Non-invasive imaging of coronary artery disease and its functional consequences

The Hybrid SPECT and CCTA approach

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- The Hybrid SPECT and CCTA approach -

Niet-invasieve beeldvorming van coronairlijden en zijn functionele consequenties

- De Hybride SPECT en CCTA benadering -
(met een samenvatting in het Nederlands)

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Aan Suleika

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Chapter 1

General introduction and outline of the thesis

For several decades invasive coronary angiography (CA) has been the reference standard in the assessment of coronary artery disease (CAD) severity. Patients with high pre-test likelihood of CAD, receive a Class 1 indication for CA [1,2]. Several factors, however, motivate the need for a reliable non-invasive imaging modality, especially in patients with a high pre-test likelihood. Not only to rule out, but also to reliably diagnose coronary stenosis with functional consequences (significant CAD) and guide therapeutic decision making.

Performance of CA in all patients with high pre-test likelihood of CAD has undeniable drawbacks. First of all, the prevalence of angiographically significant CAD in patients with high pre-test likelihood may be as low as 44-46% [3,4]. In real life, the prevalence of significant CAD in patients referred for CA is even lower at only 36.7%, according to the national cardiovascular data registry of the United States [5]. Secondly, angiographic severity of CAD does not reliably predict its main functional consequence: myocardial ischemia [6-8]. Because evidence of myocardial ischemia is needed before deciding whether revascularization is necessary, additional (non-) invasive tests are needed [2]. Finally, CA comes with high costs as a result of the need for admission to a hospital or day-care facility and a low risk (0.1%) of serious adverse events [9].

With the advent of computed tomography coronary angiography (CCTA) and the known reliability of single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) a combination of non-invasive imaging modalities became available that potentially could reliably diagnose significant CAD. The high diagnostic accuracy of this combination has previously been shown in highly selected patient populations [10-14]. Nevertheless, data demonstrating the applicability of hybrid SPECT and CCTA in diagnosing significant CAD in stable patients with an intermediate to high pre-test likelihood of CAD are still lacking. Furthermore, the contribution of these tests to therapeutic decision making in these patients is unknown. Providing evidence on both of these issues is the main objective of this thesis.

Non-invasive imaging in patients suspected of coronary artery disease

Diagnostic work-up of patients suspected of significant CAD begins with the assessment of pre-test likelihood according to risk scores (e.g. the Diamond and Forrester model or Duke Clinical Score) based on age, gender and angina typicality [15,16]. After this, cardiologists choose from wide variety of (non-) invasive imaging procedures to diagnose the presence or absence of significant CAD. From the selection of non-invasive imaging procedures SPECT, CCTA and coronary calcium scoring (CCS) can be obtained from hybrid SPECT/CT imaging.

Myocardial perfusion SPECT

Nuclear myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is known for its role in diagnosis, risk stratification and guidance of treatment decision making in patients with suspected significant CAD [17, 18]. Patients with normal perfusion and function on ECG-gated SPECT have an excellent prognosis and are best served with primary prevention [19]. Patients with a mild to moderate ischemic burden (<10% ischemic myocardium) benefit most from medical therapy whereas those with severe ischemia (>10% ischemic myocardium) benefit most from revascularization [20]. These observations are reflected in current guidelines which recommend revascularization only in patients with (non-) invasive evidence of ischemia [2].

In patients with high pre-test likelihood of CAD, the diagnostic performance of SPECT is limited with estimates of sensitivity as low as 56% and specificity between 39% and 62% [17, 21, 22]. This limited accuracy is probably due to an important fraction of non-conclusive results as a result of small perfusion defects (1-2 segments), inadequate heart rate response (e.g. failure to reach 85% of maximum predicted heart rate or 5 metabolic equivalents (MET) during exercise), and discrepant clinical data (e.g. typical angina per history or ≥2 mm ST-segment depression on ECG during exercise) [23]. Additionally, in a substantial number of patients with high-risk CAD, the severity of ischemia could be underestimated or completely undetected due to balanced ischemia [24, 25].

Coronary calcium scoring

Coronary calcium scoring (CCS) is known for its role in risk prediction in asymptomatic patients. Asymptomatic patients with CCS <10 are at low risk for major adverse cardiovascular events during follow-up [26-29]. As coronary calcium increases, so does the risk of cardiovascular events [26-29]. In patients with an intermediate predicted risk, the amount of coronary calcium is helpful in reclassifying patients into low- or high risk groups [30].

The diagnostic value of CCS in patients with anginal complaints is disputed. The negative predictive value of a CCS of zero for the presence of significant CAD is reported to be almost 100% [31-33]. However, the presence of a significant coronary stenosis as a result of non-calcified (soft) plaque is still possible in these patients. The prevalence of significant stenosis due to non-calcified plaque increases with the pre-test likelihood of CAD to 12-65% [34, 35]. In contrast, the presence of coronary calcium does not prove the presence of significant CAD [36]. According to a pooled analysis, only approximately 35% of symptomatic patients with a CCS greater than 0 were found to suffer from CAD defined by a lumen reduction of greater than 50%[37].

Coronary computed tomography angiography

Three major trials established the role of CCTA in excluding significant CAD, reporting negative predictive values (NPV) ranging from 89%-99% [38-40]. Due to a tendency to overestimate stenosis severity, positive predictive value (PPV) for significant CAD remains limited (48-83%), even with the newest generation of scanners [41]. Patients with an intermediate- to high pre-test likelihood of CAD are specifically vulnerable to false positive or non-conclusive results due to coronary calcifications, evaluation of small vessels and artifacts caused by fast heart rates and prospective scanning modes [38-40, 42, 43].

The exclusion of significant CAD by CCTA comes with an excellent prognosis in both patients with and without chest pain symptoms [44-47]. An increasingly worse prognosis is described for patients without CAD, non-obstructive CAD, non-high risk obstructive CAD and high risk obstructive CAD respectively. In these categories annual mortality rates were described of 0.65%, 1.14%, 1.41% and 2.63% respectively [44, 45]. High risk obstructive CAD was defined as 2 vessel disease (VD) including proximal left anterior descending (LAD), 3VD and left main stenosis.

While it seems straightforward to initiate a primary or secondary preventive treatment regimen for patients without CAD or non-obstructive CAD on CCTA, respectively, treatment initiation (medical therapy or revascularization) based on CCTA findings alone have not been evaluated in a prospective study. However, it was shown that the presence of high risk CAD on CCTA is associated with a benefit (lower all-cause mortality rate) from revascularization [47]. In contrast, the presence of less severe forms of CAD was found to be associated with a benefit from optimal medical therapy in the same study [47].

Hybrid myocardial perfusion SPECT and coronary CT angiography

Current guidelines on hybrid SPECT/CCTA describe the main role of hybrid SPECT/CCTA in patients with an intermediate to high risk of CAD and a non-conclusive result of either SPECT or CCTA as a standalone modality [48].

Thus far, five studies have described the diagnostic accuracy of hybrid SPECT/CCTA for significant CAD versus CA as reference standard. Sensitivity and specificity values ranging from 89%-99% and 67-95% respectively, have been reported [10-14]. However, the generalizeability of these studies is limited because hybrid imaging was studied as a standalone test in highly selected patient populations and an anatomical reference standard was used. Additionally, two studies used an obsolete imaging protocol [10-14].

Hybrid SPECT/CCTA findings can be categorized according to the concordance of a coronary stenosis on CCTA with a perfusion defect in the corresponding myocardial territory on SPECT, or vice versa. The prognostic usefulness of Hybrid SPEC/CCTA as well as it's effect on choice of treatment strategy were studied in subgroups of patients with a matched stenosis and perfusion defect, an unmatched stenosis or perfusion defect and normal findings from both SPECT and CCTA [49, 50]. A complete definition of matched, unmatched and normal hybrid SPECT/CCTA results is provided in chapter 7 of this thesis. An increased incidence of major adverse cardiac events has been found in patients with normal, unmatched and matched hybrid SPECT/CCTA findings during in a study with a median follow up of 2.8 years [49]. However, whether the imaging result had any influence on the choice of treatment strategy remained unclear [50].

Aims and outline of the thesis

This thesis aims to compare the diagnostic yield of hybrid SPECT/CCTA to the diagnostic yield of more established diagnostic procedures such as CCS and standalone SPECT or CCTA. Additionally, the effect of hybrid SPECT/CCTA on therapeutic decision making is studied.
The thesis is based on the patient population included in the High and intermediate Spect-Ct OPtimization study (HoRoSCOPe). The population for this study was prospectively acquired and the main inclusion criterion was an intermediate to high pre-test likelihood of CAD based on based on Diamond and Forrester criteria [15]. The protocol for this study is described in detail in **chapter 1.1**.

In **chapter 2,** a case report is presented that demonstrates the pitfalls of standalone anatomical imaging with CCTA and functional imaging with myocardial perfusion SPECT.

Chapters 3 to 5 describe the single test accuracy of exercise stress electrocardiography (X-ECG), CCS, SPECT and CCTA and combinations thereof for the diagnosis of CAD in the HoRoSCOPe population. In **chapter 3,** we studied whether addition of X-ECG results is of value in the diagnostic work-up after the acquisition of CCS in these patients. As stand-alone procedures, X-ECG and CCS have limited diagnostic accuracy. We evaluated whether the combination of these tests leads to a more accurate exclusion of significant CAD. In **chapter 4,** we studied whether the combination of CCS and SPECT leads to a more accurate diagnosis of significant CAD. We specifically evaluated the incremental diagnostic accuracy of CCS in addition to SPECT. In **chapter 5**, we studied the diagnostic performance of hybrid SPECT/CCTA by comparing it to a reference standard of fractional flow reserve (FFR) measurements in a subgroup of patients from the HoRoSCOPe study with non-conclusive SPECT or CCTA results. We specifically evaluated the incremental diagnostic accuracy of the complementary nature of hybrid SPECT/CCTA imaging in these patients.

Hybrid imaging has an impressive diagnostic accuracy when evaluated as a single-test. In **chapter 6,** we studied whether hybrid SPECT/CCTA improves the diagnostic work-up beyond X-ECG, CCS and standalone SPECT or CCTA in the HoRoSCOPe population.

In **chapter 7,** we studied the applicability of hybrid SPECT/CCTA imaging in the process of clinical decision making. We evaluate whether hybrid SPECT/CCTA is able to accurately guide towards (a method of) revascularization in the presence of significant CAD or a medical treatment regimen if significant CAD is ruled out.

Chapters 8 and 9 are case reports. **Chapter 8** describes hybrid SPECT/CCTA imaging in a patient with an unroofed coronary sinus without a persisting left superior vena cava. **Chapter 9** describes CCTA imaging in a patient with a pseudoaneurysm of the aortic root.

In the general discussion, **chapter 10**, we discuss the challenges of hybrid image acquisition and reconstruction. Additionally, patient selection for hybrid imaging and the value of hybrid imaging in the process of therapeutic decision making is discussed. Finally, we present recommendations for further studies.

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Chapter 1.1

The High and intermediate Risk Spect-Ct OPtimization (HoRoSCOPe) study

The current thesis is based on the High and intermediate Risk Spect-Ct OPtimization study (HoRoSCOPe). This study was conducted in the St. Antonius Hospital, Nieuwegein, The Netherlands, between September 2009 and March 2012. The main objective of the study was to evaluate the clinical value of hybrid myocardial perfusion SPECT (SPECT) and coronary computed tomography angiography (CCTA) in an unselected, prospectively acquired population. Patients with stable chest pain symptoms referred for SPECT and an intermediate to high pre-test likelihood of CAD based on Diamond and Forrester criteria were included [1]. Patients with a history of surgical revascularization, stent implantation, an unstable cardiac condition or a cardiac rhythm other than sinus rhythm were excluded.

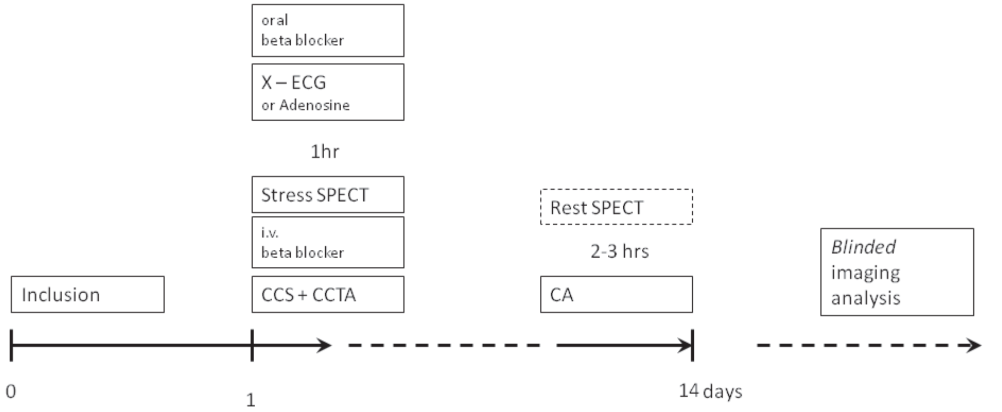

Figure 1 Sequence of diagnostic work-up. Prior to the first imaging day all patients stopped rate limiting medication. At the start of stress testing all patients received oral metoprolol tartrate. Either exercise stress electrocardiography (X-ECG) or pharmacological stress was performed prior to myocardial perfusion SPECT (SPECT) acquisition. This was directly followed by a non-enhanced CT scan to calculate coronary calcium score (CCS) and coronary CT angiography (CCTA) acquisition. On the second imaging day optional rest SPECT imaging and invasive coronary angiography (CA) including fractional flow measurements (FFR) was performed. In the presence of a normal stress SPECT (normal perfusion and gated data) the rest SPECT was omitted.

As described in Figure 1 all patients were scheduled for hybrid SPECT/CCTA imaging and invasive coronary angiography (CA) with fractional flow reserve (FFR) measurements. Non-invasive imaging acquisition was performed on a hybrid SPECT-CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands) (Figure 2). The components share a common table that is aligned to allow sequential image acquisition, without the need for the patient to physically move from one scanner to another. On day one the hybrid SPECT/CCTA imaging protocol consisted of exercise stress electrocardiography (X-ECG) or pharmacological stress preceding stress SPECT acquisition. Directly following stress SPECT, coronary calcium score (CCS) and CCTA imaging was performed. Within 14 days, on the second day of the protocol, rest SPECT acquisition and invasive CA with FFR-measurements were scheduled. In patients with a normal stress SPECT (normal perfusion and gated data) no rest SPECT was acquired. Directly following the second day, all data were available for the routine clinical heart-team meeting that would formulate a treatment advice which was actually carried out in the outpatient clinic. Subsequently, blinded imaging analysis according to the pre-defined study protocol was conducted. Also, panel sessions were held to evaluate the level of agreement of treatment decisions based on the diagnostic work-up using hybrid SPECT/CCTA imaging and the traditional diagnostic work-up using SPECT and CA.

Figure 2 Hybrid SPECT-CT system, CardioMD gamma camera in the front and Brilliance 64-slice CT scanner in the back (Philips Medical Systems, Best, The Netherlands). The components share a common table (not in the picture) that is aligned to allow sequential image acquisition.

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Chapter 2

Case report – Zero coronary artery calcium in the presence of severe isolated left main stenosis detected by CT coronary angiography in a patient with typical angina and an equivocal myocardial perfusion SPECT

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INTRODUCTION

With the advent of integrated single-photon emission computed tomography (SPECT) and Computed Tomography (CT) systems and the use of low dose coronary calcium scoring (CCS) scans for attenuation correction purposes, high quality anatomical and functional data become readily available for patients with suspected coronary artery disease (CAD) [1, 2]. Myocardial ischemia detected by nuclear perfusion imaging is associated with high CCS. Vice versa it has been suggested that a low CCS in these patients could obviate the need for further invasive testing [3, 4]. However, in patients with a normal myocardial perfusion SPECT, a high CCS could be suggestive of significant coronary artery disease [5-7]. In the current case, we present a patient with intermediate pre-test likelihood of CAD who was referred for SPECT scanning. She was enrolled in a prospective study to evaluate the additive value of CT coronary angiography (CT-A) to SPECT in the diagnosis of significant CAD. In this case no coronary calcium was present and the result of the SPECT study was equivocal. CT-A showed a severe left main stenosis, which was confirmed by invasive coronary angiography (CA).

Case Report

A 58 year-old female patient with no previous history of cardiac disease was referred for non-invasive imaging by myocardial perfusion SPECT. Several months before presentation she had developed typical anginal complaints on moderate physical exertion. Her risk profile constituted of a history of smoking, documented dyslipidaemia treated with statin therapy, diabetes mellitus and a family history of premature CAD. Physical examination revealed no relevant abnormalities. The pre-test likelihood for presence of CAD was 73% according to Diamond and Forrester criteria [8]. She underwent non-invasive imaging. Gated stress and rest SPECT and CT-A including CCS were acquired on a Hybrid SPECT-CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands). Attenuation correction was performed for all images using the CT non-enhanced calcium scan. A weight-adjusted dose of 413MBq ^{99m}Tc-sestamibi was administered during maximal bicycle exercise according to a stepwise protocol. At maximum stress of 96 Watts, 92% of the predicted capacity, she had a heart rate of 146 bpm (90% of the predicted heart rate), and a blood pressure of 154/83 mmHg. Atropine infusion was necessary to reach the target heart rate and she complained of angina pectoris during recovery from stress.

The result of exercise electrocardiography (ECG) should be considered non diagnostic. It did reveal ST segment depression at maximal exertion, although in the absence of a stable baseline. (Figure 1) After attenuation correction, SPECT showed a partially reversible mild perfusion defect in the distal anterior segment and apex, summed stress score (SSS) of 2. (Figure 2) No transient ischemic dilatation was observed. End-diastolic volumes post stress and at rest were 56 ml and 49 ml, respectively. Left ventricle ejection fraction (LVEF) post stress and at rest were similar, 68% and 71% respectively. No wall motion abnormalities were present. CT-A was performed which revealed no coronary calcifications. However, a severe left main stenosis was observed. (Figure 3) On the second day of imaging, rest SPECT images and CA were acquired. The latter confirmed the severe left main stenosis. (Figure 4) Neither CA nor CT-A revealed signs of atheroscleroses in the remainder of the coronary artery tree. The patient was scheduled for coronary bypass surgery, which was performed uneventfully. One year after the procedure she continues to do well with no relapse of anginal complaints.

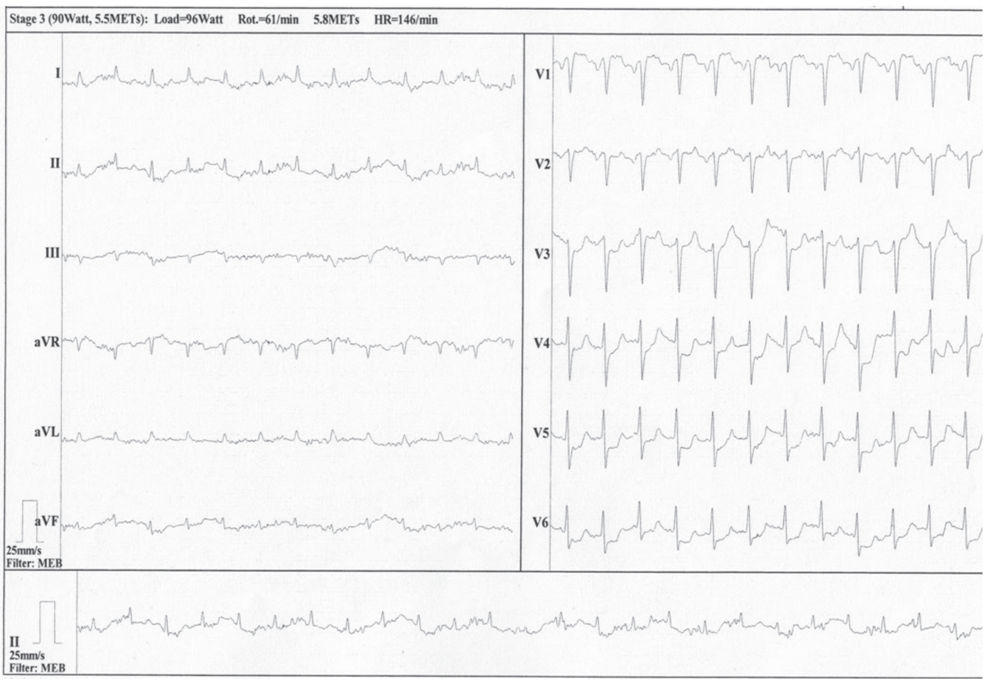

Figure 1. ECG obtained during maximum bicycle stress exercise. No anginal complaints during this stage. ECG should be considered non-diagnostic, it does reveal ST segment depression in leads V4-V6, although in the absence of a stable baseline.

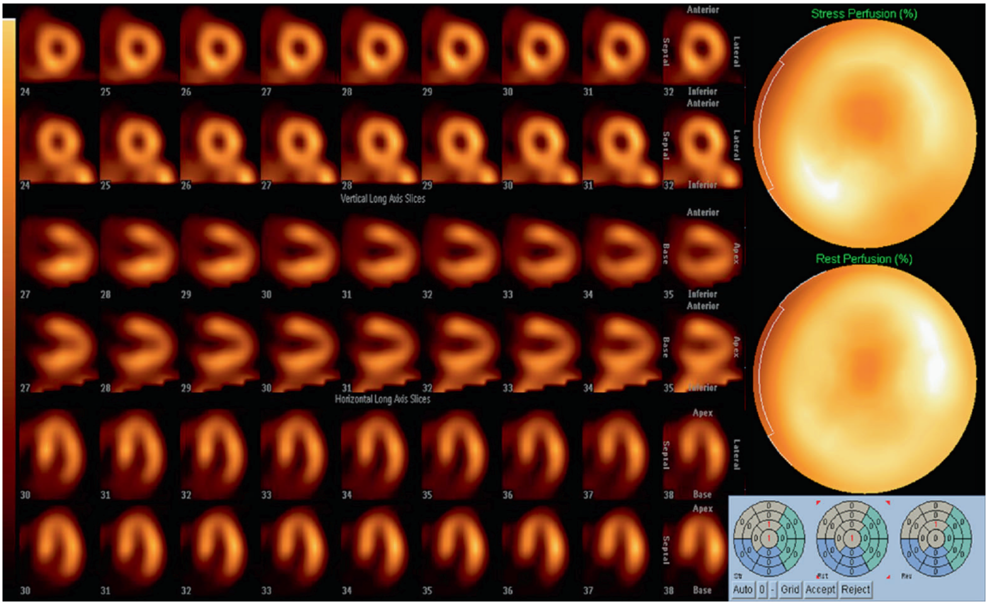

Figure 2. Attenuation corrected myocardial perfusion SPECT. After stress a mild perfusion defect is present in the distal anterior and apical region. This partially persists during rest imaging. This is suggestive of mild ischemia with an SSS of 2. Although it could be interpreted as an attenuation artefact due to breast tissue in the presence of normal wall motion and normal LVEF.

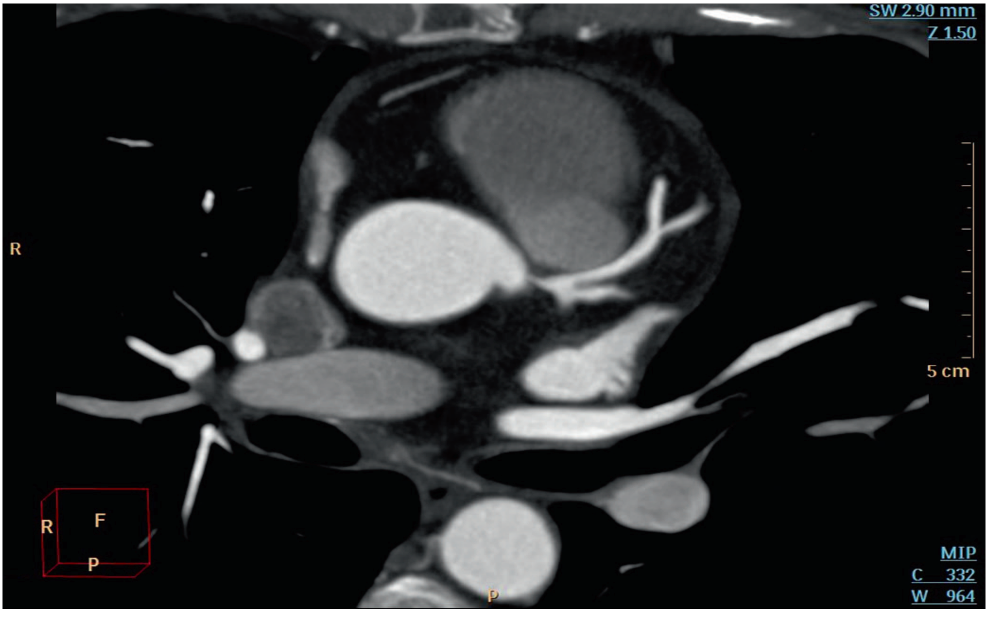

Figure 3. Axial image of CT coronary angiogram showing a severe left main coronary artery stenosis. No calcifications were present in the entire coronary artery tree.

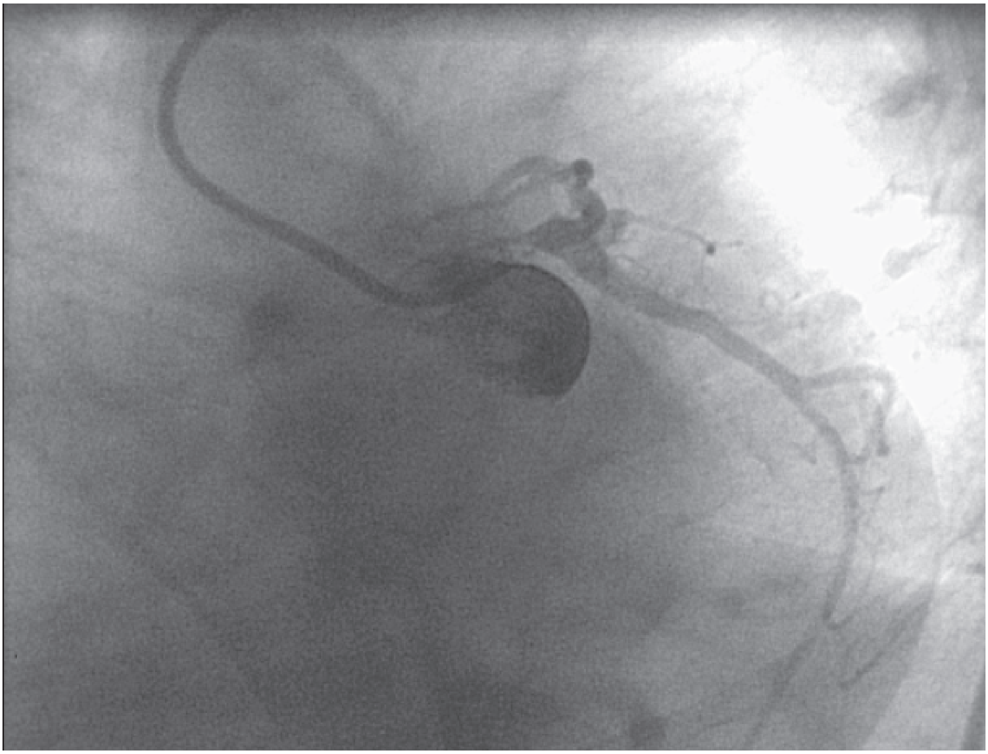

Figure 4. Left caudal view of invasive coronary angiogram confirms the presence of a severe left main coronary artery stenosis.

DISCUSSION

The current case describes the unusual case of a female patient with a CCS of zero in the presence of a severe left main stenosis, and an equivocal stress ECG and SPECT result.

Exercise ECG is known to have limited value in the work-up of women with anginal complaints, with sensitivity and specificity values of 46-79% and 48-86% respectively [9]. Therefore non-invasive imaging frequently is the first step in the diagnostic workup of women. In the overall patient population with anginal complaints, SPECT has a good diagnostic performance. Well-designed studies showed sensitivities ranging from 85-90%. If ECG gated information and attenuation correction algorithms are used, specificity values range between 80 and 90% [10, 11]. However, an important limitation is the rate of false-negative SPECT in patients with three-vessel disease or left main stenosis. Balanced ischemia has been proposed as the mechanism for the lack of perfusion defects in these patients. Due to the principle of interregional flow comparison in SPECT, patients with perfusion abnormalities in all coronary artery territories could have a false negative result. Sensitivity values of 80% to 95% have been reported for the detection of three-vessel disease by SPECT [12, 13]. Symptomatic patients with a normal exercise SPECT study have an annual cardiac death or myocardial infarction rate comparable to the asymptomatic population; 0.7% [10, 11]. The question whether our patient would have had this excellent prognosis remains unanswered. Patients with significant left main stenosis are known to have the worst prognosis of any form of CAD [14].

Our patient, however, had equivocal stress ECG and SPECT results. She had a borderline normal stress ECG and developed anginal complaints during recovery from stress. SPECT imaging was not completely normal; it was suggestive of mild ischemia with an SSS of 2. However, the perfusion defect partially persists during rest and could be interpreted as an attenuation artifact in the presence of normal wall motion and a more severe perfusion defect in the non attenuation corrected images after stress and rest. As such, the combined stress ECG and SPECT result should be regarded inconclusive. These inconclusive SPECT results have a heterogeneous set of causes. Equivocal tests due to artifacts as a result of attenuation or conduction disturbances are from a different order than discrepant tests due to abnormal clinical (typical angina during stress or significant ECG changes) or gated perfusion data (transient ischemic dilatation or loss of LVEF) [15].

With both imaging data sets available, it was postulated that in the presence of normal SPECT scans, high CCS is predictive of significant CAD. A low CCS in these patients is regarded as predictive of the absence of significant CAD [3-7]. CCS per se is known for its role in risk prediction in asymptomatic patients as well as symptomatic patients. Patients with a low to intermediate pre-test likelihood of CAD and no evidence of coronary calcifications have a very low likelihood of CAD and a low risk of adverse cardiac events [16, 17]. On the other hand, in a population of patients referred for CA, the incidence of significant CAD and a CCS of zero is 15-19% [18]. It is questionable whether the crude depiction of coronary anatomy by CCS could solve all diagnostic inaccuracy; in our patient the combined results of stress ECG, SPECT and CCS still would have resulted in a false negative test. Therefore we postulate that CCS cannot be considered definite for excluding obstructive CAD in this setting. The case demonstrates the superiority of CT-A compared to CCS, for confirmatory testing in patients with typical symptoms for CAD and equivocal results on stress ECG and SPECT MPI.

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Chapter 3

Is exercise stress electrocardiography in addition to coronary calcium scoring able to diagnose significant coronary artery disease in patients with an intermediate or high pre-test likelihood?

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Submitted

ABSTRACT

Objectives

Coronary calcium scoring (CCS) has emerged as non-invasive imaging tool to rule out coronary artery disease (CAD) in symptomatic patients. Absence of coronary calcium is associated with a very low prevalence of significant disease and favourable clinical outcome in this population. However, in symptomatic patients with an intermediate pre-test likelihood of CAD and a CCS of zero, the prevalence of significant CAD still could be 12-65%. Also, a large percentage of patients with coronary calcifications have no significant CAD. We evaluate the performance of exercise stress electrocardiography (X-ECG) in addition to CCS in predicting the presence of significant CAD.

Methods

In total, 136 patients (age 63.5±10.2 years, 62.5% male) with an intermediate to high pre-test likelihood of CAD (median 87%, range 22-95) were prospectively included in this study. Of these patients X-ECG, CCS and invasive coronary angiography (CA) were available. Patients were categorized according to three groups of CCS; >400, 0.1 – 400 and CCS 0. X-ECG was defined abnormal in the presence of positive (≥0.1mV ST-segment depression 80ms after the J-point) or non-conclusive results. A luminal loss >50% on CA served as reference standard for significant CAD.

Results

A CCS>400 (P = 0.034) and a positive X-ECG (P< 0.005) were independently predictive for the presence of significant CAD by multivariate analysis. ROC curve analysis revealed an increased diagnostic yield for significant CAD for the combination of CCS and X-ECG (AUC 0.84) versus standalone CCS (AUC 0.69) or X-ECG (AUC 0.65). However, 6 (9%) patients with CCS 0 – 400 and negative X-ECG suffered form significant CAD and 37 (54%) patients with either CCS >400 or abnormal X-ECG were free from significant CAD.

Conclusions

Despite increased diagnostic yield for the combination of CCS and X-ECG, in clinical practice a substantial number of patients without significant CAD would be unduly sent for invasive coronary angiography. Also, 9% of patients with significant CAD would remain undetected.

INTRODUCTION

Coronary calcium scoring (CCS) has emerged as non invasive tool to rule out coronary artery disease (CAD) in patients with symptoms of chest discomfort. Absence of coronary calcium in this heterogeneous population is associated with very low prevalence of significant disease and favourable clinical outcome (1, 2). Whereas increasing coronary calcium scores in these patients is associated with increased prevalence of significant CAD (3). However, in the group of symptomatic patients with (a-) typical anginal complaints and a CCS of zero, the prevalence of significant CAD might still be 12-65% (4-6). Also, in patients with an intermediate or even high pre-test likelihood of CAD, the mere presence or absence of coronary calcium is not diagnostic for significant CAD (7, 8). As such, in these patients additional (non-) invasive tests are needed.

Exercise stress ECG (X-ECG) has been in use as first line test in the evaluation of patients with symptoms of chest discomfort for decades. Guidelines still advocate its role in the majority of patients with stable symptoms since it is widely available, well established and is of low cost. On the other hand X-ECG has limited diagnostic performance and a considerable number of inconclusive results (9, 10). Comparable to the situation with CCS, an additional test is needed in many patients to reliably diagnose significant CAD.

We seek to evaluate whether the combination of these tests could serve as a non-invasive modality to rule out CAD in a population of patients with an intermediate to high pre-test likelihood of CAD.

METHODS

Patient population

For the current analysis we used a patient population enrolled in a study to evaluate hybrid myocardial perfusion single photon emission computed tomography and coronary computed tomography angiography (hybrid SPECT-CCTA) in the diagnosis of significant CAD. Of 204 patients scheduled for hybrid SPECT-CCTA, 136 (67%) had both X-ECG and CCS available and were included in this analysis (Figure 1). Pre-test likelihood was calculated according to Diamond and Forrester criteria (11). Exclusion criteria were a history of coronary artery disease, an unstable cardiac condition or a cardiac rhythm other than sinus rhythm. The study conformed to the principles outlined in the declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients.

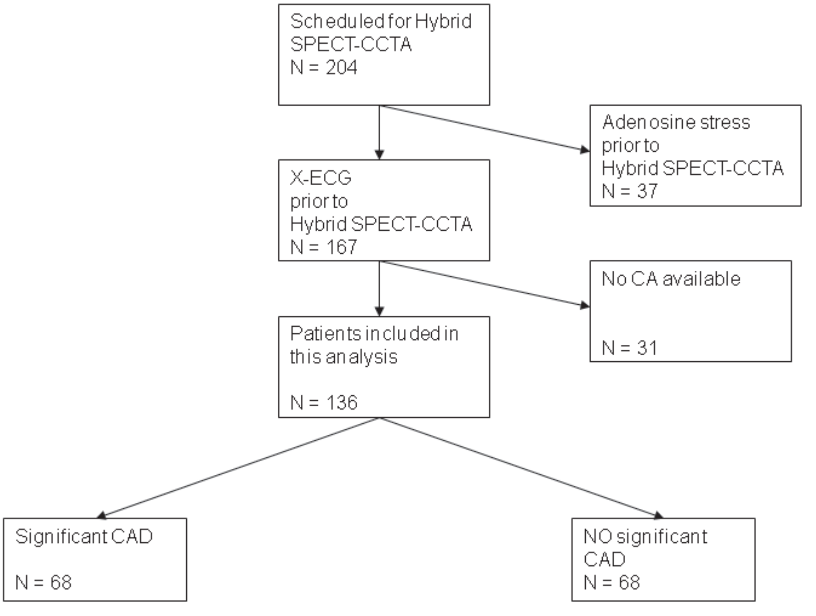

Figure 1. Flowchart for patients included in this analysis

Hybrid SPECT-CCTA=Hybrid myocardial perfusion single photon emission computed tomography and CT coronary angiography; CA = invasive coronary angiography; CAD = coronary artery disease.

Coronary calcium scoring

Imaging data were acquired on a hybrid SPECT-CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands). All patients scheduled for prospectively ECG-triggered axial CCTA received oral metoprolol tartrate at the start of the stress test preceding SPECT imaging. Patients with an initial heart rate below 60 bpm received 50mg and patients with an initial heart rate over 60 bpm received 100mg metoprolol tartrate. Preceding CT scanning additional intravenous metoprolol was administered in 79 patients (mean dose of 13.7±6.0 mg) to achieve a heart rate below 62 bpm. Prior to CCTA, a non-enhanced scan to calculate the CCS was performed with the following scanning parameters: prospective ECG triggered axial scan mode, at inspiration, 2.5mm slice thickness, 120kV tube voltage, 55mAs tube current. The CCS was obtained by multiplying each area of interest with a factor indicating peak density within the individual area, as was proposed by Agatston et al. (12). Patients were then categorized according to three groups of CCS; >400, 0.1 – 400 and CCS 0.

Exercise stress electrocardiography

Bicycle stress electrocardiography was performed according to a previously described stepwise protocol (13). Prior to stress testing all patients stopped rate limiting anti anginal medications. In 45 (33%) patients atropine was required to reach adequate heart rate response. All X-ECG results were reviewed in consensus by two physicians (JS and RMK). Positive X-ECG was defined as ≥0.1mV horizontal shift of the ST segment at 80ms after the J-point in chest leads #5 and #6. Non-conclusive X-ECG was defined as typical angina or >30mmHg decrease in systolic blood pressure during stress without electrocardiographic evidence of ischemia or uninterpretable ECG as a result of an unstable baseline or inability to reach at least 85% of the predicted heart rate (according to gender and age of the subject) without ≥0.1mV horizontal shift of the ST segment at 80ms after the J point. The predicted heart rate was corrected for length, age and sex, using a standardized table (13). Normal X-ECG was defined as the absence of any of the aforementioned criteria. Abnormal X-ECG was defined as a non-conclusive or positive X-ECG result.

Invasive coronary angiography

As part of the prospective study, CA was performed in all patients, including those with normal non-invasive test results. CA was acquired on Allura (Philips Medical Systems, Best, The Netherlands) catheterization equipment via femoral or radial artery access. In all patients biplane views were acquired from all major coronary arteries. Additional views were obtained at the discretion of the performing operator. The angiograms were visually evaluated for lesion severity according to 5 categories of diameter loss; no CAD (0% diameter loss), mild lesion severity (diameter loss 0 – 50%), intermediate lesion severity (diameter loss 50 – 70%), severe lesions (diameter loss 70 – 99%) and total occlusion. Interpretation was performed on a consensus basis by two experienced cardiologists blinded for clinical and other imaging data. Significant disease was defined as >50% luminal loss on CA.

Statistical analysis

Statistical analyses were performed with SPSS software (V. 18.0, IBM Corporation, Somers, New York, USA). Variables were expressed as mean±standard deviation (SD) or median and range, and categorical variables as frequencies and percentages. Continuous variables where compared by means of Students T test or Mann-Whitney U test where appropriate. Categorical variables were compared by means of the Chi-square test. Odds ratios for significant CAD were calculated by means of univariate and multivariate binary logistic regression analysis. As a measure of discrimination we calculated the area under the ROC curve (AUC) with 95% confidence intervals for X-ECG, CCS and the multivariate model of gender, age, pre-test likelihood according to Diamond and Forrester criteria, X-ECG and CCS. We calculated the number of patients that would have been classified as with or without significant CAD according to standalone and combined CCS and X-ECG results. For this analysis we defined the cut-off value for CCS that was found independently predictive of significant CAD abnormal. Also, we defined a positive or non-conclusive X-ECG result abnormal to resemble clinical practice. A p-value of <0.05 was considered statistically significant.

RESULTS

Study population

In total, 136 patients (mean age 63.5±10.2 years, 62.5% male) with stable angina pectoris were included in this study. Median pre-test likelihood of CAD was 87% (range 22-95). Of 204 patients scheduled for hybrid SPECT-CCTA 68 patients (33%) were excluded from the current analysis. Of these, 37 patients (18%) had no X-ECG available as a result of adenosine stress prior to hybrid SPECT-CCTA acquisition. Thirty-one patients (15%) were excluded due to the unavailability of the reference standard; in case of an unsuccessful CCTA the study protocol did not allow for further invasive imaging to limit radiation exposure and adverse events as a result of CA (Figure 1). Characteristics of the study population are presented in Table 1.

Exercise stress ECG

112 patients (82%) had a diagnostic X-ECG test. 24 patients (18%) had non-conclusive X-ECG results; one patient (1%) was unable to reach at least 85% of predicted maximum heart rate, 5 patients (4%) had an uninterpretable X-ECG as a result of an unstable baseline. Furthermore, 18 patients (13%) experienced typical anginal complaints without evidence of ischemia on stress ECG (Table 1). Of the patients with normal and positive X-ECG, 12 (18%) and 46 (68%) had significant CAD on CA respectively (Table 1). Of 24 patients with non-conclusive X-ECG 10 (42%) had significant CAD. Multivariate analysis revealed that positive X-ECG result was independently predictive of significant CAD ($P < 0.005$) (Table 1). ROC curve analysis resulted in an AUC of 0.65 (95% CI 0.55 – 0.74) for the diagnosis of significant CAD. The ROC curve crosses the reference line, resembling the fact that the presence of an uninterpretable X-ECG is suggestive of absence of significant CAD (Figure 2).

Coronary calcium scoring

A CCS of 0 was observed in 32 patients (23.5%), of these patients 6 (19%) had significant CAD on CA. Fifty four patients had a CCS of 0.1 – 400, of which 28 (52%) had significant CAD on CA. Of the patients with a CCS >400 (N = 50), 34 (68%) had significant CAD on CA. Multivariate analysis revealed that CCS >400 was independently predictive of significant CAD (P= 0.034) (Table 1). ROC curve analysis resulted in an AUC of 0.69 (95% CI 0.61 – 0.83) for the diagnosis of significant CAD (Figure 2).

Exercise stress electrocardiography in addition to coronary calcium scoring

The multivariate model of gender, age, pre-test likelihood, X-ECG and CCS had an AUC of 0.84 (95% CI 0.77 – 0.91) for the diagnosis of CAD (Figure 2).

Of 68 patients without significant CAD 37 (54%) had either a CCS >400 or an abnormal X-ECG result. Of 68 patients with significant CAD 6 (9%) patients had both a CCS of 0-400 and a negative X-ECG result (Table 2). Two patients had both a CCS of 0 and a negative X-ECG result.

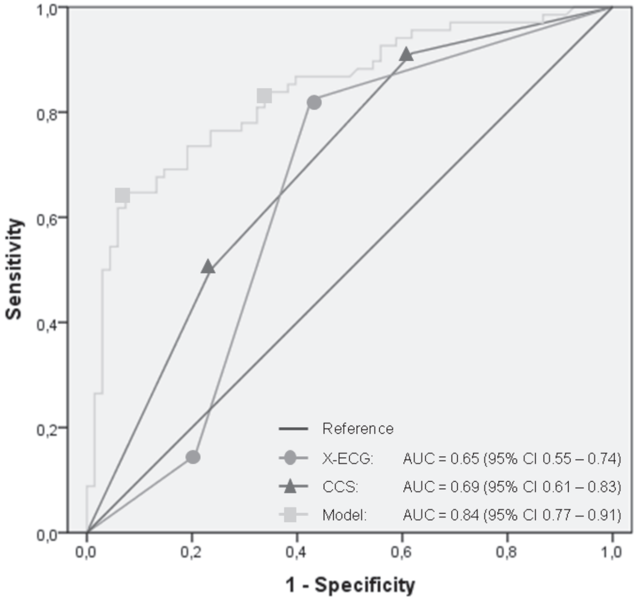

Figure 2. Incremental diagnostic yield of exercise stress ECG added to coronary calcium score in the diagnosis of coronary artery disease in an intermediate to high pre-test likelihood population ROC curves for CCS (0, 0.1-400 and >400), exercise stress ECG (X-ECG) (negative, non-conclusive and positive) and the multivariate model (Model) (age, gender, risk factors, pre-test likelihood according to Diamond and Forrester criteria, X-ECG and CCS). Differences in area under the curve (AUC) show comparable diagnostic yield of stand alone X-ECG and CCS. X-ECG added to CCS shows incremental diagnostic yield.

Table 1. Baseline patient characteristics and results of exercise stress testing and coronary calcium scoring

	No CAD N = 68	**CAD** N = 68	**Odds ratio, univariate**		**Odds ratio, multivariate**	
Age (years) *	61.3 (±10.0)	65.7 (±10.0)	1.05 (1.01 - 1.08)§	**P = 0.013**	0.99 (0.94 – 1.04)	P = 0.575
Gender, female	35 (51.5%)	16 (23.5%)	0.29 (0.14 - 0.61)	**P = 0.001**	0.79 (0.78 – 2.27)	P = 0.662
Risk factors						
Smoking	25 (37%)	22 (32%)	0.82 (0.41 - 1.67)	P = 0.589		
Hypertension	42 (62%)	48 (71%)	0.28 (0.73 - 3.04)	P = 0.278		
Diabetes mellitus	8 (12%)	15 (22%)	2.12 (0.83 - 5.40)	P = 0.114		
Dyslipidaemia	40 (59%)	49 (72%)	1.81 (0.88 - 3.70)	P = 0.106		
Family history †	45 (66%)	34 (50%)	0.51 (0.26 - 1.02)	P = 0.057		
Risk factors ≥ 3	32 (47%)	34 (50%)	1.13 (0.57 - 2.21)	P = 0.732		
Angina Pectoris						
Non-anginal	0	1 (1%)				
Atypical	30 (44%)	13 (19%)				
Typical	38 (56%)	54 (79%)				
Pre-test likelihood ‡	73.9 (22 - 95)	85.4 (22 - 95)	1.04 (1.02 - 1.07)	**P < 0.005**	1.03 (0.99 – 1.06)	**P = 0.025**
X-ECG						**P < 0.005**
Negative	39 (57%)	12 (18%)	Referent		Referent	
Positive	15 (22%)	46 (68%)	9.97 (4.17 - 23.81)	**P < 0.005**	9.00 (3.42 – 23.74)	**P < 0.005**
Non diagnostic	14 (21%)	10 (15%)	2.32 (0.82 - 6.55)	P = 0.112	2.16 (0.69 – 6.75)	P = 0.187
CCS						P = 0.105
0	26 (38%)	6 (9%)	Referent		Referent	
0.1 – 400	26 (38%)	28 (41%)	4.67 (1.66 - 13.15)	**P = 0.004**	2.75 (0.77 – 9.81)	P = 0.118
> 400	16 (24%)	34 (50%)	9.21 (3.16 - 26.80)	**P < 0.005**	4.75 (1.13 – 20.02)	**P = 0.034**

Baseline patient characteristics, exercise stress testing (X-ECG) and coronary calcium scoring (CCS), according to the presence or absence of significant coronary artery disease (CAD) on invasive coronary angiography. Multivariate analysis shows that pre-test likelihood, positive X-ECG result and CCS >400 are independently predictive of the presence of significant coronary artery disease.Values are shown as number and percentage unless otherwise noted. * Values expressed as mean ± standard deviation, † Family history of premature atherosclerosis, ‡ Values expressed as median percentage (range). § Odds ratio per year. Odds ratios were calculated by means of binary logistic regression analysis.

Table 2. Reclassification of patients after addition of X-ECG to CCS and vice versa results in significant numbers of false positive or negative test results.

		CCS >400		CCS and X-ECG		X-ECG abnormal
Significant CAD N = 68	**TP**	34	0	62	0	56
	FN	34	**28**	6	**6**	12
No Significant CAD N = 68	**TN**	52	**15**	31	**8**	39
	FP	16	0	37	0	39

Coronary calcium score (CCS) >400 was defined abnormal. Exercise stress electrocardiography (X-ECG) was defined abnormal in the presence of a positive or non-conclusive result to resemble clinical practice. As such a sensitivity, specificity, positive- and negative predictive value of 91.2% (95%CI 82-96), 45.6% (95%CI 34-57), 62.6 (95%CI 53-72) and 83.8% (95%CI 69-92) respectively, were calculated. True positive (TP), false negative (FN), true negative (TN) and false positive (FP) findings are given for each test. Numbers above or beneath the arrows indicate the number of diagnoses that evolve from a TP to a FN and a TN to a FP diagnosis and vice versa.

DISCUSSION

The principal finding of this study is that despite an increased diagnostic yield of combined CCS and X-ECG in patients with an intermediate to high pre-test likelihood of CAD, in clinical practice still a substantial number of patients without significant CAD (54%) are wrongly classified as suffering from significant CAD. In the current population 9% of patients suffered from significant CAD despite a CCS <400 and a negative X-ECG result.

With the knowledge that in a considerable number of patients referred for CA no significant CAD is found, the need for an accurate and cost-effective non-invasive diagnostic work up remains high (14). From a very diverse palette of available diagnostic procedures CCS and X-ECG probably are the most available, fast and inexpensive non-invasive diagnostic procedures that are least prone to adverse events (9, 15, 16). Previous reports have shown that in patients with low pre-test likelihood of CAD CCS was more reliable in ruling out CAD than X-ECG with cut-off value for CCS of 0 or <2 (17, 18). Diagnostic accuracy was comparable in patients with an intermediate pre-test likelihood of CAD (8, 17). Determining the absence of coronary calcium could obviate the need for further testing(17). In a study by Dedic et al, also a group of patients with high pre-test likelihood is described, defined as >70% based on the Duke Clinical Score. It was stated that these patients do not seem to benefit from either CCS or X-ECG in the exclusion from significant CAD (17). However, it remains unclear whether the combination of both sets of information could add to the diagnostic performance of each test as standalone diagnostic procedure.

With our study we were able to confirm the absence of sufficient diagnostic performance of either CCS or X-ECG as standalone diagnostic procedures in intermediate to high pre test likelihood patients. The combination of both diagnostic modalities leads to an increased diagnostic performance. The AUC for the diagnosis of significant CAD increases from 0.65 for standalone X-ECG and 0.69 for standalone CCS to 0.84 for the multivariate model of gender, age, pre-test likelihood, X-ECG and CCS. Both a positive X-ECG and a CCS > 400 are independent predictors for the presence of significant CAD, according to our multivariate analysis. The presence of these diagnostic results should make physicians alert for the presence of significant CAD. However, considerable diagnostic uncertainty remains. Not only due to inconclusive X-ECG results, that make up 18% of our population. Also, the poor diagnostic accuracy of standalone CCS and X-ECG result in a limited diagnostic accuracy of these modalities combined. As demonstrated, in clinical practice the PPV of 63% and NPV of 84% of combined CCS and X-ECG will result in a considerable number of additional invasive or non-invasive imaging procedures.

Several limitations should be taken into account when interpreting the results of this study. Acquisition of an X-ECG after imaging the amount of coronary calcium is not standard, which makes the current analysis somewhat hypothetical. The same applies to the reverse acquisition protocol, however. We have shown that the combination of both tests admittedly leads to a more reliable result when compared with the standalone tests. It is doubtful whether an AUC of 0.84 is sufficient to reliably establish or exclude CAD. The sample size for the current analysis is rather small and the possibility of selection bias cannot be excluded since a considerable number of patients from the original population were excluded from this analysis due to an unavailable X-ECG or reference standard. Gold standard in our study was a > 50%

luminal loss on CA as diagnostic for significant CAD. An anatomical parameter as reference standard has known limitations for the judgement of functional relevance of CAD (19).

CONCLUSION

In conclusion, in patients with an intermediate to high pre-test likelihood of CAD the acquisition of X-ECG after CCS results in increased diagnostic yield in the evaluation of patients for the presence of significant CAD. A high coronary calcium score (> 400) or a positive X-ECG increases the likelihood of the presence of significant CAD. However, considerable diagnostic uncertainty remains mainly due to a large number of false positive results which wilt result in additional (non-) invasive imaging procedures.

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Chapter 4

Usefulness of Coronary Calcium Scoring to Myocardial Perfusion SPECT in the diagnosis of coronary artery disease in a predominantly high risk population

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ABSTRACT

Purpose

Coronary calcium scoring (CCS) adds to the diagnostic performance of myocardial perfusion SPECT (SPECT) to assess the presence of significant coronary artery disease (CAD). Patients with a high pre-test likelihood are expected to have a high CCS which potentially could enhance the diagnostic performance of myocardial perfusion SPECT in this specific patient group. We evaluated the added value of CCS to SPECT in the diagnosis of significant CAD in patients with an intermediate to high pre-test likelihood.

Methods

In total, 129 patients (mean age 62.7±9.7 years, 65% male) with stable anginal complaints and intermediate to high pre-test likelihood of CAD (median 87%, range 22 - 95) were prospectively included in this study. All patients received SPECT and CCS imaging preceding invasive coronary angiography (CA). Fractional flow reserve (FFR) measurements were acquired from patients with angiographically estimated 50-95% obstructive CAD. For SPECT a SSS > 3 was defined significant CAD. For CCS the optimal cut-off value for significant CAD was determined by ROC curve analysis. The reference standard for significant CAD was a FFR of <0.80 acquired by CA.

Results

Significant CAD was demonstrated in 64 patients (49.6%). Optimal CCS cut-off value for significant CAD was >182.5. ROC curve analysis for prediction of the presence of significant CAD for SPECT, CCS and the combination of CCS and SPECT resulted in an area under the curve (AUC) of 0.88 (95%CI 81-94), 0.75 (95%CI 66-83%) and 0.92 (95%CI 87%-97%) respectively. The difference of the AUC between SPECT and the combination of CCS and SPECT was 0.05 (P = 0.12).

Conclusion

The addition of CCS did not significantly improve the diagnostic performance of SPECT in the evaluation of patients with a predominantly high pre-test likelihood of CAD.

INTRODUCTION

According to current guidelines invasive coronary angiography (CA) is a suitable diagnostic procedure for patients with a high pre-test likelihood of significant coronary artery disease either with or without troublesome symptoms or clinical findings [1, 2]. In this population the reported diagnostic yield of invasive CA is 44-88% [3-5]. In real life invasive CA has an even lower diagnostic yield of obstructive CAD of about 38% [6]. Non-invasive testing could be of value to defer from invasive diagnostic procedures, even in a subset of patients with an intermediate to high pre-test likelihood of CAD.

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

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

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

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

MATERIALS AND METHODS

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

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

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

A nonenhanced scan to calculate the total CCS was performed with the following scanning parameters: prospective ECG triggering, at inspiration, 2.5mm slice thickness, 120kV tube voltage, 55 mAs tube current. Agatston scores were computed using the Extended Brilliance Workspace software (Philips Medical Systems, Best, The Netherlands).

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

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

Statistical Analysis

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

RESULTS

Study population

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

Coronary angiography

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

Myocardial perfusion SPECT

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

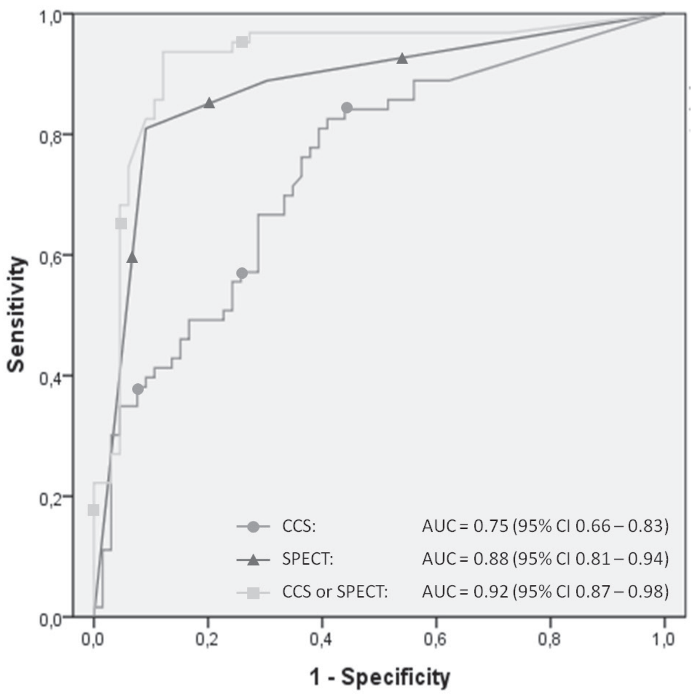

Figure. 1 ROC curve analysis for the detection of significant coronary artery disease (CAD) by the use of coronary calcium scoring (CCS), Single Photon Emission Tomography (SPECT) and the combination of CCS and SPECT. A fractional flow reserve of <0.80 was defined significant CAD. A CCS of 182.5 was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

Table 1 Characteristics of the patients included in the analysis

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

Values are shown as number and percentage unless otherwise noted. * Values expressed as mean ± standard deviation, † Values expressed as median (range). CCS, Canadian Cardiovascular Society.

Coronary Calcium Scoring

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

Combined SPECT and CCS

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

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

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

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

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

Values are shown as number and percentage unless otherwise noted. * Values expressed as mean ± standard deviation. SPECT, single photon emission computed tomography. CAD, coronary artery disease. † A fractional flow reserve of <0.80 was defined significant CAD.

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

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

Diagnostic performance of single photon emission computed tomography (SPECT), coronary calcium scoring (CCS) or combinations for the detection of significant coronary artery disease (CAD). A fractional flow reserve of <0.80 was defined significant CAD. PPP, positive predictive value. NPV, negative predictive value. TP, true positive. FP, false positive. TN, true negative. FN, false negative.

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

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

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

DISCUSSION

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

In the overall patient population with anginal complaints SPECT has a good diagnostic performance. Well-designed studies have shown sensitivities ranging from 85-90%. If ECG gated information and attenuation correction algorithms are used specificity values range between 80 and 90% [7, 8]. In 123 patients with a high pre-test likelihood of disease Groutars et al demonstrated a sensitivity of 97% and a specificity of 59% for the detection of >70% lesions on CA [3]. More recently, Hamirani et al. demonstrated a lower diagnostic performance of SPECT in a high pre-test likelihood population of 122 patients with sensitivity and specificity values of 58% and 43%, respectively [9]. Both groups used a one day dual isotope imaging protocol with ^{201}Tl rest imaging and ^{99m}Tc stress imaging. The former population was truly high risk with a mean pre-test likelihood of 92±20% and a prevalence of >70% stenosis in 80% of the patients. The latter was retrospectively constituted of patients who underwent SPECT, CT coronary angiography and CA. The prevalence of >70% stenosis was 64%, suggestive of a high risk population. In our hands SPECT had a reasonable performance with sensitivity and specificity values of 80% and 91% respectively and an AUC of 0.88 for the detection of significant CAD in a high pre-test likelihood population.

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

A false-negative SPECT in patients with balanced ischemia is a well-known pitfall for clinicians. Several authors have noted that a high CCS may have diagnostic value in this patient category [17, 22]. Schepis et al showed that in patients with an intermediate risk of CAD a CCS >709 is predictive for significant CAD (>50% stenosis) in patients with a normal SPECT. When CCS at this cut-off value was added to SPECT, the sensitivity increased from 76% to 86% and specificity remained similar (91% and 86%, respectively) when compared to SPECT alone [17]. In a selected population of 50 patients with a normal SPECT and a CCS>1000, Ghadri et al. found a 74% prevalence of stenosis >50% [22]. Our data showed that out of the 13 patients with a false-negative SPECT, 8 had a CCS > 1000. And although median CCS in patients without significant

CAD was 29, still 5% of patients with a true negative SPECT had a CCS > 1000. If we used CCS >0 as a cut-off value for CAD we observed a NPV of 88% for the exclusion of significant CAD when added to SPECT, although at the cost of a high number of false positives, PPV 59%. Adding the optimal CCS cut-off value of 182.5 to SPECT, the number of false positive results decreased. The PPV improved from 59% to 74%, the NPV of 88% increased to 92%. However, AUC as determined by ROC curve analysis did not differ significantly between the combination of CCS and SPECT and standalone SPECT. This shows that in a group of patients with high risk of CAD, excluding the presence of coronary calcifications in patients with a normal SPECT makes the exclusion of significant CAD reliable. However, a relatively low or zero CCS does not completely rule out significant CAD in these patients. One of the three patients with a CCS of zero and a negative SPECT result had a significant left main stenosis. When the presence of calcifications is proven in patients with a negative SPECT result, however, the significance of CAD is not.

4

Several limitations of our study need to be taken into account when interpreting the results. First, our study population was at predominantly high-risk of CAD. Patients with an intermediate to high pre-test likelihood were allowed to be included and over 50% of patients had a high pre-test likelihood. Thus, this study is not exemplary for the general clinical population referred for SPECT. The majority of patients with false negative results had a high pre-test likelihood of disease. Second, for each patient we chose the optimal stress protocol, either adenosine or exercise. However, adenosine stress has a known limited diagnostic performance compared to exercise stress. The reason for not being able to reach an adequate heart rate response during exercise, not only could be the reason to switch to adenosine stress; this could also be the confounding factor for the increased presence of significant CAD (f.i. peripheral atherosclerotic disease or chronic obstructive pulmonary disease). As a result of the higher prevalence of significant CAD, negative predictive value of adenosine stress SPECT could be hampered. Despite the fact that almost a quarter of the patients received adenosine stress, the diagnostic performance of SPECT alone in this population is reasonable. FFR measurements were available from 84% of patients with angiographically 50-95% obstructive disease. According to available literature it is safe to assume that lesions with <50% stenosis have no hemodynamic significance [26]. Nine patients with angiographically 70-95% obstructive disease did not receive FFR measurements, mainly for practical reasons on a busy catherization laboratory. The impact of the possible error by the assumption that these lesions were indeed hemodynamically significant is limited [26].

CONCLUSION

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

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Chapter 5

Diagnostic accuracy of hybrid myocardial perfusion SPECT and CT coronary angiography in the diagnosis of coronary artery disease

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ABSTRACT

Aims

Hybrid myocardial perfusion imaging with single photon emission computed tomography (SPECT) and CT coronary angiography (CCTA) has the potential to play a major role in patients with non-conclusive SPECT or CCTA results. We evaluated the performance of hybrid SPECT/CCTA versus standalone SPECT and CCTA for the diagnosis of significant coronary artery disease (CAD) in patients with an intermediate to high pre-test likelihood of CAD.

Methods and results

In total, 98 patients (mean age 62.5±10.1 years, 68.4% male) with stable anginal complaints and a median pre-test likelihood of 87% (range 22% – 95%), were prospectively included in this study. Hybrid SPECT/CCTA was performed prior to conventional coronary angiography (CA) including fractional flow reserve measurements (FFR). Hybrid analysis was performed by combined interpretation of SPECT and CCTA images. The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated for standalone SPECT, CCTA and hybrid SPECT/CCTA on per patient level, using a FFR <0.80 as reference for significant CAD. Significant CAD was demonstrated in 56 patients (57.9%). Non-conclusive SPECT or CCTA results were found in 32 (32.7%) patients. SPECT had a sensitivity of 93%, specificity 79%, PPV 85%, NPV 89%. CCTA had a sensitivity of 98%, specificity 62%, PPV 77%, NPV 96%. Hybrid analysis of SPECT and CCTA improved the overall performance: sensitivity, specificity, PPV and NPV for the presence of significant CAD to 96%, 95%, 96% and 95%, respectively.

Conclusions

In more than 40% of the patients with a high pre-test likelihood no significant CAD was demonstrated, emphasizing the value of accurate pretreatment cardiovascular imaging. Hybrid SPECT/CCTA was able to accurately diagnose and exclude significant CAD surpassing stand-alone myocardial SPECT and CCTA, versus a reference standard of FFR measurements.

INTRODUCTION

Cardiac hybrid myocardial perfusion imaging with single photon emission computed tomography (SPECT) and CT coronary angiography (CCTA) has been proposed in patients with an intermediate risk of coronary artery disease (CAD) [1, 2]. Hybrid cardiac imaging seems particularly useful in patients with multi-vessel disease, perfusion defects in the lateral and inferior wall, and in patients with non-conclusive results of either technique [1-4].

Diagnostic performance of stand-alone SPECT is limited in patients with intermediate to high pre-test likelihood of CAD with a broad range of reported sensitivities between 56% and 94% [5-7], probably due to an important fraction of non-conclusive results [3]. Small perfusion defects (1-2 segments), inadequate heart rate response (e.g. failure to reach 85% of maximum predicted heart rate or 5 metabolic equivalents (MET) during exercise), and discrepant clinical data (e.g. typical angina per history or ≥2 mm ST-segment depression on ECG during exercise) could be reasons to regard SPECT non-conclusive [8, 9].

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In patients with an intermediate- to high pre-test likelihood also CCTA is prone to non-conclusive results. This is mainly due to non-evaluable coronary segments as a result of coronary calcifications and artifacts that decrease diagnostic performance [10-15]. As such, even with the latest scanner generations, CCTA still has moderate specificity [10-12, 16, 17].

Evidence is emerging that the diagnostic performance of hybrid SPECT/CCTA is superior to stand alone SPECT and CCTA [15, 18]. In selected populations sensitivity and specificity values of 94-96% and 92-95% have been reported [15, 18].

In our study we focus on patients with an intermediate to high pre-test likelihood of CAD and subsequently high rates of equivocal and non diagnostic imaging results. We hypothesized that hybrid SPECT/ CCTA has incremental diagnostic accuracy over standalone SPECT or CCTA.

METHODS

Patient population and imaging schedule

We prospectively conducted a single center cross-sectional cohort study [19]. Patients with an intermediate to high pre-test likelihood of CAD were consecutively recruited for this study from September 2010 until December 2011. Boundaries for low, intermediate and high pre-test likelihood were set at <20%, 20-80% and > 80% respectively and calculated according to Diamond and Forrester criteria [20, 21]. Excluded were patients with a history of surgical revascularization, stent implantation, patients with an unstable cardiac condition or a cardiac rhythm other than sinus rhythm. The study conformed to the principles outlined in the declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients.

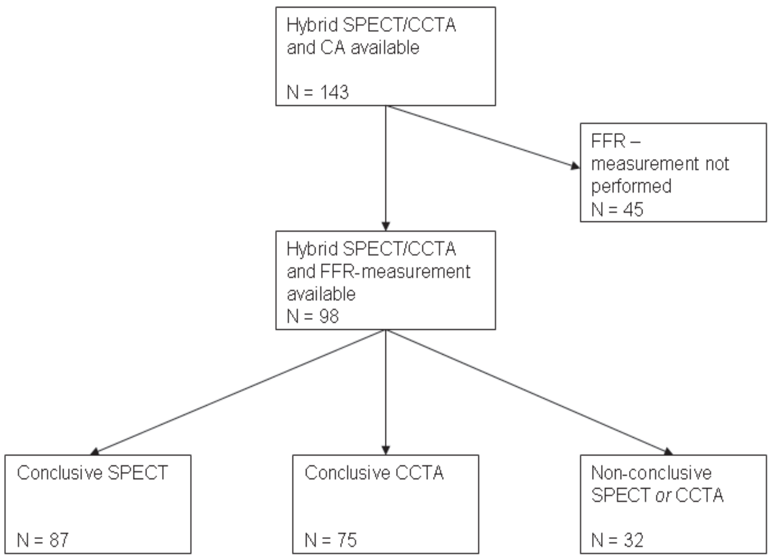


Figure 1. Flowchart for patients included in this analysis. Hybrid SPECT/CCTA, Hybrid myocardial perfusion single photon emission computed tomography and CT coronary angiography. CA, invasive coronary angiography. FFR-measurement, fractional flow reserve measurement.

Of the 143 patients that underwent hybrid SPECT and prospectively triggered CCTA, 98 patients (69%) received invasive coronary angiography (CA) and fractional flow reserve (FFR) measurements (Figure 1). Gated SPECT and CCTA data were acquired on a Hybrid SPECT-CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands). The components share a common table that is aligned to allow sequential image acquisition. On the first imaging day stress SPECT and CCTA data were acquired.

Patients started with bicycle or pharmacological stress after which stress SPECT was acquired directly followed by CCTA. In patients with a normal stress SPECT (normal perfusion and gated data) no rest SPECT was acquired. CA and FFR measurements were performed in all patients, including those with normal non-invasive test results, within 14 days from the first image acquisition. If indicated, CA was preceded by rest SPECT image acquisition.

Myocardial perfusion SPECT

SPECT images were acquired with a 2-day stress/rest MPI protocol. Of 98 patients included in the analysis 82 patients (83.7%) underwent bicycle stress according to a stepwise protocol for stress image acquisition. Sixteen (16.3%) patients underwent pharmacological stress (adenosine at standard rate of 0.14mg/kg/min over 6 min). For stress and rest SPECT a weight-adjusted dose of 400-600 MBq of ^{99m}Tc-sestamibi was used. SPECT imaging was performed using a dual headed gamma camera, equipped with low-energy, high-resolution collimators. Sixty-four projections were acquired with 40 seconds per projection and stored on a 64x64 matrix. Energy window was set at 20% around the 140-keV photon peak. Reconstruction was performed by means of filtered back projection using a Butterworth filter, to produce transverse tomograms. Short-axis, vertical and horizontal long-axis tomograms were produced from transverse tomograms by performing coordinate transformation. Attenuation correction was performed for all images using a non-enhanced CT scan. Semi-quantitative visual analysis was performed in consensus by two experienced nuclear medicine physicians. Attenuation corrected and non-attenuation corrected images and auxiliary findings (results of stress testing, gated data and semi quantitative perfusion data) were included in the analysis. Stress and rest SPECT images were interpreted as previously described according to a 17-segment model and scored for perfusion defects using a five-point scoring system (0 = normal to 4 = absence of tracer uptake) [8, 22, 23]. Gated data and semi quantitative perfusion data were assessed using the QGS/QPS software package (Cedars-Sinai Medical Center, Los Angeles, Ca, USA). The analyzing physicians were blinded for other imaging data. For the definition of normal, equivocal and abnormal myocardial perfusion on SPECT according to segmental scores we used the definition provided by Abidov et. al.[8]. SPECT with an equivocal perfusion score was regarded non-conclusive, a (probably-) normal perfusion score was regarded normal and a (probably-) abnormal perfusion score was regarded abnormal.

Coronary computed tomography angiography

All patients underwent prospectively ECG-triggered axial CCTA according to the guidelines provided by de society of cardiovascular computed angiography [24]. All participants received oral metoprolol tartrate at the start of the stress test preceding SPECT imaging. Preceding CCTA additional intravenous metoprolol was administered to achieve a heart rate below 62 bpm. Prior to CCTA, a non-enhanced scan to calculate the coronary calcium score (CCS) was performed. CCTA data were acquired with a collimation of 64 x 0.625 mm. A bolus tracking protocol was used to determine the time of optimal contrast. During CCTA 90-110ml iodinated contrast medium (Iobitridol, Xenetix 350, Guerbet) was administered, followed by a saline flush. Tube current was 500mA at 80 to 120kV for patients according to their body weight. CCTA's were read by two cardiologists for obstructive severity according to a 16-segment model and 5 categories of luminal loss: no CAD (0% area stenosis), mild lesion severity (0 – 50% area stenosis), intermediate lesion severity (50 – 70% area stenosis), severe lesions (70 – 99% area stenosis) and total occlusion. If the category of luminal loss could not be determined (e.g. due to motion artifact or severe calcifications) a segment was categorized as un-evaluable. Subsequently, a vessel-based analysis was performed from which diagnostic accuracy on a per-patient level was determined. Vessels were categorized as normal if all segments were evaluable and none had lesions >50% area stenosis. Abnormal vessels (significant CAD) were defined as vessels with at least one segment with a lesion of >50% area stenosis. Vessels with at least one severe lesion were regarded completely evaluable despite any un-evaluable segments. Non-conclusive vessels were defined as vessels with at least one un-evaluable segment, without any segments with lesions >50% area stenosis. A CCTA was defined non-conclusive if one or more vessels were un-evaluable and no vessel was abnormal.

Invasive coronary angiography

As part of the prospective study, CA and FFR-measurement was performed in all patients, including those with normal non-invasive test results. CA was acquired on Allura (Philips Medical Systems, Best, The Netherlands) catheterization equipment. FFR measurements were obtained from all patients with angiographically estimated 50-95% obstructive disease. Lesions with <50% obstructive disease (according to the interpretation on a consensus basis by two experienced cardiologists) were considered normal; no significant CAD [25]. Occluded vessels were considered abnormal. Vessels with angiographically >95% obstructive disease were considered severely stenotic with an FFR <0.80. During FFR measurement distal coronary pressure was measured with a pressure guidewire (Certus Wire, Radi Medical Systems, Uppsala, Sweden) during maximal hyperemia induced by adenosine intravenously as previously described [26]. A FFR-measurement <0.80 was defined abnormal and classified as significant CAD. A FFR-measurement >0.80 was defined normal [27, 28]. Vessel-based analysis was performed from which diagnostic accuracy on a per-patient level was determined.

Hybrid SPECT/CCTA imaging analysis

According to our pre-defined protocol all patients were included in hybrid image evaluation. Interpretation was performed by two experienced, independent physicians blinded for CA and FFR measurements. The integrated interpretation of all imaging data led to the categorization of all vessels and patients as normal or abnormal. Concordant normal or abnormal SPECT and CCTA findings led to a similar interpretation of the hybrid imaging result. Discordant SPECT and CCTA findings were interpreted as follows. In patients with normal CCTA and abnormal or non-conclusive SPECT the hybrid imaging result was defined normal. In patients with non-conclusive CCTA and normal SPECT the hybrid imaging result was defined normal. In patients with non-conclusive CCTA and abnormal SPECT the hybrid imaging result was defined abnormal. In patients with abnormal CCTA and normal SPECT, CCTA prevailed only in those patients with a definitely abnormal CCTA (Figure 5). In patients with abnormal CCTA and non-conclusive SPECT, the hybrid imaging result was defined abnormal [4].

Statistical analysis

Statistical analyses were performed with SPSS software (V. 18.0, IBM Corporation, Somers, New York, USA). Variables were expressed as mean±standard deviation (SD) or median and range, and categorical variables as frequencies and percentages. Continuous variables where compared by means of Students T test or Mann-Whitney U test where appropriate. Categorical variables were compared by means of the Chi-square test. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) with their 95% confidence intervals (CI) were calculated. A p-value of <0.05 was considered statistically significant.

RESULTS

Study population

Of a total of 143 patients that underwent hybrid imaging, 98 patients with an FFR-measurement were included in this study. During the first months of this study FFR measurement was performed at the discretion of the performing operator.

Afterwards the protocol was changed and FFR-measurement was performed in all patients. Baseline characteristics from patients excluded from this analysis (mean age 61.8±10.2 years, 73% male and median pre-test likelihood 87% (range 22-95)) did not differ significantly from patients included in the analysis. Complete characteristics of the study population are presented in Table 1. In total 32 patients (32.7%) had either a non-conclusive SPECT or CCTA (Table 2).

Table 1. Characteristics of the patients included in the analysis, n = 98.

Age (years) *	62.5 ± 10.1	
Gender, men / women	67 / 31	68.4 / 31.6 %
Risk factors		
Smoking		
Current	26	26.5%
Past	13	13.3%
Hypertension	62	63.3%
Diabetes mellitus	12	12.2%
Dyslipidaemia	59	60.2%
Family history of premature atherosclerosis	60	61.2%
Risk factors ≥ 3	44	44.9%
Angina pectoris		
Non-anginal	0	0%
Atypical	31	31.6%
Typical	67	68.4%
CCS Angina Class		
Class I	7	7.1%
Class II	80	81.6%
Class III	11	11.2%
Class IV	0	0%
Pre-test likelihood †	0.87 (0.22 – 0.95)	
Low	0	0%
Intermediate	40	40.8%
High	53	54.1%
Unknown ‡	5	5.1%

Values are shown as number and percentage unless otherwise noted. * Values expressed as mean ± standard deviation, † Values expressed as median (range). ‡ Patients with atypical angina pectoris and >70 years old. CCS, Canadian Cardiovascular Society.

Table 2. Characteristics of the imaging results of all patients, N = 98.

CT Coronary Angiogram		
Coronary Calcium Scoring		
0	26	26.5%
1 - 400	24	34.7%
>400	38	28.7%
CCS in patients with significant CAD *	497.5 (0 - 3719)	
CCS in patients without significant CAD *	1 (0 - 1966)	
CT Coronary Angiography		
Intravenous metoprolol prior to CCTA, mg †	13.1±6.1	
Heart rate during CCTA, bpm †	59.9±4.8	
Non-conclusive CCTA	23	23.5%
Calcifications	18	18.4%
Motion artifact	4	4.1%
Poor contrast opacification	1	1.0%
Myocardial Perfusion SPECT		
Exercise stress	82	83.7%
Adenosine stress	16	16.3%
Non-conclusive SPECT	11	11.2%
Non-conclusive SPECT or CCTA	32	32.7%
Conventional Coronary Angiogram with FFR - measurements		
No significant CAD §	42	42.9%
1-vessel disease §	15	15.3%
2-vessel disease §	21	21.4%
3-vessel disease or left main stenosis §	20	20.4%

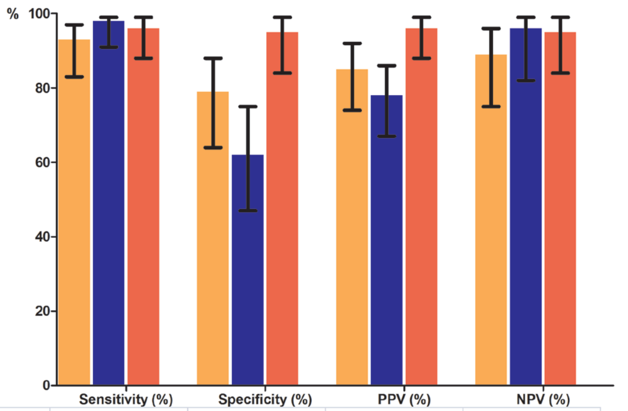
Values are shown as number and percentage unless otherwise noted. * Values expressed as median (range), significant CAD according to reference standard of fractional flow reserve (FFR) measurements. † Values expressed as mean ± standard deviation. § FFR < 0.80 was defined hemodynamically significant. CA, coronary angiography, CAD, coronary artery disease, CCS = Coronary Calcium Score, CCTA, CT coronary angiogram, ECG, electrocardiogram, SPECT, single photon emission computed tomography.

Invasive coronary angiography including FFR measurements

The CA showed significant CAD in 56 patients (57.1%). FFR-measurements were available from all patients with angiographically estimated 50-95% obstructive disease and performed in 225 vessels (57.4%), (Table 2). FFR-measurements were positive in 80 vessels (35.6%).

Myocardial perfusion SPECT

Diagnostic accuracy of SPECT in all patients is presented in Figure 2. For this analysis non-conclusive scans (n=11) were regarded abnormal. Five of these patients (45%) suffered from significant CAD. None of the patients that underwent X-ECG prior to stress SPECT (N=82) had an inadequate heart rate response, we either administered atropine in these patients (N=28, 29%) or switched to adenosine stress (N=16, 16%). No patients with normal perfusion and anginal complaints during stress suffered from significant CAD. Out of the 4 patients with positive stress ECG findings (≥2 mm ST-segment depression) and normal perfusion, 2 patients suffered from significant CAD.

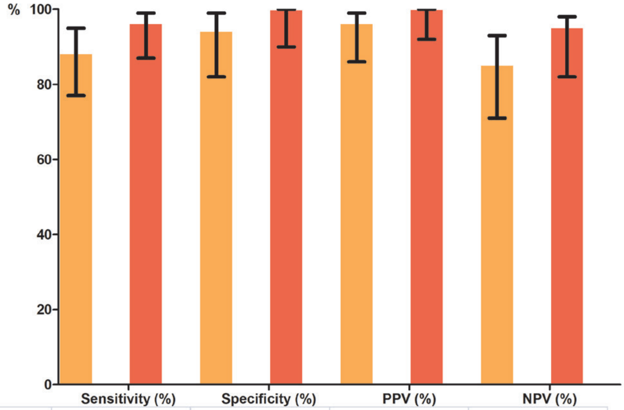


	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SPECT	93	79	85	89
CCTA	98	62	77	96
Hybrid	96	95	96	95

Figure 2. Diagnostic performance of myocardial perfusion SPECT, CT coronary angiography (CCTA) and hybrid SPECT/CCTA in all patients (N=98), using a fractional flow reserve <0.80 as reference standard. Patients with one or more non-conclusive vessels and no definitely abnormal vessels were considered abnormal. Patients with non-conclusive SPECT results were considered normal. PPV = positive predictive value. NPV = negative predictive value.

Eighty-seven (89%) patients had a conclusive SPECT, 51 (59%) of these patients suffered from significant CAD. Diagnostic performance of SPECT in patients with conclusive results is presented in Figure 3.

SPECT had a sensitivity of 62% (95%CI 52-70), a specificity of 84% (95%CI 77-88), a PPV of 70% (95%CI 60-78) and a NPV of 78% (95%CI 72-83) on a per vessel basis in all patients.



	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SPECT	88	94	96	85
Hybrid	96	99	99	95

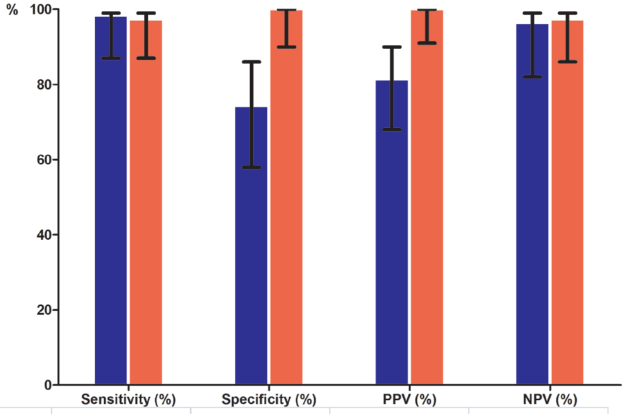
Figure 3. Diagnostic performance of standalone myocardial perfusion SPECT (SPECT) and hybrid SPECT/CCTA in patients with conclusive SPECT studies (N=87). Using a fractional flow reserve <0.80 as reference standard. PPV = positive predictive value. NPV = negative predictive value.

Coronary computed tomography angiography

Characteristics of CCTA scans are presented in Table 2. Diagnostic accuracy of CCTA in all patients is presented in Figure 2. For this analysis non-conclusive scans (n=23) were regarded abnormal. The majority of these patients (n= 17, 74%) suffered from significant CAD.

Seventy-five patients (77%) had a conclusive CCTA, 40 (53%) of these patients suffered from significant CAD. Diagnostic performance of CCTA in patients with conclusive results is presented in Figure 4.

CCTA had a sensitivity of 86% (95%CI 79-91), a specificity of 81% (95%CI 76-81) a PPV of 67% (95%CI 59-74) and a NPV of 93% (95%CI 89-93) on a per vessel basis in all patients.



	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CCTA	98	74	81	96
Hybrid	97	99	99	97

Figure 4. Diagnostic performance of standalone CT coronary angiography (CCTA) and hybrid SPECT/CCTA in patients with conclusive CCTA studies (N=75). Using a fractional flow reserve <0.80 as reference standard. PPV = positive predictive value. NPV = negative predictive value.

Hybrid SPECT/CCTA imaging

Hybrid SPECT/CCTA in all patients resulted in an improved diagnostic performance versus SPECT and CCTA as standalone imaging procedures. PPV of both SPECT (85%) and CCTA (77%) significantly improved to 96% (95%CI 88-99) for hybrid imaging analysis. NPV of SPECT (89%) improved to 95% (95%CI 84-99) if hybrid SPECT/CCTA was applied (Figure 2). Hybrid imaging analysis of 4 patients still demonstrated false positive or false negative results. Both patients with false negative results had a largely unevaluable CCTA as a result of high CCS (>1500), in combination with a normal (false negative) SPECT. Both patients with false positive results had an un-evaluable RCA with a small perfusion defect (SDS =2) in the myocardial territory subtended by this vessel. An example of the added value of hybrid imaging analysis is given in Figure 5.

In patients with conclusive SPECT results hybrid imaging analysis mainly resulted in improved NPV (85%, 95%CI 71-93 vs. 95%, 95%CI 82-98), Figure 3. A significant improvement of PPV (99%, 95%CI 91-100) was shown when hybrid imaging analysis was compared to conclusive CCTA results (PPV 81%, 95%CI 68-90), Figure 4.

Hybrid SPECT/CCTA had reliable results in patients with non-conclusive SPECT or CCTA results; PPV 91% (95%CI 72-98) and NPV 90% (95%CI 60-98), Figure 6.

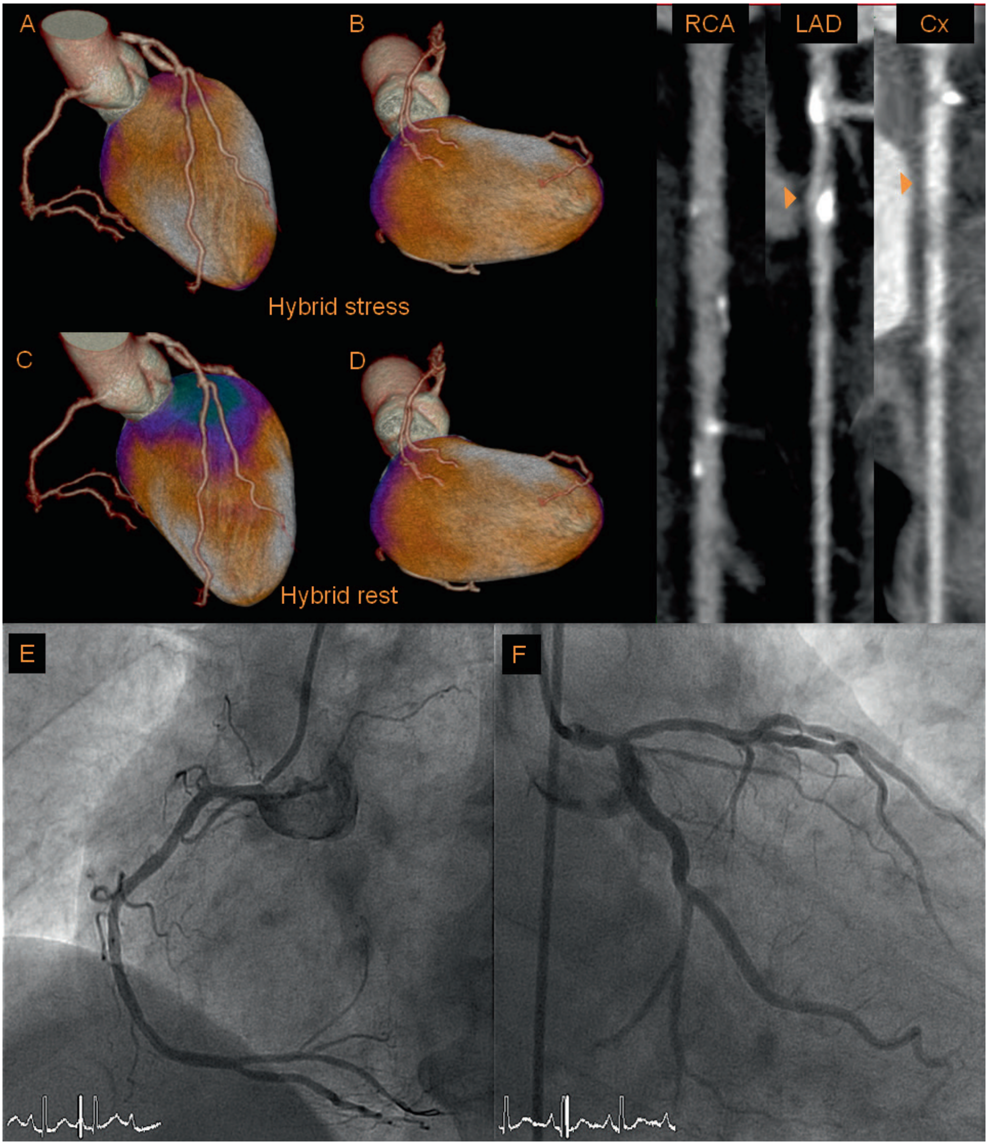


Figure 5. Example of a discordant hybrid finding with definitely abnormal CCTA and balanced ischemia on SPECT. A 61-year-old male with dypnoea during exercise. Hybrid imaging with myocardial perfusion SPECT (SPECT) showing normal perfusion (Panel A and B hybrid stress- and panel C and D hybrid rest imaging. Orange and white colours resemble normal perfusion, purple and blue colors resemble abnormal perfusion). CT coronary angiography (CCTA) showed significant left main stenosis (LM). With mild stenoses in the RCA and RCx. An intermediate lesion was visible in the proximal LAD. Coronary calcium score was 245. Conventional coronary angiography confirmed the significant LM stenosis, FFR 0.73. And mild stenosis of RCA, LAD and RCx (Panel E and F).

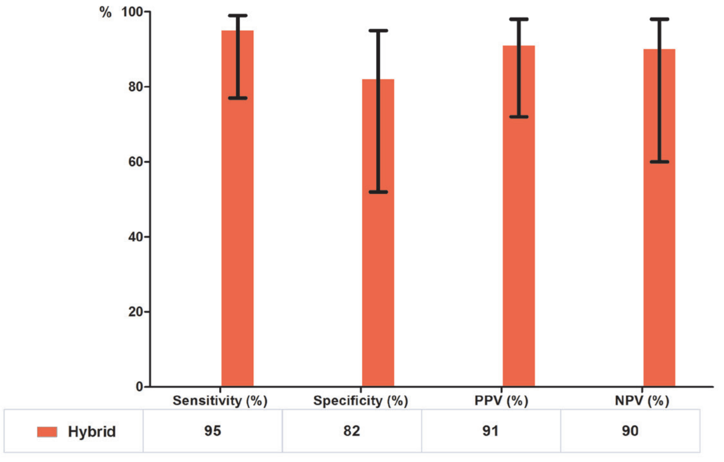


Figure 6. Diagnostic performance of hybrid myocardial perfusion SPECT (SPECT) and CT coronary angiography (CCTA) in patients with non-conclusive SPECT or CCTA studies (N=32). Using a fractional flow reserve <0.80 as reference standard. PPV = positive predictive value. NPV = negative predictive value.

Hybrid SPECT/CCTA had a sensitivity of 67% (95%CI 58-75), a specificity of 95% (95%CI 91-97) a PPV of 84% (95%CI 76-90), and a NPV of 87% (95%CI 82-90) on a per vessel basis in all patients.

Radiation dose analysis

The effective dose of the CT studies was quantified with a dose–length product conversion factor of 0.014 mSv/(mGy x cm) as described [29]. Average effective dose of the complete CT studies, was 4.3±1.1 mSv. For SPECT the effective dose was calculated using a conversion factor of 7.9^{e-3} mSv/MBq for stress and 9.0^{e-3} mSv/MBq for rest acquisition [30]. Average effective dose of SPECT per patient was 6.8±2.4 mSv. The calculated average effective dose of CA was 10.8±5.2 mSv, using a conversion factor of k = 0.22 for the registered dose area products (DAP). Mean total effective dose was 21.9±6.6 mSv per patient.

DISCUSSION

The main finding of our study is that hybrid SPECT/CCTA has excellent diagnostic performance versus a reference standard of FFR measurements. In a patient population with a high pre-test likelihood of CAD and high rates of non-conclusive results on either SPECT or CCTA, hybrid imaging analysis results in an improved PPV of 96% (versus PPV of 85% and 77% of SPECT and CCTA respectively) and a NPV of 95% (versus NPV of 89% and 96% of SPECT and CCTA respectively) on a patient level. Even in patients with either non-conclusive SPECT or non-conclusive CCTA hybrid imaging analysis results in a NPV and PPV of 91% and 90% respectively.

Current guidelines on hybrid SPECT/CCTA describe its main role in patients with an intermediate to high risk of CAD and a non-conclusive result of either modality [2]. Five studies described the increased diagnostic performance of hybrid SPECT/CCTA, with reported sensitivities and specificities ranging from 89%-99% and 67-95% respectively for the hybrid technique [15, 18, 31-33]. Besides the fact that the reference standard in all studies was CA as assessed by visual interpretation of the angiogram, these patient populations were limited in several other respects. Rispler et. al. evaluated 44 patients suspected to have CAD and scheduled for CA. Patients with unevaluable segments on CCTA however, were excluded [15]. Gaemperli et. al. evaluated 38 patients with at least one fixed or reversible perfusion defect by hybrid SPECT/CCTA. Their population resembled a high risk population due to the presence of perfusion defects as a mandatory inclusion criterion. CA was not available from all patients in this study [32]. Santana et al. performed hybrid SPECT/CCTA imaging in 50 patients evaluating its performance in a population with low to intermediate pre-test likelihood of CAD. Performance of standalone CCTA in this population was not reported. [31]. Slomka et. al. retrospectively evaluated automated co-registration, visualization and combined quantification of CCTA and SPECT from standalone scanners in 35 patients [33].

We evaluated the performance of hybrid SPECT/CCTA versus a reference standard of FFR measurements in the largest available patient cohort so far. Pre-test likelihood and diagnostic performance of each non-invasive modality versus the reference standard of FFR measurements, were prospectively acquired and available from all patients. Coronary calcium score was high in patients with CAD, median 497.5, resembling a true high risk population. At least one un-evaluable coronary segment on CCTA was present in 23.5% of the patients. Including non-conclusive SPECT results (11.2%), 33% of patients had either a non-conclusive SPECT or CCTA. Obviously, hybrid imaging was most complimentary in patients with a non-conclusive test, a false positive result of CCTA and a false negative result of SPECT imaging. As demonstrated in this manuscript the strong features of each test as standalone procedure compensate for the weaknesses of the other in a hybrid imaging setting. This results in an almost perfect diagnosis of the presence or absence of significant CAD.

The current study is limited by the fact that FFR was not measured in vessels with <50% or >95% obstructive disease. Measurement of these vessels could have resulted in improved results. However, based on available literature it is safe to assume that vessels with very mild (<50%) and very severe (>95%) obstructive disease respectively have normal and positive FFR-measurements [25, 28]. The study population is relatively small. However, hybrid SPECT/CCTA also had high diagnostic accuracy in the excluded patients with only CA as reference standard (N=45). Hybrid SPECT/CCTA had a PPV 94% (95%CI 73-99) and NPV 93% (95% CI 77-98) versus a reference standard of >50% stenosis on CA. The fact that more patients had a non-conclusive CCTA (23%) compared to the number of patients with a non-conclusive SPECT (11%) could be exemplary for the fact that CCTA is more prone to non-conclusive results due to higher CCS in patients with an intermediate- to high pre-test likelihood of disease. Hybrid imaging analysis of SPECT and CCTA is performed in several directions; both SPECT and CCTA were used as an adjunct to the other modality in conclusive and non-conclusive studies. The patient presented in Figure 5, could serve as an example in which CCTA proved to be complementary to a conclusive SPECT study. An equally compelling example could be found for a conclusive CCTA study. This leaves neither anatomical- nor functional imaging to trump the other modality and hybrid imaging without a categorical guideline for image interpretation. For each patient we chose the optimal stress protocol, either adenosine or exercise. However, adenosine stress has a known limited diagnostic performance compared to exercise stress. Despite the fact that almost a quarter of the patients received adenosine stress, the diagnostic performance of SPECT alone in this population is reasonable, and comparable to what has been reported in the past [5-7]. CCTA has a higher number of unevaluable segments and lower diagnostic performance compared to previous reports. This may be explained by the fact that patients were not excluded from further CT angiography based on the height of their CCS, which led to a high number of unevaluable segments (5.1%) [17]. Also, to limit the overall radiation dose an axial CT scan protocol without availability of multiple cardiac phases was employed, which may have contributed to the lower performance of CCTA [10-12, 17].

CONCLUSION

The advantage of hybrid imaging lies in the compensation for the weak properties of CCTA and SPECT, and the dissolution of non-conclusive results of both as standalone imaging procedures. This advantage is best reflected in a group of patients with intermediate to high risk of CAD, as is demonstrated in this study. In over 40% of this category of patients, CAD can be reliably excluded due to the complementary nature of hybrid SPECT/CCTA.

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Chapter 6

Added value of hybrid myocardial perfusion SPECT and CT coronary angiography to conventional diagnostics in discriminating between presence or absence of coronary artery disease

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Submitted

ABSTRACT

Aims

Hybrid SPECT/CCTA has only been evaluated for its diagnostic accuracy as a single test in patients suspected of significant coronary artery disease (CAD). Added value of hybrid SPECT/CCTA beyond usual clinical work-up, or use of each of these tests separately, remains unclear. We evaluated the added value of hybrid myocardial perfusion SPECT (SPECT) and coronary CT angiography (CCTA), beyond pre-test likelihood and exercise stress ECG (X-ECG), in the diagnosis of CAD.

Methods and Results

205 patients with stable angina pectoris and intermediate- to high pre-test likelihood were prospectively included. All patients underwent clinical history and examination, X-ECG, stress and rest SPECT, coronary calcium scoring (CCS) and CCTA. Fractional flow reserve measurement <0.80 or a lesion >50% on coronary angiography (CA) served as reference standard for significant CAD. Multiple imputations were used to correct for missing test results (17-20%). Added value of hybrid SPECT/CCTA to the basic model of pre-test likelihood plus X-ECG was quantified using logistic regression analysis. Model differences were then assessed using differences in C-index and in net reclassification improvement (NRI). The basic model had a C-index of 0.73 (95%CI 0.66-0.80). This significantly increased to 0.85 (95%CI 0.80-0.91) by addition of only SPECT, to 0.90 (95%CI 0.85-0.94) when adding only CCS and CCTA, and to 0.96 (95%CI 0.92-0.99) when adding hybrid SPECT/CCTA. The accompanying NRIs were 0.82 (95%CI 0.62-1.02), 0.86 (95%CI 0.66–1.06) and 1.57 (95%CI 1.11-1.59) respectively.

Conclusion

Current analysis resembles clinical routine of layered testing and shows that hybrid SPECT/CCTA imaging has a substantially higher yield than standalone SPECT or CCTA in the diagnosis of patients suspected of significant CAD.

INTRODUCTION

Patients with a high pre-test likelihood of significant coronary artery disease (CAD) have a class 1A indication for invasive coronary angiography (CA) [1]. However, only 36% of patients referred for CA prove to suffer from significant CAD [2]. A reliable non-invasive imaging technique that accurately discriminates between the presence or absence of significant CAD in these patients would be of great value.

The work-up of patients with anginal complaints in many outpatient clinics routinely starts with exercise stress electrocardiography (X-ECG) [3, 4]. Several reports describe the use of coronary calcium scoring (CCS) for diagnostic purposes in symptomatic patients [5-7]. However, according to current guidelines it is not recommended to use these tests in intermediate- to high pre-test likelihood patients (based on gender, age, clinical history and examination) [1, 7-10]. As such, many patients are referred for further non-invasive imaging to defer from CA or to exclude high risk CAD [1, 3, 4]. From all non-invasive imaging modalities, including myocardial perfusion single photon emission computed tomography (SPECT), positron emission tomography (PET), CT coronary angiography (CCTA), stress echocardiography and cardiac MRI, hybrid SPECT or PET/CCTA probably have the highest diagnostic yield. Sensitivity and specificity values of 94-96% and 92-100% for the diagnosis of significant CAD have been reported [11-17].

However, hybrid SPECT/CCTA has only been evaluated for its diagnostic accuracy as a single test. But in the routine work-up of patients with angina pectoris not only the result of the last imaging procedure is taken into account, also clinical history, examination and the results of other tests are always considered to decide whether or not to perform CA [18]. As such, the single test accuracy estimates do not indicate whether pre-test likelihood and X-ECG either in combination with standalone SPECT, with standalone CCTA, or with hybrid SPECT/CCTA is the best combination of diagnostic procedures in these patients.

We therefore performed a study to evaluate the added value of hybrid SPECT/CCTA imaging beyond pre-test likelihood, X-ECG and standalone SPECT or CCTA in patients with an intermediate- to high pre-test likelihood of significant CAD.

METHODS

Patient population

We prospectively conducted a single center cross-sectional study, in Nieuwegein, The Netherlands. Patients with chest pain symptoms and an intermediate to high pre-test likelihood of CAD were consecutively recruited for this study from September 2010 until December 2011. History was taken by physicians and chest pain was categorized according to traditional criteria [3, 19-21]. Pre-test likelihood was calculated according to Diamond and Forrester criteria [19]. The boundaries for low, intermediate and high pre-test likelihood were set at <20%, 20-80% and > 80% respectively [1, 19]. Exclusion criteria were a history of surgical revascularization (CABG), stent implantation (PCI), an unstable cardiac condition or a cardiac rhythm other than sinus rhythm. The study conformed to the principles outlined in the declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients. Furthermore, the study was conducted and reported in accord with STARD guidelines [22].

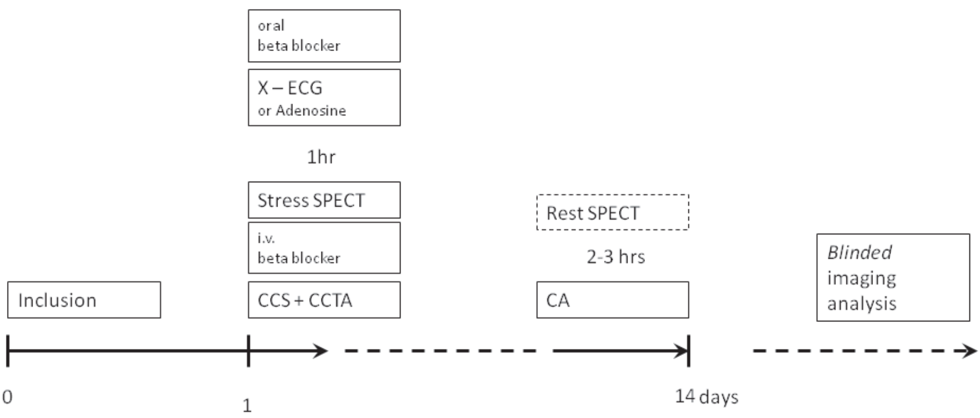
Diagnostic work-up

At day one of the diagnostic work-up all patients underwent X-ECG or pharmacological stress preceding hybrid stress SPECT and CCTA. Within 14 days, on the second day of the diagnostic work-up, rest SPECT acquisition and CA with fractional flow reserve (FFR) measurements were scheduled (Figure 1). CA and FFR measurements served as the reference test for significant CAD (see below). The interpretation of all diagnostic tests occurred blinded for all other modalities. Physicians were, however, aware of gender, age and clinical history during each test interpretation [23].

Prior to the first day of the diagnostic work-up all patients stopped rate limiting or anti-anginal medications. Stress SPECT, CCS and CCTA were acquired on a Hybrid SPECT-CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands). The components share a common table that is aligned to allow sequential image acquisition. Either X-ECG or pharmacological stress (adenosine at standard rate of 0.14mg/kg/min over 6 min) were performed prior to stress SPECT acquisition. Inability to perform bicycle stress testing or failure to reach 85% of the predicted maximum heart rate was reason to switch to pharmacological stress. Directly following stress SPECT acquisition CCS and CCTA imaging was performed. All participants presenting with baseline heart rates over 60bpm received 100mg oral metoprolol tartrate at the start of the stress test preceding SPECT imaging. Patients with an initial heart rate below 60bpm received

50mg metoprolol tartrate. Pharmacokinetics of oral metoprolol do not allow for an immediate effect that would interfere with X-ECG acquisition. Preceding CCTA additional intravenous metoprolol was administered to achieve a heart rate below 62bpm. In patients with a normal stress SPECT (normal perfusion and gated data) no rest SPECT was acquired. Inability to perform acquisition of prospectively triggered CCTA (heart rate >62-64bpm) was reason to exclude patients (N=31, 15.1%) from the study. For radiation dose saving purposes the study protocol did not allow for retrospectively gated CCTA. Mean radiation dose for SPECT was 6.3±2.5MSv and mean radiation dose for CCTA was 4.1±2.2MSv. CA and FFR measurements were performed in all patients with a completed non-invasive imaging sequence, including those with normal non-invasive test results. Mean radiation dose for CA was 10.5±4.8MSv.

Figure 1: Sequence of diagnostic work-up.



X-ECG, exercise stress electrocardiography. SPECT, myocardial perfusion SPECT. CCS, coronary calcium score. CCTA, CT coronary angiography. CA, invasive coronary angiography.

Index tests

Exercise stress electrocardiography

Bicycle stress electrocardiography was performed according to a previously described stepwise protocol [24]. All X-ECG results were reviewed in consensus by two experienced physicians blinded for all other diagnostic tests. An abnormal X-ECG was defined as ≥0.1mV horizontal shift of the ST segment at 80ms after the J-point in three consecutive beats [24, 25]. Non-conclusive X-ECG was defined as typical angina during stress, >30mmHg decrease in systolic blood pressure, uninterpretable ECG as a result of an unstable baseline or inability to reach at least 85% of the predicted heart rate without electrocardiographic evidence of ischemia. Normal X-ECG was defined as the absence of any of the aforementioned criteria. The predicted heart rate was corrected for length, age and sex, making use of a standardized table [24].

Myocardial perfusion SPECT

SPECT imaging was performed as previously described using a weight-adjusted dose of 400-600 MBq of ^{99m}Tc-sestamibi [8]. Attenuation correction was performed for all images using a non-enhanced CT scan. Stress and rest SPECT images were interpreted in consensus by two experienced nuclear medicine physicians blinded for all other diagnostic tests as previously described [8, 26, 27]. In brief, summed stress score and summed rest score were calculated after scoring for perfusion defects according to a five-point scoring system (0 = normal to 4 = absence of tracer uptake) and a 17-segment model. Gated data and semi quantitative perfusion data were assessed using the QGS/QPS software package (Cedars-Sinai Medical Center, Los Angeles, Ca, USA). For the definition of normal, non-conclusive and abnormal myocardial perfusion on SPECT according to segmental scores we used the definition provided by Abidov et al.[26]. SPECT with a non-conclusive perfusion score was regarded abnormal.

Coronary computed tomography angiography

CCTA was acquired with a prospectively ECG-triggered scan mode as previously described and according to the guidelines provided by the society of cardiovascular computed angiography [28]. Prior to CCTA, a non-enhanced scan to calculate the CCS and determine scan length was performed. CCTA's were read in consensus by two experienced cardiologists blinded for all other diagnostic tests. They categorized obstructive severity according to a 16-segment model and 5 categories of luminal loss: no CAD (0% area stenosis), mild lesion severity (0 – 50% area stenosis), intermediate lesion severity (50 – 70% area stenosis), severe lesions (70 – 99% area stenosis) and total occlusion. If the category of luminal loss could not be determined (e.g. due to motion artifact or severe calcifications) a segment was categorized as non-conclusive. Subsequently a vessel based analysis was performed from which diagnostic accuracy on a per-patient level was determined. Vessels were categorized as abnormal if at least one segment had a percent diameter stenosis >50%. All non-conclusive segments were defined abnormal.

Hybrid SPECT/CCTA imaging analysis

According to our pre-defined protocol all patients were included in hybrid imaging evaluation. Interpretation was performed in consensus by two independent experienced physicians blinded for X-ECG, CA and FFR measurements. The integrated interpretation of all imaging data led to the categorization of all vessels and patients as normal or abnormal. Concordant normal or abnormal findings by SPECT and CCTA led to a similar interpretation of the hybrid imaging result. In patients with a normal CCTA and a discordant abnormal or non-conclusive SPECT, the hybrid imaging result was defined normal. In patients with a non-conclusive CCTA, the normal or abnormal SPECT result was decisive for the hybrid imaging result. In patients with an abnormal CCTA and a discordant normal SPECT, CCTA prevailed only in those patients with a definitely abnormal CCTA. In patients with an abnormal CCTA and a discordant non-conclusive SPECT, the hybrid imaging result was defined abnormal [29].

Reference test: invasive coronary angiography

A FFR measurement <0.80 was defined abnormal and served as the reference test for significant CAD. FFR measurements were acquired in 104 patients (61%) of patients that underwent CA. All other angiograms were interpreted in consensus by two experienced cardiologists for obstructive severity according to a 16-segment model similar to the interpretation of CCTA. Interpretation occurred blinded for all other diagnostic modalities. They were aware of age, gender and clinical history [23]. Lesions with >50% obstructive disease were considered abnormal (significant CAD). Vessel-based analysis was performed from which diagnostic accuracy on a per-patient level was determined.

CA was acquired on Allura catheterization equipment (Philips Medical Systems, Best, The Netherlands) via femoral or radial artery access. Biplane views were acquired from all major coronary arteries. FFR measurements were performed as previously described [30].

Statistical analysis

First, in accordance with recent methodological recommendations, all missing test results in our study were multiply (10 times) imputed using regression techniques [31-33]. Then 4 different logistic regression models were fitted in each of the 10 individual imputed datasets and subsequently combined across imputations using Rubin's Rule [34, 35], resulting in 4 'combined' models. These 'combined' models were then used to calculate the added value measures (i.e. AUC and NRI) for each model. To resemble routine clinical work-up [36, 37] we first fitted the basic logistic regression model (model 1) including the pre-test likelihood of CAD plus X-ECG as independent diagnostic predictors (index tests) and CAD presence (yes/no) based on CA as outcome. The model's C-index or area under the receiver operating characteristics curve (Roc area) was computed. The added value of additional imaging tests (i.e. SPECT, CCS plus CCTA and hybrid SPECT/CCTA) beyond the basic model was quantified by consecutively extending the basic model with these tests and assessing the increase in C-index. The models of interest are shown in Table 1. We included CCS in the model evaluating CCTA, since acquisition of CCS is commonly performed prior to CCTA. Furthermore, the number of patients correctly reclassified after adding the various imaging modalities to the basic model, was expressed using the net reclassification improvement (NRI). This measure, summarizing the reclassification table, is calculated by subtracting the proportion of subjects classified worse by the new model from the proportion of patients that is better classified by the new model. As cut-off values for the reclassification table and related measures, we used three common CAD probability categories; low (probability <20%), intermediate (20-80%) and high (>80%) for CAD [1, 18, 38]. Data were analyzed using R (Version 2·13·1) [39].

Table 1: models of interest

Model 1: Probability of coronary artery disease (basic model*) = 1/(1+exp-(-2.496 + 0.026*Pre-test likelihood† + 1.014*X-ECG))
Model 2: Probability of coronary artery disease after adding SPECT to Model 1 = 1/(1+exp-(-2.186 + 0.008*Pre-test likelihood† + 0.800*X-ECG + 2.2628*SPECT))
Model 3: Probability of coronary artery disease after CCS and CCTA to Model 1 = 1/(1+exp-(-3.989 + 0.012*Pre-test likelihood† + 1.098*X-ECG + 0.001*CCS + 3.3160*CCTA))
Model 4: Probability of coronary artery disease after adding CCS and hybrid SPECT/CCTA to Model 1 = 1/(1+exp-(-2.450 – 0.010*Pre-test likelihood + 0.555*X-ECG + 0.001*CCS + 5.393*hybrid SPECT/CCTA

Table 1 reports the 'combined' logistic regression models 1 to 4, which were first fitted in each of the 10 individual imputed datasets and subsequently combined across imputations using Rubin's Rule. * Basic model = Pre-test likelihood + X-ECG. † Pre-test likelihood was used as a continues variable in all models. X-ECG, exercise stress electrocardiography. SPECT, myocardial perfusion SPECT. CCS, coronary calcium score. CCTA, CT coronary angiography.

RESULTS

Study population

205 adult patients were included in the study. Patient characteristics are displayed in Table 2.

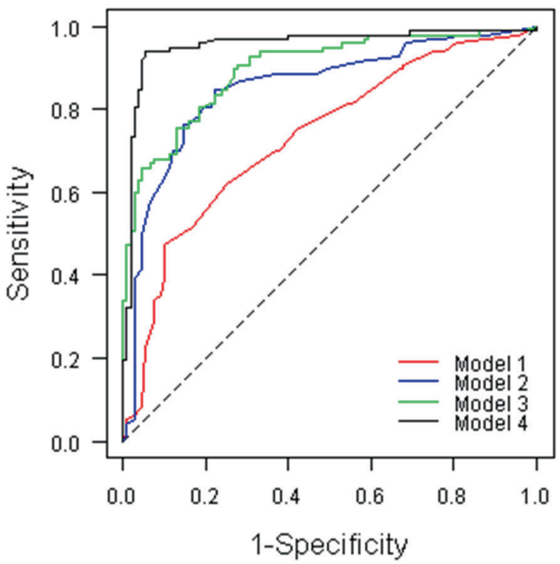
Diagnostic value of pre-test likelihood and exercise stress electrocardiography (Model 1)

In the basic multivariable model for detecting CAD the independent variables were pre-test likelihood and X-ECG. Pre-test likelihood alone, used as a continuous variable, had a C-index of 0.67 (0.59-0.74). The combination of pre-test likelihood and X-ECG (model 1; Table 1) resulted in a C-index of 0.73 (95% CI; 0.66-0.80) (Figure 2).

Added diagnostic value of SPECT, CCS+CCTA, and Hybrid SPECT/CCTA (Models 2-4)

Adding further imaging techniques, i.e. SPECT, CCS+CCTA and Hybrid SPECT/CCTA (models 2-4; Table 1) to the basic model (model 1; Table 1) resulted in a significant increase in C-index from 0.73 (95%CI; 0.66-0.80) to 0.85 (0.80 - 0.91), 0.90 (0.85 - 0.94) and 0.96 (0.92-0.99) respectively (Figure 2).

Figure 2: Areas under the receiver operator characteristics curves for all diagnostic models.



	C-index (95% CI)
Model 1: Basic model* (red line)	0.73 (0.66 - 0.80)
Model 2: Basic model + SPECT (blue line)	0.85 (0.80 - 0.91)
Model 3: Basic model + CCS + CCTA (green line)	0.90 (0.85 - 0.94)
Model 4: Basic model + CCS + Hybrid SPECT/CCTA (black line)	0.96 (0.92 - 0.99)

* Basic model = Pre-test likelihood + X-ECG. X-ECG, exercise stress electrocardiography. SPECT, myocardial perfusion SPECT. CCS, coronary calcium score. CCTA, CT coronary angiography.

Table 2: Characteristics of the patients included in the analysis, N = 205

Patient characteristics	N (%)	Missings (%)
Age (years) *	62.7 ± 9.7	0 (0)
Gender, men / women	127 (62) / 78 (38)	0 (0)
Risk factors		0 (0)
Smoking		
Current	44 (21)	
Past	35 (17)	
Hypertension	134 (65)	
Diabetes mellitus	35 (17)	
Dyslipidaemia	130 (63)	
Family history of premature atherosclerosis	120 (59)	
Risk factors ≥ 3	105 (51)	
Angina pectoris		0 (0)
Non-anginal	1 (1)	
Atypical	67 (33)	
Typical	137 (67)	
CaCS Angina Class		0 (0)
Class I	14 (7)	
Class II	172 (84)	
Class III	19 (9)	
Class IV	0 (0)	
Pre-test likelihood †	0.87 (0.22 – 0.95)	0 (0)
Low	0 (0)	
Intermediate	90 (44)	
High	103 (50)	
Unknown‡	12 (6)	
Exercise stress electrocardiography (N= 158) §		37 (18) §
Normal	119 (58)	
Abnormal	43 (21)	
Non-conclusive	6 (3)	
Coronary Calcium Score (N=204)*	536 ± 800	1(1)
Myocardial perfusion SPECT (N=204)		1 (1)
Normal	115 (56)	
Abnormal	89 (43)	

Patient characteristics	N (%)	Missings (%)
CT coronary angiography (N=163)		41 (20)
Normal	69 (34)	
Abnormal	95 (46)	
Hybrid SPECT/CCTA (N=163)		41 (20)
Normal	91 (44)	
Abnormal	73 (36)	
Invasive coronary angiography (N=171) ¶		34 (17)
Normal	85 (41)	
Abnormal	86 (42)	

Values are shown as number and percentage unless otherwise noted. * Values expressed as mean ± standard deviation, † Values expressed as median (range). ‡ Patients with atypical angina pectoris and >70 years old. § Adenosine stress was performed in 37 (18%) patients prior to stress SPECT acquisition. ¶ Of 7 patients without a completed non-invasive imaging sequence invasive coronary angiography was acquired with a clinical indication. CaCS, Canadian Cardiovascular Society.

Reclassification by Hybrid SPECT/CCTA

Using the basic model (Model 1), the estimated probability of CAD was calculated for each patient. Of the patients with a low estimated probability of CAD (<20%, n=16), 13 did not have significant CAD (negative predictive value; NPV 81%) (Table 3). In those with a high predicted probability (>80%, n=13), 8 had significant CAD (positive predictive value; PPV 62%), Table 3. Adding Hybrid SPECT/CCTA (Model 4) increased the number of patients with estimated low probability from 16 to 107, of whom 101 did not have significant CAD (NPV 94%). The number of high probability patients increased from 13 to 97, of whom 91 indeed had significant CAD (PPV 94%). Addition of Hybrid SPECT/CCTA did not change the estimated probability class (low, intermediate or high) in 22 patients (11%). Hybrid SPECT/CCTA correctly increased the estimated diagnostic probability in 83 patients with CAD, and 89 patients without CAD were correctly reclassified to lower probability groups. 5 patients with CAD were incorrectly reclassified to lower probability groups and 6 patients without CAD were incorrectly reclassified to higher probability groups (Table 3). The imaging characteristics of these patients who were incorrectly reclassified, were a very challenging CCTA (CCS >800 or motion artifacts) in combination with either a false positive or false negative SPECT (n=5), discordant SPECT and CCTA findings (n=3), or an unavailable reference test (n=3). The NRI for the addition of hybrid SPECT/CCTA was therefore 1.57 (95%CI; 1.31 - 1.83) (Table 3). The NRI for the addition of SPECT or CCS+CCTA was 0.82 (0.62-1.02) and 0.86 (0.66 – 1.06) respectively.

Table 3: Reclassification table according to low (<20%), intermediate (20-80%) and high probability (>80%) groups: basic model (model 1) versus hybrid SPECT/CCTA (model 4).

	Model 4: Basic model* + Hybrid SPECT/CCTA			
Model 1: Basic model* Patients with CAD Probability group for CAD	<20%	20-80%	>80%	Total
<20%	1	0	2	**3**
20-80%	5	0	81	**86**
>80%	0	0	8	**8**
Total	**6**	**0**	**91**	**97**
Patients without CAD Probability group for CAD	<20%	20-80%	>80%	Total
<20%	13	0	0	**13**
20-80%	84	0	6	**90**
>80%	4	1	0	**5**
Total	**101**	**1**	**6**	**108**

Reclassification improvement is 0.80 among patients with CAD (83-5 of 97) and 0.77 among patients without CAD (89-6 of 108), resulting in a net reclassification improvement of 0.80+0.77=1.57 (95% CI; 1.11-1.59). * Basic model = Pre-test likelihood + X-ECG. X-ECG, exercise stress electrocardiography. SPECT, myocardial perfusion SPECT. CCS, coronary calcium score. CCTA, CT coronary angiography. CAD, coronary artery disease. Grey shaded numbers are patients classified in agreement according to the model with and without hybrid SPECT/CT.

DISCUSSION

This study shows that in the clinical work-up of patients with an intermediate to high pre-test likelihood, addition of hybrid SPECT/CCTA imaging analysis yields the most accurate diagnosis of the presence or absence of significant CAD (C-index 0.96). Further, addition of hybrid SPECT/CCTA to pretest information and X-ECG better reclassifies patients when compared to addition of only SPECT or CCTA (NRI of 1.57 vs. 0.82 and 0.86 respectively).

Non-invasive tests beyond pre-test likelihoods are needed to correctly reclassify patients from high probability to low probability and thus correctly defer them from CA, since the clinical reality is that only 36% of patients referred for CA prove to suffer from significant CAD [1, 2]. In the subset of patients with an intermediate to high pre-test likelihood of CAD, the routinely performed X-ECG or CCS alone are not sufficient to provide adequate discrimination between patients with and without CAD [7-9]. This is also demonstrated in the current study (C-index of 0.73 and 0.75 respectively vs. pre-test likelihood alone with a C-index of 0.67. Performance of standalone SPECT or CCTA in addition to the aforementioned tests seems much more accurate (C-index of 0.85 and 0.90 respectively). However, available literature describes a limited diagnostic accuracy of SPECT or CCTA in high pre-test likelihood patients [40-42]. The high negative predictive value of CCTA could be challenged due to increased amount of coronary calcifications in high pre-test likelihood patients [43, 44]. Diagnostic performance of SPECT in these patients is known to be limited, due to a given amount of non-conclusive SPECT results due to small perfusion defects, inadequate heart rate response or discrepant clinical data (anginal complaints during stress or positive X-ECG result) [45]. The advantage of hybrid imaging lies in the compensation for the weak properties of CCTA and SPECT, and the dissolution of non-conclusive results of both as standalone imaging procedures. As such, to overcome the diagnostic uncertainty in high pre-test likelihood patients and in patients with non-conclusive imaging results, hybrid SPECT/CCTA has been proposed [11, 12, 29, 46].

The yet available studies show that when used in isolation this test has a very promising diagnostic value with a sensitivity 89%-99% and specificity of 67-95% [11-15]. The current study not only confirms this finding, but more importantly proofs that hybrid SPECT/CCTA has added value over standalone SPECT or CCTA in a high pre-test likelihood population. As such hybrid imaging is specifically relevant for the subset of patients with continued diagnostic uncertainty despite conclusive imaging results or patients with non-conclusive imaging results per se. And it has the potential to guide decisions on the necessity of revascularization [47].

Several limitations to our study should be acknowledged. Recent reports have shown that the model we used to calculate pre-test likelihood CAD (Diamond and Forrester) heavily overestimates the presence of CAD [48, 49]. The presence of a non-sinusal heart rhythm was an exclusion criterion for our study; in clinical practice this could constitute a considerable number of patients. We had missing test results and are well aware of the fact that missing data rarely occur completely at random and may therefore hamper the results. However, the number of missing data was limited and we used multiple imputations to alleviate the problem of missing test results. FFR measurements were available in 61% of patients that underwent CA, whereas for the remainder we used an anatomical reference test (>50% obstructive disease as diagnostic for significant CAD), which is known to be imperfect. According to available literature it is safe to assume that lesions with <50% stenosis have no hemodynamic significance [50]. FFR-measurements were available from 78% of patients with angiographically 50-70% and 68% of patients with 70-95% obstructive disease. We chose a boundary of 20-80% for an intermediate probability of significant CAD; this is supported by available literature [1]. However, boundaries of 10-90% or 15-85% are also commonly used. According to our analysis a boundary of 10-90% would leave 24 patients (12%) and a boundary of 15-85% would leave 1 patient (0.5%) with and without CAD in the intermediate group after hybrid SPECT/CCTA imaging analysis versus 1 patient (0.5%) if a boundary of 20-80% was used for intermediate probability. The NRI of 1.57 for the addition of hybrid SPECT/CCTA is indeed very high. In part, this is explained by the fact that these models include imaging modalities that evaluate the same characteristics of coronary artery disease. Also, this high value occurs as a result of the chosen probability thresholds of 20% and 80%, 176 of 205 patients (86%) are estimated to have an intermediate probability using the basic model (pre-test likelihood and X-ECG). The extended model is far better in predicting low probability (<20%) and high probability (>80%) patients, thus leading to a high NRI. Healthcare policies advocate a stepwise imaging protocol in the diagnostic work-up of patients, for radiation dose saving purposes and a cost effective use of diagnostic modalities. As such, a hybrid imaging approach should not be the primary imaging strategy for all patients presenting with angina pectoris.

CONCLUSIONS

Our study is the first to demonstrate the added diagnostic value of the complementary nature of hybrid SPECT/CCTA imaging. With an analysis resembling clinical routine of layered testing, the impressive diagnostic accuracy of hybrid SPECT/CCTA beyond X-ECG and SPECT or CCTA is demonstrated in intermediate to high pre-test likelihood patients. We show that these patients can be accurately reclassified into low- or high probability groups of CAD, as such deferring them from CA and probably indicate revascularization.

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Chapter 7

Hybrid myocardial perfusion SPECT/CCTA and invasive coronary angiography in patients with stable angina pectoris lead to similar treatment decisions

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ABSTRACT

Objectives

To evaluate to what extent treatment decisions for patients with stable angina pectoris can be made based on hybrid myocardial perfusion SPECT (SPECT) and CT Coronary Angiography (CCTA). It has been shown that hybrid SPECT/CCTA has good performance in the diagnosis of significant coronary artery disease (CAD). The question remains whether these imaging results lead to similar treatment decisions as compared to standalone SPECT and invasive coronary angiography (CA).

Design

We prospectively included 107 patients (mean age 62.8±10.0 years, 69% male) with stable anginal complaints and an intermediate to high pre-test likelihood for CAD. Hybrid SPECT/CCTA was performed prior to CA in all patients.

Main outcome measures

The study outcome was the treatment decision categorized as: no revascularization, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). These treatment decisions were made by a panel of two interventional cardiologists and one cardio-thoracic surgeon in two steps: first based on the results of hybrid SPECT/CCTA, and on a second occasion based on SPECT and CA. Percent agreement of treatment decisions based on both diagnostic strategies were calculated in all patients, including patients with matched, unmatched and normal hybrid SPECT/CCTA findings.

Results

Revascularization (PCI or CABG) was indicated in 54 (50%) patients based on SPECT and CA. Percent agreement of treatment decisions in all patients based on hybrid SPECT/CCTA versus SPECT and CA on the necessity of revascularization was 92%. Percent agreement of treatment decisions in patients with matched, unmatched and normal hybrid SPECT/CCTA findings was 95%, 84% and 100% respectively.

Conclusions

Panel evaluation shows that patients could be accurately indicated for and deferred from revascularization based on hybrid SPECT/CCTA.

INTRODUCTION

Current guidelines on the management of patients with stable chest pain syndromes recommend revascularization in patients with persistent limiting symptoms, high risk anatomy, or significant ischemic territory (>10% of the myocardium) [1, 2]. Since intervention of functionally irrelevant lesions is associated with the risks but not the benefits of revascularization, preferably (non-)invasive evidence of the functional significance of each lesion is available [1, 3, 4]. As such, myocardial perfusion imaging with single-photon emission computed tomography (SPECT) has been suggested as a non-invasive gatekeeper for invasive coronary angiography (CA) [5, 6]. Also, with the advent of CT coronary angiography (CCTA), reliable non-invasive anatomical information on the coronary arteries can now be obtained [7]. Like CA however, standalone CCTA lacks functional information on lesion severity and thereby is unsuitable for therapeutic decision making [8, 9].The availability of hybrid SPECT/CCTA as anatomical and functional imaging technique generated the interest in non-invasive imaging as a tool to guide therapeutic decision making, e.g. to decide on necessity of revascularization or even the choice of the method of revascularization [10-13].

Hybrid SPECT/CCTA has good diagnostic performance in patients who are evaluated for the presence of coronary artery disease (CAD) when compared to CA [10, 11, 14-16]. The value of hybrid imaging lies not only in the correlation of perfusion abnormalities on SPECT with coronary stenosis on CCTA. Rather, complimentary results of hybrid imaging may compensate for the respective diagnostic pitfalls of each technique as stand-alone imaging procedure [10, 17]. Recently, prognosis and effect on choice of treatment strategy in subgroups of patients with matched, unmatched and normal hybrid SPECT/CCTA findings have been analyzed [12, 13]. However, a direct comparison of the effect of hybrid SPECT/CCTA versus traditional work-up using SPECT and CA on the choice of treatment strategy is lacking.

For several decades, cardiologists and cardio-thoracic surgeons have been meeting in “heart- teams” to decide on the necessity of coronary revascularization based on CA and (non-) invasive evidence of myocardial ischemia [1, 2]. With the demonstrated reliability of hybrid SPECT/CCTA we hypothesized that in a similar setting, treatment decisions can be made for patients with stable angina pectoris using hybrid SPECT/CCTA just as good as with SPECT and CA. Also, we evaluated the reliability of these treatment decisions in groups of patients with matched, unmatched and normal hybrid SPECT/CCTA findings.

METHODS

Patient population

Patients with an intermediate to high pre-test likelihood of CAD were prospectively enrolled in this study from September 2010 until December 2011. Pre-test likelihood was calculated according to Diamond and Forrester criteria [18]. Exclusion criteria were a history of surgical revascularization (CABG), stent implantation (PCI), an unstable cardiac condition or a cardiac rhythm other than sinus rhythm. After acquisition of all imaging data each case was evaluated during a routine heart team meeting. Additionally, as we discuss below in more detail, a panel evaluation took place on a separate occasion. The study conformed to the principles outlined in the declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients.

Imaging procedure and interpretation

Gated SPECT and CCTA data were acquired on a hybrid SPECT/CT system, CardioMD gamma camera and Brilliance 64-slice CT scanner (Philips Medical Systems, Best, The Netherlands). On the first imaging day stress SPECT and CCTA data were acquired. Patients started with exercise (82 patients, 77%) or pharmacological (25 patients, 23%) stress after which stress SPECT was acquired. For stress and rest SPECT a weight adjusted dose of 400-600MBq ^{99m}Tc-sestamibi was used. Attenuation correction was performed on all images using a non-enhanced CT scan. Directly following stress SPECT acquisition, all patients underwent prospectively ECG-triggered axial CCTA according to the guidelines provided by de society of cardiovascular computed angiography [19]. All participants presenting with baseline heart rates over 60 bpm received 100mg oral metoprolol tartrate at the start of the stress test preceding SPECT imaging. Patients with an initial heart rate below 60 bpm received 50mg metoprolol tartrate. CA was scheduled within 14 days from the first image acquisition, preceded by rest SPECT image acquisition on the same day, only in those patients with an abnormal stress SPECT. As part of the prospective study, CA was performed in all patients, including those with normal non-invasive test results. CA was acquired on Allura (Philips Medical Systems, Best, The Netherlands) catheterization equipment via femoral or radial artery access. Biplane views were acquired from all major coronary arteries. Fractional flow reserve measurements (FFR) were performed at discretion of the performing operator and available in 72 (67%) patients.

Hybrid SPECT/CCTA data were interpreted with regard to functional relevance of coronary stenosis, in consensus by two experienced physicians blinded for other imaging procedures using dedicated software (Intellispace Portal 5.0, Philips, Best, The Netherlands). Stress and rest SPECT images were interpreted as previously described according to a 17-segment model and scored for perfusion defects using a five-point scoring system (0 = normal to 4 = absence of tracer uptake) [20-22]. CCTA images were read according to a 16-segment model and 5 categories of luminal loss: no CAD (0% luminal loss), mild lesion severity (luminal loss 0 – 50%), intermediate lesion severity (luminal loss 50 – 70%), severe lesions (luminal loss 70 – 99%) and total occlusion. Significant disease was defined as the presence of >50% luminal loss on CCTA.

Similar to a previous study on the impact of hybrid SPECT/CCTA on choice of treatment strategy [12], we assessed the panel decisions and the frequency of revascularization in patients with normal, unmatched and matched hybrid imaging findings. A matched hybrid finding was defined as a reversible defect on SPECT in a myocardial territory subtended by a stenotic coronary artery with a lesion exceeding 50% luminal loss. An ischemic finding on SPECT was defined as a SDS of ≥1 in a myocardial territory corresponding to one supplying coronary artery. An unmatched hybrid finding was defined as an ischemic SPECT finding without a lesion >50% luminal loss in the corresponding coronary artery, or as a lesion >50% luminal loss in a coronary artery on CCTA, without an ischemic finding in the corresponding myocardial territory on SPECT. If no stenosis was present on CCTA and SPECT was normal, the hybrid finding was regarded normal. Subsequently, patients were assigned to one of the following three categories: matched-, unmatched or normal hybrid SPECT/CCTA finding.

Panel evaluation

To quantify the percent agreement of treatment decisions between the new work-up including hybrid SPECT/CCTA imaging and the traditional diagnostic work-up using SPECT and CA, a design of two panel evaluations was chosen (Figure 1). The treatment decision consisted of three categories: no revascularization, PCI or CABG. The panel consisted of one cardio-thoracic surgeon (TdK) and two interventional cardiologists (BR and JVdH). First, the panel decided on the choice of treatment based on hybrid SPECT/CCTA findings. These sessions consisted of the evaluation of all available images and were chaired by two experienced readers (JS and FV). The choice for revascularisation was made in the presence of clear significant CAD, which could be an unmatched or matched hybrid SPECT/CCTA finding (Figures 2 and 3). All panel members were unaware of the CA results. Secondly, on a next occasion with a time frame of at least 4 weeks, treatment decisions were based on the evaluation of SPECT and CA images, which served as the reference method. The choice for revascularization was made in the presence of significant disease defined as a >50% luminal loss on CA with evidence of myocardial ischemia (FFR <0.80 or ischemic SPECT findings). During both sessions the panel members were supplied with anonymous baseline clinical characteristics of the patient; medical history, medication use, clinical symptoms, physical examination, risk factors and baseline ECG. Also the results of exercise stress ECGs were disclosed when available, prior to evaluation of the imaging data.

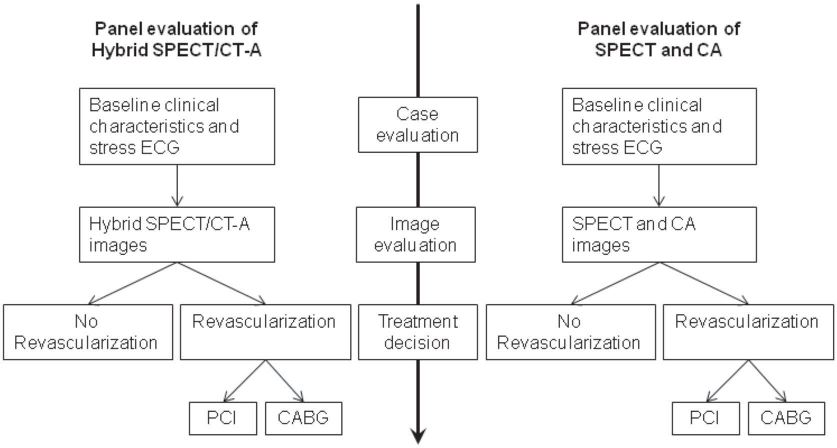

Figure 1 Panel design. The panel first decided on the treatment strategy after evaluation of hybrid single photon emission computed tomography (SPECT) and CT coronary angiography (CCTA) images. Treatment decisions were made according to three categories. 1. No revascularization, 2. Percutaneous coronary intervention (PCI) and 3. Coronary artery bypass surgery (CABG).

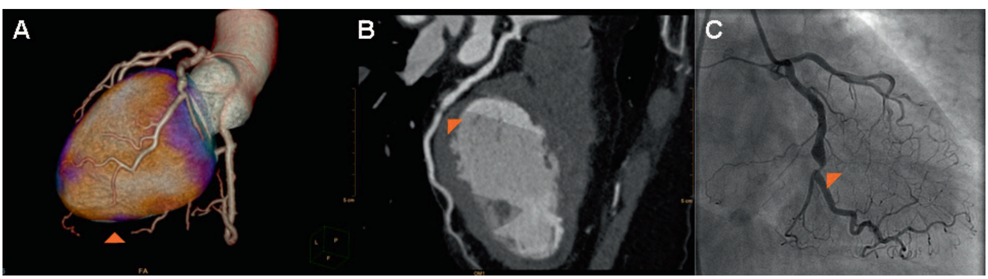

Figure 2 A 66 year-old female patient with typical anginal complaints and normal myocardial perfusion on SPECT (Panel A, stress SPECT). However, CCTA revealed severe stenosis of the circumflex artery (Panel B), which was confirmed by CA (Panel C). Based on evaluation of both hybrid SPECT/CCTA and SPECT and CA the panel decided on percutaneous coronary intervention.

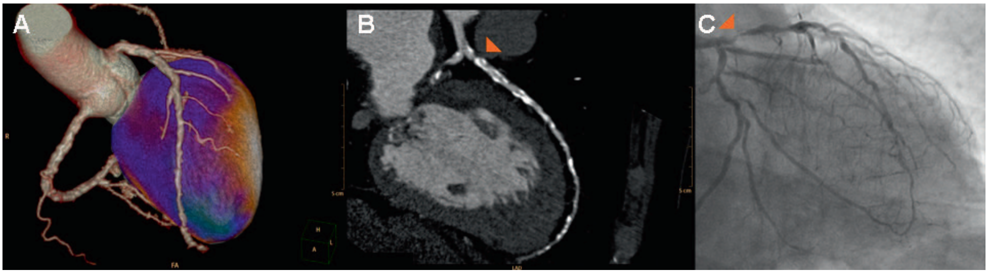

Figure 3 A 71 year-old male patient with typical anginal complaints and a severe reversible perfusion defect anterior and apical on SPECT (Panel A, stress SPECT). CCTA was largely unevaluable due to severe coronary calcifications (CCS of 2279). Although a severe stenosis in the proximal left anterior descending (LAD) artery could be suspected (Panel B). The presence of a significant stenosis in the proximal LAD was confirmed by invasive coronary angiogram (CA) (Panel C). Based on evaluation of both hybrid SPECT/CCTA and SPECT and CA the panel decided on percutaneous coronary intervention.

Statistical analysis

The primary outcome was defined as the percent agreement on the necessity of revascularization (no revascularization versus revascularization) between the new diagnostic strategy using hybrid SPECT/CCTA versus conventional SPECT and CA. Secondary outcome was defined as the percent agreement of decisions on the method of revascularization, PCI versus CABG, in patients referred for revascularization based on hybrid SPECT/CCTA. Primary and secondary outcomes were calculated for all patients combined and for the subgroups of patients with matched, unmatched and normal hybrid SPECT/CCTA findings. The Chi-square test was used to compare rates of indicated revascularizations based on SPECT and CA in the three patient groups with matched, unmatched and normal hybrid SPECT/CCTA findings. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS software (V. 18.0, IBM Corporation, Somers, New York, USA).

RESULTS

Study population

In total 107 patients (mean age 62.8±10.0 years, 69% male) with stable anginal complaints and median pre-test likelihood of CAD of 87% (range 22-95%) were included. Complete characteristics of the study population are shown in Table 1.

Hybrid SPECT/CCTA imaging findings

SPECT revealed reversible perfusion defects in myocardial segments subtended by one coronary artery in 61 (57%) patients. At least one stenosis of >50% in a coronary segment on CCTA was observed in 63 patients (59%). 40 patients (37%) showed at least one matched SPECT and CCTA finding, only unmatched findings were present in 44 patients (41%), and normal findings on both SPECT and CCTA in the remainder.

Radiation dose analysis

Average effective dose of CCTA was 4.2±1.0 mSv [23]. Average effective dose of SPECT was 6.8±2.4 mSv [24]. This brings the average effective dose for hybrid SPECT/CCTA on 11.1±2.8 mSv. The average effective dose of CA was 10.5±4.9 mSv [24]. Mean total effective dose was 21.7±6.4 mSv per patient.

Treatment decisions in all patients

The overall percent agreement of treatment decisions based on hybrid SPECT/CCTA versus SPECT and CA was 92% (95% CI; 85-96) for the primary outcome measure (No revascularization versus revascularization) (Table 2A). Overall percent agreement for the secondary outcome measure on method of revascularization (PCI versus CABG) was 74% (95% CI; 60-84) (Table 2B).

The percentage of patients with matched, unmatched and normal hybrid findings indicated for revascularization based on SPECT and CA is presented in Figure 4.

Treatment decisions in patients with matched hybrid SPECT/CCTA findings

In patients with matched findings on SPECT and CCTA the overall percent agreement of decisions based on hybrid SPECT/CCTA versus SPECT and CA was 95% (95% CI; 83-99) for the primary outcome measure (Table 3A). Two patients with a matched hybrid SPECT/CCTA result were indicated for PCI based on the hybrid findings and optimal medical treatment based on SPECT and CA. One patient had a difficultly interpretable CCTA (CCS 877) and ischemia on SPECT (SDS of 6) that turned out to be a false-positive finding.

Table 1 Characteristics of the patients included in the analysis, n = 107

Age (years) *	62.8 ± 10.0	
Gender, men / women	74 / 33	69.2 / 30.8 %
Risk factors		
Smoking		
Current	24	22.4%
Past	19	17.8%
Hypertension	68	63.6%
Diabetes mellitus	18	16.8%
Dyslipidaemia	72	67.3%
Family history of premature atherosclerosis	65	60.7%
Risk factors ≥ 3	55	51.4%
Angina pectoris		
Non-anginal	1	0.9%
Atypical	33	30.8%
Typical	73	68.2%
CaCS Angina Class		
Class I	5	4.7%
Class II	90	84.1%
Class III	12	11.2%
Class IV	0	0.0%
Pre-test likelihood †	0.87 (0.22 – 0.95)	
Low	0	0.0%
Intermediate	46	43.0%
High	56	52.3%
Unknown	5	4.7%

Values are shown as number and percentage unless otherwise noted. * Values expressed as mean ± standard deviation, † Values expressed as median (range). CaCS = Canadian Cardiovascular Society.

The second patient showed total occlusion of the proximal RCA both on CCTA and CA. Based on hybrid SPECT/CCTA the panel opted for PCI, however based on CA this segment was regarded as unsuitable for revascularization.
The percent agreement for the used method of revascularization, PCI or CABG, in patients with matched findings was 72% (95% CI; 56-84) (Table 3B).

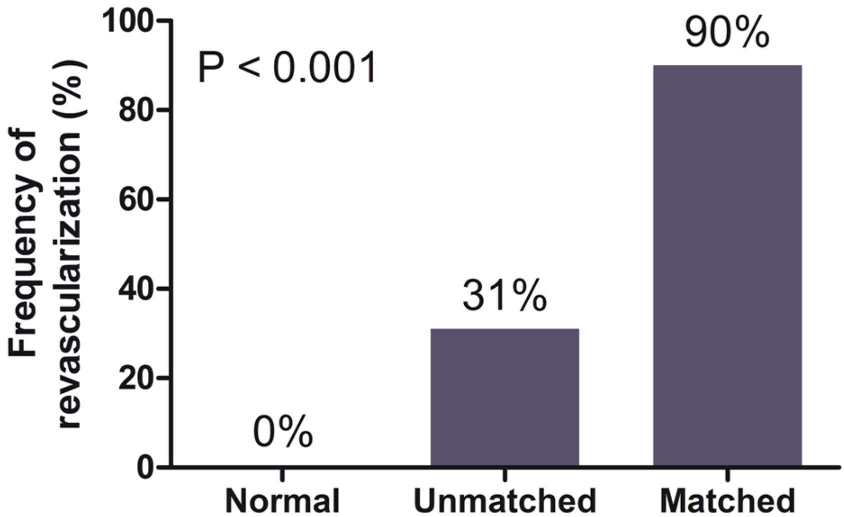

Figure 4 Frequency of revascularization as indicated by the panel based on SPECT and CA in patients with normal, unmatched and matched hybrid SPECT/CCTA findings was significantly different ($P < 0.001$ by Chi-square test).

Table 2 Treatment decisions for all patients. categorized for the necessity of revascularization.

A. Treatment decisions categorized for necessity of revascularization (N = 107).

		SPECT and CA		Percent Agreement
		Revascularization	No Revascularization	
Hybrid SPECT/ CCTA	Revascularization	50	5	
	No Revascularization	4	48	92%

B. Treatment decisions on type of revascularization (N = 50).

		SPECT and CA		Percent Agreement
		PCI	CABG	
Hybrid SPECT/ CCTA	PCI	18	10	
	CABG	3	19	74%

Agreement tables for panel decisions based on hybrid SPECT/CCTA and SPECT and CA in all patients. **Panel A.** Decisions on the necessity of revascularization (no revascularization versus PCI or CABG) in all patients. Percent agreement was 92% (95% CI; 85-96).

Panel B. Decisions on the type of revascularization (PCI versus CABG) in the group of patients indicated for revascularization based on hybrid SPECT/CCTA. Percent was 74% (95% CI; 60-84).

Table 3. Treatment decisions for patients with matched, unmatched and normal findings by hybrid SPECT/CCTA

A. Treatment decisions on necessity of revascularization.

Matched hybrid SPECT/CCTA (N = 40)				
		SPECT and CA		Percent Agreement
		Revascularization	No Revascularization	
Hybrid SPECT/ CCTA	Revascularization	36	2	
	No Revascularization	0	2	95%
Unmatched hybrid SPECT/CCTA (N = 44)				
		Revascularization	No Revascularization	
Hybrid SPECT/ CCTA	Revascularization	14	3	
	No Revascularization	4	23	84%
Normal hybrid SPECT/CCTA (N = 23)				
		Revascularization	No Revascularization	
Hybrid SPECT/ CCTA	Revascularization	0	0	
	No Revascularization	0	23	100%

B. Treatment decisions on type of revascularization.

Matched hybrid SPECT/CCTA (N = 36)				
		SPECT and CA		Percent Agreement
		PCI	CABG	
Hybrid SPECT/ CCTA	PCI	11	8	
	CABG	2	15	72%
Unmatched hybrid SPECT/CCTA (N = 14)				
		PCI	CABG	
Hybrid SPECT/ CCTA	PCI	7	2	
	CABG	1	4	79%
Normal hybrid SPECT/CCTA (N = 0)				
		PCI	CABG	
Hybrid SPECT/ CCTA	PCI	0	0	
	CABG	0	0	N.A.

Agreement tables for panel decisions based on hybrid SPECT/CCTA versus SPECT and CA. In patients with matched, unmatched and normal findings by hybrid SPECT/CCTA.

Panel A. Decisions on the necessity of revascularization (no revascularization versus PCI or CABG). Percent agreement in the matched, unmatched and normal group was 95% (95% CI; 83-99), 84% (95% CI; 71-92) and 100% (95% CI; 86-100) respectively.

Panel B. Decisions on the type of revascularization (PCI versus CABG) in the group of patients indicated for revascularization based on hybrid SPECT/CCTA. Percent agreement in the matched, unmatched and normal group was 72% (95% CI; 56-84), 79.0% (95% CI; 52-92) and not available (N.A.) respectively.

Treatment decisions in patients with unmatched hybrid SPECT/CCTA findings

In patients with unmatched findings on SPECT and CCTA the overall percent agreement of decisions based on hybrid SPECT/CCTA versus SPECT and CA was 84% (95% CI; 71-92). (Table 3A)

All three patients that would have been treated with PCI based on hybrid findings had challenging CCTA's; two as a result of high CCS and one with a motion artefact. Of four cases that would have been treated conservatively based on hybrid SPECT/CCTA and revascularized based on SPECT and CA, three patients showed

a normal SPECT probably as a result of balanced ischemia. The fourth patient suffered from very diffuse CAD resulting in very small coronary arteries, as such revascularization for this patient was almost impossible despite severe ischemia on SPECT (SDS = 11). The panel gave this patient the benefit of the doubt indicating him for PCI based on SPECT and CA.
The overall percent agreement for the used method of revascularization, PCI or CABG, in patients with unmatched findings was 79% (95% CI; 52-92) (Table 3B).

Treatment decisions in patients with normal hybrid SPECT/CCTA findings
No patients with normal non-invasive imaging findings were proven to suffer from significant CAD (N=23). As such panel decisions based on hybrid SPECT/CCTA findings were in complete agreement with decisions made based on SPECT and CA (Table 3A and B).

DISCUSSION

The current study is the first to show that similar treatment decisions can be made by a non-invasive workup using hybrid SPECT/CCTA when compared to a traditional work up using SPECT and CA. Our primary outcome measure evaluating decisions on the necessity of revascularization showed a high overall agreement (92%). Our unique study design of panel decisions on treatment strategy resembles the routine work-up of patients in so-called heart team meetings. As such it allows for conclusions on the clinical value in therapeutic decision making of this imaging procedure compared to the conventional imaging procedure including CA commonly used in clinical practice.

Specific attention should be paid to patients with unmatched hybrid SPECT/CCTA findings. Compared to the percent agreement on treatment decisions in the matched and normal group (95% and 100% respectively) the percent agreement of 84% in this group was low. Unmatched findings predominantly arise in patients with minor ischemic findings on SPECT. In these patients the high negative predictive value of CCTA should be of added value [25]. Conversely, only in patients with definite high grade stenosis on CCTA, normal or equivocal SPECT findings could be overruled. As such, the combination of a negative or equivocal SPECT and a non-conclusive CCTA (e.g. 50-70% luminal loss or high CCS) will remain most problematic. In these instances possible high risk CAD (e.g. left main or proximal LAD disease on CCTA) should be treated with great caution when evaluated on the basis of hybrid SPECT/CCTA alone. These patients should be referred for CA. Further research should explore how to reduce the incidence of unmatched hybrid SPECT/CCTA findings.

The incremental value of hybrid SPECT/CCTA in the assessment of the prognosis and impact on choice of treatment strategy in patients under the evaluation of CAD has been described recently [12, 13]. The authors demonstrated an increased incidence of revascularization procedures and adverse cardiac events in patients with matched abnormalities on SPECT and CCTA versus patients with unmatched abnormalities or normal scans. They described a patient population with an intermediate pre-test likelihood of CAD referred for hybrid SPECT/CCTA imaging. CA data were not available from all patients. Reasons for referral to or deference from CA were not described. A significantly lower number of revascularization procedures was observed in the group of patients with unmatched findings compared to the group of patients with a matched perfusion defect and anatomic abnormality on CCTA. These findings are consistent with our results. However, for a technique with excellent diagnostic performance it could be argued that the percentage of revascularization procedures, 41%, in the matched group is rather low. According to our analysis in the group of patients with matched findings on SPECT and CCTA the revascularization rate is high, up to 90%. Despite the different characteristics of our patient population, the reason for this difference remains unexplained. This should lead to further comparison of the results of hybrid SPECT/CCTA.

Several limitations to our study should be acknowledged. The panel of two cardiologists and one thoracic surgeon are very experienced members of routine clinical heart teams, but less experienced with making treatment decisions based on hybrid SPECT/CCTA imaging. The performance of SPECT or CCTA as stand alone procedure in the process of clinical decision making was not addressed in this analysis. It is reasonable to assume that in patients with normal findings on standalone SPECT or CCTA the decisions would be in high agreement with decisions based on SPECT and CA. We chose an SDS ≥1 in myocardial territory subtended by one coronary artery as threshold for significant ischemia on SPECT when evaluating the three groups of matched, unmatched and normal findings by SPECT and CCTA. This threshold is lower and different from the chosen threshold by Pazhenkottil et al. [12, 13]. In our opinion a threshold of a SSS ≥4 with a SRS ≤1 is correct for a patient based analysis. However, since matching of a reversible perfusion defect and its anatomical substrate is performed at a per vessel level a different threshold is needed. We chose the lowest possible level for reversible perfusion defect to match with coronary stenosis on CCTA. This could cause high numbers of false positive results and subsequently unnecessary referral for revascularization. However, this is not reflected in our analysis; a high percentage of patients with matched hybrid SPECT/CCTA findings was referred for revascularization based on SPECT and CA.

Current healthcare policies advocate a stepwise imaging protocol in the diagnostic work-up of patients, for radiation dose saving purposes and a cost effective use of diagnostic modalities. As such, a hybrid imaging approach should not be the primary imaging strategy for all patients presenting with angina pectoris. Patients with non-conclusive SPECT or CCTA results could be referred for either CCTA or SPECT respectively. Subsequent hybrid depiction of coronary anatomy and myocardial perfusion should lead to an adequate therapeutic decision, which is demonstrated by the current report. However, it is to be expected that only in very specific cases the surgeon will plan surgery solely based on these non-invasive imaging data [17]. Scientific proof that reliable depiction of functional relevance of CAD is feasible with CT myocardial perfusion imaging is growing [26-28]. The availability of anatomic and functional information on CAD from one imaging modality obviously has great advantages. Data on clinical benefit of hybrid SPECT/CCTA cannot be obtained from this patient subset since actual therapy was instituted after routine heart team evaluation of all clinical cases after acquisition of the CA. Randomization to different imaging strategies would be needed to address this subject.

CONCLUSIONS

Overall, our study is the first to show that with a workup including hybrid SPECT/CCTA similar treatment decisions can be reached as compared to a traditional workup including invasive coronary angiography. We show in a large prospectively acquired population that patients with an intermediate to high pre-test likelihood could be accurately deferred from, or indicated for revascularization based on hybrid SPECT/CCTA. In selected cases percutaneous and possibly surgical revascularization could even be instituted on the basis of the findings by hybrid SPECT/CCTA.

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Chapter 7.1

Letter to the Editor: Non-invasive decision making in stable angina

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Heart 2013; 99: 1136

TO THE EDITOR,

We read with great interest the study of Schaap et al [1]. During a 14-months period, they investigated patients with stable angina and compared a hybrid SPECT/CT coronary angiography (CA) versus the combination of SPECT and CA on treatment decisions. Thus, they concluded that similar decisions can be reached using the non-invasive approach. While there is great potential of such a hybrid work-up, we would like to point out some aspects of their study that may mitigate their conclusion.

They included 107 patients, aged 62.8 years, diabetes mellitus in 16.8%, most of them having a class II angina. Although these characteristics are somewhat similar to the one of patients included in the COURAGE study [2], they recommended revascularization procedures in 54/107 of the cohort, a proportion higher than expected based on recent studies on stable angina [2, 3]. In addition, we wonder whether revascularization strategy is not mainly driven by clinical characteristics, which may explain at least in part the fair overall agreement they observed between the two methods. Second, coronary artery bypass grafting (CABG) was recommended in 29/50 patients based on SPECT and coronary angiography. In the COURAGE trial, from 35539 patients selected, 2987 patients had contraindication to PCI and 947 had left main trunk stenosis, which corresponds to a maximum of 11% of the cohort with possible indication to CABG [2]. The results of the SPECT/CTCA procedure might be considered as unfair as they observed unmatched results in 41% of the patients. While they advocate that the limitation of one method is counterbalanced by the other this may be a limitation in less experimented heart teams; in addition, the agreement between the noninvasive and the invasive work-up is only of 72% in the subgroup of patients with matching results. Overall, we wonder if their conclusion is not slightly optimistic.

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Chapter 7.2

Letter to the Editor: Non-invasive decision making in stable angina - The Response

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Heart 2013; 99: 1136-1137

TO THE EDITOR,

We were intrigued by the comments from Meune et al. on our article on treatment decisions based on hybrid SPECT/CCTA for patients with stable anginal complaints [1].

Prognosis and relief of anginal complaints determine the treatment strategy for each individual patient with coronary artery disease (CAD) [2]. In patients with high-risk CAD (two-vessel disease (VD) involving the left anterior descending, three-VD, or left main disease), revascularization is associated with better outcome compared to medical therapy [3]. Moreover, CABG is the standard of care for patients with three-VD or left main disease [4]. Fifty-one percent of all included patients included in our study suffered from significant CAD, based on angiography. Of them, 37 (67%) had high-risk CAD. Twenty-two percent of patients with non-high-risk CAD were on dual anti-anginal medication. As such, despite similar baseline characteristics, the population differed from patients included in the COURAGE study with regard to severity of CAD. In patients with significant CAD, revascularization was chosen as treatment strategy for prognostic reasons in two thirds, as the next best strategy for relief of anginal complaints in 8% and for "clinical reasons" in the remainder.

As was shown in the SYNTAX trial, technical aspects of revascularization (number of lesions, lesion location, and angiographic complexity) predicts outcome after PCI or CABG [4]. Our study was designed to evaluate whether hybrid SPECT/CCTA would be able to depict the complexity of CAD with enough detail to allow for a reliable treatment decision. We demonstrated an excellent agreement (92%) of panel decisions on the necessity of revascularization. Despite unmatched SPECT and CCTA results in 41% of patients, the panel correctly appreciated the significance of CAD in these patients. Indeed, a modest agreement was found in the decision on the actual revascularization strategy. Hybrid SPECT/CCTA was not able to depict angiographic complexity of CAD to allow for a reliable choice between PCI and CABG in patients with an indication for revascularization. Of course, in heart teams with less experience in evaluating hybrid SPECT/CCTA images these findings will be different.

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Chapter 8

Case report – Hybrid SPECT/CCTA imaging of an unusual case of a completely unroofed coronary sinus without persistent left superior vena cava

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A 66-year-old male with a history of surgically closed secundum type atrial septal defect (ASD) during childhood and a percutaneous coronary intervention complained of recurrent stable angina. Clinical investigation and 12-lead ECG were unremarkable. He was referred for hybrid myocardial perfusion SPECT (SPECT) and 64-slice CT coronary angiography (CCTA). SPECT showed normal perfusion of the left ventricle (LV) and an enlarged right ventricle (RV). Gated images showed a decreased LV ejection fraction of 50% due to septal wall motion abnormalities suggestive of RV overload. Prospectively ECG-triggered CCTA revealed minor coronary atherosclerosis and a patent stent. Severe dilatation of the RV (388 mL mid-diastolic) was confirmed. By coincidence, an inferior sinus venosus defect with an unroofed coronary sinus with the right-sided superior vena cava was observed (situs solitus, atrio-ventricular, and ventriculo-arterial concordance). Middle and great ardiac veins were inserted into the roof of the left atrium and a clear left-to-right shunt was visualized by CTA. Three-dimensional transoesophageal echocardiography showed the circular ASD (14 mm) near the inferior vena cava. Right heart catheterization confirmed the left-to-right shunt (Qp:Qs 2.1) and pulmonary arterial hypertension (mean PAP 29 mmHg and PVR 106 dynes/s/cm25). Invasive oronary angiography confirmed the absence of recurrent significant CAD. This case was discussed in our grown-up-congenital-heart-disease team, and the patient underwent surgical closure of the defect, which is the treatment of choice in patients without Eisenmenger syndrome. Currently, 4 months after surgery, the patient is free from anginal complaints.

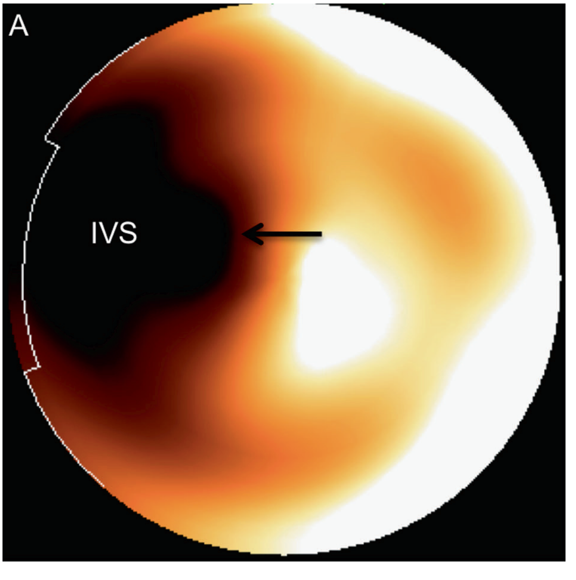

Figure 1A. Quantitative gated SPECT showing bulls eye of left ventricle (LV) motion with a septal wall motion abnormality (black arrow).

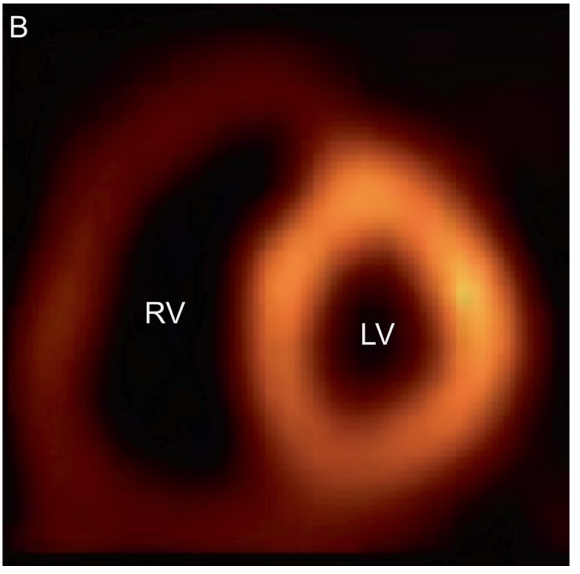

Figure 1 B. Myocardial perfusion SPECT, attenuation corrected, showing an enlarged right ventricle (RV) and normal perfusion of the LV.
IVS indicates interventricular septum, LV, left ventricle; RV, right ventricle.

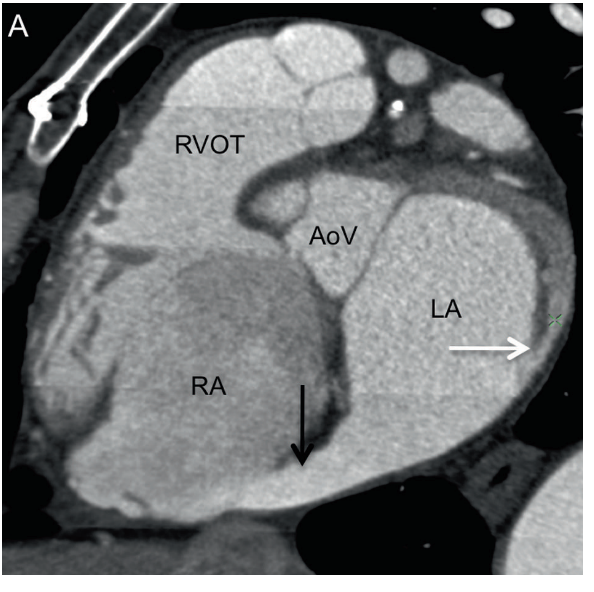

Figure 2A. Computed tomography coronary angiography showing an interatrial connection with left-to-right shunt (black arrow) and insertion of the great cardiac vein in the left atrium (LA) (white arrow).

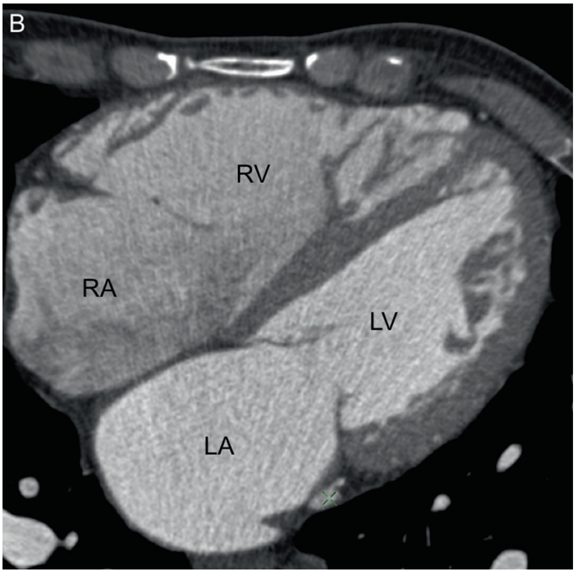

Figure 2B. Computed tomography coronary angiography showing an enlarged RV, 388ml mid-diastolic.
RVOT indicates right ventricular outflow tract; AoV, aortic valve; RA, right atrium; LA, left atrium, LV, left ventricle; RV, right ventricle.

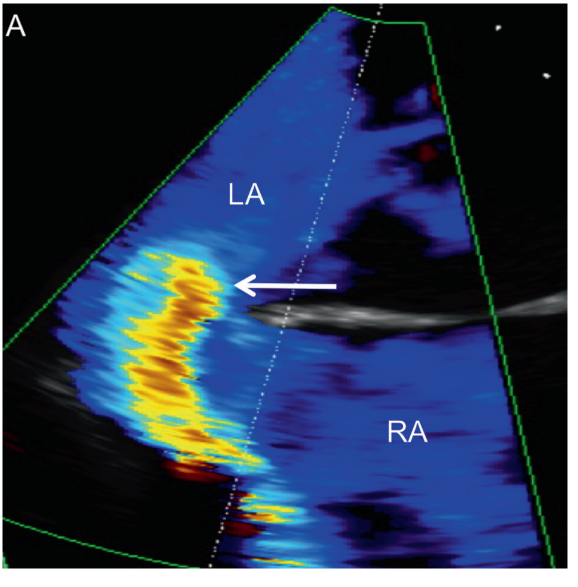

Figure 3A. Transesophageal color-doppler echocardiography showing severe interatrial left-to-right shunting (white arrow).

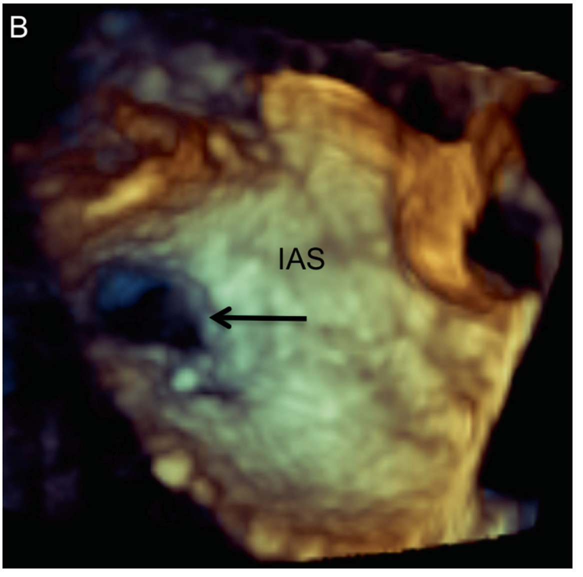

Figure 3B. Three-dimensional transesophageal echocardiography view from LA towards the interatrial septum showing an atrial septal defect (black arrow).
RA indicates right atrium; LA, left atrium;IAS, interatrial septum.

Chapter 9

Case report – Left ventricular outflow tract pseudoaneurysm compromising blood flow through the left main coronary artery after mechanical aortic valve implantation

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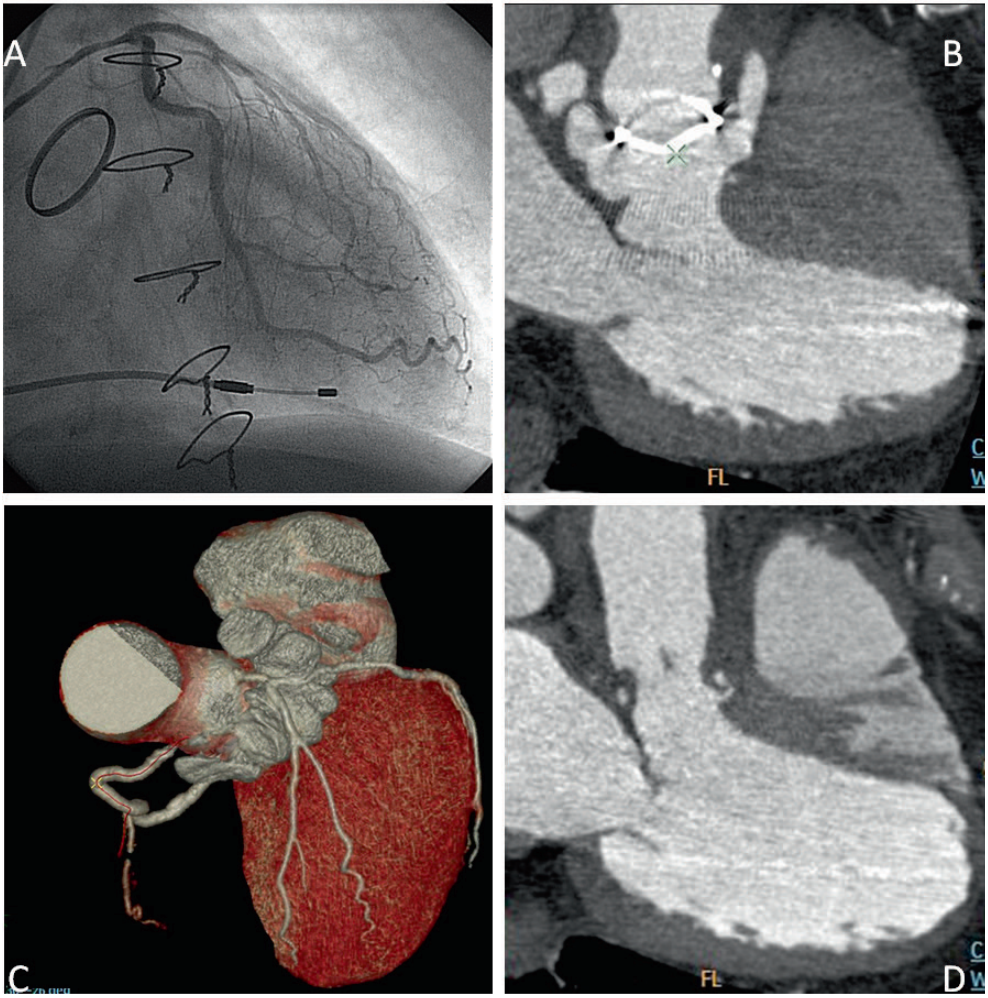
A 73-year-old male with a history of mechanical aortic valve replacement and DDD pacemaker implantation was referred to our hospital with progressive anginal complaints. Invasive coronary angiography (CA) revealed systolic compression of the left main coronary artery (LMCA), suggesting an extra-cardiac mass compromising blood flow. Single Photon Emission Computed Tomography (SPECT) and Multislice Computed Tomography – CA (MSCT-CA) were obtained which revealed a pseudoaneurysm originating from half the circumference of the left ventricular outflow tract (LVOT) extending over the aortic root. The main stem of the left coronary artery and its proximal circumflex and anterior descending branches were embedded in the aneurysm. Stress SPECT images did not reveal ischemia. The extensive dehiscence of the aortic root, also depicted by the tilting of the mechanical aortic valve on the invasive angiogram, was reason to perform a re-operation with implantation of Bentall prosthesis. A Bio Valsalva 25mm prosthesis was implanted on the remaining LVOT at the level of the mitral valve annulus. Cultures obtained during the operation grew coagulase negative staphylococci; the pseudoaneurysm might be caused by a low-grade infectious process. Post-operatively antibiotics were continued for six weeks. Currently ten months after operation the patient is doing reasonably well, follow-up MSCT-CA revealed no paravalvular cavities or valvular abnormalities.

LVOT pseudoaneurysm is a rare and serious complication after implantation of a mechanical aortic valve. It is associated with a history of endocarditis and the development of anginal complaints. Surgery is the first-line therapeutic option. Reports exist on successful stent implantation in the LMCA and percutaneous closure of the pseudoaneurysm.



Panel A. Invasive coronary angiogram right caudal view, showing systolic compression of the Left Main coronary artery.

Panel B. Multislice Computed Tomography (MSCT) image, showing a large pseudo aneurysm originating from the Left Ventricular Outflow Tract (LVOT) just below the mechanical aortic valve.

Panel C. Volume rendered MSCT coronary angiography angiography image, showing the Left Main coronary artery and its proximal anterior descending and circumflex branches embedded in the pseudo aneurysm. The pseudo aneurysm extends over half the circumference of the aortic root.

Panel D. MSCT image showing the post operative situation with the Bentall prothesis implanted at the level of the mitral valve annulus. No evidence of residual paravalvular aneurysm formation.

Chapter 10

General discussion

GENERAL DISCUSSION

With the advent of CCTA and the known reliability of myocardial perfusion SPECT a combination of non-invasive imaging modalities became available that could reliably diagnose CAD. The current thesis substantiates the role of hybrid SPECT/CCTA imaging in clinical practice. It demonstrates the applicability of the combination of SPECT and CCTA in diagnosing significant CAD in stable patients with an intermediate to high pre-test likelihood of CAD. Furthermore, non-invasive SPECT/CCTA guided therapeutic decision making in these patients is demonstrated.

However, several questions may require further discussion. Is the technique of hybrid imaging fully developed or are there remaining pitfalls? What is the exact role for hybrid imaging in the current work-up of patients with chest pain? Does hybrid SPECT/CCTA have specific advantages over other imaging modalities and what upcoming imaging modalities will challenge its role? This chapter will discuss these questions in light of the results of this thesis.

Hybrid SPECT/CCTA image reconstruction and interpretation

In the High and intermediate Risk Spect-Ct OPtimization study (HoRoSCOPe) study, a hybrid SPECT-CT system, a CardioMD gamma camera combined with a Brilliance 64-slice CT scanner were used for the acquisition of all images. The common table shared by both components allowed for sequential imaging which should have significant benefits during image reconstruction.

Hybrid SPECT/CCTA image reconstruction

The hybrid system and its nearly simultaneous image acquisition allows for a complete reduction of spatial and volumetric differences of the heart during SPECT and CCTA acquisition. This facilitates SPECT and CCTA image overlay and fusion, which is challenged by intrinsic differences in the ECG-gated CCTA and non-ECG-gated SPECT images. Nevertheless, reports exist on successful hybrid image reconstruction from images acquired from separate scanners [1-3]. Also, the workflow during image post processing allows for the introduction of significant changes in the 3D-position of the coronary tree derived from CCTA in relation to the LV volume derived from SPECT. The example shown in Figure 1 underscores the importance of a correct overlay. This patient had a subtotal stenosis in his LAD and a probably significant stenosis in a large 1st diagonal branch. SPECT showed a large area of ischemia ranging from the inferior myocardial wall, interventricular septum towards the anterior myocardial wall.

Anterolateral perfusion seemed preserved, as such excluding a hemodynamically significant stenosis in the 1st diagonal. A counterclockwise rotation of the coronary tree would position the ischemic myocardium in the area supplied by the 1st diagonal. Accurate definition and co-registration of cardiac landmarks on SPECT and CCTA images (e.g. base and apex of the heart) should allow for accurate image fusion. Nevertheless, fusion from SPECT and CCTA images will remain challenging. The fundamentally different imaging techniques cause indelible differences in the partial volume of the heart. Acquisition of both anatomic and perfusion images from one technique (e.g. CT) should eliminate this problem and allow for consistent image fusion.

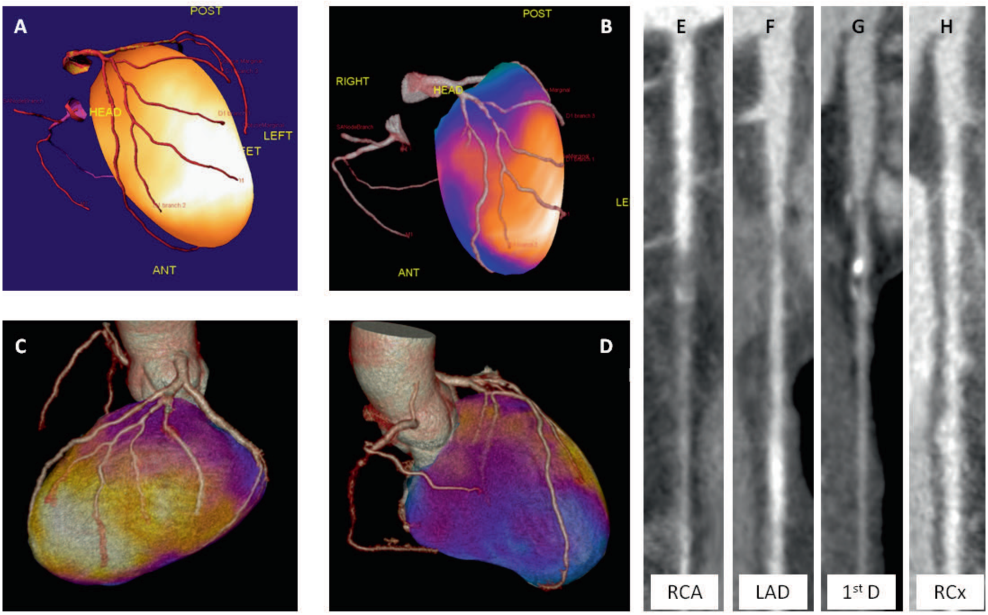


Figure 1 Evolution of hybrid imaging in the HoRoSCOPe study. Examples of hybrid stress SPECT/CCTA from one patient are shown. Panel A shows the first result of fusion of the LV volume derived from SPECT and the coronary tree derived from CCTA. The coronary arteries resembled tubes. Also exact positioning of the LV volume with respect to the coronary tree had to be performed manually (Autoquant®, Cedars-Sinai Medical Center, Los Angeles, Ca, USA). Panel B shows the 2nd generation fusion images, which shows an improvement of the visualization of the coronaries, now a 3D volume rendered image. Exact positioning of the coronaries still had to be performed manually. Panel C and D show the final generation fusion images. Both coronary artery tree and LV volume are derived from CCTA. The SPECT LV perfusion image is projected onto the CCTA LV volume. Positioning of the SPECT LV volume was performed software guided (EBW-NM® software, Philips Medical Systems, Best, The Netherlands). Panel E – F show stretched multiplanar reformats of all major coronaries.

CT attenuation correction of myocardial perfusion SPECT was shown to improve image quality and diagnostic accuracy [4-6]. Our imaging protocol consisted of the acquisition of a breath hold non-enhanced CT scan during stress SPECT and CCTA acquisition. And a non-enhanced CT scan during 20 seconds normal breathing during rest SPECT acquisition. Both acquisition methods have a different effect on the construction of an attenuation map to correct for photon attenuation during SPECT imaging. In our eyes, these differences were very small and could be neglected. Since during resampling of the attenuation map the original 0.98x0.98x5.0mm grid is recalculated into a 6.4x6.4x6.4mm grid, thereby averaging out the level of Hounsfield units in each voxel. Registration of the attenuation map with the SPECT volume should be performed with great attention to detail. Misregistration could cause significant errors in the visualization of regional tracer uptake [7-9].

Hybrid SPECT/CCTA image interpretation

According to the HoRoSCOPe protocol, all vessels and patients were either classified as normal or abnormal. We used the categorical evaluation described in Table 1. An abnormal hybrid result was defined as a perfusion defect (as defined by Abidov et al.) on SPECT with a >50% stenosis in the corresponding coronary artery [10]. This is conform previous reports on hybrid SPECT/CCTA imaging interpretation [1, 11, 12]. Pazhenkottil et al. acknowledged that patients with conflicting ("unmatched") results from SPECT and CCTA have a higher annual rate of death or non-fatal myocardial infarction compared to patients with normal findings [13, 14]. However, none of the available reports provide exact definitions for the interpretation of hybrid SPECT/CCTA in the presence of non-conclusive or conflicting results from SPECT and CCTA [1, 2, 11-15].

In the literature, robust definitions are provided on a per-patient basis for normal, equivocal and abnormal LV myocardial perfusion on SPECT [10, 16]. Still, SPECT has the drawback of underestimating the true extent of CAD. This underestimation is hypothesized to be due to balanced ischemia, emphasis on the most severe stenosis and the inability of this technique to detect non-flow limiting atherosclerosis [17-19]. Against this background, a definition should be provided for normal, abnormal and equivocal regional myocardial perfusion since hybrid SPECT/CCTA imaging analysis allows for the evaluation of myocardial perfusion according to the regional distribution of the coronaries. Available literature on hybrid SPECT/CCTA image interpretation differ in their methods of image interpretation (visual or semi-quantitative) and are largely unclear in their definitions of regional perfusion [1, 2, 11, 12, 15]. Slomka et al. were most explicit: they solely used semi-quantitative analysis and defined a threshold of >2% transient perfusion deficit in a vessel territory as significant [2].

As with all anatomical imaging techiques, CCTA precludes a definite statement on the functional relevance of a coronary stenosis. In addition, CCTA has the tendency to overestimate functional relevance, which is resembled by the limited positive predictive value for significant CAD by CCTA [20-22]. Available literature on CCTA and hybrid SPECT/CCTA predominantly defined the absence of >50% stenosis on CCTA as absence of significant CAD [1, 11, 12, 20-22]. However, it is known from CA studies that a substantial number of vessels with >50% stenosis (visual interpretation or quantitative coronary angiography) also do not show functional obstruction when evaluated using FFR-measurements [23]. Surprisingly, also a limited number of vessels with >90% stenosis on CA fail to show functional relevance [23]. As such, it should be safe to assume absence of functional relevance in the presence of <50% stenosis on CCTA. The CCTA should be regarded non-conclusive for the presence or absence of significant CAD if the coronary lumen is obscured due to artifacts or coronary calcium. And any cut-off level for significant CAD on CCTA, either >50%, >70% or even >90%, should come with some restraint.

		CCTA result		
		Normal	Non-conclusive	Abnormal
SPECT result	Normal	Normal	Normal	Normal unless definitely abnormal CCTA
	Non-conclusive	Normal	Normal or abnormal *	Abnormal
	Abnormal	Normal	Abnormal	Abnormal

Table 1 Hybrid interpretation of imaging results in the HoRoSCOPe study. Interpretation was performed on a per-vessel basis.* In the presence of non-conclusive results from both SPECT and CCTA, categorization was only performed on a per-patient basis. In these instances all available diagnostic data (e.g. X-ECG, CCS and gated SPECT data) were taken into account.

As defined in Table 1, we allowed the strengths of either SPECT or CCTA to compensate for the weaknesses of the other modality. Several aspects of this table should be discussed. Both non-conclusive and abnormal SPECT results were overruled by a normal CCTA given the high negative predictive value of standalone CCTA. In the presence of a non-conclusive CCTA result, a normal or abnormal SPECT was decisive for the hybrid diagnosis. This could result in false negative and false positive hybrid results, given the reasonable negative and positive predictive values of standalone SPECT in this patient category. An obviously abnormal CCTA was allowed to compensate for a non- conclusive or (false) negative SPECT result. The stenosis grade on CCTA could have been defined more exactly (f.i. >70% stenosis) for these patient categories. Despite the excellent diagnostic performance of hybrid SPECT/CCTA using the current scheme for image interpretation, a number of imaging combinations still did not result in a clear-cut result. In these instances, the weighed assessment of all available diagnostic information by experienced readers resulted in the final diagnosis. In general, some form of quantification is needed in these patients with conflicting or non-conclusive SPECT and CCTA results. To reach a non-invasive diagnosis on the presence or absence of significant CAD, either quantification of flow by positron emission tomography (PET) or SPECT techniques or quantification of the stenosis grade by a computed FFR from CCTA images, is needed in this select patient category (<5% of patients included in the HoRoSCOPe study) [24, 25].

The role of hybrid SPECT/CCTA in clinical practice

<u>Patient selection for hybrid SPECT/CCTA imaging</u>

Despite a median pre-test likelihood according to Diamond and Forrester criteria of 87%, approximately half of the HoRoSCOPe study population was free from significant CAD [26-29]. This overestimation of disease presence in patients referred for (non-)invasive cardiac imaging by risk scores that calculate the pre-test likelihood of CAD, has been confirmed in several publications [22, 30-33]. As such, it seems reasonable to perform non-invasive imaging as an initial step in the diagnostic work-up of patients with an intermediate to high pre-test likelihood.

It is clear that hybrid SPECT/CCTA imaging should not be the method of choice in all of these patients; in a substantial number of patients CAD can be reliably ruled out by CCTA alone. We have shown a negative predictive value of 96% from CCTA in patients with conclusive imaging results. Additionally, from standalone SPECT we demonstrated a positive predictive value of 96% in patients with conclusive imaging results; depending on the severity of ischemia a substantial number of patients could have been sent for CA without additional CCTA. Nevertheless, we demonstrated increased diagnostic accuracy and added value of hybrid SPECT/CCTA imaging, specifically in patients with non-conclusive results from either SPECT or CCTA. It is impossible to predict from pre-test likelihood calculation alone which patient will have a non-conclusive SPECT or CCTA result and/or will benefit from hybrid imaging. Additional information is needed; e.g. patients who are obese, need pharmacological stress prior to SPECT, suffer from left or right bundle branch block, have high baseline heart rates or known with high CCS are likely to benefit and could be scheduled for hybrid SPECT/CCTA imaging beforehand [34 35]. However, for the majority of patients, a step-wise imaging approach should be used so as to limit radiation exposure and minimize costs[17].

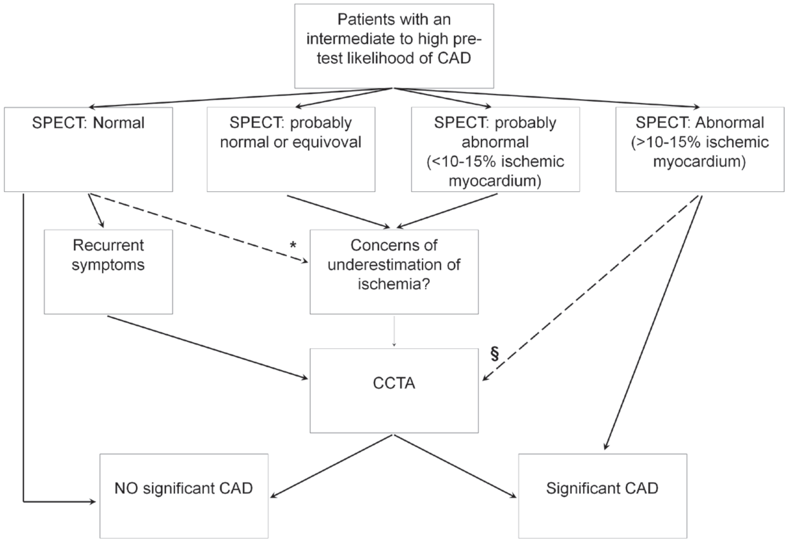


Figure 2 Proposed imaging sequence in patients with an intermediate pre-test likelihood of CAD to be used with a hybrid SPECT/CT system. Adapted from the proposed imaging sequence by Tamarappoo et al. [36]. Additional CCTA and hybrid SPECT/CCTA interpretation could be performed in patients with concerns of underestimation of the ischemic burden. * Hybrid SPECT/CCTA imaging could also be performed in patients with normal SPECT and discrepant clinical data from stress testing or poor heart rate response during exercise stress preceding SPECT acquisition. § To facilitate subsequent therapeutic decision making and guidance of the revascularization strategy, additional CCTA and hybrid SPECT/CCTA interpretation could also be performed in patients with abnormal SPECT.

10

Although we did not perform a formal health economic analysis the hybrid SPECT-CT system as we have used in the HoRoSCOPe study may facilitate a cost effective use of staff and imaging devices since it allows for a one-stop-shop imaging protocol. The main challenge for an imaging protocol with a hybrid system is the order in which SPECT and CCTA are acquired, since both modalities require specific patient preparation. For patients with a low to intermediate pre-test likelihood the high negative predictive value of CCTA justifies its use as an initial test [17, 36]. In patients with low prevalence of CAD, the high negative predictive value of CCTA allows for a reliable rule-out of CAD [36]. Subsequent non-invasive functional imaging can be applied in patients with >50% stenosis to either rule out myocardial ischemia or determine the extent of the myocardial area at risk to justify subsequent medical therapy or revascularization [36, 37]. In patients with an intermediate- to high pre-test likelihood of disease, SPECT could be used as an initial test [36]. As described in Figure 2, additional CCTA could be performed in patients with uncertainty about the result of the perfusion study[17 34, 36]. Moreover, additional CCTA in patients with an abnormal SPECT could be of value as well in the process of therapeutic decision making.

Therapeutic decision making using hybrid SPECT/CCTA imaging

The prognosis and relief of anginal complaints determine the treatment strategy for each individual patient with CAD. Both standalone SPECT and CCTA as well as hybrid SPECT/CCTA are reliable in detecting high-risk CAD [14, 37-40]. Diagnostic accuracy of standalone SPECT or CCTA to diagnose significant CAD in individual coronaries is limited, as discussed before. Therefore, it is impossible to decide on the actual treatment strategy (optimal medical treatment (OMT), PCI or CABG) for each individual patient based on these images alone. The sole exception is a (secondary) preventive treatment regimen if significant CAD is reliably ruled out. With the excellent performance of hybrid SPECT/CCTA in the diagnosis of significant CAD, the next challenge was to examine whether, based on these images, the decision could be made whether the patient needed OMT, PCI or CABG.

We evaluated the clinical applicability of hybrid SPECT/CCTA in a setting resembling the routine clinical heart team. This is fundamentally different from earlier studies that evaluated the role of imaging procedures in determining prognosis and detecting high-risk CAD [14, 37-39]. The panel meetings evaluated each case for the best treatment strategy (OMT or revascularization) to improve prognosis and relieve anginal complaints. In addition to clinical characteristics and prognosis based on available imaging, also the technical aspects of revascularization (lesion frequency, location, and angiographic complexity) were evaluated [41, 42]. As such, our evaluation of panel meetings allowed for conclusions on the clinical value in therapeutic decision making of this new imaging procedure compared to conventional imaging procedure including CA.

We found an excellent percent agreement of decisions on the necessity of revascularization. Overall, 92% of these decisions based on hybrid SPECT/CCTA images matched with the decisions based on SPECT and CA. We were unable to compare the decisions on the necessity of revascularization based on standalone

SPECT or CCTA with the reference standard of decisions based on SPECT and CA. However, it is likely that the diagnostic accuracy of both standalone techniques largely predict the agreement in treatment decisions. As such, a percent agreement of 75-85% is to be expected.

The decisions on the actual revascularization strategy (PCI or CABG) had a moderate percent agreement of 74%. This is different from the diagnostic accuracy of hybrid SPECT/CCTA on per vessel basis, which showed a PPV of 84% and a NPV of 87%. The case presented in chapter 2 is an excellent example of a patient that could have been sent for CABG based on hybrid SPECT/CCTA alone, without invasive coronary angiography prior to actual surgery. However, the limited spatial resolution of CCTA compared to CA and artifacts as a result of extensive calcifications on CCTA proved to be very challenging for the technical decision whether PCI or CABG was most suitable for the case at hand. Additionally, the tendency of SPECT to emphasize the most severe stenosis and show normal perfusion in other significant lesions was the reason that some patients were falsely diagnosed with single vessel disease and subsequently indicated for PCI based on hybrid SPECT/CCTA images. Improvement of CCTA contrast- and spatial resolution are needed before the technical treatment decision whether PCI or CABG is most appropriate, can be made for all patients based on CCTA images. Additionally, quantification of flow either by CCTA- or by PET techniques are needed to determine the true extent of multivessel CAD [18, 25].

Future challenges

Over the last decade, hybrid SPECT and PET-CT have made a great leap into clinical practice. In the fields of oncology and orthopedic surgery, the combination of structure and function images have had a great impact on diagnostics and clinical practice. Hybrid imaging in cardiology was developed on the waves of these success [17]. However, it is still challenged with respect to clinical practice and research.

Challenges for clinical practice

Regardless of the hybrid technique, uniform criteria are needed that address specific problems in image interpretation. The hybrid interpretation of non-conclusive and conflicting results from myocardial perfusion SPECT and CCTA requires specific guidelines.

One third of our patient population was excluded from further imaging due to failed acquisition of a prospectively ECG-triggered CCTA. Further modifications of the acquisition protocol, e.g. using only pharmacological stress prior to SPECT acquisition, are needed to allow for higher success rate of CCTA acquisition without the loss of SPECT diagnostic accuracy.

Challenges for further research

Obviously, acquisition of both coronary anatomy and function from one imaging technique in a stepwise imaging protocol would have great advantages. Computed tomography offers this possibility, either FFR-CT or CT myocardial perfusion in combination with CCTA are of great potential [43-46]. Further research is needed to show whether either the combination of CCTA plus FFR-CT, or myocardial perfusion studies from CT, cardiac magnetic resonance imaging, SPECT or PET has higher diagnostic accuracy and which option is most cost effective and which has the least radiation exposure.

A comprehensive health economic analysis should provide guidance towards a cost effective use of the hybrid SPECT-CT system used in the HoRoSCOPe study. This would demonstrate the cost-effectiveness of a one-stop-shop imaging protocol using a hybrid SPECT-CT system.

Finally, we evaluated whether hybrid SPECT/CCTA could play a central role in the clinical work-up of patients with anginal complaints and whether this protocol could be used to decide on the revascularization strategy. Besides improved contrast and spatial resolution of CCTA, a direct comparison of the non-invasive work-up versus the work-up including invasive CA is also needed. A trial including patients with similar characteristics as included in the HoRoSCOPe study which randomizes participants between invasive and non-invasive imaging with subsequent decisions would be of great value.

CONCLUSIONS

Our studies demonstrate the clinical usefulness of hybrid SPECT/CCTA in patients with an intermediate to high pre-test likelihood of CAD. The limited value of X-ECG and CCS and the need for advanced non-invasive imaging in these patients is also underscored. Hybrid SPECT/CCTA has excellent diagnostic accuracy and is of added value over standalone SPECT or CCTA. The strength of hybrid imaging lies in the compensation for the weak properties of standalone CCTA and SPECT, as such resolving non-conclusive results of both imaging procedures. Patients can be accurately deferred from, or indicated for revascularization based on hybrid SPECT/CCTA. In selected cases, percutaneous and possibly surgical revascularization could even be instituted on the basis of the findings by hybrid SPECT/CCTA alone.

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Chapter 11.1

Summary

SUMMARY

For several decades invasive coronary angiography (CA) has been the reference standard in the assessment of coronary artery disease (CAD) severity [1, 2]. However, several factors motivate the need for a reliable non-invasive imaging modality, especially in the patients with a high pre-test likelihood. Not only to rule out, but also to diagnose significant CAD and guide therapeutic decision making. Data demonstrating the applicability of hybrid myocardial perfusion SPECT (SPECT) and coronary computed tomography angiography (CCTA) in diagnosing significant CAD in stable patients with an intermediate to high pre-test likelihood of CAD are still lacking. Let alone, that the contribution of these tests to therapeutic decision making in these patients is known. Providing evidence on both issues was therefore the main objective of this thesis.

Chapter 1.1 describes the High and intermediate Risk Spect and Ccta OPtimization study (HoRoSCOPe). The current thesis is based on the results of this study. The main objective was to evaluate the clinical value of hybrid SPECT/CCTA in an unselected, prospectively acquired population. Patients with stable chest pain symptoms referred for myocardial perfusion SPECT and an intermediate to high pre-test likelihood of CAD based on Diamond and Forrester criteria were included [3]. Patients with a history of surgical revascularization, stent implantation and patients with an unstable cardiac condition were excluded.

Chapter 2 is a case report to introduce the advantage of the combination of SPECT and CCTA imaging, and also the strengths and weaknesses of each standalone imaging technique. We describe a female patient with typical complaints of angina pectoris, referred for SPECT. The SPECT result should be regarded non-conclusive; the subsequently performed CCTA clearly demonstrated severe left main stenosis. The catch of this case was the coronary calcium score of zero.

In **Chapter 3** the limited role of standalone exercise stress electrocardiography (X-ECG) and coronary calcium scoring (CCS) in symptomatic patients with an intermediate to high pre-test likelihood of CAD is demonstrated. Receiver operator characteristics (ROC) curve analysis revealed an increased diagnostic yield for significant CAD for the combination of CCS and X-ECG (area under the curve (AUC) 0.84) versus standalone CCS (AUC 0.69) or X-ECG (AUC 0.65). However, 6 (9%) patients with CCS 0 – 400 and negative X-ECG suffered from significant CAD and 37 (54%) patients with either CCS >400 or abnormal X-ECG were free from significant CAD.

In **Chapter 4** we evaluated the usefulness of CCS in addition to SPECT in the diagnosis of CAD. In patients with normal SPECT findings a high CCS could be suggestive of significant CAD [6-8]. CCS cut-off values of 709 and 1000 were suggested; above these values an increased incidence of significant CAD was reported in the presence of normal SPECT [6-8]. In our hands, SPECT alone had reasonable performance with a negative predictive value (NPV) of 82% and an AUC of 0.88 as determined by ROC curve analysis. By adding CCS information the NPV increased to 94%, but at the cost of a substantial number of false positives. As such the increased AUC of 0.92 did not differ significantly from SPECT as standalone procedure. Moreover, balanced ischemia and severe stenoses as a result of soft plaque (CCS of 0) caused the combination to fail in detecting significant CAD in three patients.

In **chapter 5** the incremental diagnostic accuracy of hybrid imaging is discussed. We performed hybrid SPECT/CCTA in a population with an intermediate- to high pre-test likelihood of CAD. A high number of patients had non-conclusive SPECT (11.2%) or CCTA (23.5%) results. Hybrid image interpretation led to an overall increase in diagnostic accuracy, from a NPV of 89% and positive predictive value (PPV) of 85% for SPECT and a PPV of 77% for CCTA to a NPV of 96% and PPV of 95% for hybrid imaging interpretation. In the group of patients with non-conclusive results from either SPECT or CCTA, hybrid image interpretation had a NPV and PPV of 90% and 91% respectively. We concluded that this population demonstrates the complementary nature of hybrid SPECT/CCTA imaging best; in over 40% of patients CAD could reliably be ruled out. This study demonstrated that the advantage of hybrid imaging lies in the fact that both techniques compensate for the weak properties of the other, as such dissolving non-conclusive results.

In **chapter 6** we evaluated the added value of hybrid SPECT/CCTA, beyond pre-test likelihood and X-ECG, in the diagnosis of significant CAD. In chapter 5 we demonstrated the single test accuracy of hybrid SPECT/CCTA. The added value of hybrid SPECT/CCTA beyond the usual clinical work-up, or the use of each of these tests separately, remained unclear. Added value of hybrid SPECT/CCTA to the basic model of pre-test likelihood combined with X-ECG was quantified using logistic regression analysis. Model differences were assessed using differences in C-index and in net reclassification improvement (NRI). The basic model had a C-index of 0.73 (95%CI 0.66-0.80). This significantly increased to 0.85 (95%CI 0.80-0.91) by addition of only SPECT, to 0.90 (95%CI 0.85-0.94) when adding only CCS and CCTA, and to 0.96 (95%CI 0.92-0.99) when adding hybrid SPECT/CCTA. The accompanying NRIs were 0.82 (95%CI 0.62-1.02), 0.86 (95%CI 0.66–1.06) and 1.57 (95%CI 1.11-

1.59) respectively. The current analysis resembled clinical routine of layered testing and showed that hybrid SPECT/CCTA imaging has a substantially higher yield than standalone SPECT or CCTA in the diagnosis of patients suspected of significant CAD.

In **chapter 7** we evaluated to what extend treatment decisions could be based on hybrid SPECT/CCTA images. A treatment decision was made by two interventional cardiologists and one cardiothoracic surgeon in two steps: first, based on the results of hybrid SPECT/CCTA; second, based on SPECT and CA. Percent agreement of treatment decisions (optimal medical therapy or revascularization) based on both diagnostic strategies were calculated in all patients, and in subgroups of patients with matched, unmatched and normal hybrid SPECT/CCTA findings. Revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) was indicated in 54 (50%) patients based on SPECT and CA. Percentage agreement of treatment decisions in all patients based on hybrid SPECT/CCTA versus SPECT and CA on the necessity of revascularization was 92%. Percentage agreement of treatment decisions in patients with matched, unmatched and normal hybrid SPECT/ CCTA findings was 95%, 84% and 100%, respectively. We concluded that similar treatment decisions can be made by a non-invasive workup using hybrid SPECT/CCTA when compared to a traditional work up using SPECT and CA. And that in selected cases PCI and possibly CABG could even be instituted on the basis of the findings by hybrid SPECT/CCTA alone. We demonstrated that specific attention should be paid to patients with unmatched hybrid SPECT/CCTA findings.

Chapter 8 is a case description of a male patient with a history of coronary stent implantation and recurrent angina pectoris. SPECT was true negative for myocardial ischemia of the LV; it did however show signs of right ventricle overload. CCTA very clearly showed an inferior sinus venosus defect with unroofed coronary sinus with right sided superior vena cava and no recurrent significant CAD and a patent stent.

Chapter 9 is the description of a case demonstrating the power of CCTA to depict cardiac and coronary anatomy. The patient in this report suffered from a giant pseudoaneurysm encapsulating two thirds of the aortic root and thereby also the left main coronary artery.

Chapter 10 offers a general discussion. Firstly, image hybrid SPECT/CCTA reconstruction is discussed, stressing the challenges in achieving a correct overlay and fusion of both images. Also, challenges with respect to attenuation correction of SPECT using non-enhanced CT scans are discussed. Secondly, hybrid SPECT/

CCTA image interpretation is discussed. The HoRoSCOPe protocol for hybrid image interpretation is regarded in view of available literature on SPECT and CCTA image interpretation. Thirdly, patient selection for hybrid SPECT/CCTA imaging is discussed against the background of the accuracy of standalone SPECT and CCTA imaging, pre-test likelihood estimation, and radiation dose form hybrid imaging. A proposition for an imaging sequence using a hybrid SPECT-CT system is given. Fourthly, therapeutic decision making using hybrid SPECT/CCTA imaging is discussed. Finally, recommendations for further studies are given, followed by the conclusions of this thesis.

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Chapter 11.2

Samenvatting

SAMENVATTING

Sedert enkele decennia is invasieve coronaire angiografie (CA) de referentie standaard voor de beoordeling van de ernst van coronairlijden (CAD) [1, 2]. Echter, verschillende factoren onderbouwen de noodzaak voor betrouwbare niet-invasieve beeldvorming, met name voor patiënten met een hoge voorafkans op CAD. Niet alleen om uit te sluiten, maar zeker ook om hemodynamisch significant CAD aan te tonen. Gegevens die de toepasbaarheid van hybride myocard perfusie SPECT (SPECT) en CT coronaire angiografie (CCTA) demonstreren in een stabiele patiënten populatie met een intermediaire tot hoge voorafkans op hemodynamisch significant CAD, ontbreken nog. Laat staan dat bekend is wat de bijdrage is van deze tests aan de therapeutische besluitvorming bij deze patiënten. Het wetenschappelijk onderbouwen van deze beide zaken was het belangrijkste doel van dit proefschrift.

Hoofdstuk 1.1 beschrijft de "High and intermediate Risk Spect and Ccta OPtimization study" (HoRoSCOPe). Dit proefschrift is volledig gebaseerd op de gegevens die uit deze studie werden verkregen. Het belangrijkste doel van de studie was de evaluatie van de klinische waarde van hybride SPECT/CCTA in een prospectief verkregen patiëntenpopulatie. Patiënten met stabiele symptomen van thoracale pijn en een intermediaire- tot hoge voorafkans op significant coronairlijden op basis van Diamond and Forrester criteria werden geïncludeerd [3]. Patiënten met daarentegen een voorgeschiedenis van chirurgische myocard revascularizatie (CABG), coronaire stent implantatie (PCI) of een onstabiele cardiale toestand werden geëxcludeerd.

Hoofdstuk 2 betreft de beschrijving van een patiëntencasus om zowel de voordelen van de combinatie van beeldvorming met SPECT en CCTA, als de voor- en nadelen van deze technieken als alleenstaande modaliteit, te introduceren. We beschrijven de casus van een patiënte met een blanco voorgeschiedenis en typische angina pectoris. Het resultaat van het SPECT onderzoek, waar zij voor was verwezen, was niet-conclusief. Het vervolgens gemaakte CCTA liet echter een ernstige stenose van de hoofdstam van de linker coronair. Het bijzondere aan deze casus was dat deze stenose werd veroorzaakt door "zachte plaque"; de coronaire calciumscore (CCS) was 0.

In **hoofdstuk 3** beschrijven we de beperkte waarde van inspannings electrocardiografie (X-ECG) en CCS voor de diagnostiek van significant CAD bij symptomatische patiënten met een intermediaire tot hoge voorafkans. Analyse met behulp van "receiver operator characteristics" (ROC) grafieken liet wel een toegenomen diagnostische opbrengst zien voor de combinatie van CCS en X-ECG in de diagnostiek naar significant coronairlijden (oppervlakte onder de curve (AUC) 0.84) versus alleen CCS (AUC 0.69) of X-ECG (AUC 0.65). Echter, 6 (9%) patiënten met een CCS 0 – 400 en een negatief X-ECG leden aan significant CAD. Ook waren 37 (54%) patiënten met of een CCS >400 of een abnormaal X-ECG vrij van significant CAD.

In **hoofdstuk 4** evalueren wij de toegevoegde waarde van CCS aan SPECT in de diagnostiek van significant CAD. Bij patiënten met een normale SPECT kan een hoge CCS een aanwijzing zijn voor het bestaan van significant CAD [6-8]. Afkapwaarden voor CCS van 709 en 1000 zijn beschreven, hierboven werd een toegenomen incidentie van significant CAD waargenomen ondanks een normale SPECT [6-8]. In onze handen had SPECT een redelijke diagnostische accuratesse met een negatief voorspellende waarde (NPV) van 82% en een AUC van 0.88 zoals bepaald door analyse van ROC grafieken. Door het toevoegen van CCS nam de NPV toe tot 94%, maar dit ging ten koste van een groot aantal vals positieven. Zodoende verschilde de toegenomen AUC van 0.92 voor de combinatie van SPECT en CCS niet significant van de AUC van SPECT als enkele test. Bovendien veroorzaakte gebalanceerde ischaemie als gevolg van ernstige stenoses door "zachte plaque" (CCS van 0), dat de combinatie van SPECT en CCS faalde in het detecteren van significant CAD in drie patiënten.

In **hoofdstuk 5** bediscussiëren wij de diagnostische accuratesse van hybride beeldvorming. Hybride SPECT/CCTA werd verricht bij patiënten met een intermediaire- tot hoge voorafkans op significant CAD. Van deze patiënten had een groot percentage niet-conclusieve bevindingen bij SPECT (11.2%) of CCTA (23.5%). Hybride interpretatie van SPECT en CCTA beelden leidde in de gehele populatie tot een toegenomen diagnostische accuratesse; van een NPV van 89% en positief voorspellende waarde (PPV) van 85% voor SPECT en een PPV van 77% voor CCTA naar een NPV van 96% en een PPV van 95% voor de hybride interpretatie. In de groep van patiënten met niet-conclusieve bevindingen bij SPECT of CCTA had de hybride interpretatie respectievelijk een NPV en een PPV van 90% en 91%. Wij concluderen dat in onze populatie het complementaire karakter van hybride SPECT/CCTA beeldvorming optimaal tot uiting komt; in meer dan 40% van de patiënten kon CAD betrouwbaar worden uitgesloten. Deze studie demonstreert dat het voordeel van hybride beeldvorming ligt in het feit dat beide technieken kunnen compenseren voor de zwakke eigenschappen van de ander, waardoor niet-conclusieve bevindingen worden verholpen.

In **hoofdstuk 6** evalueren wij de toegevoegde waarde van hybride SPECT/CCTA aan de vooraf kans op CAD en X-ECG, in de diagnostiek van significant CAD. In hoofdstuk 5 hebben we de diagnostische accuratesse beschreven van hybride SPECT/CCTA als enkele test. De toegevoegde waarde van hybride SPECT/CCTA aan de gebruikelijke klinische work-up en SPECT of CCTA als enkele tests bleef echter onopgehelderd. De toegevoegde waarde van hybride SPECT/CCTA aan het basis model van voorafkans en X-ECG werd gekwantificeerd met behulp van logistische regressie analyse. De verschillen tussen de modellen werden onderzocht met behulp van de verschillen in C-index en netto verbetering van de reclassificatie (NRI). Het basismodel had een C-index van 0.73 (95%CI 0.66-0.80). Dit verbeterde significant naar 0.85 (95%CI 0.80-0.91) na toevoegen van SPECT, naar 0.90 (95%CI 0.85-0.94) na toevoegen van CCS en CCTA, en naar 0.96 (95%CI 0.92-0.99) na toevoegen van hybride SPECT/CCTA. Be bijbehorende NRI's waren respectievelijk 0.82 (95%CI 0.62-1.02), 0.86 (95%CI 0.66–1.06) en 1.57 (95%CI 1.11-1.59). De huidige analyse lijkt sterk op de klinische praktijk van gelaagd testen en demonstreert dat hybride SPECT/CCTA een aanzienlijk groter diagnostisch bereik heeft dan SPECT of CCTA als enkele test in de diagnostiek van coronairlijden.

In **hoofdstuk 7** evalueren we in hoeverre therapeutische besluiten kunnen worden gebaseerd op hybride SPECT/CCTA beelden. Therapeutische besluiten werden in twee stappen genomen door een panel van twee interventiecardiologen en een cardio-thoracaal chirurg; eerst op basis van de bevindingen bij hybride SPECT/CCTA en in tweede instantie op basis van SPECT en CA. Het percentage overeenkomende therapeutische besluiten (optimale medicamenteuze therapie of revascularizatie) op basis van beide diagnostische strategieën werden berekend voor alle patiënten en subgroepen van patiënten met een gematchte abnormale SPECT en CCTA, een niet-gematchte abnormale SPECT of CCTA en normale bevindigen bij zowel SPECT als CCTA. Revascularizatie (PCI of CABG) was noodzakelijk voor 54 (50%) patiënten op basis van de bevindingen bij SPECT en CA. Voor alle patiënten was het percentage overeenkomende therapeutische besluiten gebaseerd op hybride SPECT/CCTA versus SPECT en CA voor wat betreft de noodzaak van revascularizatie 92%. Voor subgroepen van patiënten met gematchte abnormale SPECT en CCTA, niet-gematchte abnormale SPECT of CCTA en normale bevindigen bij zowel SPECT als CCTA was het percentage overeenkomende therapeutische besluiten respectievelijk 95%, 84% en 100%. Wij concluderen dat op basis van niet-invasieve beeldvorming tot overeenkomende therapeutische besluiten kan worden gekomen vergeleken met de gebruikelijke invasieve beeldvorming met behulp van CA en SPECT. En ook dat in geselecteerde casus tot PCI en mogelijk CABG kan worden besloten op basis van alleen de bevindingen bij hybride SPECT/CCTA. Wel moet speciale aandacht worden geschonken aan patiënten met niet-gematchte bevindingen bij hybride SPECT/CCTA.

Hoofdstuk 8 betreft de beschrijving van de casus van een patiënt met een voorgeschiedenis van coronaire stent implantatie en recidief angina pectoris. SPECT was correct negatief voor ischaemie van het linker kamer myocard, het liet echter wel tekenen van rechterkamer volume en/of druk overbelasting zien. CCTA liet zeer duidelijk een sinus venosus inferior defect zien met een ontbrekend dak van de sinus coronarius. Er was sprake van een normale rechtszijdige vena cava superior en geen recidief significant coronairlijden, ook de stent was fraai open.

Hoofdstuk 9 betreft de beschrijving van een casus die de kracht van CCTA in het afbeelden van de cardiale en coronaire anatomie demonstreert. De patiënt die in dit hoofdstuk wordt beschreven leed aan een groot pseudoaneurysma dat ca. 2/3^{e} van de aortawortel omsloot en daarmee ook de hoofdstam van de linker coronair.

Hoofdstuk 10 betreft de generale discussie. Allereerst wordt de reconstructie van hybride SPECT/CCTA beelden bediscussieerd. De uitdagingen voor het verkrijgen van een juiste fusie van de beelden worden benadrukt. Ook worden de uitdagingen met betrekking tot verzwakkingcorrectie van SPECT met behulp van CT beelden bediscussieerd. Als tweede wordt de interpretatie van de hybride SPECT/CCTA beelden behandeld. Het HoRoSCOPe protocol voor de interpretatie van deze beelden wordt beschouwd in het licht van de beschikbare literatuur over dit onderwerp. Ten derde, wordt de patiënten selectie voor hybride SPECT/CCTA bediscussieerd tegen de achtergrond van de inschatting van de voorafkans, de diagnostische accuratesse van SPECT en CCTA als afzonderlijke beeldvormingsmodaliteiten, en de stralingsdosis die gepaard gaat met hybride beeldvorming. Een voorstel voor een beeldvormingsprotocol met een hybride SPECT-CT systeem wordt beschreven. Als vierde wordt de therapeutische besluitvorming met behulp van hybride SPECT/CCTA beelden bediscussieerd. Tenslotte worden aanbevelingen voor volgende studies gegeven gevolgd door de conclusies van dit proefschrift.

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Chapter 11.3

Dankwoord

DANKWOORD

Daar waar het onderwerp van mijn onderzoek slechts hybride is, daar is de totstandkoming van dit proefschrift een perfect samenspel geweest van een veelheid aan disciplines en personen. Mijn dank is bijzonder groot aan iedereen die aan dit proefschrift heeft meegewerkt. In het bijzonder wil ik de volgende personen noemen.

Zoals ieder klinisch onderzoek zou ook de HoRoSCOPe studie nooit mogelijk zijn geweest zonder de bereidheid van **patiënten** om deel te nemen. Mijn eerste dank is aan hen.

Mijn promotor, **Prof. Dr. J.F. Verzijlbergen**. Beste Fred, jouw gaves om te inspireren en te motiveren gaan hand in hand met je talent voor mensenkennis en cynische commentaren. Hierdoor ben ik op de juiste momenten voorzien van een extra peper en behoed voor het gevoel dat ik het Nobelprijs Comité alvast een briefje moest gaan sturen. Je visie dat non-invasieve cardiale beeldvorming alleen door de combinatie van vorm en functie op het hoogste niveau te krijgen is, is de basis geweest voor dit onderzoek. We hebben helaas even geduld moeten hebben voordat de “First of a Kind” Hybride SPECT-CT werd geïnstalleerd, maar daarna liet je me direct volledig vrij met deze machine en op jouw afdeling. Hierdoor is mijn promotietraject niet alleen wetenschappelijk, maar zeker ook op persoonlijk vlak enorm leerzaam geweest. Dat jijzelf de afgelopen jaren ook een paar maal promotie hebt gemaakt, is gelukkig nooit een te grote hobbel voor dit boekje gebleken; het is een enorme eer dat je nu niet mijn co-, maar mijn promotor bent.

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Dr. B.J.W.M. Rensing. Beste Benno, jij hebt me op het pad van dit promotie onderzoek gezet. Ik kwam met de ambitie om te promoveren en “bij het begin te beginnen”, dat heb ik geweten. Je steun in woord en daad waren onontbeerlijk voor het welslagen van dit project, bedankt. Gelukkig lardeer je een gesprek niet zelden met een vergeten songtekst of citaat van Drs P., anders waren onze gesprekken nog korter en bondiger geweest.

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Dr. J.A. de Groot. Beste Joris, precies op het juiste moment werd je mijn vraagbaak voor de laatste statistische mogelijkheden en stand van zaken. Je hebt me een paar maal moeten uitleggen dat voor een vraag die ik wilde beantwoorden waarschijnlijk het 10-voudige aantal patiënten geïncludeerd had moeten worden. Toch hebben we een paar fraaie analyses op papier gezet; zonder jouw hulp had ik het niet uit kunnen rekenen.

De **leden van de beoordelingscommissie**, Prof. Dr. B.L.F. van Eck – Smit, Prof. Dr. D.J.G.M. Duncker en Prof. Dr. P.J. de Feyter wil ik danken voor hun snelle en deskundige beoordeling van het manuscript.

Dr. M.C. Post. Marco, misschien is dit "Plokkeren"? Altijd oprecht vol optimisme over het welslagen van deze promotie, nooit te beroerd met raad en daad terzijde te staan, en een neus en feilloos inzicht voor een goede hypothese. In ieder geval beheers je dit met een hoofdletter P. Enorm bedankt, je bemoedigende woorden zijn van wezenlijk belang geweest om niet gedesillusioneerd te raken.

De **maatschap Cardiologie van het St. Antonius Ziekenhuis** ben ik veel dank verschuldigd. De in dit boekje beschreven beeldvorming was volledig nieuw, en niet geheel vanzelfsprekend, voor het St. Antonius Ziekenhuis. Toch heb ik als niet-invasieve beeldvormer alle ruimte en ondersteuning gekregen om het protocol in de praktijk te brengen. In het bijzonder wil ik Dr. H.W. M., Thijs, Plokker danken. Je hebt van begin tot eind aandacht gehad voor het welslagen van dit project. De electrofysiologen Dr. L.V.A. Boersma, Dr. M.C.E.F. Wijffels en Dr. E.F.D. Wever wil ik bedanken voor de gelegenheid die zij mij hebben geboden de laatste fase van het onderzoek te combineren met een fellowship device therapie.

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Dr. S.M. Boekholdt en Dr. W.B. Meijboom. Beste Matthijs en Bob, enorm veel dank dat jullie je expertise op het gebied van coronaire CT angiografie in dienst hebben willen stellen van mijn promotie. Dank voor de uren die jullie hebben geïnvesteerd in het beoordelen van de, niet al te gemakkelijke, CT angiogrammen.

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R. M. Kauling. Beste Martijn, je bent een waardig en veelbelovend opvolger. Ik weet zeker dat er nog een boek te schrijven is op basis van de database. Deze was er niet geweest zonder al jouw inspanningen bij de inclusie van patiënten en het invoeren van gegevens.

Nog voordat ik op het pad van de hybride beeldvorming was beland, was er het telefoontje van **Dr. Arend Mosterd**, ik denk op een vrijdag namiddag, met Benno Rensing. Niet alleen als kruiwagen maar vooral als opleider en rolmodel heb ik enorm veel geluk gehad met de **cardiologen en internisten in het Meander Medisch Centrum**. Zoals met iedereen die het promoveren "er even bij doet", ben ook ik in de spagaat van de combinatie van kliniek en wetenschap gekomen. Mijn eerste drie jaar opleiding bij jullie hebben me geleerd dat de combinatie van uitstekende klinische zorg én vooruitstrevende wetenschap op een soms hilarische manier te maken is.

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De "Hybride" laboranten van de nucleaire geneeskunde. Marion Schwillens, Rob van der Boor, Aldrick Peterson, Martine van Rutte en Kirsten Poelma. Wat is het een enorm feest geweest om met jullie samen te werken. Jullie bereidwilligheid en leergierigheid om je een nieuwe techniek eigen te maken en werkelijk tot in de puntjes te beheersen, is zeldzaam. Naast jullie waren Paddy Okletey, Harold "Chief" Eugenia, Kees Roeterdink, Mariska Karremans een genot om mee samen te werken.

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De secretariaten cardiologie en nucleaire geneeskunde. Dames wat zijn jullie een partij flexibel geweest. Niet zelden moest er iets verzet, nog snel een brief verzonden, een extra postzegel geleend, ja zelfs langs een brievenbus gefietst worden om de hele keten van inclusie en beeldvorming intact te houden. Met name het geduld en incasseringsvermogen van Carola, Sandra, Arda en Irene met deze hongerige promovendus is legendarisch, dank-jullie-wel!

Dear **Christiana**, thank you for your valuable comments on the introduction and general discussion.

De **Bredase Maatschap Cardiologie.** Dank voor jullie warme belangstelling voor de voortgang van mijn proefschrift en jullie flexibiliteit in de laatste fase van het schrijfwerk. Ik ben bijzonder blij nu ruim een jaar deel uit te mogen maken van deze maatschap en heb enorm veel zin iets moois te maken van de toekomst van de Bredase cardiologie!

Mijn **vrienden en vriendinnen**. Tussen het promoveren door waren jullie graag bereid de broodnodige ontspanning te bieden. Al heb ik een paar etentjes, zeilweekenden en dispuutborrels moeten laten schieten. Ik heb me wel eens afgevraagd of dat het nu allemaal waard was. In ieder geval is het moment aangebroken dat deze offers niet meer gebracht hoeven worden.

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Paul en Mien, mijn **schoonouders**, en Keanu en Jaimiro mijn **zwagers**, dank voor de familie die jullie voor me zijn. En dank voor het slechts optrekken van een wenkbrauw op de momenten dat ik bijvoorbeeld tijdens een skivakantie achterbleef om een middag te typen.

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Mijn vrouwen **Suleika, Naomi en Esmée**. Dames, zonder jullie was dit alles niet mogelijk geweest. Naomi en Esmée hebben, gelukkig, weinig meegekregen van de uren die in dit boekje zijn gaan zitten. Mijn kleine ogen hadden ook net zo goed van een nachtelijke fles kunnen zijn. Suleika, liefde van mijn leven, het is onmogelijk in woorden te vatten wat je allemaal voor me betekent. Ongelooflijk hoe je me steunt en de gelegenheid geeft te doen wat ik leuk vind. Pas als dit boekje verdedigd is zal ik je vragen waar je het geduld (wist niet dat je het in je had) vandaan hebt gehaald. We hebben een paar fantastische tropenjaren achter de rug die ons ongeveer alles hebben gebracht wat we wilden bereiken. Laten we afspreken dat 2014 een jaar wordt in een lagere versnelling zodat we hier iets vaker bij stil kunnen staan. Ik hou van je.

Chapter 11.3

List of publications

LIST OF PUBLICATIONS

Does radioiodine therapy have disadvantageous effects in non-iodine accumulating differentiated thyroid carcinoma?
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Is exercise stress electrocardiography of incremental value after coronary calcium scoring?
Schaap J, Kauling RM, Post MC, Kelder JC, Van der Heyden JA, de Kroon TL, Rensing BJ, Verzijlbergen JF.
Submitted

Added value of hybrid myocardial perfusion SPECT and CT coronary angiography in the diagnosis of coronary artery disease.
Schaap J, de Groot JA, Nieman K, Meijboom WB, Boekholdt SM, Kauling RM, Post MC, Van der Heyden JA, de Kroon TL, Rensing BJ, Moons KG, Verzijlbergen JF.
Submitted

Chapter 11.3

Curriculum Vitae

CURRICULUM VITAE

The author of this thesis was born on the 10th of August 1977 in Amersfoort. In 1996 he earned his Athenaeum diploma from the Corderius College, also in Amersfoort. During the same year he started medical school at the Leiden University in Leiden. In 1999 he had his first experience with clinical research under the guidance of Prof. Dr. J.W.A. Smit at the department of endocrinology of the Leiden University Medical Center. This opened the opportunity for a 7-month encounter with basic medical research at the laboratory of Prof. Dr. S.M. Jhiang in Columbus, United States, in 2001. He graduated Cum Laude from medical school in 2003. During this year he started his career in cardiology as a "physician not-in-training" at the cardiology department of the Hofpoort Hospital in Woerden. In 2004 he was accepted as a trainee in cardiology at the St. Antonius Hospital in Nieuwegein. He started his residencies in the Meander Medical Center in Amersfoort, the first year for a cardiology residency under the guidance of Dr. P.J. Senden. In 2005 he continued with a two-year residency in internal medicine under the guidance of Prof. Dr. C.A.J.M. Gaillard, in the same hospital. In 2007 he returned to the St. Antonius Hospital in Nieuwegein to finish his training in cardiology, tutor Dr. W.J. Jaarsma. In 2007 he started with the preparations for the "High and intermediate Risk Spect-Ccta OPtimization study (HoRoSCOPe) under the guidance of Prof. Dr. F.J. Verzijlbergen. Inclusion started in September 2009 and reports from this study resulted in this thesis. After finishing his cardiology training in 2010 he continued his career with a fellowship non-invasive cardiac imaging and device therapy, tutor Dr. L.V.A. Boersma, in the St. Antonius Hospital. From March 2012 he has been working as a cardiologist with a special interest for non-invasive cardiac imaging in the Amphia Hospital in Breda.
Jeroen is married to Suleika Leenknegt. They have two daughters; Naomi was born in 2011 and Esmée in 2012.

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SPECT/CCTA vs Conventional Angiography in Angina

Schaap et al. from St. Antonius Hospital (Nieuwegein, The Netherlands) reported on October 19 ahead of print in *Heart* on a study comparing the effect of hybrid myocardial perfusion SPECT/CT coronary angiography (SPECT/CCTA) with that of SPECT alone plus invasive coronary angiography in treatment and management decisions for patients with stable angina pectoris. The study included 107 patients (mean age, 62.8 ± 10.0 y; 69% men, 31% women) with stable anginal complaints and an intermediate-to-high pretest likelihood for coronary artery disease. Hybrid SPECT/CCTA imaging was performed before conventional angiography in all patients. Treatment outcomes were classified as no revascularization, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Treatment decisions were made by 2 interventional cardiologists and a cardiothoracic surgeon based first on the results of hybrid SPECT/CCTA and second on results from SPECT alone plus conventional angiography. Revascularization (either PCI or CABG) was indicated in 54 (50%) patients using data from SPECT and CA. SPECT/CCTA agreed with SPECT and conventional angiography on the need for revascularization in 92% of patients. The percentage agreements of treatment decisions in patients with matched, unmatched, and normal hybrid SPECT/CCTA findings was 95%, 84%, and 100%, respectively. The authors concluded that "that patients could be accurately indicated for and deferred from revascularization based on hybrid SPECT/CCTA."

Heart