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EDITORIAL COMMENT

Women and Ischemic Heart Disease

Paradox and Pathophysiology*

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In the U.S., more than a quarter of a million women die each year from ischemic heart disease (IHD), and current projections indicate that this will increase with our aging population and epidemics of obesity, metabolic syndrome, and diabetes mellitus. Notably, IHD is the leading killer of women at all ages, with annual mortality rates affecting greater numbers of younger and older women than breast cancer. Furthermore, resource consumption patterns in women are characterized by more frequent angina diagnosis, more office visits, more avoidable hospitalizations, higher myocardial infarction (MI) mortality, and higher rates of heart failure as compared with men (1). Clear sex differences in the presentation, pathophysiology, and treatment of IHD underscore the need for more study of women.

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Three paradoxes are evident with regard to sex differences in IHD (2). First, women have a higher prevalence of angina compared to men, yet have an overall lower prevalence of atherosclerosis and obstructive coronary artery disease (CAD). Second, symptomatic women undergoing coronary angiography have less extensive and severe CAD, despite being older with a greater risk factor burden, compared to men. Third, despite relatively less CAD, women have a more adverse prognosis compared to men. These 3 paradoxical findings suggest an alternative, sex-specific pathophysiology for IHD in women, given our traditional understanding that the majority of angina and adverse cardiovascular outcomes stem from obstructive CAD.

Advanced cardiac imaging can be used to further our understanding of the pathophysiology of these paradoxes of ischemic heart disease in women (Fig. 1). Identification of nonobstructive atheroma is increasingly important and can be visualized and quantified now by intravascular coronary ultrasonography, coronary artery calcium (CAC) score, and computed tomography angiography, the latter 2 using fast computed tomography scanning. The gold standard identification for microvascular coronary dysfunction (MCD) which is a common concomitant of nonobstructive atherosclerosis, is invasive coronary reactivity testing for measurement of both endothelial- and nonendothelial-dependent reactivity (3). Additional advanced imaging modalities that show promise for the noninvasive assessment of this include magnetic resonance (MR) angiography of the coronary artery and transthoracic echocardiography Doppler coronary artery

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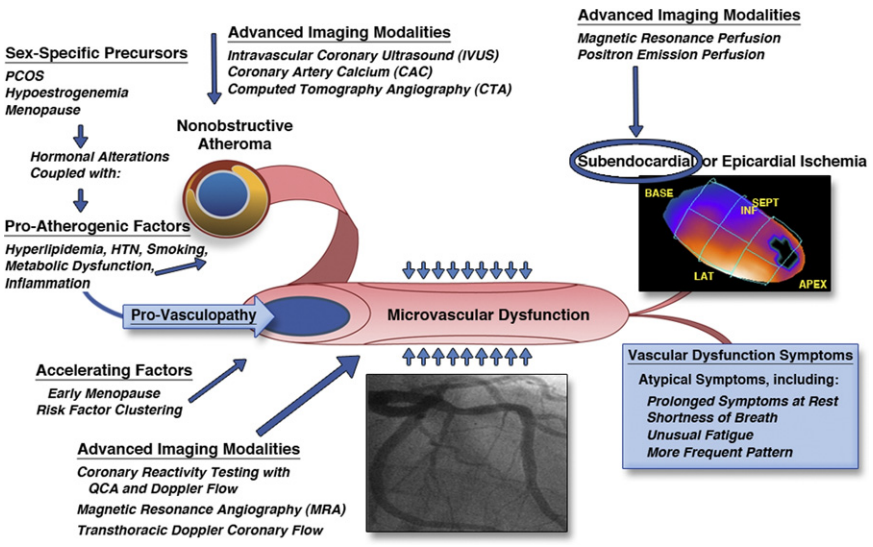

Figure 1. Advanced Imaging Modalities to Detect Abnormalities of Microvascular Angina

Adapted, with permission, from Shaw et al. (11). HTN = hypertension; INF = inferior; LAT = lateral; PCOS = polycystic ovary syndrome; QCA = quantitative coronary angiography; Sept = septal.

flow, both in response to pharmacological stressors. Finally, assessment of the nonsegmental myocardial perfusion abnormalities associated with MCD can be measured by cardiac MR perfusion imaging, and absolute myocardial blood flow reserve by positron emission tomography. Identification of nonobstructive CAD (4), MCD (5), and abnormal nonsegmental perfusion abnormalities (6) are associated with an elevated risk of adverse events similar to obstructive CAD. Cardiac MR perfusion imaging is uniquely able to visualize epicardial versus subendocardial myocardium; prior work has provided evidence of subendocardial perfusion abnormalities in women with signs and symptoms of ischemia but no obstructive CAD (7). The National Heart, Lung, and Blood Institute-sponsored WISE (Women's Ischemia Study Evaluation) study has additionally documented the presence of myocardial ischemia in these patients using cardiac MR spectroscopy (8). Because of the relatively high frequency of MCD in symptomatic women with and without CAD (9,10), this constellation of findings suggests that MCD plays a central role in the genesis of symptoms and ischemia, and may be a global estimator of outcome in female IHD pathophysiology, as outlined in Figure 1 (11).

The current findings published from the Dallas Heart Study by Banks et al. (12) provide additional novel data that further support this unfolding understanding of an alternative sex-specific pathophysiology for IHD in women. Using the advanced cardiac imaging technique of CAC, these investigators found, in a relatively large community-based population that oversampled with African Americans, that angina was not related to atherosclerosis measured by CAC, but was related to novel risk factors, including central obesity, insulin resistance, serum inflammatory markers, and reduced aortic compliance. The Dallas Heart study used robust methods of subject sampling, standardized definitions, and core laboratory measures, and so provides a good estimate of angina, atherosclerosis, and other marker prevalence in women. While noncalcified atherosclerosis can be present in women and younger adults, the confirmatory MR imaging-measured aortic atherosclerosis findings are reassuring that this did not likely confound the results.

What can we learn from this new work regarding the 3 paradoxes of IHD in women? Among the women in the Dallas Heart study with angina and/or CAC (n = 318) (Table 1) (12), the largest subgroup (64%) had atherosclerosis without angina, consistent with our understanding of the relatively large burden of asymptomatic atherosclerosis among women in the community (1). The prevalence of symptomatic atherosclerosis was the lowest (7%) subgroup, supportive of the finding that a majority of women with CAD do not have classic angina symptoms (2), which contributes to underdiagnosis or misdiagnosis in women. Notably, the second most prevalent subgroup was women with angina in the absence of atherosclerosis (29%)—

consistent with the accumulated literature documenting that as many as one-third of women have signs and symptoms of myocardial ischemia without evident CAD (13). While there are >6 million women in the U.S. with clinically documented CAD, we have estimated the prevalence of signs and symptoms of IHD in the absence of CAD using the National Cardiovascular Data Registry database to be 2 to 3 million women (1), again consistent with these new community population data.

Notably, the investigators document that, whereas the presence of atherosclerosis measured by CAC was associated with traditional risk factors, angina without CAC was not, and had a paradoxically greater clustering of more novel risk factors including central obesity, insulin resistance, vascular inflammation, and aortic compliance. Although multivariate analyses identified only African-American ethnicity, family history of myocardial infarction, and central obesity as independent risk factors, the risk factor clustering captured by the National Cholesterol Program Adult Treatment Panel 3 term "metabolic syndrome" is known to be a convenient clustering of traditional and novel risk factors that are difficult to separate. This pattern of risk-clustering data supports the WISE study hypotheses outlined in figure 1 (11), suggesting a pathophysiological link between angina and nonatherosclerotic-mediated vascular reactivity.

Regrettably, but by design, the current study did not include either measures of endothelial, nonendothelial, or myocardial perfusion reserve testing. We, therefore, cannot add specifically to our knowledge regarding the second paradox listed, and whether endothelial, nonendothelial, or both vascular reactivity pathophysiological pathways contribute to myocardial ischemia and thereby angina in women with a relatively lesser extent and severity of angiographic CAD. The WISE study data, which evaluated higher risk, symptomatic subjects, documented a high prevalence of atherosclerosis by intravascular coronary ultrasonography in women associated with MCD—additional community data using advanced imaging are needed to confirm whether this relation holds true or whether they are unrelated to each other. Although the vascular inflammatory markers measured (soluble intracellular adhesion molecule-1, soluble vascular cell adhesion molecule) have been correlated with endothelial dysfunction, as cited by the Dallas Heart investigators, prior WISE study work failed to demonstrate links to vascular reactivity in women. The coronary flow reserve did not correlate with levels of high-sensitivity C-reactive protein, interleukin-6, interleukin-18, tumor necrosis factor-α, transforming growth factor-β1, and soluble intracellular adhesion molecule-1 (14), although serum amyloid high-sensitivity C-reactive protein was a strong predictor of adverse cardiac events (15,16). These combined data suggest the hypothesis that vascular inflammation may promote endothelial dysfunction and atherosclerotic plaque destabilization, but potentially not nonendothelial smooth muscle pathophysiological pathways in women. More work is needed.

And what about the third and final paradox? Why do women have more adverse outcomes despite less extensive CAD and better ventricular function? The literature suggests that when women look like men (with typical symptoms and obstructive CAD), they are more likely to be treated like men and benefit from aggressive interventional and medical therapies. As characterized by the "Yentl" syndrome depicted in the Barbra Streisand movie of the same name, Healy (17) used this term to call attention to the paradox of adverse outcomes of women with IHD in preparation for the National Institutes of Health Women's Health Initiative. This literature documents that interventional strategies are equally effective in biomarker positive women and men in the setting of obstructive CAD (11).

But what do these new data tell us about the one-third of women with signs and symptoms of ischemic but no obstructive CAD? These new Dallas Heart Study data combined with prior work suggests that this sizable group contributes to the adverse morbidity and mortality experienced by women in part related to MCD. Because MCD is paradoxically poorly predicted by traditional cardiovascular disease risk factors (10), the current diagnosis is challenging to physicians, and knowledge regarding potential preventive or treatment strategies lacks an evidence base. The current strategy, which aims to detect obstructive coronary stenosis, is less effective in women with a greater prevalence of signs and symptoms of ischemia unrelated to obstructive CAD. Alternative strategies using tools to detect the "vulnerable patient" should be more useful and may be preferentially helpful in women. Novel imaging strategies aimed at pathophysiological pathways, including measures of nonendothelial, endothelial function, vascular and myocardial compliance, as well as myocardial perfusion and flow reserve are actively being investigated as useful risk markers and diagnostic strategies. Noninvasive,

nonionizing radiation strategies are needed for this purpose, as invasive study has documented the feasibility of identifying future risk by pathophysiological evaluation in women with no obstructive CAD (18). Further closure of knowledge gaps related to the paradox and the pathophysiology of IHD in women is one of our highest priorities to improve the health of the 51% of the population that is female.

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