Cardiovascular magnetic resonance imaging and computed tomography in patients with suspected coronary artery disease

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Chapter 3

Positive predictive value of computed tomography coronary angiography in clinical practice

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ABSTRACT

Background: Several studies have investigated the diagnostic performance of computed tomography coronary angiography (CTCA) for the detection of significant coronary artery disease (CAD). These studies were performed in patients that were already referred for invasive coronary angiography (ICA) and prevalence of significant CAD was high. Although the negative predictive value of CTCA was consistently high, a wide range of positive predictive values (PPV) was reported. Thus, the PPV of CTCA in patients that undergo CTCA as part of a clinical diagnostic evaluation remains unclear. This study investigated the PPV of CTCA for the detection significant CAD of in clinical practice.

Methods: A total of 181 patients with low to intermediate pre-test probability CAD that were referred for non-invasive evaluation of chest pain underwent 64-slice CTCA. CTCA was scored per segment as normal, non-obstructive CAD or obstructive CAD (>50% diameter stenosis). All patients with obstructive CAD according to CTCA, underwent ICA. Significant CAD was defined as >50% diameter stenosis on ICA.

Results: According to CTCA, 65 (35.9%) patients had obstructive CAD. In 26 (14.4%) patients, significant CAD was found by ICA. The PPV for detection of significant CAD per patient, per vessel and per segment were 40.0% (26/65, 95% CI: 30.6-50.2%), 31.3% (36/115, 95% CI: 24.7-38.8%) and 25.5% (42/165; 95% CI: 20.3-31.4%), respectively.

Conclusions: The PPV of CTCA for detection of significant CAD in patients with low to intermediate probability CAD that are clinically referred for non-invasive evaluation of chest pain is markedly lower than generally reported.

INTRODUCTION

Multiple studies have investigated the diagnostic performance of computed tomography coronary angiography (CTCA) for the detection of significant coronary artery disease (CAD).(1-7) CTCA is a sensitive technique with excellent negative predictive value (NPV) and is therefore especially useful to exclude CAD in patients at low risk of having CAD. (8) However, a wide range of positive predictive values has been reported. In a recent large multicenter study, the positive predictive value (PPV) was only moderate (64 %). (9) This overestimation of plaque severity is predominantly caused by beam hardening artifacts originating from calcified atherosclerotic plaques.(10;11) The majority of studies were performed in patients that were already referred for invasive coronary angiography (ICA), despite a reported low to intermediate pre-test probability of CAD. Accordingly, the reported prevalence of significant CAD in these patient groups was high (58-67%, as reported in 4 meta-analyses).(12-15) However, this may not reflect clinical practice, where patients with low to intermediate probability CAD will first undergo non-invasive tests (such as CTCA). As the diagnostic performance of a test depends on the prevalence of disease in the patient population that is tested (16), the diagnostic performance of CTCA in patients not yet referred for invasive ICA remains unclear.

The aim of this study was therefore to investigate the PPV of CTCA for the detection of CAD in symptomatic patients with low to intermediate pre-test probability CAD, who were clinically referred for non-invasive evaluation of chest pain, but who were not yet referred for ICA.

MATERIALS AND METHODS

Patients and study protocol

During a 24-month period consecutive patients were prospectively recruited from the outpatient clinic of our hospital. Inclusion criteria were chest pain, low to intermediate pre-test probability CAD according to the previously described Diamond/Forrester and CASS scale (17-19) and referral for non-invasive evaluation of suspected CAD. Exclusion criteria were any prior history of CAD (prior documented myocardial ischemia, myocardial infarction, percutaneous coronary intervention or cardiac surgery), significant arrhythmia, pregnancy, renal insufficiency (serum creatinine > 110µmol/L) or known allergy to iodinated contrast agents. All patients underwent CTCA. Only patients with obstructive CAD were referred for ICA. The study protocol was approved by the local ethics committee and written informed consent was obtained.

Computed tomography coronary angiography

CTCA was performed using a 64-slice CT scanner (Sensation 64, Siemens, Erlangen, Germany). The radiation exposure was estimated using dedicated software (ImPACT, version 0.99x, St George's Hospital, London, UK). When resting heart rate was > 65 beats

per minute, 50 mg metoprolol was administered orally one hour before start of CTCA. When the heart rate persisted 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.
Data were acquired using a scan collimation of 64x0.6 with a flying z-focus (rotation time 370ms) at 900mAs and 120 kV. Injection of 100 ml non-ionic contrast agent (Ultravist300, 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 an attenuation threshold value of 150 HU. Using retrospective ECG triggering, data were 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 per coronary artery. 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 2 experienced observers, blinded to ICA 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.(20) Each segment was graded by visual assessment on a 4 point scale: normal (no stenosis); non-obstructive (0-50% diameter stenosis); obstructive (>50% diameter stenosis) and non-diagnostic (severe motion artifacts that impaired adequate image interpretation). In an intention to diagnose approach, non-diagnostic segments were regarded as positive for having obstructive CAD.
To evaluate the impact of plaque composition on PPV, all segments with obstructive CAD were divided in the following categories: calcified plaque (defined as plaque with a higher attenuation than the contrast enhanced lumen), non-calcified plaque (defined as plaque with a higher attenuation than the epicardial fat and connective tissue surrounding the vessel wall, but a lower attenuation than the contrast enhanced lumen) and mixed plaque (plaque consisting of both non-calcified and calcified plaque).

Invasive coronary angiography

Invasive coronary angiography was performed according to standard clinical protocols. An invasive cardiologist blinded to CTCA data evaluated the angiograms. The coronary arteries were subdivided according to the same model as was used for CTCA images. All segments that were estimated visually as having at least one diameter stenosis > 20%, were quantitatively assessed using quantitative coronary analysis (QCA) software (Inturis, CIVP, Philips, Best, the Netherlands). Significant CAD was defined as more than 50% diameter stenosis in two orthogonal directions.

Statistical analysis

All data are presented as mean ± standard deviation for continuous data. A true positive CTCA was defined as > 50% diameter stenosis on CTCA and significant CAD on ICA in the same patient, coronary artery or segment. PPV of CTCA for detection of significant CAD was obtained from two-by-two tables and confidence intervals were calculated in binomial expression using Wilson's approximations.(21) For each plaque category, the PPV for detection of significant CAD was determined on a per segment level. Categorical variables were compared using a Chi-square test. Statistical analysis was performed using a standard software package, SPSS version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 192 consecutive patients met the inclusion criteria. In 10 patients CTCA was not performed because of persistent heart rates above 65 beats per minute. In 1 patient CTCA was unsuccessful due to severe breathing artifacts. The remaining 181 patients were included in the analysis. The patient flow chart is shown in figure 1. Mean interval time between CTCA and ICA was 32 ± 13 days (interquartile range 22 days). Detailed patient characteristics are listed in Table 1. Mean pre-test probability according to the combined Diamond/Forrester and CASS scale was 37% ± 25% (median 27%).

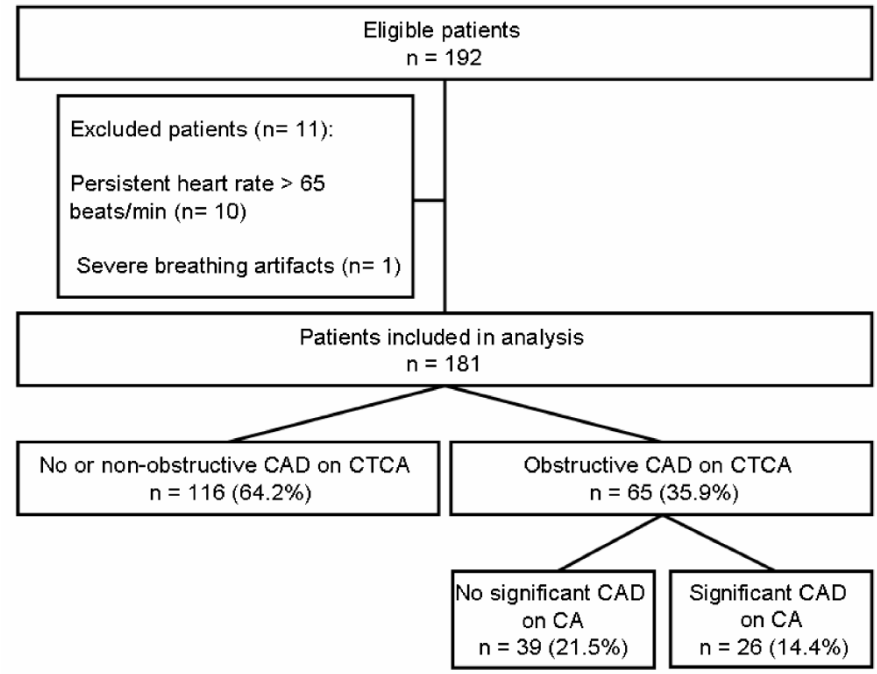

Figure 1. Patient flow chart.

Table 1. Patient characteristics.

Patients	181
Male	89 (49.2)
Mean age (yrs)*	56 ± 10
Body mass index (kg/m²)*	26 ± 4
Symptoms	
non-anginal chest pain	78 (43.1)
atypical chest pain	80 (44.2)
typical chest pain	23 (12.7)
Risk factors for CAD	
Diabetes	21 (11.6)
Hyperlipidaemia	44 (24.3)
Hypertension	68 (37.6)
Family history	68 (37.6)
Current or former smoker	49 (27.1)

Note: unless otherwise stated data are expressed as number of patients with percentages within parentheses. * Mean ± standard deviation.

Computed tomography coronary angiography

In 86 (47.4%) patients beta-blocker was administered intravenously prior to scanning. Mean heart rate at data acquisition was 59 ± 6 beats per minute. The estimated radiation exposure for CTCA was 17.0 mSv.

Of 2896 segments, 18 (0.6%) segments were non-diagnostic due to motion artifacts and subsequently were classified as having obstructive CAD. According to CTCA, 81 (44.8%) patients and 505 (69.8%) vessels did not have any CAD. Non-obstructive CAD was detected in 35 (19.4%) patients and 104 (14.4%) vessels. Sixty-five (35.9%) patients and 115 (15.9%) vessels were scored as having obstructive CAD. (See figure 2) Single vessel disease was detected in 32 (17.7%) patients, two-vessel disease in 18 (9.9%) patients, 13 (7.2%) patients had three-vessel disease and 2 (1.1%) patients had three-vessel CAD with left main disease.

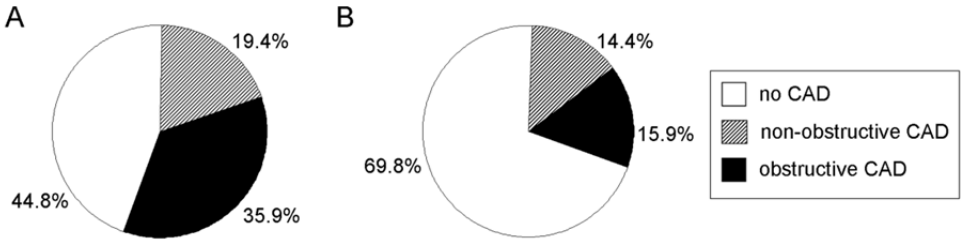

Figure 2. Prevalence of coronary artery disease (CAD) per patient (A) and per vessel (B) according to computed tomography coronary angiography.

Invasive coronary angiography

Invasive coronary angiography was performed in all 65 patients with obstructive CAD according to CTCA. No complications were observed. Significant CAD was detected in 26 (26/181, 14.4%) patients and 39 (39/724, 5.4%) vessels. Single vessel disease was found in 16 (16/181, 8.8%) patients, two-vessel disease in 7 (7/181, 3.9%) patients and three-vessel disease in 3 (3/181, 1.7%) patients.

CTCA compared to ICA

Of 65 patients with obstructive CAD on CTCA, 26 patients had significant CAD on ICA, resulting in a PPV of CTCA for detection of significant CAD of 40.0% (95% CI: 30.6-50.2%). Of 115 vessels with obstructive CAD on CTCA, 36 vessels had significant CAD on ICA, resulting in a PPV per vessel of 31.3% (95% CI: 24.7-38.8%). The PPV per segment was 25.5% (42/165; 95% CI: 20.3-31.4%). Figure 3 shows typical case examples.

Of all patients that underwent ICA, absence of significant CAD was confirmed by ICA in 142 of 145 (97.9%) vessels and 869 of 875 segments (99.3%) without obstructive CAD on CTCA. In 3 vessels (2 distal right coronary arteries, 1 mid circumflex coronary artery) significant CAD was found by ICA, whereas these vessels were falsely scored as having non-obstructive CAD by CTCA.

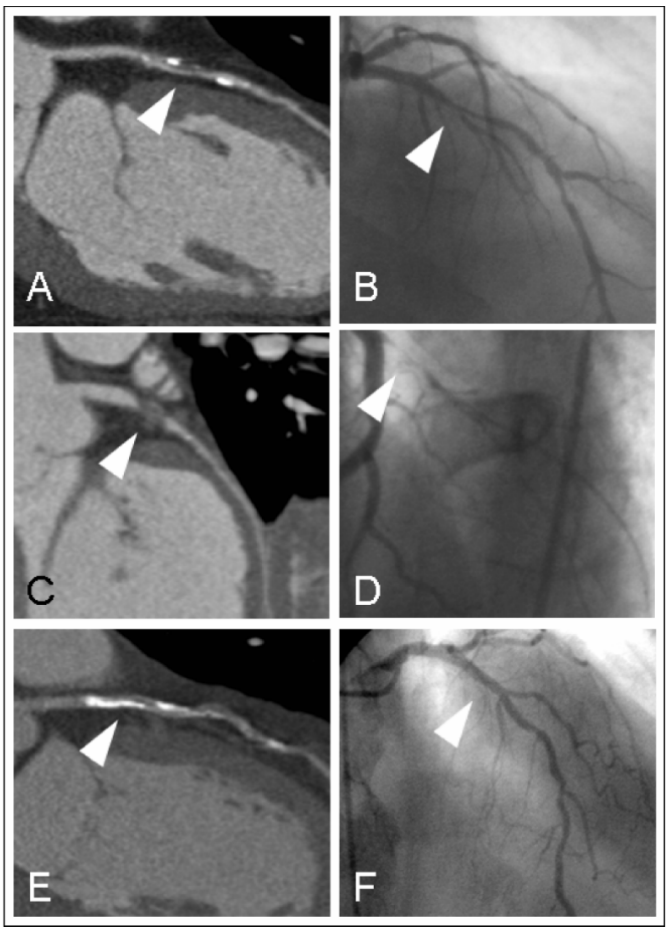

Figure 3. Case examples of curved multiplanar reconstruction images of computed tomography coronary angiography showing obstructive coronary artery disease (A, C, E) and invasive coronary angiography (B, D, F) images of the identical vessels. Obstructive mixed plaque in the proximal left anterior descending coronary artery (LAD), which was confirmed by invasive coronary angiography (A, B, arrowheads). Obstructive non-calcified plaque in circumflex coronary artery, which was confirmed by invasive coronary angiography (C, D, arrowheads). Obstructive calcified plaque in proximal LAD on computed tomography coronary angiography, which was not significant on invasive coronary angiography (E, F, arrowheads).

Plaque composition and significant CAD

According to CTCA, obstructive CAD was observed in 147 segments. The plaque composition was calcified in 46 (31.3%) segments, mixed in 89 (60.5%) segments and non-calcified in 12 (8.2%) segments. The PPV for detection of significant CAD in segments with non-calcified plaque (6/12; 50%) was significantly higher than in segments with calcified plaque (17%; 8/46), p=0.019. There was a trend towards a higher PPV in segments with non-calcified plaque compared to segments with mixed plaque (27/89; 30%), p=0.17. (See figure 4.) All patients with obstructive non-calcified plaque also had mixed or calcified plaques in 1 or more coronary vessels.

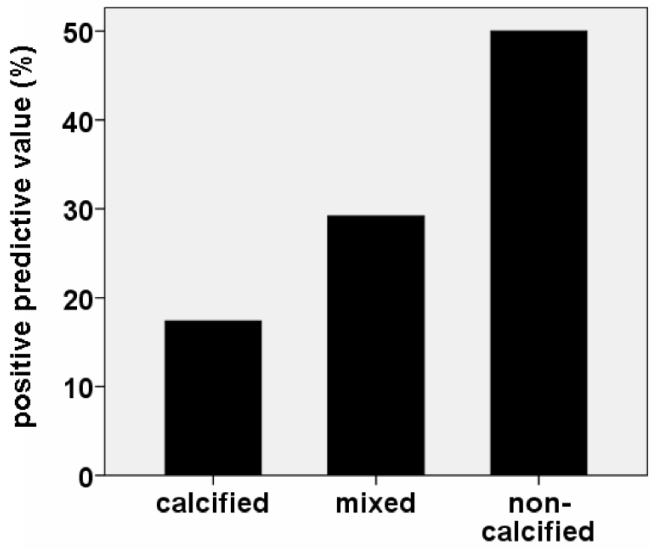

Figure 4. Positive predictive value of computed tomography coronary angiography for detection of significant coronary artery disease per plaque morphology category.

DISCUSSION

This study investigated the PPV of CTCA for detection of significant CAD in patients with low to intermediate probability CAD that were clinically referred for non-invasive evaluation of chest pain. Our main finding was that the PPV of CTCA in this patient group was markedly lower than reported so far.

Several studies have investigated the diagnostic accuracy of CTCA for detection of significant CAD. Generally, the prevalence of significant CAD in these studies was high (58-67%) and the per patient PPV was excellent, 93% (12;14;15). In a recent multicenter study that included lower risk patients, the prevalence of significant CAD, and accordingly PPV, were reduced, 25% and 64%, respectively.(9)

The low PPV of CTCA in the present study (40%) can be explained by the clinical profile of our study patients, who had low to intermediate pre-test probability of disease, but who, in contrast to previous studies, had not been already referred for ICA. Therefore, the proportion of patients with significant CAD in the present study was lower than in most other studies investigating the diagnostic performance of CTCA. Since we investigated patients that were clinically referred for non-invasive evaluation of chest pain, our findings, better reflect daily clinical practice. Other studies investigating patients undergoing CTCA for clinical indications found even lower numbers for prevalence of obstructive CAD (19-21%).(8;22) However, in these studies no data of ICA were reported.

Our data demonstrated the importance of plaque composition in this patient group, which significantly influenced the PPV of CTCA. This is in line with other studies in patients with a higher pre-test likelihood of CAD, that showed the poor agreement between CTCA and ICA for the prediction of stenosis severity in calcified plaques.(23;24) Previously, other studies have shown that the distribution of plaque composition may vary among different patient groups.(25-27) These studies showed that non-calcified plaque is less frequent in patients with stable angina than in patients presenting with acute coronary syndromes. Our study showed that, in this low to intermediate risk patient group, most obstructive lesions observed by CTCA consisted of mixed or calcified plaque and only a small proportion (8.2%) was non-calcified. Consequently, the large number of mixed and calcified plaques might additionally explain the overall low PPV found in our patients.

Clinical implications

This study showed that the PPV of CTCA for detection of significant CAD in clinical practice is low. Direct referral of all patients who have obstructive CAD on CTCA for ICA would lead to a large number of unnecessary invasive diagnostic procedures. Therefore, additional non-invasive functional testing should be performed when obstructive CAD is observed. In this way, CTCA can safely rule-out CAD in the majority of patients and in a smaller number additional functional testing may further define the hemodynamic significance of CAD. When there are no signs of myocardial ischemia, the patient should receive optimal medical therapy and no further invasive measurements will be needed. Although this strategy provides a comprehensive non-invasive assessment of coronary

anatomy and function, its prognostic value and cost-effectiveness needs to be investigated, particularly in comparison to other non-invasive modalities.

Study limitations

Only patients with obstructive CAD on CTCA underwent ICA. Due to this design, sensitivity and NPV of CTCA for detection of significant CAD could not be determined. However, many studies have consistently found high values for sensitivity and NPV. Furthermore, as the prevalence of CAD in the present study was low, it can be expected that these values will be even higher. Therefore, it was considered unethical to perform ICA in these low-risk patients with normal CTCA. An indication of the excellent NPV is provided by our finding that absence of significant CAD was confirmed by ICA in 98% of the vessels without obstructive CAD on CTCA that were visualized by ICA. Additionally, verification bias might have influenced the study results. In contrast to other studies, the standard of reference, ICA, was only performed in patients with obstructive CAD on CTCA. This is in line with clinical practice, in which CTCA acts as gatekeeper before ICA. However, observers might have overestimated stenosis severity in some cases to verify their findings against ICA. Furthermore, we only investigated the PPV of CTCA for detection of anatomical relevant CAD on ICA. We did not compare CTCA findings to functional techniques such as fractional flow reserve measurements, or to patient outcome. Finally, CTCA images were acquired using retrospective gating. Consequently, this resulted in a higher radiation dose than when prospective triggering was applied.

In conclusion, this study shows that the PPV of CTCA for detection of significant CAD in patients with low to intermediate probability CAD that are clinically referred for non-invasive evaluation of chest pain is markedly lower than generally reported.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (28).

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