

EDITORIAL COMMENT

Invasive Coronary Vasoreactivity Testing to Diagnose Microvascular Dysfunction in Women*

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Fundamental gaps still exist in our understanding of cardiovascular disease in women. Women are more likely to suffer from coronary heart disease due to a higher prevalence of very old age relative to men. Women tend to be protected from the development and complications of coronary artery disease (CAD) at younger ages, perhaps due to the beneficial effects of estrogen on the vasculature. A number of sex-related physiological differences might affect coronary vascular function, including sex-based variations in vessel anatomy, biomechanical properties (1), and endothelial function. The vascular endothelium, in particular, plays a key protective role in terms of preventing thrombosis, smooth muscle cell proliferation, and vasoconstriction.

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In 1996, the National Institutes of Health launched the WISE (Women's Ischemia Syndrome Evaluation) study to provide scientific evidence about presentation, diagnosis, and progression of heart disease in women. Designed as a multicenter cohort study, WISE followed more than 900 women for an average of nearly 4 years after clinically indicated coronary angiography (2). Women presenting with chest pain suggestive of angina and/or with abnormal stress tests more often have nonobstructive CAD than their male counterparts. A key finding from the WISE study was

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the high burden of coronary microvascular dysfunction in women presenting with ischemic symptoms but angiographically normal vessels (3); up to one-half of symptomatic women had coronary microvascular dysfunction in the absence of significant CAD. The impact of impaired coronary vasoreactivity in women without obstructive CAD can be significant: many experience persistent symptoms or cardiovascular events that necessitate expenditure of healthcare resources and affect their quality of life (4,5). Previous results from the WISE study demonstrated that impaired endothelial-mediated vasodilatation in the absence of overt CAD predicts long-term adverse cardiovascular events in women (4).

Microvascular dysfunction might involve both smooth muscle cells or the endothelium (or both) and can be measured in vivo by monitoring the vasodilator response to pharmacological or mechanical (flow) challenge in either peripheral or coronary vessels. Coronary reactivity can be measured with invasive testing of endothelial function with intracoronary infusion of acetylcholine, which promotes the release of nitric oxide and endothelium-dependent vasodilation followed by intracoronary administration of sodium nitroprusside or adenosine, to assess endothelial-independent function. Previously, the WISE investigators validated an approach of assessing the functional integrity of the coronary microvasculature in symptomatic women by measuring coronary flow velocity response to adenosine and monitoring coronary flow velocity reserve (CFR), defined as the ratio of hyperemic time-averaged peak flow after adenosine to time-averaged peak flow at baseline (6).

In this issue of *JACC: Cardiovascular Interventions*, Wei et al. (7) report on the safety of invasive coronary reactivity testing in women to diagnose microvascular disease. Among 293 symptomatic women without obstructive CAD who underwent testing, 4 total adverse events occurred—2 of which were deemed serious: a coronary dissection, and an episode of coronary spasm leading to acute myocardial infarction. Over the course of >5-year follow-up, the overall rate of major adverse cardiac events in the population was 8.2%. The investigators rightly conclude that the immediate risk of testing is relatively low in comparison with the overall event rate in this population.

The results of the procedure should change patient management to justify performing an invasive test that carries albeit a small (<1%), but real risk of serious harm. The strongest evidence in support of testing comes from the documented benefit of angiotensin-converting enzyme inhibition in this population. In a subset of women in the WISE study with microvascular dysfunction, randomization to therapy with quinapril for 16 weeks improved both CFR and symptoms, as compared with placebo therapy (8). The benefit was observed in women with the most severe microvascular dysfunction, as evidenced by the lowest CFR. Given the strong link between inflammation and endothe-

lial dysfunction, women with microvascular dysfunction might additionally benefit from high-dose statin therapy. In patients with normal coronary arteries, high C-reactive protein levels occur in association with abnormal coronary vasoreactivity (9). In an isolated perfusion system, C-reactive protein attenuates endothelial-dependent vasodilatation of porcine coronary arterioles (10). Statins as a class might exert beneficial pleiotropic effects on inflammation and endothelial function, thus rendering them useful in the setting of microvascular dysfunction, although this benefit remains theoretical at present. And certainly, regardless of symptoms, women should be counseled to adopt healthy lifestyle habits that have been shown to delay the development of obstructive CAD as well as improve markers of endothelial dysfunction. These would include total abstinence from tobacco, moderate physical activity, and achievement of an ideal weight.

Are there other less invasive procedures that could substitute for invasive coronary reactivity testing to establish the diagnosis of coronary microvascular dysfunction? Lipid and hormone levels, blood pressure, and left ventricular function do not seem to predict coronary velocity response to intracoronary adenosine, although age and years after menopause might (3). Overall, traditional atherosclerotic risk factors account for <20% of the observed variability in CFR in this patient population (11). Several methods for noninvasive peripheral measurements exist on the basis of Doppler or finger arterial-pulsatile volume changes. Digital reactive hyperemia peripheral arterial tonometry correlates with nonobstructive CAD in women with symptoms of angina referred for coronary angiography (12), and is inexpensive, portable, and easy to use. However, the technique provides only a surrogate marker for coronary function without all the information that can be obtained from direct, invasive measurements. Eventually, imaging modalities such as cardiac magnetic resonance imaging with pharmacological stress and gadolinium as a flow tracer, might replace invasive testing but at present invasive coronary reactivity remains the gold standard. By providing an estimate of the risk in women with angina, the WISE study continues its remarkable impact on advancing understanding of the heart health of women and sex-based differences in ischemic vascular disease.

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