Heart Metab. (2015) 67:15-20

High biomarkers, but normal angiogram: what next?

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Abstract

Myocardial infarction (MI) with nonobstructed (<50% stenosis) coronary arteries (MINOCA) represents a diagnostic and therapeutic dilemma. Potential diagnoses include both MI- and non-MI–related etiologies. A diagnostic algorithm that starts in the catheterization lab and incorporates cardiovascular magnetic resonance imaging and computed tomography narrows the differential diagnosis, allowing a targeted therapeutic approach that ultimately may improve prognosis. ■ *Heart Metab*. 2015;67:15-20

Keywords: acute myocardial infarction; angiography; cardiovascular magnetic resonance imaging; computed tomography; nonobstructed coronary arteries; normal coronary arteries

Myocardial infarction (MI) with nonobstructed (<50% stenosis) coronary arteries (MINOCA) occurs in approximately 6% of patients with suspected MI and represents a diagnostic and therapeutic dilemma.[1] The prevalence may be even higher in the era of high-sensitivity cardiac troponin (cTn) assays, because of their lower specificity to diagnose acute MI. It typically occurs in younger patients and an unsatisfying number of patients are ultimately discharged without a clear etiology for their episode of myocardial injury. Importantly, patients have an adverse outcome that may be related to inappropriate diagnosis and treatment.[2]

The underlying causes of MINOCA are heterogeneous and include plaque rupture with spontaneous coronary recanalization and/or distal embolization of plaque debris, coronary spasm, myocarditis, stress cardiomyopathy, pulmonary embolism, microvascular dysfunction, and others (*Table I*). Given this wide spectrum of potential diagnoses, it follows that the pathology is not exclusively related to MI, but includes non-MI diagnoses as well.

A crucial question is whether MINOCA is associated with vulnerable plaques or not. In more than half of patients with MINOCA, some degree of coronary artery disease (CAD) can be found, including outward/positively remodeled atherosclerotic plaque within a coronary artery.[3] Although MI is frequently triggered by atherosclerotic plaques which previously did not cause severe stenosis,[4] holding such plaques responsible for the index event in patients with MINOCA is jumping to conclusions. This "smoking gun" theory is also challenged by the observation that an equal burden of CAD can be found in matched healthy controls without known cardiovascular disease[5] and that MI is finally diagnosed in only 20% of patients.[1]

Abbreviations

CAD: coronary artery disease; **CT:** computed tomography; **cTn:** cardiac troponin; **IVUS:** intravascular ultrasound; **MINOCA:** myocardial infarction with nonobstructed coronary arteries; **MRI:** magnetic resonance imaging; **OCT:** optical coherence tomography; **WMA:** wall motion abnormality

The presence of minimal CAD can merely be a coincidental finding. Alternatively, microvascular disease as a result of coronary vasomotor dysfunction and/or decreased intramyocardial capillary density in hypertensive or diabetic patients or in hypertrophic cardiomyopathy, are increasingly recognized entities.[6]

Other non-MI diagnoses should be taken into account and inappropriate treatment and stigmatization of patients, as having suffered a MI, should be avoided. Current guidelines do not provide recommendations on how to deal with these patients,[7,8] but additional diagnostic testing is often needed to narrow the differential diagnosis.

MI related	Non-MI related
Plaque rupture or erosion and spontaneous recanalization	Myocarditis
Coronary spasm in setting of - Endothelial dysfunction - Cocaine abuse - Ephedrine-containing drug abuse - Withdrawal from calcium antagonists	Stress cardiomyopathy
	Pulmonary embolism
	Dilated cardiomyopathy
	Hypertrophic cardiomyopathy
	Microvascular dysfunction (syndrome X)
(Paradoxical) coronary embolism - Myocardial tumor (myxoma) - Myocardial thrombus (post-MI, atrial fibrillation) - PFO or ASD	Pheochromocytoma
	Sarcoidosis
	Connective tissue disease (SLE)
Hypercoagulable status - Factor V Leiden - Prothrombin G20210A gene mutation - Protein C deficiency - Protein S deficiency - Antithrombin deficiency - Hyperhomocysteinemia - Antiphospholipid antibody syndrome	
Myocardial bridging	
Demand ischemia - Tachycardia (eg, atrial fibrillation) - Severe hypertension (>200 mm Hg systolic) - Congestive heart failure	

Table I *Potential causes of myocardial infarction with nonobstructed coronary arteries (MINOCA).*
Abbreviations: *ASD, atrial septal defect; MI, myocardial infarction; PFO, patent foramen ovale; SLE, systemic lupus erythematosus.*

Initial diagnostic evaluation

The interventional cardiologist is often the first to be confronted with MINOCA. Myocardial bridging, spontaneous coronary dissection, and missed proximally occluded side-branches should carefully be excluded. Provocative testing using intracoronary ergonovine or acetylcholine can be performed to exclude coronary vasospasm as a result of endothelial dysfunction and concealed atherosclerosis. Because coronary angiography does not allow visualization of the vessel wall, vulnerable plaques could be sought using either intravascular ultrasound (IVUS) or optical coherence tomography (OCT) while the patient is still in the catheterization lab. A thin fibrous cap, large plaque burden, large lipid core, and small lumen area are morphological characteristics of ruptured and vulnerable coronary plaques.[9] However, an extensive and "blind" exploration of the complete coronary tree in search for concealed atherosclerosis is impractical, time-consuming and not without risk. Restricted availability, expertise, higher costs, and additional radiation exposure for patients further limit widespread use of OCT and IVUS. Moreover, far too many patients are sent back to the ward without further invasive testing, leaving the clinician in despair.

Clinical characteristics are not specific, but can be useful to narrow the differential diagnosis. The presence of multiple risk factors for atherosclerosis (smoking, abnormal lipid profile, positive family history, diabetes, hypertension) increases the likelihood of concealed atherosclerosis. A family or personal history of hypercoagulability and thromboembolism may warrant a search for hereditary thrombophilia, such as factor V Leiden, prothrombin G20210A gene mutation, protein C, protein S, antithrombin deficiency, hyperhomocysteinemia, or the antiphospholipid antibody syndrome. Routine blood testing may reveal elevated inflammatory parameters or elevated D-dimer levels that may suggest myocarditis or pulmonary embolism, respectively. However, the information received from history or additional blood tests often lacks specificity and provides evidence too circumstantial to be clinically useful. Additional noninvasive imaging may further narrow the differential diagnosis.

Noninvasive imaging

Cardiac magnetic resonance imaging

Although a single test that untangles all different etiologies in patients with MINOCA is not available, cardiac magnetic resonance imaging (MRI) may differentiate between potential causes. A comprehensive cardiac MRI examination provides information on myocardial function (cine imaging), inflammation (T2-weighted imaging), and fibrosis (delayed enhancement imaging), and allows categorization of potential etiologies, both MI- and non-MI–related.[10]

Cardiac cine MRI accurately and reproducibly provides assessment of cardiac function, volumes, mass, and morphology. Consequently, regional wall motion abnormalities (WMAs) that are confined to a corresponding coronary artery territory are highly suspicious, but not diagnostic for MI. WMAs outside a single coronary artery territory or extending over multiple territories occur with either myocarditis or stress cardiomyopathy. Dilated or hypertrophic cardiomyopathy can also be suggested from cardiac cine MRI.

T2-weighted cardiac MRI enables visualization of myocardial edema (T2-hyperintensity) and may be used to detect acute MI, myocarditis, or stress cardiomyopathy.[11] In acute MI, edema is typically subendocardial or transmural, and sometimes accompanied with intramyocardial hemorrhage (central hypoenhancement within hyperenhanced area) (*Figure 1, case 1)*. In myocarditis, T2-hyperintensity is mostly patchy, mid-wall, or epicardial, and located in the septal and/or basal inferolateral segments (*Figure 1, case 2)*. A cardinal feature of stress cardiomyopathy (also "takotsubo cardiomyopathy" or "transient apical ballooning") is reversible regional WMAs and edema that extends beyond a single

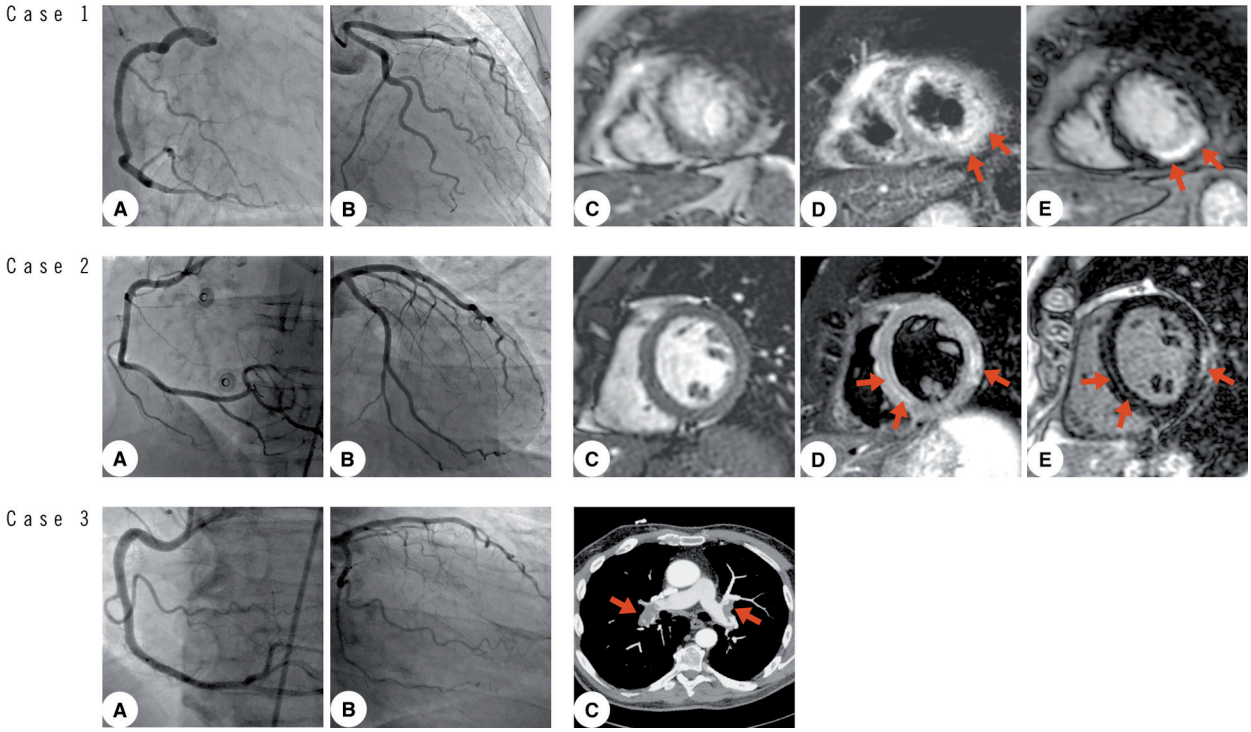

Fig. 1 *Patient examples.* ***Case 1.*** *An 82-year-old woman who presented with acute chest pain and diaphoresis. The electrocardiogram (ECG) showed ST-segment elevation in inferolateral, and ST-segment depression in anteroseptal, leads. High-sensitivity cardiac troponin T (cTnT) levels were elevated (40 ng/L and 317 ng/L at presentation and 3-hour follow-up, respectively). Urgent invasive coronary angiography showed vessel wall irregularities of both left and right coronary arteries (**A, B**). Cardiac magnetic resonance imaging (MRI) is consistent with an acute subendocardial myocardial infarction: akinesia on cardiac cine MRI (**C**), subendocardial increased signal intensity on the T2-weighted (edema) imaging (**D**), and delayed enhancement (scar) (**E**) in the apical mid-inferolateral segments (arrows).* ***Case 2.*** *A 31-year-old man who presented with acute chest pain and flu-like symptoms. The ECG showed ST-segment elevation in the lateral leads and high-sensitivity cTnT level was elevated (1572 ng/L) at presentation. Invasive coronary angiography revealed normal coronary arteries (**A, B**). A subsequent cardiac MRI examination is consistent with myocarditis: hypokinesia on cardiac cine MRI (**C**), focal mid-wall to epicardial increased signal intensity on the T2-weighted (edema) (**D**), and the delayed enhancement images (scar) (**E**) in the mid-inferolateral segments (arrows).* ***Case 3.*** *A 66-year-old man who presented with acute chest pain. The ECG showed inverted T-waves in the anterior leads. High-sensitivity cTnT and D-dimer levels were elevated (34 ng/L and >10000 ng/mL, respectively). Urgent invasive coronary angiography revealed normal coronary arteries (**A, B**). Transthoracic echocardiography was judged as normal. A computed tomography (CT) scan was deemed more appropriate than cardiac MRI, and showed bilateral pulmonary emboli (**C**).*

coronary artery in the absence of myocardial scar and is often triggered by emotional or physical stress.[11]

Delayed enhancement cardiac MRI is capable of visualizing small scars that cannot be detected by other imaging techniques and allows differentiation between MI- and non-MI–related etiologies.[10] Based on the concept that ischemic necrosis proceeds as a "wavefront" from the subendocardium to the epicardium with increasing occlusion time, it follows that hyperenhancement patterns that spare the subendocardium are likely to be nonischemic in origin. Thus, ischemic damage from CAD typically involves the endocardium,[10] whereas mid-wall to epicardial scar (either patchy or linear) is consistent with myocarditis or dilated or hypertrophic cardiomyopathy. In such cases, the coronary angiogram should be reassessed for proximally occluded side branches that may have been missed initially.

A specific diagnosis can be provided by cardiac MRI in up to 75% of patients with MINOCA[12] and include MI (5% to 29%), myocarditis (7% to 63%), stress cardiomyopathy (2% to 22%), pericarditis (0% to 5%), amyloidosis (0% to 5%), and hypertrophic or dilated cardiomyopathy (0% to 4%).[13] Nonetheless, a large subset of patients do not have any abnormalities on cardiac MRI.[1] This may be explained by an insufficient resolution of cardiac MRI to detect limited myocardial damage, disease recovery (eg, stress cardiomyopathy [for this reason cardiac MRI should be performed early]), or other etiologies for MINOCA undetectable by cardiac MRI. New developments, such as T1- and T2-mapping techniques may further increase cardiac MRI's diagnostic accuracy, but validation is still awaited.[14] The diagnostic role of adenosine stress-perfusion cardiac MRI to detect microvascular disease is still debated.

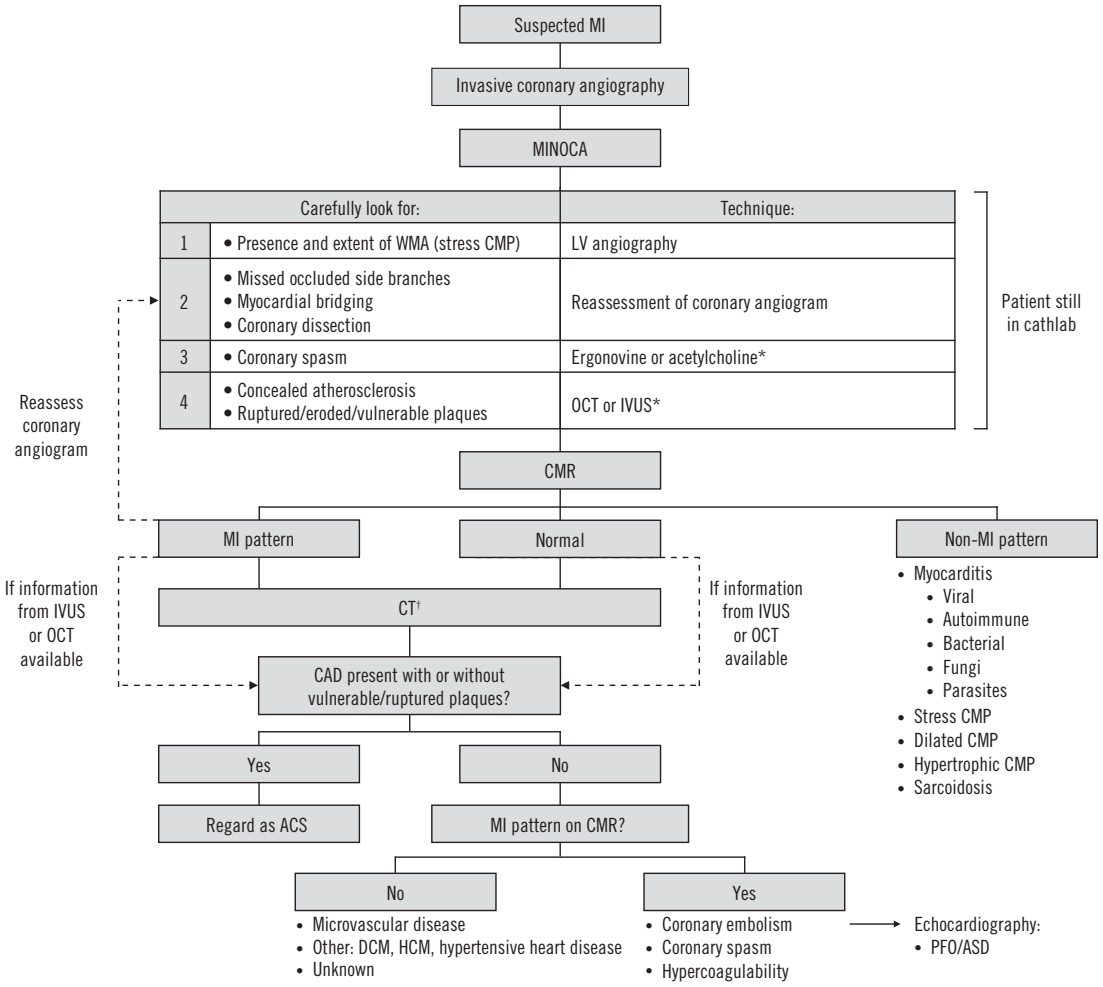

Fig. 2 *Potential diagnostic strategy in patients with MINOCA. *When available. †Perform "triple rule out" CT when high suspicion for pulmonary embolism or acute aortic dissection (elevated D-dimer).*

Abbreviations: *ACS, acute coronary syndrome; ASD, atrial septal defect; CAD, coronary artery disease; CMP, cardiomyopathy; CMR, cardiac magnetic resonance imaging; CT, computed tomography; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IVUS, intravascular ultrasound; LV, left ventricle; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructed coronary arteries; OCT, optical coherence tomography; PFO, patent foramen ovale; WMA, wall motion abnormalities.*

Computed tomography angiography

Atherosclerosis may be present, but concealed on routine invasive coronary angiography because of outward remodeling of atherosclerotic plaques. Computed tomography (CT) angiography is very sensitive in detecting CAD and rules out atherosclerosis with high confidence.[15] Initial noncontrast enhanced CT scanning may identify calcified coronary plaques, but when absent, does not rule out the existence of noncalcified plaques.[3] Therefore, iodine contrast agents are usually administered to visualize the coronary lumen, the vascular wall, and (noncalcified) plaques. Completely normal coronary arteries on CT angiography and a zero calcium score exclude atherosclerotic CAD as a cause for MINOCA.

In the presence of atherosclerosis, CT angiography allows characterization of plaques. In general, vulnerable plaques are noncalcified, have a large plaque area, a large lipid core, and more frequently show outward remodeling.[3] The high resolution of CT angiography allows identification of ruptured plaques, but is insufficient to detect the thinned fibrous cap of eroded plaques.[16] Even though there are no distinct characteristics for plaque erosion, the presence of a ruptured or vulnerable plaque may be sufficient to indicate a plaque-related etiology in a patient with MINOCA.

In addition to coronary artery evaluation, specific contrast bolus protocols allow opacification of coronary arteries, the aorta, and the pulmonary arteries in a single CT angiography scan ("triple rule out" protocol). Using this comprehensive scanning protocol may be beneficial in selected patients to quickly rule out CAD, aortic dissection, and pulmonary embolism (*Figure 1, case 3*).[17] Furthermore, CT may identify other clinically important diagnoses such as a coronary anomaly, malignancy, or pneumonia.[17]

Conclusion

Diagnosing patients with MINOCA remains challenging and includes both MI- and non-MI–related diagnoses. The diagnostic algorithm should start in the catheterization lab, followed by a staged use of noninvasive imaging techniques (*Figure 2*). Cardiac MRI plays a crucial role in narrowing the differential diagnosis. In combination with results from the history, and invasive (OCT or IVUS) or noninvasive techniques (CT), CAD is ruled out or becomes more plausible. In the setting of MI without CAD, a thorough search should be performed for (paradoxical) coronary embolism (exclude atrial fibrillation, myocardial tumor or thrombus, patent foramen ovale, or atrial septal defect) or hypercoagulability disorders. Unfortunately, in an unsatisfying number of patients, the etiology remains unknown. ■

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