JACC: CASE REPORTS VOL. 4, NO. 5, 2022

EDITORIAL COMMENT

Is Vasospastic Coronary Disease More Common Than We Realize?*

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Myocardial infarction with nonobstructive coronary arteries (MINOCA) is characterized by criteria for acute myocardial infarction, absence of obstructive coronary artery disease (>50% stenosis), and no other obvious cause for presentation (such as myocarditis, Takotsubo and other types of cardiomyopathies, and noncardiac pathologies such as pulmonary embolism).[1] Potential underlying causes of MINOCA typically include coronary vasospasm, microvascular dysfunction, spontaneous coronary thrombosis and emboli with recanalization, plaque disruption, and spontaneous coronary artery dissection (SCAD).[2] MINOCA is usually diagnosed with initial coronary angiography, demonstrating no obstructive disease, sometimes followed by provocative testing and cardiac magnetic resonance (CMR) imaging.[2]

In addition, both intravascular ultrasound (IVUS) and optical coherence tomography (OCT), when available, can often be helpful in further evaluating the underlying cause of ischemia in patients with MINOCA.[3,4] In one series of patients with MINOCA, the combination of OCT plus CMR was able to identify a cause of the MINOCA in 85% of patients (with 64% having an ischemic cause and 21% having a nonischemic cause), but no cause was able to be identified in 15%.[5]

Vasospastic disease is a common cause of MINOCA, perhaps up to 46% of cases per one series.[3] At time of coronary angiography, intracoronary administration of nitroglycerin is commonly used to prevent or treat vasospasm. Nitroglycerin is an endothelium-independent vasodilator. When diagnosis of vasospastic disease is uncertain, provocative testing can be useful to make the diagnosis so that patients can be initiated on appropriate medical therapy.

In this issue of *JACC: Case Reports*, Mizutani et al[6] present a case of a post-menopausal woman with chest pain and elevated troponin, found to have no obstructive coronary disease and, initially, negative provocative testing with intracoronary ergometrine (also known as ergonovine). The patient subsequently showed endomyocardial enhancement of the inferior wall on late gadolinium-enhancement (LGE) on CMR, consistent with subendocardial ischemia. Early after hospital discharge, the patient developed recurrent chest pain and elevated troponin, or MINOCA, and this time invasive provocative testing with acetylcholine confirmed coronary vasospasm. CMR following her second event showed transmural LGE, suggesting completed infarct. The patient was treated with dihydropyridine calcium channel blockers (CCBs) (benidipine and amlodipine) that can be used for treatment of MINOCA.[3] Note that non-dihydropyridine CCBs, such as diltiazem and verapamil, can also be used for vasospastic angina. However, she did not experience relief with CCBs and ultimately was treated with nicorandil, which has the dual properties of being a nitrate and potassium-channel agonist, which leads to smooth muscle cell relaxation and coronary artery dilation.

Recently, studies have evaluated the safety and prognostic value of coronary provocative testing using invasive methods in the clinical setting. One large study performed in Japan evaluated patients who underwent either ergometrine or acetylcholine

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2022.01.014

provocation testing in the catheterization laboratory immediately following coronary angiography for the diagnosis of coronary vasospasm.[7] The multicenter study consisting of more than 1,200 patients reported a prevalence of provocation-induced arrhythmic side effects of 6.8%, which the authors note is approximately the prevalence during spontaneous angina caused by vasospasm (7%). The presence of mixed diffuse and focal vasospasm was independently predictive of adverse cardiovascular events, whereas the presence of arrhythmic side effects was not. Furthermore, in this study, an abnormal provocative test occurred significantly more frequently in each vessel in patients tested with acetylcholine compared with those tested with ergometrine. This is possibly because of differences in the mechanism of action of the vasoactive agents. Therefore, in the case presented by Mizutani et al,[6] these findings fit in with the clinical picture of a negative ergometrine test but positive acetylcholine test in a patient presenting with MINOCA.

In terms of the mechanism of provocative agents, acetylcholine is a cholinergic agonist that elicits an endothelial dependent response of the coronaries, whereas ergometrine affects vascular smooth muscle constriction and is endothelial independent. Whether a particular agent is used over the other depends on the mechanism of interest to be tested and comfort level and expertise of the institution. In the United States, acetylcholine is available and used for provocation testing, typically in specialized tertiary-care centers. In addition, newer noninvasive techniques to test coronary endothelial function using MRI have been studied.[8,9] In general, coronary provocative testing is recommended for the workup of MINOCA after careful review of the angiography films (and when available, review of IVUS) and when other diagnostic studies (CMR, echo) do not yield a specific etiology or diagnosis.

How does coronary vasoreactivity testing affect treatment? Once the diagnosis of coronary vasospasm is made, a trial of CCBs should be started, as with the patient presented. However, CCBs alone may be insufficient to adequately control symptoms, and long-acting nitrates can also be tried in conjunction with standard background medical therapy. A recent study (CorMicA trial) showed that treatment based on invasive coronary functional testing lead to better outcomes in terms of quality of life and angina after 1 year compared with a control group without testing-guided therapy.[10] This is likely due to making the correct diagnosis and implementing the appropriate targeted treatments. At present, clinical trials are underway to evaluate the efficacy of different treatment approaches in patients with coronary vasospasm and coronary microvascular dysfunction in MINOCA.

Further, recurrent presentation with myocardial ischemia or infarction (MI) is more frequent after MINOCA than in the population without this history, with up to 25% of patients reported to have recurrent angina within 12 months.[11] Studies are mixed on whether recurrence in MINOCA is comparable with or lower than in obstructive coronary artery disease, with some reporting similar incidence, whereas others report lower incidence.[12,13] Clinicians should be mindful of the noninsignificant risk of recurrence of ischemia among patients with MINOCA.

The clinical importance of MINOCA is becoming increasingly recognized, and this case effectively highlights several key issues in patients presenting with MI in this setting. It illustrates the importance of the diagnostic work-up, the role coronary functional testing, and the incidence of recurrent events after the initial diagnosis of MINOCA.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS atrial fibrillation, coronary angiography, myocardial Infarction