Nonatherosclerotic Cardiovascular Diseases in Women

Reviewing the clinical presentation, pathophysiology, diagnostic pathway, and treatment of MINOCA, SCAD, and microvascular dysfunction in female patients.

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Acute coronary syndrome (ACS) presentations are often complex and multifaceted. Some are associated with established risk factors, some with novel risk factors, and some as the result of female sex–specific risk factors.[1] Nonatherosclerotic cardiovascular disease is more often found in women with ACS and may be due to spontaneous coronary artery dissection (SCAD) or coronary microvascular dysfunction (CMD).[2,3]

MYOCARDIAL INFARCTION WITH NONOBSTRUCTIVE CORONARY ARTERIES

The term myocardial infarction with nonobstructive coronary arteries (MINOCA) is an umbrella term used to describe myocardial infarction (MI) (rise and fall in troponin, with either confirmed symptoms of ischemia, electrocardiogram (ECG) changes, or imaging-confirmed MI or on angiography) with nonobstructive coronary arteries on angiography (≤ 50% stenosis) and without an overt cause for the MI, such as cardiac trauma or injury, sepsis, pulmonary embolism, or myocarditis.[3] Patients with MINOCA represent 5% to 25% of all patients with a clinical diagnosis of MI.[3,4] MINOCA is associated with a significant 1-year mortality of 0.6% compared to a mortality of 2.3% for an MI with obstructive coronary artery disease.[5,6]

Clinical Presentation

Consideration of the diagnosis begins with patients presenting with cardiac-sounding chest pain, troponin elevation, and ECG changes suggestive of an acute MI, without an identifiable culprit lesion on coronary angiography.[4,7]

Pathophysiology

MINOCA may result from several different pathologies, including plaque rupture, ulceration or erosion, CMD, vasomotor dysfunction, SCAD, and coronary thromboembolism.[2,3,8-11]

Diagnostic Pathway

Blood tests, including blood count, renal function, electrolytes, glucose, C-reactive protein, serial troponins, B-natriuretic peptide, clotting screen, and D-dimer, should be performed.[7]

A left ventriculogram is helpful to assess for Takotsubo cardiomyopathy, but an echocardiogram will suffice and may also provide additional information, such as source of emboli or regional wall motion abnormalities.

Obtaining the diagnosis in MINOCA is key, and hence the coronary angiogram is the start of the investigative process, not the finish. Angiography is followed by intravascular imaging, including intravascular ultrasound or optical coherence tomography, to enhance the detection of plaque abnormalities (found in up to 40% of MINOCA cases[10,11]) such as rupture, erosion, ulceration, or even hemorrhage within the plaque.[9-12]

After excluding significant plaque pathology with intravascular imaging, the patient should be assessed with coronary pressure wire to identify CMD or vasospastic disease.[13] This should include measurements of coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR). Further detail regarding coronary physiology assessments is provided later in the CMD

section. Tests for vasospasm are often deferred until the convalescent phase.

Cardiac MR (CMR) with gadolinium contrast should be performed in all patients to determine potential causes of MINOCA presentations.[2] Late gadolinium enhancement (LGE) on CMR enables assessment of the localization and size of the infarct in MINOCA. The extent of LGE allows differentiation between MI and myocarditis with typical subendocardial/transmural and subepicardial/mid-wall pattern, respectively. The diagnostic precision of CMR is increased when imaging is undertaken within 7 to 14 days of presentation. Delayed imaging may result in certain pathologic changes, such as myocardial edema in myocarditis no longer being apparent.

Treatment

Treatment is dependent on the causation of the MINOCA presentation. In general, there is evidence of benefit of treatment with statins and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and some benefit with β-blockers.[13-15] MINOCA resulting from plaque disruption should additionally be treated with dual antiplatelet therapies,[2] and in those with coronary embolism, with some form of anticoagulation or antiplatelets.[16] Calcium-channel blockers are useful in vasospastic MINOCA, as are long-acting oral nitrates and potassium-channel activators.

SPONTANEOUS CORONARY ARTERY DISSECTION

SCAD is a less common but increasingly recognized cause of ACS (16% of all causes)[9] and may fall within a MINOCA classification, as not every case of SCAD results in complete vessel occlusion. The diagnosis of SCAD may be missed at the time of angiography as the changes may be subtle or in a distal location and, on occasion, misinterpreted as atherosclerotic stenosis. Ninety percent of SCAD patients presenting with acute STEMI are women.[11] Recognition of, and heightened suspicion for, SCAD is important as conservative management is ideal in the absence of refractory symptoms and/or ST-segment elevation.[17]

SCAD usually occurs in younger women (aged < 50 years) and is responsible for up to 34% of ACS presentations in women.[18,19] The risk of recurrence is 27% at 5 years.[20] Despite an initial description of a case in 1931,[21] SCAD has been underrecognized and underdiagnosed for decades. Recently, better recognition and awareness, along with greater use of intravascular imaging, have resulted in improved detection.

Although SCAD was initially described in peripartum women, the peripartum clinical setting represents < 10% of all SCAD cases.[19,20,22] That said, 50% of ACS in peripartum women is a result of SCAD.[23] SCAD is associated with fibromuscular dysplasia, which should be screened for once SCAD is diagnosed.[24-28]

Clinical Presentation

SCAD should be suspected in young or middle-aged women who have few traditional cardiovascular risk factors presenting with MI. Acute chest pain is reported in 60% to 90% of SCAD cases.[29-31]

Pathophysiology

SCAD results from either a rupture of the vaso vasorum into the media or an intimal tear, either of which result in an intramural hematoma that compromises coronary flow.[32]

Diagnosis

The first-line diagnostic examination remains the invasive coronary angiogram. Despite its inherent limitations as a "lumenogram," different SCAD patterns have been described, and Saw et al proposed an angiographic classification[33] that is now widely adopted. In the case of nondiagnostic coronary angiography, intracoronary imaging may be considered to facilitate the diagnosis of SCAD[34,35] and then to tailor the medication appropriately. Coronary CT angiography may also be considered but may not have the sensitivity and visual resolution to detect intimal flaps or distal dissections.[36]

Treatment

Coronary angiography is the most helpful tool for diagnosis. However, the recommended management is usually conservative. In most cases, spontaneous healing occurs.[17,27] The recommended conservative strategy includes in-hospital monitoring. Percutaneous interventions should be avoided and only undertaken if there is vessel occlusion and ongoing symptoms for fear of propagation of the intramural hematoma. Coronary artery bypass grafting has been reported in extreme cases. Of note, extension of the intramural injury or a new SCAD have been reported in 5% to 10% of the cases.[19,37] No randomized control trials of management have been completed to date, although at least one is planned. Therefore, current guidelines are derived from consensus expert opinion.[17]

There is variable opinion on the utility of dual antiplatelet therapy after a SCAD event, given that many cases occur in the absence of atherosclerosis, but aspirin is often a mainstay of therapy. Statins have not been shown to impact SCAD recurrence: β-blocker therapy is the only therapy to date that has been shown to reduce SCAD recurrence.[38] ACE/ARBs are recommended if there is any

evidence of left ventricular impairment. Antianginals, including nitrates, calcium antagonists, and ranolazine, may be considered for symptomatic patients.[17]

Prognosis

The initial prognosis appears to be more favorable than observed in atherosclerotic ACS, particularly in conservatively treated patients.[27] However, rates of major adverse cardiac events and SCAD recurrence vary considerably in the literature, highlighting the need for longer-term follow-up and further dedicated studies.

CORONARY MICROVASCULAR DYSFUNCTION

The coronary vessels supply the myocardium with oxygenated blood via the larger epicardial arteries (the macrocirculation) that are visible angiographically and the smaller pre-arterioles, arterioles, and capillaries. Smaller vessels (< 200 mm in diameter) comprise the coronary microcirculation and are responsible for the majority of vascular resistance, particularly under coronary vasodilatory circumstances.[39] CMD is defined as elevated microvascular resistance leading to abnormal coronary microvascular vasodilation, impaired myocardial flow during hyperemia, and myocardial ischemia without evidence of epicardial coronary artery disease.[40] Impaired coronary microcirculatory function can manifest as anginal symptoms and objective ischemia, even in the absence of epicardial coronary disease, known as ischemia with nonobstructive coronary arteries (INOCA).[41]

Epidemiology/Clinical Presentation

CMD is estimated to affect 41% of patients with nonobstructive coronary disease, as defined by invasive angiography, and is more common in women than in men.[42] Common symptoms include chest pain or discomfort, dyspnea, heart failure, exercise intolerance, or generalized fatigue.[43] The presence of CMD predicts major adverse cardiac events, including death, hospitalization for heart failure, and nonfatal MI.[44]

Associated Conditions

Risk factors for the development of CMD overlap with risk factors for atherosclerotic coronary artery disease. CMD has been demonstrated in patients with diabetes,[45] hyperlipidemia,[46] and tobacco use[47] and increases with age. CMD has been linked to sudden cardiac death and systolic dysfunction in patients with hypertrophic cardiomyopathy,[48] and it is postulated to play a role in heart failure with preserved ejection fraction (HFpEF)[49] and, when present, is associated with worse outcomes.[50] CMD is thought to be present after ischemic insult, with vasoconstriction attributed to increased sympathetic tone and reperfusion injury.[51]

Pathophysiology

CMD is caused by structural and/or functional abnormalities of the microvasculature. Structural changes, such as intimal thickening, vascular smooth muscle cell hypertrophy, or proliferation, and increased fibrosis of the extracellular matrix may all contribute to impaired vasodilation. These structural changes have been described in the setting of chronic arterial hypertension, aortic stenosis, and hypertrophic cardiomyopathy.[52] Impaired vasodilatory function may be provoked by endothelial dysfunction, vascular smooth muscle cell dysfunction, and/or imbalance of vasoactive mediators, including nitric oxide, prostacyclin, and endothelin.[53] Chronic tobacco use, hyperlipidemia, and diabetes result in endothelial dysfunction and an increase in vasoreactivity, whereas arterial hypertension and hypertrophic cardiomyopathy can cause dysfunction of smooth muscle cells.[52-54]

Physiologic Assessment and Diagnosis

The diagnosis of CMD is made when a patient presents with symptoms suggestive of ischemia, there is objective evidence of ischemia in the absence of obstructive coronary artery disease, and abnormal coronary microvascular blood flow has been confirmed by noninvasive or invasive methods. Both noninvasive and invasive methods aim to estimate coronary blood flow by calculating CFR, which is a measure of capacitance of the epicardial coronary arteries and coronary microvasculature. Because resistance in the coronary circulation is mainly a function of the microvascular circulation, in the absence of epicardial coronary disease, the ratio of coronary blood flow at maximal vasodilation (hyperemia) to flow at rest demonstrates the ability of the microvasculature to respond to a stimulus. A CFR ratio of < 2.5 is considered abnormal in invasive assessments, ratios between 2 to 2.4 are considered to be in the grey area.[43] When assessed noninvasively, a myocardial perfusion reserve score < 2 is considered abnormal.[51]

Noninvasive Assessment

Cardiac positron emission tomography can be used for the diagnosis of microvascular disease. Using an injected radioisotope, it can assess perfusion across all coronary beds at rest and stress. With postimaging processing, both regional and global CFR can be calculated.[55] Similarly, CMR imaging can also be used to evaluate perfusion at rest and stress with a gadolinium-based contrast agent.[55] Although postprocessing of the images is technically challenging and time consuming, the lack

of ionizing radiation provides an advantage over other methods of assessment. Doppler echocardiography of the proximal left anterior descending artery can also be used to calculate CFR[56]; however, it is prone to greater operator variability. Dynamic myocardial perfusion CT uses iodinated contrast and provides superior spatial resolution, but it does confer a higher radiation dose.[55]

Invasive Assessment

Increasingly, CMD is being diagnosed invasively during routine diagnostic coronary angiography. Invasive evaluation for CMD for those with INOCA has a class IIa recommendation in both the 2021 "AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain" and the 2019 "ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes."[31,57] After ruling out obstructive coronary artery disease and evidence of congestive heart failure, CMD may be measured via a Doppler or thermodilution method, the latter of which is currently more widely available. Invasive measurement of CMD involves placement of a thermodilution wire in a coronary artery. After anticoagulation, pressure equalization of the wire in the aorta, and flushing the catheter with saline, the thermodilution wire (PressureWire X, Abbott) is placed in a coronary artery via a 6-F guide catheter, typically into the distal left anterior descending artery but occasionally into other vessels if there is a specific territory of interest. Nitroglycerin is administered, and then three injections of 3-mL saline at room temperature are flushed into the coronary artery to measure a transit time. The same procedure is performed with hyperemia, usually using intravenous adenosine. By measuring the mean transit time of blood at rest and at hyperemia, CFR can be calculated. In addition to CFR, when the thermodilution method is used, the index of microvascular resistance (IMR) is calculated using mean transit time at hyperemia in addition to distal coronary pressure. Fractional flow reserve (FFR) and resting full-cycle ratio are also reported with CFR. IMR is a measurement specific to microvascular blood flow.[58] IMR calculations assume that coronary blood flow is equal to myocardial blood flow, and the contribution of collateral blood flow is negligible.[59] CMD is diagnosed with an FFR > 0.80, CFR < 2.5, and IMR ≥ 25. Invasive assessments for CMD are sometimes paired with an assessment of epicardial coronary vasospasm, which has been described elsewhere.[60]

Treatment

Aggressive management of risk factors for coronary disease, such as hyperlipidemia, diabetes, and hypertension, are mainstays in the management of CMD. Exercise and weight loss[61] in obese patients can improve CFR in addition to cardiovascular outcomes. Pharmacologic therapy includes the use of traditional antianginal medications, such as β-blockers and calcium channel blockers.[62] Medications such as ranolazine, ivabradine, trimetazidine, and nicorandil have also been studied, with mixed benefit.[62] SGLT2 inhibitors have shown clear clinical benefit in HFpEF and have been shown to improve CFR in murine models but require further study in humans.[63]

CONCLUSION

INOCA and MINOCA are common and are becoming increasingly recognized. The etiology of MINOCA can be traced in many circumstances. The ability to harness existing diagnostic tools, including coronary angiography, intravascular imaging, invasive and noninvasive physiology, and cardiac imaging with cardiac MRI are all critically important to providing patients with a diagnosis, guidance, and treatment recommendations. ■

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