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Microvascular Dysfunction: Genetic Polymorphisms Suggest Sex-Specific Differences in Disease Phenotype

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Keywords

microvascular dysfunction; single nucleotide polymorphisms; vascular stiffness

Microvascular dysfunction is an underrecognized contributor to chest pain syndromes in patients with documented ischemia and angiographically normal or minimally diseased epicardial coronary arteries. The relationship between microvascular dysfunction and myocardial ischemia has been confirmed. Studies performed in symptomatic patients using dobutamine stress-cardiac magnetic resonance imaging (MRI) demonstrated a correlation between coronary flow reserve and reversible perfusion defects. This study, however, identified reversible perfusion defects in only 56% of patients with microvascular dysfunction [1]. Another study that utilized ^{31}P -nuclear magnetic resonance spectroscopy to provide metabolic evidence of ischemia in patients with microvascular dysfunction found that only ~20% of patients with chest pain and angiographically normal coronary arteries had decreased phosphocreatine-to-ATP ratios indicative of myocardial ischemia [2]. Thus, these studies indicate that microvascular dysfunction is not a uniform disease and does not always result in ischemia detectable by conventional or advanced methodologies. Instead, microvascular dysfunction appears to be a widely variable entity within the spectrum of coronary vascular pathologies that includes endothelial dysfunction, inflammation, and atherosclerosis.

When present, microvascular dysfunction in symptomatic patients is not a benign finding and is a predictor of adverse clinical outcomes. In a large population-based study of 11,223 patients who had insignificant or no coronary artery disease at coronary angiography, symptomatic patients (male and female) with normal coronary arteries had an increased risk of major adverse cardiovascular events (pooled hazard ratio 1.52; 95% CI 1.27–1.83) compared to asymptomatic individuals [3]. The prevalence of microvascular dysfunction is higher in women than men and there are sex-specific differences in clinical outcomes. In the first year after diagnostic angiography for angina, symptomatic women with insignificant coronary disease were found to have a 3.5-fold higher risk of major adverse events, including death, myocardial infarction, stroke, and heart failure compared to women without any disease. By contrast, the hazard risk for men with insignificant coronary disease was not different than that for men with normal coronary arteries [4]. This risk did not diminish over

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time and after 5-years women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study with symptomatic microvascular dysfunction and normal coronary arteries were shown to have a 3-fold increase in major adverse events compared to asymptomatic age-matched women [5]. When taken together, these observations support the idea that microvascular dysfunction may be a different disease in women as compared to men.

At present our understanding of the pathobiological mechanisms that mediate coronary microvascular dysfunction is limited and it remains unclear if there are sex-based differences in the cellular and molecular processes that contribute to the disease. There is evidence to indicate that microvascular dysfunction may occur as a result of impaired microvascular vasodilatory reserve owing to an imbalance between vasodilator and vasoconstrictor agents (e.g., nitric oxide, endothelin-1, reactive oxygen species, or ion channel-mediated regulation of K^+ or Ca^{2+} levels); microvascular structural remodeling with increased vessel muscularization, extracellular matrix deposition, or calcification to increase local vascular stiffness; autonomic dysregulation; insufficient microvascular density to supply to the myocardium; or innate differences in the caliber of the coronary vessels (i.e., smaller in women than men even after adjustment for body size) (reviewed in [6]).

In this issue of *Coronary Artery Disease*, Yoshino *et al.* provide additional mechanistic insight into the pathogenesis of microvascular dysfunction by identifying an underlying genetic basis for the disease [7]. The investigators genotyped 643 patients with microvascular dysfunction and examined 1,536 single nucleotide polymorphisms (SNPs) occurring in 76 biologically relevant genes. Analysis of the genetic data revealed that SNPs in the *VEGFA* and *CDKN2B-AS1* genes were highly associated with microvascular dysfunction in the entire study population. They also identified a SNP-sex interaction that may explain some of the pathophysiological differences observed between men and women with microvascular dysfunction. Interestingly, they found that SNPs within the *MYH15*, *VEGFA*, and *NT5E* genes were associated with microvascular dysfunction in men but there were no candidate SNPs that associated with the disease in women. Although this study examined only a relatively small number of SNPs and genes, the findings are highly novel as prior studies of SNPs associated with microvascular dysfunction relied on retinal vessel caliber as an indicator of microvascular disease and did not perform the sophisticated coronary microvascular functional phenotyping as reported in the current study [8].

The SNPs found to associate with microvascular dysfunction in this study support the involvement of cellular and vascular remodeling as key mediators in the pathogenesis of microvascular disease. For example, the biological consequences of loss-of-function SNPs in *VEGFA* are a decrease in vascular endothelial cell proliferation, migration, and angiogenic potential while a similarly functioning SNP in the long noncoding RNA *CDKN2B-AS1* would promote cellular senescence. This, in turn, may lead to smaller caliber microvessels, a decrease in microvascular density, or a limited angiogenic response to myocardial ischemia that would manifest clinically as a chest pain syndrome [9]. The additional SNPs found to associate with microvascular dysfunction in men may also contribute to microvascular dysfunction by regulating vascular stiffness. The *MYH15* gene has been linked to the maintenance of tonic force in vascular smooth muscle cells [10]. Whether or not this is applicable to endothelial cells or achieves importance for endothelium

that undergoes endothelial-to-mesenchymal transition as may occur under the biochemical conditions associated with microvascular dysfunction is unknown. A SNP in *NTE5* would promote vascular calcification and thereby contribute to overall microvessel stiffness. It is interesting to speculate that the fact that these SNPs are linked to microvascular dysfunction in men indicate that in men this is a disease of microvascular stiffness while the disease phenotype in women is not as well characterized.

The importance of the study by Yoshino *et al.* is that it lays the groundwork for future investigations designed to elucidate the genetic basis of microvascular dysfunction. In the current “-omics” era, these studies should take advantage of the comprehensive platforms available to perform an all-inclusive genetic analysis of patients with microvascular dysfunction that has been carefully phenotyped. Moreover, the results from these studies should be subjected to novel analytical methods, such as systems biology and network analysis, for the discovery of previously unknown genetic factors and related signaling pathways that contribute to disease pathogenesis. These analyses may also identify targets unique to microvascular dysfunction that can be exploited for pharmacotherapeutic intervention [11].

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