Non-obstructive coronary artery disease upon multi-detector computed tomography in patients presenting with acute chest pain—Results of an intermediate term follow-up

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Aims

Multi-detector computed tomography (MDCT) has emerged as an efficient tool for detection of obstructive coronary artery disease (CAD) and assessment of patients with acute chest pain. MDCT may detect premature, non-obstructive atherosclerotic lesions which otherwise would not have been detected upon functional cardiac imaging tests. Currently, there is scarce data regarding the clinical significance of these lesions. The purpose of this study was to prospectively analyse the intermediate term outcome of patients admitted to chest pain unit (CPU) with findings of non-obstructive CAD upon MDCT.

Method and results

The study comprised 444 patients admitted to the CPU at Sheba Medical Center and underwent evaluation by MDCT for complaints of acute chest pain. Studies were classified as: normal; non-obstructive CAD (defined as any narrowing $\leq 50\%$ diameter stenosis); obstructive CAD (narrowing of $\geq 50\%$ diameter stenosis); or non-diagnostic. Patients were followed up for a minimum of 1 year and outcomes were compared between the non-obstructive ($n = 115$) and the normal ($n = 266$) MDCT groups in regard to MACE [coronary revascularization, acute coronary syndrome (ACS), and death]. Comparing the groups, those with non-obstructive CAD were older, more likely to be males, and dyslipidaemic. During an intermediate term follow-up (2.5 $\pm$ 0.4 years) MACE was equally low between the two groups (1% for both groups; $P = 0.9$).

Conclusion

Among patients evaluated by MDCT for acute chest pain, during an intermediate term follow-up, those with non-obstructive CAD had a benign clinical outcome compared with those with normal coronary arteries.

Keywords

MDCT • Coronary artery disease • Chest pain • Prognosis

Introduction

Cardiac multi-detector computed tomography (MDCT) has emerged as an excellent diagnostic modality to assess for coronary artery disease (CAD) in low- to moderate-risk patients1–3 or in patients presenting with acute chest pain in which cardiac biomarkers are negative and no other objective evidence of myocardial ischaemia exists.4

In the setting of acute chest pain, coronary MDCT can detect premature, non-obstructive, atherosclerotic plaques that may or may not be related to patient’s symptoms. Patients with evidence of atherosclerosis are often recommended to be treated in a secondary prevention manner namely lifestyle modification, aspirin and statins with the aim of significant lowering of LDL-cholesterol levels.

To date, no study has evaluated the long-term prognostic role of non-obstructive CAD with cardiac MDCT, in patients presenting with acute chest pain. The aim of the present study was to examine the prognostic significance of non-obstructive CAD.
cardiac MDCT in patients with acute chest pain by prospectively comparing the intermediate term prognosis of patients with non-obstructive CAD to patients with a normal exam.

Methods

Subjects

The study cohort consists of 444 consecutive patients who presented to the emergency room with acute chest pain and were admitted to the chest pain unit (CPU) between May 2006 and December 2007. All patients were referred for cardiac MDCT within 24 h of their admission.

Inclusion criteria for CPU admission included: (i) age above 20 years; (ii) acute chest pain that was (a) considered by the attending physician to be suggestive of cardiac origin or in order to rule out an ACS; (b) not explained by local trauma; (iii) absence of baseline ECG changes suggesting acute ischaemia or myocardial infarction; (iv) absence of elevated cardiac troponin I on admission.

Patients are monitored and observed for a minimum of 12 h followed by repeated ECG and cardiac biomarkers measurements. Each patient in the CPU is monitored by an ST-segment analyzer and evaluated by a cardiologist at the end of the observation period. Patients were hospitalized for further evaluation if one of the following was found during observation in CPU: (i) new ischaemic ECG changes; (ii) re-occurring elevated troponin levels; (iii) ST-analyzer changes suggestive of myocardial ischaemia; (iv) ongoing chest pain assumed to be ischaemic by the evaluating cardiologist. Patients free of the above symptoms were referred to cardiac MDCT (using a 64-slice scanner) or thallium myocardial perfusion scintigraphy. Patients were excluded from MDCT and referred for a perfusion scan if: (i) age >70 years; (ii) prior history of CAD (iii) weight >120 kg; (iv) absence of sinus rhythm; (v) known contra-indication to iodine contrast administration; (vi) abnormal renal function (serum creatinine ≥1.4 mg/dL); (vii) chronic therapy with metformin. All tests were interpreted by staff cardiologists and roentgenologists. Results were classified as normal coronary arteries, non-obstructive CAD, and obstructive CAD (see precise definitions below). Patients with obstructive CAD by MDCT were referred for invasive coronary angiography and treated accordingly. Patients with non-obstructive CAD received a recommendation to be treated with lipid-lowering agents (statins) with LDL-cholesterol target ≤100 mg/dL. Follow-up was performed by either outpatient clinic visit or by a telephone call after receiving informed consent from patients. Pre-specified clinical endpoints were: recurrent episodes of chest pain, repeated hospitalizations for chest pain, or ACS; coronary angiography and/or coronary revascularization, and death. For patients whose follow-up was not available, records of the Ministry of Interior were reviewed to ascertain their vital status.

Protocol of cardiac multi-detector computed tomography

All MDCT scans were performed using a 64-slice scanner (Brilliance 64, Philips Medical Systems, Cleveland, OH, USA) with retrospective ECG gating. The heart rate control was achieved by oral beta-blocker administration (propranolol 50–100 mg) 1 h prior to the scan. Intravenous beta-blocker administration (metoprolol 5–15 mg) was added if the heart rate rose >70 bpm. The first scan was acquired with prospective gating for calcium score evaluation, with scan volume starting at the lung apices and ending at the level of the diaphragm. Per protocol patients with high calcium score (Agatston score >800) were excluded from further analysis, however, none of our patients had a high calcium score. The contrast-enhanced scan was acquired with retrospective gating. A mean bolus of 80 mL (range 70–110) of non-ionic contrast medium (Iomeron) was injected into an ante-cubital vein at a flow rate of 4–6 mL/s. Scanning parameters included: voltage—120 kV (increased to 140 kV in patients weighing >100 kg); effective tube current—800 to 1235 mA; slice collimation 64 × 0.625 mm; gantry rotation time—400 ms; pitch—0.2 (reduced to 0.17 in patients weighing >100 kg). Dose modulation (full radiation dose only during 40–80% of the R–R interval) was applied whenever possible in order to decrease radiation exposure. The actual radiation dose was 6.5 mSv and dose modulation was performed in 80% of patients. Diastolic phases (70–80% of the R–R interval) were used if the heart rate rose above 70 bpm. Each vessel was reconstructed using curved multi-planar reformats (extended workspace, Philips Medical Systems, Cleveland, OH, USA). All studies were analysed and interpreted by experienced radiologists (O.G., E.K) and cardiologists (S.M.) specializing in cardiovascular imaging. As stated before, patients were divided into four groups: (i) completely normal coronary arteries with no evidence of atherosclerosis; (ii) non-obstructive CAD (coronary lesions of ≤50% luminal narrowing); (iii) obstructive CAD (luminal narrowing >50%); (iv) inconclusive test due to technical difficulties.

Statistical analysis

All data were analysed using SPSS 12 (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared using χ² tests. Student’s independent t-tests were used for comparison of continuous variables. A statistically significant difference was considered with a P-value < 0.05.

Results

Study population

The study comprised 444 consecutive patients that presented to the emergency department with acute chest pain were admitted to the CPU, and were further evaluated by MDCT. Figure 1 illustrates the distribution of patients between the two groups—266 (60%) patients had completely normal coronary arteries and 115 (26%) patients had non-obstructive CAD. Thirty-two (7%) patients had an un-interpretable scan due to technical difficulties which included breathing artefacts, arrhythmia and accelerated
heart rate, blooming artefacts due to gross coronary calcification, or body habitus. Thirty-one (7.2%) patients had obstructive CAD and per protocol were referred for invasive coronary angiography, of whom 18 (62%) underwent subsequent revascularization (17 with percutaneous intervention and 1 with bypass surgery). Thus, 381 patients with technically adequate study and non-obstructive CAD were the subject of the current analysis—266 (70%) patients revealed normal coronary arteries, and 115 (30%) obstructive CAD were the subject of the current analysis—266 (70%) patients revealed normal coronary arteries, and 115 (30%) had non-obstructive CAD.

Outcomes

Follow-up was available at a mean duration of 2.4 ± 0.4 and 2.6 ± 0.5 years in 89 and 92% of the patients in the non-obstructive group and normal group, respectively (P = 0.56). Baseline characteristics are shown in Table 1. Patients with non-obstructive were significantly older, more likely to be male, dyslipidaemic, hypertensive and with a higher C-reactive protein level. Table 2 summarizes the clinical outcomes of the two study groups of patients. Patients with non-obstructive CAD required more additional functional tests such as stress echocardiography and myocardial perfusion scintigraphy during the follow-up period (in order to exclude the possibility of CAD responsible for their acute chest pain, 33 vs. 20%, P = 0.01). Both groups had similar rates of re-admissions due to chest pain or suspected ACS. MACE rates death, ACS, and/or coronary revascularization were extremely low and similar in both groups (1.1 vs. 0.9%, P = 0.9). Since follow-up data were available in 91% of patients, we compared baseline characteristics of patients with and without follow-up and found no significant differences (data not shown).

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Non-obstructive CAD, n = 115</th>
<th>Normal MDCT, n = 266</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>53 ± 9.1</td>
<td>48 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>89 (79)</td>
<td>156 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>43 (38)</td>
<td>81 (31)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>61 (54)</td>
<td>89 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (5.3)</td>
<td>20 (7.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>37 (33)</td>
<td>57 (21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Family Hx, n (%)</td>
<td>38 (34)</td>
<td>85 (32)</td>
<td>0.69</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL ± SD)</td>
<td>6.03 ± 10.3</td>
<td>3.54 ± 4.47</td>
<td>0.026</td>
</tr>
<tr>
<td>LDL</td>
<td>117 ± 25</td>
<td>110 ± 24</td>
<td>0.031</td>
</tr>
<tr>
<td>HDL</td>
<td>41 ± 10</td>
<td>45 ± 11</td>
<td>0.005</td>
</tr>
<tr>
<td>TG</td>
<td>152 ± 92</td>
<td>126 ± 62</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 2 Clinical outcomes

<table>
<thead>
<tr>
<th>Metric</th>
<th>Non-obstructive CAD, n = 102/115</th>
<th>Normal MDCT, n = 244/266</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available follow-up (%)</td>
<td>89</td>
<td>92</td>
<td>0.54</td>
</tr>
<tr>
<td>Follow-up duration, years (mean ± SD)</td>
<td>2.4 ± 0.5</td>
<td>2.6 ± 0.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Additional tests during follow-up, n (%)</td>
<td>33 (33)</td>
<td>46 (19)</td>
<td>0.004</td>
</tr>
<tr>
<td>Recurrent chest pain, n (%)</td>
<td>27 (27)</td>
<td>58 (24)</td>
<td>0.56</td>
</tr>
<tr>
<td>Re-admission due to chest pain, n (%)</td>
<td>10 (9.9)</td>
<td>15 (6.1)</td>
<td>0.234</td>
</tr>
<tr>
<td>Re-admission due to suspected ACS, n (%)</td>
<td>2 (2)</td>
<td>5 (2.2)</td>
<td>1</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>1 (0.9)</td>
<td>2 (0.9)</td>
<td>1</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1 (0.9)</td>
<td>1 (0.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>ACS</td>
<td>0</td>
<td>2 (0.9)</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
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</tbody>
</table>
exclusion of CAD. However, when non-obstructive CAD is detected, several therapeutic and diagnostic dilemmas appear: Should these patients be further evaluated by functional tests? Should these patients be treated in a secondary prevention manner, i.e., long-term aspirin and statins? What is the morphology of these non-obstructive coronary lesions—stable or unstable, and should it influence our therapeutic strategy?

Currently in patients presenting with acute chest pain having non-obstructive coronary lesions, one can assume that some are vulnerable plaques that may lead to future acute coronary events. Our data showing a very low event rate in this population contradicts this theory as long as patients are treated in a secondary prevention manner. It should be noted that the accuracy of cardiac MDCT to morphologically detect non-obstructive vulnerable plaques is limited. We know that the likelihood of plaque rupture is based on plaque composition rather than plaque volume. Most ruptures occur in plaques containing a soft, lipid-rich core covered by a thin, inflamed fibrous cap. A thin fibrous cap is on the order of 70 μm, which is 10 times beyond the present in-plane resolution of MDCT (750 μm).

Data on the prognostic value of invasive coronary angiography detecting non-obstructive CAD are also limited. Severity of CAD as measured by left main disease and two- to three-vessel CAD involving proximal left anterior descending artery and assessed by invasive angiography correlates with worse prognosis. Yet, clinical outcome of angiographically non-significant coronary lesions with a morphology of unstable, ruptured plaques is unknown. Only a very small study by Ohlmann et al. examined this issue. In patients with non-obstructive ruptured coronary plaques (proven by intravascular ultrasound) treated conservatively, death rate was as high as 6% and MACE rate was 18%. Moreover, the FAME (Fractional Flow Reserve vs. Angiography in Multivessel Evaluation) study pointed out the inaccuracy of coronary angiography to detect haemodynamically significant lesions, where 20% of lesions assessed by angiography to be significant (diameter stenosis >70%) were found to be non-significant by fractional flow reserve (FFR). A recent study by Sarno et al., which examined the severity of lesions detected by both MDCT and coronary angiography by FFR showed the limitation of both modalities in detecting haemodynamically significant lesions.

**Study limitations**

Our study has several limitations. Complete clinical follow-up was available in 91%; however, mortality data were available for the entire study population. Moreover, baseline characteristics of patients without clinical follow-up were similar for all groups (data not shown). For all patients discharged from CPU with the diagnosis of non-obstructive CAD based on MDCT statin therapy was recommended with a target LDL level of below 100. Unfortunately we do not have data on the percentages of patients fulfilling this recommendation at follow-up. These data may potentially influence the long-term outcome especially in patients with unstable coronary plaques. Our study is observational and therefore may be biased by immeasurable factors. Moreover, our data consist of univariate analysis due to very low MACE rates in both groups (1%). This may limit the interpretation of MACE rates reported in this study.

**Conclusions**

This is one of the few studies examining the prognostic significance of non-obstructive CAD upon cardiac MDCT in patients with acute chest pain. Patients admitted to a specifically designed CPU undergoing cardiac MDCT and having non-obstructive CAD have a favourable outcome throughout a 2-year follow-up, which is comparable with those with normal coronary arteries. Larger randomized studies are required to examine secondary prevention measures in patients with non-obstructive CAD upon cardiac MDCT.

**Conflict of interest:** none declared.

**References**


Acute inflammatory aortitis: utility of hybrid imaging with positron emission tomography/computed tomography in diagnosis and follow-up

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A 63-year-old lady presented with abdominal pain, night sweats, and headache. She had a maculopapular rash, diastolic murmur, and fever. Urinalysis was positive for blood and she was treated as endocarditis. Transoesophageal echocardiography (TOE) revealed small mobile densities on the aortic leaflets (Supplementary data online, Video S1), suspicious for vegetations and moderate regurgitation. Blood cultures were negative and she continued to spike fevers with elevated inflammatory markers despite prolonged antibiotics. Erythrocyte sedimentation rate (ESR) was 135 mm/h. There was no temporal artery tenderness. Positron emission tomography/computed tomography (PET/CT), using F18 Flurodeoxyglucose (FDG 18) showed intense uptake of FDG 18 involving the ascending aorta, arch, and descending aorta to the iliac bifurcation (Panels A and B). Temporal artery biopsy revealed low-grade arteritis with mononuclear infiltrate but no giant cells (Panel C). Repeat PET/CT after high-dose steroids demonstrates dramatic resolution of FDG 18 uptake (Panel D). Repeat TOE has shown resolution of the vegetation-like structures on the aortic leaflets and progressive aortic regurgitation (Supplementary data online, Video S2). She is being maintained on prednisone and azathioprine with excellent symptomatic improvement.

Based on the American College of Rheumatology classification criteria of giant cell arteritis (GCA), this patient can be diagnosed with GCA based on age of onset > 50 years, ESR > 50 mm/h, and abnormal artery biopsy, with a sensitivity of 94% and a specificity of 91%.

FDG 18 PET/CT imaging can be very useful in such cases to aid diagnosis and monitor response to therapy. This case is a reminder that aortitis can have an acute presentation which can mimic endocarditis.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.