Acute coronary syndrome without coronary obstructions: diagnosis and treatment

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Abstract
Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) is a syndrome with different causes. Its prevalence ranges between 5% and 25% of all myocardial infarctions. The prognosis is extremely variable, as it strictly depends on the cause of MINOCA. Clinical history, electrocardiography, cardiac enzymes, echocardiography, coronary angiography, and left ventricular angiography represent first-level diagnostic investigations to identify the causes of MINOCA. This preliminary step helps divide patients presenting with epicardial or microvascular patterns and to perform specific additional tests for an adequate management workflow. This article will focus on the diagnosis and treatment of MINOCA.

Keywords: acute myocardial infarction; microcirculation; no obstructive coronary atherosclerosis

Introduction
Myocardial infarction (MI) with no obstructive coronary atherosclerosis (MINOCA) is characterized by clinical evidence of MI with normal or near-normal coronary arteries on angiography (stenosis severity <50%). The prevalence ranges between 5% and 25%,1,2 with a prevalence up to 25% among women and up to 10% among men who present with non–ST-segment elevation MI (NSTEMI).3

The first-level diagnostic investigations for MINOCA include clinical history, electrocardiography (ECG), cardiac enzymes, echocardiography, coronary angiography, and left ventricular (LV) angiography (Figure 1 and Table I).4 Regional wall motion abnormalities at LV angiography that are limited to a single epicardial coronary artery territory identify an “epicardial pattern,” whereas regional wall motion abnormalities that extend beyond a single epicardial coronary artery territory identify a “microvascular pattern.” Epicardial causes of MINOCA include coronary artery spasm and positive remodeling of unstable plaque, but no obstructive atherosclerosis. Takotsubo syndrome, coronary microvascular spasm, myocarditis mimicking MI, and coronary embolism can be considered microvascular causes of MINOCA (Figure 1).4

The rate of all-cause mortality during admission ranged from 0.1% to 2.2% and the 1-year post–MINOCA ranged from 2.2% and 4.7%.3,5 This article will focus on the diagnosis and treatment of MINOCA (Table I).
Epicardial causes of MINOCA

Coronary artery spasm

Coronary artery spasm occurs in 3% to 95% of patients with MINOCA; the extreme variability depends on the stimuli used to trigger the spasm (ergonovine vs acetylcholine), the definition of spasm, and ethnic reasons. Patients with coronary artery spasm typically have angina at rest, during the night, or early in the morning, which is associated with a transient ST-segment elevation at ECG. In the absence of ECG documentation, the diagnosis is based on an intracoronary provocative test and defined as a reduction of at least 75% of the vessel caliber together with symptoms/signs of myocardial ischemia. While the intracoronary ergonovine test is a standardized procedure, the dosage of intracoronary acetylcholine can vary from 2 to 200 µm for the left coronary artery and from 2 to 80 µm for the right coronary artery. The prevalence of coronary artery spasm is higher in the Japanese population compared with the Caucasian population, and it results in a poor outcome. Standard treatment includes nonspecific vasodilators, such as nitrates and calcium channel blockers. In cases that are refractory to standard treatment (10% to 20%), high doses of calcium channel blockers can be used. Fasudil, a Rho-kinase inhibitor, is effective in Japanese patients. Other potential treatments include β1-adrenergic receptor agonists and antioxidant therapy with vitamin E and C, and, in selected cases, stent implantation or partial sympathetic denervation can be considered. In patients at a high risk of spasm-related cardiac death, the use of an implantable cardiac defibrillator is required.

No obstructive coronary atherosclerosis with positive remodeling

The presence of eccentric plaques with positive remodeling resulting in a lack of obstructive coronary

**Fig. 1** Diagnostic algorithm of myocardial infarction with no obstructive coronary atherosclerosis.

Abbreviations: EBM, endomyocardial biopsy; IVUS, intravascular ultrasound; LV, left ventricular; OCT, optical coherence tomography; TEE, transesophageal echocardiography.

artery disease represents another epicardial cause of MINOCA. These lesions frequently show characteristics of vulnerability, ie, a large lipid pool and thin fibrous cap. Of note, hypercoagulability might enhance the detrimental consequences of these lesions. The instability of a nonobstructive unstable plaque can be caused by rupture of a thin fibrous cap (73%) or by plaque erosion (23%).

Coronary angiography can underestimate eccentric plaque with positive remodeling, thus justifying the use of intravascular imaging modalities, eg, intravascular ultrasound and optical coherence tomography. In particular, optical coherence tomography is more sensitive than intravascular ultrasound for identifying plaques with a large lipid pool and thin fibrous cap. These lesions are associated with a risk of cardiovascular events at follow-up that is comparable to that of patients with acute coronary syndrome and obstructive atherosclerosis. An observational study in the SWEDHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) that included 9466 consecutive, unique patients with MINOCA, showed long-term beneficial effects of treatment with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, a trend toward a positive effect with β-blocker treatment, and a neutral effect with dual antiplatelet therapy.

### Microvascular causes of MINOCA

#### Takotsubo syndrome

One of the microvascular causes of MINOCA is takotsubo syndrome. Its prevalence ranges between 1.2% and 2.2% of all cases of acute coronary syndrome. Although several etiopathogenetic mechanisms have been proposed, reversible coronary microvascular dysfunction seems to represent a common pathophysiological determinant of takotsubo syndrome.

Takotsubo syndrome is characterized by a high prevalence of postmenopausal females reporting a recent physical or emotional stress. The most common ECG abnormalities (eg, ST-segment elevation and T wave inversion) are usually observed during the acute and subacute phases. Typically, all patients exhibit marked LV dysfunction on admission, with a sizeable proportion showing a dramatic functional improvement over a period of days to weeks. Left ventriculography, after documentation of MINOCA, allows takotsubo syndrome to be diagnosed. These patients typically have hypokinesia or akinesia in the mid and apical segments, with preserved or hyperkinetic functions in the basal regions. However, other variants of takotsubo syndrome have been described. Myocardial contrast echocardiography with adenosine may confirm the diagnosis by showing reversible coronary microvascular constriction. Cardiac magnetic reso-
nance with contrast medium shows a typical LV dysfunction without detectable myocardial necrosis after gadolinium administration. Intra-hospital mortality varies from 0% to 8% and 1-year mortality is about 5.6% per patient-year.

LV dysfunction may require the prescription of β-blockers, angiotensin-converting enzyme inhibitors, and diuretics, sometimes together with anticoagulant therapy in patients who are at risk of a ventricular mural thrombus. Antiarrhythmic drugs play a crucial role in the acute and subacute phases of takotsubo syndrome. In patients with cardiogenic shock, intravascular treatment with inotropic agents, intra-aortic balloon pumping, and utilization of LV assist devices are mandatory.

**Coronary microvascular spasm**

Coronary microvascular spasm is characterized by transient transmural myocardial ischemia, as indicated by ST-segment changes during spontaneous or provoked angina and in the presence of normal epicardial coronary arteries. It accounts for approximately 25% of cases of acute coronary syndrome with MINOCA. Microvascular angina can be diagnosed when an intracoronary acetylcholine test reproduces the symptoms usually experienced by the patients and triggers ischemic ECG changes (ie, ST-segment depression or ST-segment elevation that is ≥0.1 mV or T-wave peaking in at least 2 contiguous leads), in the absence of epicardial spasm (≥75% diameter reduction). The long-term prognosis of these patients needs to be explored in adequate studies. The standard first-line treatment is the use of calcium channel blockers; however, in the case of refractory angina (25%), fasudil may be considered a possible alternative treatment.

**Myocarditis mimicking a myocardial infarction**

Acute myocarditis mimicking an MI represents a microvascular cause of MINOCA in about one-third of patients. The clinical presentation seems to be related to the type of virus. In particular, parvovirus B19 (PVB19) may cause myocarditis-mimicking MINOCA, probably because it targets endothelial cells through the blood group P antigen. Patients with myocarditis are usually young and with a recent history of fever or respiratory infection. The ECG findings vary from nonspecific T wave and ST-segment changes to ST-segment elevation. An endomyocardial biopsy is the gold-standard method for the in vivo diagnosis of myocarditis, which also provides prognostic information. It should be performed in patients with suspected myocarditis mimicking an MI and in the setting of unexplained new-onset heart failure (<2 weeks), with hemodynamic compromise and an uncertain etiology. Cardiac magnetic resonance is emerging as a useful method to detect global and regional wall motion abnormalities and to provide a differential diagnosis from takotsubo syndrome. Of note, late gadolinium enhancement reveals two common patterns of myocardial damage—an intramural, rim-like pattern in the septal wall or a subepicardial patchy distribution in the free left ventricle lateral wall.

The prognosis of patients with myocarditis strictly depends on clinical presentation. Treatment of a myocarditis-mimicking MI that is characterized by LV dysfunction is based on the use of β-blockers and angiotensin-converting enzyme inhibitors. Of note, Frustraci et al demonstrated that, in patients with active lymphocytic myocarditis with circulating cardiac autoantibodies and no viral genome in the myocardium, treatment with prednisone and azathioprine for 6 months caused a prompt improvement in LV ejection fraction.

**Coronary embolism**

Coronary embolism is included as a microvascular cause of MINOCA because it usually involves the microcirculation, although an angiographically visible embolization of the epicardial coronary artery branches may occur.

A paradoxical embolism can be related to a patent foramen ovale (PFO), a large atrial septal defect, or a coronary arteriovenous fistula. It should be suspected in patients presenting with MINOCA and one of the conditions associated with a high risk of systemic embolism. Of note, a hypercoagulable state might predispose the patient to thrombus formation. The criteria for the diagnosis of a paradoxical embolism include 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. Transthoracic, transesophageal, and contrast-enhanced echocardiogra-
phy are the cornerstone methods for detecting the cardiac sources of embolism as a cause of MINOCA. Importantly, the coronary angiography needs to be analyzed carefully for the identification of an amputation of the distal coronary branches. The standard treatment for MINOCA due to coronary embolism remains individualized and depends on multiple factors. When the thrombus has a systemic origin, therapy with warfarin will be prescribed. Aspirin and clopidogrel will also be used for the secondary prevention of coronary thrombi. The efficacy and safety of triple anticoagulation therapy (warfarin + aspirin and clopidogrel) will also be used for the secondary prevention of coronary thrombi. The efficacy and safety of triple anticoagulation therapy (warfarin + dual antiplatelet therapy) in the treatment and prevention of coronary embolisms remains unclear at this point. Regarding an atrial septal defect, paradoxical thromboembolism requires transcatheter device closure or surgical repair. If the cause of paradoxical embolization is a patent foramen ovale, the options for the secondary prevention of cryptogenic embolism consist of administering antithrombotic medications or percutaneous closure, although there is contrasting evidence for these methods.

Conclusions

MINOCA is frequently detected in patients admitted to the hospital with a diagnosis of MI. Our article shows that identifying the causes of MINOCA is the first step in guiding risk stratification and adequate management of these patients.

REFERENCES

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