Original Article

Characteristics and Risk Factors of Yemeni Patients Presenting with Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA)

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ABSTRACT

Background: Myocardial infarction with non-obstructive coronary artery (MINOCA) is a syndrome, which requires both clinical documentation of ST-elevation myocardial infarction (STEMI) (abnormal cardiac biomarker, ischemic symptoms, and electrocardiography changes) and detection of nonobstructive coronary arteries. The purpose of this study is to determine the incidence of and characteristics of patients with MINOCA in the Yemeni population.

Methods: Consecutive patients admitted between January and June 2019 at Al-Thawra Hospital, Sana'a (Yemen), with STEMI diagnosis were enrolled in this study. Demographic, clinical, echocardiographic, and coronary angiography characteristics of patients were noted.

Results: MINOCA was identified in 63 patients (25%) out of 249 admitted with STEMI diagnosis at Al-Thawra Hospital. The mean age of MINOCA patients was similar to obstructive coronary group; however, they were more often females and less frequently with diabetes and family history of coronary artery disease. Other risk factors like smoking, arterial hypertension, dyslipidemia, and oral tobacco were similar. Conversely, the percentage of Khat chewers was significantly higher in the MINOCA patients ($P < 0.01$) as compared to obstructive group.

Conclusions: The relatively high incidence of MINOCA in our country and the long list of multiple potential causes of MINOCA should open further working diagnosis after coronary angiography and further efforts for defining the cause of myocardial infarction in each individual patient in Middle East countries.

Key words: Coronary angiography, myocardial infarction, nonobstructive coronary artery disease

INTRODUCTION

Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) was first documented >75 years ago when autopsy reports detailed myocardial necrosis in the absence of significant coronary atherosclerosis.[1,2] Over the last 30 years, the diagnosis and management of acute myocardial infarction (AMI) has substantially progressed due to two innovations: (1) the development of the troponin assay which has provided a more accurate diagnostic marker of myocardial injury and is now the cornerstone of contemporary AMI definitions[3] and (2) the studies by DeWood *et al*.[4] that involved

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undertaking coronary angiography during AMI. This group demonstrated that ST elevation myocardial infarction (STEMI) was typically associated with an occluded coronary artery.[5] These data were subsequently confirmed in several large AMI registries.

There was a large meta-analysis in which 6% of AMIs occurred in the absence of obstructive coronary artery disease (CAD).[6] Thus, some patients with AMI and elevated troponins have no significant CAD on angiography. This syndrome, consisting of clinical evidence of AMI[3] (abnormal cardiac biomarker and either ischemic symptoms or ischemic electrocardiography [ECG] changes) with normal or near-normal coronary arteries on angiography, has been referred as MI with normal coronaries).[5] However, it may be more appropriately termed MINOCAs. Many studies have included patients with nonobstructive lesions (<50%) on angiography.

Although patients with MINOCA are more readily identified by contemporary AMI assessment strategies, few studies have investigated determinants, clinical characteristics, and outcomes of this condition.[5]

Data from large AMI registries[6-8] suggest a prevalence of MINOCA, between 2% and 10%, depending on the cohort studied and diagnostic criteria utilized. The CRUSADE registry, the largest of these studies, reported that female gender and a younger age were the only independent clinical predictors of MINOCA.[8] Further analyses of these databases confirm that MINOCA patients have better outcomes than those with obstructive CAD, both in relation to in-hospital and 12-month mortality.[8] Furthermore, mortality rates were similar for those who had normal angiography and those with minor disease,[9] justifying the merger of these subgroups into the clinical syndrome of MINOCA.

The pathophysiology of MINOCA is multifactorial and poorly understood with several proposed mechanisms.[10,11] This makes diagnostics and treatment of MINOCA challenging in daily clinical practice. That is why the problem of MINOCA diagnostics was highlighted in the recent European Society of Cardiology Clinical Practice Guidelines on STEMI.[12]

It is imperative that the diagnosis of MINOCA be considered as a working diagnosis to elucidate the underlying cause of the clinical presentation. This needs to be undertaken at two levels, to (1) exclude disorders mimicking an AMI and (2) identify the underlying cause responsible for the MINOCA.[13]

Few data are available about MINOCA in Middle Eastern countries. The aim of the present study was to assess incidence and characteristics of MINOCA patients in Yemen.

METHODS

Consecutive patients admitted between January and June 2019 (6 months) at Al-Thawra Hospital, Sana'a (Yemen) with STEMI diagnosis, documented by clinical and ECG findings, were enrolled in this study. Personal data, clinical findings, and details of electrocardiographic, echocardiographic, and coronary angiography findings were recorded. STEMI patients not undergoing to coronary angiography at hospital admission were excluded from the study. The traditional cardiovascular risk factors (smoking, hypertension, Khat chewing, family history and diabetes mellitus, dyslipidemia) were noted. All medical procedures were performed according to current medical standards. MINOCA patients were identified if having the diagnosis of STEMI or NSTEMI with nonobstructive CAD visualized in angiography, and no previous coronary revascularization.[10]

Statistical analysis

Categorical variables were presented as percentages. Continuous variables were expressed as median and interquartile range. Normality was assessed by the Kolmogorov–Smirnov–Lilliefors test. Equality of variances was assessed using the Levine's test. Differences between groups were compared using the Student's or the Welch's *t*-test depending on the equality of variances for normally distributed variables. The Mann–Whitney U test was used for nonnormally distributed continuous variables. Ordinal variables were compared using the Cochran–Armitage test. Nominal variables were compared by the Pearson's Chi-squared test or by the Fisher's exact test if 20% of cells had expected count <0.05. All analyses were carried out with IBM SPSS®, v20.0.0 (IBM SPSS version 20 NY, USA).

RESULTS

Out of 249 patients initially admitted with STEMI, 63 (25%) were classified as MINOCA. The mean age was not statistically different in patients with MINOCA as compared to patients in the obstructive group (53 ± 11 vs. 56 ± 10 years, respectively, $P = 0.10$) [Table 1].

Patients with MINOCA were more often women comparing to patients with obstructive CAD (59% vs. 19%, $P < 0.01$). Diabetes and family history of CAD were less frequent in MINOCA patients than in the obstructive group (16% vs. 32%; $P < 0.05$ and 14% vs. 28%, $P < 0.05$, respectively). Dyslipidemia (21% vs. 22%), hypertension (37% vs. 40%), smoking (48% vs. 51%), and oral tobacco (30% vs. 24%) were not statistically associated with MINOCA; conversely, the incidence of Catha edulis (Khat) chewers was significantly higher in MINOCA group (90% in MINOCA vs. 64% in obstructive group, $P < 0.01$). Finally, MINOCA patients were less likely to receive antiplatelet and antithrombotic treatment before angiography [Table 1].

Table 1: Clinical characteristics of myocardial infarction with nonobstructive coronary artery patients as compared to obstructive coronary artery disease

	Obstructive CAD, *n* (%)	MINOCA, *n* (%)	*P*	Total, *n* (%)
Number of cases (*n*)	186	63		249
Age (years), mean	56±10	53±11	0.10	
Gender				
Female	35 (19)	37 (59)		72 (29)
Male	151 (81)	26 (39)		177 (71)
Family history of CAD	52 (28)	9 (14)	<0.05	61 (24)
Diabetes	59 (32)	10 (16)		69 (28)
Dyslipidemia	40 (22)	13 (21)	0.01	53 (21)
Hypertension	74 (40)	14 (37)		88 (35)
Smoking	95 (51)	30 (48)		125 (50)
Oral tobacco	45 (24)	19 (30)		59 (24)
Catha edulis	119 (64)	57 (90)		176 (71)

CAD: Coronary artery disease, MINOCA: Myocardial infarction with nonobstructive coronary artery

Transthoracic echocardiography pattern in MINOCA

Similar occurrence of segmental wall motion abnormalities by transthoracic echocardiography was detected in MINOCA and obstructive group (90 vs. 89%) [Table 2]. The percentage of patients with normal ejection fraction was slightly higher in MINOCA in comparison to obstructive group (63% vs. 56%, *P* value = 0.22) [Table 3]; however, there was no significant difference between the mean ejection fraction in the two groups which was slightly higher in MINOCA group (53% vs. 51%, ns).

Mitral regurgitation and MINOCA

The most common mitral valve regurgitation grade was grade II, occurring in 49% of MINOCA patients and in 39% of obstructive group (*P* = 0.304) [Table 4].

DISCUSSION

In this study, we showed that MINOCA patients represent a significant proportion of MI patients referred to invasive assessment in our daily practice. We found MINOCA in about 25% of patients. This incidence is much higher than recently published report from SWEDEHEART Registry (about 8%) as well as a meta-analysis of clinical studies (about 6%).[6,14]

In particular, our study confirms that MINOCA patients were more frequently female, without diabetes and family history of CAD. Interestingly, the majority of MINOCA patients were Khat chewers (90% vs. 64% in CAD subgroup) and this finding may potentially explain the particularly high incidence of MINOCA in Yemen. MINOCA is just an initial and general diagnosis, which does not describe underlying pathophysiology. Potential pathophysiological mechanisms of this clinical condition are quite complex, including both coronary and noncoronary pathologies.[14]

The coronary causes comprise several different mechanisms. Thromboembolism may be an underlying pathological factor by itself or may be caused by plaque rupture or coronary spasm. This includes also thrombotic disorders (hereditary or acquire).[6] Plaque disruption may be caused by erosion, ulceration, plaque rupture, and intraplaque hemorrhage. Coronary artery spasm may be present not only due to endogenous causes but may be provoked by exogenous substances like cocaine[15-17] or cathinon in Catha edulis (khat) which is a very common social habit among Yemenis,[16,18-21] and this could explain the significant high incidence of MINOCA in our patients. Montone *et al*.[22] showed acetylcholine and ergonovine tests to be safe in patients with MINOCA and suspected coronary vasomotor abnormalities. Moreover, test results correlated with clinical symptoms and outcome in follow-up. In the meta-analysis of MINOCA studies, coronary artery spasm was inducible in 27% of patients.[6]

Noncoronary etiologies are also frequent in MINOCA patients. It is important to recognize well-defined diseases with described etiopathologies like myocarditis, pulmonary embolism, or Takotsubo cardiomyopathy in patients initially described as MINOCA. Importantly, some of those causes are treatable, so a well-planned diagnostic seems to be crucial for the final diagnosis, treatment selection, and outcome of these patients. According to the 2017 European Society of Cardiology Clinical Practice Guidelines on STEMI, failure to identify the underlying cause may result in inadequate and inappropriate therapy in MINOCA patients.[3]

The diagnostic algorithm based on suspected diagnosis and corresponding diagnostics modalities (noninvasive and invasive) was proposed. This includes myocarditis (with echocardiography, cardiac magnetic resonance, and end myocardial biopsy), coronary epicardial/microvascular etiology (with intravascular ultrasound (IVUS), ergonovine/acetylcholine test, pressure/Doppler wire), myocardial disease (with echocardiography and cardiac magnetic resonance), pulmonary embolism (with D-dimer,

Table 2: Distribution of segmental wall motion abnormalities in myocardial infarction with nonobstructive coronary artery versus obstructive coronary artery disease group

	Obstructive CAD, *n* (%)	MINOCA, *n* (%)	Total
SWMA			
No	20 (11)	6 (10)	26
Yes	166 (89)	57 (90)	223
Total	186	63	249

CAD: Coronary artery disease, MINOCA: Myocardial infarction with nonobstructive coronary artery, SWMA: Segmental wall motion abnormality

Table 3: LV ejection fraction in myocardial infarction with nonobstructive coronary artery versus obstructive coronary artery disease group

	Obstructive CAD, *n* (%)	MINOCA, *n* (%)	Total
Ejection fraction (%)			
<50	80	23	103
>50	106 (56)	40 (63)	146
Total	186	63	249

CAD: Coronary artery disease, MINOCA: Myocardial infarction with nonobstructive coronary artery, LV: Left ventricle

Table 4: Degree of mitral regurgitation in myocardial infarction with nonobstructive coronary artery versus obstructive coronary artery disease group

	Mitral regurgitation degree					Total
	I	II	III	IV	*n*	
Obstructive CAD	60	74	28	1	23	186
MINOCA	21	31	4	0	7	63
Total	81	105	32	1	30	249

CAD: Coronary artery disease, MINOCA: Myocardial infarction with nonobstructive coronary artery

computed tomography scan, thrombophilia screening), and type 2 MI (with extra cardiac investigation including investigations for anemia, selected secondary etiologies of arterial hypertension, some possible infectious etiologies).[10]

In a large meta-analysis, myocarditis was detected in one third of patients with suspected MINOCA undergoing cardiac magnetic resonance, whereas 21% had infarction.[23] Intracoronary imaging is important in selected cases since plaque rupture, ulceration, erosion, or intraplaque hemorrhage are rarely visible in angiography in nonobstructive CAD. Reynolds *et al*.[24] showed that plaque disruption confirmed by IVUS was observed in 38% of women with MINOCA.

Interestingly, in some cases, plaque rupture was identified by IVUS even in angiographically normal appearing segments.[22] In addition, in patients with MINOCA, invasive coronary provocative tests may be considered.

In line with previous reports, our study showed that MINOCA patients in Yemen were more often female comparing to patients with obstructive CAD (59% vs. 19%, Chi-square = 27.7, $P < 0.01$) and incidence of MINOCA in women (40%) was higher than previously reported in a meta-analytic study.[6] In agreement with previous studies,[6] there was no significant difference in arterial hypertension, diabetes mellitus, smoking, and family history of CAD comparing to obstructive CAD patients. Patients with MINOCA have lower mortality comparing to obstructive CAD patients with MI in 12-month follow-up.

However, in-hospital mortality of about 1% and 3.5% at 12-month is still high especially as compared to stable non-MI patients with normal coronaries in angiography.[6] This underlines the need for precise diagnosis and dedicated treatment of MINOCA patients. Unfortunately, our study did not drop by this follow-up.

Limitations

Our study has some limitations. An independent image analysis in a core laboratory was not done and angiograms were assessed by local operators. In majority of cases, the operators were not following the patients after coronary angiography has done, and they did not finalize the patients diagnosis. In addition, there is a potential bias from unmeasured confounding factors not included in this analysis. In particular, new imaging modulates for further evaluation, such as CMR and IVUS, were not available in our country. Despite all these limitations, this study reflects the "real-world" of MINOCA in Yemen.

CONCLUSIONS

This study reported for the first time the incidence and characteristics of MINOCA in a referral hospital in Yemen. These preliminary results seem to demonstrate that this particular type of myocardial infarction occurs more frequently in Yemen as compared to Europe and North America. The extremely high number of Khat chewers in MINOCA patients in our country might open new research fields to better understand the pathophysiology of this complex and multifactorial disease.

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Conflicts of interest

There are no conflicts of interest.

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