SPECT and CT imaging in
stable coronary artery disease
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SPECT and CT imaging in stable coronary artery disease

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doors

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Voor mijn ouders
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CHAPTER 1

Introduction and outline of the thesis
Despite advances in primary and secondary prevention, cardiovascular disease remains the leading cause of death worldwide [1-3]. In patients suspected of coronary artery disease (CAD), assessment of the presence and extent of coronary atherosclerosis is mandatory to determine the appropriate clinical management. Coronary anatomy and the degree of vascular pathology have traditionally been defined and identified by invasive coronary angiography (ICA). Nowadays, additional intracoronary pressure-derived fractional flow reserve (FFR) can be measured in the same session to assess the functional significance of coronary stenoses [4]. However, the invasive nature of ICA carries a non-negligible risk and adds significant costs. Furthermore, the low diagnostic yield of ICA demonstrates the need for better selection methods using the non-invasive tests [5].

Current guidelines and appropriate use criteria documents recommend the use of non-invasive cardiac imaging in numerous clinical scenarios in order to provide diagnostic and prognostic information. The goal of such imaging is to guide therapeutic decision making and to enhance risk stratification, especially in patients with an intermediate pre-test probability [6-9].

With the recent advent of combined single photon emission computed tomography (SPECT) and computed tomography (CT) into hybrid SPECT/CT devices, attenuation correction of SPECT myocardial perfusion images can now easily be obtained. More importantly, traditional SPECT results can now be complemented with the anatomic information obtained from coronary artery calcium scoring (CACS) and coronary computed tomography angiography (CCTA) in a single session. Although initial studies report a synergistic effect of this SPECT/CT combination in selected populations [10,11], real-world clinical data for stable low-intermediate risk patients are still lacking. Furthermore, the clinical implications of a stepwise approach with this kind of hybrid imaging are unknown.

Non-invasive imaging in suspected stable coronary artery disease

Non-invasive testing is important to exclude CAD on the one hand, and to detect the presence of CAD with its functional consequence on the other hand. For optimal decisions, high diagnostic performance of these tests is required. Non-invasive imaging for diagnosis of CAD is currently focused on functional imaging to assess the haemodynamic consequences of obstructive CAD, and on anatomical imaging to visualize the coronary artery tree. Traditional exercise electrocardiography testing is a
widely available, well-established and cost-effective means to assess ischaemic heart
disease. However, it has a limited diagnostic accuracy and a substantial rate of
inconclusive test results [12]. Alternatively, several non-invasive functional tests are
currently available that may be more useful, such as myocardial perfusion imaging
with SPECT or positron emission tomography (PET), stress echocardiography and
cardiac magnetic resonance imaging (MRI). For anatomical imaging CACS and CCTA
are used. An interesting recent development is the possibility to combine functional
with anatomical tests in a single machine. The following paragraphs provide an update
with regard to imaging by using SPECT, CACS and CCTA, and a combination of these
tests.

SPECT myocardial perfusion imaging

Non-invasive testing with SPECT myocardial perfusion imaging is widely available
and extensively validated in stable angina. It provides valuable diagnostic information
with reasonable accuracy and also provides prognostic information. SPECT results
improve patient selection for invasive angiography and coronary revascularisation [13].
The reported sensitivity of SPECT for the detection of angiographically relevant CAD
is high (87–89%) [14,15], although a wide range of diagnostic performance has been
reported. SPECT has traditionally been done with gamma cameras based on sodium
iodide crystals and photomultipliers.

Recently, a new generation of gamma cameras with novel semiconductor
cadmium-zinc-telluride (CZT) detector technology has been developed. The high
intrinsic sensitivity and resolution of these CZT detectors allow direct digital
conversion of scintillation events. This eliminates the need for photomultiplier tubes
and facilitates considerable down-sizing of the gantry. The CZT detectors enable
improved image quality and reduced imaging time because of improved count
sensitivity and image contrast [16,17]. However, clinical experience with the CZT
SPECT camera is limited.

Coronary artery calcium scoring

Coronary artery calcifications are highly specific for the presence of coronary
atherosclerosis and represent the total atherosclerotic plaque burden present in the
epicardial coronary arteries [18]. CACS is a clinical tool used for the early non-
invasive detection of coronary atherosclerosis and has shown to be a reliable,
independent risk predictor for cardiovascular events [19,20]. However, the role of
CACS in symptomatic patients is currently less clear. The absence of coronary
calcifications has a high negative predictive value to exclude obstructive CAD in
appropriately selected patients [21,22], while high CACS values are generally
associated with more advanced coronary sclerosis and a higher likelihood of ischaemia
[23,24] or stenotic lesions [25].

Coronary computed tomography angiography

CCTA allows reliable visualization of the coronary arteries and is able to detect the
presence of coronary stenosis in addition to general cardiac anatomy and anomalies.
The high negative predictive value in low-intermediate risk patients enables a reliable
exclusion of obstructive CAD [26]. Due to technical limitations accurate assessment of
the degree of stenosis is difficult. An inherent limitation, therefore, remains the
inability to predict the severity and functional relevance of intermediate grade stenoses
and calcified lesions. Consequently, positive predictive values in detecting haemo-
dynamically relevant coronary artery stenoses vary between 32 and 60% [27].

SPECT imaging combined with calcium scoring and/or coronary
CT angiography

The growing availability of multi-slice CT scanners and the recent advent of hybrid
SPECT/CT and PET/CT scanners have increased the interest in simultaneous perfusion
imaging and CACS or CCTA in patients with suspected CAD. The possible
improvement using CZT cardiac SPECT scanners has further increased the interest in
this hybrid approach. The CACS enables diagnosing and quantification of the degree of
coronary atherosclerosis irrespective of MPI results, improving the detection of
relevant CAD [28], while also providing additional long-term prognostic information
[29-31]. Hybrid SPECT and CCTA imaging has shown to improve the diagnostic and
prognostic performance and has the potential to enable a more appropriate selection of
patients who may benefit from ICA with subsequent revascularization [32]. However,
the optimal combination of these new tests is currently unclear. Important aspects in
combining these tests are the overall clinical effectiveness and the minimization of the total cost as well as radiation dose.

In summary, SPECT myocardial perfusion imaging provides relevant functional information in patients with suspected CAD, although it does not give anatomical information for targeting revascularization. CCTA is able to detect coronary atherosclerosis at its earliest stages with a high sensitivity and negative predictive value, although it is unable to assess the haemodynamical relevance of depicted stenoses. Therefore, SPECT imaging and CCTA should be considered complementary approaches rather than exclusive in the evaluation of the patient at risk for CAD. In addition, the role of CACS in symptomatic patients in clinical daily practice remains unclear.

In 2009, we have implemented (as the first hospital in Europe) a dedicated cardiac hybrid 64-slice SPECT/CT device in clinical daily practice. In 2010, the gamma camera was upgraded with latest CZT detector technology. We have implemented a sequential diagnostic approach for hybrid cardiac imaging in stable low-intermediate risk patient starting with stress SPECT imaging and CACS as initial tests. In case of normal perfusion findings further testing was omitted, while additional rest SPECT imaging and/or CCTA were performed in those with equivocal or abnormal stress SPECT findings. However, the implementation of CZT SPECT detector technology and the real-world implications of this stepwise diagnostic algorithm required clinical evaluation and validation.

Outline of the thesis

The aim of this thesis was to study the clinical value and potential role of combining SPECT, CACS and CCTA imaging in a real-world everyday clinical setting. For this purpose we developed a stepwise algorithm for patients with suspected stable CAD. Additionally, the clinical implications of SPECT imaging by using a CZT gamma camera were studied. These research questions were assessed by using data from a large cohort registry of low-intermediate risk patients without prior CAD referred for non-invasive SPECT/CT imaging because of suspected stable anginal complaints.

In Chapter 2, the impact of the CZT SPECT camera for myocardial perfusion imaging is described. Chapter 3 describes the degree of concordance between CZT SPECT
imaging and invasive pressure-derived fractional flow measurements in stable patients with intermediate degree coronary stenoses. CCTA allows reliable visualization of the coronary arteries and is also able to detect general cardiac anatomy and coronary anomalies including myocardial bridging. Myocardial bridging is a congenital coronary anomaly caused by muscles overlying the intramyocardial course of an epicardial coronary artery and may cause symptoms as chest pain due to systolic compression of the tunnelled segment. In CHAPTER 4, we studied the value of CCTA in assessing the prevalence of myocardial bridging in patients referred for a clinically indicated CCTA.

CHAPTERS 5 to 8 of this thesis focus on the impact of simultaneous CACS and CCTA in stable low-intermediate risk patients referred for SPECT myocardial perfusion imaging. CHAPTER 5 describes our real-world clinical experience with an individualized stepwise approach for hybrid SPECT/CT imaging in stable patients with suspected CAD. In CHAPTER 6, we investigated the influence of CACS knowledge on the visual interpretation of SPECT. In CHAPTER 7, we describe the ability of a zero calcium score to exclude flow-limiting CAD in our homogeneous population referred for SPECT imaging on clinical grounds. Finally, the impact of SPECT imaging in symptomatic patients with extreme coronary calcifications (CACS ≥1000) is addressed in CHAPTER 8.
Introduction and outline of the thesis

References


Introduction and outline of the thesis


CHAPTER 2

Impact of a new ultrafast CZT SPECT camera for myocardial perfusion imaging: fewer equivocal results and lower radiation dose

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Abstract

**Purpose:** The new ultrafast cardiac single photon emission computed tomography (SPECT) cameras with cadmium-zinc-telluride (CZT)-based detectors are faster and produce higher quality images as compared to conventional SPECT cameras. We assessed the need for additional imaging, total imaging time, tracer dose and 1-year outcome between patients scanned with the CZT camera and a conventional SPECT camera.

**Methods:** A total of 456 consecutive stable patients without known coronary artery disease underwent myocardial perfusion imaging on a hybrid SPECT/CT (64-slice) scanner using either conventional (n=225) or CZT SPECT (n=231). All patients started with low-dose stress imaging, combined with coronary calcium scoring. Rest imaging was only done when initial stress SPECT testing was equivocal or abnormal. Coronary CT angiography was subsequently performed in cases of ischaemic or equivocal SPECT findings. Furthermore, 1-year clinical follow-up was obtained with regard to coronary revascularization, non-fatal myocardial infarction or death.

**Results:** Baseline characteristics were comparable between the two groups. With the CZT camera, the need for rest imaging (35% vs 56%, \(p<0.001\)) and additional coronary CT angiography (20% vs 28%, \(p=0.025\)) was significantly lower as compared with the conventional camera. This resulted in a lower mean total administered isotope dose per patient (658±390 MBq vs 840±421 MBq, \(p<0.001\)), and shorter imaging time (6.39±1.91 vs 20.40±7.46 min, \(p<0.001\)) with the CZT camera. After 1 year, clinical outcome was comparable between the two groups.

**Conclusions:** As compared to images on a conventional SPECT camera, stress myocardial perfusion images acquired on a CZT camera are more frequently interpreted as normal with identical clinical outcome after 1-year follow-up. This lowers the need for additional testing, results in lower mean radiation dose and shortens imaging time.

Introduction

Non-invasive testing is often employed for the detection of suspected obstructive coronary artery disease (CAD). Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is widely used and has proven to provide valuable diagnostic and prognostic information [1-4]. A stress-only protocol
Ultrafast CZT SPECT camera for myocardial perfusion imaging has been proposed to lower radiation dose and imaging time, in which rest imaging is omitted when the stress images are normal [5]. To improve image quality and reduce imaging time, a new generation of gamma cameras with novel semiconductor cadmium-zinc-telluride (CZT) detector technology has been developed [6,7]. However, clinical experience with the CZT camera is limited and there are no data on stress-only protocols with the CZT camera as compared with the conventional camera [8-14].

Using a stress-only protocol, we compared the CZT camera with the conventional camera with regard to the need for additional rest imaging, total imaging time, mean total tracer doses and the 1-year outcome.

Materials and methods

STUDY POPULATION
From January to July 2010, a total of 456 consecutive patients with suspected CAD, and a low to intermediate pre-test likelihood for CAD according to Diamond and Forrester criteria, underwent SPECT/CT imaging using an individualized stepwise decision algorithm (Fig. 1) [15]. The aim of this algorithm was to provide a

![Fig. 1. Single-day individualized stepwise decision algorithm. SPECT single photon emission computed tomography, CCTA coronary computed tomography angiography.](image-url)
comprehensive patient-tailored assessment of possible CAD in each patient in a single day. Results allowed rapid selection of appropriate treatment or discharge. From January until March 2010, patients (n=225) were scanned on a conventional SPECT/CT camera (Ventri-LightSpeed VCT XT, GE Healthcare), and from May until July 2010, patients (n=231) were scanned with a CZT-based SPECT/CT camera (Discovery NM/CT 570c, GE Healthcare).

We applied an individualized approach starting with low-dose stress SPECT and assessment of the coronary artery calcium score (CACS) as initial screenings tests in all patients. After acquisition and post-processing, data were immediately analysed by two experienced nuclear cardiology reviewers. In case of normal stress perfusion further tests were omitted regardless of the CACS. However, patients with equivocal or abnormal stress perfusion were referred for rest SPECT. In case of equivocal or abnormal stress/rest SPECT results and a suitable CACS, coronary computed tomography angiography (CCTA) was performed in the absence of contraindications. The CACS was considered suitable when <1000 in the absence of multiple severely calcified segments. At the end of the day, the same reviewers evaluated all tests performed and a final conclusion was drawn.

**SPECT-MPI DATA ACQUISITION**

All patients underwent a 1-day $^{99m}$Tc-Tetrofosmin MPI protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 h before the test. Pharmacological stress was induced by intravenous administration of adenosine (97% of the patients, continuous infusion at a rate of 140 μg/kg per minute for 6 minutes) or dobutamine (3% of the patients, starting with 10 μg/kg per minute and increased at 3-minute intervals to a maximum of 50 μg/kg per minute until 85% of the predicted heart rate had been reached). Whenever possible, patients performed additional low-level bicycle exercise to reduce side effects of adenosine. ECG and blood pressure were monitored before, throughout and following the infusion. A weight-adjusted dose of $^{99m}$Tc-Tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. Patients scheduled for rest imaging received a dose of $^{99m}$Tc-Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). For both stress and rest SPECT images were acquired 45–60 minutes after tracer injection.

On the conventional dual-detector gamma camera (Ventri, GE Healthcare), images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 x 64 matrix, and an elliptical orbit with step-and-shoot
acquisition at 6º intervals over a 180º arc (45º anterior oblique to 45º left posterior oblique) with 30 steps (30 views). All patients were imaged in the supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images.

The CZT-based SPECT images were acquired using a multi-hole camera (Discovery NM/CT 570c, GE Healthcare) and 19 stationary detectors simultaneously imaging the heart. Each detector contained 32 x 32 pixelated (2.46 x 2.46 mm) CZT elements. A 20% symmetrical energy window at 140.5 keV was used as previously described [16]. All patients were imaged in the supine position with arms placed above the head. Acquisition time was 5 minutes for the stress images and 4 minutes for the rest images. This was derived from the recommendations of the manufacturer, published experience and our own qualitative assessment in heart phantom studies and our initial experience in patients [9,16].

Gated SPECT analysis to calculate left ventricular volumes, ejection fraction and to assess wall motion abnormalities was done in nearly all patients when feasible, usually at stress but in some cases at rest [6,7,17]. In all 456 patients, stress and rest SPECT studies were followed by an unenhanced low-dose CT scan during a breath-hold to provide the attenuation map for attenuation correction. These scans covered the entire chest with scanning parameters: 5.0-mm slice thickness using a reconstruction algorithm with a 512 x 512 matrix and 800-ms rotation times at 120 kV and 20 mA. Emission images as well as attenuation map data were entered in a dedicated reconstruction algorithm to provide 3D volume data (available in a Xeleris workstation, GE Healthcare). These were reorientated in the standard way and displayed in the three traditional cardiac axes.

SPECT MPI ANALYSIS
Teams of experienced cardiologists and nuclear medicine physicians unblindedly analysed the images using MPI polar maps. Segments were scored by consensus of two readers using a 20-segment model for the left ventricle using following 5-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction in radiotracer uptake and 4 = absence of detectable tracer in a segment) [18,19].

Perfusion defects were identified on the stress images (a segment with a score ≥2 was considered to have a defect). A stress study was interpreted as normal if perfusion was assessed to be homogeneous throughout the myocardium and less than two segments had stress scores >2 [18-20]. Subsequent rest imaging was performed if the stress images did not fulfil these criteria and were therefore deemed to be either
abnormal or equivocal. A reversible perfusion defect was defined as one in which a stress defect was associated with a rest score $\leq 1$ or a stress defect score of 4 with a rest score of 2 [18,19]. Irreversible defects were considered scar tissue when persistent despite applying CT-based attenuation correction together with abnormal wall motions in the corresponding segments [21].

Image quality for all 456 stress studies was assessed retrospectively by two independent experienced blinded readers employing a visual 4-point grading scale (1 = poor, 2 = fair, 3 = good and 4 = excellent). The following parameters were considered: myocardial count density and uniformity, endocardial and epicardial edge definition, visualization and definition of the right ventricle, and background noise.

CACS AND CCTA DATA ACQUISITION
All CACS and CCTA scans were acquired using the CT of the integrated SPECT/CT device. All patients with heart rates $>70$ bpm received oral beta-blocker therapy (50 or 100 mg metoprolol, Astra Zeneca BV, Zoetermeer, The Netherlands) prior to the CACS scan [22]. For the CACS scans an unenhanced, ECG-gated scan was performed prospectively triggered at 75% of the RR interval using the following scan parameters: $4 \times 2.5$ mm, gantry rotation time 330 ms, tube voltage 120 kV and tube current 250 mA. Post-processing of the CACS was performed on dedicated workstations (Advantage Windows 4.4, GE Healthcare).

With regard to the CCTA, exclusion criteria were known hypersensitivity to iodinated contrast agents, renal insufficiency or irregular heart rhythms. All patients received a single dose of nitroglycerine (0.4 mg) just before the CCTA scan. If necessary, patients received oral (50–200 mg) and/or intravenous beta-blocker therapy (5–30 mg) in order to achieve a target heart rate below 65 bpm [23]. An unenhanced scan was first obtained, followed by the CT angiographic acquisition using the following parameters: 64 slices per rotation, 0.625-mm detector collimation, gantry rotation time 330 ms, effective temporal resolution 165 ms, spatial resolution 0.4 mm$^2$, tube voltage 100–140 kV (depending on the patient’s body weight) and tube current of 450–800 mA. Contrast-enhanced CCTA was acquired with prospective ECG triggering (86%) or helical scanning (14%). All images were acquired during an inspiratory breath hold of approximately 10–12 s.

CACS AND CCTA ANALYSIS
The computer software for coronary calcium scoring (Smart Score, GE Healthcare) automatically defined the presence of calcified lesions as those greater than 130 HU.
The total calcium burden in the coronary arteries was manually depicted and allocated to the corresponding coronary artery by an experienced reader using the Agatston method for quantification of the CACS [24].

Image interpretation of the CCTA was performed on axial images, multiplanar and curved reformations, and thin-slab maximum intensity projections. Coronary arteries were subdivided according to a 15-segment model as proposed by the American Heart Association [25]. Each segment was evaluated on at least two planes, and the degree of diameter stenosis was visually graded by consensus of the two readers.

CLINICAL FOLLOW-UP
Clinical outcome data were obtained by reviewing hospital records, by performing telephone interviews with the patients and by contacting patients’ general practitioners. The time between the stress test and the date of the final examination or consultation was used to determine follow-up length. Events that were noted during follow-up where death, non-fatal myocardial infarction and unstable angina requiring revascularization. The minimal follow-up duration was 9 months for those without an event. Clinical outcomes in patients imaged by the two cameras were categorized based on MPI results (normal or abnormal).

STATISTICAL ANALYSIS
Statistical analysis to compare baseline characteristics, acquisition times, injected tracer doses, the need for additional rest imaging and final SPECT results, was performed with chi-squared and one-way analysis of variance (ANOVA) as available in SPSS software (version 16.0 for Windows; SPSS Inc., Chicago, IL, USA). Comparison of continuous data between both groups was performed using the two-sided Student’s t-test. Quantitative variables were expressed as mean±SD and categorical variables as frequencies or percentage. A p value of less than 0.05 was considered as statistically significant.

Results

BASELINE CHARACTERISTICS
The mean age of the 456 patients was 60±12 years, 49% was male and the mean body mass index (BMI) was 28±5 kg/m². The main indications for SPECT/CT imaging were chest pain (73%) and dyspnoea (12%). Other indications were palpitations (5%),
screening (3%), abnormal resting ECG (3%), syncope (2%), preoperative clearance (1%) or fatigue (1%). In 444 patients (97%) pharmacological stress was induced with adenosine and in 12 patients (3%) with dobutamine. A total of 231 patients (51%) was scanned with the CZT camera and 225 (49%) with the conventional camera. The baseline characteristics of the two groups are summarized in Table 1.

**Table 1.** Baseline characteristics of 456 stable patients with suspected CAD referred for SPECT imaging by either a new CZT camera or a conventional camera

<table>
<thead>
<tr>
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<th>CZT (n=231)</th>
<th>Conventional (n=225)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59.9±13</td>
<td>60.9±12</td>
<td>0.44</td>
</tr>
<tr>
<td>Male gender</td>
<td>48</td>
<td>51</td>
<td>0.46</td>
</tr>
<tr>
<td>Current smoker</td>
<td>23</td>
<td>16</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>14</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>49</td>
<td>52</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63</td>
<td>63</td>
<td>0.91</td>
</tr>
<tr>
<td>Family history</td>
<td>39</td>
<td>44</td>
<td>0.20</td>
</tr>
<tr>
<td>Aspirin</td>
<td>41</td>
<td>41</td>
<td>0.96</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>52</td>
<td>50</td>
<td>0.71</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>141±20</td>
<td>143±22</td>
<td>0.36</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85±13</td>
<td>88±12</td>
<td>0.013</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71±12</td>
<td>74±14</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28±5</td>
<td>28±5</td>
<td>0.40</td>
</tr>
<tr>
<td>LBBB</td>
<td>6</td>
<td>4</td>
<td>0.56</td>
</tr>
<tr>
<td>Creatinine level (μmol/l)</td>
<td>77±26</td>
<td>76±16</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Data are percentages or mean±standard deviation.

SPECT, single photon emission computed tomography; CZT, cadmium zinc telluride; BP, blood pressure; BMI, body mass index; LBBB, left bundle branch block.

**Table 2.** Results of SPECT imaging with a new CZT camera vs a conventional camera in 456 stable patients with suspected CAD

<table>
<thead>
<tr>
<th></th>
<th>CZT (n=231)</th>
<th>Conventional (n=225)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Calcium score = 0</td>
<td>23</td>
<td>28</td>
<td>0.24</td>
</tr>
<tr>
<td>Calcium score</td>
<td>228±597</td>
<td>306±661</td>
<td>0.76</td>
</tr>
<tr>
<td>Normal perfusion</td>
<td>86</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fixed defect</td>
<td>5</td>
<td>7</td>
<td>0.38</td>
</tr>
<tr>
<td>Ischaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>3</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Definite</td>
<td>7</td>
<td>10</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Data are percentages or mean±standard deviation.

SPECT, single photon emission computed tomography; CZT, cadmium zinc telluride.
IMAGING RESULTS
Results of SPECT imaging with the CZT camera versus the conventional camera are summarized in Table 2. There were no differences in the calcium score between the two groups. Image quality of the stress scans was graded good or excellent in 210 of the 231 patients (91%) scanned with the CZT camera and in 179 of the 225 patients (80%) scanned with conventional SPECT ($p=0.001$). In addition, with the CZT camera, there were significantly more normal scans and significantly fewer equivocal scans. The normalcy rate in patients with a <10% likelihood of CAD was 95% for the CZT group (n=40) and 86% for the conventional group (n=28) ($p=0.22$). Table 3 summarizes the need for additional imaging after coronary calcium score and stress imaging with the CZT camera as compared with the conventional camera. After use of the CZT camera, the need for either additional rest imaging or CCTA was significantly less (35% vs 56%, $p<0.001$).

As a direct result, the mean total $^{99m}$Tc-Tetrofosmin dose received per patient in the CZT group was $658\pm390$ MBq versus $840\pm421$ MBq in the conventional SPECT group ($p<0.001$). The mean total acquisition time for SPECT imaging per patient was $6.39\pm1.91$ minutes in the CZT group compared to $20.40\pm7.46$ minutes in the conventional SPECT group ($p<0.0001$).

CLINICAL FOLLOW-UP
Follow-up was assessed in 99% of the patients. There were no deaths or patients with myocardial infarction during a mean follow-up of $13\pm3$ months (Table 4). A total of 16 patients (7%) scanned with CZT camera and 24 patients (11%) scanned with the conventional camera had coronary revascularization ($p=0.21$).

Table 3. Need for additional imaging after CACS and stress imaging with a new CZT camera vs a conventional camera in 456 stable patients with suspected CAD

<table>
<thead>
<tr>
<th></th>
<th>CZT (n=231)</th>
<th>Conventional (n=225)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No additional imaging</td>
<td>65</td>
<td>44</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Rest imaging (total)</td>
<td>35</td>
<td>56</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Rest imaging, without CCTA</td>
<td>15</td>
<td>28</td>
<td>0.001</td>
</tr>
<tr>
<td>Rest SPECT + CCTA</td>
<td>20</td>
<td>28</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Data are percentages. CACS, coronary artery calcium score; CZT, cadmium zinc telluride; CCTA, coronary computed tomography angiography; SPECT, single photon emission computed tomography.
Table 4. One-year clinical follow-up of 456 stable patients with suspected CAD referred for SPECT imaging by either a new CZT camera or a conventional camera

<table>
<thead>
<tr>
<th></th>
<th>CZT (n=231)</th>
<th>Conventional (n=225)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal SPECT</td>
<td>86</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>2</td>
<td>2</td>
<td>0.99</td>
</tr>
<tr>
<td>Myocardial infarction / death</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal SPECT</td>
<td>14</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>5</td>
<td>9</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction / death</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are percentages.
SPECT, single photon emission computed tomography; CZT, cadmium zinc telluride; NS, not significant.

Discussion

This clinical study in 456 consecutive stable patients with suspected CAD showed that the use of a new CZT camera for myocardial perfusion imaging yields significantly more scans interpreted as normal reducing the need for additional imaging. This was mostly due to a significantly lower number of equivocal scans. The reduced need for additional imaging resulted in a significant reduction in mean acquisition time and lower radiation dose. There were no differences in 1-year clinical outcome between patients imaged by the new camera as compared to those imaged by the conventional camera.

CZT cameras use a different imaging technique as compared to conventional SPECT cameras, with a stationary multi-pinhole design focused on the heart. This new geometric design and the new detector material combined with novel reconstruction algorithms led to improved diagnostic performance. Since the introduction of the novel dedicated cardiac CZT gamma camera in 2006, this has been confirmed in several clinical studies. Although the design and sample size of these studies vary and the number of reports is still limited, all studies including this one describe superior image quality with significantly shorter acquisition times because of improved count sensitivity and image contrast (Fig. 2) [6-12]. It seems that by using the CZT camera, imaging time can be shorter with the same injected dose or the injected dose can be reduced. Diagnostic accuracy of CZT SPECT for detecting clinically significant CAD
in comparison to invasive coronary angiography was demonstrated to be high [12,13]. Recently, the combined CZT SPECT/64-slice CT device (as used in our study) was validated using invasive angiography as the reference standard [26]. Furthermore, one study proved the feasibility of attenuation correction in this novel CZT camera with strong clinical agreement as compared to attenuation correction of MPI on a conventional camera [14].

**Fig. 2.** Attenuation corrected stress/rest CZT SPECT images demonstrate large reversible perfusion defects of the anterior, apical and septal walls in a 66-year-old man with atypical anginal chest pain. Acquisition times were 5 minutes for low-dose stress images and 4 minutes for high-dose rest images providing excellent image quality.
One of the applications of CCTA in hybrid imaging is the further analysis of equivocal SPECT cases [27]. The decreased frequency of equivocal results with the CZT camera also reduced the need for additional CCTA imaging in our study, allowing a more efficient use of CCTA and further reduction of the mean radiation dose. Nevertheless, hybrid SPECT/CCTA images are still possible with the CZT camera to combine anatomical and physiological findings [28].

Our study had several limitations. It concerned an unblinded, non-randomized single-centre study with a relatively small population. However, although we used a historical control population, both groups were very comparable concerning baseline characteristics. Another limitation may be that we investigated only a stable patient population with low or intermediate risk without known prior CAD. Furthermore, it must be stated that subjects in our cohort had a mean BMI of 28±5 kg and image quality may be substantially lower in severely obese patients. Therefore, our results must be read with caution when extrapolating them to populations with many obese subjects. However, this reflects normal clinical daily practice in a nuclear department. The additional diagnostic information obtained from the CCTA was not analysed and our findings were not externally validated by invasive angiography with fractional flow reserve measurement. However, in a low to intermediate risk population, it could be questioned whether invasive angiography for scientific validation purposes only would be considered ethical. Finally, although we had clinical follow-up up to 1 year regarding myocardial infarction, revascularization or death, data on anginal complaints after 1 year were not available.

Conclusion

As compared to images on a conventional SPECT camera, stress myocardial perfusion images acquired on a CZT camera are more frequently interpreted as normal with identical clinical outcome after 1-year follow-up. This lowers the need for additional testing, results in lower mean radiation dose and shortens imaging time.
References


Ultrafast CZT SPECT camera for myocardial perfusion imaging


CHAPTER 3

Myocardial perfusion imaging with a cadmium zinc telluride-based gamma camera versus invasive fractional flow reserve

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Stoffer Reiffers
Ad H.J. Oostdijk
Menko-Jan de Boer
Pieter L. Jager

Abstract

**Purpose:** Recently introduced ultrafast cardiac SPECT cameras with cadmium zinc telluride-based (CZT) detectors may provide superior image quality allowing faster acquisition with reduced radiation doses. Although the level of concordance between conventional SPECT and invasive fractional flow reserve (FFR) measurement has been studied, that between FFR and CZT-based SPECT is not yet known. Therefore, we aimed to assess the level of concordance between CZT SPECT and FFR in a large patient group with stable coronary artery disease.

**Methods:** Both invasive FFR and myocardial perfusion imaging with a CZT-based SPECT camera, using $^{99m}$Tc-Tetrofosmin as tracer, were performed in 100 patients with stable angina and intermediate grade stenosis on invasive coronary angiography. A cut-off value of <0.75 was used to define abnormal FFR.

**Results:** The mean age was 64±11 years, and 64% were male. SPECT demonstrated ischaemia in 31% of the patients, and 20% had FFR <0.75. The concordance between CZT SPECT and FFR was 73% on a per-patient basis and 79% on a per-vessel basis. Discordant findings were more often seen in older patients and were mainly (19%) the result of ischaemic SPECT findings in patients with FFR >0.75, whereas only 8% had an abnormal FFR without ischaemia as demonstrated by CZT SPECT.

**Conclusions:** Only 20–30% of patients with intermediate coronary stenoses had significant ischaemia as assessed by CZT SPECT or invasive FFR. CZT SPECT showed a modest degree of concordance with FFR, which is comparable with previous results with conventional SPECT. Further investigations are particularly necessary in patients with normal SPECT and abnormal FFR, especially to determine whether these patients should undergo revascularisation.

Introduction

Non-invasive testing with single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is well-validated in stable angina and provides valuable diagnostic and prognostic information improving patient selection for invasive coronary angiography (ICA) and coronary revascularisation [1-3]. The new generation of SPECT cameras with semiconductor cadmium zinc telluride (CZT) detector technology may provide superior image quality, reduced acquisition times, lower radiotracer doses, and higher diagnostic accuracy as compared to ICA [4-12].
Similarly, intracoronary pressure-derived fractional flow reserve (FFR) measurement is a well-established invasive method for the assessment of the functional significance of coronary stenoses, facilitating decision making regarding coronary revascularization [13-15]. FFR is frequently performed for determining the functional significance of coronary stenoses [16], and adds value to anatomical measurements on ICA. Previous studies have shown that the degree of concordance between conventional SPECT and FFR is 60–90% [17], but most studies included a limited patient population, and all studies were performed with conventional SPECT cameras.

The aim of our study was to assess the degree of concordance between CZT SPECT imaging and invasive FFR measurement in a larger cohort of patients with intermediate coronary stenoses.

Materials and methods

STUDY POPULATION
From September 2010 to December 2012, we included 100 consecutive stable symptomatic patients (mean age 66±11 years, 64 men) who were (1) scheduled for elective FFR measurement of intermediate anatomical coronary lesions demonstrated by recent invasive angiography, and (2) without previous non-invasive ischaemia detection in a prospective registry. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients. Inclusion criteria were referral for elective FFR measurement of target lesions with a reduction in diameter of 40–80% as determined during previous coronary angiography. Patients with concomitant severe coronary stenoses (>80%), serial coronary stenoses or prior myocardial infarction in the territory of the target lesion were excluded. All patients underwent SPECT using an ultrafast CZT-based gamma camera 1 day prior to the scheduled FFR measurement. FFR values <0.75 were considered positive for ischaemia and FFR values ≥0.75 were considered negative [13].

CLINICAL INFORMATION
At the time of examination, all patients completed a questionnaire regarding demographic information, prior medical history, cardiac risk factors and current medication use. Hypertension was defined as a blood pressure of ≥140/90 mmHg or the use of antihypertensive medication. Hypercholesterolaemia was defined as a total cholesterol level of ≥5 mmol/l or treatment with cholesterol-lowering medication.
Patients were classified as having diabetes if they were receiving treatment with oral hypoglycaemic drugs or insulin. A positive family history of coronary artery disease (CAD) was defined as the presence of CAD in first-degree relatives younger than 60 years. These data were verified and complemented with demographic and clinical information collected from medical records. Furthermore, information regarding patient age, gender, weight, height, blood pressure, heart rate and symptoms were prospectively obtained by a medical nurse.

CZT SPECT DATA ACQUISITION

All patients underwent a 1-day $^{99m}$Tc-Tetrofosmin SPECT protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 h before the test. In 97% of the patients, pharmacologic stress was induced by intravenous administration of adenosine at a continuous rate of 140 μg/kg/min for 6 min. In patients with a contraindication to the use of adenosine (3%), stress was induced using dobutamine (starting with 10 μg/kg/min and increasing at 3-minute intervals to a maximum of 50 μg/kg/min until 85% of the predicted heart rate had been reached). Whenever possible, patients performed additional low-level bicycle exercise to reduce side effects of adenosine. ECG and blood pressure were monitored before, throughout, and following the infusion. A weight-adjusted dose of $^{99m}$Tc-Tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. Patients scheduled for rest imaging received a dose of $^{99m}$Tc-Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). Both stress and rest SPECT images were acquired 45–60 minutes after tracer injection.

Patients were scanned with a hybrid 64-slice SPECT/CT. The CZT-based SPECT images were acquired using a multi-pinhole camera (Discovery NM/CT 570c; GE Healthcare) and 19 stationary detectors simultaneously imaging the heart. Each detector contained 32 x 32 pixelated (2.46 x 2.46 mm) CZT elements. A 20% symmetrical energy window at 140 keV was used as previously described [9]. All patients were imaged in the supine position with arms placed above the head. The acquisition time was 5 minutes for the stress images and 4 minutes for the rest images, as used previously [9]. Gated SPECT analysis to calculate left ventricle ejection fraction and to assess wall motion abnormalities was done in nearly all patients when feasible, usually during stress but in some patients at rest. Attenuation correction was not performed.
CZT SPECT versus FFR

CZT SPECT ANALYSIS
Two blinded nuclear cardiac readers (each with more than 10 years experience) visually interpreted the images, including MPI polar maps. Segments were scored semiquantitatively by consensus using a 17-segment model for the left ventricle and a five-point scoring system (0, normal; 1, mild reduction in radiotracer uptake; 2, moderate reduction; 3, severe reduction; and 4, absence of detectable tracer in a segment) [18,19]. Perfusion defects were identified on the stress images (a segment with a score >2 was considered to have a defect). A stress study was interpreted as normal if perfusion was assessed as homogeneous throughout the myocardium and fewer than two segments had a stress score ≥2 [18,19]. An ischaemic perfusion defect was defined as one in which a stress defect was associated with a rest score ≤1 or a stress defect score of 4 with a rest score of 2 [18,19]. Anterior and septal perfusion defects were allocated to the left anterior descending coronary artery, lateral defects to the left circumflex coronary artery, and inferior defects to the right coronary artery according to current convention [20].

FFR MEASUREMENT
By ICA, a 0.014-inch pressure monitoring wire (PressureWire®; RADI Medical Systems, Uppsala, Sweden) was set to zero, calibrated, advanced through a guiding catheter, introduced into the coronary artery and positioned distal to the stenosis under investigation. Adenosine (140 μg/kg/min) was infused continuously through a 5 F sheath in the femoral vein to obtain maximal coronary blood flow, corresponding to minimal distal coronary pressure. After maximal hyperaemia had been achieved, FFR was calculated as the ratio of the mean distal intracoronary pressure measured by the pressure wire to the mean arterial pressure measured through the coronary guiding catheter.

AGREEMENT BETWEEN CZT SPECT AND FFR
Concordance on a per-patient basis between SPECT and FFR was present if ischaemic changes on the stress-rest SPECT test were observed in the presence of a coronary lesion with a FFR value of <0.75. Concordance on a per-lesion basis between SPECT and FFR was present if ischaemic changes on the stress-rest SPECT test were observed in the perfusion territory of a coronary lesion showing a FFR value of <0.75. In addition, concordance was also present when no ischaemic changes were observed in coronary lesions with FFR values ≥0.75.
STATISTICAL ANALYSIS
Statistical analysis was performed with a commercially available software package (SPSS, version 20.0, for Windows; SPSS, Inc.). Quantitative variables are expressed as means±SD and categorical variables as frequencies, or percentage. Quantitative data were compared using an unpaired two-tailed Student’s t-test or the Mann-Whitey U-test where appropriate. Categorical data were compared using the Chi-squared test and one-way analysis of variance to compare baseline characteristics and end-points.

Table 1. General patient characteristics in relation to the SPECT result

<table>
<thead>
<tr>
<th></th>
<th>Ischaemic SPECT (n=31)</th>
<th>Non-ischaemic SPECT (n=69)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±8</td>
<td>65±12</td>
<td>0.412</td>
</tr>
<tr>
<td>Male gender</td>
<td>58</td>
<td>43</td>
<td>0.200</td>
</tr>
<tr>
<td>Prior infarction or revascularization</td>
<td>30</td>
<td>39</td>
<td>0.413</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>20</td>
<td>19</td>
<td>0.867</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47</td>
<td>24</td>
<td>0.027</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>57</td>
<td>69</td>
<td>0.253</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70</td>
<td>66</td>
<td>0.676</td>
</tr>
<tr>
<td>Family history</td>
<td>53</td>
<td>60</td>
<td>0.536</td>
</tr>
<tr>
<td><strong>Current cardiac medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>73</td>
<td>79</td>
<td>0.568</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>77</td>
<td>80</td>
<td>0.708</td>
</tr>
<tr>
<td>ACEi / ARB</td>
<td>57</td>
<td>59</td>
<td>0.860</td>
</tr>
<tr>
<td>Statin</td>
<td>67</td>
<td>74</td>
<td>0.437</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>141±22</td>
<td>136±18</td>
<td>0.359</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>84±17</td>
<td>81±14</td>
<td>0.946</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68±12</td>
<td>66±12</td>
<td>0.707</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30±5</td>
<td>28±4</td>
<td>0.054</td>
</tr>
</tbody>
</table>

Data are percentages or mean±standard deviation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
CZT SPECT versus FFR

Results

The mean age of the patients was 64±11 years, 64% were men and the mean body mass index (BMI) was 28±5 kg/m². The prevalence of coronary risk factors was high as 31% of patients had diabetes, 65% had hypercholesterolaemia and 67% had hypertension. CZT SPECT demonstrated ischaemia in 31% (31) of the patients. Patients with ischaemia had a higher prevalence of diabetes but other general characteristics were comparable between the two groups (Table 1). FFR values ranged from 0.44 to 0.99 with a mean value of 0.83±0.09. The FFR was <0.75 in 20 patients. Differences between patients with and without FFR values <0.75 are shown in Table 2. Patients with FFR <0.75 were often men and less often had hypertension; all other general characteristics were comparable between the two groups. FFR was measured in 128 lesions.

| Table 2. General patient characteristics in relation to FFR |
|-----------------------------------|-----------------------------------|-----------------|
|                                   | FFR <0.75 (n=20)                  | FFR ≥0.75 (n=80) | \( p \) value |
| Age (years)                       | 66±11                             | 66±11           | 0.793         |
| Male gender                       | 75                                | 41              | 0.007         |
| Prior infarction or revascularization | 30                              | 38             | 0.532         |
| Cardiovascular risk factors       |                                   |                 |               |
| Current smoking                   | 25                                | 18             | 0.444         |
| Diabetes                          | 25                                | 33             | 0.517         |
| Hypercholesterolaemia             | 40                                | 71             | 0.009         |
| Hypertension                      | 50                                | 71             | 0.071         |
| Family history                    | 50                                | 60             | 0.418         |
| Current cardiac medication        |                                   |                 |               |
| Aspirin                           | 70                                | 79             | 0.406         |
| Beta-blocker                      | 80                                | 79             | 0.902         |
| ACEi / ARB                        | 55                                | 59             | 0.761         |
| Statin                            | 60                                | 75             | 0.181         |
| Blood pressure (mmHg)             |                                   |                 |               |
| Systolic                          | 142±20                            | 137±20         | 0.168         |
| Diastolic BP                      | 87±17                             | 81±15          | 0.033         |
| Heart rate (bpm)                  | 67±12                             | 67±12          | 0.750         |
| BMI (kg/m²)                       | 29±5                              | 28±4           | 0.911         |

Data are percentages or mean±standard deviation.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
According to FFR, 20% (20) of the patients were considered to have ischaemia. On a per-patient basis, there was concordance between SPECT and FFR in 73% (Fig. 1). On a per-vessel basis, the concordance between SPECT and FFR was 79%. The concordances between SPECT and FFR on a per-patient basis and on a per-vessel basis were 70% and 76%, respectively, using a cut-off FFR value of <0.80 for abnormality.

The mean FFR in patients with ischaemic SPECT was 0.77±0.12 as compared to 0.83±0.07 in patients without ischaemia on SPECT ($p=0.001$). Patients with discordant findings were older (69±9 years vs. 64±11 years, $p=0.043$), but other general characteristics were comparable. Among the 27 patients with discordant findings 7 were found to have serial stenoses, and 20 had a focal stenosis. Also after reviewing images after FFR measurement, there remained clear differences between SPECT and FFR (Fig. 2). Patients with abnormal FFR values without ischaemia on SPECT were less likely to have hypertension (25% vs 71%, $p=0.015$). In contrast, CZT SPECT showed ischaemia in 19 patients with FFR values $\geq 0.75$. These patients had a higher BMI (31±5 vs. 28±4, $p=0.027$).

All patients with concordant ischaemic SPECT and abnormal FFR findings underwent subsequent coronary revascularization. None of the patients with concordant non-ischaemic SPECT and FFR findings underwent coronary revascularization. Seven of eight patients with discordant abnormal FFR values without
CZT SPECT versus FFR

ischaemia on SPECT underwent coronary revascularization. Six of 19 patients with discordant ischaemic SPECT with FFR values ≥0.75 (all with FFR value <0.80) underwent coronary revascularization.

Fig. 2. Discordance between nonischaemic stress-rest CZT SPECT perfusion images and FFR positivity of a lesion of the left anterior descending coronary artery (FFR 0.61) in a patient with single-vessel disease.
Discussion

In this observational study in 100 patients with stable angina and intermediate anatomical coronary lesions without previously detected ischaemia, only 20–30% had ischaemia as assessed by either CZT SPECT imaging or invasive FFR measurement. The concordance between CZT-based SPECT and FFR was comparable with previous results with conventional SPECT cameras. Discordance was most often the result of abnormal SPECT but normal FFR (19%) and less frequently the result of normal SPECT with abnormal FFR (8%).

MPI is the best validated non-invasive imaging modality, has proven diagnostic and prognostic value, and may be a gatekeeper in patients with intermediate risk stable angina [1-3]. The recently introduced CZT camera may produce better image quality with reduced acquisition times and lower tracer doses because of improved count sensitivity and image contrast [4-12]. However, the performance of the CZT camera has been less well studied than that of the conventional camera. In particular, it is not yet known how well results with the CZT camera agree with those from invasive measuring of the severity of a coronary stenosis. Of course, because SPECT and FFR are two different methods, there will always be discordance between them [17]. The rate of discordance of relative MPI PET imaging was found to be 27%, but quantitative PET analysis with absolute myocardial blood flow quantification had a substantially higher concordance rate of 92% [21]. These results together suggest an intrinsic factor as the main cause of discordance between FFR and MPI by either SPECT or PET. This can be easily understood as MPI provides a measure of relative tissue perfusion, which is physiologically quite different from a poststenotic pressure difference in an epicardial vessel. This may also provide an explanation as to why discordances are usually the result of ischaemic SPECT (tissue) with limited stenotic pressure difference.

In addition, both FFR and SPECT have limitations. FFR may be less accurate in patients with collateral circulation, serial stenoses, microvascular disease, prior myocardial infarction, elevated central venous pressure or left ventricle hypertrophy [16,22]. SPECT may be more difficult in obese patients and CT-based attenuation correction may result in improved images [23,24]. Furthermore, discordant findings have been found more often in patients with multivessel disease [25,26]. Melikian et al. studied the correlation between SPECT and FFR in patients with multivessel disease and found concordance in 61% on a per-patient basis [26]. They concluded that SPECT tends to ‘underestimate’ or ‘overestimate’ the functional importance of coronary
stenotheses using FFR as the reference test. However, it should be emphasized again that this reference test (FFR) was initially validated against non-invasive tests including thallium SPECT imaging in which discordant results have also been reported in single-vessel disease (22%) [13]. Unfortunately, the clinical significance of such discrepant findings is not yet known.

An important finding in our study was that only 20–30% of patients had ischaemia as assessed by either CZT SPECT or invasive FFR, confirming previous observations [27]. Several studies have shown only an improved clinical outcome after revascularization in patients with proven functionally relevant CAD based on SPECT or FFR, while coronary interventions can be safely deferred in patients without ischaemia [28-31]. However, despite guidelines and recommendations, approximately half of the patients referred for elective coronary revascularization have no objective proof of ischaemia [32-34]. Although both SPECT and FFR may independently provide information about ischaemia, it remains unknown which technique is better for determining whether revascularization should be performed. Despite this uncertainty, FFR measurement is considered by many cardiologists to be the most accurate test for depicting ischaemia, while also providing additional prognostic information [16,28-31]. Therefore, FFR plays a major role in patient selection for coronary revascularization, especially in those with intermediate coronary stenoses with undetermined functional significance. However, the invasive nature of FFR measurement accompanies a non-negligible risk with incremental procedure times. It also adds significant costs with a low diagnostic yield in patients with intermediate degree coronary stenosis [29], as also shown in this study.

Our study had several limitations. Although the study sample was larger than in many previous studies, the study cohort was too small to perform subanalyses in specific patient groups. Furthermore, with our sample size it was not possible to perform long-term follow-up, to determine whether specific patients (such as those with abnormal FFR but normal SPECT) have a different prognosis. Another limitation was that seven of the study patients selected had serial stenoses, and therefore we cannot exclude the possibility that results may be different in a less selected patient population. We did not compare the results obtained using the CZT camera with those obtained using a conventional camera in our patients. Also, comparison of the results obtained using other non-invasive methods of ischaemia detection, such as PET or MR perfusion, could have been of value. In addition, only a small number of patients in our study had an abnormal FFR and the presence of microvascular disease in our patients cannot be excluded. Finally, the potential impact of attenuation correction in CZT SPECT imaging was not assessed. As long as no single test can be considered a perfect
gold standard, long-term outcome studies are warranted, particularly in patients with discrepant SPECT and FFR findings.

**Conclusion**

In only 20–30% of patients with intermediate coronary stenosis was the stenosis functionally relevant as assessed by CZT SPECT or invasive FFR. CZT SPECT and FFR were concordant in 73% on a per-patient basis and in 79% on a per-vessel basis, which is comparable with previous results with conventional SPECT cameras. Findings were most discordant in patients with ischaemia on SPECT but normal FFR. Further investigations are necessary particularly in patients with normal SPECT and abnormal FFR, especially to determine whether these patients should have revascularisation.
References


CZT SPECT versus FFR

CHAPTER 4

Prevalence and predictors of bridging of coronary arteries in a large Indonesian population, as detected by 64-slice computed tomography scan

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Yahya B. Juwana
Menko-Jan de Boer
Harry Suryapranata

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Abstract

**Background:** Coronary computed tomography angiography (CCTA) can be used to detect myocardial bridging (MB) of coronary arteries. However, most published studies included small cohorts and did not collect data about predictors. We investigated prevalence and predictors of MB in an Indonesian population.

**Methods:** All patients who had CCTA at Cinere Hospital, Jakarta, Indonesia between 2006 and 2009 were included in a prospective registry. MB was defined when at least half of the coronary artery was imbedded within the myocardium with a normal epicardial course of the proximal and distal portion.

**Results:** Of the 934 patients (mean age 53 years, 37.8% female), MB could be observed in 152 patients (16.3%). Patients with MB were younger compared with those without MB. Coronary risk factors were not different between the two groups. Coronary calcifications and moderate to severe coronary stenoses were less prevalent in patients with MB, also after adjusting for differences in age. At the time of diagnosis, only a few patients with MB were treated with beta-blockers (35%) or calcium-channel blockers (13%).

**Conclusions:** Prevalence of myocardial bridging as detected by CCTA is relatively high. Patients with MB were younger and had a lower prevalence of coronary sclerosis. MB could be the cause of their unexplained symptoms. Follow-up studies are necessary to assess the symptoms of these patients, their response to treatment and the incidence of (coronary) events. CCTA can be used to identify patients for potential new treatment strategies.

Introduction

Although mortality and morbidity of coronary artery disease is usually caused by atherosclerotic processes, congenital anomalies of coronary arteries may also cause symptoms in a subset of patients. Myocardial bridging (MB) of coronary arteries is caused by muscles overlying the intramyocardial course of an epicardial coronary artery. It is characterised by systolic compression of the tunnelled segment, commonly affecting the mid-portion of the left anterior descending coronary artery (LAD). Although, in general, MB is a benign condition, it may cause symptoms as chest pain and has been associated with impairment in endothelium-dependent vasorelaxation [1]
and clinical events such as myocardial infarction [2]. The deep intramural LAD has even been associated with sudden death [3].

Previously, the diagnosis of MB was made by coronary angiography with a typical angiographic ‘milking effect’. Also intravascular ultrasound (IVUS) and intracoronary Doppler (ICD) can be helpful in diagnosing the severity of MB [4]. Interestingly, IVUS studies have shown that despite the strong association between MB and endothelial dysfunction, bridging segments are relatively spared from atherosclerotic plaque formation [5]. However, non-invasive imaging may detect the existence of MB even better than coronary angiography with lower risks for general patients [6,7]. Although there are now several publications on MB in patients who underwent coronary computed tomography angiography (CCTA) of the heart, most studies had a small sample size (<300–400). Furthermore, most studies did not collect data on predictors or risk factors [8,9]. Data about prevalence and predictors in an Indonesian population are not available. The aim of our study was to assess the prevalence and predictors of MB in a large cohort of consecutive patients who had undergone CCTA at a non-university hospital in Indonesia.

Methods

All consecutive patients who were referred to our hospital for non-invasive angiography of coronary arteries by CCTA for suspected or known coronary artery disease were eligible for this prospective registry. At baseline, eligible patients completed a questionnaire on current medication use and risk factors for coronary artery disease. Height, weight, blood pressure and pulse were measured. In addition, data on treadmill ECG stress testing performed before the CCTA examination were collected when available.

CCTA IMAGING

A beta-blocker was administered to all patients with a heart rate over 65 beats/min (metoprolol 100 mg orally or 5 to 10 mg intravenously, 1 hour or immediately before scanning, respectively). A coronary computed tomographic angiography was obtained with a 64-slice multidetector CT scanner (Brilliance 64, Philips Medical Systems). Non-enhanced CT for calcium scoring was performed from 1 cm below the level of the tracheal bifurcation to the diaphragm in a craniocaudal direction. Contrast medium (Iopamiro 370/100) of 100 ml was injected intravenously at a rate of 5–6 ml/s.
CCTA Analysis

The CCTA data were analysed by an experienced cardiologist at the site (JW) and independently also by second investigators. If the diagnoses were different, the pictures were re-assessed. Disagreement was solved by a consensus reading.

The calcium scoring study was evaluated using an established analysis program (Heartbeat-CS, EBW, Philips Medical Systems). Agatston scores were determined and recorded on case report forms. Using retrospective electrocardiographic gating, reconstructions were performed routinely at 75% phases of the R-R interval period. Depending on the coronary morphology and quality of the scan other phases were applied to assess the coronary arteries. Analysis of scans was performed on a dedicated workstation (Philips Extended Brilliance Workspace). The dataset was evaluated in terms of contrast opacification, assessability, stenoses and plaques. Coronary arteries were assessed using axial and multi-planar reconstructions. Coronary stenosis was graded according to severity. Coronary stenosis was defined as absent (no coronary stenosis), mild stenosis (<40%), moderate stenoses (40–70%) and severe stenosis (>70%).

MB was defined when at least half of the coronary arterial diameter was imbedded within the myocardium and with the proximal and distal portions of the coronary artery coursing through epicardial fat. Arterial segments located in a deep gorge but covered only by a thin layer of muscle or fibrous-fatty tissue were included because it was reported that they may also be compressed during systole by the surrounding muscle.

The length and depth of the MB was measured: depth was defined as the diameter of the coronary artery in the MB plus the muscle width.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0.1). Continuous data were expressed as mean±standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by Student’s t-test and the Chi-squared or Fisher’s exact test were used as appropriate for dichotomous data. Binary logistic regression analysis was performed to test the independent association between several characteristics and MB. Analysed variables that were significant are reported with their respective odd ratios and 95% confidence intervals. For all analyses, statistical significance was assumed when the two-tailed probability value was <0.05.
Prevalence and predictors of myocardial bridging

Table 1. Coronary location of myocardial bridging in 152 patients as measured by 64-slice CCTA

<table>
<thead>
<tr>
<th>Location of bridging</th>
<th>% (n=152)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal LAD</td>
<td>13.2</td>
</tr>
<tr>
<td>Mid LAD</td>
<td>77.6</td>
</tr>
<tr>
<td>Distal LAD</td>
<td>9.2</td>
</tr>
<tr>
<td>Proximal RCX</td>
<td>0.7</td>
</tr>
<tr>
<td>Mid RCX</td>
<td>2.6</td>
</tr>
<tr>
<td>Distal RCX</td>
<td>2.6</td>
</tr>
<tr>
<td>RCA</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate branch</td>
<td>2</td>
</tr>
</tbody>
</table>

* Some patients had MB on more locations.
LAD, left anterior descending coronary artery; RCX, ramus circumflexus; RCA, right coronary artery.

Results

During the study period, a total of 934 patients were referred to our hospital for CCTA imaging. Mean age was 53 years (range 23–82), 37.8% were female and 13.4% had diabetes. Mean systolic blood pressure before CCTA was 132 mmHg (±18.4) and mean diastolic blood pressure 82 mmHg (±10.7). Beta-blockers were used by 43% of patients and 13% of the patients used calcium antagonists. MB could be observed in 152 patients (16.3%). The distribution of the coronary location of MB is listed in Table 1. The majority of MB was located in the LAD, particularly in the mid-LAD. There were no patients with MB of the right coronary artery (RCA).

Differences between patients with and without MB are summarized in Table 2. Patients with MB were younger than those without MB. There were no differences in traditional coronary risk factors, including diabetes, smoking, dyslipidaemia and hypertension, between patients with and without MB. The clinical symptoms were comparable between the two patient groups. There were significant differences in the prevalence of atherosclerosis between patients with and without MB. Coronary sclerosis as assessed by coronary calcification was less prevalent in patients with MB and the presence of moderate to severe coronary stenoses was also significantly lower in this patient group (Tables 2 and 3). After adjustments for age, MB was still strongly associated with a lower prevalence of moderate to severe coronary stenoses (HR 0.37; 95%CI: 0.22–0.61, p< 0.001).
Table 2. Differences between patients with and without bridging as measured by 64-slice CCTA

<table>
<thead>
<tr>
<th></th>
<th>Without bridging (n=782)</th>
<th>With bridging (n=152)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.6±11.0</td>
<td>51.3±9.3</td>
<td>0.015</td>
</tr>
<tr>
<td>BMI</td>
<td>25.9±4.1</td>
<td>25.9±3.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
<td>60%</td>
<td>0.62</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132±18</td>
<td>129±19</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82±10</td>
<td>81±12</td>
<td>0.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.5%</td>
<td>13.2%</td>
<td>0.91</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>35%</td>
<td>37.5%</td>
<td>0.57</td>
</tr>
<tr>
<td>High lipids</td>
<td>44%</td>
<td>51%</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28%</td>
<td>24%</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking</td>
<td>21%</td>
<td>16%</td>
<td>0.18</td>
</tr>
<tr>
<td>Complaints for referral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>46%</td>
<td>40%</td>
<td>0.21</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.3%</td>
<td>4.3%</td>
<td>0.24</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>9.9%</td>
<td>10.7%</td>
<td>0.79</td>
</tr>
<tr>
<td>Palpitations</td>
<td>10.6</td>
<td>9.2</td>
<td>0.64</td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>18.5</td>
<td>21.8</td>
<td>0.40</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>44.6</td>
<td>35</td>
<td>0.05</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>19</td>
<td>13</td>
<td>0.11</td>
</tr>
<tr>
<td>Total calcium score</td>
<td>152±423</td>
<td>127±769</td>
<td>0.57</td>
</tr>
<tr>
<td>Calcium score = zero</td>
<td>50%</td>
<td>62%</td>
<td>0.007</td>
</tr>
<tr>
<td>Calcium score &gt;400</td>
<td>11%</td>
<td>3%</td>
<td>0.003</td>
</tr>
<tr>
<td>Moderate / severe stenosis</td>
<td>34.0%</td>
<td>14.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Of the 934 patients, 668 (72%) underwent treadmill ECG stress testing because of suspected coronary artery disease prior to referral for non-invasive coronary angiography by CT, of whom 181 (27%) had a positive ECG stress test. Treadmill ECG stress test was positive for ischaemia in 34 of 119 patients (29%) with MB compared with 147 of 549 patients (27%) without MB (p=0.69).
Prevalence and predictors of myocardial bridging

Table 3. Percentage of moderate and severe stenosis in patients with and without bridging as measured by 64-slice CT scan

<table>
<thead>
<tr>
<th></th>
<th>Without bridging (n=782)</th>
<th>With bridging (n=152)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate stenosis</td>
<td>22.4</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>6.7</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>RCX</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Moderate stenosis</td>
<td>7.7</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>2.4</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Moderate stenosis</td>
<td>9.2</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>5.3</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; RCX, ramus circumflexus; RCA, right coronary artery.

Discussion

In this large cohort, it is demonstrated that CCTA is an easy and reliable tool for comprehensive in vivo diagnosis of the intramuscular course of coronary arteries. We found a prevalence of MB as detected by CCTA of 16.3%. Patients with MB were younger than those without MB. There were no differences in coronary risk factors or stress testing results between patients with and without MB, but the prevalence of coronary artery disease was higher. After adjustments for differences in age, patients with MB still had less coronary stenoses.

Previous studies

The estimated frequency that has been reported varies from 1.5 to 16% when assessed by coronary angiography, but in some autopsy series, it is as high as 80% [10,11]. Kramer et al. reviewed 658 normal coronary angiograms of patients with normal left ventricular function and found that 81 (12%) had a myocardial bridge of the LAD [12]. In a larger study, assessing 7467 consecutive coronary angiograms, only 61 (<1%) of the patients had a myocardial bridge of the LAD [13].
A few studies investigated the association between traditional coronary angiography and CCTA in detecting MB [6,7,14]. It was shown that the diagnosis of MB was more often made with CCTA, suggesting that CCTA is superior to traditional angiography although differences in the definition of MB may play a role. With CCTA, different prevalences of MB have been reported (Table 4), ranging from 5.7% to 33% [6-8,14-32].

We did not find MB in the RCA in any of our patients. Although MB of RCA has been described [33], it is probably very rare.

<table>
<thead>
<tr>
<th>First author [reference]</th>
<th>Number of patients</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu [7]</td>
<td>53</td>
<td>30.2</td>
</tr>
<tr>
<td>De Rosa [8]</td>
<td>242</td>
<td>18.7</td>
</tr>
<tr>
<td>Lubarsky [9]</td>
<td>300</td>
<td>33</td>
</tr>
<tr>
<td>Kim [14]</td>
<td>311</td>
<td>58.0</td>
</tr>
<tr>
<td>Cademartiri [15]</td>
<td>543</td>
<td>10.9</td>
</tr>
<tr>
<td>Ko [16]</td>
<td>401</td>
<td>5.7</td>
</tr>
<tr>
<td>Konen [17]</td>
<td>118</td>
<td>30.5</td>
</tr>
<tr>
<td>Kawawa [18]</td>
<td>148</td>
<td>15.8</td>
</tr>
<tr>
<td>Johansen [19]</td>
<td>152</td>
<td>32.2</td>
</tr>
<tr>
<td>Jacobs [20]</td>
<td>506</td>
<td>10.5</td>
</tr>
<tr>
<td>Wang [21]</td>
<td>51</td>
<td>54.9</td>
</tr>
<tr>
<td>Duran [22]</td>
<td>725</td>
<td>4.0</td>
</tr>
<tr>
<td>Kantarci [23]</td>
<td>626</td>
<td>3.5</td>
</tr>
<tr>
<td>Hwang [25]</td>
<td>1275</td>
<td>42.0</td>
</tr>
<tr>
<td>Koşar [26]</td>
<td>700</td>
<td>37.0</td>
</tr>
<tr>
<td>La Grutta [27]</td>
<td>277</td>
<td>29.6</td>
</tr>
<tr>
<td>Rodriguez-Granillo [28]</td>
<td>577</td>
<td>17.3</td>
</tr>
<tr>
<td>Liu [29]</td>
<td>3011</td>
<td>5.8</td>
</tr>
<tr>
<td>Atar [30]</td>
<td>169</td>
<td>17</td>
</tr>
<tr>
<td>Kim [31]</td>
<td>607</td>
<td>6</td>
</tr>
<tr>
<td>Chen [32]</td>
<td>276</td>
<td>8.7</td>
</tr>
</tbody>
</table>
Prevalence and predictors of myocardial bridging

MYOCARDIAL BRIDGING AND CORONARY LESIONS
In our study, the number of stenoses in the different coronary arteries was lower in patients with MB. There may be several explanations for these findings. Patients with MB were younger. However, after correction for age the association between bridging and a lower prevalence of coronary artery disease remains evident. Another explanation might be that MB was responsible for chest pain complaints, which led to the decision to perform a CCTA. In patients without MB, coronary artery disease as a cause for chest pain complaints is more likely. An alternative explanation could be that MB might be protective for the development of coronary artery disease. Several pathology studies have been performed assessing the extent of atherosclerosis, particularly within the bridge, in patients with MB [34]. Altogether, the data suggest that MB is associated with the decreased development of atherosclerosis under and proximal to the tunnelled artery, although it is unclear whether this is an independent factor [35]. It seems that MB located within 5 cm from the left coronary ostium may prevent atherosclerosis in the proximal part of LAD [36].

MYOCARDIAL BRIDGING AND STRESS TESTING
Although several prior studies have assessed the frequency of MB detected by invasive angiography and CCTA, only limited data are available describing the relationship between MB and non-invasive stress test results. In our study, 29% of the patients with MB had a positive exercise stress test, which is in line with previous work by Bourassa et al. [37], who reported ischaemic ECG findings in 28–67%. However, higher rates were found by others, especially in the presence of left ventricular hypertrophy or severely bridged coronary segments [38,39].

TREATMENT
It may be difficult to decide what to do with patients with MB as diagnosed by CCTA, particularly if they have symptoms. In general, therapeutic approaches that have been attempted for myocardial bridging include beta-blockers, calcium-channel blockers, stents, coronary artery bypass grafting (CABG), percutaneous coronary interventions (PCI) and surgical myotomy. In a small study (n=29), it was shown that coronary stent placement for medically refractory symptomatic myocardial bridging failed to relieve severe angina and was associated with high clinical restenosis [40]. In emergency situations, as in patients with myocardial infarction due to occlusion of the coronary vessel at the site of MB, percutaneous coronary intervention can be performed [41].
Nitrates should be avoided because they may increase the angiographic degree of systolic narrowing and can lead to worsening of the symptoms. Until now, no specific treatments have been proven to be beneficial in randomised controlled trials. It is possibly that now more patients have a diagnosis of MB, as demonstrated by non-invasive imaging, randomised controlled trials will be performed with as endpoint both clinical events and symptoms.

LIMITATIONS
We have no follow-up data of our patients and did not perform routine invasive coronary angiography. We have no specific data with regard to the location of coronary stenosis in relation to the location of myocardial bridging. Furthermore, the presence of inducible ischaemia on myocardial perfusion imaging was not assessed and we did not study the relationship between the depth of the bridges and the severity of complaints.

Although we describe a large cohort, we could not perform subgroup analyses, such as in females or those with hypertension.

Conclusions
CCTA offers a good possibility to diagnose MB. The prevalence is about 16%. Patients with MB may appear to have a lower prevalence of coronary stenosis, but this should be confirmed in other studies. Also, follow-up studies should be performed to find subsets of patients with MB who are at risk of complications. Finally, randomised controlled trials are necessary to assess which treatment should be given.
References

Prevalence and predictors of myocardial bridging


CHAPTER 5

Cardiac hybrid SPECT/CT imaging in patients with suspected coronary artery disease: clinical evaluation of a stepwise algorithm

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Jorik R. Timmer
Stoffer Reiffers
Ad H.J. Oostdijk
Siert Knollema
Pieter L. Jager

Submitted
Abstract

**Purpose:** Hybrid cardiac imaging with single photon emission computed tomography (SPECT) combined with coronary CT angiography (CCTA) allows detection of anatomical coronary abnormalities and their physiologic consequences in a single setting offering improved diagnostic information. We aimed to prospectively assess the feasibility of a single-day individualized stepwise approach for hybrid SPECT/CT imaging in consecutive stable patients with suspected coronary artery disease (CAD).

**Methods:** Between January 2009 and July 2011 a total of 2411 patients without known CAD were referred for hybrid SPECT/CT imaging. Patients underwent initial stress SPECT imaging and coronary calcium scoring. In case of normal perfusion findings further tests were omitted regardless of the calcium score. Additional rest SPECT and CCTA (when feasible) were performed in those with abnormal stress SPECT. In addition, clinical follow-up was recorded with regard to coronary revascularization, nonfatal myocardial infarction and death.

**Results:** Of the 2411 patients (mean age 61±12 years, 43% male) calcium scoring was performed in 2339 (97%) and 53% had normal stress SPECT findings in whom additional testing could be omitted. Among the 1144 patients who underwent additional rest imaging, SPECT was still considered to be normal in 555 patients (49%). Additional CCTA was performed in 618 patients (26%) ruling out obstructive CAD in 73% of patients with abnormal SPECT findings, including 50% of the patients with ischaemic SPECT results. After a median follow-up of 29 months (25th–75th percentile 18–38), annual cardiac event rate was 0.5% for the stress-only group, 3.4% for patients who underwent additional rest imaging without CCTA, and 4.8% for patients who underwent complete SPECT with CCTA imaging \( (p<0.001) \).

**Conclusions:** Our individualized approach, using flexible SPECT/CT imaging provides both anatomical and functional information in a single session. This method can be preferred over methods employing SPECT alone, CCTA alone, or a fixed combination of stress/rest SPECT and CCTA in all patients. Moreover, in this approach SPECT and CCTA seem to compensate each other’s shortcomings.

Introduction

Accurate detection of functionally relevant coronary artery disease (CAD) remains a challenging task. Therefore, great efforts have been made to develop new non-invasive
approaches for imaging. Stress myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) is an established method for assessment of the functional significance of coronary stenoses and risk stratification, although it does not give anatomical information for targeting revascularization [1-3]. More recently, coronary computed tomography angiography (CCTA) is increasingly being used as an alternative diagnostic tool allowing visualisation of the coronary arteries and stenosis with a high negative predictive value (NPV) although it does not provide functional information on lesion severity [4,5].

With the recent advent of hybrid SPECT/CT devices, attenuation corrected MPI scans can be complemented with anatomical information obtained from coronary artery calcium scoring (CACS) and CCTA in a single session [6]. The improved diagnostic and prognostic performance of hybrid SPECT/CT imaging has the potential to enable a more appropriate selection of patients who may benefit from revascularization [7-9]. For overall clinical effectiveness and minimization of the total cost and radiation dose a sequential diagnostic approach seems most practical for clinical practice. However, clinical data are limited [10]. Therefore, the aim of the present study was to prospectively assess the feasibility of an individualized stepwise approach for hybrid SPECT/CT imaging starting with low-dose stress SPECT and CACS as initial screenings tests in consecutive new stable patients with suspected CAD.

Materials and methods

STUDY POPULATION
From January 2009 to July 2011, a total of 2411 consecutive patients with suspected but unconfirmed CAD, and a low to intermediate pre-test likelihood for CAD according to Diamond and Forrester criteria [11], underwent SPECT/CT imaging using an individualized stepwise decision algorithm. Patients were referred from the cardiology outpatient clinics of our hospital, which is a large cardiovascular center with a local, regional, and supraregional catchment area. The aim of this algorithm was to provide a comprehensive patient-tailored assessment of possible CAD in each patient in a single day. Results allowed rapid selection of appropriate treatment or discharge. From January 2009 until April 2010, patients (n=977) were scanned on a conventional SPECT/CT camera (Ventri-LightSpeed VCT XT, GE Healthcare), and from May 2010 until July 2011, patients (n=1434) were scanned with a cadmium zinc telluride (CZT)-based SPECT/CT camera (Discovery NM/CT 570c, GE Healthcare).
We applied an individualized approach starting with low-dose stress SPECT and assessment of the CACS as initial screenings tests in all patients. After acquisition and post-processing, data were immediately analyzed by two experienced nuclear cardiology reviewers. In case of unequivocally normal stress perfusion further tests were omitted regardless of the CACS. All patients with equivocal or abnormal stress perfusion were referred for rest SPECT with or without CCTA. However, CCTA was only performed in case of a suitable CACS and absence of any contra-indications. The CACS was considered suitable when <1000 in the absence of large clustered calcified segments. At the end of the day, the same reviewers evaluated all performed tests and a final conclusion was drawn. All procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients.

CLINICAL INFORMATION
At the time of examination, all patients completed a questionnaire regarding demographic information, prior medical history, cardiac risk factors and current medication use. These data were verified and complemented with demographic and clinical information collected from medical records. Furthermore, information regarding patient age, gender, weight, height, blood pressure, heart rate and symptoms were prospectively obtained by a medical nurse. Pre-test likelihood of CAD was assigned according to Diamond and Forrester criteria, with a risk threshold of <13.4% for low risk, between 13.4 and 87.2% for intermediate risk, and >87.2% for high risk [11].

SPECT-MPI DATA ACQUISITION
All patients underwent a 1-day $^{99m}$Tc-Tetrofosmin MPI protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. Pharmacologic stress was induced by intravenous administration of adenosine (continuous infusion at a rate of 140 μg/kg/min for 6 minutes) or dobutamine in case of contra-indication for adenosine (starting with 10 μg/kg/min and increased at 3-minute intervals to a maximum of 50 μg/kg/min until 85% of the predicted heart rate had been reached). Whenever possible, patients performed additional low-level bicycle exercise to reduce side-effects of adenosine. ECG and blood pressure were monitored before, throughout, and following the infusion. A weight-adjusted dose of $^{99m}$Tc-Tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. Patients scheduled for rest imaging received a dose of $^{99m}$Tc-
Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). For both, stress and rest SPECT images were acquired 45–60 min after tracer injection.

On the conventional dual-detector gamma camera (Ventri, GE Healthcare), images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 x 64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals over a 180° arc (45° anterior oblique to 45° left posterior oblique) with 30 steps (30 views). All patients were imaged in supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images.

The CZT-based SPECT images were acquired using a multi-pinhole camera (Discovery NM/CT 570c, GE Healthcare) and 19 stationary detectors simultaneously imaging the heart. Each detector contained 32 x 32 pixelated (2.46 x 2.46 mm) CZT elements. A 20% symmetrical energy window at 140 keV was used as previously described [12]. All patients were imaged in supine position with arms placed above the head. Acquisition time was 5 minutes for the stress images and 4 minutes for the rest images [12]. Gated SPECT analysis to calculate left ventricular volumes, ejection fraction and to assess wall motion abnormalities was done in nearly all patients when feasible, usually at stress but in some cases at rest. In all 2411 patients, stress and rest SPECT studies were followed by an unenhanced low-dose CT scan during a breath-hold to provide the attenuation map for attenuation correction. These scans covered the entire chest with scanning parameters: 5.0-mm slice thickness using a reconstruction algorithm with a 512 x 512 matrix, and 800 ms rotation times at 120 kV and 20 mA.

Emission images as well as attenuation map data were entered in a dedicated reconstruction algorithm to provide 3D volume data (available in a Xeleris workstation, GE Healthcare). These were reorientated in the standard way and displayed in the three traditional cardiac axes.

SPECT MPI ANALYSIS
Two experienced nuclear cardiac readers interpreted the images including MPI polar maps. Segments were scored by consensus of two readers using a 17-segment model for the left ventricle using following five-point scoring system (0, normal; 1, mild; 2, moderate; 3, severe reduction in radiotracer uptake; and 4, absence of detectable tracer in a segment) [13,14].

Perfusion defects were identified on the stress images (a segment with a score ≥2 was considered to have a defect). A stress study was interpreted as normal if perfusion was assessed to be homogeneous throughout the myocardium and less than two
segments had stress scores ≥2 [13,14]. Subsequent rest imaging was performed if the stress images did not fulfill these criteria and were therefore deemed to be either abnormal or equivocal. A reversible perfusion defect was defined as one in which a stress defect was associated with a rest score ≤1 or a stress defect score of 4 with a rest score of 2 [13,14]. Reversible defects not meeting these criteria were considered equivocal for ischaemia as previously described [15]. Irreversible defects were considered scar tissue when persistent despite applying CT based attenuation correction together with abnormal wall motions in the corresponding segments [16]. Radiation dose for SPECT MPI was calculated as $^{99m}$Tc-tetrofosmin activity times 7.9 mSv/GBq.

CACS AND CCTA DATA ACQUISITION

All CACS and CCTA scans were acquired using the CT of the integrated SPECT/CT device. All patients with heart rates >70 beats/minute received oral beta-blocker therapy (50 or 100 mg Metoprolol tartrate, Astra Zeneca BV, Zoetermeer, The Netherlands) prior to the CACS scan. If the final heart rate was >70 beats /min, CACS measurement was not performed. For the CACS scans an unenhanced, ECG-gated scan was performed prospectively triggered at 75% of the RR-interval using the following scan parameters: 48 sections and 2.5-mm section thickness; gantry rotation time 330 ms; tube voltage 120 kV; and a tube current ranging from 125 to 250 mA, depending on patient size. Post-processing of the CACS was performed on dedicated workstations (Advantage Windows 4.4, GE Healthcare).

With regard to the CCTA, exclusion criteria were known hypersensitivity to iodinated contrast agents, renal insufficiency or irregular heart rhythms. All patients received a single dose of nitroglycerine (0.4 mg) just before the CCTA scan. If necessary, patients received oral (50 to 200 mg) and/or intravenous beta-blocker therapy (5 to 30 mg) in order to achieve a target heart rate below 65 beats/minute [17]. A scout view of the chest was first obtained, followed by the CT angiographic acquisition using the following parameters; 64 slices per rotation, 0.625 mm detector collimation, gantry rotation time 330 ms, effective temporal resolution 165 ms, spatial resolution 0.4 mm$^3$, tube voltage 100–140 kV (depending on the patient’s body weight), tube current of 450–800 mA. Contrast-enhanced CCTA was acquired with prospective ECG triggering (70%) at 75% of the RR interval or with retrospective data acquisition (30%) with ECG-based tube current modulation (full tube current was applied from 40–80% of the RR interval). All images were acquired during an inspiratory breath hold of approximately 10 to 12 seconds. Effective radiation dose for CCTA was estimated as dose-length product times a conversion coefficient for the chest k (0.017 mSv/mGy/cm).
Stepwise approach for cardiac hybrid SPECT/CT imaging

CACS AND CCTA ANALYSIS
The computer software for coronary calcium scoring (Smart Score, GE Healthcare) automatically defined the presence of calcified lesions as those greater than 130 Hounsfield Units. The total calcium burden in the coronary arteries was manually depicted and allocated to the corresponding coronary artery by an experienced reader using the Agatston method for quantification of the CACS [18].

Image interpretation of the CCTA was performed on axial images, multiplanar and curved reformations, and thin-slab maximum intensity projections. Coronary arteries were subdivided according to a 15-segment model as proposed by the American Heart Association [19]. Each segment was evaluated on at least two planes according to Society of Cardiovascular Computed Tomography guidelines [20], and the degree of diameter stenosis was visually graded by consensus of the two readers. Obstructive CAD was defined when narrowing of the coronary lumen was 50% or greater.

HYBRID IMAGE FUSION
Images of patients who underwent complete SPECT MPI with CCTA could be fused into hybrid three-dimensional SPECT/CT images, using the CardiQ Fusion software package (GE Healthcare) as described in the literature [21]. The use of the fusion software was left to the discretion of the readers.

CLINICAL FOLLOW-UP
Clinical outcome data were obtained by reviewing hospital records, by performing telephone interviews with the patients and by contacting patients’ general practitioners. Event free survival was defined as survival without myocardial infarction or coronary revascularization. The time between the stress test and the date of the final examination or consultation was used to determine follow-up length. Events that where noted during follow-up where death, nonfatal myocardial infarction and unstable angina requiring revascularization. Minimal follow-up time was 1 year for those without an event.

STATISTICAL ANALYSIS
Statistical analysis was performed with a commercially available software package (SPSS, version 20.0 for Windows; SPSS Inc., Chicago, IL, USA). Quantitative variables are expressed as mean±SD and categorical variables as frequencies, or percentages. Quantitative data were compared using an unpaired two-tailed Student’s t-test or the Mann-Whitney U-test where appropriate. Categorical data were compared using Chi-squared test or Fisher’s exact test as appropriate. Differences in event-free
survival over time were analyzed by the Kaplan-Meier method. The log-rank test was used to compare the survival curves. We calculated annualized event rates on the basis of events per patient-year. Two sided \( p \) values of less than 0.05 were considered to indicate a significant difference.

Results

**BASELINE CHARACTERISTICS**

Of the 2411 patients, mean age was \( 61 \pm 12 \) years, 43% were male, 14% were diabetic and the mean body mass index (BMI) was \( 28 \pm 5 \) kg/m\(^2\). The main indications for referral were atypical chest pain and dyspnea. Pre-test likelihood was considered to be low in 212 patients (9%), intermediate in 1738 (72%) and high in 461 patients (19%). Pharmacologic stress was induced by intravenous administration of adenosine in 2339 patients (97%) and by administration of dobutamine in 72 patients (3%). The mean effective radiation dose for the entire cohort was \( 8.9 \pm 5.7 \) mSv. The mean total effective radiation dose in patients who underwent stress-only imaging was \( 4.4 \pm 0.4 \) mSv and \( 14.0 \pm 4.6 \) mSv in patients who underwent additional imaging \( (p<0.001) \).

**Fig. 1.** Additional imaging in patients after stress SPECT and coronary artery calcium scoring

SPECT: single photon emission computed tomography; CACS: coronary artery calcium score; CCTA: coronary computed tomography angiography
IMAGING RESULTS
CACS was assessed in 2339 patients (97%) whereas stress MPI was performed in all patients. In 72 patients (3%) CACS was not assessed because of elevated heart rate. Mean CACS of our cohort was 280±579, median CACS was 35 (interquartile range 0.01–265). A zero CACS was found in 606 patients (26%), 198 patients (9%) had CACS >1000. Stress SPECT revealed unequivocally normal myocardial perfusion findings in 1267 patients (53%). After the initial measurements and evaluation, these patients with normal SPECT were immediately discharged, while the remaining 1144 patients (47%) were scheduled for additional imaging (Fig. 1). Patients who underwent additional testing were more likely to be male, to have more cardiovascular risk factors, higher CACS, higher BMI, were more often scanned with a conventional SPECT camera, and to have more often left bundle branch block (LBBB, Table 1).

Table 1. Comparison between patients with stress-only imaging versus patients requiring additional imaging

<table>
<thead>
<tr>
<th>Total cohort (n=2411)</th>
<th>Stress-only SPECT (n=1267)</th>
<th>Additional testing (n=1144)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59.2±12</td>
<td>62.0±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>36</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15</td>
<td>17</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>43</td>
<td>45</td>
<td>0.455</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59</td>
<td>65</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>48</td>
<td>50</td>
<td>0.746</td>
</tr>
<tr>
<td>Mean number risk factors</td>
<td>1.8±1.1</td>
<td>1.9±1.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>137±21</td>
<td>141±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84±12</td>
<td>83±12</td>
<td>0.323</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±13</td>
<td>71±12</td>
<td>0.015</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>27±4</td>
<td>29±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBBB</td>
<td>1</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine level (μmol/L)</td>
<td>76±45</td>
<td>80±37</td>
<td>0.028</td>
</tr>
<tr>
<td>CACS (mean)</td>
<td>168±428</td>
<td>405±690</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal SPECT</td>
<td>0</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CZT SPECT</td>
<td>71</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are percentages or mean±standard deviation.
SPECT, single photon emission computed tomography; BP, blood pressure; bpm: beats per minute; BMI, body mass index; LBBB, left bundle branch block; CACS, coronary artery calcium score; CZT, cadmium zinc telluride.
Table 2. Comparison between patients with SPECT imaging without CCTA versus patients who underwent complete SPECT with CCTA imaging

<table>
<thead>
<tr>
<th></th>
<th>Stress-rest SPECT, no CCTA (n=526)</th>
<th>Stress-rest SPECT with CCTA (n=618)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.8±12</td>
<td>59.6±11</td>
<td>0.006</td>
</tr>
<tr>
<td>Male gender</td>
<td>40</td>
<td>53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>14</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>13</td>
<td>0.374</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>44</td>
<td>44</td>
<td>0.900</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62</td>
<td>61</td>
<td>0.503</td>
</tr>
<tr>
<td>Family history</td>
<td>49</td>
<td>50</td>
<td>0.743</td>
</tr>
<tr>
<td>Mean number risk factors</td>
<td>1.87±1.1</td>
<td>1.89±1.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139±20</td>
<td>139±19</td>
<td>0.161</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84±12</td>
<td>83±11</td>
<td>0.007</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±13</td>
<td>70±11</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28±5</td>
<td>28±5</td>
<td>0.197</td>
</tr>
<tr>
<td>LBBB</td>
<td>3</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine level (μmol/l)</td>
<td>78±47</td>
<td>76±15</td>
<td>0.016</td>
</tr>
<tr>
<td>CACS (mean)</td>
<td>315±639</td>
<td>180±339</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are percentages or mean ± standard deviation. SPECT: single photon emission computed tomography; CCTA: coronary computed tomography angiography; BP: blood pressure; bpm: beats per minute. BMI: body mass index; LBBB: left bundle branch block; CACS: coronary artery calcium score.

Among all 1144 patients who underwent additional rest SPECT imaging 555 patients (49%) had normal perfusion results and 589 patients abnormal stress-rest SPECT imaging findings. A total of 165 patients (14%) showed irreversible perfusion defects, 203 patients (18%) had equivocally reversible SPECT findings and 221 patients (19%) had findings clearly suggestive for ischaemia.

Additional CCTA was performed in 618 patients referred for rest imaging. Patients who underwent CCTA were more likely to be male and smokers and they had a lower heart rate, lower creatinine values and lower CACS, while they were less likely to have diabetes or hypertension as compared to patients who underwent additional rest SPECT imaging without CCTA (Table 2). Additional CCTA was performed in 351 (60%) of 589 patients with abnormal stress-rest SPECT imaging findings. In the remaining 238 patients CCTA was not performed because of extensive coronary atherosclerosis (n=132), renal insufficiency (n=40), irregular or elevated heart rate (n=38), or the presence of small atypical perfusion defects suspicious for an artefact.
Stepwise approach for cardiac hybrid SPECT/CT imaging

(n=28). In those patients who underwent additional CCTA, the presence of obstructive CAD was ruled in 73% of patients with abnormal SPECT findings, including 50% of the patients with ischaemic SPECT results. Conversely, CCTA revealed obstructive coronary lesions with ≥50% lumen obstruction in 45 of 264 patients (17%) with normal SPECT findings, in 13 of the 101 patients (13%) with persistent SPECT defects, in 24 of 132 patients (18%) with equivocally reversible defects and in 60 of 121 patients (50%) with ischaemic SPECT findings.

FOLLOW-UP

Follow-up was assessed in 2393 patients (99%). The mean follow-up period was 29±12 months (median follow-up 29 months, interquartile range 18–38 months). During follow-up 447 patients (19%) underwent invasive coronary angiography (ICA), 317 patients (13%) early (≤60 days) after non-invasive imaging and 130 patients (5.4%) late (> 60 days). Coronary revascularization was performed in 198 patients (8.2%), including 21 patients from the stress-only group. Nonfatal myocardial infarction occurred in 11 patients (0.5%), including 4 patients from the stress-only group. In total 6 patients (0.2%) died from a cardiac cause, including 2 patients from the stress-only group.

A choice to perform ICA was more common in the group with additional imaging (31%) as compared to patients in the stress-only group (7.1%, p<0.001). In addition, referral for ICA occurred more often in men and in those with diabetes, hypertension or dyslipidaemia, and in patients with abnormal SPECT perfusion results. Of these patients who underwent ICA, obstructive CAD was demonstrated in 29% in the stress-only group versus 54% in the group who underwent additional testing (p<0.001). Coronary revascularization was performed in 21 (1.7%) patients in the stress-only group and in 177 (15%) patients in the additional testing group (p<0.001). Among patients with abnormal perfusion results, coronary revascularization was performed more frequently (32% of the patients) when CCTA was not acquired as compared to patients who underwent additional CCTA (8.4% of the patients, p<0.001). Among the patients with abnormal perfusion results who underwent additional CCTA coronary revascularization during follow-up was performed in 0.8% of the patients (2 of 257) without obstructive CAD at CCTA as compared to 29% (28 of 97) of the patients with obstructive CAD at CCTA (p<0.001).

In patients from the stress-only group, the annual total cardiac event rate was 0.5%, whereas for patients who underwent additional rest SPECT imaging without CCTA and patients who underwent complete SPECT/CCTA imaging, the respective values were 3.4 and 4.8% (p<0.001, Fig. 2).
The annual total cardiac event rates for all patients in our cohort with normal SPECT perfusion results was 0.8%, whereas for patients with equivocal findings and patients with abnormal SPECT results, the respective values were 3.9% and 8.8% \( (p<0.001) \), Fig. 3.

Among patients with normal SPECT perfusion findings, those who underwent stress-only imaging had a lower annual event rate (0.5%) as compared to the patients who required additional rest SPECT imaging (1.5%, \( p=0.003 \)).
Discussion

This large prospective observational study shows that a one-day stepwise algorithm for hybrid cardiac SPECT/CT imaging with additional imaging for patients with equivocal or abnormal findings is feasible and allows an ‘all-in-one’ approach in a single day. Such an approach provides anatomical and functional information in a single-session allowing stress-only imaging with an excellent short-term prognosis in more than half of all patients. Simultaneous CACS in patients referred for MPI has the potential to increase readers’ interpretative certainty [22], provides incremental diagnostic and prognostic information [23-27], and may influence medical treatment strategy [28,29]. Furthermore, this algorithm allows acquisition of an additional CCTA in the same

Figure 3. Kaplan Meier analysis of event-free survival (without coronary revascularization, myocardial infarction and death) based on SPECT results (Log rank $p<0.001$). SPECT: single photon emission computed tomography; CCTA: coronary computed tomography angiography.
setting for patients with equivocal or abnormal MPI findings that has the potential to depict false positive MPI findings [30,31].

Several studies have documented the complementary information provided by CCTA and SPECT MPI. Additional MPI provides functional information about obstructive coronary stenoses found in patients referred for CCTA [10,32,33]. Conversely, CCTA for symptomatic low-intermediate risk patients with abnormal MPI results is able to depict patients without obstructive CAD in whom a potential ICA can be deferred [26,27] and may result in significant cost savings [34]. The improved diagnostic and prognostic performance of hybrid imaging allows a more appropriate patient selection for coronary revascularization [7-10,33].

For overall clinical and economical effectiveness of non-invasive hybrid imaging a sequential diagnostic approach seems most practical for daily clinical practice. Several diagnostic algorithms for hybrid cardiac imaging have been proposed [10,35,36]. However, so far the best initial test remains unknown and may depend on the population studied. The ability to correctly rule out CAD renders CCTA an attractive tool for starting the diagnostic algorithm in low-intermediate risk patients. However, approximately 50% of the patients require additional SPECT or PET perfusion imaging after initial CCTA [10,33]. Furthermore, in clinical practice up to 30% of the segments may be non-evaluable for the readers on CCTA [37,38] and extensive coronary atherosclerosis may hamper a reliable evaluation of coronary lesion severity [39].

Therefore, we have implemented an algorithm starting with stress SPECT and CACS first. In our study, stress SPECT could be assessed in all patients while CACS was feasible in 97%. Interestingly, in 53% of all patients further tests could be omitted after an unequivocally normal stress MPI with an excellent short-term prognosis. This reflects the high NPV for coronary revascularization or hard cardiac events of SPECT, which was demonstrated in earlier studies [1,3]. In our cohort, additional imaging could be more often omitted in younger patients, women, those with a low CACS, those scanned with a CZT SPECT camera, and in patients without diabetes or LBBB. Such patients may benefit from a stress-only SPECT protocol as a potential alternative to CCTA for the exclusion of CAD.

Although complete hybrid imaging with both CCTA and MPI provides optimal diagnostic and prognostic information, the high cumulative effective radiation dose and cost restrict the large scale use in clinical practice. Furthermore, several studies have shown that hybrid imaging provides additional information only in selected patients [10,33]. Recent technical improvements in hardware and software for CCTA and SPECT MPI have enabled high quality imaging with reduced radiation dose [12,40-
As a result, hybrid imaging can now be achieved with an effective radiation dose even lower than that for traditional MPI or retrospectively gated CCTA [44,45]. Similarly, the mean total effective radiation dose per patient in our entire cohort was lower as compared to the average radiation dose associated with traditional stress-rest SPECT MPI [46].

Although our study reflects a real-world experience and all consecutive patients were studied, we have to acknowledge several limitations. First, this was a single centre study in patients without prior CAD predominantly at low or intermediate pre-test likelihood. Therefore, our findings must be read with caution when extrapolating them to other populations. Furthermore, our findings were not externally validated by ICA with fractional flow reserve measurement. However, in a low to intermediate risk population, it could be questioned whether ICA for scientific validation purposes only would be considered ethical. In addition, we obtained clinical follow-up in the cohort in our study with low event-rates for patients with normal SPECT findings. We do, however, recognize that the relatively short follow-up may have resulted in under-reporting of adverse cardiac events. Patient referrals, clinical postimaging medical management and downstream utilization of invasive testing were left to discretion of the treating physicians, each with their own opinions and backgrounds. Therefore it was not standardized and revascularization during follow-up may have been influenced by other factors. We have included a relatively small population relating to a low risk population. Furthermore, appropriate selection of patients in the cohort in our study who would benefit from additional CCTA could have been improved by implementing an additional evaluation immediately after the rest SPECT scan. Finally, we did not perform a head to head comparison with a CCTA first approach and the cost-effectiveness of this algorithm still has to be studied.

Conclusion

We evaluated a one-day stepwise approach for hybrid cardiac SPECT/CT imaging in stable symptomatic low-intermediate risk patients starting with stress MPI and CACS. Such an approach provides anatomical and functional information in a single-session allowing stress-only imaging with an excellent prognosis in more than half of all patients. Acquisition of an additional CCTA for patients with equivocal or abnormal MPI findings has great potential to depict false positive MPI findings improving patient selection for coronary revascularization.
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CHAPTER 6

The influence of coronary calcium score on the interpretation of myocardial perfusion imaging

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Pieter L. Jager

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Abstract

**Purpose:** Coronary artery calcium (CAC) scores influence the pre-test likelihood of ischaemia in patients undergoing myocardial perfusion imaging (MPI). We investigated the influence of CAC score knowledge on the visual interpretation of MPI in patients referred for the diagnostic work-up of suspected coronary artery disease.

**Methods:** We retrospectively analyzed symptomatic patients who were referred for MPI. For the current analysis, we selected 151 patients who underwent SPECT MPI with simultaneous CAC scoring. MPI was visually interpreted in two separate sessions, first without and then with knowledge of the CAC score. MPI results were classified into four groups: normal, fixed defects, ischaemia, and equivocal.

**Results:** Mean age of the patients was 64±11 years, 56% were male. Without knowledge of the CAC score MPI was evaluated as normal in 36%, compared to 40% with knowledge of the CAC score ($p=0.636$). Overall, the addition of the CAC score changed the interpretation of MPI in 56 patients (37%). Importantly, the frequency of equivocal MPI interpretations decreased from 21% without knowledge of CAC score to 9% with knowledge of CAC score ($p=0.002$).

**Conclusions:** Knowledge of the CAC score has a major impact on the interpretation of MPI, increasing the interpretative certainty.

Introduction

Myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) provides valuable diagnostic and prognostic information in patients referred for non-invasive detection of myocardial ischaemia [1-4]. However, image quality may influence both readers’ diagnostic certainty and overall diagnostic accuracy [5-7]. Availability of additional (clinical) data and knowledge of the pre-test likelihood of ischaemia can improve reading [8].

The coronary artery calcium (CAC) score is a relatively new technique to estimate the amount of coronary atherosclerosis [9-11]. Simultaneous CAC scoring with SPECT may offer incremental diagnostic and prognostic information over SPECT imaging alone [12-15]. This is of particular importance as concomitant CAC scoring will become increasingly available with the recent introduction of both hybrid positron emission tomography (PET)/CT and SPECT/CT devices. We hypothesized that knowledge of CAC score can influence reading of SPECT images, with a higher
Impact of calcium score on MPI evaluation

diagnostic certainty of interpretation. Therefore, the aim of our study was to assess the influence of CAC scores on the visual interpretation of SPECT images in a population referred for the diagnostic work-up of suspected coronary artery disease (CAD).

Materials and methods

STUDY POPULATION
For this study we selected patients who were referred to our hospital over a 1-year period (January 2009 to December 2009) for a clinically indicated MPI, and out of these we retrospectively selected patients without a previous history of CAD who underwent simultaneous CAC scoring using a hybrid 64-slice SPECT/CT device (n=151). All procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients.

CLINICAL INFORMATION
At the time of examination, all patients completed a questionnaire regarding demographic information, prior medical history, cardiac risk factors and current medication use. These data were verified and complemented with demographic and clinical information collected from medical records. Furthermore, information regarding patient age, gender, weight, height, blood pressure, heart rate and symptoms were prospectively obtained by a medical nurse. Pre-test likelihood of CAD was assigned according to Diamond and Forrester criteria, with a risk threshold of <13.4% for low risk, between 13.4 and 87.2% for intermediate risk, and >87.2% for high risk [16].

SPECT-MPI DATA ACQUISITION
All patients underwent a 1-day $^{99m}$Tc-Tetrofosmin MPI protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. In 149 patients (99%) pharmacologic stress was induced by intravenous administration of adenosine (continuous infusion at a rate of 140 μg/kg/min for 6 minutes), while dobutamine was used in two patients (1%) with a contra-indication for adenosine (starting with 10 μg/kg/min and increased at 3-minute intervals to a maximum of 50 μg/kg/min until 85% of the predicted heart rate had been reached). Whenever possible, patients performed additional low-level bicycle exercise to reduce
side effects of adenosine. ECG and blood pressure were monitored before, throughout, and following the infusion. A weight-adjusted dose of $^{99m}$Tc-Tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. Patients scheduled for rest imaging received a dose of $^{99m}$Tc-Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). For both, stress and rest SPECT images were acquired 45–60 minutes after tracer injection.

For SPECT/CT imaging we used a dual-detector gamma camera (Venti, GE Healthcare) equipped with a 64-slice CT scanner (LightSpeed VCT XT, GE Healthcare). SPECT images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 x 64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals over a 180° arc (45° anterior oblique to 45° left posterior oblique) with 30 steps (30 views) [17]. All patients were imaged in supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images. Gated SPECT analysis was done in nearly all patients when feasible at high-dose rest acquisition in order to assist the readers in discerning artifacts from perfusion abnormalities. In all patients, stress and rest SPECT studies were followed by an unenhanced low-dose CT scan during a breath-hold to provide a map for attenuation correction. These scans covered the entire chest with scanning parameters: 5.0 mm slice thickness using a reconstruction algorithm with a 512 x 512 matrix, and 800 ms rotation times at 120 kV and 20 mA. Emission images as well as attenuation map data were entered in a dedicated reconstruction algorithm to provide 3D volume data (available in a Xeleris workstation, GE Healthcare). These were reorientated in the standard way and displayed in the 3 traditional cardiac axes.

CAC IMAGING
All cardiac CT studies were acquired using the 64-slice CT scanner of the integrated SPECT/CT device. All patients with heart rates >70 beats/minute received oral beta-blocker therapy (50 or 100 mg metoprolol tartrate, Astra Zeneca BV, Zoetermeer, The Netherlands) prior to the CAC scan. For the CAC scans an unenhanced, ECG-gated scan was performed prospectively triggered at 75% of the RR-interval using the following scan parameters: A section thickness of 2.5 mm; gantry rotation time 330 ms; tube voltage 120 kV; and a tube current ranging from 125–250 mA depending on patient size. Post-processing of the CAC scan was performed on dedicated workstations (Advantage Windows 4.4, GE Healthcare).
The computer software for CAC scoring (Smart Score, GE Healthcare) automatically defined the presence of calcified lesions as those greater than 130 Hounsfield Units. The total calcium burden in the coronary arteries was manually depicted and allocated to the corresponding coronary artery by an experienced reader using the Agatston method for quantification of the CAC [18].

SPECT MPI INTERPRETATION AND DATA ANALYSIS
Two experienced nuclear cardiac readers (each with >10 years of experience in reading MPI) qualitatively analyzed the attenuation corrected SPECT MPI images in two separate reading sessions. The total set of 151 SPECT studies was displayed in random order to avoid bias. During the first session the readers were asked to read the SPECT scans without knowledge of the CAC scores. During the second reading session (after 8 weeks), the readers (also blinded to their initial MPI interpretations) received information on the total CAC score and the distribution of CAC per coronary vessel. The blinded interpreters scored the SPECT studies in consensus in both sessions as normal, equivocal, or abnormal with discrepancies resolved by a third reader. An equivocal result was defined as persistent diagnostic uncertainty whether the scan could be regarded definitely normal or abnormal, as agreed upon by both readers. If the study was considered abnormal, the presence of reversible or irreversible defects was recorded. Both readers had >3 years of experience in coronary CT angiography. Importantly, the readers were not further instructed how to handle CAC values or cut-off levels and the synthesis of imaging results with CAC score information was left to their individual discretion.

We analyzed changes in diagnostic interpretation between the two reading sessions. The changes induced by the knowledge of CAC score were defined as minor or major depending on the type of change in interpretation. Major changes were defined as a change in the overall conclusion of the study, e.g., a conclusion changing from ‘ischaemia’ to ‘no ischaemia’ or vice versa was considered a major change. Other changes were considered minor.

FOLLOW-UP
Data regarding downstream invasive angiography within 6 months were obtained for patients with a change in MPI interpretation by reviewing hospital records, by performing telephone interviews with the patients and by contacting patients’ general practitioners. Patients were referred for invasive coronary angiography on clinical grounds or for research purposes. Invasive angiography was performed according to
standard clinical protocols. Angiograms were evaluated by certified interventional cardiologists who were aware of the SPECT and CAC imaging results. The presence of obstructive CAD was defined as >70% luminal narrowing in a major coronary vessel or >50% stenosis in the left main coronary artery.

**Statistical Analysis**
Statistical analysis was performed with a commercially available software package (SPSS version 18.0 for Windows; SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean±SD and categorical variables as frequencies, or percentage. Comparisons were performed with unpaired Student’s t-tests, Fisher’s exact tests or Chi-square tests, as appropriate. Two-sided p values of less than 0.05 were considered as statistically significant.

**Results**

**Baseline Characteristics**
Mean age of the 151 patients was 64±11 years, 56% were male and the mean body mass index (BMI) was 29±5 kg/m². Baseline characteristics are summarized in Table 1.

**Table 1. Characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>64±11</td>
</tr>
<tr>
<td>Male</td>
<td>84 (56)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>29±5</td>
</tr>
<tr>
<td>CAC score, median (interquartile range)</td>
<td>307 (111–926)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (22)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>69 (46)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>117 (77)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>81 (54)</td>
</tr>
<tr>
<td>First degree relative &lt;60 years with CAD</td>
<td>83 (55)</td>
</tr>
<tr>
<td>Pre-test likelihood*</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>88 (58)</td>
</tr>
<tr>
<td>High</td>
<td>57 (38)</td>
</tr>
</tbody>
</table>

Data are numbers (percentages) of patients, unless otherwise indicated. CAC, coronary artery calcification; CAD, coronary artery disease. *Pre-test likelihood according to Diamond & Forrester criteria [16].
Impact of calcium score on MPI evaluation

Availability of the CAC score altered the initial diagnostic interpretation in 37% of the cases (56/151, \( p < 0.0001 \)), with a major change in 39 patients (26%). There was a 59% decrease in the number of equivocal SPECT findings, a 9% increase in the number of scans interpreted as normal, a 26% increase in the number of scans interpreted as positive for ischaemia and a 17% decrease in the number of scans with persistent perfusion defects (Fig. 1). The addition of the CAC scores reduced the number of equivocal SPECT findings from 32 (21%) to 13 (9%, \( p = 0.002 \)). Baseline characteristics in patients with equivocal findings or change in MPI interpretation were similar as compared to those with unequivocal findings or unchanged MPI reading, respectively.

A CAC score of zero was found in ten patients, of which two were interpreted as having a definitely normal scan during the first reading, changing to seven after the

![Fig. 1. Interpretation of myocardial perfusion scans in 151 patients without and with knowledge of CAC scores. Data are percentages. MPI, myocardial perfusion imaging; CAC, coronary artery calcium; NS, not significant.](image-url)
second reading when CAC scores were available ($p=0.07$). Conversely, thirty patients had a CAC score $>1000$, of whom 15 patients had findings definitely suggestive for ischaemia during the first reading, changing to 23 in the second session with knowledge of the CAC score ($p=0.06$). Four patients with CAC score $>1000$ and initial equivocal SPECT interpretation were reclassified as having ischaemia when the CAC scores were presented.

Follow-up revealed that all 56 patients with an altered SPECT interpretation underwent invasive angiography within 6 months after SPECT on clinical grounds or for research purposes. The changes induced by CAC score knowledge and the findings at subsequent invasive angiography are presented in Table 2. Among the 39 patients in which the change was considered major, 24 readings improved and 15 readings deteriorated.

### Table 2. Changes in SPECT interpretation induced by CAC score knowledge and findings at invasive coronary angiography

<table>
<thead>
<tr>
<th>No.</th>
<th>CAC score</th>
<th>SPECT without CAC score</th>
<th>SPECT with CAC score</th>
<th>Obstructive CAD at invasive angiography*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4186</td>
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<tr>
<td>2</td>
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<td>normal</td>
<td>no</td>
</tr>
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<td>5</td>
<td>581</td>
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</tr>
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<td>6</td>
<td>46</td>
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</tr>
<tr>
<td>9</td>
<td>5</td>
<td>equivocal</td>
<td>fixed defect</td>
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</tr>
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<td>10</td>
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<td>730</td>
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<tr>
<td>23</td>
<td>520</td>
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*Table continues on next page.*
### Impact of calcium score on MPI evaluation

#### Table 2 continued from previous page.

<table>
<thead>
<tr>
<th>No.</th>
<th>CAC score</th>
<th>SPECT without CAC score</th>
<th>SPECT with CAC score</th>
<th>Obstructive CAD at invasive angiography*</th>
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</tr>
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</table>

#### Discussion

Our study shows that knowledge of clinical data, in our case the CAC score, influences interpretation of myocardial perfusion scans in patients without a history of coronary artery disease. Most importantly, the changes in our study triggered by CAC score knowledge have a major effect on final interpretation in 26% of the cases and leads to a significant reduction of equivocal SPECT interpretations. These data suggest a potential role for simultaneous CAC scoring to improve the interpretative diagnostic
certainty, however, the implications for diagnostic accuracy of MPI in detecting obstructive CAD and eventual patient management still need to be studied.

The widespread availability of multi-slice CT scanners and the recent advent of hybrid SPECT/CT and PET/CT scanners have increased the interest in understanding the direct impact of simultaneous CAC scoring in patients referred for MPI. The CAC score enables diagnosing and quantification of the degree of coronary atherosclerosis irrespective of MPI results, providing additional diagnostic and prognostic information that could improve post-imaging clinical management and patient behaviour [12-15,19]. However, future studies are warranted to elucidate whether the aggressive management of risk factors based on CAC scores averts future adverse cardiovascular events.

We tried to extend the potential role of simultaneous CAC scoring by assessing the direct impact of CAC score knowledge on the interpretation of myocardial perfusion scans. Equivocally abnormal SPECT findings may be reclassified as normal when accompanied by a very low CAC score due to the high NPV of CAC scoring [20-23]. Also in a recent study from our center, none of the patients with equivocal or abnormal SPECT findings had obstructive CAD at subsequent invasive follow-up when the CAC score was zero [24]. On the other hand, very high CAC scores may depict obstructive CAD undetected by SPECT [12,25]. Readers might interpret borderline SPECT findings as abnormal, therefore increasing sensitivity of their interpretation in the presence of very high CAC scores. In our study readers were not instructed how to handle equivocal findings when CAC score values were also present, so this study also describes our initial experience in handling CAC score. In case of CAC scores below 100 and over 1500 the interpreters tend to adjust indefinite MPI conclusions toward definitely normal and definitely abnormal respectively. However, this obviously requires more study.

One could question whether interpretation of myocardial perfusion scans (or other diagnostic imaging test) should be done independently of clinical data. However, use of clinical data may improve sensitivity of radiological studies [26,27]. Similarly, knowledge of routine clinical data influences MPI interpretation [8]. Hence, guidelines recommend to consider inclusion of clinical data in the interpretation of myocardial perfusion scans [28].

The small patient number, the retrospective design and the highly selected population represent the major limitations of current study. In addition, the extreme selection bias and lack of comparison with invasive fractional flow reserve measurements in all patients impede a reliable calculation of the sensitivity and specificity as reflection of the diagnostic performance. However, the aim of this study
Impact of calcium score on MPI evaluation

was to assess the influence of CAC scores on the visual interpretation of SPECT. The relatively high number of equivocal findings may be perceived as possible limitation. We cannot completely exclude an underlying bias (although unlikely) to interpret more studies as equivocal during first reading session. In addition, the interpretation of MPI images without the availability of raw SPECT data or gated SPECT data may lead to a strong bias in favor of additional CAC scoring. As another limitation, we performed an additional scan for CAC scoring that accompanies an additional radiation exposure of 1.1 mSv [29]. However, attenuation maps from CAC scans allow accurate attenuation correction of MPI [30] and CAC can be visually assessed from low-dose attenuation CT scans [31]. In this way additional radiation exposure can be minimized, yet delivering valuable additional anatomical information. Although our main focus was to assess the changes induced by CAC scoring on the SPECT interpretations, the main question should of course be whether use of clinical data, including CAC score, leads by improving diagnostic accuracy of MPI to better patient outcome. Additional prospective studies with a larger sample size should address this question.

Conclusion

Knowledge of the CAC score has a major impact on the interpretation of MPI, increasing the interpretative certainty.
References


Impact of calcium score on MPI evaluation


Coronary artery calcium scoring to exclude flow-limiting coronary artery disease in symptomatic stable patients at low or intermediate risk

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Jorik R. Timmer
Stoffer Reiffers
Ad H.J. Oostdijk
Siert Knollema
Jan Paul Ottervanger
Pieter L. Jager

Radiology 2013;269:77-83
Abstract

**Purpose:** To assess the capability of a zero coronary artery calcium (CAC) score to help exclude flow-limiting coronary artery disease (CAD) in a homogeneous population with stable anginal complaints and a low-to-intermediate pretest likelihood.

**Materials and methods:** The study protocol had institutional ethics committee approval, with written informed consent from all patients. Between 2009 and 2011, a total of 3501 consecutive stable patients without known CAD underwent prospectively simultaneous myocardial perfusion imaging and CAC scoring on a hybrid, 64-section single photon emission computed tomography (SPECT)/computed tomography (CT) scanner. In 868 (25%) of 3501 patients, the CAC score was zero, and these patients constituted the current study population. When feasible, additional coronary CT angiography was performed in those with abnormal SPECT findings. Clinical follow-up was recorded with regard to invasive coronary angiography, coronary revascularization, non-fatal myocardial infarction, or death. Results were analyzed by using descriptive statistics.

**Results:** In 868 patients (mean age, 54 years ±11 [standard deviation]; 610 [70%] female, 258 [30%] male), SPECT findings were normal in 766 (88%) and abnormal in 102 (12%), with equivocal results in 41 (5%), persistent defect in 35 (4%), and ischaemia in 26 (3%). In the group with abnormal SPECT findings, additional coronary CT angiography was performed in 93 patients (91%), showing non-obstructive CAD in eight patients (9%) and normal coronary arteries in 85 patients (91%). In the other nine patients (9%), invasive angiography was used to exclude obstructive CAD. At a median follow up of 17 months (25th percentile, 11; 75th percentile, 24 months), no coronary events were recorded.

**Conclusions:** A CAC score of zero in stable patients at low or intermediate risk excludes flow-limiting CAD. These findings support the possibility of CAC scoring as a simple and safe tool to select patients for additional testing or discharge, as recommended in the literature.

Introduction

Coronary artery calcium (CAC) scoring is a well-validated clinical tool for the early detection of coronary artery atherosclerosis and provides valuable prognostic information [1,2]. In symptomatic patients, the absence of measurable CAC has a high
negative predictive value for the exclusion of obstructive anatomic coronary artery disease (CAD) [3-4]. The absence of CAC also helps exclude inducible ischaemia at functional testing such as myocardial perfusion positron emission tomography (PET) in patients at low or intermediate risk of CAD [5]. Consequently, a clinical expert consensus report states that the absence of measurable CAC may be an effective selection tool in symptomatic patients before further testing, such as stress nuclear imaging, invasive diagnostic coronary angiography, and hospital admission [6]. In their guidelines, the Chest Pain Guideline Development Group [7] recommends CAC scoring as the initial test in stable patients when the likelihood of CAD is 10–29%, and they recommend no further testing when the CAC score is zero.

Despite these guidelines, investigators in several studies [8-12] again questioned the capability of CAC scoring to help rule out obstructive CAD. In these studies [8-12], higher rates of obstructive non-calcified plaques (6–39%) or inducible ischaemia (16%) were reported, especially in populations at higher risk and in patients with unstable chest complaints who present themselves at the emergency department. Many of these studies included heterogeneous populations or were conducted retrospectively. Prospective clinical studies in which CAC scoring with myocardial perfusion imaging was compared in large homogeneous groups of symptomatic stable patients with low or intermediate likelihood of CAD are limited [5]. Hence, data on the prevalence of flow-limiting CAD in patients with a CAC score of zero in such groups are largely lacking; therefore, the aim of our study was to assess the capability of a zero CAC score to help exclude flow-limiting CAD in a homogeneous population with stable anginal complaints and a low to intermediate pretest likelihood of CAD.

Materials and methods

STUDY POPULATION

From January 2009 to December 2011, a total of 3501 consecutive stable patients (mean age, 61 years ±12 [standard deviation]; 1983 [57%] female patients; 1518 [43%] male patients) who were suspected of having CAD but in whom it was unconfirmed and who had a low to intermediate pretest likelihood for CAD, according to Diamond and Forrester [13] criteria, underwent myocardial perfusion imaging on a hybrid 64-section single photon emission computed tomography/computed tomography (SPECT)/computed tomography (CT) scanner with simultaneous assessment of the CAC score in all. Patients were referred from the cardiology outpatient clinics of our
hospital, which is a large cardiovascular center with a local, regional, and supraregional catchment area. In the case of equivocal or abnormal stress-rest SPECT findings, coronary CT angiography was performed afterward in the absence of contraindications. Experienced nuclear cardiac reviewers (A.H.J.O., P.L.J., S.K. and J.P.O., all with more than 10 years of experience, and J.R.T., with more than 5 years of experience) evaluated all test results and drew a final conclusion. In total, 868 patients (25% of 3501) had a CAC score of zero. These patients constitute the population of the current study. All procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients.

CLINICAL INFORMATION
Demographic and clinical information were collected from medical records. Furthermore, information in regard to age, sex, weight, height, blood pressure, heart rate, current medication use, and symptoms was obtained prospectively by a medical nurse. Pretest likelihood of CAD was assigned according to Diamond and Forrester (13) criteria, with a risk threshold of less than 13.4% for low risk, a risk threshold between 13.4% and 87.2% for intermediate risk, and a risk threshold of more than 87.2% for high risk.

SPECT MYOCARDIAL PERFUSION DATA ACQUISITION
All patients underwent imaging with a 1-day technetium 99m (99mTc)-Tetrofosmin myocardial perfusion imaging protocol. Patients were instructed to refrain from drinking caffeine-containing beverages for at least 24 hours before the test. In 98% (851 of 868) of the patients, pharmacologic stress was induced by means of intravenous administration of adenosine at a continuous rate of 140 μg/kg of body weight per minute for 6 minutes. In the case of contraindication for adenosine (17 [2%] of 868), dobutamine was administered, starting with 10 μg/kg per minute, and the dose was increased at 3-minutes intervals to a maximum of 50 μg/kg per minute, until 85% of the predicted heart rate had been reached. Whenever possible, patients performed additional low-level bicycle exercise to reduce the adverse effects of adenosine. Electrocardiographic measurements and blood pressure were monitored before, during, and after the infusion. A weight-adjusted dose of 99mTc-Tetrofosmin (standard dose, 370 MBq; dose for patients >100 kg, 500 MBq) was injected after 3 minutes of adenosine infusion.
Patients scheduled for rest imaging received a dose of $^{99m}$Tc-Tetrofosmin (standard dose, 740 MBq; dose for patients >100 kg, 1000 MBq). Stress and rest SPECT images were acquired 45 to 60 minutes after tracer injection. Patients underwent scanning with a conventional gamma camera (before May 1, 2010, n=289) or with a cadmium zinc telluride (CZT) gamma camera (after May 1, 2010, n=579).

With the conventional dual-detector gamma camera (VentrI; GE Healthcare, Milwaukee, WI, USA), images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 x 64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals over a 180° arc (45° anterior oblique to 45° left posterior oblique) with 30 steps (30 views). All patients underwent imaging in a supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images.

The CZT-based SPECT images were acquired using a multi-pinhole camera (Discovery NM/CT 570c; GE Healthcare) and 19 stationary detectors simultaneously imaging the heart. Each detector contained 32 x 32 pixelated (2.46 x 2.46 mm) CZT elements. A 20% symmetrical energy window at 140 keV was used [14]. All patients underwent imaging in a supine position with arms placed above the head. Acquisition time was 5 minutes for the stress images and 4 minutes for the rest images.

Gated SPECT analysis to calculate left ventricular volumes and ejection fraction and to assess wall motion abnormalities was performed in nearly all patients when feasible, usually at stress but in some patients at rest [14]. In all patients, stress and rest SPECT studies were followed by unenhanced low-dose CT scan during a breath hold to provide the attenuation map for attenuation correction. These scans covered the entire chest, with the following scanning parameters: 5.0-mm section thickness by using a reconstruction algorithm with a 512 x 512 matrix, and 800-ms rotation times at 120 kV and 20 mA. Typical dose-length product was 34 mGy·cm and typical volume CT dose index was 1.4 mGy. Emission images and attenuation map data were entered in a dedicated reconstruction algorithm to provide three-dimensional volume data available at a workstation (Xeleris; GE Healthcare). These were reorientated in the standard way and displayed in the three traditional cardiac axes.

SPECT MYOCARDIAL PERFUSION IMAGING ANALYSIS
Two experienced nuclear cardiac readers (P.L.J., A.H.J.O., S.K., each with more than 10 years of experience) interpreted the images, including myocardial perfusion imaging polar maps. Segments were scored in consensus by using a 20-segment model for the left ventricle using a five-point scoring system: score 0, normal; score 1, mild; score 2,
moderate; score 3, severe reduction in radiotracer uptake; and score 4, absence of detectable tracer in a segment) [15,16].

Perfusion defects were identified on the stress images (a segment with a score ≥2 was considered to have a defect). Stress study results were interpreted as normal if perfusion was assessed to be homogeneous throughout the myocardium and fewer than two segments had stress scores of two or greater [15,16]. An ischemic perfusion defect was defined as one in which a stress defect was associated with a rest score of one or less or a stress defect score of four with a rest score of two [15,16]. Reversible defects that did not meet these criteria were considered equivocal for ischaemia, as previously described [17]. Irreversible defects were considered as scar tissue when they were persistent despite CT-based attenuation correction together with abnormal wall motions in the corresponding segments [18].

**CAC SCAN ACQUISITION**

All cardiac CT studies were performed by using the 64-section CT scanner of the integrated SPECT/CT scanner (LightSpeed VCT XT; GE Healthcare). All patients with heart rates greater than 70 beats per minute received oral β-blocker therapy, with 50 or 100 mg of metoprolol tartrate (Astra Zeneca, Zoetermeer, The Netherlands) before to the CAC scan. For the CAC scans, an unenhanced, electrocardiographically gated scan was obtained prospectively, triggered at 75% of the R-R interval by using the following scanning parameters: 40 sections and 2.5-mm section thickness; gantry rotation time, 330 msec; tube voltage, 120 kV; and a tube current ranging from 125–250 mA, depending on patient size. Postprocessing of the CAC scan was performed at a dedicated workstation (Advantage Windows 4.4; GE Healthcare).

**CAC SCAN INTERPRETATION**

The CAC scoring computer software (Smart Score; GE Healthcare) automatically defined the presence of calcified lesions as those greater than 130 HU. The total calcium burden in the coronary arteries was depicted manually and allocated to the corresponding coronary artery by an experienced reader by using the Agatston method for quantification of the CAC [19]. All CAC scans were read by two nuclear cardiac readers (P.L.J., S.K., J.P.O., A.H.J.O. or J.R.T., all with more than 3 years of experience in CAC scoring) at the time of SPECT interpretation.
CORONARY CT ANGIOGRAPHY ACQUISITION
With regard to coronary CT angiography, exclusion criteria were known hypersensitivity to iodinated contrast agents, pregnancy, renal insufficiency, or irregular heart rhythm. All patients received a single dose of nitroglycerine (0.4 mg) just before coronary CT angiography. If necessary, patients received oral (50–200 mg) and/or intravenous (5–30 mg) β-blocker therapy (metoprolol) to achieve a target heart rate below 65 beats per minute. A scout view of the chest was obtained first during an inspiratory breath hold followed by the CT angiographic acquisition with the following parameters: 64 sections per rotation; detector collimation, 0.625 mm; gantry rotation time, 330 ms; effective temporal resolution, 165 ms; spatial resolution, 0.4 mm³; tube voltage, 100 to 140 kV (depending on the patient’s body weight); and tube current, 450 to 800 mA. All images were acquired during an inspiratory breath hold of approximately 10–12 s. Contrast material-enhanced (Optiray 350; Mallinckrodt Medical BV, Petten, The Netherlands) coronary CT angiography was acquired with prospective electrocardiographic triggering (71 [76%] of 93 patients) at 75% of the R-R interval or with retrospective data acquisition (22 [24%] of 93 patients) with electrocardiographically based tube current modulation (full tube current was applied from 40% to 80% of the R-R interval).

CORONARY CT ANGIOGRAPHIC IMAGE INTERPRETATION
Image interpretation of coronary CT angiographic results was performed (P.L.J., S.K., J.P.O., A.H.J.O. or J.R.T., all with more than 3 years of experience in coronary CT angiography) by using axial images, multiplanar and curved reformations, and thin-slab maximum intensity projections according to Society of Cardiovascular Computed Tomography guidelines [20]. Each segment was evaluated on at least two planes, and the degree of diameter stenosis was graded visually with the consensus of two readers as none (0% luminal stenosis), mild (1% to 49% luminal stenosis), moderate (50% to 69% luminal stenosis), or severe (>70% luminal stenosis). Obstructive CAD was defined when narrowing of the coronary lumen was 50% or greater.

CLINICAL FOLLOW-UP
Clinical outcome data were obtained by reviewing hospital records, performing telephone interviews with the patients, and contacting patients’ general practitioners. The interval between the examination date and the date of the final consultation was used to determine the follow-up length. Events that were recorded were invasive diagnostic coronary angiography, coronary revascularization, non-fatal myocardial infarction, and death.
Statistical analysis to compare baseline characteristics was performed with Chi-squared and one-way analysis of variance (ANOVA) (SPSS, version 18.0 for Windows; SPSS, Chicago, Ill). Quantitative variables were expressed as mean±standard deviations, and categorical variables were expressed as frequencies or percentage. Normality of data distribution was assessed by using the Kolmogorov-Smirnov test. Differences in age between men and women were compared by using the unpaired two-tailed Student’s t-test, as appropriate. Two-sided p values of less than 0.05 were considered to indicate a significant difference.

Table 1. Baseline characteristics in 868 stable patients suspected of having CAD

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54±11</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>610 (70)</td>
</tr>
<tr>
<td>Male</td>
<td>258 (30)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>151 (17)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>61 (7)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>295 (34)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>451 (52)</td>
</tr>
<tr>
<td>Family history</td>
<td>495 (57)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>269 (31)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>391 (45)</td>
</tr>
<tr>
<td>Statin</td>
<td>200 (23)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>131±18</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82±12</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71±12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26±4</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Creatinine level (μmol/l)</td>
<td>72±19</td>
</tr>
<tr>
<td>Pre-test likelihood</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>260 (30)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>608 (70)</td>
</tr>
</tbody>
</table>

Note: The patients had a CAC score of zero and were referred for SPECT imaging.

* Data are the means ± standard deviations.

\(^{1}\) Data are the numbers of patients; numbers in parentheses are percentages, and percentages were rounded.

\(^{2}\) Data are the numbers of patients; numbers in parentheses are percentages. Pretest likelihood according to Diamond & Forrester [13] criteria.
Calcium scoring for the exclusion of coronary artery disease

Results

The mean age of the 868 patients who were suspected of having CAD was 54 years ±11 (age range, 27–91 years); 610 (70%) were women and 258 (30%) were men, and the mean body mass index (BMI) was 26 kg/m² ±4. The mean age for women was 55 years ±11 (age range, 28–91 years) compared with a mean age of 50 years ±11 (age range, 27–78 years) for men ($p<0.001$). The baseline characteristics are summarized in Table 1.

The results of SPECT in 868 patients with a CAC score of zero are summarized in Table 2. Seven hundred sixty-six (88%) of 868 patients had normal SPECT myocardial perfusion findings. Persistent perfusion defects were found in 35 (4%), equivocal results in 41 (5%), and ischaemia in 26 (3%) of 868 patients. Patients who underwent scanning with the CZT camera had fewer equivocal SPECT findings (15 [3%] of 579 patients) than did patients who underwent scanning with the conventional gamma camera (28 [10%] of 289 patients, $p<0.001$). Subsequent coronary CT angiography was performed in 93 (91%) of 102 patients with equivocal or abnormal SPECT findings and revealed normal coronary arteries in 85 (91%) patients and non-obstructive CAD in the remaining eight patients (9% of those with abnormal SPECT findings), excluding obstructive CAD in all of these patients. The nine patients (9%) with equivocal or abnormal SPECT findings in whom coronary CT angiography could not be performed were referred subsequently for invasive coronary angiography, which revealed normal coronary arteries in all of them.

<table>
<thead>
<tr>
<th>Normal</th>
<th>766 (88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent defect</td>
<td>35 (4)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>41 (5)</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>26 (3)</td>
</tr>
</tbody>
</table>

Note: Data are the numbers of patients; numbers in parentheses are percentages, and percentages were rounded.
Complete follow-up data were available in 858 (99%) of 868 patients. The results in 10 patients were missing. The median follow-up was 17 months (25th and 75th percentiles, 11 and 24 months, respectively). There were no patients with myocardial infarction during this period, and two patients died from a non-cardiac cause. Including the previously mentioned nine patients, 31 (4%) of 868 patients were referred for invasive coronary angiography during follow-up, and the findings thereof helped to exclude the presence of obstructive CAD in all 31 patients. No patients in this cohort had flow-limiting CAD (95% confidence interval: 0–0.01%).

Discussion

This single-centre, observational study in a large and homogeneous group of stable symptomatic patients at low to intermediate risk for CAD showed that a CAC score of zero excludes flow-limiting CAD in all patients without a single exception. Although SPECT myocardial perfusion imaging findings were abnormal in 12% (102 of 868) of the patients, including reversible defects in 3% (26 of 868 patients), no obstructive stenoses were found in the coronary arteries at coronary CT angiography or invasive angiography in these patients. These findings support the use of CAC scoring as a first-line test in stable patients at low to intermediate risk for CAD, as has been suggested [6,7].

The prevalence of obstructive CAD in the presence of a CAC score of zero depends strongly on the population studied. An overview is provided in Table 3. In asymptomatic patients with a CAC score of zero the prevalence of obstructive CAD is lower than 1% [31]. Similarly, in symptomatic patients, a CAC score of zero is associated with a low likelihood (1–3%) of obstructive CAD in several studies [3,4]. On the other hand, in groups that contain patients presenting at emergency departments or groups of patients with unstable angina or acute coronary syndromes, higher prevalences of obstructive CAD were reported. However, in none of the prior studies did the investigators assess the hemodynamic significance of lesions detected in patients with a CAC score of zero [3,4,8-11,22-31]. Furthermore, the long-term prognostic effect of these lesions remains unclear, although several studies did not show increased rates of hard cardiac events (non-fatal myocardial infarction or death) at mid-term (3 year) follow-up [4,27].
Table 3. Overview of prevalences of obstructive CAD among symptomatic patients with a CAC score of zero obtained from diagnostic studies of CAC scoring

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Reference test</th>
<th>Total No. of patients</th>
<th>No. of male patients (%)</th>
<th>CAC score of zero (%)</th>
<th>Obstructive CAD in patients with a CAC Score of Zero (%)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarwar et al. [3] (2009)</td>
<td>Invasive coronary angiography</td>
<td>NA</td>
<td>1053</td>
<td>19 (94%)</td>
<td>7 (13%/19%)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Villines et al. [4] (2011)</td>
<td>Coronary CT angiography</td>
<td>10037</td>
<td>56 (5621)</td>
<td>51 (528%)</td>
<td>3 (179/5128)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Estevez et al. [5] (2011)</td>
<td>PET</td>
<td>206</td>
<td>36 (75)</td>
<td>48 (99)</td>
<td>1 (199%)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Schenker et al. [12] (2008)</td>
<td>PET</td>
<td>621</td>
<td>40 (249)</td>
<td>34 (213)</td>
<td>16 (34213)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Drosch et al. [21] (2010)</td>
<td>Coronary CT angiography</td>
<td>500</td>
<td>74 (371)</td>
<td>12 (61)</td>
<td>26 (1661)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Yoon et al. [22] (2012)</td>
<td>Coronary CT angiography</td>
<td>136</td>
<td>58 (79)</td>
<td>68 (92)</td>
<td>15 (1492)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Dedic et al. [23] (2011)</td>
<td>Coronary CT angiography</td>
<td>756</td>
<td>51 (387)</td>
<td>37 (281)</td>
<td>4 (10281)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Ergun et al. [24] (2011)</td>
<td>Coronary CT angiography</td>
<td>883</td>
<td>43 (376)</td>
<td>100 (883)</td>
<td>5 (43883)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Merita et al. [25] (2012)</td>
<td>Coronary CT angiography</td>
<td>2160</td>
<td>51 (1110)</td>
<td>47 (1019)</td>
<td>2 (241019)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Sonnkowski et al. [26] (2011)</td>
<td>Coronary CT angiography</td>
<td>166</td>
<td>37 (61)</td>
<td>100 (166)</td>
<td>2 (3166)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Unetet et al. [27] (2011)</td>
<td>Coronary CT angiography</td>
<td>1119</td>
<td>51 (576)</td>
<td>100 (1119)</td>
<td>1 (201119)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Malfit et al. [28] (2011)</td>
<td>Coronary CT angiography, invasive coronary angiography</td>
<td>1500</td>
<td>62 (928)</td>
<td>27 (407)</td>
<td>18 (73407)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
<tr>
<td>Cheng et al. [29] (2007)</td>
<td>Coronary CT angiography</td>
<td>554</td>
<td>65 (358)</td>
<td>75 (416)</td>
<td>1 (2416)</td>
<td>Included patients with acute coronary syndrome</td>
</tr>
</tbody>
</table>

Note. NA, not available. Numbers in parentheses were used to calculate the percentages.

* The denominator used to calculate each percentage is the total number of patients in each study.
Although there remains some controversy about the capability of CAC scoring to help rule out obstructive CAD, when strictly implemented in stable patients at low to intermediate risk, as suggested by the guidelines, the CAC score still may function as an effective first-line selection tool before further diagnostic evaluation. The negative predictive value of a CAC score of zero is even higher than the negative predictive value of exercise testing [23] and of myocardial perfusion imaging with PET [5]. Because exercise and nuclear stress testing are well accepted first-line diagnostic modalities in populations at low to intermediate risk for CAD in which patients have stable chest complaints, CAC scoring is an attractive alternative. A zero CAC score in patients with intermediate risk that is based on conventional risk assessment could be used to reclassify such patients into a low-risk category [32]. However, we believe additional testing is still necessary in patients with unstable complaints, in patients with acute problems at emergency departments, in patients with possible coronary spasms or patients who are suspected of having coronary anomalies, and in patients with a substantially higher pretest probability [8-11,21-23].

We acknowledge several limitations of our study. First, because only patients with equivocal or abnormal SPECT findings underwent additional coronary CT angiography, the prevalence of non-calcified plaque could not be assessed in patients with normal SPECT findings, and potential critical stenoses accompanied by false-negative SPECT findings theoretically could have been missed. However, our results are in line with those of Esteves et al. [5] who also found normal myocardial perfusion imaging findings in patients without detectable CAC. Furthermore, it is questionable whether performing complete SPECT with coronary CT angiography only for scientific validation purposes in a population at low risk would have been ethical and clinically acceptable. As a partial solution for this potential problem, we obtained data on clinical follow-up in the cohort in our study, and we did not find any cardiac events that could have been related to potentially false-negative SPECT findings. In addition, a normal myocardial perfusion scan confers an excellent short-term prognosis [33], and patients with a CAC score of zero have slow progression of CAD across time [34]. Although false-negative SPECT findings remain possible in the cohort in our study with relatively short follow-up, we still believe our findings to be valid, but more studies are welcomed to confirm these findings and also to assess the influence of non-calcified plaques on patient treatment and long-term prognosis.

Second, we used the Diamond and Forrester [13] criteria to determine the pretest likelihood of CAD in the patients in our study. However, results from one study showed that such traditional criteria for assessing the pretest probability (although recommended by several guidelines [7,35] evidently led to overestimation of the actual
prevalences found in patients referred for non-invasive coronary CT angiography [36]. Therefore, our results may have been influenced by the fact that the population in our study possibly had a lower risk than we had defined before testing. This issue is of paramount interest because a uniform definition of the pretest probability appears crucial in the appropriate selection of patients for whom CAC scoring may be an effective first-line test. In addition, future prospective cost-effectiveness studies are warranted.

In conclusion, the absence of coronary calcification in stable patients at low or intermediate risk helps exclude flow-limiting CAD. These findings support published recommendations and the usefulness of CAC scoring as a simple and safe tool to select patients for additional testing or discharge.
References


Calcium scoring for the exclusion of coronary artery disease


CHAPTER 8

Myocardial perfusion imaging in stable symptomatic patients with extensive coronary atherosclerosis

Mohamed Mouden
Jan Paul Ottervanger
Jorik R. Timmer
Stoffer Reiffers
Ad H.J. Oostdijk
Siert Knollema
Pieter L. Jager

Abstract

**Purpose:** High coronary artery calcium (CAC) scores are associated with a high likelihood of ischaemia and obstructive coronary disease. Myocardial perfusion imaging (MPI) is a key investigation to determine the need for revascularization. However, the value of MPI in presence of extensive CAC has so far only been demonstrated in asymptomatic patients, whereas its value in symptomatic patients remains largely unclear. Therefore, we studied the impact of MPI in symptomatic patients with a CAC score $\geq 1000$.

**Methods:** We included 282 patients (mean age 69±9 years, 63% men) without a history of coronary disease with suspected stable angina referred for MPI and with a CAC score $\geq 1000$. On follow-up at 18 months invasive angiography, coronary revascularization, non-fatal myocardial infarction and death were recorded.

**Results:** MPI was normal in 54%, equivocal in 10% and abnormal in 37% (fixed defect 9% and ischaemia 28%). More abnormal MPI findings were observed in men, smokers and those with even higher CAC scores. During follow-up, 1 patient (with non-ischaemic MPI) died of cardiac cause, 1 patient (with ischaemic MPI) suffered a myocardial infarction and 92 patients (33%) underwent revascularization. Ischaemia on MPI was a strong predictor of coronary revascularization (odds ratio 13.1; 95% CI 7.1–24.3; $p<0.001$).

**Conclusions:** Ischaemia on MPI is observed in approximately 30% of patients with a CAC score $\geq 1000$, and is a strong predictor of coronary revascularization. However, non-ischaemic MPI does not exclude revascularization, and patients with persisting complaints should be considered for invasive angiography.

Introduction

Myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) provides valuable diagnostic and prognostic information in patients referred for non-invasive detection of myocardial ischaemia [1,2]. However the presence or absence of atherosclerosis remains undetected. Furthermore, the diagnostic accuracy of MPI may be impaired in patients with balanced ischaemia due to flow-limiting three-vessel coronary artery disease (CAD) or left main stenosis [3], while this group is particularly prone to adverse cardiac events [4,5].
Coronary artery calcium (CAC) scoring is a clinical tool for the early non-invasive detection of coronary atherosclerosis [6,7]. Higher CAC scores are generally associated with more advanced coronary sclerosis and a higher likelihood of ischaemia [8,9] or stenotic lesions [10]. Nevertheless, according to several studies, the presence of extreme CAC scores is accompanied by a normal MPI in the majority of both asymptomatic and symptomatic patients [11,12]. Recent studies indicate that patients with normal MPI but with high CAC scores are at increased risk for future coronary events as compared to patients with no CAC. Such patients may have obstructive CAD despite normal MPI results [9,13,14]. With the recent advent of hybrid SPECT/CT devices, MPI and CAC scoring can be easily combined and performed in a single session. However, the value of MPI in symptomatic patients with a very high CAC score and the resulting implications for treatment and short-term prognosis remain largely unclear.

Therefore, the aims of this study were to assess the impact of MPI in patients with a low/intermediate risk of a coronary event with suspected but unconfirmed CAD who subsequently presented with a high CAC score (>1000) and to evaluate the resulting clinical and prognostic implications.

Materials and methods

STUDY POPULATION
We retrospectively evaluated all patients who presented to our hospital over a 3-year period (January 2009 to December 2011) for a clinically indicated MPI with a hybrid 64-slice SPECT/CT device. Only patients without a previous history of CAD, and a low to intermediate pre-test likelihood of CAD with a very high CAC score (>1000) were included in the current analysis. All procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients.

CLINICAL INFORMATION
At the time of examination, all patients completed a questionnaire regarding demographic information, prior medical history, cardiac risk factors and current medication use. These data were verified and complemented with demographic and clinical information collected from medical records. Furthermore, information
regarding patient age, gender, weight, height, blood pressure, heart rate and symptoms were prospectively obtained by a medical nurse. The pretest likelihood of CAD was assigned according to the criteria of Diamond and Forrester, with a risk threshold of <13.4% for low risk, between 13.4 and 87.2% for intermediate risk, and >87.2% for high risk [15].

SPECT-MPI DATA ACQUISITION
All patients underwent a 1-day $^{99m}$Tc-Tetrofosmin MPI protocol. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. Pharmacological stress was induced by intravenous administration of adenosine (continuous infusion at a rate of 140 μg/kg/min for 6 minutes). In patients with a contraindication for adenosine, stress was induced using dobutamine (starting with 10 μg/kg/min and increased at 3-minute intervals to a maximum of 50 μg/kg/min until 85% of the predicted heart rate had been reached). Whenever possible, patients performed additional low-level bicycle exercise to reduce the side effects of adenosine. ECG and blood pressure were monitored before, throughout, and following the infusion. A weight-adjusted dose of $^{99m}$Tc-Tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was injected after 3 minutes of adenosine infusion. Patients scheduled for rest imaging received a dose of $^{99m}$Tc-Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). Both stress and rest SPECT images were acquired 45–60 minutes after tracer injection. Patients were scanned with a hybrid 64-slice SPECT/CT device that included a conventional gamma camera (before 1 May 2010, 85 patients) or a cadmium-zinc-telluride (CZT) gamma camera (after 1 May 2010, 197 patients).

With the conventional dual-detector gamma camera (Ventri; GE Healthcare), images were acquired using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 x 64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals over a 180° arc (45° anterior oblique to 45° left posterior oblique) with 30 steps (30 views). All patients were imaged in the supine position with arms placed above the head. Acquisition time was 12 minutes for the stress images and 15 minutes for the rest images.

The CZT-based SPECT images were acquired using a multipinhole camera (Discovery NM/CT 570c; GE Healthcare) and 19 stationary detectors simultaneously imaging the heart. Each detector contained 32 x 32 pixelated (2.46 x 2.46 mm) CZT elements. A 20% symmetrical energy window at 140 keV was used as previously described [16]. All patients were imaged in the supine position with arms placed above
the head. Acquisition time was 5 minutes for the stress images and 4 minutes for the rest images as previously reported [16]. Gated SPECT analysis to calculate left ventricular volumes and ejection fraction, and to assess wall motion abnormalities was done in nearly all patients when feasible, usually during stress but in some cases during rest. Stress and rest SPECT studies were followed by an unenhanced low-dose CT scan during breath-hold to provide the attenuation map for attenuation correction. These scans covered the entire chest with the following scanning parameters: 5.0-mm slice thickness using a reconstruction algorithm with a 512 x 512 matrix, and 800 ms rotation times at 120 kV and 20 mA. Emission images as well as attenuation map data were entered into a dedicated reconstruction algorithm to provide 3D volume data (available in a Xeleris workstation; GE Healthcare). These were reorientated in the standard way and displayed in the three traditional cardiac axes.

SPECT MPI ANALYSIS
Experienced nuclear cardiac readers (each with more than 10 years experience) non-blindly interpreted the images including MPI polar maps. Segments were scored by consensus of two readers using a 20-segment model for the left ventricle using the following five-point scoring system: 0, normal; 1, equivocal; 2, moderate reduction in radiotracer uptake; 3, severe reduction in radiotracer uptake; 4, no detectable tracer in a segment) [17,18].

Perfusion defects were identified on the stress images (a segment with a score > 2 was considered to have a defect). A stress study was interpreted as normal if perfusion was assessed to be homogeneous throughout the myocardium and fewer than two segments had a stress score > 2 [17-19]. Subsequent rest imaging was performed if the stress images did not fulfil these criteria and were therefore deemed to be either abnormal or equivocal. A reversible perfusion defect was defined as one in which a stress defect was associated with a rest score ≤ 1 or a stress defect score of 4 with a rest score of 2 [17,18]. Irreversible defects were considered scar tissue when persistent despite applying CT-based attenuation correction together with abnormal wall motions in the corresponding segments [20].

UNENHANCED CAC SCAN ACQUISITION
All cardiac CT studies were acquired in a single session immediately after MPI using the 64-slice CT scanner of the integrated SPECT/CT device (LightSpeed VCT XT; GE Healthcare). All patients with a heart rate > 70 beats/minute received oral beta-blocker therapy (50 or 100 mg metoprolol; Astra Zeneca BV, Zoetermeer, The Netherlands)
prior to the CAC scan. For the CAC scans an unenhanced, ECG-gated scan was performed prospectively triggered at 75% of the RR interval using the following scan parameters: 4 x 2.5 mm, gantry rotation time 330 ms, tube voltage 120 kV, and a tube current ranging from 125–250 mA depending on patient size. Postprocessing of the CAC scan was performed on dedicated workstations (Advantage Windows 4.4; GE Healthcare).

UNENHANCED CAC SCAN INTERPRETATION
The computer software for CAC scoring (Smart Score; GE Healthcare) automatically defined the presence of calcified lesions as those with radiodensity greater than 130 HU. The total calcium burden in the coronary arteries was manually depicted and allocated to the corresponding coronary artery by an experienced reader using the Agatston method for quantification of CAC [21].

CLINICAL FOLLOW-UP
Clinical outcome data were obtained by reviewing hospital records, by performing telephone interviews with the patients and by contacting patients’ general practitioners. The time between the examination date and the date of the final consultation was used to determine follow-up length. Events that were recorded during follow-up were diagnostic invasive coronary angiography (ICA), coronary revascularization, non-fatal myocardial infarction and death.

STATISTICAL ANALYSIS
Statistical analysis to compare baseline characteristics was performed with Chi-squared and one-way analysis of variance (ANOVA) as available in SPSS software (version 18.0 for Windows; SPSS Inc., Chicago, IL, USA). Comparison of continuous data between groups was performed using the two-sided Student’s t-test. Quantitative variables are expressed as means±SD and categorical variables as frequencies, or percentage. p values of less than 0.05 were considered statistically significant.
Results

BASELINE CHARACTERISTICS
The baseline characteristics of the patients are shown in Table 1. The mean age of the entire cohort of 282 patients was 69±9 years, 63% were men and their mean body mass index (BMI) was 28±5 kg/m². In 269 patients (95%) pharmacological stress was induced with adenosine and in 13 patients (5%) with dobutamine. The mean CAC score for the entire cohort was 1857±862 (median 1586, interquartile range 1235–2169). The mean CAC score in patients ≥70 years of age (1959±898) was higher than that in patients <70 years (1754±814, p=0.046).

Table 1. Baseline characteristics of 282 stable patients with suspected CAD and CAC score ≥1000 referred for SPECT imaging

<table>
<thead>
<tr>
<th>Age (years), mean±SD</th>
<th>69±9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>63</td>
</tr>
<tr>
<td>Cardiovascular risk factors (%)</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>53</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71</td>
</tr>
<tr>
<td>Family history</td>
<td>48</td>
</tr>
<tr>
<td>Number of risk factors, mean±SD</td>
<td>2.2±1.2</td>
</tr>
<tr>
<td>Current cardiac medication (%)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>55</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>63</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor / angiotensin receptor blocker</td>
<td>52</td>
</tr>
<tr>
<td>Statin</td>
<td>56</td>
</tr>
<tr>
<td>Pretest likelihood a</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>12</td>
</tr>
<tr>
<td>Intermediate</td>
<td>88</td>
</tr>
<tr>
<td>Blood pressure (mmHg), mean±SD</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>147±21</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84±13</td>
</tr>
<tr>
<td>Heart rate (bpm), mean±SD</td>
<td>72±12</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean±SD</td>
<td>28±5</td>
</tr>
<tr>
<td>Left bundle branch block (%)</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine level (μmol/l), mean±SD</td>
<td>86±48</td>
</tr>
</tbody>
</table>

a According to the criteria of Diamond and Forrester [15].
SPECT RESULTS
SPECT revealed normal perfusion in 151 patients (54%). Stress-only imaging was performed in 73 patients (26%) with unequivocally normal stress SPECT findings. Additional rest SPECT imaging was performed in 209 patients (74%). The mean left ventricle ejection fraction was 62±12%. Equivocal findings were found in 27 patients (10%), while abnormal perfusion was found in 104 patients (37%), of whom 26 (9%) showed fixed defects and 78 (28%) had findings suggestive of ischaemia. Patients with abnormal findings were more likely to be men, to be a current smoker and to have an even higher CAC score (Table 2). Patients who underwent scanning with the CZT camera had fewer equivocal SPECT findings (6% vs 18%, p=0.002) and more often underwent stress-only imaging (30% vs 16%, p=0.0018).

Table 2. Comparison between normal and abnormal SPECT findings in patients with CAC scores ≥1000

<table>
<thead>
<tr>
<th>Total cohort (n=282)</th>
<th>Normal SPECT (n=151)</th>
<th>Abnormal SPECT (n=131)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>69.5±9</td>
<td>68.9±9</td>
<td>0.585</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>55</td>
<td>72</td>
<td>0.004*</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>12</td>
<td>21</td>
<td>0.047*</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27</td>
<td>28</td>
<td>0.838</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>56</td>
<td>50</td>
<td>0.378</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>70</td>
<td>73</td>
<td>0.488</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>48</td>
<td>50</td>
<td>0.746</td>
</tr>
<tr>
<td>Number risk factors, mean±SD</td>
<td>2.1±1.1</td>
<td>2.2±1.2</td>
<td>0.453</td>
</tr>
<tr>
<td>Current medication (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>52</td>
<td>60</td>
<td>0.184</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>60</td>
<td>66</td>
<td>0.351</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor / angiotensin receptor blocker</td>
<td>53</td>
<td>51</td>
<td>0.758</td>
</tr>
<tr>
<td>Statin</td>
<td>58</td>
<td>53</td>
<td>0.481</td>
</tr>
<tr>
<td>Blood pressure (mmHg), mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>149±21</td>
<td>144±21</td>
<td>0.098</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85±13</td>
<td>83±12</td>
<td>0.277</td>
</tr>
<tr>
<td>Heart rate (bpm), mean±SD</td>
<td>72±12</td>
<td>71±12</td>
<td>0.542</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean±SD</td>
<td>29±6</td>
<td>28±5</td>
<td>0.548</td>
</tr>
<tr>
<td>Left bundle branch block (%)</td>
<td>3</td>
<td>4</td>
<td>0.819</td>
</tr>
<tr>
<td>Creatinine level (μmol/l), mean±SD</td>
<td>90±69</td>
<td>81±17</td>
<td>0.151</td>
</tr>
<tr>
<td>CAC score, mean±SD</td>
<td>1761±737</td>
<td>1969±977</td>
<td>0.043*</td>
</tr>
</tbody>
</table>

*p<0.05.
Follow-up examinations were performed in 281 patients (99%). The minimal follow-up time was 1 year, with a mean of 24±11 months (median 23 months, interquartile range 16–31 months). Overall, 132 patients (47%) underwent ICA during follow-up, of whom 93 (33%) were referred for early (<60 days) ICA and 39 (14%) for late (≥60 days) ICA. ICA was chosen more commonly in patients with ischaemic SPECT findings (86%) than in those with non-ischaemic SPECT findings (32%, \( p<0.001 \)).

Of the 204 patients with non-ischaemic SPECT findings, 65 (32%) underwent ICA because of persisting complaints, of whom 39 (19%) were early and 26 (13%) late referrals. Of these 65 patients, 22 had non-significant CAD and 43 had obstructive CAD (defined as ≥70% luminal narrowing in a major coronary vessel, ≥50% stenosis in the left main coronary artery or fractional flow reserve value ≤0.80). Subsequent revascularization was performed in 35 patients. Single-vessel disease was found in 16 patients, two-vessel disease in 9 and three-vessel disease in 18. Left main stem stenosis was found in 2 patients. Among the 78 patients with ischaemic SPECT findings, 67 (86%) were referred for ICA, of whom 54 (69%) underwent early and 13 (17%) late ICA. Of these patients who underwent ICA, obstructive CAD was confirmed in 60, of whom 57 underwent revascularization. Single-vessel disease was found in 15 patients, two-vessel disease in 13 and three-vessel disease in 31. Isolated left main stem stenosis was found in one other patient, while four patients had concurrent left main involvement. Ischaemia on MPI was a very strong predictor of coronary revascularization (odds ratio 13.1, 95%CI 7.1–24.3; \( p<0.001 \)) during follow-up.

In patients with confirmed obstructive CAD the revascularization rate was higher in the group with ischaemia (95% vs 81%, \( p=0.048 \)). After excluding early revascularizations, there were 13 late revascularizations in the cohort with non-ischaemic SPECT findings compared to 10 late revascularization in those with ischaemic SPECT findings (\( p=0.077 \)). One patient without ischaemia on MPI died of acute myocardial infarction, while one patient with ischaemia on MPI suffered an acute myocardial infarction requiring primary percutaneous intervention. Six patients died from a non-cardiac cause. Analysis of event-free survival is shown in Fig. 1.
Discussion

In this single-centre, observational study in symptomatic stable patients with suspected CAD and a very high CAC score, myocardial perfusion was normal in more than 50% of the patients. Of the 32% of patients with non-ischaemic MPI who were referred for ICA, 54% underwent subsequent revascularization. The proportion of downstream invasive testing and revascularization following a non-ischaemic MPI study in this highly selected cohort was higher than in a similar population with lower CAC scores [16], again confirming the value of CAC scoring combined with MPI. Now the question is what should be the strategy in patients with normal myocardial perfusion but very high CAC score.

The relation between MPI and CAC has been studied, but most of the previous studies focused mainly on asymptomatic cohorts and included only few patients with CAC scores ≥1000. In four studies that included predominantly asymptomatic subjects,
the probability of myocardial ischaemia increased with higher CAC scores, but as in our study, the majority of those with a high CAC scores had normal perfusion [8,22-24]. A lower frequency (29%) of normal MPI results among 28 asymptomatic diabetic subjects with CAC scores ≥1000 was observed, probably indicating the higher-risk profile in that cohort [25]. In three large studies that included symptomatic patients, the MPI findings were normal in the majority of the patients with CAC scores ≥1000 (Fig. 2) [9,11,12]. Summarizing all studies, the majority of patients without prior CAD but a high CAC score have normal MPI, with a higher prevalence of abnormal MPI in symptomatic patients and high-risk groups.

Several studies have assessed the prognostic value of CAC scoring over MPI alone. Patients with both a high CAC score and high-risk MPI findings show higher mortality rates than patients with only a high CAC score [24]. Similar higher long-term event rates have been found among asymptomatic individuals with normal SPECT and more extensive atherosclerosis. With regard to the short-term, higher risk cohorts with a CAC score ≥1000 suffer more adverse events [9,25]. Conversely, as in our study, patients with a low/intermediate risk have a low annual severe short-term event rate even in the presence of elevated CAC scores [12,23,24]. Time-point analysis indeed showed an initially low annual event rate in subjects with normal SPECT and a severe CAC score with separation of the survival curves for total cardiac events at 3 years and for death/myocardial infarction at 5 years after initial testing [23]. Therefore, it may be hypothesized that MPI could provide better short-term risk assessment, while CAC scoring may provide a better estimate longer-term prognosis because of its ability to detect varying degrees of coronary atherosclerosis before the development of stress-induced myocardial ischaemia [23]. Summarizing the published studies, in patients with a low/intermediate risk with a very high CAC score a normal MPI confers a benign short-term prognosis, while the long-term risk of a severe cardiac event is increased.

Potentially, CAC scoring could improve postimaging clinical management and patient behaviour. Two prior studies have investigated whether the knowledge of present coronary atherosclerotic burden affects medical treatment strategy in patients without evidence of abnormal myocardial perfusion. In consecutive patients with non-ischaemic MPI findings who underwent CAC scoring in the same setting or shortly after MPI, subsequent initiation or optimization of medical therapy for CAD was more likely to occur in those found to have CAC as compared to those without CAC [26,27]. However, whether the aggressive management of risk factors induced by CAC scores averts future adverse cardiovascular events, especially in patients with extensive CAC, is currently unclear.
The question arising from our results is why patients with extensive CAC and normal MPI findings are frequently referred for downstream invasive testing with subsequent coronary revascularization despite the lack of ischaemia. The detection of very high CAC scores is associated with a high likelihood of ischaemia and obstructive CAD [8-10]. Therefore, these patients may have a higher pretest likelihood than we defined prior to testing. As for most diagnostic tests, a normal MPI study in such patients with a high pretest probability should be interpreted with caution. This may be particularly relevant in patients with suspected three-vessel CAD or left main stenosis. Visual analysis of MPI images provides information on relative rather than absolute perfusion for each myocardial region. Therefore, global but uniform reduction in coronary vasodilator reserve may result in a homogeneous distribution of radiotracer, potentially leading to false-negative MPI results [28,29]. In addition, the collateral circulation could maintain adequate myocardial perfusion, leading to underestimation of the angiographic severity of coronary lesions. Several other factors may contribute to

Fig. 2. Prevalence of normal myocardial perfusion in symptomatic patients with coronary artery calcium scores >1000 in our study and three previous studies (Schenker et al. [9], Berman et al. [11], Rozanski et al. [12]).
false-negative MPI findings including insufficient coronary vasodilatation due to unrecognized ingestion of caffeine-containing products, attenuation and motion artifacts and plateauing of myocardial tracer uptake at high flow rates [29-36].

Although the incorporation of several non-perfusion imaging findings seems to significantly improve the detection of balanced ischaemia [37], a recent study still found obstructive CAD in 76% of patients with extensive CAC and a normal MPI [14]. Interestingly, in less than one-third of these patients three-vessel disease was found as a possible explanation for the lack of perfusion defects. Similarly, in our study in only 42% of patients with obstructive CAD despite the non-ischaemic MPI findings could the CAD be attributed to three-vessel coronary disease.

In summary, the high probability of obstructive CAD in symptomatic patients with extreme CAC scores, the possibility of false-negative MPI findings, and the recommendation for coronary revascularization for any stenosis >50% in patients with limiting angina unresponsive to optimal medical treatment could be explanations for the high referral rate for ICA despite the absence of objective ischaemia [38]. Based on our findings, we do not believe that all symptomatic patients with a very high CAC score and non-ischaemic MPI result should routinely undergo invasive testing. However, in patients with persistent symptoms in whom clinical suspicion would places them at a higher risk of significant CAD ICA should be considered.

Our study had several limitations. First, this was a retrospective study. Second, we used SPECT rather than PET imaging that may have a higher diagnostic accuracy, especially in relation to the well-known difficulty in finding balanced ischaemia. However, SPECT is more widely available and there is longer experience with its use. Further, the use of pharmacological stress and a 20-segment model for the left ventricle instead of the recommended 17-segment model could be a limitation. Furthermore, since this was a single centre study in a selected MPI referral cohort with no prior CAD at low or intermediate pre-test likelihood, our findings must be read with caution before extrapolating to other populations. Patient referrals, clinical postimaging medical management and downstream utilization of invasive testing were left to the discretion of the treating physicians, which could have been a source of bias. However, the findings do reflect general cardiac patient care. Another limitation includes the definition of obstructive CAD and the determination of the need for revascularization. They were mainly based on visual assessment of the severity of coronary stenoses on ICA, as pressure-derived fractional flow reserve measurement was only used in a few patients. Finally, we also recognize that the relatively short follow-up period may have resulted in under-reporting of adverse cardiac events.
Conclusion

Approximately 50% of the symptomatic patients with a high CAC score have normal MPI. In most of those with ischaemia on MPI, ICA confirms coronary obstructions. In patients without ischaemia on MPI but persisting complaints, the prevalence of obstructive CAD as demonstrated by ICA is also high. In all symptomatic patients with a high CAC score, the incidence of cardiac events is low, whereas the occurrence of coronary revascularization is high. However, more prospective studies are needed to assess the long-term prognostic value of severe CAC in symptomatic patients referred for MPI.
Myocardial perfusion imaging in patients with extreme calcium scores

References


Chapter 9

Summary, Conclusion
and
Future perspectives
The correct identification of patients who may benefit from invasive coronary revascularization requires both anatomical and functional information [1]. The non-negligible procedural risk, high costs and low diagnostic yield associated with conventional ICA demonstrates the need for improvement in non-invasive testing for appropriate patient-selection [2,3]. Currently, each cardiac imaging modality has its own advantages and limitations and none can be considered suitable for all patients.

The non-invasive clinical assessment of CAD and subsequent patient management can be improved with complementary information obtained from SPECT, CACS and CCTA. Although initial studies have shown incremental diagnostic and prognostic value, real-world clinical data for multimodality and hybrid imaging in stable low-intermediate risk patients are still lacking. Furthermore, the clinical implications of a one-day stepwise approach for cardiac hybrid imaging are unknown, and clinical experience with recently introduced high-speed SPECT gamma cameras with CZT detector technology is limited.

Therefore, the aims of this thesis were to study the clinical value and potential role of combining SPECT, CACS and CCTA in daily practice using a stepwise algorithm for patients with suspected stable CAD, and to assess the clinical implications of a recently introduced CZT-based SPECT gamma camera.

In CHAPTER 1, the general introduction provides a brief introduction on the subject and the background of the thesis.

The latest gamma cameras equipped with CZT detector technology provide superior image quality and allow shorter acquisition times because of improved count sensitivity and image contrast. However, CZT cameras are dedicated to perfusion imaging of the heart and are more expensive, while the incremental clinical value remains unknown. Therefore, in CHAPTER 2, we compared the clinical implications of SPECT imaging using the new CZT-based SPECT camera with a conventional SPECT camera. A total of 456 consecutive stable patients underwent stress-first SPECT imaging. The first half was studied using conventional SPECT (n=225), the second half using CZT SPECT (n=231). We found out that additional rest SPECT imaging was performed in only 35% of the patients scanned with CZT SPECT, whereas in those scanned with conventional SPECT, rest imaging was concluded to be necessary in 56% (p<0.001). From these data it was calculated that the mean amount administered radioactive dose per patient was 22% lower in those scanned with the new camera: 658±390 MBq in the CZT group and 840±421 MBq in the conventional group (p<0.001). The mean total imaging time per patient was also significantly shorter with
the new camera: 6.39±1.41 minutes in the CZT group and 20.40±7.46 minutes in the conventional group (p<0.001). After 1 year, clinical outcome was comparable between both highly comparable groups.

These findings show that stress SPECT images acquired with a CZT camera are more frequently interpreted as normal with identical clinical outcome. As a result, CZT SPECT imaging lowers the need for additional testing, results in lower mean radiation dose and shortens imaging time.

As stated above it is crucial to obtain functional information in patients with anatomic stenosis. Although SPECT imaging is one of the modalities to assess the haemodynamic consequences of coronary stenoses, there is also a recent trend to use invasive pressure-derived FFR measurement for depicting ischaemia. FFR is a guide wire-based procedure that can accurately measure blood pressure and flow through a specific part of the coronary artery. Currently, many cardiologists consider FFR to be the most accurate test for depicting ischaemia, while also providing additional prognostic information. Previous studies have shown a moderate degree of concordance between conventional SPECT and FFR, however, the agreement between CZT SPECT and FFR is not known. In CHAPTER 3, we prospectively assessed the concordance between CZT-based SPECT imaging and invasive FFR measurement in 100 stable patients with intermediate grade coronary stenoses. Thirty-one percent of the patients showed ischaemic SPECT findings, while FFR depicted ischaemia in 20%. The concordance between CZT SPECT and FFR was 73% on a per-patient basis and 79% on a per-vessel basis.

This study shows a modest concordance between CZT SPECT and FFR which is comparable with previous results with conventional SPECT. In addition, most coronary stenoses of intermediate degree severity were found to be functionally irrelevant.

Therefore we conclude that the discordance between FFR and SPECT is intrinsic and that these tests measure two different phenomena: a pressure gradient over a stenosis measured with a catheter versus tissue perfusion measured with a flow tracer. Which of the two is ultimately correct remains controversial.

Apart from the new type of SPECT camera studied in this thesis, we also studied clinical aspects of CCTA. In contrast to ICA, CCTA also shows several aspects of the myocardial wall, such as calcifications, but it may also detect congenital coronary anomalies including myocardial bridging. Myocardial bridging is caused by muscles overlying the intramyocardial course of an epicardial coronary artery and may cause chest pain by systolic compression of the tunnelled segment. However, studies
assessing the prevalence of myocardial bridging as detected by CCTA in symptomatic patients referred for the diagnostic work-up of stable CAD are scarce. In CHAPTER 4 we studied therefore the prevalence and predictors of myocardial bridging in 934 patients who underwent a clinically indicated CCTA. In 152 patients (16%) myocardial bridging could be observed. Patients with myocardial bridging were younger and had a lower prevalence of coronary sclerosis. The prevalence of myocardial bridging as detected by CCTA is higher as compared to the reported frequencies for ICA, and myocardial bridging could be an explanation for symptoms and ischaemia in some patients without obstructive CAD.

In CHAPTER 5, we described the clinical experience of our individualized sequential approach combining SPECT, CACS and CCTA in the setting of the Isala Clinics, as a large secondary and tertiary referral hospital for cardiac patients. We performed hybrid cardiac SPECT/CT imaging in stable patients with suspected CAD. In total 2411 consecutive patients without a history of CAD underwent simultaneous stress-first SPECT imaging and CACS. Normal stress SPECT results were found in 53% of patients in whom additional testing could be omitted. Among the 1144 patients who underwent additional rest imaging, 618 patients required additional CCTA. Obstructive CAD could be ruled out by CCTA in 71% of patients with abnormal stress-rest SPECT, including 49% of patients with ischaemic SPECT results. At follow-up after 19 months these patients had an excellent prognosis.

This stepwise approach provides both anatomical and functional information and it appears that the combination of SPECT with CCTA, minimalizes shortcomings of either SPECT or CCTA. Therefore, this method can be preferred over SPECT or CCTA alone. It also is preferable to an approach with both stress and rest SPECT or to approaches with CCTA in all patients.

We believe that the Zwolle fast-track algorithm uses the techniques in a wise and conservative fashion, while yet producing all required clinical information in a single day. We chose the approach starting with SPECT as it fits best in the clinical protocols that have been applied here over the past 20 years based on a unique and sound cooperation between the departments of cardiology and nuclear medicine. Other approaches may also be possible, as long as both physiological and anatomical information is obtained.

With our cameras being able to do SPECT with CT, calcium scoring with its relative simplicity was also performed routinely and studied in this thesis. This adds completely new information to SPECT and several aspects of the combination were studied.
Coronary artery calcifications are highly specific for the presence of coronary atherosclerosis and represent the total atherosclerotic plaque burden present in the epicardial coronary arteries.

One aspect was our hypothesis that CACS may improve SPECT readings. Therefore, we investigated in CHAPTER 6 the influence of CACS knowledge on the visual interpretation of SPECT imaging in 151 patients referred for the diagnostic work-up of suspected CAD. SPECT images were visually interpreted in two separate sessions, first without and then with knowledge of the CACS. Overall, the addition of the CACS changed the interpretation of SPECT in 56 patients (37%). Importantly, the frequency of equivocal SPECT interpretations decreased from 21% without knowledge of CAC score to 9% with knowledge of CAC score ($p=0.002$). These findings show that knowledge of CACS has a major impact on the qualitative interpretation of SPECT, increasing the interpretative certainty.

Another aspect of CACS was the study of the subgroup without any coronary calcium. CHAPTER 7 describes the ability of a zero calcium score to exclude flow-limiting CAD in a homogeneous population with stable anginal complaints and a low to intermediate pre-test likelihood. We included 868 stable patients without known CAD who prospectively underwent simultaneous SPECT imaging and CACS. Additional CCTA was performed in those with abnormal SPECT findings when feasible. SPECT was completely normal in 88% of patients, while additional CCTA (11%) or invasive coronary angiography (1%) ruled out obstructive CAD in those with abnormal SPECT findings. At a median follow-up of 17 months (25th–75th percentile: 11–24 months), no coronary events were recorded. The findings of this study show that a zero calcium score in stable low-intermediate risk patients may help exclude flow-limiting CAD. This supports the possibility of CACS as a simple and safe tool to select patients for additional testing or discharge.

Besides the apparent strong clinical value of a zero calcium score, we were also interested in the opposite, the value of a very high CACS in patients referred for SPECT imaging.

Therefore, we assessed the impact of SPECT imaging in symptomatic patients with extreme coronary calcifications (defined as a CACS $\geq 1000$) in CHAPTER 8. We retrospectively identified 282 stable patients without a history of CAD who underwent simultaneous SPECT imaging and CACS, in whom a CACS $\geq 1000$ was concurrently detected. SPECT was normal in 54%, equivocal in 10% and abnormal in
37%. We found more abnormal SPECT findings in males, smokers and those with even higher CACS. Ischaemia was demonstrated in approximately 30% of patients with CACS ≥1000, and ischaemia is a strong predictor of coronary revascularization (odds ratio 13.1; 95% CI 7.1, 24.3; p<0.001).

We concluded that the majority of symptomatic patients with a CACS ≥1000 had normal perfusion findings. However, as we have demonstrated, patients with normal SPECT findings but with extreme coronary calcification should be watched closely, as we demonstrated that persistent complaints are often still based on relevant CAD and many of such patients ultimately required revascularization. Therefore, the degree of suspicion for severe CAD during follow-up should remain high even with normal SPECT findings, and such patients with persisting complaints should be considered for invasive angiography.

Future perspectives and directions

The studies described in the present thesis explored the clinical value and potential role of non-invasive cardiac imaging including SPECT imaging with latest CZT detector technology and hybrid imaging combining SPECT, CACS and CCTA using a stepwise algorithm for patients with suspected stable CAD. However, several possibilities exist to extend the work described in this thesis.

MYOCARDIAL PERFUSION IMAGING

This thesis has shown the value of CZT SPECT imaging in clinical practice. However, future studies are needed to assess the long-term prognostic value of CZT SPECT and the incremental diagnostic value of dynamic myocardial blood flow quantification with high-speed CZT SPECT. Currently, the widespread use of PET for myocardial perfusion imaging is hampered by several factors including high costs and the necessity for an on-site cyclotron or Rubidium generator. However, new tracer development will facilitate dissemination of quantitative cardiac PET [4,5]. Prospective comparative studies between attenuation corrected CZT SPECT imaging and other non-invasive functional tests such as myocardial perfusion imaging with PET or MRI need to be conducted to assess diagnostic and prognostic value, and the cost-effectiveness of these modalities. Furthermore, more studies are warranted in patients with discrepant myocardial perfusion results and FFR findings to determine optimal treatment strategy and long-term outcome.
Summary, Conclusion and Future perspectives

MYOCARDIAL PERFUSION IMAGING WITH CALCIUM SCORING

This thesis has also demonstrated the role of simultaneous CACS in symptomatic patients referred for SPECT imaging. However, future studies are needed to assess the diagnostic and prognostic value of myocardial perfusion imaging with simultaneous CACS. Furthermore, the long-term impact of clinical management based on CACS knowledge in patients with normal MPI findings need to be studied.

ALGORITHMS FOR MULTIMODALITY AND HYBRID IMAGING

Although we have showed the feasibility of a stepwise algorithm starting with stress SPECT imaging and CACS, different diagnostic algorithms can be used alternatively for multimodality or hybrid imaging. Future studies should assess the optimal initial test in different patient populations and the various imaging strategies require prospective comparison.

Possibly, initial CACS has the potential to determine optimal imaging strategy for a sequential approach. In such a strategy patients with a CACS <400 will most likely benefit from CCTA owing to the high negative predictive value, while patients with CACS >400 will benefit from a functional test. In addition, patients with extensive coronary calcification (i.e. CACS >700) may be referred for PET perfusion imaging when available due to the higher accuracy in detecting relevant CAD due to improved temporal and spatial resolution, more accurate attenuation correction, and the potential for absolute myocardial blood flow quantification [6,7].

Future studies will put more focus on combining CCTA with CT perfusion results and non-invasive FFR measurement derived from coronary CT, while CCTA images can also be fused into 3D hybrid images without additional radiation with MRI perfusion or stress echocardiography images [8,9]. Finally, the impact of multimodality and hybrid cardiac imaging on downstream ICA and coronary revascularization rates need to be studied.

The non-invasive diagnostic work-up of patients with suspected stable CAD has considerably improved in recent years, with rapid developments in various cardiac imaging modalities. At the same time, important advances have been made in the integration of different imaging modalities. Non-invasive testing will play an increasing role in which a patient-tailored approach is recommended to accurately exclude relevant CAD, and to improve selection of patients who may benefit from coronary revascularization to improve survival and to relieve persisting symptoms.
Chapter 9

References


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CHAPTER 10

Samenvatting
Zowel anatomische als functionele informatie zijn nodig voor de optimale selectie van patiënten die baat kunnen hebben bij een invasieve behandeling van hun coronarialijden [1]. De risico’s, hoge kosten en lage diagnostische opbrengst van traditionele invasieve coronair angiografie benadrukken het belang van verbeteringen in de huidige niet-invasieve diagnostiek [2,3]. Iedere diagnostische modaliteit heeft zijn voor- en nadelen en vooralsnog is geen enkele techniek perfect geschikt voor alle patiënten. De niet-invasieve klinische beoordeling van coronarialijden en het hieruit volgende klinische beleid kunnen worden verbeterd middels de complementaire informatie verkregen door SPECT, CACS en CCTA. Initiële studies hebben de aanvullende diagnostische en prognostische waarde aangetoond voor multimodaliteitsdiagnostiek danwel hybride beeldvorming. Echter, de waarde in de klinische dagelijkse praktijk voor stabiele patiënten met een laag tot intermediair risico blijft onbekend. Voorts zijn de klinische consequenties van een eendaags stapsgewijs protocol voor cardiale hybride diagnostiek onbekend. Daarnaast is er nog weinig bekend over de klinische waarde van de recent geïntroduceerde SPECT camera’s met CZT detectoren.

De doelen van dit proefschrift waren derhalve om de klinische waarde en de potentiële rol van recent geïntroduceerde CZT SPECT camera’s en multimodaliteitsdiagnostiek te beoordelen. Hierbij hebben we gebruik gemaakt van een stapsgewijs algoritme voor SPECT, CACS en CCTA in de dagelijkse praktijk.

In HOOFDSTUK 1 wordt een introductie van het onderwerp en de achtergrond van dit proefschrift gegeven.

De laatste generatie gamma camera’s, die gebruik maken van CZT detectoren, leveren superieure beeldkwaliteit en maken een kortere scantijd mogelijk door de verbeterde sensitiviteit en beeldcontrast. Daarentegen zijn de CZT camera’s duurder en enkel geschikt voor perfusiescintigrafie van het hart, waarbij de toegevoegde klinische waarde van deze camera’s grotendeels nog moet blijken.

In HOOFDSTUK 2 hebben we de klinische consequenties van SPECT myocard-perfusiescintigrafie van de nieuwe CZT SPECT camera vergeleken met die van een conventionele SPECT camera. In totaal hebben 456 patiënten een stress SPECT ondergaan. De eerste helft van de patiënten werden gescand met een conventionele SPECT camera (n=225), terwijl de andere helft een SPECT scan op de CZT camera kregen (n=231). Indien nodig geacht werd een aanvullende rust SPECT scan verricht, hetgeen nodig bleek in slechts 35% van de patiënten gescand met de CZT SPECT camera in tegenstelling tot 56% van de patiënten gescand met de traditionele SPECT
Samenvatting

camera ($p<0.001$). De gemiddelde hoeveelheid toegediende radiotracer per patiënt was 22% lager in de groep van patiënten gescand met de nieuwe CZT camera: 658±390 MBq in de CZT groep en 840±421 MBq in de conventionele groep ($p<0.001$). Ook bleek de gemiddelde totale scantijd per patiënt significant lager met de nieuwe camera: 6.39±1.41 minuten in de CZT groep en 20.40±7.46 minuten in de conventionele groep ($p<0.001$). De 1 jaar prognose in beide groepen was identiek.

Deze bevindingen tonen dat stress SPECT beelden gemaakt met een CZT camera vaker als normaal worden geïnterpreteerd. Hierdoor is een aanvullende rust scan minder vaak nodig voor patiënten gescand met een CZT camera, hetgeen resulteert in lagere stralingsdoses en kortere scantijden.

Zoals reeds eerder werd vermeld is het essentieel om functionele informatie te verkrijgen in patiënten met kransslagadervernauwingen gedetecteerd middels een anatomische test. SPECT myocardperfusiescintigrafie is één van de modaliteiten om het hemodynamische belang van coronarialijden te beoordelen. Tegenwoordig wordt de invasieve FFR meting in toenemende mate toegepast om ischemie aan te tonen. FFR is een invasieve procedure om de bloeddruk en de doorstroming door een specifiek gedeelte van een kransslagader te meten. Momenteel wordt de FFR meting door vele cardiologen als de meest accurate test gezien voor de detectie van ischemie, waarbij tevens prognostische informatie wordt verkregen. Uit eerdere studies blijkt de mate van overeenkomst tussen traditionele SPECT en FFR matig te zijn, echter, de uitkomsten van de nieuwe CZT SPECT camera en FFR zijn nog niet eerder vergeleken. In HOOFDSTUK 3 hebben we de concordantie tussen de CZT SPECT uitslagen en invasieve FFR bepalingen bepaald in 100 stabiele patiënten met een intermediaire coronairstenose. Ischimische SPECT bevindingen bleken aanwezig in 31% van de patiënten, terwijl FFR ischemie detecteerde in 20% van de patiënten. De concordantie tussen CZT SPECT en FFR bedroeg 73% op patiënt niveau, terwijl de concordantie 79% bedroeg bij analyse van alle coronairvaten waarbij een FFR werd verricht.

Deze studie toont een matige concordantie tussen CZT SPECT en FFR, hetgeen overeenkomt met eerdere bevindingen voor conventionele SPECT. Voorts bleken de meeste intermediaire coronairvernauwingen niet functioneel van belang te zijn.

Hieruit concluderen wij dat de discordantie tussen FFR en SPECT intrinsiek is en dat beide onderzoeken verschillende fenomenen onderzoeken: een drukgradiënt over een stenose gemeten met een katheter versus weefselperfusie gemeten met een flow tracer. Het blijft nog onduidelijk welke test uiteindelijk correct zal blijken.
Naast de nieuwe type SPECT camera, hebben we tevens de klinische aspecten van CCTA bestudeerd. In tegenstelling tot invasieve luminografie is CCTA tevens in staat om verschillende aspecten van de vaatwand te tonen zoals calcificaties, echter CCTA is ook in staat om congenitale anomalieën zoals myocardiale bridging te detecteren. Bij bridging verloopt een deel van de coronairarterie intramyocardiaal, waarbij pijn op de borst kan optreden door systolische compressie door het myocard. Voorts is er weinig studie gedaan naar de prevalentie van myocardiale bridging in symptomatische patiënten verwezen voor CCTA wegens een verdenking op stabiel coronairlijden. Derhalve hebben wij in HOOFDSTUK 4 onderzoek gedaan naar de prevalentie en voorspellers van myocardiale bridging in 934 patiënten die een klinisch geïndiceerde CCTA hebben ondergaan. Myocardiale bridging kon worden gedetecteerd in 152 patiënten (16%). Deze patiënten met bridging waren jonger en hadden een lagere prevalentie van coronairsclerose. De prevalentie van myocardiale bridging gedetecteerd door CCTA is hoger in vergelijking met de gepubliceerde frequenties voor invasieve coronairangiografie, en de aanwezigheid van myocardiale bridging zou een verklaring kunnen zijn voor de symptomen in sommige van de patiënten zonder obstructief coronairlijden.

In HOOFDSTUK 5 beschrijven wij de klinische ervaringen met ons geïndividualiseerde, stapsgewijze algoritme waarbij wij gebruik maken van SPECT, CACS en eventueel CCTA. Hybride cardiale SPECT/CT diagnostiek werd toegepast in patiënten met een verdenking op stabiel coronairlijden. In totaal ondergingen 2411 patiënten zonder coronare voorgeschiedenis stress SPECT perfusiescintigrafie met gelijktijdig CACS. Een normale stress SPECT uitslag werd gevonden in 53% van alle patiënten, waarvoor aanvullende onderzoeken achterwege kon worden gelaten. Van de 1144 patiënten die een aanvullend onderzoek ondergingen werd een CCTA verricht in 618 patiënten. Door een aanvullende CCTA kon obstructief coronairlijden worden uitgesloten in 73% van de patiënten met een abnormale stress-rest SPECT, waaronder 50% van de patiënten met evidente ischemische SPECT bevindingen. Na een follow-up van 29 maanden hadden deze patiënten een uitstekende prognose.

Dit stapsgewijze algoritme levert zowel anatomische als functionele informatie en het blijkt dat de combinatie van SPECT met CCTA de tekortkomingen van elk onderzoek afzonderlijk minimaliseert. Derhalve is deze methode te prefereren boven SPECT danwel CCTA als afzonderlijke test. Dit algoritme lijkt tevens te verkiezen boven een standaard stress-rest SPECT protocol, danwel een standaard compleet SPECT/CCTA protocol.
Samenvatting

Wij zijn van mening dat het ‘Zwolle fast track’ algoritme de modaliteiten op een verstandige en conservatieve wijze toepast, waarbij desalniettemin alle benodigde klinische informatie binnen 1 dag kan worden verkregen. We hebben gekozen voor een stapsgewijze benadering met initieel stress SPECT scintigrafie, wegens de toepasbaarheid hiervan in onze bestaande klinische protocollen, welke reeds ruim 20 jaar gebaseerd zijn op een unieke en solide samenwerking tussen de afdelingen van de cardiologie en nucleaire geneeskunde. Andere algoritmes zijn uiteraard mogelijk, zolang zowel anatoomsch als fysiologische informatie kan worden verkregen.

Met de 64-slice hybride SPECT/CT camera is het mogelijk om zowel SPECT als CT onderzoeken te verrichten. De relatief gemakkelijk te verkrijgen informatie van de CACS hebben we routinematig bepaald naast de SPECT perfusiescintigrafie in onze patiënten hetgeen we hebben bestudeerd in deze thesis. Dit levert nieuwe aanvullende informatie op bovenop de SPECT en hierbij werden diverse aspecten van gecombineerd SPECT en CACS diagnostiek bestudeerd. Coronaire calcificaties zijn zeer specifiek voor de aanwezigheid van atherosclerose in de coronairvaten.

Een van dergelijke aspecten was onze hypothese dat CACS de SPECT beoordeling zou kunnen verbeteren. Derhalve hebben we in HOOFDSTUK 6 de invloed van CACS kennis op de visuele SPECT beoordeling onderzocht in 151 patiënten met een klinische verdenking op stabiel coronairlijden. De SPECT beelden werden beoordeeld in 2 aparte sessies, eerst zonder kennis en nadien met kennis van de CACS. De kennis van de CACS bleek de SPECT beoordeling te beïnvloeden in 56 patiënten (37%). Noemenswaardig is het feit dat het aantal dubieuze SPECT uitslagen hierdoor afnam van 21% naar 9% ($p=0.002$). Hieruit blijkt dat kennis van de CACS een belangrijke impact heeft op de visuele SPECT beoordeling, waardoor de diagnostische zekerheid van de beoordelaars toeneemt.

Daarnaast hebben we gekeken naar de subgroep van patiënten zonder enige detecteerbare coronair calcificaties.

HOOFDSTUK 7 beschrijft het vermogen van een calcium score van 0 voor het uitsluiten van functioneel relevant coronairlijden in een homogene populatie met stabiele angineuze klachten en een laag tot intermediaire vooraf kans. In deze studie werden 868 patiënten zonder coronair voorgeschiedenis geïncludeerd, die zowel SPECT perfusiescintigrafie als CACS ondergingen. In patiënten met abnormale SPECT resultaten werd een aanvullende CCTA verricht indien mogelijk. De SPECT scan bleek volstrekt normaal in 88% van de patiënten, terwijl middels een aanvullende
CCTA (11%) of invasieve coronair angiografie (1%) de aanwezigheid van obstructief coronairlijden kon worden uitgesloten in de patiënten met een abnormale SPECT scan. Na een mediane follow-up van 17 maanden (IQR: 11–24 maanden) bleken er geen coronair events te zijn opgetreden. De bevindingen van deze studie tonen dat een calcium score van 0 kan helpen om obstructief coronairlijden uit te sluiten in stabiele laag-intermediair risico patiënten. Dit ondersteunt de mogelijkheid van CACS als een simpele en veilige test om patiënten te selecteren voor eventueel aanvullend onderzoek danwel ontslag.

Naast de relevante klinische waarde van een calcium score van 0, waren wij tevens geïnteresseerd in juist het tegenovergestelde, de waarde van een sterk verhoogde CACS in patiënten verwezen voor SPECT scintigrafie.

Derhalve onderzochten wij de impact van SPECT perfusiescintigrafie bij symptomatische patiënten met extreme coronaire calcificaties (gedefinieerd als een CACS $>1000$) in HOOFDSTUK 8.

Wij hebben 282 stabiele patiënten zonder coronaire voorgeschiedenis retrospectief geïdentificeerd die gelijktijdig een SPECT en CACS hebben ondergaan bij wie een CACS $\geq 1000$ was gedetecteerd. De SPECT bleek normaal in 54% van de mensen, dubieus in 10% en abnormaal in 37% van de patiënten. Een abnormale SPECT uitslag werd met name gezien in mannen, rokers en de patiënten met een nog hogere CACS. In ongeveer 30% van deze patiënten met een CACS $\geq 1000$ toonde de SPECT aanwijzingen voor ischemie, waarbij de aanwezigheid van ischemie een sterke voorspeller voor revascularisatie blijkt (odds ratio 13.1; 95%CI 7.1, 24.3; $p<0.001$).

Hieruit concludeerden wij dat de meerderheid van de symptomatische patiënten met een CACS $\geq 1000$ een normale SPECT perfusiescintigrafie heeft. Echter, patiënten met normale SPECT bevindingen met extreme coronaire calcificaties dienen intensief te worden vervolgd, daar de persistierende klachten vaak toch gebaseerd zijn op relevant coronairlijden waarvoor uiteindelijk revascularisatie is vereist. Concluderend, de verdenking op ernstig coronairlijden bij deze patiënten dient hoog te blijven gedurende de follow-up ondanks de normale SPECT uitslagen. Bij dergelijke patiënten met persistierende klachten dient een invasieve coronair angiografie te worden overwogen.
Samenvatting

Toekomstperspectieven

De studies beschreven in dit proefschrift tonen de klinische waarde van CZT SPECT en hybride SPECT/CT diagnostiek in patiënten met een verdenking op stabiel coronariaalijden. Het beschreven werk in dit proefschrift vormt een basis voor diverse nieuwe toekomstige onderzoeken.

MYOCARDPERFUSIESCINTIGRAFIE
Onze studies tonen de waarde van CZT SPECT diagnostiek voor de dagelijkse praktijk. Toekomstige studies zijn echter nodig om de lange termijn prognostische waarde van CZT SPECT aan te tonen. Daarnaast zal tevens de aanvullende diagnostische waarde van kwantitatieve myocardscintigrafie middels dynamische CZT SPECT verder onderzocht worden. Momenteel wordt het grootschalig gebruik van PET voor myocardscintigrafie beperkt door verschillende factoren, waaronder de hoge kosten en de noodzaak voor een cyclotron (= deeltjesversneller) of een Rubidium generator. De beschikbaarheid van recent ontwikkelde nieuwere PET perfusietracers zal het klinische gebruik van PET perfusiescintigrafie aanzienlijk doen toenemen [4,5]. Prospectief opgezette studies om CZT SPECT en andere non-invasieve functionele testen, zoals PET en MRI perfusiescintigrafie, te vergelijken, zullen de diagnostische en prognostische waarde onderzoeken, almede ook de kosteneffectiviteit van de diverse onderzoeksmodaliteiten. Bovendien zijn er meer studies nodig om de optimale therapie en de hiermee gepaard gaande lange termijn prognose te bepalen voor patiënten met discrepante FFR en perfusie resultaten.

SPECT IN COMBINATIE MET CALCIUMSCORE
Dit proefschrift beschrijft tevens de toegevoegde waarde van het gelijktijdig verrichten van CACS in patiënten verwezen voor een SPECT onderzoek. De toegevoegde diagnostische en prognostische informatie van CACS in deze patiënten dient verder te worden onderzocht. Daarnaast dient het effect van de gelijktijdige acquisitie van SPECT en CACS op de uiteindelijke therapiekeuze van de hoofdbehandelaar te worden onderzocht.

NON-INVASIEVE CARDIALE HYBRIDE DIAGNOSTIEK
In onze studie tonen wij de toepasbaarheid van een stapsgewijs algoritme beginnend met stress SPECT diagnostiek en CACS. Er zijn echter diverse alternatieve strategieën.
mogelijk. In de toekomst dient de optimale initiële test te worden onderzocht voor verschillende patiëntendemografie.

Wellicht dat het verrichten van een initiële CACS kan helpen om de optimale strategie te bepalen. Hierbij zullen patiënten met een CACS <400 waarschijnlijk het meeste baat hebben bij een CCTA vanwege de hoge negatieve voorspellende waarde van CCTA. Daarnaast kunnen patiënten met een sterk verhoogd CACS (bijvoorbeeld >700) geselecteerd worden om (indien beschikbaar) een PET perfusiescan te ondergaan vanwege de betere detectie van gebalanceerde ischemie [6,7].

Toekomstige studies zullen zich meer gaan focussen op het combineren van CCTA met CT perfusiescintigrafie en non-invasieve FFR metingen. Bovendien kunnen CCTA beelden tegenwoordig gefuseerd worden tot 3D hybride beelden zonder additionele stralingsbelasting door gebruik te maken van MRI perfusie of stress echocardiografie beelden [8,9]. Tot slot, dient de impact van multimodaliteit en hybride diagnostiek op therapeutische keuze verder te worden onderzocht.

De detectie van stabiel coronarylijden is de afgelopen jaren aanzienlijk verbeterd met snelle ontwikkelingen van de verschillende beschikbare non-invasieve onderzoeksmodaliteiten. Daarnaast is er een grote vooruitgang geboekt met de integratie van de verschillende diagnostische testen. Non-invasieve diagnostiek zal in toenemende mate een rol gaan spelen. Hierbij kan een patiënt-specifieke benadering worden aangeraden om zo accuraat mogelijk obstructief coronarylijden uit te sluiten, en daarnaast de juiste patiënten te selecteren voor een invasieve behandeling om de overleving te verbeteren en de klachten te verlichten.
List of publications

Dankwoord

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Dankwoord

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The author of this thesis was born on January 17th, 1982 in Winterswijk, The Netherlands. He attended the ‘scholengemeenschap de Driemark’ in Winterswijk and graduated in 2000. During the same year he started studying medicine at the Erasmus University in Rotterdam. During his medical training in 2004 he was selected to perform clinical research for a 5-month term under the guidance of prof. dr. M.J. Krasna at the department of Cardiothoracic Surgery in Baltimore, United States. He obtained his medical degree in January 2007 after finishing a 4-month cardiology clerkship at the Erasmus Medical Center under guidance of dr. A.P.J. Klootwijk. He started working at the cardiology department in Reinier de Graaf hospital in Delft for 6 months, and in September 2007 he continued his cardiology career in Zwolle. From November 2008 until December 2012 he worked as a PhD-student in which he was involved with the implementation and optimisation of a dedicated cardiac SPECT/CT imaging program for stable patients suspected of having coronary artery disease. The registration of these patients including subsequent follow-up and analysis have resulted in this thesis. In January 2013 he was accepted as a trainee in cardiology and started his residency at the department of Cardiology in Zwolle under the guidance of dr. A.R. Ramdat Misier. He started his two-year residency in internal medicine in January 2014 under the guidance of dr. P.H.P. Groeneveld.