



## We have a greater understanding of ‘cardiac syndrome X,’ but questions remain

There was a time when diagnosing coronary artery disease and managing its clinical expression of angina and myocardial infarction focused almost entirely on the lumens of the major coronary vessels. Culprit stenoses needed to be recognized and rectified, mainly via bypass or an endovascular procedure. Medical therapy was adjunctive or preventative. Improved understanding of the biologic nature of the stenosing plaque and proliferating and remodeling vascular tissue led to the implementation of still-evolving approaches directed at plaque stabilization and shrinkage, as well as antithrombotic and antiproliferative therapies. We also saw that some patients experienced classic angina with imaging or electrocardiographic evidence of myocardial ischemia and sometimes infarction in the absence of significant epicardial coronary artery obstructive lesions. The pathogenesis was unclear, and these patients were thus diagnosed as having “cardiac syndrome X.” In current parlance, they have ischemia and no obstructive coronary artery disease (INOCA). Greater understanding of this condition, which can clinically mirror obstructive coronary artery disease (CAD) until coronary angiography is performed, has led to the recognition that many of these patients have coronary microvascular dysfunction (CMD).<sup>1</sup>

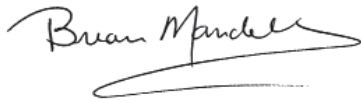
As discussed by Tjoe et al<sup>2</sup> in this issue of the *Journal*, INOCA-related syndromes are most commonly precipitated by coronary spasm or by CMD. Definitive diagnosis requires accurate epicardial coronary imaging to exclude significant obstruction and epicardial coronary spasm, and then physiologic assessment of the coronary microvasculature. Physiologic assessment, as Tjoe et al describe in detail, includes measurement of coronary flow reserve and interventional evaluation of endothelial function. These procedures may not be available in all catheterization laboratories.

CMD seems to be more common in women than men and is not benign, as it is associated with the presence or future development of atherosclerotic obstructive CAD. But even in the absence of coexistent obstructive CAD, there is an association with heart failure with preserved ejection fraction, with acute coronary syndromes, and with several comorbidities including diabetes, chronic kidney disease, and hypertension, and perhaps with some systemic inflammatory and autoimmune diseases.

As I was thinking through these associations and the independent role that CMD might play in clinical outcomes, I wondered if its more common presence in women (for reasons I do not fully understand) might contribute to the variably described protective effects of aspirin in women vs men, assuming a nonthrombotic pathophysiology for CMD. Perhaps CMD could also explain some of the increased cardiovascular risk, incompletely accounted for by traditional cardiac risk factors, attributed to autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus—perhaps as a result of the effect of inflammatory cytokines or activated cells on regulatory control of the coronary microvasculature, in addition to the underlying biologic effects attributable to the female host. (Recall that these 2 conditions occur more commonly in women.)

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Another interesting observation regarding patients with CMD is that patients (66% female) initially screened for participation in the CIAO-ISCHEMIA trial<sup>3</sup> who had angina with ischemia but no coronary obstruction on angiography were followed over a year's time and underwent repeat stress echocardiographic testing along with angina questionnaires. The patients received medical treatment at the discretion of their physicians. After 1 year, the stress echo was normal in approximately half of the patients, and angina had improved in 43% and worsened in 14%, but the changes in imaging did not correlate with the changes in angina.<sup>4</sup> Apparently, we still have a lot to learn about the nature and expression of pain, even in a pain syndrome like angina, which we think we understand.



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