Adjunctive value of CT coronary angiography in the diagnostic work-up of patients with typical angina pectoris

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Aims To determine the adjunctive value of CT coronary angiography (CTCA) in the diagnostic work-up of patients with typical angina pectoris.

Methods and results CTCA was performed in 62 consecutive patients (45 male, mean age 58.8 ± 7.7 years) with typical angina undergoing diagnostic work-up including exercise-ECG and conventional coronary angiography. Only patients with sinus heart rhythm and ability to breath hold for 20 s were included. Patients with initial heart rates > 70 beats/min received β-blockers. We determined the post-test likelihood ratios, to detect or exclude patients with significant (> 50% lumen diameter reduction) stenoses, of exercise-ECG and CTCA separately, and of CT performed after exercise-ECG testing. The prevalence of patients with significant coronary artery disease (CAD) was 74%. Positive and negative likelihood ratios for exercise-ECG were 2.3 [95% confidence interval (CI): 1.0–5.3] and 0.3 (95% CI: 0.2–0.7) and for CTCA 7.5 (95% CI: 2.1–27.1) and 0.0 (95% CI: 0.0–8), respectively. CTCA increased the post-test probability of significant CAD after a negative exercise-ECG from 58 to 91%, and after a positive exercise-ECG from 89 to 99%, while CT correctly identified patients without CAD (probability 0%).

Conclusion Non-invasive CTCA is a potentially useful tool, in the diagnostic work-up of patients with typical angina pectoris, both to detect and to exclude significant CAD.

KEYWORDS Imaging; Coronary artery disease; Computed tomography; Coronary angiography; Exercise-ECG test

Introduction Stress-testing is useful in selecting patients for coronary angiography and can help guide subsequent revascularization strategies. Current guidelines recommend stress-testing in the work-up of patients with stable angina and a treadmill exercise-ECG is the first-choice stress-test in the majority of patients.¹–⁴ CT coronary angiography (CTCA) is a non-invasive technique that can reliably detect significant coronary stenoses in selected patient populations.⁵–¹⁴ However, the value of CTCA in addition to exercise-ECG in the diagnostic work-up of patients with typical angina pectoris in the clinical setting is yet unknown.

We sought to establish the diagnostic value, to detect or exclude significant coronary artery disease (CAD), of exercise-ECG and CTCA, alone and in combination, in a consecutive cohort of patients with typical angina pectoris.

Methods

Study population During a 1-year period, we studied 62 (45 male, mean age 58.8 ± 7.7 years) consecutive patients who fulfilled all of the following criteria: first history of typical angina pectoris, and two specific CT criteria: sinus heart rhythm and ability to breath hold for > 20 s. Of 103 patients eligible for inclusion, 41 patients were excluded with contra-indications (known allergy, serum creatinine > 120 μmol/L, or thyroid disorders) to iodinated contrast (n = 4), baseline ECG abnormalities precluding reliable exercise-ECG interpretation ( > 1 mm rest ST-depression, complete left bundle-branch block, n = 6), and inability to perform CTCA before conventional angiography for logistic reasons (n = 23); eight patients refused to participate in the study. Patients were recruited in a community hospital where the diagnostic work-up including exercise-ECG and conventional coronary angiography (CCA) was performed. CTCA was performed in the university hospital on an outpatient basis. The study complies with the Declaration of Helsinki. The institutional review boards of both hospitals approved the study protocol and all patients gave informed consent.

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Clinical research

Imaging

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Patient preparation
Patients with a heart rate above 70 beats/min received a single oral dose of 100 mg metoprolol ≥ 45 min before the scan, unless contraindicated (e.g. overt heart failure or chronic obstructive pulmonary disease).

Scan protocol, image reconstruction, and evaluation
All patients were scanned using a second generation 16-slice CT-scanner (Sensation16 Straton®, Siemens, Forchheim, Germany). Scan parameters were: 16 × 0.75 mm collimation, rotation time 375 ms, temporal resolution 188 ms, table feed 3.0 mm/rotation, tube voltage 120 kV, and 600 mAs; tube modulation was not applied. Radiation exposure was estimated as 11.8–16.3 mSv (WinDose®, Institute of Medical Physics, Erlangen, Germany). A bolus of 100 ml contrast material (Iomeron® 400, Bracco, Milan, Italy) was injected through an arm vein (4 ml/s) using a bolus-tracking technique to initiate the CT-scan (mean scan time: 18.2 ± 1.0 s). Datasets were reconstructed using ECG gating and high image quality was generally obtained when datasets were reconstructed during the mid-to-end diastolic phase. All available ≥ 2 mm coronary branches were independently analysed by two observers, unaware of the results of CCA, using conventional post-processing techniques. Patients with at least 1 ≥ 50% stenosis were considered as having significant CAD on the CT-scan.

Quantitative coronary angiography (QCA)
All CT-scans were performed within 4 weeks of CCA. A single observer, unaware of the results of CTCA, determined the diameter of all coronary branches using a quantitative algorithm (CAAS, Pie Medical, Maastricht, The Netherlands). All ≥ 2 mm coronary branches were included for comparison with CT. Stenoses were evaluated in two orthogonal views, and classified as significant if the mean lumen included for comparison with CT. Stenoses were evaluated in two orthogonal views, and classified as significant if they had at least one significant coronary stenosis.

Diagnosis of significant CAD was based on the presence of greater than or equal to one significant stenosis as determined by QCA, which was considered as the gold standard. Agreement between CCA and CTCA was calculated using κ-statistics.

Exercise-ECG
All exercise tests were performed prior to CTCA to avoid the influence of β-blockers on the diagnostic accuracy of exercise-ECG. Exercise-ECG was performed using a cycle ergometer and a protocol starting with an initial workload of 25 W, followed by increments of 25 W every 2 min. Heart rate and blood pressure were recorded at rest and at the end of each stage of exercise. A 12-channel electrocardiogram was obtained each minute and 3-channel monitoring of cardiac rhythm was performed continuously. Exercise-ECG examinations were classified as positive where there was horizontal or downsloping ST-segment depression of ≥ 1 mm at 80 ms after the J-point occurring during or after exercise. An exercise-ECG tests in patients who did not reach the reference exercise capacity presenting with high (> 70 beats/min) heart rates. One CT-examination was classified as inconclusive due to the presence of extensive motion artifacts (mean heart rate: 84 beats/min). CCA revealed absence of significant stenoses in 26% (16/62), single vessel disease in 32% (20/62), and multi-vessel disease in 42% (26/62) of patients. Thus, the prevalence of significant CAD was 74%. The pre-test likelihood was estimated as 81 ± 17% (see the Statistical analysis section).

Diagnostic performance of exercise-ECG and CTCA
Nine exercise-ECG tests were classified as inconclusive. Sensitivity of exercise-ECG to detect significant CAD in the remaining 53 patients was 78% (95% CI: 62–89), specificity was 67% (95% CI: 34–90), and positive and negative predictive value was 89% (95% CI: 73–96) and 47% (95% CI: 28–65), respectively. The post-test likelihood of a significant CAD was 28% if the pre-test likelihood was 50%.

Statistical analysis
Descriptive statistics were used to evaluate the diagnostic performance of exercise-ECG and CTCA to detect patients with significant CAD, including sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios. These diagnostic parameters were expressed with a 95% confidence interval (CI) calculated with binomial expansion. The pre-test likelihood was estimated using the Duke Clinical Score, which includes Diamond-Forrester criteria and clinical variables that are known to have prognostic value. Post-test likelihoods after exercise-ECG and CTCA were calculated using Bayes’ theorem (post-test odds = pre-test odds × likelihood ratio). Patient characteristics between included and excluded patients were compared using unpaired, two-sided T-test (continuous variables) or Pearson χ² test (dichotomous variables).

Prevalence of significant CAD was based on the presence of greater than or equal to one significant stenosis as determined by QCA, which was considered as the gold standard. Agreement between CCA and CTCA was calculated using κ-statistics.

Results
Patient characteristics of those included and excluded from the study are shown in Table 1. There were no significant differences between the two groups. Fifty per cent (31/62) of the patients received a pre-scan β-blocker; mean heart rate during scanning was 59.3 ± 8.3 beats/min. No contra-indications to β-blockers were present in patients presenting with high (> 70 beats/min) heart rates. One CT-examination was classified as inconclusive due to the presence of extensive motion artifacts (mean heart rate: 84 beats/min). CCA revealed absence of significant stenoses in 26% (16/62), single vessel disease in 32% (20/62), and multi-vessel disease in 42% (26/62) of patients. Thus, the prevalence of significant CAD was 74%. The pre-test likelihood was estimated as 81 ± 17% (see the Statistical analysis section).

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Included patients (n = 62)</th>
<th>Excluded patients (n = 41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (± SD)</td>
<td>60.4 ± 9.3</td>
<td>59.5 ± 9.2</td>
<td>0.643</td>
</tr>
<tr>
<td>Risk factors n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>43(69)</td>
<td>27(66)</td>
<td>0.589</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>42(68)</td>
<td>24(59)</td>
<td>0.271</td>
</tr>
<tr>
<td>Smoking</td>
<td>25(40)</td>
<td>18(44)</td>
<td>0.797</td>
</tr>
<tr>
<td>Family history of premature CAD</td>
<td>23(37)</td>
<td>17(41)</td>
<td>0.728</td>
</tr>
<tr>
<td>Obese (BMI ≥ 30)</td>
<td>16(26)</td>
<td>11(27)</td>
<td>0.965</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>8(13)</td>
<td>4(10)</td>
<td>0.597</td>
</tr>
<tr>
<td>Medication n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>59(95)</td>
<td>37(90)</td>
<td>0.185</td>
</tr>
<tr>
<td>β-blocker</td>
<td>51(82)</td>
<td>34(84)</td>
<td>0.866</td>
</tr>
<tr>
<td>ACE inhibitors/AT-II antagonist</td>
<td>20(32)</td>
<td>10(24)</td>
<td>0.351</td>
</tr>
<tr>
<td>Calcium-antagonist</td>
<td>20(32)</td>
<td>14(34)</td>
<td>0.909</td>
</tr>
<tr>
<td>Nitrates (systemic)</td>
<td>18(29)</td>
<td>9(22)</td>
<td>0.385</td>
</tr>
<tr>
<td>Statins</td>
<td>43(69)</td>
<td>28(68)</td>
<td>0.773</td>
</tr>
<tr>
<td>Prevalence of significant CAD</td>
<td>46(74)</td>
<td>30(75)</td>
<td>0.755</td>
</tr>
</tbody>
</table>

BMI, body mass index. P-values < 0.05 were considered significant.

References
Sensitivity of CTCA to detect significant CAD in 61 patients (one patient was classified as inconclusive) was 100% (95% CI: 92–100), specificity was 87% (95% CI: 59–98), and positive and negative predictive value was 96% (95% CI: 85–99) and 100% (95% CI: 75–100), respectively. Agreement between CCA and CTCA on a per-patient level was high (κ-value: 0.91).

Positive and negative likelihood ratios to detect or exclude significant CAD were: 2.3 (95% CI: 1.0–5.3) and 0.3 (95% CI: 0.2–0.7) for exercise-ECG; 7.5 (95% CI: 2.1–27.1) and 0.0 (95% CI: 0.0–∞) for CTCA, respectively. Figure 1 shows the diagnostic impact on the probability of significant CAD of exercise-ECG. Figure 2 shows the diagnostic impact on the probability of significant CAD after CTCA.

**Diagnostic performance of CTCA in addition to exercise-ECG to detect significant stenoses**

The prevalence of significant CAD after a positive exercise-ECG test of 89% (with an estimated post-test likelihood of 91%) was refined by CTCA to respectively 100% after a positive CT-scan [with an estimated post-test likelihood of 99%] and 0% after a negative CT-scan [with an estimated post-test likelihood of 0% (Figure 3)]. The prevalence of significant CAD after a negative exercise-ECG test of 53% (with an estimated post-test likelihood of 58%) was refined by CTCA to respectively 90% after a positive CT-scan [with an estimated post-test likelihood of 91% (Figure 4)] and 0% after a negative CT-scan [with an estimated post-test likelihood of 0%]. The prevalence of significant CAD after CTCA in patients with an inconclusive exercise-ECG test was respectively 83% after a positive CT-scan [with an estimated post-test likelihood of 96% (Figure 5)] and 0% after a negative CT-scan [with an estimated post-test likelihood of 0%].

**Discussion**

Exercise-ECG testing is safe, inexpensive, and widely available. Current guidelines recommend documentation of exercise- or stress-induced ischaemia in patients with stable angina who are evaluated for revascularization. Patients with a positive exercise-ECG test will be further evaluated by diagnostic CCA to determine further management with percutaneous intervention, bypass surgery, or pharmacological treatment. Patients with a negative exercise-ECG require (depending on the level of clinical suspicion of the presence of CAD based upon history, physical examination, and rest-ECG) either further non-invasive diagnostic work-up, or referral for CCA, or a regular clinical follow-up on an outpatient basis.

In our study, we evaluated the diagnostic value of exercise-ECG alone, of CTCA alone, and in particular the additional value of CTCA after exercise-ECG in 62 consecutive patients with typical angina and an intermediate-to-high pre-test probability of significant CAD. We only included patients with typical symptoms of stable angina pectoris. The prevalence of significant CAD in our patient cohort was 74%, which is in line with the estimated pre-test likelihood of 81 ± 17% using clinical variables such as age, gender, symptoms, and cardiovascular risk factors. Our results show that exercise-ECG was able to correctly predict the presence or absence of significant CAD in 65% (40/62) of patients, whereas CTCA correctly classified all patients with significant CAD (n = 46), but misclassified 19% (3/16) of patients without significant CAD.

The post-test probability of significant CAD after a negative exercise-ECG test was 58%, which represents such a high diagnostic uncertainty level that further diagnostic work-up is required. In this context, CTCA proved particularly useful; a positive CTCA increased the probability of significant CAD to 91% whereas a negative CTCA decreased it to

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**Figure 1** The diagnostic impact on the probability of significant CAD of exercise-ECG.
Thus, the additional diagnostic information provided by CTCA is of particular use in patients with an intermediate likelihood of having significant CAD (e.g. patients with typical angina and a negative stress-test).

The estimated post-test probability of significant CAD after a positive exercise-ECG test was 91%. The subsequent step in such patients, where indicated, is conventional diagnostic angiography, as the high probability of significant CAD in patients with typical angina pectoris and a positive stress test makes further non-invasive diagnostic work-up unhelpful. However, despite this high probability of disease, CTCA was able to even further perfect this to a prevalence

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**Figure 2** The diagnostic impact on the probability of significant CAD of CTCA.

**Figure 3** The diagnostic impact on the probability of significant CAD of CTCA as an adjunct to exercise-ECG.

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1 Estimation using Duke clinical Score (including Diamond-Forrester criteria and prognostic clinical variables).
2 Based on conventional coronary angiography (≥1 significant coronary stenosis as determined by QCA).
3 Calculated using Bayes’ theorem (pre-test odds = post-test odds x likelihood ratio).
of 100% in case of a positive CT-scan and to 0% in case of a negative CT-scan.

The question remains what would be the role of CTCA in the diagnostic work-up of patients with a (very) high pre-test likelihood of significant CAD. According to the guidelines, the majority of patients with a high pre-test likelihood should undergo non-invasive testing, followed by diagnostic CCA to refer these patients for appropriate therapy. Some investigators suggest that these patients should immediately be referred for a diagnostic coronary angiogram, followed in the same session by percutaneous intervention, thereby obviating the need for further non-invasive diagnostic tests including CTCA. In keeping with current guidelines, such an ad hoc approach has important disadvantages when compared with a staged approach, which allows time to inform the patient about risks, benefits, and alternatives of the selected therapy as well as optimal hydration and pre-treatment with oral anti-platelet agents before coronary intervention. This immediate approach does not allow general discussion between the general cardiologist, interventional cardiologist, and cardiac surgeon to reach consensus about the most optimal treatment strategy. In addition, a single session approach may result in a considerable kidney contrast burden and associated contrast induced nephrotoxicity. Moreover, such approach may result in a high diagnostic workload with a significant burden on the availability of percutaneous interventional laboratories. In fact, the majority of patients who undergo elective percutaneous revascularization procedures in the Netherlands—as in many other European countries—are being sent to referral hospitals after a complete diagnostic work-up, including CCA in a community hospital without percutaneous intervention facilinations. The findings of our pilot study suggest that CTCA may be used as an 'intermediate' step to guide referral for diagnostic angiography followed by percutaneous intervention in the same session (patients with one- or two-vessel disease) or bypass surgery (left main or three-vessel disease). Our results also indicate that CTCA may even function as a 'gatekeeper' for diagnostic coronary angiography in patients with an intermediate-to-high likelihood of significant CAD. For these reasons, CTCA may still be of use in patients with a high pre-test likelihood of significant CAD.

We have studied a relatively small number of patients who are at high risk of having significant CAD and excluded a significant number of patients because of logistic inability to perform CTCA before the conventional angiogram. The main reason was the short interval between exercise-ECG and conventional angiography (3–7 days) which in some cases did not allow timely CT examination (e.g. no available

Figure 4 Example of CT vs. CCA in a patient with single vessel disease and a negative exercise-ECG test. Volume-rendered CT images (coloured images) provide a nice anatomical overview of a dominant right coronary artery (RCA). Maximum intensity projected (MIP) and two orthogonally curved multiplanar reconstructed (cMPR) CT images indicate the presence of a significant stenosis at the proximal RCA (arrowhead), which was confirmed on the conventional coronary angiogram (CCA).
time slots, CT maintenance, or not able to contact the patient). It is of note that these patients could have been examined by CT in a clinical setting because of the elective nature of diagnostic angiography in stable patients. Moreover, we did not find significant differences in patient characteristics between included and excluded patients (Table 1). Larger prospective studies are needed evaluating the diagnostic value of CTCA in addition to stress testing in patients with a low or intermediate pre-test likelihood of significant CAD (e.g. patients with atypical angina or non-anginal chest pain). These patients may potentially benefit more from CTCA whereas the impact of CT as 'gatekeeper' for diagnostic coronary angiography may be higher. If such studies would confirm our initial results, CTCA may become a routinely used technique in the diagnostic work-up of patients suspected of having CAD.

Limitations

We have classified stenoses with a mean lumen diameter reduction of $\geq 50\%$ as determined by QCA as 'significant'. It is known that this threshold is the best-chosen anatomical threshold that correlates with myocardial ischaemia. However, it is of note that some $\geq 50\%$ stenoses on the conventional angiogram may have been haemodynamically non-significant, and that a negative stress-test in these patients incorrectly was classified as false negative, thereby stressing that the cut-off values of anatomy and function do not always result in concordant outcomes.

CTCA has specific limitations; it is only reliable in selected patients with a slow (<70 beats/min, spontaneous or β-blocker induced) and regular heart rhythm, who are able to breath hold for at least 20 s. Furthermore, the high radiation exposure associated with CTCA [11.8–16.3 (male/female) mSv] is a matter of concern and significantly higher when compared to diagnostic conventional angiography (3–6 mSv).

Conclusions

While exercise-ECG testing provides important information that aids in the management of patients with typical angina, it is of limited diagnostic value for the detection of significant coronary disease. A combined diagnostic work-up of exercise-ECG testing and CTCA markedly improved the post-test probability of the presence or absence of significant CAD.

Conflict of interest: none declared.

References


