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REVIEW

Clinical update

Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management

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Myocardial infarction (MI) with no obstructive coronary atherosclerosis (MINOCA) is a syndrome with different causes. Its prevalence ranges between 5 and 25% of all MIs. The prognosis is extremely variable, depending on the causes of MINOCA. Clinical history, echocardiography, coronary angiography, and left ventriculography represent the first-level diagnostic investigations. Nevertheless, additional tests are required in order to establish its specific cause, thus allowing an appropriate risk stratification and treatment. We review pathogenesis, diagnosis, prognosis, and therapy of MINOCA and propose an algorithm for its management.

Keywords Acute myocardial infarction • No obstructive coronary atherosclerosis

Introduction

According to the universal definition of myocardial infarction (MI) proposed by European Society of Cardiology,[1] MI is identified by the detection of 'rise and/or fall' of troponin associated with at least one of the following: (i) symptoms of ischaemia, (ii) electrocardiographic (ECG) changes indicative of new ischaemia, (iii) evidence of new loss of viable myocardium or new regional wall motion abnormality, and (iv) identification of intra-coronary (IC) thrombus by angiography or autopsy.[1]

Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) is a syndrome with different causes,[2] characterized by clinical evidence of MI with normal or near normal-coronary arteries on angiography (stenosis severity $<50\%$). Data from large MI registries suggest a prevalence between 5 and 25%,[2–5] but the most recent study, in a contemporary cohort of patients, reported a prevalence of 8.8%,[9] which appears to reflect daily clinical experience. Previous studies have shown a prevalence of MINOCA between 10 and 25% among women and between 6 and 10% among men who present with no-ST elevation MI (NSTEMI).[6] An analysis of patients with NSTEMI included in the CRUSADE registry showed that female sex and younger age were independent clinical predictors of MINOCA.[3]

Clinical history, ECG, cardiac enzymes, echocardiography, coronary angiography, and left ventricular (LV) angiography represent the first-level diagnostic investigations to identify the causes of MINOCA (*Figure 1* and *Table 1*). In particular, regional wall motion abnormalities at LV angiography limited to a single epicardial coronary artery territory identify an 'epicardial pattern', whereas regional wall motion abnormalities extended beyond a single epicardial coronary artery territory identify a 'microvascular pattern'.

The prognosis of MINOCA is not as benign as reported by early cohort studies and as commonly assumed by physicians.[4] Indeed, the rate of all-cause mortality during admission and at 12-month follow-up ranged between 0.1 and 2.2% and between 2.2 and 4.7%, respectively.[7,8] Of note, a recent retrospective analysis of patients enrolled in the ACUITY trial[9] showed that, compared with NSTEMI patients with obstructive coronary artery disease (CAD), patients with MINOCA had a higher adjusted risk of mortality at 1 year (5.2 vs. 1.6%; HR 3.44, CI 1.05–11.28; $P = 0.04$).

In spite of its high prevalence and poor outcome, current guidelines do not specifically address the management of MINOCA. Thus, in this article, we review pathogenesis, diagnosis, prognosis, and therapy of MINOCA and propose an algorithm for its management.

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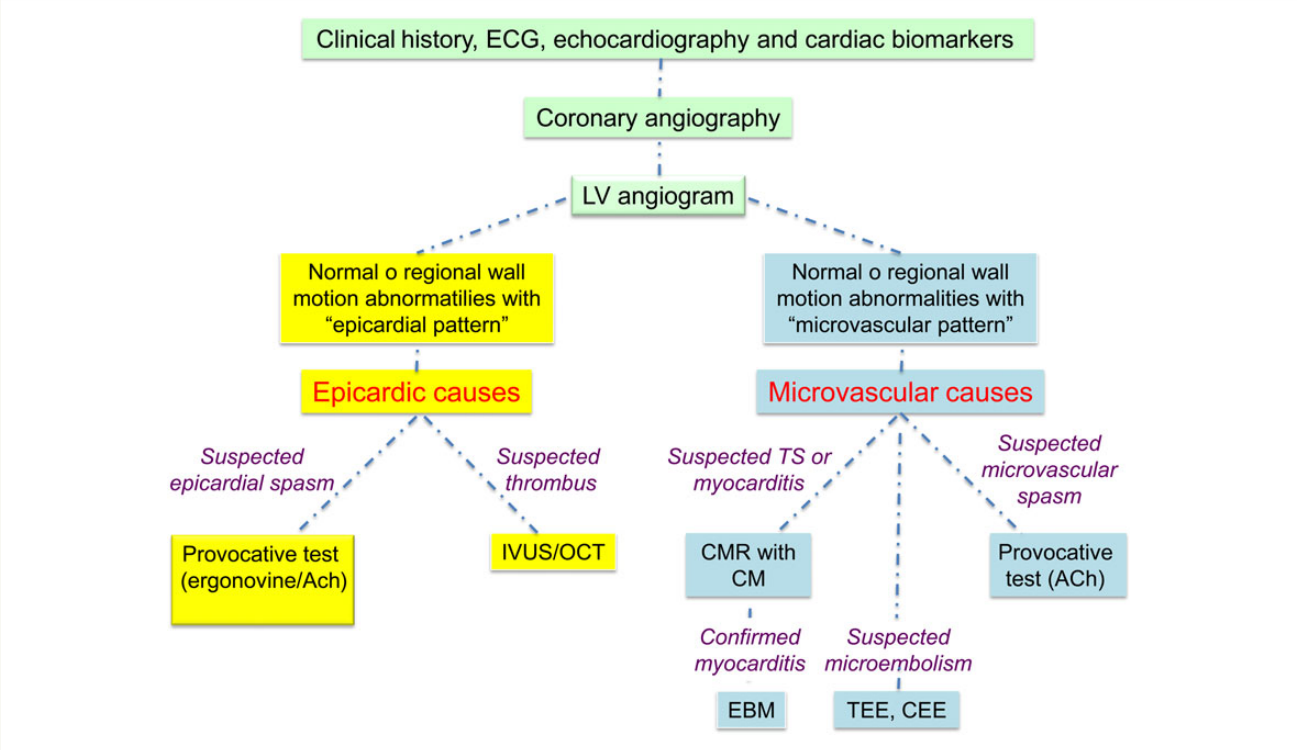

Figure 1 Diagnostic algorithm of myocardial infarction with no obstructive coronary atherosclerosis. First step is represented by clinical history, electrocardiography, cardiac enzymes, echocardiography, coronary angiography, and left ventricular (LV) angiography. Regional wall motion abnormalities with an 'epicardial pattern' indicate an epicardial cause of myocardial infarction with no obstructive coronary atherosclerosis: if clinical data suggest coronary artery spasm, intra-coronary acetylcholine (Ach), or ergonovine test should be performed and if there is a clinical doubt of thrombus, intra-vascular ultrasound (IVUS), or optical coherence tomography (OCT) are required. Regional wall motion abnormalities with a 'microvascular pattern' indicate a microvascular cause of MINOCA. If clinical data and left ventriculography suggest Takotsubo syndrome (TS) or PVB19 myocarditis, cardiac magnetic resonance (CMR) with contrast medium (CM) is needed. If the latter shows evidence of myocarditis, endomyocardial biopsy (EMB) can be performed to ascertain the aetiology. If clinical data suggest coronary microembolism, TEE, and/or CEE are required to detect a cardiac source of embolism. Finally, if microvascular spasm is suspected, IC Ach test is needed. TEE, transesophageal echocardiography; CEE, contrast-enhanced echocardiography.

Table 1 Diagnostic tests, prognostic characteristics, and therapeutic treatments stratified for specific causes of myocardial infarction with no obstructive coronary atherosclerosis

Mechanism	Diagnosis	Prognosis	Therapy
Epicardic causes			
Vasospasm	IC ergonovine or Ach test	Variable	Calcium antagonist, nitrates, Rho kinase inhibitors?
Eccentric plaque	IVUS and OCT	Variable	Control of cardiovascular risk factors and dual antiplatelet therapy
Microvascular causes			
Takotsubo syndrome	Ventriculography CMR with CM	Favourable	Heart failure treatment
Microvascular spasm	IC Ach test	Favourable	Rho kinase inhibitors?
PVB19 myocarditis	CMR with CM EMB	Variable	Heart failure treatment
Coronary embolism[a]	Coronary angiography Identification of an embolic source	Depends on the underlying cause	Depends on the underlying cause

IC, intra-coronary; Ach, acetylcholine; IVUS, intra-vascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; CMR, cardiac magnetic resonance; CM, contrast medium; EMB, endomyocardial biopsy.
[a]Coronary embolism can also cause macrovascular obstruction.

Epicardial causes of MINOCA

Coronary artery spasm

Coronary artery spasm (CAS) represents an important epicardial cause of MINOCA. It usually occurs at a localized segment of an epicardial artery, but sometimes involves two or more segments of the same (multifocal spasm) or of different (multi-vessel spasm) coronary arteries, or may involve diffusely one or multiple coronary branches.[10] The prevalence ranges between 3 and 95% of MINOCA patients; this wide difference depends on the stimuli used to trigger spasm, definitions of spasm, and ethnic reasons.[11] Coronary artery spasm results from the interaction of two components: (i) an usually localized, but sometimes diffuse, hyper-reactivity of vascular smooth muscle cells (VSMCs) and (ii) a transient vasoconstrictor stimulus acting on the hyper-reactive VSMCs. The main cause of VSMCs hyper-reactivity seems to be enhanced Rho kinase activity.[12]

Patients with CAS typically refer angina at rest, during the night or early in the morning, associated with a transient ST segment elevation. In the absence of ECG documentation, the diagnosis is based on an IC provocative test, whereas CAS is generally defined as reduction of at least 75% of the vessel calibre together with symptoms/signs of myocardial ischaemia (*Figure 2A* and *B*).[13–16] While the IC ergonovine test is a well-standardized procedure,[13] the provocative test with IC acetylcholine (Ach) is performed in different ways in different countries[13–16] (Supplementary material online, *Table S1*).

The prognosis is variable. Apart from multi-vessel CAS,[17] other independent predictors of cardiovascular outcome emerged from studies on the Japanese population: history of out-of-hospital cardiac arrest, smoking, angina at rest alone, organic coronary stenosis, ST-segment elevation during angina, and β-blockers use.[18] However, it is difficult to extrapolate these findings to Caucasian populations; indeed, while the prevalence of CAS is higher in the Japanese population, its outcome is better in the Caucasian population.[18]

Non-specific vasodilators such as nitrates and calcium channel blockers constitute the standard treatment. In case of refractory vasospastic angina (ranging from 10 to 20% of cases), fasudil has been found effective in Japanese patients, although these positive findings cannot be directly extrapolated to Caucasian patients. In selected cases, stent implantation or partial sympathetic denervation[10] can be employed. Implantable cardiac defibrillators are needed in patients at high risk of spasm-related cardiac death.

No obstructive coronary atherosclerosis with positive remodelling

Another epicardial cause of MINOCA is the presence of eccentric plaques with positive remodelling resulting in lack of obstructive CAD. These lesions frequently show characteristics of vulnerability: large lipid pool and thin fibrous cap,[19] which may increase the susceptibility to plaque rupture.[20] Of note, hypercoagulability might enhance the detrimental consequences of these lesions.[21] Plaque rupture followed by a transient and partial thrombosis, followed by spontaneous fibrinolysis, may cause distal embolization leading to MINOCA. Of note, in case of plaque erosion, the loss of surface endothelium, the high concentration of hyaluronan, and the increased expression of its receptor, CD44, seem to be responsible

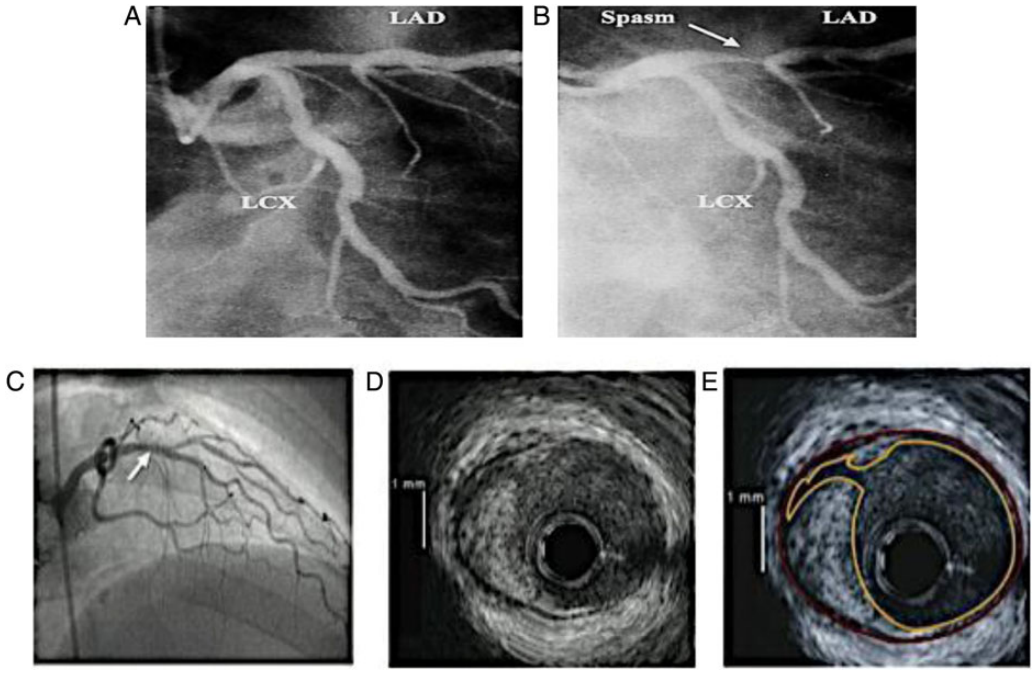

Figure 2 Epicardial causes of MINOCA. (*A* and *B*) Acute coronary artery spasm of the left anterior descending coronary artery (LAD) (white arrow) induced by intra-coronary ergonovine test. (*C–E*) Representative angiographic and intra-vascular ultrasound (IVUS) of plaque disruption. The site of plaque rupture or ulceration is marked with an arrow (*C*); the right side for the IVUS image (*E*) shows the outline of the luminal border (yellow) and external elastic lamina (red) corresponding to the IVUS image on left side (*D*).

for thrombosis.[19,20] Furthermore, neutrophils could play a crucial role in the 'destabilization' of eroded plaques.[22]

Rupture/erosion of eccentric plaques with positive remodelling is more common in women with cardiovascular risk factors.

In this setting, considering the limits of coronary angiography, the use of intra-vascular imaging modalities seems mandatory.[23,24] In particular, Reynold *et al.*[25] identified plaque fissure by intra-vascular ultrasound (IVUS) in ~40% of women with MINOCA (*Figure 2C–E*). Of note, optical coherence tomography (OCT) is probably more sensitive than IVUS.[23] Indeed, previous studies showed that OCT has a sensibility of 92% and a specificity of 75% in the identification of plaques with large lipidic pool and thin fibrous cap.[24] The finding of ruptured plaque without thrombus detected by intra-vascular imaging modalities might be due to spontaneous fibrinolysis or might represent a coincidental finding. Accordingly, in a recent study, Di Vito *et al.*[26] demonstrated that ruptured plaques may remain stable over 6-month period despite a deep wall defect and thin fibrous cap. At the other extreme, thrombus in the absence of plaque fissure might be the marker of a plaque erosion responsible for MINOCA.

These lesions are associated to a risk of cardiovascular events at follow-up comparable with that of patients with acute coronary syndromes (ACS) and obstructive atherosclerosis.[27] Thus, these patients require dual antiplatelet treatment for 12 months and statins. In particular, long-term lipid-lowering therapy with statins after MI is associated to a significant increase in the fibrous-cap thickness paralleling the reduction of the lipid content of the plaque.[28]

Microvascular causes of MINOCA

Takotsubo syndrome

A microvascular cause of MINOCA is represented by Takotsubo syndrome (TS). Its prevalence is reported to range between 1.2 and 2.2% of all ACS.[29] Although several aetiopathogenetic mechanisms have been proposed (e.g. multi-vessel epicardial spasm, catecholamine-induced myocardial stunning, spontaneous coronary thrombus lysis, and acute microvascular spasm), the causes of TS are still debated. A previous study demonstrated that, irrespective of its aetiology, reversible coronary microvascular dysfunction is a common pathophysiological determinant of TS.[30] Indeed, the extent of myocardial hypoperfusion at myocardial contrast echocardiography, was similar in patients to TS and in patients to ST elevation MI, whereas a transient significant improvement of myocardial perfusion and of LV function during adenosine infusion was observed in the former only.

Takotsubo syndrome is characterized by a high prevalence of post-menopausal females reporting recent physical or emotional stress. The most common ECG abnormalities (e.g. ST-segment elevation and T wave inversion) are usually observed during the acute and sub-acute phases.[31] Typically, all patients exhibit marked LV dysfunction on admission, while a sizeable proportion exhibits a dramatic functional improvement over a period of days to weeks. They mainly show hypokinesia or akinesia of mid and apical segments of the left ventriculography, with preserved or hyperkinetic function of basal regions (*Figure 3A* and *B*). However, Shimizu *et al.*[32] reported three other 'patterns' of TS: 'reverse Takotsubo' with basal akinesia and

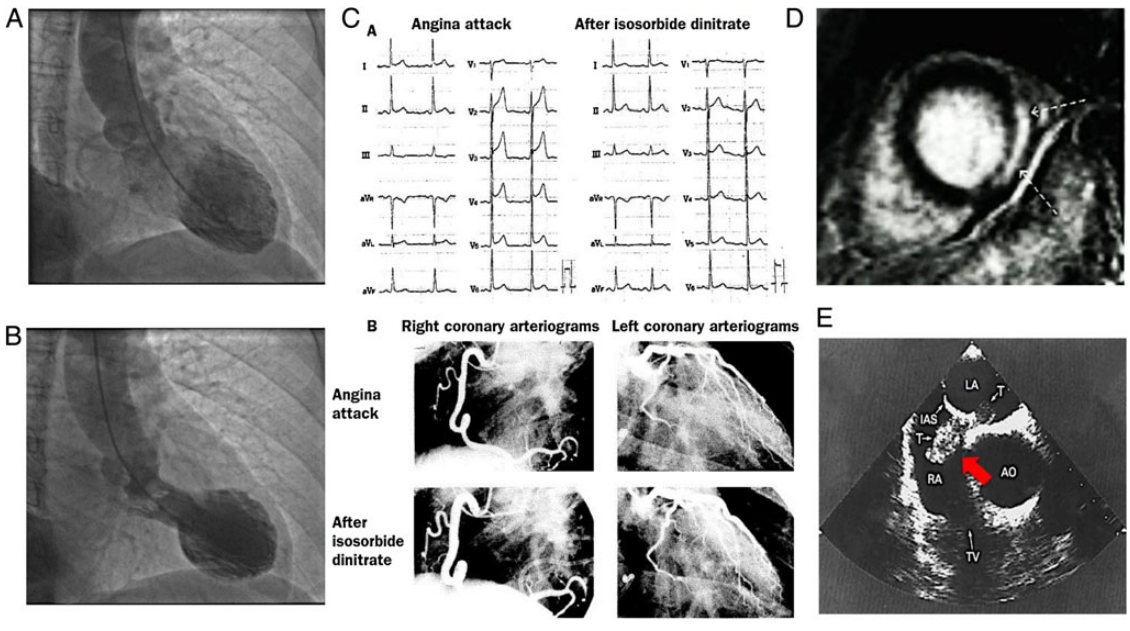

Figure 3 Microvascular causes of myocardial infarction with no obstructive coronary atherosclerosis. (*A* and *B*) Takotsubo syndrome during diastole (*A*) and systole (*B*). (*C*) Spontaneous ST segment elevation and angina in the absence of epicardial spasm relieved by nitrate administration in a patient with coronary microvascular spasm. (*D*) Late gadolinium-enhanced (LGE) imaging in a patient with myocarditis; typical pattern of hyper-enhanced areas (dotted arrows), suggesting fibrotic tissue in the mid-inferolateral segments in short-axis orientation. (*E*) Thrombus (red arrow) in transit through a patent foramen ovale at two-dimensional transoesophageal echocardiography. (Ao, aorta; TV, tricuspid valve; LA, left atrium; RA, right atrium).

apical hyperkinesia, 'mid-ventricular type' with medio-ventricular ballooning and basal and apical hyperkinesia, 'localized type' with ballooning of a limited number of myocardial regions. Left ventriculography after documentation of MINOCA allows the diagnosis of TS. Myocardial contrast echocardiography with adenosine may confirm the diagnosis by showing reversible coronary microvascular constriction.[30] Cardiac magnetic resonance (CMR) with contrast medium (CM) shows the typical LV dysfunction without detectable myocardial necrosis after gadolinium administration.[33]

The long-term prognosis is extremely variable. In particular, Elesber *et al.*[34] reported a 4-year survival not different from that in an age- and sex-matched population (11.4%). However, intra-hospital mortality varies from 0 to 8%, whereas 1-year mortality is ~1–2%.[34] Major complications typically occur in the first phase, mostly related to heart failure, ventricular arrhythmias, rupture of the LV free wall, LV mural thrombus, and following risk of systemic embolization.

In TS, LV dysfunction may require prescription of β-blockers, angiotensin-converting enzyme inhibitors (ACEI) and diuretics, sometimes together with anticoagulant therapy in patients at risk of ventricular mural thrombus.[29,31] In patients with cardiogenic shock, intra-vascular treatment with inotropic agents, intra-aortic balloon pumping, and utilization of LV assist devices might be necessary.[31] Treatment of ventricular arrhythmias is also important.

Coronary microvascular spasm

Coronary microvascular spasm is characterized by transient transmural myocardial ischaemia, as indicated by ST-segment changes, during spontaneous or provoked angina, in the presence of normal epicardial coronary arteries (*Figure 3C*). It may be considered the unstable presentation of microvascular angina.[35] About 25% of patients with ACS and no obstructive CAD have evidence of microvascular spasm, although an increase of troponin is unfrequent.[36]

In this context, microvascular angina can be diagnosed when IC Ach test reproduces the symptoms usually experienced by the patients and triggers ischaemic ECG changes (i.e. ST-segment depression or ST segment elevation of ≥0.1 mV or T-wave peaking in at least two contiguous leads), in the absence of epicardial spasm (≥75% diameter reduction).[35]

Long-term prognosis of patients with coronary microvascular spasm seems to be good with regard to mortality; however, angina persists in about one-third of patients in spite of treatment with calcium channel blockers.[37] In this case, Fasudil may be considered a possible alternative treatment.

Myocarditis mimicking MI

In about one-third of patients, MINOCA is caused by acute myocarditis mimicking MI. Adenoviruses, parvovirus B19 (PVB19), human herpes virus 6, and Coxsackie virus are considered the most common causes of viral myocarditis. Previous studies suggested that the clinical presentation is related to the type of virus.[38] In particular, PVB19 myocarditis may mimic MINOCA. Indeed, endothelial cells represent PVB19-specific targets, probably through blood group P antigen.[39,40] Thus, symptoms of chest pain and ST segment elevation at ECG in patients with viral myocarditis but no obstructive CAD may be caused by intense coronary microvascular constriction, as a result of myocardial inflammation and/or PVB19 infection of vascular endothelial cells and microvascular dysfunction. Accordingly, Yilmaz *et al.*[40] demonstrated that, after administration of Ach, patients with myocarditis mimicking MINOCA showed constriction of the distal segment of epicardial vessel, with probable extension to coronary microcirculation.[39,40] Thus, the infection of coronary endothelial cells with PVB19 may cause a kind of 'coronary vasculitis', which may constitute a major determinant of the clinical course and of the myocardial spread of inflammation.[40]

Patients with myocarditis are usually young and with a recent history of fever or respiratory infection. Electrocardiographic findings vary from non-specific T wave and ST-segment changes to ST-segment elevation.[37] Left ventriculography and CMR are useful to detect global and regional wall motion abnormalities and to allow differential diagnosis with TS. In acute myocarditis diagnosis, CMR provides a sensibility of 100% and a specificity of 90%.[41] In particular, the late gadolinium enhancement reveals two common patterns of myocardial damage: either an intramural, rim-like pattern in the septal wall or a sub-epicardical patchy distribution in the free left ventricle lateral wall[41] (*Figure 3D*). Endomyocardial biopsy remains the gold standard for *in vivo* diagnosis of myocarditis, also providing prognostic information.[36] According to the guidelines, it should be performed in patients with suspected myocarditis mimicking MI and in the setting of unexplained new-onset heart failure of <2 weeks, with haemodynamic compromise and of uncertain aetiology.[42]

The prognosis of patients with myocarditis strictly depends on clinical presentation.[37,38] In a previous study enrolling 24 patients mimicking MI,[39] the persistence of virus genome was associated with progression of LV dysfunction and persistence of angina. Kindermann *et al.*[43] showed that, among patients with suspected myocarditis, advanced New York Heart Association functional class, immune-histological signs of inflammation, and lack of β-blocker therapy were independent predictors of death or transplantation at 5-year follow-up.

Treatment of myocarditis mimicking MI and characterized by LV dysfunction is based on the use of β-blockers and ACEI.[43]Recently, some trials tested more specific therapeutic approaches. In one study, in patients with enteroviral-associated myocarditis with LV dysfunction, virus clearance spontaneous or obtained by interferon-β administration was associated with a more favourable prognosis compared with those with virus persistence.[44]

Coronary embolism

Coronary embolism is included in microvascular causes of MINOCA as it usually involves microcirculation, although an angiographically visible embolization of epicardial coronary artery branches may occur. Of note, in this latter case, the coronary arteries are obviously not normal due to the evidence of either an abrupt vessel stump or thrombotic material inside epicardial coronary artery.

Coronary embolism should be suspected in patients with MINOCA and one of the following conditions associated with high risk of systemic embolism: prosthetic heart valves, chronic atrial fibrillation, dilated cardiomyopathy with apical thrombus, infective endocarditis, and mixoma.[45,46] In all these cases, a hypercoagulable state might predispose to thrombus formation.[47]

Paradoxical embolism (PE) is a rare cause of MINOCA. Paradoxical embolism can be related to a patent foramen ovale (PFO), a large atrial septal defect or a coronary arteriovenous fistula.[45–47] Of note, PE is more likely to be a cause of cryptogenic stroke more than of MI.[47] The criteria for PE diagnosis include the following:

evidence of arterial embolism in the absence of a source in the left heart, source of embolism in the venous system, and the communication between venous and arterial circulation.[48] However, unless a clear evidence is found like a thrombus transiting form the right to the left atrium (*Figure 3E*), it is difficult to ascribe occurrence of MINOCA to PE. In this context, transthoracic, transoesophageal, and contrast-enhanced echocardiography are the cornerstone methods for detection of cardiac sources of embolism as causes of MINOCA. Of note, Wohrle *et al.*[49] demonstrated subclinical MI in 10.8% of patients with PFO undergoing CMR after a first cryptogenic cerebral ischaemic event. Importantly, in patients in whom PE is suspected, coronary angiography needs to be carefully analysed for the identification of amputation of distal coronary branches.

Prognostic data of patients with PE and MINOCA are derived mostly from case reports and are mainly determined by the underlying cause that needs to be carefully identified as well as for cases caused by thrombus formation on left-side structures.

The treatment should be individualized and mostly focused on multiple factors including patient characteristics, time of presentation, and presence or absence of other embolic sites. With specific regard to atrial septal defect, PE requires transcatheter device closure or surgical repair.[45] The options for secondary prevention of PFO-induced cryptogenic embolism consist in the administration of anticoagulants or in percutaneous closure of PFO.[50] In this context, a recent trial showed that closure of PFO with the Amplatzer PFO Occluder for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of embolic events or death, when compared with medical therapy alone.[50] Anticoagulation is indicated for the treatment of the remaining cardiac causes of coronary embolism.

Conclusions

Myocardial infarction with no obstructive coronary atherosclerosis, a syndrome with several causes, is frequent in patients admitted with the diagnosis of MI. An accurate and systematic diagnostic work-up, summarized in *Figure 1*, is crucial for the identification of the cause of MINOCA in each individual patient, and then for risk stratification and for the implementation of the most appropriate forms of treatment. Yet, patients with MINOCA, in particular those with angiographically normal-coronary arteries, are frequently labelled as 'non-cardiac patients', thus missing the opportunity to appropriately treat patients with an outcome worse than previously believed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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