

# Management of myocardial infarction with Nonobstructive Coronary Arteries (MINOCA): a subset of acute coronary syndrome patients

Anthony G. Matta<sup>1,2</sup>, Vanessa Nader<sup>1,3</sup>, Jerome Roncalli<sup>1,\*</sup>

<sup>1</sup>Department of Cardiology, Toulouse University Hospital, 31059 Toulouse, France

<sup>2</sup>Faculty of Medicine, Holy Spirit University of Kaslik, 446 Jounieh, Lebanon

<sup>3</sup>Faculty of Pharmacy, Lebanese University, 13-5033 Beirut, Lebanon

\*Correspondence: [roncalli.j@chu-toulouse.fr](mailto:roncalli.j@chu-toulouse.fr) (Jerome Roncalli)

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Myocardial infarction with non-obstructive coronary artery disease (MINOCA) represents a significant proportion (up to 15%) of acute myocardial infarction (AMI) population. MINOCA is diagnosed in patients who fulfilled the fourth universal definition of AMI in the absence of significant obstructive coronary artery disease on coronary angiography. MINOCA is a group of heterogeneous diseases with different pathophysiological mechanisms requiring multimodality imaging. Left ventriculography, cardiac magnetic resonance imaging and intra-coronary imaging (IVUS, OCT) are useful tools playing a pivotal role in the diagnostic work-up. There are no standard guidelines on the management of MINOCA patients and the therapeutic approach is personalized, thereby detecting the underlying aetiology is fundamental to initiate an early appropriate cause-targeted therapy.

## Keywords

MINOCA; Management; Myocardial infarction; Atherosclerosis

## 1. Introduction

Myocardial infarction with non-obstructive coronary artery disease (MINOCA) represents a significant proportion (up to 15%) of acute myocardial infarction (AMI) population [1, 2]. This term on top of others such as INOCA (ischemia and no obstructive coronary artery disease) [3], MINCA (myocardial infarction with normal coronary arteries) [4], TP-NOCA (troponin-positive non-obstructive coronary arteries) and ACSNNOCA (acute coronary syndrome with normal or near normal coronary arteries) [5] were used to describe a sole clinical entity incorporating myocardial damage in the absence of significant obstructive coronary artery disorder. While MINOCA includes a group of miscellaneous diseases, the underlying aetiology and pathophysiological mechanisms remain unclear in large patient series [6]. Coronary angiography is the crucial exam for making the diagnosis of MINOCA which requires to exclude the presence of significant coronary artery stenosis ( $\geq 50\%$  luminal narrowing) and an alternative cause of the acute presentation in the setting of AMI [6, 7]. The fourth universal definition

of myocardial infarction requests a rise and/or fall of high-sensitive cardiac troponine (hs-CT) with one value above the 99-percentile upper reference limit [7]. Compared to CAD-AMI (significant coronary artery disease- acute myocardial infarction) population, MINOCA patients were younger and have lower prevalence of cardiovascular risk factors including dyslipidemia, hypertension, diabetes mellitus, and smoking [8, 9]. Even though, MINOCA patients were preponderantly females and previous studies showed that the incidence of MINOCA in women presenting with AMI is twofolds higher than that of men [8, 9]. Atherosclerosis has a limited burden in MINOCA patients unlike CAD-AMI population, thereby playing a minor role in the pathophysiology of AMI in MINOCA cases. Noteworthy that according to aforementioned MINOCA diagnostic criterias, clinical entities resulting in increased level of hs-CT such as stroke, pulmonary embolism, sepsis, adult respiratory distress syndrome and end-stage renal failure must be excluded in the work-up [6, 7]. MINOCA clinically manifests as no ST-elevation myocardial infarction rather than ST-elevation myocardial infarction (2/3 vs 1/3 of cases) [10]. The long-term prognosis is usually better but not trivial among MINOCA patients compared to those with CAD-AMI [10, 11]. Reduced left ventricle ejection fraction [11–13], increased C-reactive protein [14], elevated level of hs-CT [15, 16], female sex [12, 17] and mild three-vessels or left main atherosclerosis (30–50% luminal stenosis) [14] are independent predictors of adverse events in MINOCA patients. Herein, we focus on the therapeutic approach and management of MINOCA: a specific subset of acute coronary syndrome population.

## 2. Causes of MINOCA

The main causes of MINOCA could be divided into two groups: ischemic and non-ischemic.

## 2.1 The ischemic causes

The ischemic causes include spontaneous coronary artery dissection (SCAD), plaque disruption, coronary spasm, microvascular dysfunction, coronary thrombus or embolism and supply-demand mismatch.

Coronary artery dissection is a tear separating the inner layers of the coronary artery from the outer layers not always revealed by coronary angiography [3, 18]. However, intramural haematoma without intimal tear is detected by intracoronary imaging in some cases [19]. Fibromuscular dysplasia is commonly found in other vessels of SCAD-MINOCA patients [20]. It is more often in women accounting for 25% of all acute coronary syndromes in women aged below 50-year-old [21]. The impacts of hormonal changes, pregnancy and delivery on vascular wall (intima-media) were implicated [21]. In SCAD, the external compression of coronary true lumen results in myocardial infarction or MINOCA. It is the consequence of blood accumulation in the tunica media after an endothelium-intimal tear formation “inside-out mechanism” or microvessel rupture in the vascular wall “outside-in mechanism” [22, 23]. A recent OCT based study found that the absence of fenestration in SCAD increases the pressure in false lumen and subsequently the external compression of the true lumen [24].

MINOCA accounts for up to 20% of type 1 AMI enrolling plaque rupture and erosion [6, 25] which were detected by IVUS among 40% of MINOCA cases [26, 27]. Thromboembolism, superadded coronary spasm, thrombosis and an association of these processes are the main mechanisms of myocardial necrosis in MINOCA patients with plaque rupture. Plaques with thin fibroatheromatous cap ( $<65\ \mu\text{m}$ ) and infiltrated by macrophages are at risk for rupturing [28]. Activation of the sympathetic nervous system is the main trigger for plaque rupture while hypercoagulable state amplifies the thrombotic response [29]. Plaque erosion results in thrombus formation without rupture, thereby the internal elastic lamina and underlying media are intact unlike plaque rupture [30]. Thus, spontaneous coronary thrombolysis has been proposed as an internal protective mechanism avoiding thrombus formation in case of plaque rupture or erosion [26].

The prevalence of coronary artery spasm defined as a reversible diffuse or focal vascular smooth muscle hypersensitivity to vasoconstrictive endogenous or exogenous stimuli varies between 3 to 95% of MINOCA cases [31, 32]. It is well known that modifications in coronary vasomotor tone participate in the pathogenesis of myocardial infarction. Then, it has been demonstrated that a mutation (V734I) in the nucleotide binding domain binding 1 of ABCC9 affects the susceptibility to AMI by altering the vasomotor response to intracellular nucleotides [33]. Coronary microvascular spasm or dysfunction altering myocardial perfusion and contractility has been found in 25% of MINOCA patients [34]. It induced transient myocardial ischemia with electrical modifications (ST segment), clinical manifestation (angina) and troponin elevations without angiographic reduction in coronary

lumen [35–37]. Despite the lack of epicardial obstructive disease, there can be microvascular obstruction which is a cause of MINOCA.

Acquired thrombotic disorders (antiphospholipid syndrome, myeloproliferative diseases), hereditary thrombotic disorders (Protein C, S and factor V Leiden deficiencies) and predisposing hypercoagulable states (atrial fibrillation, cardiac tumor, valvular vegetations or calcifications) result in coronary thromboembolism [10]. Structural heart disease like right-left shunts, patent foramen ovale, atrial septal defect and coronary fistula may lead to paradoxical embolism which is relatively a rare cause of MINOCA [38–40]. Lastly, conditions provoking oxygen supply-demand mismatch by either increasing oxygen demand through promoting systolic wall tension, myocardial contractility and heart rate or reducing oxygen supply through decreasing coronary blood flow and oxygen-carrying capacity are responsible for type 2 AMI [41–43].

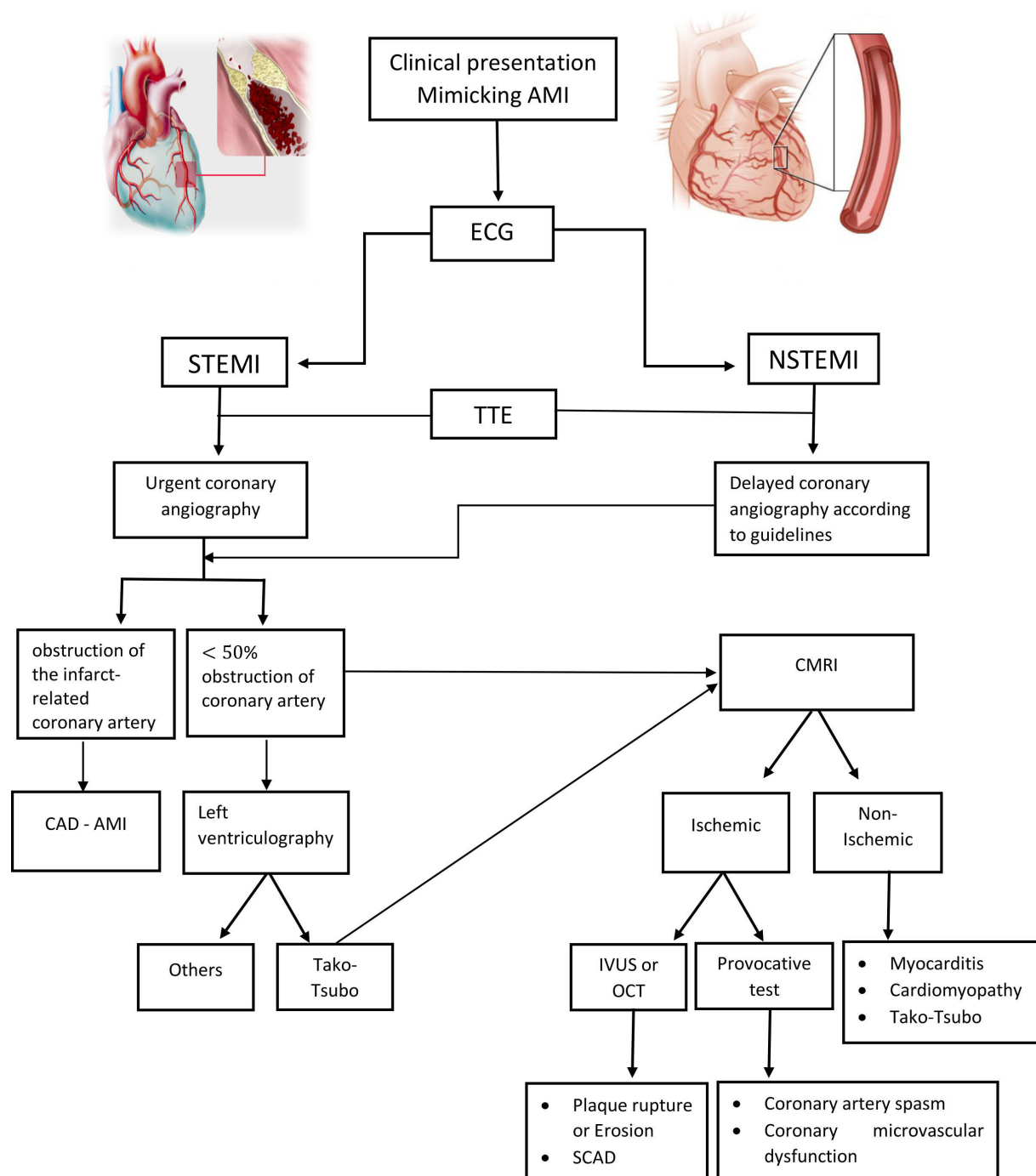
## 2.2 The non-ischemic causes

The non-ischemic causes include myocarditis, tako-tsubo cardiomyopathy, hypertensive heart disease, tachyarrhythmias, cardiotoxins or chemotherapeutic agents and cardiomyopathies. Myocarditis are likely to present as acute coronary syndrome accounting for 33% of MINOCA cases [44] especially when parvovirus B19 is the underlying causative agent [45]. Parvovirus B19 has predilection to endothelial cells due to blood group P antigen inducing intense vasoconstriction of coronary microcirculation and subsequent ST segment elevation in the setting of myocardial inflammation [46, 47]. This finding was confirmed by Yilmaz *et al.* [47] who showed an epicardial spasm limited to the distal part of coronary artery after the injection of acetylcholine in MINOCA patients with myocarditis [46, 47]. Viral infections with adenoviruses, coxsackie virus, parvovirus B19 and human herpes virus 6 are the most common cause of myocarditis [45].

Toxins, drugs, chemotherapeutic agents, auto-immune (sarcoidosis, lupus) and endocrine diseases are another causes of myocarditis [48–50]. Myocardial involvement during autoimmune disorders could be the sole clinical presentation or a part of systemic reaction [51]. Early diagnosis of myocarditis in the context of MINOCA is important for its prognostic value and to establish an appropriate treatment [52]. Indeed, a poor prognosis was attributed to eosinophilic myocarditis, cardiac sarcoidosis and giant cell myocarditis [52].

Tako-tsubo cardiomyopathy known as stress-induced reversible cardiomyopathy generally affects post-menopausal women. The exact pathophysiological mechanisms remain unclear, thereby several hypotheses such as diffuse spasm, spontaneous coronary thrombus and lysis, catecholamine-induced myocardial stunning have been proposed. However, coronary microvascular dysfunction is a common finding among tako-tsubo syndromes [53].

Lastly, illicit drug use such as cocaine and MDMA can also result in MINOCA.



**Fig. 1. Algorithm showing the work-up for the management of MINOCA.** Coronary angiography is immediately recommended in STEMI patients while it could be postponed according to risk stratification in NSTEMI patients. Then, CMRI is recommended in all patients with non-significant CAD followed by endovascular imaging (OCT and IVUS) or provocative test depending on clinical history in the presence of evidence of ischemia. \*CAD, coronary artery disease; AMI, acute myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary artery disease; CMRI, cardiac magnetic resonance imaging; STEMI, ST segment elevation myocardial infarction; NSTEMI, no ST segment elevation myocardial infarction; TTE, transthoracic echocardiography; SCAD, spontaneous coronary dissection.

### 2.3 Novelties in MINOCA causes

In the era of COVID-19 (coronavirus disease 2019) pandemic, COVID-19 infection was found as a potential causative agent for MINOCA or ACSNNOCA. COVID-19 positive patients are likely to develop tako-tsubo cardiomy-

opathy (stressful situation), myocarditis (viral inflammation), AMI (thrombo-embolism, vasospasm and plaque rupture) and non-cardiac conditions such as pulmonary embolism and sepsis [54]. A pro-thrombotic effect ensuing from local and systemic inflammatory reactions, endothelial cells infection

and cytokines storm has been currently attributed to COVID-19 [55–57].

Recently, a correlation between MINOCA and myocardial bridge has been hypothesized by our group via a large observational cohort [58]. In fact, myocardial bridge has the potential to activate and enhance the all suggested pathophysiological mechanisms of MINOCA. The mechanical compression called systolic milking effect of MB predisposed to atherosclerotic plaque rupture [59] or contributed to SCAD [60]. Moreover, the tunneled coronary segments are prompt to vasospasm with hyper-contractility response to vasoconstrictive agents [61]. The continuous transient dynamic compression of vascular wall results in increasing the shear wall stress which harm endothelial cells [62, 63]. Data from literature showed that myocardial infarction could be a pertinent clinical manifestation of myocardial bridge with milking effect [64–66] and recent published study revealed a significantly higher angiographic prevalence of myocardial bridge in MINOCA rather than CAD-AMI (coronary artery disease acute myocardial infarction) populations [58, 66]. It is worthy to mention that myocardial bridge is associated with proximal atherosclerotic plaque despite sparing of the bridge, so it remains to be seen if the bridge and/or combination of bridge and non-obstructive CAD result in MINOCA.

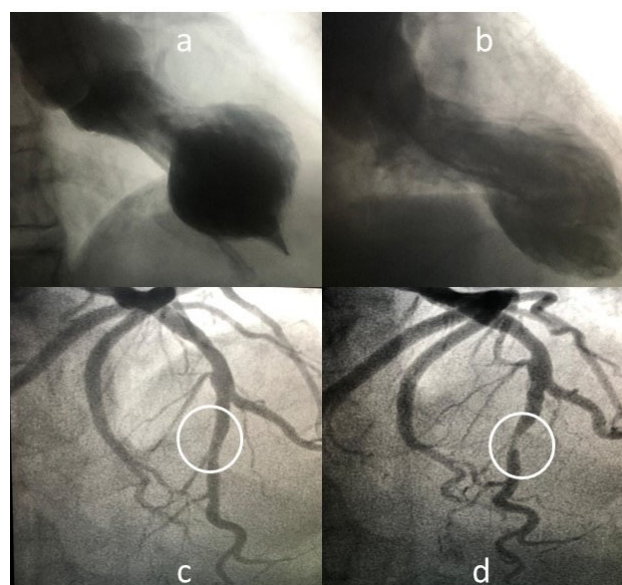
### 3. Management of patients suspected of MINOCA

MINOCA should be considered as «working diagnosis» rather than «true diagnosis», thereby performing further diagnostic evaluation is fundamental. Coronary angiography is urgently recommended in patients with ST-segment elevation myocardial infarction while it could be delayed according to cardiovascular risk stratification in those with No ST-segment elevation myocardial infarction. Screening for AMI mechanical complications, transthoracic echocardiography is routinely performed before undergoing cardiac catheterization laboratory. In the absence of significant coronary artery stenosis on coronary angiogram, C-MRI should be performed to differentiate ischemic from non-ischemic causes. According to clinical context, either IVUS/OCT or provocative test is required in the presence of evidence in favor of ischemic origin (Fig. 1).

Excluding non-cardiac disorders that mimickAMI like pulmonary embolism, sepsis and forms of type 2 myocardial infarction (anaemia and hyperthyroidism) is an important step. Thus, detailed clinical history, electrocardiogram, critical laboratory tests (D-dimer, red and white blood cells counts, creatinine, thyroide stimulating hormone) and pulmonary CT-angiography are useful tools depending on clinical presentation. However, Collste *et al.* [4] did not reported any case of pulmonary embolism after performing CT-angiography in 100 consecutive MINOCA patients. Screening for drug consumption including sympathomimetic agents (cocaine and methamphetamines) and for hypercoagulable state may be helpful in a number of patients [10]. The preva-

lence of inherited thrombophilia disorders like factor V Leiden, Protein C and S deficiencies detected among MINOCA patients is 14% [10].

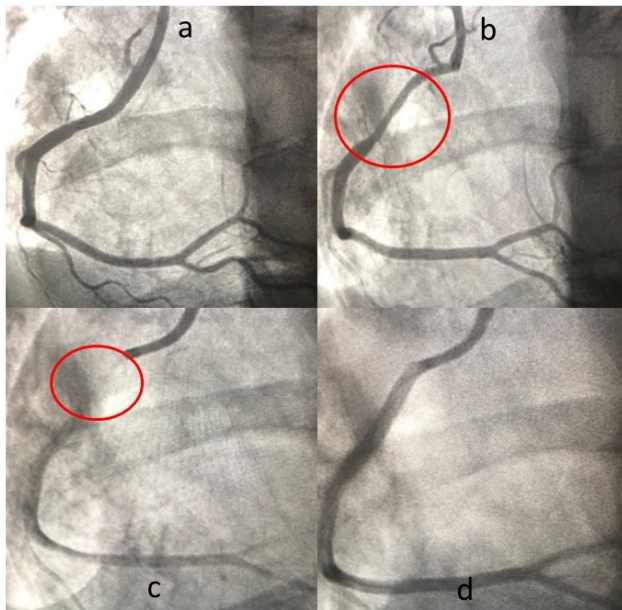
Transthoracic echocardiography is an essential non-invasive exam systematically performed in the acute setting to detect AMI-complications, structural heart disease, intra-cardiac thrombus, cardiac tumor (myxoma), tako-tsubo features and wall motion abnormalities [67]. In the setting of MINOCA, interventional cardiologist routinely accomplished coronary angiography with left ventriculogram searching for the angiographic features of apical or mid-ventricular Tako-Tsubo like fisherman's pot or Hawk's beak appearance, respectively [68] (Fig. 2).



**Fig. 2. Left ventriculogram and coronary angiography.** Left ventriculogram showing mid-ventricular tako-tsubo with hawk's beak appearance (a) and apical tako-tsubo with fisherman's pot feature (b) in 2 MINOCA patients. Left coronary angiogram showing patent coronary arteries (c) and severe systolic milking effect of myocardial bridge (d) in MINOCA patient.

Then, cardiac magnetic resonance imaging (C-MRI) is the key diagnostic tool to differentiate ischemic from non-ischemic causes in MINOCA patients. C-MRI is very important in the diagnosis. Subendocardial late gadolinium enhancement (Fig. 3a) is most consistent with infarct [3]. Non-ischemic causes are likely mid-wall or sub-epicardial. However, they can be subendocardial as well in cases of sarcoidosis, amyloid. Myocardial edema shows inflammation. That can be present in infarct as well as in non-specific inflammation from many causes of MINOCA [3–23]. Furthermore, C-MRI is the recommended imaging modality of choice to confirm myocardial involvement according to the ESC (European Society of Cardiology) guidelines and it was favourably compared to the gold standard endomyocardial biopsy [48, 52, 69–72]. It is worthy to mention that C-MRI is normal in a large proportion of MINOCA patients

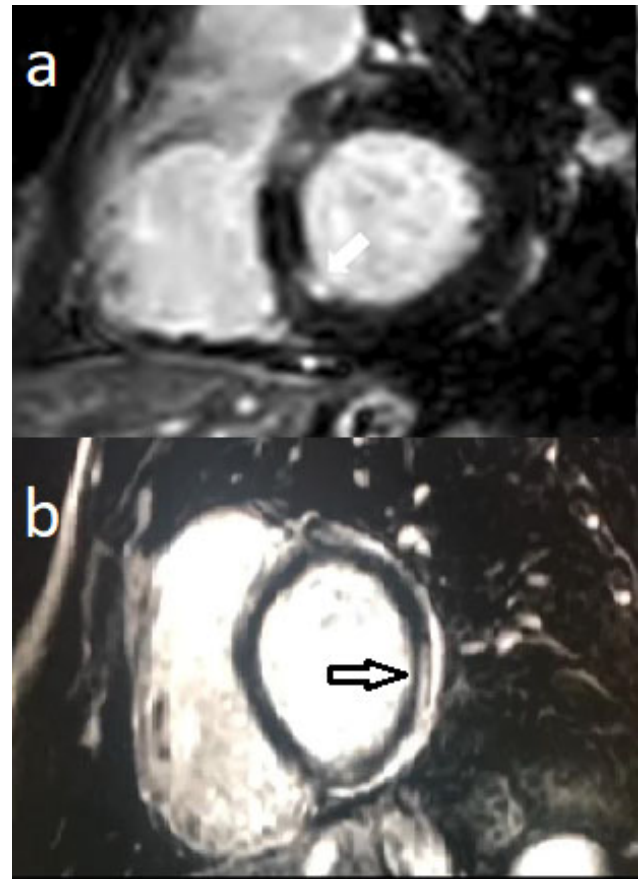




**Fig. 3. Cardiac magnetic resonance imaging.** Short-axis gadolinium enhanced cardiac magnetic resonance imaging showing an acute sub-endocardial necrosis on the infero-septo-basal segment in MINOCA patient with plaque rupture (a) and sub-epicardial enhancement of the lateral wall in MINOCA patient with acute myocarditis (b).

(8–67%), thereby raising the reconsideration for alternative non-cardiac disorders or undetectable small infarct or little widely distributed necrotic myocytes [4, 73–79]. Performing C-MRI within 7 days from clinical presentation is the optimal time to increase the diagnostic yield [73, 75, 76]. Leurent *et al.* [73] who did C-MRI at a mean delay of 6.9 days in 107 MINOCA patients were able to find a definitive diagnosis in 90% of cases (60% myocarditis (Fig. 3b), 16% AMI and 14% cardiomyopathy). However, the overall diagnostic yield of C-MRI performed within 4 weeks after hospital admission in MINOCA patients was 71% (33% myocarditis, 12% takotsubo cardiomyopathy, 2% hypertrophic cardiomyopathy, 2% dilated cardiomyopathy and 3% other) [74–83]. Recently, Dastidar *et al.* [84] assessed the prognostic role of C-MRI in MINOCA patients and identified C-MRI diagnosis of cardiomyopathy as an independent predictor of mortality.

Intracoronary imaging like optical coherence tomography (OCT) and at lesser extent intravascular ultrasound (IVUS) are important tools for the diagnosis of coronary plaque disruption, spontaneous coronary dissection and coronary thrombosis. Plaque disruption including rupture, hemorrhage, ulcer and erosion was found in 40% of MINOCA cases [26]. Documented plaque rupture on OCT was correlated to major adverse cardiac events [85]. Given that plaque erosion is not detected by IVUS, OCT is the preferred intravascular imaging modality [86]. A recent study by Reynold *et al.* [87] identified a culprit lesion (plaque rupture) by using OCT in 46.2% of total 145 participating women. They also noticed that multimodality imaging combining C-MRI and



**Fig. 4. Intracoronary reactivity testing.** Intracoronary reactivity testing performed in MINOCA patient: coronary angiogram showed a patent right coronary artery (a) with proximal vasospasm in response to methergin administration (b,c) that resolves after injection of nitroglycerine (d).

OCT were more powerful to determine the underlying cause of MINOCA than each modality alone [87].

Lastly, provocative spasm testing maybe considered in some MINOCA patients who were likely to have vasospastic angina. Recurrent episodes of rest angina with circadian pattern that respond to nitrates are in favor of vasospasm [88]. Inducible major epicardial coronary spasm was revealed in 43 to 54% of MINOCA patients [89, 90] (Fig. 4). Montone *et al.* [89] recommended intracoronary reactivity testing in all MINOCA patients. He also showed that provocative test could be safely performed in the acute phase following coronary angiography [89, 90]. Currently, Reynolds *et al.* [87] have identified coronary artery spasm as underlying cause of MINOCA in 46 women over 145 by using OCT. To complete, it is worthy to mention that coronary microvascular spasm (vessels <0.5 mm diameter) was revealed in about 16% to 54% of MINOCA patients [52, 89, 91]. Ischemic ECG changes with chest discomfort after intracoronary injection of acetylcholine without angiographic epicardial coronary artery spasm direct towards microcirculatory spasm [92, 93]. Multiple invasive and non-invasive techniques such as CMRI, doppler transthoracic echocardiography, positron emission tomography and hyperaemic absolute

coronary flow measurement are useful to assess coronary microcirculation accounting for 70% of total coronary resistance in the absence of obstructive disease [94, 95].

#### 4. Therapeutic approach

Since MINOCA involved several pathophysiological mechanisms and various clinical entities, the therapeutic strategy varies depending on the underlying aetiology. However, it remains unclear if treatment strategy for AMI is suitable for MINOCA patients without an identifiable cause. Lifestyle modification including smoking cessation, regular physical activity, weight loss and mediterranean diet was recommended in all MINOCA patients [96]. The beneficial effects of renin-angiotensin converting enzyme inhibitors (ACEI) on reducing mortality and major adverse cardiac events in MINOCA have been reported by previously conducted studies [97–99] while conflicting results were observed with statins [65, 97, 98, 100]. A neutral effect was linked to antiplatelet therapy which can also be harmful to some MINOCA patients [101, 102].

##### 4.1 Ischemic causes

The management of MINOCA patients with plaque disruption should be in accordance to the guidelines for AMI [7, 103]. Indeed, dual antiplatelet therapy is recommended for 1 year followed by lifelong single antiplatelet therapy. For MINOCA patients with spontaneous coronary artery dissection, a conservative approach is preferred because coronary intervention or stenting contributes to the propagation of the dissection and mural hematoma [104].  $\beta$ -blockers and aspirin are the mainstay medical therapy while the role of anticoagulant and dual-antiplatelet remains controversial [105, 106]. Some researchers hypothesized that using P2Y<sub>12</sub> inhibitors could be beneficial view the prothrombotic state triggered by the intimal tear [22] while others reported that these agents increased the risk of bleeding and subsequently the progression of intramural hematoma [97]. Statins were not recommended unless atherosclerotic disease is present in SCAD patients [107]. Calcium channel blockers and nitrates were used as first line therapy for the treatment of MINOCA patients with vasospastic angina [90]. Combining dihydropyridine and non dihydropyridine calcium channel blockers or adding nicorandil (potassium channel activator) is indicated for refractory vasospastic angina [88]. Dipyridamole [108] and ranolazine [109] which promote microcirculatory vasodilation and visceral analgesic agents like imipramine [110] and aminophylline [111] are of potential benefits in MINOCA patients with microvascular dysfunction. We highlight on the lack of consensus for secondary prevention implantable cardiac defibrillators in extreme cases of coronary spasm or other causes of MINOCA resulting in sudden cardiac death, although it is likely reasonable.

##### 4.2 Non-ischemic causes

MINOCA patients with myocarditis were conventionally treated with diuretics, ACEI or angiotensin receptor block-

ade (ARB) and  $\beta$ -blockers [52]. Intravenous inotropic agents or mechanical cardiopulmonary support were required if they are hemodynamically unstable [52]. To date, there are no guidelines on medical treatment for MINOCA with Tako-tsubo cardiomyopathy, and heart failure therapies ( $\beta$ -blockers and ACEI/ARB) were routinely used. Finally, approved medicines for secondary prevention after MI like statins, ACEI or ARB,  $\beta$ -blockers and dual antiplatelet agents were recommended in MINOCA patients with unclear aetiology [93, 112, 113].

#### 5. Prognosis

A recent large nation-wide study showed a comparable mid-term prognosis between MINOCA and CAD-AMI patients [98]. Data from literature are conflicting because while some studies reported a lower mortality rate and cardiovascular events in MINOCA population [98, 114–117], others revealed similar adverse clinical outcomes between MINOCA and CAD-AMI [118–120]. Except for revascularization which was more commonly observed among CAD-AMI patients, there are no significant difference in adverse clinical outcomes including death from any cause, cardiac and non-cardiac deaths at 2-years follow-up between MINOCA and CAD-AMI populations [98]. Similarly, the frequencies of in-hospital events were comparable [99]. The use of statins in the presence of mild atherosclerotic disease and ACE/ARB was associated with prolonged survival [2, 91–94, 98, 113, 114] whereas advanced age, diabetes mellitus, atypical manifestations, STEMI presentation and killip class IV were independent predictors of mortality in MINOCA patients [98, 121].

#### 6. Conclusions

MINOCA is a common clinical entity accounting up to 15% of AMI population and incorporating numerous pathophysiological mechanisms. It could be considered as a working diagnosis and additional multimodality imaging diagnostic approach (Left ventriculogram, Echocardiography, C-MRI, IVUS, OCT) is usually needed. Since the therapeutic management differs among MINOCA patients, determining the underlying aetiology is fundamental to perform cause-targeted therapy.

#### Author contributions

AM contributed to conception, design and writing of the report; VN contributed to conception and design of the report; JR contributed to design and writing of the report and provided important intellectual contributions to the manuscript.

#### Ethics approval and consent to participate

Not applicable.

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## Conflict of interest

The authors declare no conflict of interest.

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