

EDITORIAL COMMENT

Coronary Microvascular Dysfunction

Does Sex Matter?*

Alexandra J. Lansky, MD, Cody Pietras



In this issue of *JACC: Cardiovascular Interventions*, Kobayashi et al. (1) investigate sex differences in invasive measures of microvascular function and challenge the widely held view that microvascular dysfunction is the primary cause of the high prevalence of angina in the absence of obstructive coronary artery disease (CAD) in women.

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HISTORICAL PERSPECTIVE

An estimated 10.2 million Americans have angina (2). Women in particular have a consistent excess of angina in the United States and worldwide, seemingly indicative of an inherent sex-based disparity in the biological basis for chest pain (3). Among symptomatic patients without previous known CAD referred for cardiac catheterization, more than 60% are found to have nonobstructive CAD (<50% diameter stenosis [DS]), and 39% have “normal” coronary arteries (<20% DS); women account for 55% of patients without obstructive CAD and only 34% with significant stenosis (4). Women consistently demonstrate less obstructive coronary artery disease compared with men, irrespective of presentation with stable or unstable coronary syndromes (5,6).

Among outpatients with known CAD, anginal symptoms predict mortality: the mortality rate increases by 27%, 61%, and 250% for mild, moderate, and severely limiting angina, respectively (7). In women with nonobstructive CAD in the WISE

(Women’s Ischemia Syndrome Evaluation) study, angina itself conferred a worse prognosis: the 5-year annualized cardiovascular event rate (death, myocardial infarction, stroke, and hospitalization for heart failure) was 16% for symptomatic women with nonobstructive CAD, 8% for symptomatic women with normal coronaries, and 2.4% for asymptomatic women without CAD (8-10).

Further investigation by the WISE into the mechanisms of angina in women with nonobstructive CAD (N = 159) revealed that almost one-half of women had abnormal coronary flow reserve (CFR), indicating that microvascular dysfunction may be a root cause of angina (11). Furthermore, both endothelium-dependent (12) and -independent (13) abnormal CFR was associated with an increased incidence of adverse cardiac events.

Another WISE substudy demonstrated that at least 20% of women with angina and nonobstructive CAD had evidence of myocardial ischemia by nuclear magnetic resonance spectroscopy (MRS), again postulated to be due to atherosclerosis-related microvascular dysfunction. Women with abnormal MRS had a higher 3-year composite event rate, driven primarily by rehospitalization for unstable angina, which was associated with repeat catheterization and higher health care costs (9). Similar findings were noted in a smaller series of women with angina and “normal” coronaries, 20% of whom displayed myocardial ischemia on MRS (14). Although microvascular or endothelial dysfunction is thought to be the most plausible mechanism, other potential physiological mechanisms include coronary vasospasm and increased left ventricular diastolic pressure due to impaired myocardial relaxation. The main takeaway from the WISE studies has been that microvascular dysfunction is central to the pathobiology of non-obstructive ischemic heart disease in women and accounts for their symptoms and prognosis.

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From the Division of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

CONTRIBUTION OF THE CURRENT STUDY

The current study by Kobayashi et al. (1) clarifies 2 important points in our understanding of women with angina and nonobstructive CAD. First, microvascular function measured by the index of microvascular resistance (IMR) was similar between the sexes. IMR is a direct measure of microvascular function that eliminates the variability of resting vascular tone by incorporating only hyperemic parameters, making it more reproducible than CFR (15). Second, CFR was lower in women due to a shorter resting mean transit time. CFR, defined as hyperemic coronary flow divided by resting coronary flow, is subject to substantial variation due to resting hemodynamic changes (e.g., blood pressure, heart rate, myocardial contractility) and epicardial artery pathology. In this study, both hypertension and small coronary vessel size predicted reduced resting transit time and therefore contributed to abnormal CFR. These important observations suggest that women have increased resting coronary flow—possibly related to a higher prevalence of hypertension and possibly to smaller vessels—rather than more abnormal microvascular function. These findings shed important new light on the pathobiology of ischemic heart disease in women in whom vascular dysfunction was thought to be central (16). Based on the current study—the first to include men for direct comparison—microvascular function appears to be similar between the sexes.

This study also provides insight into nonatherosclerotic contributors to the adverse prognosis associated with the abnormal CFR observed in the WISE study. Reduced resting coronary flow was associated with hypertension and small vessel caliber, both of which are more common in women. In the setting of smaller vessels, hypertension (particularly prevalent in elderly women) and diastolic dysfunction may precipitate ischemia and anginal symptoms, leading to the observed prognosis. The complex interplay of nonobstructive atherosclerosis, hypertension, and diastolic dysfunction, compounded by other risk factors common to women including insulin resistance, metabolic syndrome, and diabetes, likely contributes to the symptoms and functional limitations observed in women.

OTHER CLINICAL CONSIDERATIONS

Most studies evaluating the prognosis of angina and measures of CFR were conducted exclusively in women and included patients with angiographically defined nonobstructive disease (<50% DS) as well as

normal coronary arteries (<20% DS). Intravascular ultrasound (IVUS) studies have illuminated the enormous burden and diffuse nature of atherosclerosis in patients with nonobstructive CAD: in a WISE substudy, 80% of women with nonobstructive CAD had a mean atheroma volume of $30 \pm 8\%$ involving more than 40% of the interrogated vessel length, and 73% had evidence of positive remodeling, indicating that angiography significantly underestimates the extent of disease (17). The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial demonstrated the substantial incremental impact of even mild angiographic lesions (2.6% to 34% DS) on IVUS plaque burden (46% to 51%) and subsequent cardiovascular events (ranging from 0.3% to 5.1%), in addition to residual angina (18). Furthermore, women may be more vulnerable to intermediate lesions with thin-cap fibroatheroma, as detected by virtual histology IVUS (19). These observations alone may be sufficient to explain the increased incidence of cardiovascular events in women with angina despite the absence of obstructive CAD, without invoking fundamental sex-based biological differences in the pathophysiology of angina.

SUMMARY

As Kobayashi et al. (1) point out in their elegant study, the emphasis on microvascular dysfunction as the primary cause of the sex differences in anginal symptoms in the absence of obstructive CAD may have been misguided. Based on these new data, it appears unlikely that the fundamental pathophysiology of ischemic heart disease is different between the sexes; rather, sex-based disparities in the prevalence and combination of known risk factors result in different manifestations of disease in women compared with men. The degree to which microvascular dysfunction is a contributor to sex differences remains to be determined in larger comparative studies that include both men and women. Future efforts should be directed at elucidating the relative contributions of known risk factors including disease severity and burden to abnormal coronary flow to better tailor effective therapies to each patient.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Alexandra J. Lansky, Division of Cardiovascular Medicine, Yale University School of Medicine, PO Box 208017, New Haven, Connecticut 06520-8017. E-mail: alexandra.lansky@yale.edu.

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