Assessment of coronary calcification by electron-beam computed tomography in symptomatic patients with normal, abnormal or equivocal exercise stress test

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Aims Exercise stress testing is often used as the initial non-invasive diagnostic test in symptomatic patients with suspected obstructive coronary artery disease. Positive standard ECG criteria are quite specific for obstructive coronary artery disease, but there may be a substantial number of false negative tests, including patients with severe coronary artery disease. Also, exercise stress tests frequently yield equivocal results. Instead of detecting the functional consequences, electron-beam computed tomography visualized atherosclerotic plaque disease directly, but its relationship to functional testing has not been clearly delineated. It was the aim of the current study to examine electron-beam computed tomography for the identification of obstructive coronary artery disease in patients with a normal, abnormal, or equivocal exercise stress test.

Methods and Results Symptomatic patients referred for coronary angiography were prospectively included in a consecutive manner if they had no prior diagnosis of coronary artery disease and an unremarkable resting ECG. All patients underwent both exercise stress test and electron-beam computed tomography on the day before coronary angiography. Standard protocols and ECG criteria to diagnose inducible ischaemia were used for the exercise stress test. The electron-beam computed tomography-derived total calcium score was computed according to standard Agatston criteria. Of the 323 patients (mean age, 55 ± 11 years; 77% male), 179 (55%) had obstructive coronary artery disease, defined angiographically as luminal diameter narrowing ≥ 50%. A normal exercise stress test was documented in 105 patients (32.5%), an abnormal exercise stress test (‘diagnostic for ischaemia’) in 113 (35%), and an equivocal exercise stress test (‘inadequate exercise or non-diagnostic ECG-changes’) in 105 (32.5%). Multivariate analysis indicated that exercise stress test and electron-beam computed tomography yielded independent information for predicting obstructive coronary artery disease. Sensitivity, specificity and overall accuracy of the exercise stress test were 71%, 75% and 73%, respectively, if equivocal tests were not included, and 50%, 84% and 65% if they were included. Irrespective of the cut-point regarded as ‘positive’, the overall accuracy of the electron-beam computed tomography-derived calcium score remained approximately 80% in patients with a normal, abnormal or equivocal exercise stress test. In patients with an equivocal and — to a lesser degree — with a normal exercise stress test, electron-beam computed tomography was able to significantly improve classification regarding obstructive coronary artery disease. Electron-beam computed tomography added no incremental predictive value in patients with an abnormal exercise stress test.

Conclusion In patients who are judged to have an intermediate post-test probability of disease after exercise stress test, electron-beam computed tomography scanning may be a meaningful strategy for further stratification regarding the likelihood of obstructive coronary artery disease.

Key Words: Myocardial ischaemia, coronary atherosclerosis, coronary artery disease, diagnostic testing, atherosclerotic plaque.
Introduction

The diagnostic evaluation of patients with chest pain syndromes and an intermediate likelihood of obstructive coronary artery disease usually includes exercise stress testing for increasing or decreasing the post-test probability of disease\(^{[1-3]}\). Standard exercise stress testing, either using a treadmill or a cycle, is designed to detect myocardial ischaemia as a result of flow-limiting epicardial coronary stenoses. The test is readily available and safe. In general, exercise stress testing, if clearly abnormal, is relatively specific for underlying coronary artery disease, whereas a negative test result does not necessarily rule out angiographically obstructive coronary artery disease\(^{[4]}\).

Recently, electron-beam computed tomography as a modality to diagnose coronary atherosclerosis has been included in guidelines for the management of patients with chronic stable angina\(^{[2]}\). Instead of imaging the physiological consequences, electron-beam computed tomography provides for direct visualization of coronary atherosclerosis by virtue of detecting the calcification associated with atherosclerotic plaque formation\(^{[4]}\). Because calcification is often observed in the absence of luminal obstruction, electron-beam computed tomography does not permit prediction of stenoses in a site-specific manner\(^{[5]}\). Consequently, it is a sensitive, but not a very specific, method for predicting obstructive coronary artery disease.

In patients presenting to the emergency room with chest pain and no initial objective signs of myocardial ischaemia, patients with a negative electron-beam computed tomography did not suffer subsequent major cardiac events, and electron-beam computed tomography had a negative predictive value in the range of 98–100\(^{[6,7]}\). In symptomatic patients undergoing coronary angiography, electron-beam computed tomography was highly predictive of subsequent events and in direct comparison performed better than coronary angiography itself in this respect\(^{[8]}\). The combination of sensitive detection of obstructive coronary artery disease and ability to predict cardiac events may render electron-beam computed tomography valuable as a non-invasive imaging technique in symptomatic patients.

Symptomatic status and/or objective evidence of inducible ischaemia are the most common basis for deciding upon the need for selective coronary angiography. In a subset of patients with indeterminate symptoms and equivocal or negative exercise stress test, further non-invasive testing by an imaging technique is usually advocated\(^{[5]}\). It was the aim of the current investigation to evaluate electron-beam computed tomography as a modality for further diagnostic stratification of patients with an intermediate likelihood of coronary artery disease who have undergone exercise stress testing, and to use direct angiography as the reference standard.

Methods

Patients

Symptomatic patients with two or more cardiovascular risk factors referred for selective coronary angiography to evaluate coronary artery disease were included in a consecutive manner if they fulfilled the following criteria: (1) no prior clinical manifestation or angiographic documentation of coronary artery disease; (2) unremarkable resting electrocardiogram (ECG) with no evidence of prior myocardial infarction, left ventricular hypertrophy, left or right bundle branch block, ST-segment shifts or changes, or repolarization abnormalities; (3) angina-like chest pain; (4) stable symptoms; (5) ability to exercise; (6) no digitalis use; (7) informed consent to undergo both an exercise stress test and electron-beam computed tomography scan on the day before coronary angiography.

There has been special interest in symptomatic patients with angiographically normal or near-normal coronary arteries at the Essen Department of Cardiology, and patients are often specifically referred there for that reason\(^{[9-11]}\). This allowed recruitment of patients with a lesser probability of coronary artery disease than usual to be seen in a catheterization laboratory. Because the electron-beam computed tomography scanner was located in a different institution, access to this test was limited to certain times in a week. Between May 1994 and May 1998, 323 patients were prospectively included in the study. Conventional cardiovascular risk factors were measured as reported previously\(^{[12]}\).

Exercise stress test

Symptom-limited exercise stress testing was done in accordance with the guidelines of the American Heart Association\(^{[13]}\). Patients exercised upright on an electrically braked cycle calibrated in Watts. A 12-lead ECG was recorded at rest and continuously during exercise. After a warm-up phase, exercise began at 50 W and was increased every 2 min in a stepwise fashion. ST depression was measured from the isoelectric PR level and was considered abnormal if horizontal or downsloping, \(\geq 0.10 \text{ mV}\), and for \(\geq 80 \text{ ms}\). Because subjects with Q waves on the resting ECG were not included, ST-segment elevation was also considered an abnormal response. In the absence of ECG changes diagnostic for ischaemia or other mandatory end-points\(^{[13]}\), exercise was terminated upon maximum exertion (that is, exhaustion, dyspnoea). Mandatory end-points were a drop in systolic blood pressure, increasing anginal pain, symptoms of central nervous system infection, clinical signs of poor perfusion, serious arrhythmias, technical difficulties related to the procedure and the patient’s request to stop\(^{[13]}\).

It was appreciated that maximum heart rate may vary considerably among individuals. However, because a subjective rating of perceived exertion was not available,
heart rates <85% of the predicted maximum were considered likely to indicate an inadequate level of exercise. The test results were classified into three groups: (1) a normal exercise stress test with maximum exertion; (2) an abnormal test with significant ECG signs of ischaemia as described above; (3) an equivocal test either due to inadequate exercise (heart rate <85% of predicted maximum) or non-diagnostic ECG changes. Withdrawal of medications prior to the test was not required. Medication use was documented.

**Electron-beam computed tomography**

Non-enhanced electron-beam computed tomography scans were performed with a Siemens Evolution scanner (Imatron Inc, South San Francisco, U.S.A.) in the single slice mode with an image acquisition time of 100 ms and a section thickness of 3 mm, as described previously[14,16]. A 26 cm² field of view was used. Patients were positioned supine and, after localization of the main pulmonary artery, 30–40 contiguous slices down to the apex of the heart were obtained with electrocardiographically gated triggering at 80% of the RR interval.

For each study, a calcium score was determined using the methods of Agatston et al[19]. This algorithm has been widely used in research and clinical studies. The calcium score is the product of the area of coronary calcification (at least four contiguous pixels with a CT density ≥ 130 Hounsfield Units) and a factor rated from 1 to 4 dictated by the maximum CT density within that lesion. Calcified lesions were encircled manually by a physician and included in the analysis only if strictly in the trajectory of the coronary arteries.

**Coronary angiography**

Coronary angiography was done with a minimum of five views of the left coronary system and two views of the right coronary artery, as described previously[14,16]. The angiograms were analysed without knowledge of the result of electron-beam computed tomography, whereas the outcome of exercise stress testing was generally known to the observer. A narrowing of the lumen diameter by 50% or more, by visual assessment, was defined as obstructive stenosis and documented for each of the major coronary arteries (left main, left anterior descending, left circumflex and right coronary artery). Off-line quantitative coronary angiography (Medis, Reiber, The Netherlands) was used to confirm categorization of lesions with borderline narrowing[10]. Patients were classified according to the presence of obstructive stenoses in one, two or three of the major coronary arteries. Patients with significant left main stem disease were automatically classified as ‘3-vessel disease’.

**Statistics**

Statistical analyses were performed using the SPSS software package (version 8.0, SPSS Inc, Chicago, Illinois). Values are reported as mean ± SD unless noted otherwise. To minimize the statistical influence of extreme values due to the non-normal distribution of calcium scores, a logₑ{(x+1)} transformation was made.

The use of age- and sex-specific percentile values of the calcium score has been reported to be superior to absolute score values in some settings[17]. Therefore, we assigned percentile values derived from a published independent cohort of asymptomatic patients[18] to the absolute score values of each patient and analysed the predictive usefulness of these percentiles in comparison with the absolute score values.

Continuous variables were compared between three groups of patients using one-way analysis of variance with a post-hoc Bonferroni test. Proportions were compared using chi-squared analysis. McNemar’s test was employed to detect significant differences in the number of patients classified correctly by exercise stress testing or electron-beam computed tomography. To analyse the ability of the electron-beam computed tomography-derived calcium score to predict angiographically obstructive coronary artery disease, a cut-point indicating a ‘positive’ score had to be chosen. We used two approaches to define this cut-point. One was to adopt cut-points established in an independent (but also largely caucasian and male) population[9]. The other was to retrospectively determine optimal cut-points in the current population by receiver-operating characteristic curve analysis. The cut-points for optimized combination of sensitivity and specificity were 80 in the independent population[10] and 67 in the current population. The cut-points yielding a sensitivity of 90% — associated lesser specificity — were 37[9] and 15, respectively. Multivariate logistic regression analysis was used to determine independent predictors of obstructive coronary artery disease. A two-tailed P value <0.05 was considered significant.

**Results**

**Patient demographics and test results**

Characteristics of the 323 study patients are given in Table 1. A normal exercise stress test was seen in 105 (32.5%) patients. One hundred and thirteen (35%) patients had a clearly positive test. In 105 (32.5%) patients, the test result was equivocal. The mean product of maximum heart rate and systolic blood pressure in all patients was 25 697 ± 6646 (median 25 725; 25th and 75th percentile, 20 085 and 31 031; range, 29 570), the mean work level achieved was 124 ± 43 W. This corresponded to a mean metabolic equivalent of 7.0 ± 2.4. Table 2 shows that patients with a normal test result achieved a higher workload and increased double product compared with patients who had an abnormal or equivocal test result. There were no differences between the groups for calcium antagonist and angiotensin-converting enzyme inhibitor use. Nineteen (17%)
patients with an abnormal exercise stress test were on beta-blocking medication compared with 38 (36%) with a normal and 32 (30.5%) with an equivocal exercise stress test ($P=0.004$). Twelve (11%) patients with an abnormal exercise stress test were on nitrate medication compared with 34 (32%) with a normal and 18 (17%) with an equivocal exercise stress test ($P<0.001$).

The mean electron-beam computed tomography-derived Agatston calcium score was 346 ± 661. The median score was 105, and the 25th and 75th percentile scores were 3 and 393, respectively. The calcium score was significantly higher in patients with an abnormal than in patients with a normal exercise stress test, as given in Table 2. Obstructive coronary artery disease was found in 179 (55%) patients, 112 (63%) of whom had multi-vessel disease (Table 3).

**Table 1 Demographics of the 323 study patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>250 (77)</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>142 (44)</td>
<td></td>
</tr>
<tr>
<td>Positive family history</td>
<td>38 (12)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (11)</td>
<td></td>
</tr>
<tr>
<td>Smoking: never</td>
<td>114 (35)</td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>128 (40)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 11</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg . dl$^{-1}$)</td>
<td>224 ± 40</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein (mg . dl$^{-1}$)</td>
<td>46 ± 18</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein (mg . dl$^{-1}$)</td>
<td>149 ± 39</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg . dl$^{-1}$)</td>
<td>176 ± 109</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg . m$^{-2}$)</td>
<td>26.3 ± 3.6</td>
<td></td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>89 (30)</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>64 (20)</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>58 (18)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>56 (17)</td>
<td></td>
</tr>
<tr>
<td>Lipid lowering agents: statins</td>
<td>51 (16)</td>
<td></td>
</tr>
<tr>
<td>others</td>
<td>9 (3)</td>
<td></td>
</tr>
</tbody>
</table>

**Prediction of obstructive coronary artery disease**

Angiographic findings in the three categories of exercise stress test results are given in Table 3. If only unequivocal exercise test results were considered, sensitivity for

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**Table 2 Exercise load and total Agatston calcium score (log$_e$-transformed) of patients with a clearly normal or abnormal or equivocal stress test**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exercise stress test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=105)</td>
</tr>
<tr>
<td>Maximum (W)</td>
<td>152 ± 44*</td>
</tr>
<tr>
<td>Metabolic equivalent</td>
<td>8.6 ± 2.5*</td>
</tr>
<tr>
<td>Double product</td>
<td>28 924 ± 5823*</td>
</tr>
<tr>
<td>Calcium score</td>
<td>254.9 ± 6343.2†</td>
</tr>
<tr>
<td>Calcium score (log$_e$-transformed)</td>
<td>3.1 ± 2.5†</td>
</tr>
</tbody>
</table>

* $P<0.001$ vs ‘abnormal’ and vs ‘equivocal’, respectively; † $P<0.05$ vs ‘abnormal’ (ANOVA, post hoc Bonferroni).

**Table 3 Exercise stress test results and angiographic documentation of obstructive coronary artery disease**

<table>
<thead>
<tr>
<th>Coronary angiography</th>
<th>Exercise stress test*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=105)</td>
</tr>
<tr>
<td>Obstructive CAD (n=179)</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>No obstructive CAD (n=144)</td>
<td>69 (66%)</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>7 (7%)</td>
</tr>
</tbody>
</table>

*The percentage of patients in parentheses refers to the exercise stress test categories, that is, within columns.

CAD=coronary artery disease.

Due to rounding of the percentage values, a sum >100% is possible.
predicting angiographically obstructive coronary artery disease
was 71%, specificity 75% and overall accuracy 73%. If all tests were considered, sensitivity was 50%,
specificity 84% and overall accuracy 65%. Only age and
total cholesterol levels were significant in multivariate
logistic regression analysis to test the additional contri-
bution of risk factors for predicting obstructive cor-
nonary artery disease versus a positive exercise test. The
odds ratio was $5.2 \cdot 10^9$ for a positive exercise test, $2.1 \cdot 10^6$ for every 10 years of higher
age, and $1.3 \cdot 10^7$ for every 25 mg . dl$^{-1}$ of higher
total cholesterol. Overall accuracy (regarding correct
classification) was 72%. Beta-blocking agents
were used by 40 (33%) of 121 patients with a false negative
(normal or equivocal) test result and by 49
(24%) of the 202 other patients ($P=0.11$). Nitrate medi-
cation was used by 30 (25%) of 121 patients with a false negative test result and by 34 (17%) of the 202 other
patients ($P=0.12$).

Table 4 demonstrates that overall accuracy was very
similar for all four calcium score cutpoints, although, as
expected, sensitivity and specificity differed somewhat.
The use of percentile values instead of absolute score
values led to a decreased ability to separate patients. The
area under the curve was $0.86 \pm 0.02$ (± SEM) for absolute score values and $0.77 \pm 0.03$ (± SEM) for per-
centile values ($P<0.001$ for difference of the areas under the curve by z-statistics) (Fig. 1).

In multivariate logistic regression analysis to test the
additional contribution of risk factors for predicting
obstructive coronary artery disease versus a positive
calculator score, only total cholesterol levels were signi-
cant. Using a calculator score cut-point $>37$, for example,
the odds ratio was $2.1 \cdot 10^3$ (1.1–39.2) for a positive calculator
score and $1.3 \cdot 10^2$ (1.1–7.1) for every 25 mg . dl$^{-1}$ of higher
total cholesterol. Overall accuracy with this model
was 82%.

When both calculator score and exercise testing were
entered into the logistic regression model, both were
significant predictors of obstructive coronary artery
disease. Total cholesterol levels were also significant,
but not age. The odds ratios remained largely identical
compared with those noted above.

**Electron-beam computed tomography and exercise testing**

Electron-beam cumputed tomography provided inde-
pendent information compared with the exercise stress
test. Table 5 shows that in patients with normal, abnor-
mal, or equivocal exercise stress test, electron-beam
computed tomography yielded similar results for the
classification of patients with coronary artery disease.
With the electron-beam computed tomography-derived
cut-points defined in an independent patient population,
approximately 80% of the patients were classified cor-
rectly, regardless of the result of the exercise stress test.

**Figure 1** Receiver-operating characteristic (ROC) curve
analysis comparing absolute calculator score values and
percentile values adopted from Sullivan et al.[19] The
area under the ROC curve was significantly greater for
absolute calculator score values than for percentile values.

Table 4 Accuracy of various cut-points of the calculator score* to identify patients
with obstructive coronary artery disease

<table>
<thead>
<tr>
<th>Coronary angiography</th>
<th>Calcium score cut-points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$&gt;80$</td>
</tr>
<tr>
<td>Obstructive CAD (n=179)</td>
<td>140</td>
</tr>
<tr>
<td>No obstructive CAD (n=144)</td>
<td>26</td>
</tr>
</tbody>
</table>

*The rationale for the specific cut-points is explained in the text.

**Figure 2** shows the ability of exercise stress test and
electron-beam computed tomography (calculator score
cut-point of 37) to separate patients according to the
presence of obstructive coronary artery disease, stratifi-
ced in terms of the result of the exercise stress test.
Electron-beam computed tomography led to significantly improved classification of patients with regard to obstructive coronary artery disease in the group with an equivocal exercise stress test. In patients with a normal exercise stress test, electron-beam computed tomography also demonstrated superior performance, but with a lower level of significance. Electron-beam computed tomography appeared to offer no advantage in patients with a positive exercise stress test.

The combination of exercise stress testing and electron-beam computed tomography in the case of a negative or equivocal exercise stress test was evaluated in the total study population as given in Table 6. To illustrate the difference achieved with combining exercise testing and electron-beam computed tomography, calculations were done using a calcium score cut-point of 37 in analogy to Fig. 2. However, the total population was included and not exercise stress test subgroups. Considering the electron-beam computed tomography result in patients with a negative or equivocal exercise stress test, 75 of 89 (84%) patients who were classified false negative on the basis of exercise testing alone were classified correctly as having obstructive coronary artery disease. Twenty-six of 121 (21.5%) patients correctly classified by the exercise test alone as having no obstructive coronary artery disease were now classified false positive. Sensitivity was increased by 42% (95% CI for parameter of binomial distribution, 35%–49.5%), and specificity was decreased by 18% (95% CI, 12%–25%). Overall, 49 (15%) more patients were classified correctly on the basis of the combined tests. It should be noted that 53 (90%) of 59 patients with 3-vessel and/or left main disease were correctly identified compared with 38 (64%) when using exercise stress testing alone.

**Discussion**

In the present investigation, exercise stress testing and electron-beam computed tomography provided independent information on the probability of obstructive coronary artery disease in symptomatic patients. The ability of electron-beam computed tomography to predict obstructive coronary artery disease was constant in patients with a normal, abnormal or equivocal exercise stress test. Because the post-test probability of disease remained intermediate in the case of an equivocal exercise stress test (‘inadequate exercise or non-diagnostic ECG-changes’), the incremental value of electron-beam computed tomography was greatest in this group of patients with a normal exercise stress test.
Computed tomography in the case of a negative or equivocal exercise stress test in the absence of an abnormal exercise stress test, who had no prior myocardial infarction and who had no resting ECG abnormalities. Another factor may have been the use of anti-ischaemic medications, but this was not different for patients with a false negative test and the other patients. It is interesting that the performance of the standard ECG criteria evaluated in the current investigation was very similar to estimates of its sensitivity was consistent with previous work-up bias.

**Table 6 Accuracy of the combination of exercise stress testing and electron-beam computed tomography in the case of a negative or equivocal exercise stress test in the total study population**

<table>
<thead>
<tr>
<th>Coronary angiography</th>
<th>Exercise stress testing and electron-beam computed tomography: calcium score cut-points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;80</td>
</tr>
<tr>
<td>Obstructive CAD (n=179)</td>
<td>157</td>
</tr>
<tr>
<td>No obstructive CAD (n=144)</td>
<td>42</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88%</td>
</tr>
<tr>
<td>Specificity</td>
<td>71%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>80%</td>
</tr>
</tbody>
</table>

Total study population = 323. Different cut-points of the calcium score yielded comparable overall accuracy. CAD = coronary artery disease.

**Exercise stress test**

In concordance with diagnostic guidelines, it is current clinical practice to perform exercise stress testing as the initial test in asymptomatic patients with an intermediate likelihood of obstructive coronary artery disease. A number of reasons can be listed in support of exercise testing as the initial test. These are most notably (1) the opportunity to obtain objective evidence of myocardial ischaemia, which is potentially treatable by revascularization, (2) the wealth of information apart from ECG changes provided by the exercise test, in particular concerning cardiorespiratory fitness and blood pressure response [13,20], and (3) the ability to evaluate the workload a patient can bear without symptoms or signs of myocardial ischaemia, which can be used to assess the short-term risk of the patient and which can be extrapolated with reasonable sureness to activities of daily life [13]. The ability of patients to exercise conveys a favourable prognosis compared with those too frail to do so [1].

Considering equivocal test results as well (which mirrors the clinical situation), a sensitivity of 50% and a specificity of 84% for predicting obstructive coronary artery disease was obtained. Sensitivity was thus in the low range of that of published results from symptomatic patients, whereas specificity was consistent with previous results [31]. This may partly be explained by the selection of patients who were all to undergo coronary angiography, even in the absence of an abnormal exercise stress test, who had no prior myocardial infarction and who had no resting ECG abnormalities. Another factor may have been the use of anti-ischaemic medications, but this was not different for patients with a false negative test and the other patients. It is interesting that the performance of the standard ECG criteria evaluated in the current investigation was very similar to estimates of its sensitivity was consistent with previous work-up bias.

**Electron-beam computed tomography**

For clinical purposes, calcification detected by electron-beam computed tomography can be considered a specific expression of underlying atherosclerotic plaque disease [25]. Compared with exercise stress testing, anatomical disease is visualized and not its functional consequences. No reliable diagnosis can be made regarding the degree of luminal narrowing which is associated with an individual calcified lesion [22]. However, the probability of obstructive coronary artery disease increases with the amount of calcification [5]. Regardless of the cut-point used to determine a ‘positive calcium score’ in the current investigation, the ability to discriminate patients with obstructive coronary artery disease did not change substantially. The overall accuracy was high enough to render age insignificant in a multivariate regression analysis evaluating independent predictors of obstructive coronary artery disease. This is consistent with the concept that the electron-beam computed tomography-derived calcium score may reflect the biological age of an individual’s coronary arteries and might thus supplant age as a parameter in risk assessment algorithms [23,24].

The strength of electron-beam computed tomography may lie in its ability to measure the overall extent of coronary atherosclerosis, which is a powerful predictor of subsequent events [25]. In symptomatic patients, electron-beam computed tomography (calcium score >100) predicted death and myocardial infarction.
independently of coronary angiography (number of major coronary arteries with obstructive disease)\(^\text{[6]}\). It is increasingly recognized that major cardiac events are mostly caused by non-obstructive or intermediate coronary lesions. Because electron-beam computed tomography visualizes calcified plaques directly, irrespective of the degree of luminal obstruction, it may be able to provide for prognostic stratification beyond information on the likelihood of obstructive coronary artery disease.

**Comparison of exercise stress testing and electron-beam computed tomography**

For direct comparisons with exercise stress testing, a cut-point of 37 was consistently used. This cut-point was derived not from the present study population but from the independent study by Rumberger et al\(^\text{[5]}\), thus avoiding an inherent bias against the exercise stress test. The exercise stress test and the electron-beam computed tomography scan provided independent information about the probability of obstructive coronary artery disease. Consistent with the only previous direct comparisons of the two methods\(^\text{[26]}\), electron-beam computed tomography was superior in predicting obstructive coronary artery disease. In multivariate regression analysis, inclusion of both exercise stress testing and calcium scores did not improve identification of obstructive coronary artery disease compared with calcium scores alone. It has been discussed above that exercise stress testing remains the standard initial test in symptomatic patients. A recent cost-effectiveness analysis comparing exercise stress testing and electron-beam computed tomography for the evaluation of chest pain in patients with low to intermediate pre-test probability of coronary artery disease did not directly examine the sensitivity and specificity of these tests for angiographic examination but used published data from independent laboratories\(^\text{[27]}\). On the basis of a Bayesian model, the authors concluded that a diagnostic pathway starting with electron-beam computed tomography instead of stress testing might provide substantial cost savings. However, this analysis did not consider the importance of evaluating exercise capacity in symptomatic patients.

Because of the high specificity of a positive exercise stress test observed in the current study (84%), it does not seem worthwhile to perform both tests in all patients. But, patients with an unchanged intermediate post-test probability of obstructive coronary artery disease might benefit from undergoing electron-beam computed tomography as an additional test. This may pertain in particular to the identification of patients with severe 3-vessel and/or left main disease, who frequently had a normal or equivocal exercise stress test.

The addition of cardiac imaging to stress testing, for example radionuclide perfusion or echocardiographic imaging, results in improved performance regarding the prediction of obstructive coronary artery disease. Such techniques were not available in the current study. Two recent reports on the direct comparison of electron-beam computed tomography and radionuclide perfusion imaging indicated superior prediction of angiographic coronary artery disease by electron-beam computed tomography compared with the modified stress test\(^\text{[25,50]}\).

**Limitations**

The study was done at a tertiary referral centre specialized in complex invasive coronary diagnostic and interventional procedures\(^\text{[9,11,14,16]}\). Among all patients referred for coronary angiography, the study population was carefully selected on the basis of clinical history, symptoms, resting ECG and medication. We believe that we were able to examine patients who might also be seen at less specialized centres or in primary care practice, but it is difficult to evaluate this aspect formally. Extrapolation of the present results to a more general patient population should be made with caution.

Withdrawal of medications prior to the exercise test was not required. The use of an exercise stress test in patients who are continuously taking their actual medications may often be able to document the maximally tolerated exercise with that regimen. For diagnostic purposes, it is usually preferable to ask patients to discontinue their anti-ischaemic medications prior to the test, but it has been acknowledged that this may not always be feasible in clinical practice\(^\text{[1]}\). Although we did not find an increased rate of false negative stress tests in patients on beta-blocking or nitrate medications, we cannot exclude that the diagnostic performance of standard ECG criteria was underestimated in our study.

**Clinical implications**

A number of extracoronary diseases can cause angina-like chest pain, most prominently aortic valve stenosis, diseases of the upper gastrointestinal system and functional cardiac complaints\(^\text{[28–30]}\). Coronary microcirculatory diseases in the absence of epicardial coronary artery disease are an additional mechanism of chest pain\(^\text{[16,31]}\). Because most of these diseases are associated with a favourable prognosis compared with coronary artery disease, it is important to establish or rule out this diagnosis with reasonable certainty. Exercise stress testing represents the standard initial non-invasive diagnostic procedure. The test allows for stratification of patients according to a high or low post-test probability of obstructive coronary artery disease. However, in many patients, the post-test probability of obstructive disease remains at an intermediate level, and some patients with severe coronary artery disease are not identified.

Electron-beam computed tomography allows for direct visualization of coronary atherosclerotic plaques. It is very sensitive for predicting obstructive coronary artery disease\(^\text{[4,5,26]}\), and in a symptomatic population predicts myocardial infarction and death short-term\(^\text{[6–7]}\).
and long-term[9]. In the current investigation electron-beam computed tomography provided independent information concerning the prediction of obstructive coronary artery disease in symptomatic patients, compared with exercise stress testing, and had incremental value in patients with an equivocal, or to a lesser degree normal, stress test. Therefore, electron-beam computed tomography scanning may be a meaningful strategy for further testing in symptomatic patients who, after exercise stress testing, are still judged to have an intermediate probability of obstructive coronary artery disease.

References


