Original Research Article

Coronary computed tomography angiography in patients with myocardial infarction and non-obstructed coronary arteries

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Abstract

Background: Cardiovascular disease (CVD) is the number one cause of death worldwide. In India almost 30,000 people suffer an acute myocardial infarction (AMI) each year and, despite the greatly improved survival after AMI, CVD remains the leading cause of death among women and men. During the last decade, there has been increasing awareness of the significant minority of patients with acute myocardial infarction, for whom invasive coronary angiography (ICA) does not show any coronary artery stenoses. This condition is called myocardial infarction and non-obstructed coronary arteries (MINOCA) and is still incompletely understood.

Aim of the study: To investigate whether patients with MINOCA had a greater coronary plaque burden determined by coronary CTA than a control group matched by age and gender.

Materials and methods: Totally 100 patients were included in the study Patients presenting to the department of cardiology, SRM Medical College Hospital and Research Institute Kattangulathur, Kanchipuram District, Chennai with an ACS between January 2018 to May 2019. In the first step, patients with MINOCA were screened for the SMINC study Patients were eligible to take part in the study if they were between 35 and 70 years old, fulfilled the criteria for acute myocardial infarction (AMI) according to the universal definition of AMI and underwent ICA showing no or minimal signs

of atherosclerosis (defined as the presence of plaque discernible on ICA, but no stenosis exceeding 30% by visual estimation). All patients also underwent cardiovascular magnetic resonance (CMR) imaging at a median of 12 days after hospital admission.

Results: MINOCA patients did not have more CAD than healthy controls, matched by age and gender. A large proportion of MINOCA patients had no signs of CAD at coronary CTA.

Conclusion: Thus, MINOCA should not be considered a definitive diagnosis, but rather a working diagnosis, warranting additional diagnostic evaluation. Myocarditis is one of the conditions that may manifest itself as MINOCA. Findings of the SMINC study, where myocarditis was excluded by CMR, suggest that TS is an important cause of MINOCA. Other potential causes include CAD with rupture of a non-stenotic lesion, coronary artery spasm, thrombotic disorders, and microvascular dysfunction.

Key words

MINCA- Myocardial infarction and normal coronary arteries, MINOCA Myocardial infarction and non-obstructed coronary arteries, SMINC -Stockholm Myocardial Infarction with Normal Coronaries, AMI - Acute myocardial infarction.

Introduction

Cardiovascular disease (CVD) is the number one cause of death globally. According to the World Health Organization (WHO) more than 17 million people died from CVD in 2012, representing approximately one-third of all global deaths. An estimated 7.5 million of these deaths were due to coronary heart disease. In a significant minority of patients with AMI, invasive coronary angiography (ICA) shows no significant stenoses of the coronary arteries [1]. The condition is called myocardial infarction with non-obstructed coronary arteries (MINOCA) and is still incompletely understood. The studies of this thesis have been conceived and realized in a setting of rapid technological advancements and a constantly expanding field of knowledge [2]. Important advances in computed tomography (CT) technology have enabled the safe and accurate non-invasive imaging of the heart and the coronary arteries. There has been an increasing awareness of MINOCA, for which there are currently no therapeutic guidelines. Another condition that has gained increasing attention during the last decade and for which underlying mechanisms are largely unknown is the Takotsubo syndrome (TS), also referred to as stress-induced cardiomyopathy or the "broken heart syndrome" [3]. Coronary CTA has very good accuracy for diagnosing stenoses of the coronary arteries, compared to ICA. In particular, an excellent negative predictive value has been demonstrated in several meta-analyses. Coronary CTA has proven highly sensitive in detecting atherosclerotic plaques in the proximal segments of the coronary arteries, as compared to intravascular ultrasound [4]. A histopathologic study showed that coronary CTA detected all advanced plaques, but missed many of the very early lesions (Stary I-II). In contrast to ICA, coronary CTA not only shows the lumen of the coronary arteries, but also the vessel wall and what lies beyond it [5]. Coronary CTA thus allows for the detection and characterization of coronary atherosclerotic plaques even when they do not give rise to stenoses and whether they are calcified or not. Accordingly, coronary CTA makes it possible to assess atherosclerotic plaques undetected by ICA. The atherosclerotic process is complex and involves a number of local and systemic factors, including local hemodynamics, endothelial dysfunction, hyperlipidemia and widespread inflammation Development of an atherosclerotic lesion is a gradual process [6]. The earliest imaging sign is diffuse intimal thickening, which may later progress to a localized atheroma with a fibrous cap. If the lipid core enlarges and the fibrous cap thins, the lesion is called a 3 thin-cap fibroatheroma. This plaque phenotype is associated with an increased risk of plaque

rupture [7]. At a later stage, increasing calcification leads to the formation of a fibrocalcific plaque, which is considered to be more stable. Even though these plaques rarely cause thrombosis and acute coronary syndromes they may cause chronic ischemic symptoms due to gradual lumen narrowing [8].

Materials and methods

Totally 100 patients were included in the study Patients presenting to the department of cardiology, SRM Medical College Hospital and Research Institute, Kattangulathur, Kanchipuram District, Chennai with an ACS between January 2018 to May 2019. In the first step, patients with MINOCA were screened for the SMINC study Patients were eligible to take part in the study if they were between 35 and 70 years old, fulfilled the criteria for acute myocardial infarction (AMI) according to the universal definition of AMI and underwent ICA showing no or minimal signs of atherosclerosis (defined as the presence of plaque discernible on ICA, but no stenosis exceeding 30% by visual estimation). All patients also underwent cardiovascular magnetic resonance (CMR) imaging at a median of 12 days after hospital admission. Exclusion criteria were myocarditis (based on CMR findings or clinical diagnosis), a clinical diagnosis of pulmonary embolism, non-sinus rhythm on admission, pacemaker use, and a patient history of structural or coronary heart disease, chronic obstructive lung disease or renal disease. After patient inclusion, the coronary angiograms, as well as the clinical AMI diagnoses, were re-evaluated by an additional independent investigator. A control group, matched by age and gender, was recruited Randomly selected persons of matching age and gender to MINOCA. Subjects who were willing to participate and who had no known CVD underwent an exercise stress test. If the test was normal they were invited to take part in the study. In the second step, MINOCA patients and controls of the SMINC study were recruited to the coronary CTA substudy. Additional exclusion criteria for the coronary CTA study were age under 45, an estimated glomerular filtration rate (GFR) < 50 ml/min/1.73 m^2 (based on serum creatinine), previous adverse reaction to an iodine-based contrast agent and an irregular heart rate (jeopardizing the diagnostic quality of the CT scan).

Coronary computed tomography angiography [9, 10]

Examinations were performed on a 64-slice computed tomography scanner (Light Speed VCT XT; GE Healthcare, Milwaukee, WI, USA). A prospectively ECG-triggered scan protocol was used: detector configuration 64 x 0.625 mm, rotation time 350 ms (temporal resolution 175 ms), tube potential 120 kVp, tube current 450-650 mA (according to patient size). The scans were performed in diastole, in general at 70-75% of the RR interval, with 0-200 ms padding (depending on heart rate and variability). Two patients, however, were examined using a retrospectively ECG-gated scan protocol (dose modulation, 100 kVp, 200-450 mA), as a slightly irregular heart rate might otherwise have compromised image quality. The intravenous contrast medium (CM) used was the iso-osmolar iodixanol 320 mg I/mL.

Statistical analyses

Student's t-test (for normally distributed variables) and the Mann-Whitney U-test (in the case of non-normal distribution) were used in order to test differences between two independent groups. The Pearson test (for normally distributed variables) or the Spearman test (in the case of non-normal distribution) were used to test the correlation between continuous variables. The 5% level of significance was considered (two-tailed $p<0.05$).

Results

Baseline characteristics were similar in MINOCA patients and controls, apart from current smoking and treated hypertension, which was more common in the MINOCA group (**Table – 1**). At presentation, 50 MINOCA patients had no signs of heart failure (Killip class 1) and only one had heart failure (Killip class 2).

Signs of acute ischemia (ST-T changes or left bundle branch block) on admission ECG were present in 31 (54%) out of whom 10 had ST elevations. The median (interquartile range) peak troponin level was 18 (7-43) times the upper limit of normal. Myocardial infarction was detected by CMR in 11 (19%) patients. The criteria for TS were fulfilled in 15 (26%).

Table – 1: Clinical characteristics of the study group (MINOCA and controls).

	MINOCA patients	**Controls**	***P***
	n=50	**n=50**	
Age (years)	60 ± 5	61 ± 6	*ns*
Female	42 (74%)	39 (67%)	*ns*
Smoking habits			0.04
Never smoked	29 (52%)	33 (57%)	*ns*
Previous smoker	17 (30%)	23 (40%)	*ns*
Current smoker	10 (18%)	2 (3%)	*ns*
Family history of CAD	16 (28%)	14 (24%)	*ns*
BMI (kg/m^2)	25.8 ± 3	25.8 ± 3	*ns*
Diabetes mellitus*	1 (2%)	0 (0%)	*ns*
Treated hypertension	19 (33%)	6 (10%)	0.003
Treated hyperlipidemia	8 (14%)	3 (5%)	*ns*
SBP (mm Hg)	144 (129-161)	129 (115-140)	<0.001
GFR ($ml/min/1.73m^2$)	77.9 ± 12	78.1 ± 13	*ns*
FRS			*ns*
low	22 (39%)	31 (53%)	*ns*
intermediate	22 (39%)	18 (31%)	*ns*
high	13 (23%)	9 (16%)	*ns*

Table – 2: Coronary CTA plaque burden per segment.

		MINOCA patients 765 segments	**Controls 781 segments**	***P***
Severity of CAD	No CAD	684 (89%)	687 (88%)	<0.01*
	Stenosis <20%	68 (9%)	58 (7%)	
	Stenosis 20-50%	13 (2%)	35 (4%)	
	Stenosis ≥50%	0 (0%)	1 (0.1%)	
Plaque size	No CAD	684 (89%)	687 (88%)	0.04*
	Small	41 (5%)	31 (4%)	
	Medium	24 (3%)	29 (4%)	
	Large	16 (2%)	34 (4%)	
Plaque composition	No CAD	684 (89%)	687 (88%)	0.04*
	Non-calcified plaque	10 (1%)	10 (1%)	
	Mixed plaque	10 (1%)	28 (4%)	
	Calcified plaque	61 (8%)	56 (7%)	

On a per-patient level, there were no statistically significant differences in severity or extent of CAD (**Table – 2**). Twenty-four (42%) MINOCA patients and 25 (43%) controls had no signs of CAD. When analyzing the data on a per segment level, however, there were statistically significant differences regarding the degree of stenosis, plaque size, and plaque composition. Compared

to controls, MINOCA patients had fewer segments with stenosis ≥20%. They also had fewer large and mixed type plaques. The CAC scores within each group were diverse, but no significant differences were found between the groups. There were no differences regarding coronary CTA plaque burden when subgroups of MINOCA patients were compared with controls (MINOCA patients with AMI detected by CMR, with ST elevations or with TS).

Table – 3: Comparison between groups with and without CAD at coronary CTA (clinically healthy subjects).

	No CAD	**CAD**	***P***
	n=25	**n=25**	
RHI	2.2 (1.4-4.9)	2.1 (1.4-3.6)	*ns*
IMT (mm)	0.70 (0.53-0.99)	0.71 (0.49-0.99)	*ns*
CAC	0 (0-4)	36 (0-1882)	<0.001

Table – 4: Myocardial bridging in MINOCA and TS patients and in matched controls.

	MINOCA patients	**TS subgroup**	**Control group**	***P***
	n=50	**n=50**	**n=50**	
MB (coronary CTA)	28 (49%)	18 (53%)	26 (45%)	*ns*
Type of MB				*ns*
Partial encasement	11 (19%)	12 (13%)	10 (17%)	
Full encasement	17 (30%)	6 (40%)	16 (28%)	
Location of MB				*ns*
Proximal LAD	1 (2%)	1 (7%)	0	
Mid LAD	23 (40%)	7 (47%)	20 (34%)	
Distal LAD	4 (7%)	0 (0%)	6 (10%)	
Length of MB (mm)	14.5 (2.0-51.0)	6.03	13.5 (3.8-45.0)	*ns*
Thickness of MB (mm)*	0 (0-4.8)	0 (0-2.0)	0 (0-5.0)	*ns*

When comparing the groups with and without evidence of CAD at coronary CTA, no statistically significant differences were found concerning RHI or IMT (**Table – 3**). Nor was there any correlation between the number of diseased segments on coronary CTA and RHI (r_s=0.13) or IMT (r_s=0.098). Not surprisingly, there was a statistically significant difference in CAC score when comparing the groups with and without CAD demonstrated by coronary CTA (p<0.001). Similarly, there was a strong correlation between the CAC score and the number of diseased coronary segments (r_s=0.86, p<0.001).

Table - 4 shows the prevalence, type and location of MB in the different study groups. There were no statistically significant differences between MINOCA patients or the TS subgroup and the control group regarding the prevalence or type of MB. Nor were there any differences between the groups regarding the location, the length or the thickness of MB. Nine MINOCA patients had no signs of CAD or MB. Out of these 9 patients, 3 were diagnosed with TS.

Discussion

Coronary plaque burden in patients with MINOCA, with a control group matched by age and gender for comparison. We aimed to find out whether MINOCA patients had more CAD than controls, which might indicate that CAD is an underlying mechanism of MINOCA [11]. Instead, we found a similar prevalence of CAD in patients

with MINOCA and controls. In addition, a large proportion of MINOCA patients (42%) did not have any signs of CAD at coronary CTA, which strongly suggests there are other underlying causes for a significant number of MINOCA patients. This finding was further supported by the fact that MINOCA patients had a lower rate of large size and mixed type coronary artery plaques; plaque characteristics that have been shown to imply a more vulnerable plaque type, more prone to rupture [12]. Coronary CTA has proven to be highly sensitive for detecting atherosclerotic plaques of the coronary arteries Still, there are limitations to its spatial resolution, which makes it uncertain to assess very small plaques, in particular, is located distally in the coronary arteries [13]. Hence, early CAD, with subtle changes of the vessel wall, as well as distal lesions might remain undetected by coronary CTA. In this thesis, a semi-quantitative method that relied on visual assessment was used for coronary CTA plaque analysis. It could be debated whether an automated, non-user dependent method would have been more reliable [14]. There were however no robust and validated automated methods available when this study was conducted. In contrast, semi-quantitative methods for plaque assessment have been described in several studies, demonstrating small inter- and intraobserver variability [15]. In a recent study, an automated coronary plaque quantification algorithm was compared to expert and non-expert semi-automatic plaque assessment, with intravascular ultrasound as the gold standard. The performance of the fully automated method was good and comparable to non-expert readers but inferior to expert readers. There was a high agreement between expert readings and intravascular ultrasound measurements for all parameters analyzed [16]. Only segments with sufficient CTA and intravascular ultrasound image quality were included in the study and performance of an automated method in the real world scenario with motion, calcifications and other artefacts still need to be established. Substantial efforts have been made to search for imaging markers of plaque instability that might allow us to identify vulnerable plaques before they rupture and thereby possibly prevent plaque rupture and AMI or sudden death [17]. Pathologic studies have identified the thin- cap fibroatheroma as a vulnerable plaque type with prognostic implications. Studies using intravascular ultrasound and optical coherence tomography have reported that a large necrotic core, a thin fibrous cap, and positive vascular remodeling are signs of plaque instability [18]. Several coronary CTA plaque characteristics have been associated with a vulnerable plaque type: positive vascular remodeling, low-attenuation plaque (<30 HU), large plaque area and non-calcified or mixed plaque types [19]. There are several limitations when attempting to identify vulnerable plaques by coronary CTA. Examinations were performed by dedicated radiographers using a 64-detector scanner, in a center with several years' experience of coronary CTA. Evaluation of coronary CTA scans was performed by two experienced readers, separately and in consensus. Our findings partly contradict the findings of a previous study in which only 16% of MINOCA patients did not have signs of CAD when examined with coronary CTA [20]. However, this difference can probably be explained by the difference in the inclusion criteria. In the previous study, patients with <50% angiographic diameter stenosis were included, whereas in our study a more rigorous definition was used, including only patients with no or minimal signs of atherosclerosis (<30%). Patients with plaque disruption had a higher degree of stenosis (median degree of stenosis 40%) compared to patients without plaque disruption [21]. Pathology studies of acute coronary death have demonstrated that the average culprit lesion has a diameter stenosis of approximately 50%, and rarely below 3 %. This further supports our conclusion that, for the present study group, CAD is most likely not an important cause of MINOCA [22].

Conclusion

Thus, MINOCA should not be considered a definitive diagnosis, but rather a working

diagnosis, warranting additional diagnostic evaluation. Myocarditis is one of the conditions that may manifest itself as MINOCA. Findings of the SMINC study, where myocarditis was excluded by CMR, suggest that TS is an important cause of MINOCA. Other potential causes include CAD with rupture of a non-stenotic lesion, coronary artery spasm, thrombotic disorders, and microvascular dysfunction.

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