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## Novel imaging aspects in the management of patients with acute coronary syndromes

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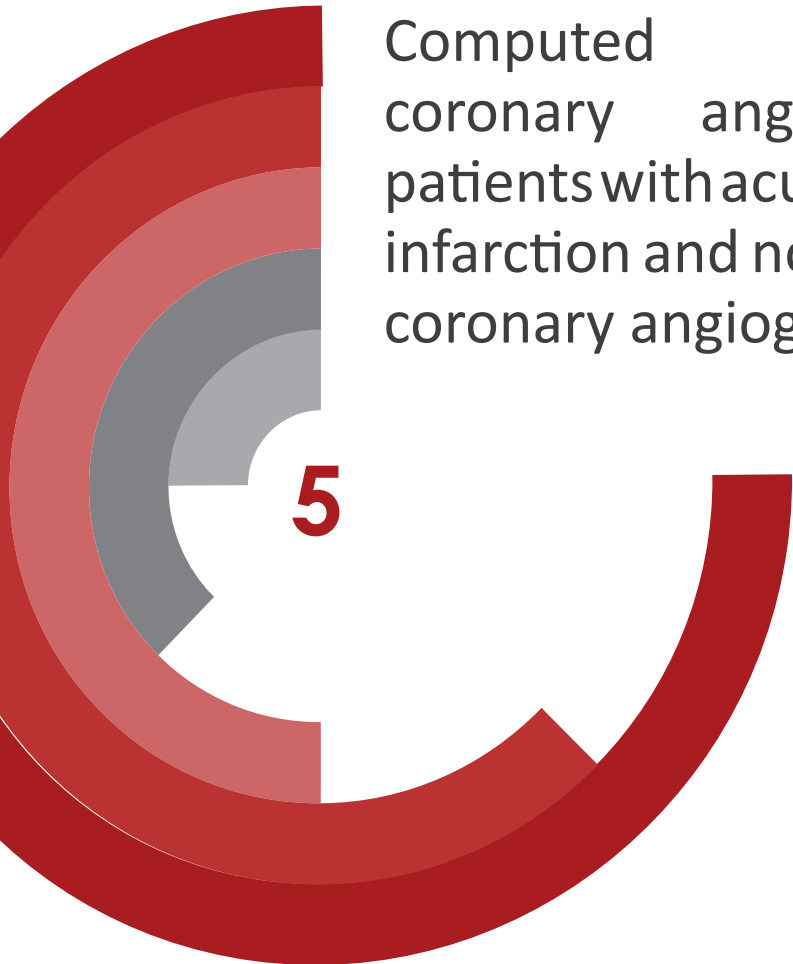
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# Computed tomography coronary angiography in patients with acute myocardial infarction and normal invasive coronary angiography

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## Abstract

**Aims:** Three to five percent of patients with AMI, have normal coronary arteries on invasive coronary angiography (ICA). The aim of this study was to assess the presence and characteristics of atherosclerotic plaques on computed tomography coronary angiography (CTCA) in this group of patients.

**Methods and Results:** Thirty patients with AMI without visible coronary plaques on ICA underwent CTCA after ICA. Echocardiography was performed in the majority of patients. Twenty-eight patients presented with NSTEMI and two with STEMI. Mean age was 60.2 years and 23/30 were women. The prevalence of risk factors of CAD was low. 452 coronary segments were analysed. Eighty percent (24/30) had normal coronary arteries and twenty percent (6/30) had coronary atherosclerosis on CTCA. In case of atherosclerosis the median number of segments with plaque per patient was one. Echocardiography was normal in 12/26 patients, 11/26 patients had only wall motion abnormalities (WMA), 2/26 patients had WMA with minimal pericardial effusion and 1 patient had only minimal pericardial effusion.

**Conclusion:** Despite a diagnosis of AMI, 80% of patients with normal ICA showed no coronary plaques on CTCA. The remaining 20% had only minimal non-obstructive atherosclerosis. The previously proposed mechanism of AMI due to rupture of a non-obstructive-, invisible on ICA-, plaque could only account for a minority (20%) of this study population. Our data suggest that most patients either had AMI caused by a mechanism not involving plaque rupture or did not have an infarction at all.

## Introduction

Acute myocardial infarction (AMI) usually results from thrombotic occlusion of a coronary artery due to a ruptured atherosclerotic plaque. However, some patients, about 3 to 5%<sup>1,2</sup> fulfil criteria for myocardial infarction but have angiographically normal coronary arteries (MINCA). The pathogenetic mechanisms that cause AMI in the patient with no visible coronary atherosclerosis on the invasive coronary angiography (ICA) are unknown. Alterations in the endothelium and/or of components in the blood promoting endothelial dysfunction and the formation of thrombotic occlusion have been suggested<sup>3, 4</sup>. According to Glagov<sup>5</sup> atherosclerotic plaques can cause outward remodelling of the coronary vessel without significant obstruction and therefore can be invisible on ICA. However, such plaques are prone to rupture and the development of an acute myocardial infarction<sup>6</sup>. If this is the case also in patients who show no visible changes on a conventional ICA, in spite of a diagnosis of myocardial infarction, remains unclear. Other proposed mechanisms are coronary dissection, embolism and vasospasm<sup>7-9</sup>.

Although ICA has been the gold standard for the diagnosis of coronary artery disease, lumenography provides merely an image of the internal arterial lumen and lacks the capability to adequately depict the vessel wall with its developing atherosclerotic plaque. Previous studies analysing serial angiograms from patients presenting with ACS have suggested that in nearly two thirds of the culprit lesions, the coronary angiogram obtained a few months before the acute event demonstrated a non significant stenosis<sup>10</sup>.

Imaging of the coronary vessels with computed tomography has been proposed as a method for qualitative imaging of vessel wall changes<sup>11</sup>. Computed tomography coronary angiography (CTCA) has a high negative predictive value, but tends to overestimate the degree of stenosis<sup>12-14</sup>. Previous studies have shown that CTCA is comparable to IVUS for classifying plaques<sup>15-17</sup>. The aim of the current study was to assess the presence and characteristics of atherosclerotic plaques on CTCA in patients with acute myocardial infarction who have a completely normal coronary angiogram on ICA. We hypothesise that plaques are present in patients with acute myocardial infarction and normal coronary arteries on ICA. This group of patients with acute myocardial infarction and angiographically normal coronary arteries is broadly recognized and described in several series. They are often described as being younger than the "classical" myocardial infarction patients and with lower burden of cardiovascular risk factors but the pathogenesis of this kind of presentation of myocardial infarction is still debatable.

## Methods

### *Study design and population*

This was a multi-center, prospective, descriptive study carried out in 3 hospitals in southeast Sweden, Linköping, Kalmar and Jönköping from November 2008 to January 2011. Patients were included at the local hospital where they presented with myocardial infarction and after they underwent an ICA. After the inclusion they were forwarded to University Hospital in Linköping for the CTCA part of the study. Inclusion criteria for the study were: myocardial infarction according to the ESC guidelines of 2007, with no visible atherosclerosis on ICA as assessed by two independent experienced operators<sup>18</sup>. The exclusion criteria were: inability to perform CTCA (contraindications to beta-blockers or nitroglycerine, allergy to contrast medium, pregnancy and permanent atrial fibrillation), renal dysfunction (creatinine clearance <60 ml/min) or risk factors for contrast induced acute kidney injury (treatment with metformin, high dose diuretics), recent major trauma, surgery or PCI, or the lack of informed consent. From November 2008 to January 2011, 30 patients were enrolled in the study. Clinical characteristics are displayed in Table 1. Twenty-eight patients presented with NSTEMI and two with STEMI. Mean age of the study population was 60.2 years (51.3 - 69.1) and 23/30 (77%) were female. 17/30 (57%) were previous or active smokers, 7/30 (23%) had hypertension, 5/30 (17%) had hypercholesterolemia and none had diabetes. There were 3/30 (10%) patients who were previously diagnosed with myocardial infarction. CTCA was performed within three days after ICA. Echocardiography was not part of the study protocol and was performed in routine clinical practice upon the discretion of the treating physician.

The study complies with the Declaration of Helsinki. Approval was obtained from the Regional Ethical Review Board in Linköping. All participants gave written informed consent.

### *Computed Tomography Coronary Angiography: image acquisition*

CTCA was performed at the University Hospital Linköping using a 64-slice or a 128-slice dual source CT scanner (Somatom Definition or Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). During CTCA acquisition non-ionic contrast medium was administered, 60-50ml, 370 mg I/ml, 5ml/sec, Jopromid. Intravenous beta-blockers were administered if not contraindicated, for optimal image quality. Additionally, nitroglycerine was administered to all patients before the scan. Strategies to reduce radiation dose, including electrocardiogram gated tube current modulation, prospective triggering and reduction of tube voltage were used whenever feasible. The following scan parameters were used: 1. for 64 slice

**Table 1.** Patient characteristics

No. of patients	N=30	
Mean age , years	60.2 ± 8.9	
Males	7 (23%)	
Females	23 (77 %)	
Risk factors		
Previous or present smoker	17 (57 %)	
Median BMI	25 (23 –28)	
Diabetes mellitus	0 (0 %)	
Hypertension	7 (23 %)	
Hyperlipidaemia	5 (17 %)	
Previous myocardial infarction	3 (10 %)	
Previous stroke	0 (0 %)	
Clinical presentation		
NSTEMI	28 (93 %)	
STEMI	2 (7 %)	
Medication		
	on admission	at discharge
Acetyl salicylic acid	4 (13 %)	28 (93 %)
Clopidogrel	1 (3 %)	22 (73 %)
Beta blocker	5 (17 %)	25 (83 %)
Calcium antagonist	1 (3 %)	2 (7 %)
ACEI/ARB	2 (7 %)	15 (50 %)
Statin	4 (13 %)	28 (93 %)
Diuretics	1 (3 %)	1 (3 %)
Laboratory results		
Creatinine on admission	75,0 (61,0 –81,3)	
Creatinine at 3 months follow -up	75,0 (64,0 –78,8)	
Peak Troponin I (ng/mL) (N=18)	1,6 (0,6 –6,3)	
Peak Troponin T (ng/mL) (N=5)	0,2 (0,1 –0,9)	
Peak hs-Troponin T (ng/L) (N=7)	873,0 (183,0 –1160,0)	
Number of patients with elevated Troponin	30 (100%)	
ApoA1	1,5 (1,3 -1,6)	
ApoB	0,9 (0,7 -1,1)	
Triglycerids	1,2 (0,8 -1,6)	
Cholesterol	5,2 (4,8 -6,1)	
HDL - cholesterol	1,6 (1,2 -2,1)	
LDL - cholesterol	3,1 (2,5 -3,9)	

The data are mean±SD, median, IQR, or numbers (%). ACEI = Angiotensin-converting enzyme inhibitor; Apo = Apolipoprotein; ARB = angiotensin receptor blocker; BMI = body mass index; IQR = interquartile range; HDL = high density lipoprotein; LDL = low density lipoprotein; NSTEMI = non ST-elevation myocardial infarction; SD = standard deviation; STEMI = ST-elevation myocardial infarction.

CT scanner: 64 x 2 slices with 0.6 mm collimation, gantry rotation time of 330 ms, tube voltage 100 or 120 mV, and effective tube current of 320 to 412 mAs; 2. for the 128-slice CT scanner: 128 x 2 slices with 0.6 mm collimation, gantry rotation time of 280 ms, tube voltage 100 or 120 mV, and effective tube current of 320 to 370 mAs.

### *Computed Tomography Coronary Angiography: image analysis*

CTCA datasets were evaluated on a remote workstation with dedicated software (QAngio CT, Medis Medical Imaging Systems, Leiden, the Netherlands)<sup>49</sup>. Evaluation

**Table 2.** Findings on ICA, echocardiography and CTCA

Invasive coronary angiography	N=30
Normal coronary arteries	30 (100)
Wall irregularities	0 (0)
Coronary stenoses	0 (0)
Coronary anomaly	2 (7 %)
Aberrant Cx origin from right sinus Valsalva	1 (3.5%)
Aberrant RCA origin from left sinus Valsalva	1 (3.5%)
 Echocardiography	 N=26
Wall motion abnormalities	11 (42 %)
Wall motion abnormalities and pericardial effusion	2 (8 %)
Pericardial effusion	1 (4 %)
 Computed tomography angiography	 N=30
Coronary arteries	
Normal coronary arteries	24 (80 %)
Coronary atherosclerosis	6 (20 %)
If atherosclerosis, number of segments with plaque	1 (1–2)
Coronary anomaly (same as on ICA)	2 (7 %)
Other findings	
Pericardial thickening or effusion	9 (30 %)
Aortic valve calcification	2 (7 %)
Aortic calcifications	1 (3 %)
Aorta ascendens dilatation	1 (3 %)
Hiatal hernia	1 (3 %)
Liver cysts and post-infectious lung findings	1 (3 %)
Lung fibrosis	1 (3 %)
COPD	1 (3 %)
Nonspecific lung findings	2 (7 %)
Vertebral compression	1 (3 %)

The data are median, IQR, or numbers (%). IQR = interquartile range, ICA= invasive coronary angiography, CTCA: computed tomography coronary angiography

was performed side by side in consensus by two experienced observers blinded to baseline patient characteristics and ICA results. Lumen and plaque analysis were performed at a predefined window and level setting (window 900, level 250 Hounsfield units)<sup>20</sup>. If considered necessary, display settings were manipulated in order to achieve optimal discrimination of vessel lumen and plaque components and minimize blooming artifacts of calcified plaques. Coronary segments were visually scored for the presence of plaques. Seventeen segments were differentiated, according to a modified American Heart Association classification<sup>21</sup>. Tissue structures >1 mm<sup>2</sup> either within the coronary artery lumen or adjacent to the coronary artery lumen which could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen, were defined as coronary plaques. Degree of stenosis of atherosclerotic lesions was quantified by visual estimation. Plaques with ≥50% luminal narrowing were classified as obstructive. Plaques were classified according to their composition into three types: 1. noncalcified plaque (plaques with lower density compared to contrast-enhanced lumen), 2. calcified plaque (plaques with high density structures compared to contrast-enhanced lumen), or 3. mixed plaque (noncalcified and calcified elements in single plaque). In addition, thickening of the pericardium and/or the presence of pericardial effusion was evaluated<sup>22</sup>.

#### *Troponin analysis*

Three different troponin assay methods were used during the course of the study according to local routines. Troponin I (ULN: <0,04 µg/L), Troponin T (ULN: 0,01 µg/L) and hs-Troponin T (ULN: 15 ng/L).

#### *Statistical analysis*

Continuous variables are presented as mean±SD when normally distributed and as medians with interquartile range (IQR) when skewed. Categorical variables are presented as numbers and percentages. Statistical analyses were performed using SPSS version 20 (Chicago, IL).

## **Results**

### *Clinical*

Troponin levels of all patients were elevated (Table 1). Troponin I was used in 18 patients with mean peak value 1.6 µg/mL (IQR 0.6–6.3 µg/mL). Troponin T was used in 5 patients with mean peak value 0.2 µg/mL (IQR 0.1–0.9 µg/mL). hs-Troponin T was used in 7 patients with mean peak value 873.0 ng/L (183.0–1160.0 ng/L). ICA showed no atherosclerosis in all patients (Table 2). None of the patients had atrial



fibrillation/flutter or other type of supraventricular or ventricular tachycardia at presentation or during hospitalization.

#### *Computed Tomography Coronary Angiography*

The CTCA was performed a median of 3 days after ICA. A total number of 452 segments were analyzed. All coronary artery segments were of diagnostic image quality. A total of 24 patients had normal coronary arteries, and 6 patients had coronary atherosclerosis. In case of atherosclerosis, the median number of segments with plaque per patient was one. On CTCA thickening of pericardium or minimal pericardial effusion was present in 9 patients. Additional findings included coronary anomalies, aortic calcifications and dilatation, hiatus hernia and lung disorders (Table 2).

#### *Echocardiography*

Echocardiography was performed in 26 patients during hospitalization according to local routines. The echocardiographical examinations were reviewed once again during the analysis of study data but not based on a predefined protocol. A total of 12 patients had completely normal echocardiography results (Table 2). Eleven patients had only wall motion abnormalities, two patients had wall motion abnormalities with minimal pericardial effusion and one patient had only minimal pericardial effusion. Among patients with wall motion abnormalities there were three patients with wall motion abnormalities that could fit a takotsubo pattern (apical ballooning), one of these patients also had minimal pericardial effusion.

#### *Pharmacological treatment*

At the time of discharge from the hospital the majority of patients had been treated with acetyl salicylic acid, statin, beta-blocker and clopidogrel. Half of the patients were discharged with ACE-inhibitor or ARB. At the time of admission only a small percentage of patients had any medication (Table 1).

## **Discussion**

In opposition to our hypothesis and previous study findings<sup>23</sup>, we found that the majority of our patients (80%), who were diagnosed with AMI without visible atherosclerosis on a routine invasive coronary angiography, had totally normal coronary arteries on CTCA as well. The remaining 20% of patients had only minimal, one-segment, non-obstructive atherosclerosis. It appears unlikely that eccentrically remodelled atherosclerotic plaques that were invisible in ICA caused an AMI in

our patients since these plaques should be visible on CTCA<sup>23</sup>. The limited extent of atherosclerosis found in the remaining 20% of patients makes the plaque hypothesis less likely even in this subgroup.

In our population the majority of patients (27/30) were diagnosed with a first time myocardial infarction. The mean age was 60.2 years which is in accordance with previously observed age for first time AMI<sup>24, 25</sup>. The prevalence of risk factors was however lower from what was observed in large epidemiological studies<sup>18</sup> where the prevalence of diabetes, hypertension and hyperlipidaemia was 18.5%, 39.0% and 90% respectively. In our small study the prevalence was 0% for diabetes, 23% for hypertension and 17% for hyperlipidaemia. Most patients were women, 77% (23/30), which is in accordance with previous analyses where female sex was the strongest predictor of insignificant CAD in patients with NSTEMI<sup>26</sup>. The most frequent cause of AMI in similar female populations with non-obstructive CAD was previously found to be plaque rupture and ulceration<sup>27</sup>. However 80% of our population had no atherosclerosis at all (either on ICA or on CTCA), leaving mechanisms like vasospasm, dissection, embolism and impaired coagulation and fibrinolysis as possible causes of AMI. Even if these patients fulfilled diagnostic criteria for myocardial infarction, alternative explanations for chest pain and positive biomarkers as in myocarditis may have been overlooked. It has been shown before that up to 50% of patients with raised troponin, and unobstructed coronary arteries had myocarditis as diagnosed by cardiac MRI.<sup>28</sup>

Echocardiography was performed in the majority of patients (26/30). Fifty per cent of them (13/26) showed wall motion abnormalities (WMA), a finding that is compatible with a diagnosis of AMI but other conditions, like myocarditis, can have similar WMA. Among the patients with wall motion abnormalities there were 3 patients where apical hypokinesia was distributed over several coronary perfusion territories that could support the diagnosis of takotsubo cardiomyopathy. Minimal pericardial effusion was found in 3 patients, a finding that is not specific but it could be a sign of perimyocarditis.

Most patients were prescribed acetyl salicylic acid (93%) and a great proportion of them were sent home with dual antiplatelet therapy (73%), beta-blocker (83%) and statin (93%), thus being treated as “classical” AMI patients. We do know however, that patients with AMI and insignificant coronary atherosclerosis have a lower incidence of adverse outcomes compared with patients with significant coronary artery disease<sup>26</sup>. With their lower burden of risk factors in mind, such extensive medication may be inappropriate.

The important implications a diagnosis of acute myocardial infarction can have

for the psychological well-being of the patient<sup>29, 30</sup> for classification of risk in health insurance and the consequences for society because of sick leave, pension- and insurance claims<sup>31</sup>, underscore the need for using additional imaging such as MRI in this group of patients.

In a recent study<sup>32</sup> where 152 patients with MINCA underwent cardiac MRI, the findings were normal in two thirds of the patients, 7% had signs of myocarditis and about 20% signs of myocardial necrosis. Amongst patients with normal MRI, 32% had typical clinical signs and symptom of Takotsubo cardiomyopathy and reversible wall motion abnormalities. Interestingly, the initial diagnosis of AMI was changed in two thirds of the patients after the MRI examination. These findings suggest that a significant part of this population actually has other diagnoses than AMI and more extensive evaluation than just coronary angiography is needed.

### *Study limitations*

During the course of the study the three centers used different troponin assay methods excluding comparisons of the level of troponin rise. Another limitation of the study is that echocardiography was not part of the study protocol and it was left to the treating physician to decide if an echocardiographical examination was necessary and when to perform it. Though we finally had access to echocardiography in the majority of patients, the content of the examinations and the parameter analysis was not predefined.

### *Conclusions*

Despite a diagnosis of AMI, based on ESC guideline criteria, the majority of patients with a completely normal ICA showed no coronary plaques on CTCA. A few patients had only minimal non-obstructive atherosclerosis. Our data suggest that most patients either had AMI caused by a mechanism not involving plaque rupture or did not have an infarction at all. Having in mind what consequences a diagnosis of AMI confers to the patient it is reasonable to extend the diagnostic evaluation of these patients to cardiac MRI for excluding myocarditis and/or intravascular imaging (optical coherence tomography or intravascular ultrasound) to provide information about some mechanisms of coronary damage (i.e. dissection).

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