Chapter 2

Comparison of exercise electrocardiography with magnetic resonance myocardial perfusion imaging and computed tomography coronary angiography in patients with suspected coronary artery disease

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Submitted

ABSTRACT

Purpose: To investigate the relationship between exercise electrocardiography (X-ECG) and functional and anatomical imaging modalities for the diagnostic evaluation of patients with suspected coronary artery disease (CAD).

Methods: Patients (n=71 mean age 54 ± 9; 68% male) with chest pain and without prior history of CAD underwent X-ECG, adenosine stress and rest magnetic resonance myocardial perfusion imaging (MRMPI) and 64-slice computed tomography coronary calcium scoring (CCS) and angiography (CTCA). Sensitivity and specificity of X-ECG for detection of myocardial ischemia on MRMPI or obstructive CAD on CTCA (>50% diameter stenosis) were determined for conclusive X-ECG results.

Results: The X-ECG was normal in 47, positive in 13 and inconclusive in 11 patients. In 10 of 11 patients with inconclusive X-ECG, MRMPI and CTCA provided diagnostic images. Mean coronary calcium scores were not significantly different among patients with negative, positive and inconclusive X-ECG, 52 ± 95, 98 ± 162 and 107 ± 216, respectively (p=0.32).

Sensitivity and specificity of X-ECG for detection of myocardial ischemia on MRMPI were 39% (95% CI: 20%-61%) and 83% (95% CI: 72%-90%), respectively. Sensitivity and specificity of X-ECG for detection of obstructive CAD on CTCA were 36% (95% CI: 18%-61%) and 81% (95% CI: 70%-89%), respectively. Receiver operating characteristic curve analysis showed that CTCA had significant higher diagnostic accuracy for the detection of myocardial ischemia on MRMPI than X-ECG: area under the curve 0.83 ± 0.06 (95% CI: 0.72-0.95) and 0.60 ± 0.08 (95% CI: 0.46-0.75), respectively (p=0.0056).

Conclusions: X-ECG did not correlate to anatomical and functional imaging modalities for the diagnostic evaluation of CAD. Particularly the sensitivity of X-ECG for detection of anatomically or hemodynamically relevant CAD in this patient group was low.

INTRODUCTION

Exercise electrocardiography (X-ECG) is the most frequently used modality for the initial evaluation of patients with suspected coronary artery disease (CAD) in daily clinical cardiology practice. It is fast, safe and its prognostic value has been validated extensively. (1) However, its ability to detect or exclude significant CAD is only moderate, particularly in patients with single vessel disease. (2) Furthermore, in a large proportion of patients results are inconclusive due limited exercise capacity or abnormal baseline electrocardiography. Recently, non-invasive anatomical imaging tests are increasingly used for the evaluation of patients with suspected CAD. Computed tomography coronary calcium scoring (CCS) is an independent predictor of major adverse cardiac events. (3) Computed tomography coronary angiography (CTCA) accurately visualizes atherosclerotic plaques in the coronary arteries and correlates well with invasive coronary angiography. (4) As the negative predictive value for detection of significant CAD is excellent, CTCA is particularly useful to exclude significant CAD in low to intermediate risk patients. (5) However, in case of obstructive CAD on CTCA, assessment of the hemodynamic relevance of CAD is still needed to direct further patient management. Myocardial perfusion imaging modalities provide detailed information about the location and extent of myocardial ischemia. In recent years, magnetic resonance myocardial perfusion imaging (MRMPI) is increasingly used in clinical practice for the detection of myocardial ischemia. As it does not involve any ionizing radiation and provides information about ventricular function, stress and rest myocardial perfusion, and myocardial viability in one single scan session, it is a promising new imaging modality for the diagnostic evaluation of patients with suspected CAD. Several studies have shown its capability to detect hemodynamically relevant CAD and it has been validated against nuclear myocardial perfusion imaging modalities, invasive coronary angiography and fractional flow reserve measurements. (6-8) However, studies comparing MRMPI with X-ECG are scarce.

Therefore, in this study the relationship between X-ECG and these new non-invasive anatomical and functional imaging modalities for the diagnostic evaluation of patients with suspected CAD was investigated.

METHODS

Patients and study protocol

Patients with chest pain and low to intermediate pre-test probability CAD that underwent X-ECG, CTCA and MRMPI as part of their clinical evaluation of suspected CAD were recruited from our outpatient cardiology clinic. The study population is a shared population with a previous publication in which patients underwent both CTCA and MRMPI. [9] In the present study patients were retrospectively included when they had undergone routine X-ECG in addition to CTCA and MRMPI, as part of their clinical work-up. The study protocol was approved by the local ethics committee and written informed consent was

obtained in all patients. Exclusion criteria were: prior history of CAD (prior documented myocardial ischemia, myocardial infarction, percutaneous coronary intervention or cardiac surgery), abnormal baseline electrocardiography, significant arrhythmia, pregnancy, renal insufficiency (serum creatinine > 110μmol/L), known allergy to ionated contrast material and any change in clinical status during the time interval between X-ECG, CTCA and MRMPI. The pre-test probability of CAD was calculated according to the previously described Diamond/Forrester and CASS scale. (10-12)

Exercise electrocardiography

The X-ECG was performed on a bicycle ergometer using a symptom-limited modified Bruce protocol. The X-ECG data were scored positive, negative or inconclusive by a cardiologist blinded to CCS, CTCA and MRMPI data. The X-ECG was scored positive if the electrocardiogram showed significant ST segment depression (≥1 mm (0,1 mV) horizontal or downsloping ST-depression 80 ms after the J point in ≥3 consecutive beats and ≥2 leads). The X-ECG was scored negative when at least 85% of the maximum predicted heart rate was achieved without significant ST segment changes. The X-ECG was considered inconclusive if 85% of the maximal predicted heart rate was not achieved and no significant ST segment depression was observed.

Computed tomography coronary angiography

CTCA was performed using a 64-slice CT scanner (Sensation 64, Siemens, Erlangen, Germany). When resting heart rate was > 65 beats per minute, 50 mg metoprolol was administered orally one hour before start of CTCA. In case of persistent heart rate above 65 beats per minute, metoprolol (5-15 mg) was administered intravenously immediately before image acquisition. All patients received 0.4 mg nitroglycerin sublingual before start of the scan. First a non-contrast scan was performed at 150 mAs and 120 kV. Using dedicated software (Syngo Calciumscoring, Siemens, Germany) the Agatston calcium score was calculated by an experienced observer, blinded to X-ECG, CTCA and MRMPI data.

The coronary angiography scan was performed using a scan collimation of 64x0.6 with a flying z-focus at 900mAs and 120 kV. Injection of 100 ml non-ionic contrast agent (Ultravist 300, Bayer, Germany) through a cannula in the antecubital vein (flow rate 5 ml/s) was followed by 40 ml of saline flush. Automated bolus tracking was used by drawing a region of interest in the ascending aorta on a single axial slice located at the bifurcation of the pulmonary trunk. The CTCA scan was started automatically when the contrast level in the region of interest reached a threshold value of 150 HU. Using retrospective ECG triggering, data were initially reconstructed at 65% of the RR interval (slice thickness 0.75 mm, increment 0.4 mm). In case of motion artifacts, axial reconstructions for the entire RR interval (10% steps) aimed at the region of interest were acquired and analysed to determine the interval with optimal image quality. Subsequently a new reconstruction of the full dataset was made at this RR interval. CTCA data were transferred to an offline workstation and analysed in consensus by a radiologist and a cardiologist blinded to the X-

ECG and MRMPI data. Analysis was performed on the original axial dataset and on curved multiplanar reconstructions. The coronary tree was evaluated according to a 16-segment coronary artery model modified from the American Heart Association. (13) Each segment was graded by visual assessment on a 4 point scale: normal (no stenosis); intermediate CAD (0-50% diameter stenosis); obstructive CAD (>50% diameter stenosis) and non-diagnostic (severe motion artifacts that impaired adequate image interpretation).

Magnetic resonance myocardial perfusion imaging

All imaging was performed on a 1.5T whole body MRI scanner (Sonata/Avanto, Siemens, Erlangen, Germany) with the patient in supine position using an eight-element phased array cardiac receiver coil. Patients were instructed to refrain from caffeinated drinks and other competitive antagonists of adenosine 24 hours before the examination. All images were acquired with electrocardiographic triggering and expiration breath holding. First pass myocardial perfusion was assessed using a dynamic single shot saturation recovery gradient-echo planar pulse sequence (TR/TE = 5.6/1.1 ms, saturation time 110 ms, flip angle 18^{o}, echo-planar factor 4, matrix-size 160 x 144 and voxel size 2.5 x 2.5 x 10 mm^3), accelerated by parallel imaging with a factor two using TSENSE, during the administration of 0.1 mmol/kg body weight of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany) flushed with 15 mL of 0.9% saline (flow rate 3 mL/s). Every heartbeat 3 left ventricle short axis slices (basal, mid and apical) were acquired. After 3 minutes of continuous intravenous infusion of adenosine (140 µg/kg/min) the stress scan was started and simultaneously the contrast agent was injected and flushed with saline; the adenosine was stopped immediately after completion of the scan. Blood pressure and heart rate were monitored during adenosine infusion. The rest scan was acquired at least 10 minutes after the stress scan, with identical scan parameter setting, contrast dose and slice positions.

MRMPI data were analysed visually by a cardiologist, blinded to X-ECG and CTCA data. Both stress and rest images were analysed simultaneously on one workstation. The myocardium of the 3 short axis orientations during stress and rest were divided into segments using a 16 segment model as described previously (14) and all segments were scored normal or ischemic. Ischemia was defined as myocardial hypoperfusion during > 3 consecutive images after arrival of the contrast agent in the left ventricular cavity in at least 1 myocardial segment.

Statistical analysis

All data were presented as mean ± standard deviation for continuous data.

Differences between groups were tested by Chi-square and paired t-tests. Correlations between coronary calcium scoring and conclusive X-ECG results, CTCA or MRMPI were tested by Spearman's correlation. Receiver operating characteristic (ROC) curves were calculated of X-ECG for detection of obstructive CAD on CTCA and myocardial ischemia

on MRMPI. Sensitivity and specificity of conclusive X-ECG results for detection of CAD on CTCA and myocardial ischemia on MRMPI were obtained from two-by-two tables. Ninety-five percent confidence intervals (CI) were calculated from binomial expression using Wilson's approximations. (15) The ROCs were compared using the method of the DeLong et al. (16) Statistical analysis was performed using a standard software package, SPSS version 15.0 SPSS, Chicago, IL, USA) and SAS version 9.2 (SAS institute, Inc., Cary, NC, USA).

RESULTS

A total of 71 patients met the inclusion criteria. Detailed patient characteristics are listed in table 1. The most common reason to terminate the X-ECG was fatigue. The mean exercise time was 8:40 min. The X-ECG was negative in 47 (66%) patients and positive in 13 (18%) patients. The X-ECG was inconclusive in 11 (16%) patients.

Table 1. Clinical characteristics

Patients	71
Male	43 (61)
Mean age (yrs)*	54 ± 9
Body mass index (kg/m²)*	27 ± 4
Symptoms	
non-anginal chest pain	24 (33)
atypical chest pain	34 (47)
typical chest pain	13 (18)
Risk factors for CAD	
Diabetes	6 (8)
Hyperlipidaemia	15 (21)
Hypertension	28 (39)
Family history	31 (43)
Smoking	12 (17)
Pre-test probability of CAD†*	44 ± 24

Note: unless otherwise stated data are expressed as number of patients with percentages within parentheses. * Mean ± standard deviation.
† According to the combined Diamond/Forrester and CASS scale. (10-12)
CAD indicates coronary artery disease.

Mean coronary calcium score was 69 ± 133 (inter-quartile range 0-59). The calcium score was zero in 31 (44%) patients. CTCA was not performed in 1 patient due to persistent heart rates above 65 beats per minute. Mean heart rate at data acquisition was 59 ± 6 beats per minute. The image quality was non-diagnostic in 10 of 1120 (0.9%) segments due to motion artifacts and these were subsequently excluded from the analysis. According to CTCA, 31 (44%) patients did not have CAD. Intermediate CAD was detected in 15 (21%)

patients and obstructive CAD in 24 (34%) patients. Single vessel disease was detected in 12 (17%) patients, two-vessel disease in 8 (11%) patient and 4 (6%) patients had three-vessel disease.

MRMPI could not be performed in 2 patients (one patient had prior unknown claustrophobia and one patient had reversible tachycardia of > 160 beats /min during adenosine infusion). In 15 (21%) patients myocardial ischemia was observed by MRMPI. Figure 1 shows a typical case example.

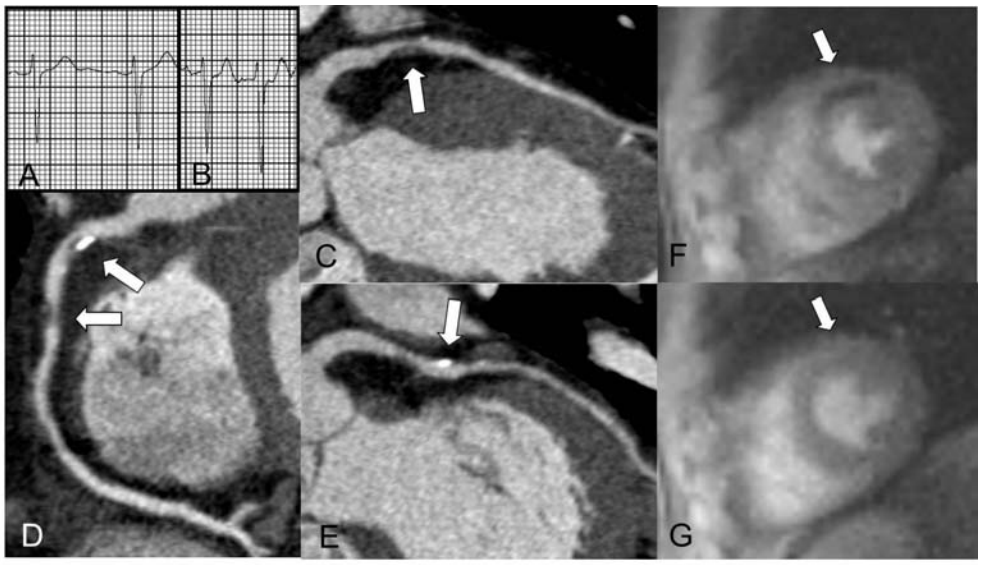

Figure 1. Case example of a 58 year old male patient with atypical chest pain. Exercise electrocardiography was negative (A rest, B exercise stress). Computed tomography coronary angiography showed obstructive coronary artery disease in the proximal left anterior descending coronary artery (C) and intermediate coronary artery disease in the right (D) and the circumflex coronary artery (E). During adenosine stress and rest magnetic resonance myocardial perfusion imaging a reversible perfusion defect was observed in the anterior myocardial wall on a mid ventricular short axis orientation (F adenosine stress, G rest).

Relationship between X-ECG and imaging modalities

No significant correlation was found between CCS and X-ECG (r=0.13, p=0.34). Although there was a trend towards lower mean coronary calcium scores in patients with negative X-ECG results than in patients with positive or inconclusive results, there was no significant difference due to the large variance of coronary calcium scores (52 ± 95, 98 ± 162 and 107 ± 216, p=0.32, respectively). Among patients with a coronary calcium score of zero, the X-ECG was negative in 68% (21/31), positive in 16% (5/31) and inconclusive in 16% (5/31) of patients. The area under the curve (AUC) of CCS using a cut-off value of zero (CCS0), for prediction of a positive X-ECG was 0.56 ± 0.08 (95% CI: 0.41-0.71; p=0.44).

In figure 2 the CTCA findings among patients with negative, positive and inconclusive X-ECG results are presented. The AUC of X-ECG for detection of obstructive CAD on CTCA was 0.56±0.06 (95% CI: 0.44-0.68; p=0.32). The sensitivity and specificity of X-ECG for detection of obstructive CAD on CTCA were 30% (6/20; 95% CI: 16%-48%) and 82% (32/39; 95% CI: 70%-90%), respectively.
In figure 3 the MRMPI findings among patients with negative, positive and inconclusive X-ECG results are presented. The AUC of X-ECG for detection of myocardial ischemia on MRMPI was 0.61±0.08 (95% CI: 0.46-0.75; p=0.16). The sensitivity and specificity of X-ECG for detection of myocardial ischemia on MRMPI were 39% (5/13; 95% CI: 20%-61%) and 83% (38/46; 95% CI: 72%-90%), respectively.

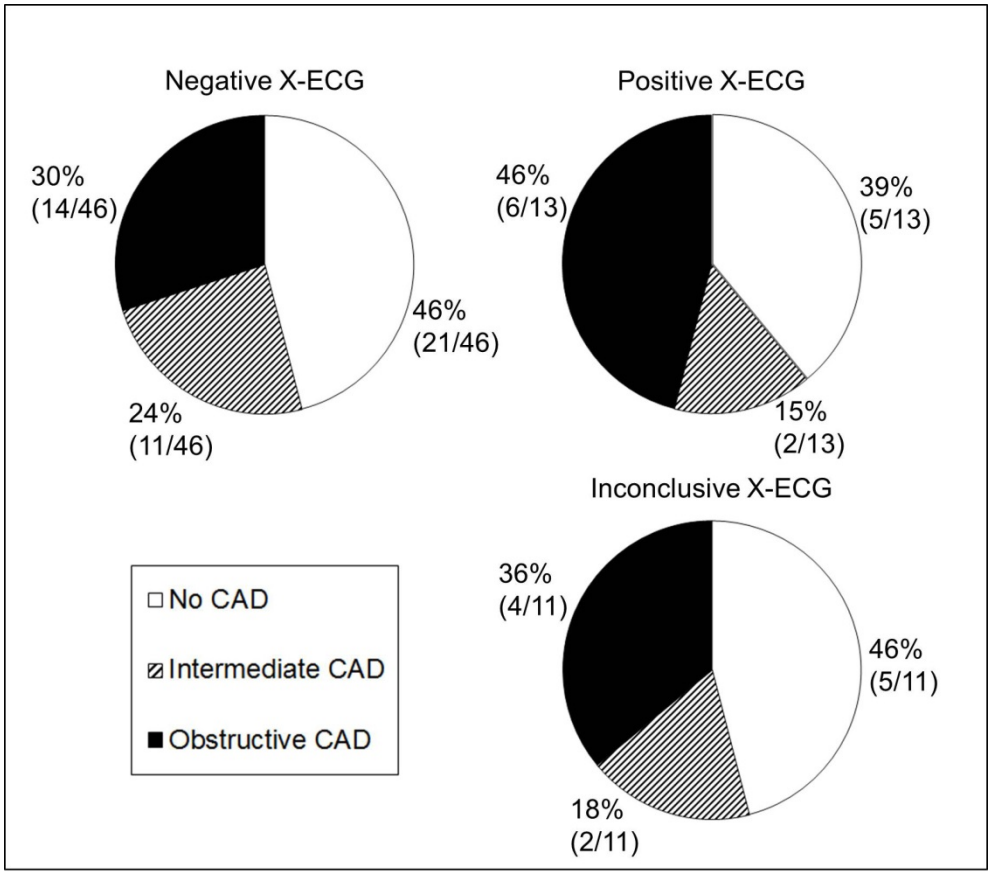

Figure 2. The relationship between exercise electrocardiography (X-ECG) and findings on computed tomography coronary angiography. Data are expressed as percentage of patients with number of patients within parentheses.

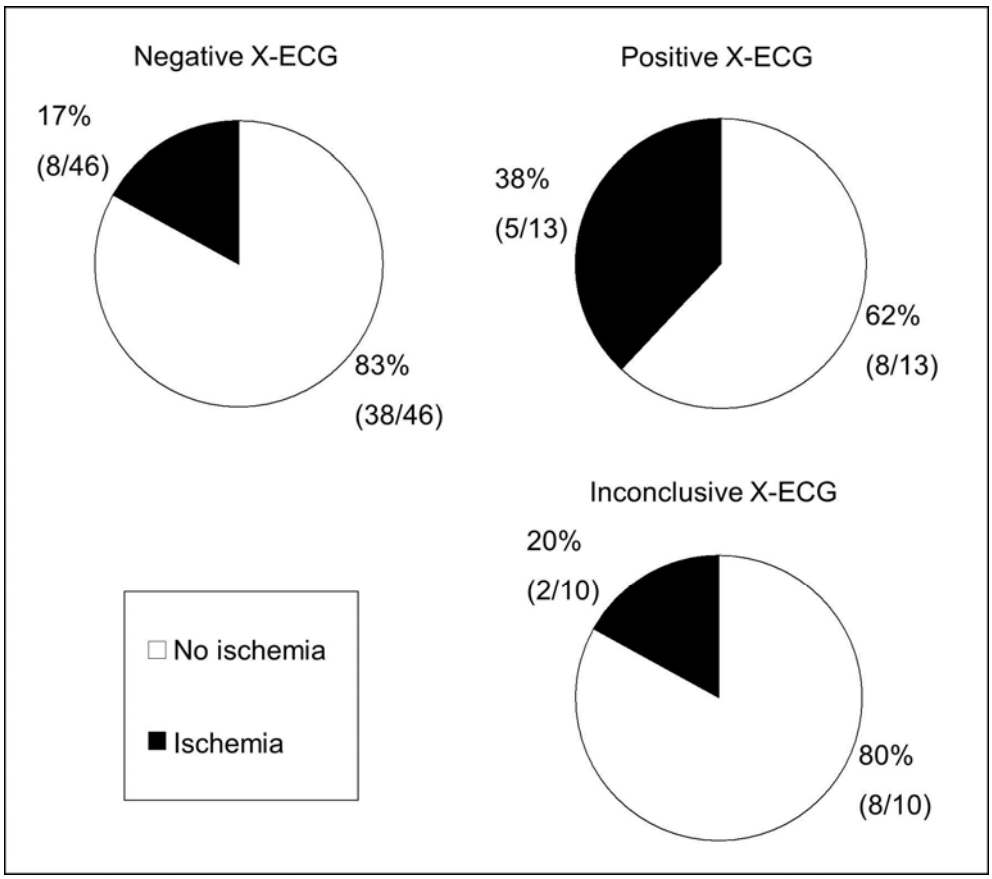

Figure 3. The relationship between exercise electrocardiography (X-ECG) and findings on magnetic resonance myocardial perfusion imaging. Data are expressed as percentage of patients with number of patients within parentheses.

Relationship between anatomical and functional imaging modalities.

A significant correlation was found between CCS and intermediate CAD ($r=0.65$, $p<0.001$), obstructive CAD on CTCA ($r=0.56$, $p<0.001$) and myocardial ischemia on MRMPI ($r=0.45$, $p<0.001$). Mean coronary calcium scores were significantly different among patients without CAD, mild CAD, intermediate and obstructive CAD, 0 ± 0, 68 ± 77, 60 ± 71 and 232 ± 211, respectively ($p < 0.0001$). The area under the curve (AUC) of coronary calcium score using a cut-off value of zero, for detection of obstructive CAD on CTCA was 0.80 ± 0.04 (95% CI: 0.73-0.88; $p<0.0001$). Furthermore, mean coronary calcium scores were significantly different between patients with normal myocardial perfusion and patients with myocardial ischemia on MRMPI, 46 ± 114 and 150 ± 171, respectively ($p=0.007$). The area under the curve (AUC) of coronary calcium score using a cut-off value of zero, for

detection of myocardial ischemia on MRMPI was 0.67 ± 0.06 (95% CI: 0.56-0.79; p=0.022). Among patients with a coronary calcium score of zero, the majority (29/31 patients, 94%) had no or only mild CAD and normal myocardial perfusion on MRMPI.
The AUC of CTCA (>50%) for detection of myocardial ischemia on MRMPI was 0.80 ± 0.06 (95% CI: 0.68-0.91; p<0.0001). The sensitivity and specificity of CTCA for detection of myocardial ischemia on MRMPI were 80% (12/15; 95% CI: 52%-96%) and 79% (42/53; 95% CI: 66%-89%), respectively.
Among patients with conclusive results for all tests (n=58) the AUC of CTCA for detection of myocardial ischemia was significantly higher than X-ECG, 0.83 ± 0.06 (95% CI: 0.72-0.95) and 0.60 ± 0.08 (95% CI: 0.46-0.75), respectively (p=0.0056). No significant difference was observed between AUC of X-ECG and CCS0 for detection of myocardial ischemia on MRMPI, 0.60 ± 0.08 (95% CI: 0.46-0.75) and 0.66 ± 0.06 (95% CI: 0.53-0.78), respectively (p=0.54). See figure 4.

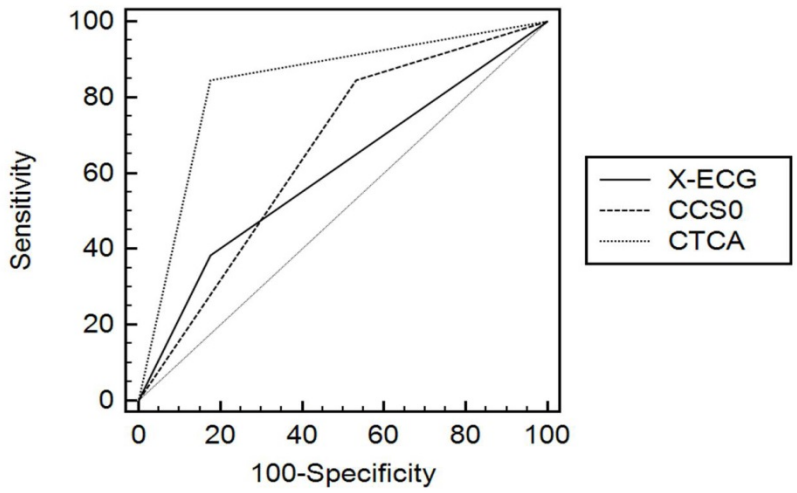

Figure 4. Receiver operating characteristic (ROC) curves of exercise electrocardiography (X-ECG), coronary calcium scoring with cut-off value of zero (CCS0) and CT coronary angiography (CTCA) for detection of myocardial ischemia on magnetic resonance myocardial perfusion imaging.

DISCUSSION

This study investigated the relationship between X-ECG and non-invasive anatomical and functional imaging techniques for the diagnostic evaluation of patients with suspected CAD. It is the first study that directly compared findings on X-ECG with CTCA and MRMPI. Our results show a lack of correlation between either X-ECG and CCS, CTCA and MRMPI. Particularly the sensitivity of X-ECG for detection of anatomically and hemodynamically relevant CAD was low. More than 50% of patients with normal X-ECG did have CAD on CTCA and 17% had myocardial ischemia. Furthermore, in over 20% of patients with inconclusive X-ECG, obstructive CAD or ischemia was observed. Our results showed that in contrast to X-ECG, CCS and CTCA did correlate to MRMPI.

Previous studies investigating the relationship between X-ECG and either CTCA or nuclear myocardial perfusion imaging have shown similar results. Rubinshtein et al (17) found that among patients with negative X-ECG results the prevalence of obstructive CAD on CTCA was 22%, and the prevalence was even higher among patients with inconclusive X-ECG (39%). In a study by Mollet et al (18) obstructive CAD was detected by CTCA in 47% of patients with a negative X-ECG and 67% of patients with inconclusive X-ECG. Bokhari et al compared the diagnostic performance of X-ECG to exercise gated single photon emission computed tomography myocardial perfusion imaging (SPECT) for detection of significant CAD on invasive coronary angiography in 218 symptomatic patients. (19) The overall sensitivity of X-ECG (36%) was significantly lower than that of SPECT (81%). Although the sensitivity of X-ECG in patients with multi-vessel CAD was higher, the sensitivity of SPECT again was superior to X-ECG (88% versus 58%, respectively). In contrast to previous studies, patients in the present study underwent X-ECG and CTCA as well as myocardial perfusion imaging. To our knowledge only one study has yet compared X-ECG with MRMPI. (20) Greulich et al compared X-ECG, MRMPI and invasive coronary angiography in 68 women with suspected CAD. Similarly, they found a poor correlation between X-ECG and MRMPI. Of 45 patients with negative X-ECG results, MRMPI detected myocardial ischemia in 11(24%) patients. Furthermore, of 23 patients with positive X-ECG, MRMPI was normal in 14 (61%) patients. Moreover, 10 (22%) patients with negative X-ECG had significant CAD on ICA. Overall, the diagnostic accuracy of MRMPI was significantly higher that X-ECG for detection of significant CAD on ICA, 91% versus 66% ($p=0.0007$).

The low diagnostic accuracy of X-ECG for detection of significant CAD can be explained by the position of electrophysiologic changes in the ischemic cascade. (21) This cascade is initiated by a mismatch of oxygen supply and demand in the presence of a hemodynamically significant epicardial coronary stenosis caused by an atherosclerotic plaque. As a result of this mismatch, relative myocardial perfusion is reduced and subsequently diastolic and systolic dysfunction decline. If this mismatch persists, electrophysiologic changes can be detected and ultimately the patient may feel chest discomfort. Each diagnostic modality can be placed in this perspective. CCS detects any

calcified coronary atherosclerotic plaque and CTCA can visualize the degree of coronary stenosis. Myocardial perfusion imaging visualizes the perfusion defect. Finally, X-ECG detects electrocardiographic changes. As a result of this order of events, anatomical tests such as CCS and CTCA are very sensitive modalities for the detection of any atherosclerosis, but are less specific for detection of hemodynamically relevant CAD. Although myocardial perfusion imaging does not detect mild atherosclerosis that is not (yet) hemodynamically significant, it is able to detect small regions of myocardial ischemia caused by (distal) single vessel CAD. X-ECG can quite accurately detect electrocardiographic changes caused by larger areas of myocardial ischemia (as in multi-vessel disease) but is obviously less sensitive in detecting smaller areas of ischemia as in single vessel disease. The prevalence of three-vessel disease in the present study was very low (6%). This may have reduced the sensitivity of X-ECG even more.

Present results show the limited diagnostic value of X-ECG in the evaluation of patients with suspected CAD. Although X-ECG is a good prognostic tool, it lacks sensitivity and specificity to detect significant CAD. Imaging tests can provide additional information about the presence of CAD and may subsequently direct further treatment.

The presence of any referral bias could not be excluded in the present study. Furthermore, the small sample size is a limitation. Therefore no differentiation between gender and other potential confounders (e.g. diabetes) of the accuracy of X-ECG for detection of CAD could be made.

In conclusion, exercise electrocardiography did not correlate to anatomical and functional imaging modalities for the diagnostic evaluation of CAD. Particularly the sensitivity of X-ECG for detection of anatomically or hemodynamically relevant CAD in this patient group was low.

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