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Role of optical coherence tomography in clinical management of myocardial infarction with nonobstructive coronary arteries

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ABSTRACT Myocardial infarction without angiographic moderate to severe stenosis (> 50%) and any other related diagnosis on clinical presentation is defined as myocardial infarction with nonobstructive coronary arteries (MINOCA). Common causes of MINOCA working diagnosis includes plaque disruption, spontaneous coronary artery dissection, coronary artery spasm, coronary thromboembolism, Takotsubo cardiomyopathy, and myocarditis. Clinical history, assay of myocardial enzymes, electrocardiogram, echocardiography, coronary angiography, and left ventriculography facilitate the initial diagnosis of MINOCA and reveal the underlying causes, while cardiovascular magnetic resonance and optical coherence tomography (OCT) are used to confirm the diagnosis. Although cardiovascular magnetic resonance is the gold standard noninvasive diagnostic tool for MINOCA, its ability to diagnose the cause and mechanism underlying this condition in the coronary arteries is limited because of its image resolution. Observational studies have demonstrated that OCT can be used to determine the underlying cause of MINOCA by investigating the characteristics of the culprit lesions and to predict the prognosis of the patients. In this article, we review the current diagnostic approach for MINOCA focusing on each imaging tool. Furthermore, we reevaluate the role of OCT in the clinical management of MINOCA. Identifying the cause of MINOCA through OCT might help select optimal and effective drug treatments and improve prognosis.

Acute myocardial infarction (AMI) is a leading cause of mortality worldwide.[1] However, diagnosis and treatment of patients with AMI without significant epicardial coronary obstruction is challenging.[2]

High-sensitivity cardiac troponin assay is used to diagnose AMI based on the presence of at least one troponin with a concentration exceeding the 99th percentile upper reference limit.[3] Suspected AMI is typically confirmed with coronary angiography (CAG) as the upstream investigation to determine the presence of epicardial coronary obstruction and guide decision-making for revascularization and medical therapies. The absence of obstructive coronary artery disease (CAD) in major epicardial vessels (stenosis severity < 50%) on CAG leads to a working diagnosis of myocardial infarction with nonobstructive coronary arteries (MINOCA).[4–6]

Common causes of MINOCA working diagnosis include plaque disruption, spontaneous coronary artery dissection, coronary artery spasm, coronary thromboembolism, Takotsubo cardiomyopathy, and myocarditis. The European Society of Cardiology (ESC) and American Heart Association guidelines recommend that the final diagnosis of the cause underlying MINOCA should be determined by cardiovascular magnetic resonance (CMR) and several kinds of intravascular imaging.[7,8] A study using optical coherence tomography (OCT) revealed variations in the prognoses of MINOCA with different underlying pathophysiologies.[9] The poor prognosis of MINOCA is often due to an inaccurate diagnosis of its underlying causes, resulting in inappropriate drug treatments. During the diagnostic process for MINOCA, patients with nonischemic origins were not clearly excluded, and most studies have been conducted on heterogeneous populations. Recent reports have suggested that early CMR can identify more accurate patient groups,[10] and may be useful for future investigations of MINOCA. However, delayed intracoronary ima-

ging evaluation due to early CMR might overlook hyperacute findings of thrombus or plaque disruption. Additionally, OCT may offer greater diagnostic accuracy than CMR for ischemic causes of MINOCA. Therefore, diagnosing the underlying cause of MINOCA using OCT may help in determining the appropriate drug treatment and improving prognosis. Herein, we review the current diagnostic approaches, describing each technique and reevaluating the role of OCT in the clinical management of MINOCA.

CURRENT DIAGNOSTIC APPROACHES TO MINOCA

The term MINOCA was first coined by John Beltrame in 2013 to replace the former terminology for myocardial infarction with normal coronaries, which included only patients without atherosclerosis of the epicardial vessels and excluded those with angiographic stenoses between 1% and 50%.[11] The 2015 ESC guidelines for patients with acute coronary syndrome without persistent ST-segment elevation emphasized that nonobstructive CAD is detected in 5%–20% of cases on CAG.[12] In 2023, the ESC updated their guidelines for acute coronary syndrome management to include a dedicated section for MINOCA.[7]

These guidelines recommend excluding clinically overt and systemic causes of myocardial injury, such as sepsis, pulmonary embolism, cardiac contusion, and other noncardiac causes, despite elevated levels of cardiac troponins in high-sensitivity cardiac troponin assays and including cardiac causes, such as structural myocardial dysfunction- and ischemic myocardial injury-related conditions to diagnose MINOCA. Suspected cases of MINOCA are confirmed by a diagnostic algorithm (Figure 1). Initial MINOCA diagnosis is based on clinical history, examination of myocardial enzymes, electrocardiogram, echocardiography, CAG, and left ventriculography. Coronary spasm provocative testing, CMR, and OCT are employed to determine the underlying causes of MINOCA and confirm the final diagnosis. Some reports have advocated for early CMR in investigating the causes of MINOCA. Mileva, *et al*.[10] suggested that early CMR should be conducted on patients suspected of MINOCA without stenosis of 50% or more. After being differentiated from those with non-ischemic patterns, patients with ischemic patterns should undergo further examination with

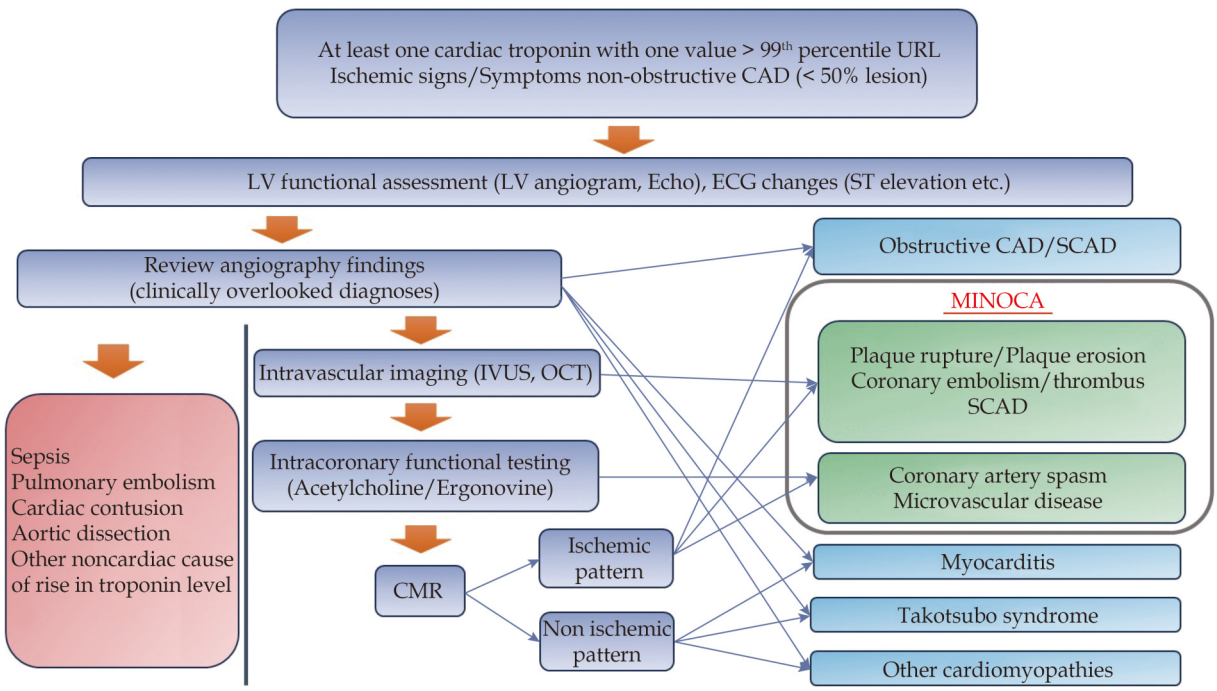

Figure 1 Diagnostic algorithm for MINOCA. Diseases in which cardiac troponin levels are elevated due to noncardiac causes, such as sepsis and pulmonary artery thromboembolism, are excluded (red). In suspected MINOCA cases (light blue), IVUS/OCT, acetylcholine provocation testing, and CMR are used to rule out non-ischemic heart diseases like Takotsubo cardiomyopathy and myocarditis. Thus, a true diagnosis of MINOCA is obtained (green). CAD: coronary artery disease; CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; IVUS: intravascular ultrasound; MINOCA: myocardial infarction with nonobstructive coronary arteries; OCT: optical coherence tomography; SCAD: spontaneous coronary artery dissection.

OCT and other methods. This approach addresses the issue of non-ischemic origins not being clearly excluded from the MINOCA patient population, leading to studies on heterogeneous groups. Early CMR can help identify a more accurate patient demographic, which is beneficial for MINOCA research. However, early CMR screening may delay OCT examination, potentially missing significant findings, such as thrombus and plaque disruption in the hyperacute phase. Additionally, OCT has identified causative lesions in 40% of patients without abnormal CMR findings.[13] This has suggested that many MINOCA patients might be incorrectly classified as non-ischemic by CMR. Therefore, relying on early CMR screening could result in missing true MINOCA cases and is considered an inappropriate diagnostic process. Our diagnostic algorithm recommends performing CMR to confirm the underlying mechanism only after excluding vascular causes through OCT and coronary spasm provocative testing.

Coronary Angiography

CAG is the typical upstream diagnostic test for AMI. For patients with obstructive CAD, the diagnosis is clear, and the treatment plan can be selected according to the CAG findings. Obstructive CAD may involve plaque disruption or coronary artery embolism in small coronary artery branches, leading to complete occlusion, or ≥ 50% distal stenosis in a major epicardial artery. On the other hand, the diagnostic criteria for MINOCA include having non-obstructive coronary arteries on angiography (< 50% stenosis). Therefore, CAG findings are crucial and should be thoroughly rechecked for any oversights before proceeding with further examinations. In MINOCA, coronary atheromatous plaque tends to develop eccentrically, and CAG mostly shows normal findings or mild stenosis.[14] Although CAG may indicate plaque disruption, it cannot determine the exact pathogenic mechanism underlying MINOCA.[15–19] Moreover, since myocardial injury may be induced by distal thromboembolism and/or vasospasm, a complete vascular occlusion may not be visible with CAG alone.[20]

Left Ventriculography

In cases of acute myocardial injury, left ventriculography or echocardiography are performed to assess wall motion abnormality, enabling clinicians to diagnose Takotsubo cardiomyopathy.[21] Since left ventricular wall motion evaluation by echocardiography may be insufficient, left ventriculography is recommended. In patients with suspected MINOCA, cardiac ventriculography rules out stress cardiomyopathy, or Takotsubo cardiomyopathy, which has a prevalence of 2% in suspected AMI cases.[22] Figure 2 shows the left ventriculography of a patient with Takotsubo cardiomyopathy. Enhanced sympathetic activity with catecholamine-induced toxicity in cardiomyocytes, triggered by emotions and/or physical stressors, underlie acute myocardial injury.[23] Because such acute myocardial injury is nonischemic, Takotsubo cardiomyopathy is not considered MINOCA.[4] Takotsubo cardiomyopathy diagnosis by cardiac ventriculography is limited by the lack of unique diagnostic characteristics. Nevertheless, Takotsubo cardiomyopathy has several distinct features, including apical ballooning and midventricular, basal, and focal patterns, with potential transitions across types and varying clinical presentations.[24,25] Concomitant CAD has been reported in 10%–29% of patients with Takotsubo cardiomyopathy, and AMI is a trigger for this condition.[4,26] Although cardiac ventriculography is traditionally regarded as the diagnostic gold standard for excluding Takotsubo cardiomyopathy in patients with suspected MINOCA, conclusive differentiation from AMI, myocarditis, and other cardiomyopathies is only possible with CMR.[21]

Coronary Spasm Provocative Testing

Provocative testing with intracoronary acetylcholine or ergonovine administration enables the evaluation of epicardial coronary spasm as a cause of MINOCA.[27–36] A positive response to acetylcholine or ergonovine spasm provocation testing is defined by transient occlusion or narrowing (> 90%) of a coronary artery with signs and symptoms of myocardial ischemia (angina/ST changes).[37] Figure 3 shows patients with MINOCA due to coronary spasm and administration of acetylcholine caused 99%

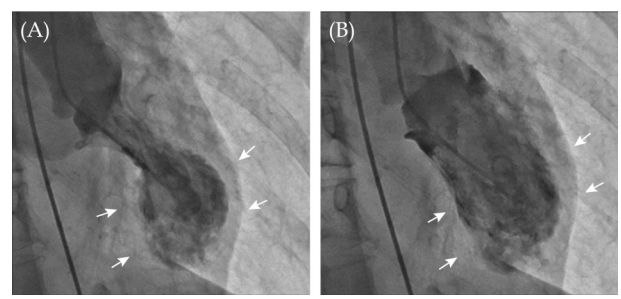

Figure 2 Left ventriculography of Takotsubo cardiomyopathy. Left ventriculography during the acute stage of Takotsubo cardiomyopathy shows apical ballooning (A: systole, B: diastole). Typical apical ballooning was observed during diastole.

stenosis of the left anterior descending coronary artery. Coronary spasm provocative tests have been reported to be safe even in the case of AMI.[38,39] A study comparing 84 patients with acute coronary syndrome who underwent acetylcholine provocation testing during emergency CAG with 445 patients tested in a non-emergency setting found no difference in serious complications or mortality between the groups.[40] Therefore, under carefully monitored conditions, acetylcholine provocation testing is considered safe for patients suspected of MINOCA, after excluding causes, such as plaque rupture. Prior research has indicated that a positive provocative test is predictive of adverse clinical outcomes in MINOCA,[38] with 43%–54% of patients showing coronary vasospasm.[41] Therefore, coronary spasm provocative tests are important for identifying patients with poor prognosis in MINOCA. This will help in determining appropriate medical interventions to improve prognosis of MINOCA with coronary spasms.

Cardiovascular Magnetic Resonance

CMR provides accurate visualization of abnormalities in regional wall motion, allowing precise quantification of left and right ventricular functions. T2-weighted and late gadolinium enhancement (LGE) sequences are used to assess both myocardial edema and scar formation. Myocardial edema marks the site of acute injury, and LGE is crucial in distinguishing acute ischemic damages from nonischemic injuries; intramyocardial or subepicardial LGE suggests a nonischemic cause, typically myocarditis, while subendocardial (partial thickness) or transmural involvement (full thickness) suggests an ischemic cause.[42,43] Considering the ability of CMR to detect various pathophysiological effects of reversible (e.g., inflammation and edema) and irreversible (e.g., necrosis and fibrosis) acute myocardial injury, it is the gold standard among noninvasive tools for diagnosis of MINOCA.[44] Moreover, CMR is invaluable in assessing Takotsubo cardiomyopathy, in which the absence of LGE, uniform regional distribution of edema, and specific wall motion abnormalities characterized by apical ballooning, midventricular, basal, and focal patterns.[45] However, CMR is not able to determine characteristics of coronary culprit lesion-causing acute myocardial injury. A previous study showed that despite normal CMR findings, the culprit lesion was identified by OCT in 40% of MINOCA.[13] Hence, the diagnostic capacity of CMR for MINOCA may be limited.

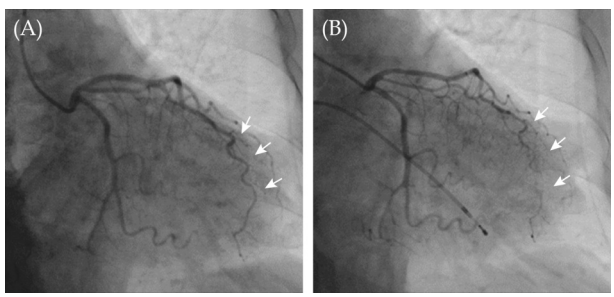

Figure 3 Coronary spasm provocative testing. Changes in coronary angiograms of the left coronary artery. (A): Pre-acetylcholine, normal coronary; and (B): during intracoronary acetylcholine infusion, 99% stenosis of the left anterior descending.

ROLE OF OCT IN CLINICAL MANAGEMENT OF MINOCA

OCT is a high-resolution tool for understanding of plaque characterization.[46] It can distinguish between the different components of plaque and thrombus by exploiting the unique optical properties of each tissue, such as fibrous, lipidic, and calcified components.[20] Coronary thrombosis is the most frequent final event leading to an acute coronary syndrome in patients with obstructive CAD. Autopsy studies have revealed that plaque rupture of thin-cap fibroatheroma, plaque erosion, and calcified nodule are the most common underlying mechanisms leading to thrombus formation, and that OCT can characterize the culprit plaque associated with these three pathologies.[47] Representative OCT images are shown in Figure 4. Because of its high resolution, OCT is useful in the management of obstructive CAD.[48,49] However, its use in the diagnosis of MINOCA is still limited. Figure 5 shows a representative patient with MINOCA whom OCT was useful for identifying the underlying cause. Despite CAG showed no significant stenosis, thrombus formation in the left main trunk was detected by OCT. Based on OCT findings, plaque erosion and subsequent thrombus formation probably be the cause of MINOCA in this case.

Observational studies have shown that OCT can be used to determine the underlying cause of MINOCA by visualizing plaque disruption or thrombus, thereby confirming the final diagnosis, and to predict prognosis. In the study using both OCT and CMR, 40% of patients without abnormal findings on CMR had an OCT-identified culprit lesion.[13] This finding underlines the importance of OCT in the diagnosis of MINOCA and supports the gu-

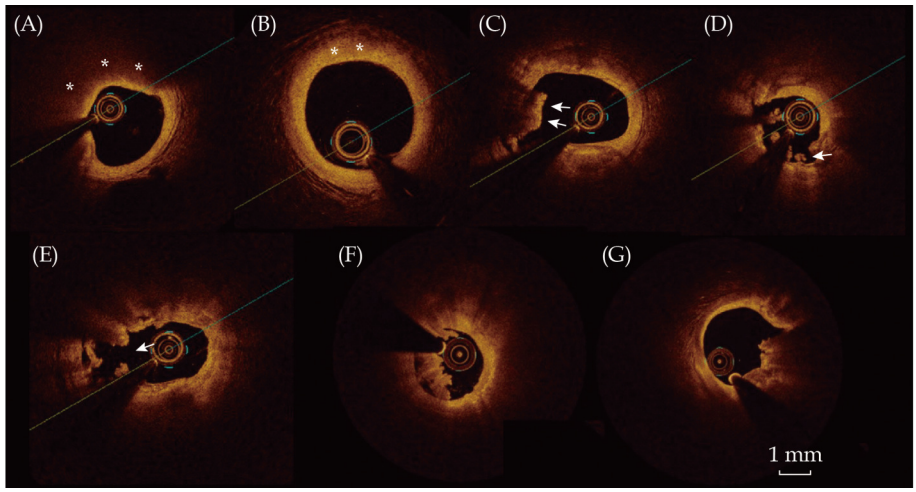

Figure 4 Representative optical coherence tomography images. (A): Lipid plaque; (B): fibrous plaque; (C): red thrombus; (D): white thrombus; (E): plaque rupture; (F): plaque erosion; and (G): calcified nodule.

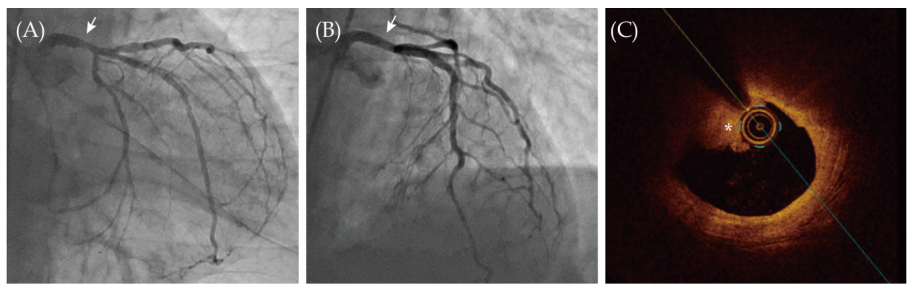

Figure 5 Coronary angiography and OCT in MINOCA. (A & B): Coronary angiography of a patient diagnosed with MINOCA. Coronary angiography showed no stenosis > 50%, but OCT revealed a thrombus in the main trunk of the left coronary artery. (A) right anterior oblique 30°/caudal 20°, (B) right anterior oblique 0°/cranial 30°; and (C): OCT image of the main trunk of the left coronary artery. Asterisk represents thrombus in the main trunk of the left coronary artery. MINOCA: myocardial infarction with nonobstructive coronary arteries; OCT: optical coherence tomography.

idelines recommending multimodal imaging in patients with MINOCA. Zeng, *et al.*[50] studied 190 patients with MINOCA using OCT and found atherosclerotic causes of MINOCA (plaque erosion, plaque rupture, and nodule calcification) in 64 patients (33.7%). Nonatherosclerotic causes of MINOCA (spontaneous artery dissection and coronary spasm) were found in 91 patients (47.9%). Compared to patients with nonatherosclerotic causes of MINOCA, those with atherosclerotic causes had worse clinical outcomes, higher incidence of major adverse cardiac events (15.3% *vs.* 4.5%, $P = 0.015$), and more frequent target lesion revascularization (6.1% *vs.* 0%, $P = 0.030$). Taruya, *et al.*[9] investigated the utility of OCT in predicting the prognosis of MINOCA and found that patients with high-risk lesions detected by OCT had poorer prognoses. Treatment with statins and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker can reduce major adverse cardiac events in patients with MINOCA by 23% and 18%, respectively.[51] Thus, regardless of the cause, anti-atherosclerotic drugs are effective in treating MINOCA. In contrast, dual antiplatelet therapy, which is commonly used to prevent myocardial infarction with CAD, did not significantly reduce major adverse cardiac events in that study.[51] Thus, patient selection for antiplatelet therapy based on the characteristics of the coronary culprit lesion on OCT may be required. Identification of the precise cause of MINOCA using OCT potentially help select optimal and effective drug treatments, thereby improving prognosis.

In another study, Usui, *et al.*[51] used OCT to identify differences between MINOCA and obstructive coronary lesions in women. While recently ruptured plaque and intraplaque hemorrhage were more prevalent in patients with MINOCA, plaque rupture with a persistent cavity and thrombus were more frequently found in patients with obstructive coronary lesions. These findings suggest a different etiopathogenetic mechanism underlying MINOCA, as highlighted by OCT.

CONCLUSIONS

MINOCA is a group of heterogeneous diseases with various underlying causes. Although CMR is the gold standard noninvasive diagnostic tool for MINOCA, its ability to diagnose the underlying cause and mechanism of MINOCA is limited. Despite the absence of obvious coronary stenosis in MINOCA, some patients with this disease have a high risk for adverse cardiovascular events. To improve prognosis in patients with MINOCA, precisely identifying the underlying cause is important. OCT plays an important role in diagnosing and understanding the mechanism of MINOCA. It is particularly useful in identifying the culprit lesions and their characteristics as atherosclerotic lesions. If the underlying causes of MINOCA can be precisely identified, optimal and effective drug treatments may be selected for patients, and improving their clinical outcomes finally.

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