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Abstract

The term myocardial infarction with non-obstructive coronary arteries (MINOCA) applies to patients who have clinical evidence of AMI but coronary angiography reveals no coronary obstructions and an alternative diagnosis is not possible. It is a heterogeneous group of disease. Its prognosis, predictors of mortality and optimum management is unclear. In this review, we present a disease overview for MINOCA including the clinical features, adopted definitions, prevalence, diagnosis, treatment, and prognosis.

Keywords: Coronary artery disease, Myocardial infarction, Non-obstructive, Coronary angiography

1. Introduction

Worldwide, acute myocardial infarction (AMI) is associated with high mortality [1,2]. The management of AMI has evolved over the last few decades. Management strategies such as early coronary angiography and catheter-based reperfusion have changed the outlook in cases of AMI. Early in 1980, DeWood et al. [3] demonstrated that ST-segment-elevation myocardial infarction (STEMI) was associated with an occluded epicardial artery in >90% cases, but this was not the case with non-ST segment-elevation myocardial infarction (NSTEMI) [4]. Although obstructive coronary artery disease was evident in a majority of the patients with NSTEMI, complete occlusion was not a predominant feature. Historically, absence of obstructive lesions in coronary arteries on angiography in patients with STEMI and/or NSTEMI triggered a diagnostic dilemma which withheld any further investigations and treatment. The term myocardial infarction with non-obstructive coronary arteries

(MINOCA) applies to patients who have clinical evidence of AMI but coronary angiography reveals no coronary obstructions and an alternative diagnosis is not possible. Our understanding of MINOCA has evolved in the recent past yet many uncertainties persist regarding its pathophysiology, management, and prognosis. In this review, we present a disease overview for MINOCA including the clinical features, adopted definitions, prevalence, diagnosis, treatment, and prognosis.

2. Definition

Various terminologies including MINOCA, MINCA (Myocardial infarction with normal coronary arteries) [5] and INOCA (ischemia and no obstructive coronary artery disease) [6,7] have been used for AMI/acute coronary syndrome (ACS) with normal or near normal coronary arteries. Pasupathy et al. [8] proposed a new term 'troponin-positive non-obstructive coronary arteries (TP-NOCA)' that includes patients with coronary disorders resulting in ischemic necrosis, and myocardial and non-cardiac disorders resulting in myocardial injury.

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Regardless of the underlying cause, TP-NOCA refers to all conditions with elevated troponin levels. MINOCA is a subset of TP-NOCA where myocardial ischemia, possibly due to plaque rupture or coronary dissection, is the cause for myocardial injury [9].

According to the 4th Universal Definition of MI, MINOCA is AMI in the absence of obstructive coronary artery disease (<50% coronary artery stenosis) on angiogram (Table 1) [10–13].

Angiographic features of non-obstructive coronary disease include normal coronary arteries, minimal luminal irregularities (<30% stenosis) and mild to moderate coronary atherosclerosis (30–50%).

3. Prevalence

Available evidence in literature suggests 5–15% prevalence of MINOCA [12,14]. This wide range in prevalence is mainly attributed to differences in study population and the heterogeneity in adopted definitions. Reported prevalence may be even higher in the era of high sensitivity cardiac troponin assays. The VIRGO study [15] reported 11.1% prevalence of MINOCA whereas the SWEDEHEART study [16] reported a 8.0% prevalence. Another observational study in Japan reported a prevalence of 10.2% [17]. When compared to MI in patients with obstructive coronary artery disease (CAD), higher prevalence of MINOCA was found in younger patients (58.8% vs. 61.3%, $p < 0.001$) and in females (43% vs. 24%, $p < 0.001$) [18]. MINOCA is also predominant in patients presenting with non-STEMI (78% vs. 51%, $p < 0.0001$) when compared to AMI with obstructive CAD [19]. Similar findings have been reported in other studies [15,20–22].

4. Clinical characteristics

Patients with MINOCA are less likely to have traditional risk factors. Old age, male sex, obesity, smoking, and diabetes are negative predictors of

Abbreviation list

AMI	Acute myocardial infarction
ACS	Acute coronary syndrome
ACEi	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
CAD	Coronary artery disease
CMR	Cardiac magnetic resonance
ESC	European Society of Cardiology
INOCA	Ischemia and no obstructive coronary artery disease
IVUS	Intravascular ultrasound
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MINCA	Myocardial infarction with normal coronary arteries
MRI	Magnetic resonance imaging
NSTEMI	Non-ST segment-elevation myocardial infarction
OCT	Optical coherence tomography
STEMI	ST-segment-elevation myocardial infarction
TP-NOCA	Troponin-positive non-obstructive coronary arteries

MINOCA while peripheral vascular disease, cerebrovascular disease, liver disease, renal disease and malignancy were identified as positive predictors [17]. Based on findings reported in different studies, it seems MINOCA tends to affect young females more often than men. Patients generally have fewer or similar cardiovascular risk factors compared to MI with obstructive CAD [15,17,18].

5. Diagnosis of MINOCA

MINOCA can present with ST-elevation MI (STEMI) or non-STEMI (NSTEMI). MINOCA should be considered as a working diagnosis when there is no obvious cause at presentation for elevated troponin. So, in the assessment, the first step is to exclude non-ischemic causes of an elevated troponin level. A position paper on MINOCA from the Dutch ACS working group of

Table 1. 4th universal definition of myocardial infarction.

Acute myocardial infarction includes the following criteria:

1. Acute myocardial injury with clinical evidence of acute myocardial ischemia, and
2. With detection of a rise and/or fall of cardiac troponin with at least one value above the 99th percentile upper reference limit, and
3. With at least one of the following:
 - Symptoms of myocardial ischemia
 - New ischemic changes on electrocardiogram
 - Development of pathological Q waves
 - Imaging evidence of new loss of viable myocardium or regional wall motion abnormality in a pattern consistent with an ischemic etiology
 - The identification of a coronary thrombus by angiography or autopsy

Reference: Thygesen et al. (2018) [10].

the Netherlands Society of Cardiology [14] considered MINOCA as dynamic working diagnosis to help clinicians to further evaluate the underlying mechanism and individualized management of patients with MINOCA. If coronary angiography during a suspected AMI shows non-obstructive coronary arteries and there is no obvious cause for the clinical presentation/elevated troponin like sepsis, pulmonary embolism, hypotension, myocarditis, then a working diagnosis of MINOCA is used. Every effort must be made to determine the specific cause as prognosis and management vary according to etiology. To reveal the underlying cause of MINOCA, the European Society of Cardiology (ESC) working group proposed a diagnostic algorithm which included a thorough history, physical examination, laboratory testing, imaging, and invasive investigations [13]. This comprehensive approach should help physicians to manage MINOCA in a patient more appropriately.

Vasospastic angina, characterized by transient ST changes during chest pain that respond to nitrates, is caused by coronary artery spasm leading to transient coronary artery obstruction [7]. When there is suspicion of coronary vasospasm as the cause of MINOCA, coronary vasospasm provocation test with ergonovine and acetylcholine should be considered at the time of coronary angiography whenever it is available. The diagnosis of vasospastic angina has prognostic value as it is associated with increased mortality [23]. Optical coherence tomography (OCT) or intravascular ultrasound (IVUS) imaging helps to rule out plaque disruption as the cause of MI in cases where coronary angiography failed to show obstructive lesions. Invasive functional coronary angiography with a diagnostic guidewire and adenosine test may be needed to establish a confirmatory diagnosis of epicardial vasospastic and microvascular angina [7].

Coronary microvascular dysfunction, defined as increased in coronary blood flow less than 2.5-fold in response to adenosine, has been associated with ACS. Coronary microvascular dysfunction may or may not be associated with coronary artery or myocardial diseases. It may also be associated with interventional cardiac revascularization procedures. The underlying pathophysiological mechanisms include coronary plaque erosion, microembolization, autonomic imbalance, endothelial dysfunction, inflammation, and vascular smooth muscle abnormalities [24]. Microembolism from mural thrombosis of a coronary plaque (whether fibrous cap rupture or erosion) may be an important cause. This may lead to microvascular angina.

Demonstration of slow coronary flow on coronary angiography is the marker of microvascular dysfunction. Most of the symptoms in patients with nonobstructive CAD may be due to coronary microvascular dysfunction. Cardiac magnetic resonance imaging (MRI) can be done to detect a microvascular obstruction. Functional imaging including positron emission tomography and myocardial perfusion imaging, and coronary computed tomographic angiography can help establish a diagnosis of coronary microvascular dysfunction [7].

Congenital thrombophilia (Protein C deficiency, Factor V Leiden) and acquired thrombophilia associated with connective tissue diseases and oral contraceptive pills can lead to thrombotic occlusion of coronary arteries. These account for 12% and 3%, respectively for MINOCA without evidence of an obstructive atheroma [25]. These are not common but important entities as these need anti-thrombotic therapy.

Cardiac magnetic resonance (CMR) plays a pivotal role for the diagnosis of patients with MINOCA. The utility of CMR imaging is its ability to identify infarcted tissue by late gadolinium enhancement imaging, inflamed tissue by T2 weighted imaging, and regional wall motion abnormalities. However, the diagnosis remains inconclusive in a significant number of patients. A recent study by Lintingre et al. [26], demonstrated high diagnostic value of high-resolution late gadolinium CMR in patients with MINOCA. Collste et al. [5] have provided an important insight in the assessment of MINOCA by performing CMR imaging. The CMR studies revealed myocarditis in 7% patients with a typical myocarditis infarct pattern in 19%, and no significant abnormality in 67% of MINOCA patients. Of particular significance were myocarditis cases detected on CMR imaging despite the clinically overt cases being excluded from study. These findings support the importance of CMR imaging in the assessment of MINOCA and mandate this imaging modality as essential in the evaluation of patients with MINOCA.

6. Differential diagnosis

MINOCA is a heterogenous entity with a clinical diagnosis of AMI. The diagnosis of MINOCA should exclude other overt causes for elevated troponin (Table 2). This may also include obstructive coronary artery disease like distal stenosis or occluded small branches and non-ischemic causes for myocardial injury.

Table 2. Clinical conditions associated with elevated troponin levels.

Coronary conditions	Non-coronary cardiac conditions	Non- coronary non- cardiac (non- ischemic) conditions
Plaque rupture or erosion	Myocarditis	Stroke
Coronary artery spasm	Takotsubo cardiomyopathy	Pulmonary embolism
Spontaneous coronary dissection	Cardiomyopathies	Sepsis
Aortic dissection with coronary artery involvement	Cardiac trauma	Adult respiratory distress syndrome
Coronary microvascular disorder	Strenuous exercise	End stage renal failure
Thrombophilia	Tachyarrhythmias	
Sympathomimetic agents	Cardiotoxins	

Plaque disruption is common in MINOCA and comprises plaque rupture, plaque erosion and calcific nodules. It leads to MI by thrombus formation with transient complete arterial occlusion with spontaneous thrombolysis or distal embolization [27]. OCT or IVUS imaging may be helpful when coronary angiography reveals nonobstructive CAD to rule out plaque disruption as the cause of MI.

The diagnosis of coronary spasm is particularly important as optimum therapy with calcium channel blocker can improve prognosis. Varying prevalence rates are reported for coronary spasm in patients with MINOCA. Deyama et al. [28] reported 71.4% prevalence of coronary spasm in MINOCA after acetylcholine provocation test. Similar prevalence (71.3%) of coronary spasm was reported in another study [29]. On the contrary, the VIRGO study [15] reported a prevalence of 3.7% for coronary spasm in MINOCA patients. Moreover, an early detection can help to improve prognosis as vasospasms are generally associated with transient ischemia which may not lead to myocardial necrosis.

Spontaneous coronary artery dissection may sometimes appear as non-obstructive coronary artery disease on angiography and should be considered as a cause of MINOCA. Coronary embolism in patients with thrombophilia may deceptively appear as MINOCA on angiography. Coronary microvascular dysfunction usually presents as stable CAD but may also present as ACS and be a cause of MINOCA. Lastly, MINOCA may have an uncertain origin.

7. Treatment

Patients with MINOCA represent a major therapeutic challenge. Management of MINOCA is based on limited evidence and there are no prospective, randomized, controlled trials. A study has shown that use of renin-angiotensin system blockers and statins has mortality benefits in patients with MINOCA [30]. Lindahl et al. [16] reported beneficial

effects of statins and renin-angiotensin system blockers in MINOCA patients. But dual antiplatelets and beta-blockers failed to show significant reduction in major cardiac events. Although it was an observational study, it was the first study to evaluate secondary prevention strategy in large number of patients (n = 9466) with MINOCA. The ongoing randomized MINOCA BAT trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03686696) Identifier: NCT03686696), designed to evaluate beta-blockers and angiotensin converting enzyme inhibitors (ACEi)/Angiotensin II receptor blockers (ARBs) in MINOCA patients, should provide information on best treatment strategy for these patients. In clinical practice, it may be reasonable to administer ACEi/ARBs, statins, and antiplatelet agents to most patients with MINOCA. Optimum therapy with calcium channel blockers is the treatment of choice for coronary spasm in patients with vasospastic angina. There are currently no effective therapies for microvascular dysfunction.

8. Prognosis

There are conflicting data regarding the prognosis of MINOCA. Overall, the prognosis of MINOCA is not very favorable. Available data should be interpreted with caution since the outcomes of MINOCA depend on the underlying cause. Pasupathy et al. [18] reported better prognosis in MINOCA patients compared to AMI with obstructive CAD. In-hospital mortality was 1.1% in the MINOCA group and 3.2% in the AMI with obstructive CAD group (p = 0.001) whereas the 12-month mortality was 3.5% and 6.7% (p = 0.003), respectively. Another study reported similar 1- and 12-month mortality in both MINOCA and AMI with obstructive CAD (1 month: 1.1% and 1.7%, respectively, p = 0.043; 12 month: 0.6% and 2.3%, respectively, p = 0.68) [15]. Bainey et al. reported a lower 1-year composite of death and/or reinfarction rate among MINOCA patients with no angiographic evidence of CAD (3.9%) when compared to MINOCA with stenosis <50% (36.1%) (p = 0.028) [31]. On the other hand, Smilowitz et al.

[32] reported favorable prognosis for patients with MINOCA. In an analysis of a nation-wide, multi-center, prospective registry, Choo et al. [30] reported comparable clinical outcomes both in patients with MINOCA and in patients with MI-CAD. Patients with MINOCA (n = 396) and myocardial infarction with obstructive CAD (n = 10 871) showed no significant differences for risks of cardiac death (Hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.53–1.28; p = 0.38), noncardiac death (HR, 1.55; 95% CI, 0.93–2.56; p = 0.09) and reinfarction (HR, 1.23; 95% CI, 0.65–2.31; P = 0.38), incidence of all-cause death (HR, 1.04; 95% CI, 0.74–1.45; p = 0.83). In an observational study on more than 9000 MINOCA patients, Nordenskjold et al. [33] reported 24% major adverse cardiovascular events (MACEs) and 14% mortality during a mean follow-up of 4.5 years. The average time to readmission in patients with MINOCA was 17 months and this was mainly due to reinfarction. Another observational study in elderly population in Japan [17], found poor short-term prognosis in patients with MINOCA compared to those with MI-CAD. A Korean registry reported similar incidence of all-cause death in patients with MINOCA and MI-CAD (9.1% vs. 8.8%; HR, 1.04; p = 0.83). The incidence of all-cause death was lower in patients with positive vasospasm than in those with negative vasospasm. Non-use of renin-angiotensin system blockers (HR, 2.63; 95% CI, 1.08–6.25; p = 0.033) and statins (HR, 2.17; 95% CI, 1.04–4.54; p = 0.039) was a significant predictor of all-cause death in MINOCA patients [30]. Retrospective analysis of a multicenter trial showed that patients with MINOCA had a higher adjusted risk of mortality at 1 year compared with patients with non-ST elevation MI (5.2% vs. 1.6%) [34]. Mortality rates in patients with MINOCA are said to be related to the type of atherosclerotic plaques (calcified plaque 1.4%, mixed plaque 3.3%, non-calcified plaque 9.6%) [35]. In a systematic review (>36,000 patients in 44 studies), the annual mortality rate in patients with MINOCA was 2% [36]. There was a reduced ejection fraction and ST depression at presentation. The use of beta blockers at follow up were associated with poor long-term prognosis. Patients with MINOCA are reported to have worse short and long-term survival compared with people in the general population when matched for age and sex [37].

9. Conclusions

In evaluation of patients with MINOCA, a systematic approach should be used to establish

underlying etiology/mechanism especially for conditions that have effective therapies. MINOCA should not be considered as a benign condition and should receive same attention as MI-CAD. Based on available evidence in literature, it is reasonable to consider antiplatelets, statins, ACEi/ARBs for MINOCA patients and individualize the treatment based on underlying mechanisms. Further randomized studies with adequate sample size are required to evaluate the optimal therapies for patients with MINOCA.

Declarations

Ethics approval and consent to participate.

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

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Acquisition of data: Fahad Shamsi, Khwaja Y. Hasan, Shahrukh Hashmani, Syed F. Jamal, Samer Ellaham.

Data collection: Fahad Shamsi, Khwaja Y. Hasan, Shahrukh Hashmani, Syed F. Jamal, Samer Ellaham.

Drafting of manuscript: Fahad Shamsi.

Revising and editing the manuscript critically for important intellectual contents: Fahad Shamsi, Samer Ellaham.

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