assessment of the hemodynamic significance of coronary stenoses determined by visual CTCA does not correlate well with the functional assessment of intracoronary fractional flow reserve (FFR) [16, 17]. The negative and positive predictive values indicate that MSCT angiography cannot completely replace conventional CAG at present [14].

MPI SPECT using ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin is a well-established and widely accepted test for the diagnostic evaluation of patients with known or suspected CAD [18, 19]. Sometimes MPI SPECT quality may be hampered by scatter and attenuation artifacts. In a large study of 2,560 patients the sensitivity and specificity of MPI SPECT compared to CAG was 91 and 87%, respectively [20]. In patients with known or suspected CAD, a normal MPI SPECT study identifies a low-risk group with an annual rate of death or nonfatal myocardial infarction <1%. Among patients with nonischemic MPI SPECT studies, high CAC scores do not confer an increased risk for cardiac events. Thus, although patients with high CAC scores may be considered for intensive medical therapy to prevent future CAD events, a normal MPI SPECT study in such patients suggests no need for more aggressive interventions [21]. Several newly designed dedicated cardiac SPECT systems were recently introduced with the goals of achieving higher spatial resolution and sensitivity, while significantly shortening the scan time and

improving patient comfort. By limiting the field of view of the camera to encompass the predictable location of the heart, and changing the crystals, detector, and collimator design, these new SPECT systems are smaller in size and allow simultaneous data acquisition of the heart from all angles. Beyond the changes in hardware, advances in software development for image reconstruction, computer-aided analysis, and image interpretation will likely increase the value of nuclear cardiac imaging.

SPECT after a screening CAC measurement

In terms of prognostic value, CAC is most useful in populations at intermediate risk in symptomatic patients [22, 23]. Because CAC is an easily obtained surrogate for plaque burden, it is a potential tool for predicting cardiovascular risk in persons in whom atherosclerosis is developing. Especially its negative predictive value has been stressed. A CAC score of 100 Agatston units is commonly used as the cutoff value with a significant increase of coronary event rate in patients [24], and additional age- and sex-adjusted percentiles are commonly used. Ischemia extension on MPI SPECT was small however, and no intervention was necessary. Additional FFR measurements also yielded a near to normal flow reserve and the patient was treated conservatively [17, 25].

He et al. [26] concluded that below a threshold of 400 Agatston units the probability of abnormal perfusion findings was low on MPI SPECT: 0.9% for CAC score <100 Agatston units, 9.8% for CAC score of 100–399 Agatston units, and 47.6% for CAC score >400 Agatston units. Furthermore, below the threshold of 400 Agatston units, most of the perfusion defects were minor and not of prognostic significance. Schepis et al. showed that combining MPI SPECT with CAC at a cutoff of 709, and not at the critical level of 400, improved the accuracy of SPECT for the detection of CAD [27]. The vast majority of patients for whom true-negative findings were obtained by the combination of SPECT and CT nevertheless had substantial calcifications, although the CAC score was below the cutoff for coronary risk. This finding highlights the fact that the presence of atherosclerosis does not necessarily result in perfusion abnormalities on MPI SPECT and the cutoff level of 400 is debatable; however, to prevent misdiagnosing of CAD the cutoff level of 400 is maintained.

CAC after a screening SPECT

The clinical strength of MPI SPECT is its strong negative predictive value for subsequent cardiac events even in patients with known CAD [28, 29]. However, this negative predictive value is lower in certain high-risk groups such as diabetic patients, and MPI SPECT techniques also have well-recognized limitations and a finite rate of false-negative findings, for example, in patients with main stem stenosis and three-vessel disease [30, 31]. CAC measurement may also play a significant role in clarifying equivocal MPI SPECT results, due to attenuation artifacts, scatter, or when stress ECG and MPI SPECT results are disparate. In contrast, previous studies reported that approximately 70% of patients with a normal MPI SPECT will have a CAC above 0 with about 50% having a CAC above 100 and up to 30% a severe score (> 400) [26, 27, 32–35]. However, with increasing severity of the CAC score, more patients will have abnormal SPECT results as well as more severely abnormal SPECT findings [26, 27, 33, 34]. Early detection of CAD allows appropriate medical therapy and risk modification [36]. CAC identifies additional patients that will benefit from optimal pharmacotherapy compared to SPECT findings alone. Both parameters are important for cardiovascular risk: CAC is related to the long-term risk (> 5 years), and MPI SPECT is more related to the short-term risk (< 1 year) of cardiovascular events. Although CAC can be very low or negative, obstructive coronary lesions can be present, due to non-calcified plaques [37]. Vice versa CAC can be elevated without functional consequences for myocardial perfusion [33]. Therefore, coronary morphology is often not correlated to functional myocardial perfusion [17].

SPECT and CTCA

Calcifications or stents represent major causes for overestimation of luminal narrowing on CTCA. Motion, noise, and contrast-related image deterioration are the main reasons for false-negative CTCA findings. The positive predictive value of CTCA is therefore suboptimal. At present, the main clinical advantage of CTCA seems to be related to its high negative predictive value, which allows for the exclusion of obstructive CAD. CTCA detects the presence of multiple coronary lesions, but the hemodynamic consequences of these abnormalities, which are important for adequate therapeutic decisions, might be equivocal. In patients with multiple lesions, identification of the culprit lesion is not possible. To avoid these potential clinical limitations, integration of the anatomic information provided by CTCA with hemodynamic information provided by MPI SPECT is needed and seems to be of value. MPI SPECT and MSCT provide different and complementary information on CAD, namely, detection of atherosclerosis versus detection of ischemia [2, 38].

Table 1 SPECT/CT protocol outline: algorithm of integrated SPECT/CT findings of MPI, CAC, and CTCA in patients with suspected CAD

		CAC			
		< 10 or <25th percentile	11-100 or 25-50th percentile	101-400 or 50-75th percentile	>400 or >75th percentile
MPI SPECT	Normal	Provide reassurance	Expectative	Expectative or angiography	Angiography
	Mild	Expectative	Expectative or angiography	Angiography	Angiography
	Moderate	Expectative or angiography	Angiography	Angiography	Angiography
	Extensive	Angiography	Angiography	Angiography	Angiography

Table readout needs to be combined with the pre-risk for CAD. However, patients with high risk profile and typical anginal complaints with normal CAC and MPI SPECT or conflicting results (low risk readout or low read out combined with moderate to high risk by the table, respectively) may need further workup with angiography. Uncalcified, substenotic vulnerable lesions can not be excluded.

CAC: coronary artery calcium scoring

MPI SPECT: myocardial perfusion imaging categorized according to ischemia extent. Markings: light blue: very low risk, light green: low risk, orange: moderate risk, red: high risk group. For all categories: risk factor management should be considered. Pharmacological risk reduction in case no angiography is performed should be tailored to the patient's needs depending on the outcome of the SPECT/CT investigation.

Combined SPECT/CT

Hybrid SPECT/CT cameras have already been introduced commercially in the clinical setting. A study by Thilo et al. [39] demonstrated that fast assessment of CAD is possible with an integrated SPECT/CT system. The combination of CAC and MPI SPECT is needed for optimal evaluation of CAD [40, 41]. Combined SPECT/CT acquisition is more patient friendly, and only one visit to the imaging department is requested. Hybrid imaging will need less personnel compared with two stand-alone machines and may result in reduced healthcare costs. Fusion of MPI SPECT with CT angiography with dedicated software is another good option. The combination of MPI SPECT, CAC and CTCA (if a 64-slice CT is available) will offer the clinician MPI SPECT, left ventricle ejection fraction (LVEF) and function, left ventricle volumes (end-systolic and end-diastolic volumes), attenuation transmission maps, CAC, and CT angiography. With the hybrid imaging system, attenuation correction can also be performed with minimal effort by using the CAC scoring CT examination [42]. One should have in mind that CTCA cannot replace conventional CAG, but be used for equivocal or conflicting MPI SPECT and CAC results. A point of concern is the high radiation burden of CTCA of an estimated dose of 12 mSv on average [43]. A basic principle of radiation protection is to keep radiation exposure “as low as reasonably achievable” (ALARA principle). Combination of SPECT and CAC alone will reduce radiation burden significantly. SPECT scanning can be limited to stress MPI SPECT alone, combined with CAC, resulting in 4 and 1.5 mSv radiation burden, respectively. Inconclusive MPI SPECT stress scans need, however, to be completed with a rest MPI SPECT. Nuclear medicine physicians need to be “cross-over” trained to be familiar with CTCA reading and CAC interpretation.

Approximately 761 per million of population (pmp) MPI SPECT studies are performed yearly in Europe [44]. The combination of SPECT/CT parameters may prove to be important from a diagnostic and therapeutic point of view in several clinical scenarios.

The integration of MPI SPECT and CAC score is an interesting strategy for the diagnostic work-up of patients with suspected CAD. CAC score using the Agatston score, and age and gender risk percentiles, can be integrated with the MPI SPECT results of normal, mild ischemia, moderate ischemia, and extensive ischemia of the LV surface. As cardiovascular disease remains the largest healthcare problem around the world despite

increasing healthcare spending, there is growing interest to enhance the use of cost-effective diagnostic tools, especially in using new diagnostic systems like SPECT/CT. Cost-effectiveness studies are lacking at this moment, but are needed to estimate the financial costs for society.

A practical 1-day work-up of patients with intermediate risk for CAD can be as follows: patients start with stress MPI SPECT and CAC scoring, if needed rest MPI SPECT, and if needed finished by CTCA at the end of a 1-day procedure. For this purpose a 64-slice SPECT/CT system is preferable, but SPECT/CT systems with less than 64 slices can also be combined with CT of 64 slices PET/CT systems in the same department. The cross tabulation of possible SPECT MPI and CAC results in patients with intermediate risk for CAD directs further clinical work-up as proposed in the refined Table 1: (1) provide reassurance to the patient and no further risk assessment in this very low-risk group, (2) lifestyle adaptation or coronary risk reduction with medication in the low-risk group, (3) pharmacological coronary risk reduction or angiography (CTCA or conventional CAG) in the intermediate-risk group, and (4) angiography in the high-risk group [45, 46]. The table readout should be combined with the pre-risk of CAD.

Conclusion

Combined SPECT/CT findings of physiological and morphological aspects may not just complement the work-up and assessment of CAD, but may also direct impending therapeutic strategies. Cardiac SPECT/CT is a patient-friendly method due to the one-stop-shop hallmark. Cost-effectiveness studies need to be explored.

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