The Prevalence of Microvascular Dysfunction, Its Role Among Men, and Links With Adverse Outcomes
Noninvasive Imaging Reveals the Tip of the Iceberg

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Considerable evidence has accumulated to counter older concepts of a categorical definition of ischemic heart disease as simply the presence or absence of a flow-limiting stenosis. Revised concepts increasingly recognize ischemic heart disease as a continuous spectrum that is not limited to obstructive plaque seen by angiography in an epicardial coronary artery. Included in this spectrum are functional disorders of the large and smaller coronary blood vessels. These smaller vessels, collectively the coronary microcirculation, comprise most of the coronary blood vessels and control the volume and distribution of blood flow to the myocardium.

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Although not visualized by angiography, the coronary microcirculation may be indirectly assessed from the speed of radiographic contrast movement as the corrected thrombolysis in myocardial infarction (TIMI) frame count. This simple, objective, continuous index is accurate, reproducible, highly correlated with Doppler blood flow measurements, and provides information for risk stratification.1–3 The microcirculation can be directly assessed, in the absence of flow-limiting stenoses, by coronary flow reserve (CFR) and also by the index of microvascular resistance. Noninvasive methods, such as positron emission tomography (PET), Doppler echocardiography, and gadolinium perfusion cardiac magnetic resonance imaging, are increasingly being used to evaluate microvascular function.

Patients with symptoms and signs of ischemia, referred for invasive coronary evaluation, increasingly appear without obstructive epicardial coronary artery disease (CAD).4,5 We and others identified that symptomatic patients with nonobstructive CAD may have an elevated risk of adverse outcomes compared with cohorts without symptoms or signs of ischemic heart disease.5 Unfortunately, because of lack of evidence-based results on treatment, management of these symptomatic patients is often frustrating for the patients and their physicians. As a result, these individuals consume medical resources rivaling those for patients with obstructive CAD.5 Approximately 45% to 60% of such patients have coronary vascular dysregulation (endothelial or nonendothelial dependent macrovascular or microvascular dysfunction) capable of causing ischemia with provocative testing.4,7 Numerous reports linked coronary vascular dysregulation, usually referred to as coronary microvascular dysfunction (CMD), with adverse clinical outcomes,8–10 but these data have mostly been derived from cohorts of women. Indeed, the finding from the National Heart, Lung, and Blood Institute-sponsored Women’s Ischemic Syndrome Evaluation (WISE) that CMD predicted adverse outcomes9 has been termed a “milestone” in furthering our understanding of ischemic heart disease among women.11 This finding has resulted in multiple attempts to link CMD with female reproductive hormones and other female-specific issues, with variable results.

However, the role of CMD among men has been open to question because relatively few studies included large numbers of men. In the current issue of Circulation, Murthy et al12 report investigations of the prevalence and prognosis of CMD among women and men referred for evaluation of suspected CAD. Patients were assessed with whole-body PET–computed tomography, and studies were analyzed semiquantitatively to identify perfusion defects suggestive of obstructive CAD. PET studies were further processed to determine myocardial blood flow at rest and after stress. Patients without a history of CAD or evidence of a significant perfusion defect at stress (summed stress score <3) were presumed not to have obstructive CAD and were included in the prognosis analysis.

The strengths of this work included a large sample size of both men (n=405) and women (n=813) lack of referral for coronary angiography bias, quantification of CFR, and collection of objective outcomes (cardiac death, myocardial infarction, late revascularization, and heart failure hospitalization) that were adjudicated masked to other findings. Using a CFR<2.0 to define CMD, they found that, in both sexes, CMD was highly prevalent (>50%) and significantly associated with adverse outcomes. Even in the presence of subclinical CAD (eg, coronary calcification), CFR remained significantly associated with adverse outcomes. The adjusted hazard decreased ~20% for every 10% increase in CFR. These new data confirm and extend the authors’ previous findings about the high prevalence of CMD and predictions of adverse outcomes in women and extend them to men. The findings are highly relevant for clinical trials evaluating therapeutic agents because this field lacks evidence-based data to inform patient management. Future study is also necessary to determine whether CMD significantly strengthens the prediction of adverse outcomes beyond that provided by traditional risk models, such as the Framingham risk score.
Although the prevalence and associated adverse prognosis of CMD in those patients with a normal perfusion scan included in this cohort are impressive, the true prevalence of CMD is likely to be even higher. Patients with perfusion defects were excluded from the current study, because their perfusion defect was presumed to be caused by obstructive CAD. However, others have shown that 70% of patients with an abnormal myocardial perfusion study but angiographically “normal” epicardial coronaries had CMD. Therefore, some of the patients excluded from this study likely also had CMD.

The high prevalence of CMD is noteworthy because CMD likely contributes not only to chest discomfort but also to ischemia-related left-ventricular dysfunction. Diastolic dysfunction is the earliest functional abnormality documented in patients with ischemia secondary to vascular smooth muscle dysfunction (spontaneously occurring coronary spasm). In our studies from the WISE, which included a high prevalence of CMD among women with normal left-ventricular systolic function at baseline, a heart failure hospitalization was the most prevalent adverse outcome during follow-up. Patients with endothelial dysfunction, related to microvascular inflammation/dysregulation, have a high incidence of left-ventricular diastolic dysfunction, and this likely contributes to the symptoms of patients with heart failure with preserved ejection fraction. Similarly, in the study by Murthy et al, patients with a CFR < 2.0 were 2 times more likely to have a heart failure hospitalization versus those with a CFR ≥ 2.0. Thus, CMD is a potentially important therapeutic target for the growing population of patients with heart failure with preserved ejection fraction.

Because of its high prevalence and associated adverse prognosis, it is important to consider testing for CMD in patients with chest discomfort or left-ventricular dysfunction of unclear cause. The investigators used a well-validated method to determine absolute myocardial blood flow reserve with PET. Their study design exemplified the importance of considering absolute or regional measures of flow compared with relative distribution of flow. Although a large proportion of patients had documented impairment in CFR, all patients included in the current study had “normal” relative perfusion by PET perfusion imaging. Therefore, when considering a more diffuse process, such as CMD, it is important to use a test that can evaluate absolute myocardial blood flow. In the WISE, we performed coronary reactivity testing using a Doppler guide wire in a proximal left coronary artery branch. Change in blood flow velocity in response to intracoronary adenosine is used to determine CFR, and change in coronary flow and coronary cross-sectional area in response to intracoronary acetylcholine are used to define endothelial-dependent vascular function. However, because most of these patients also have endothelial dysfunction, there is very limited flow-mediated dilation in response to adenosine, so coronary velocity provides a very good estimate of the absolute change in blood flow.

In addition to the PET techniques described by these investigators, there are other noninvasive methods available for the evaluation of coronary blood flow and CFR to assess CMD. Transthoracic Doppler echocardiography provides assessment of coronary blood flow velocity in the left anterior descending coronary that can be used to determine CFR after hyperemia. Doppler echo–derived measures of CFR were shown to correlate significantly with invasive measures of CFR. In contrast to PET, Doppler echo does not require radiation exposure and is available at most centers. A limitation of transthoracic Doppler echo–determined CFR is the feasibility of detecting left anterior descending flow in all of the patients. Studies reported that as few as 34% and as many as 96% of patients included in various cohorts had successful evaluation of left anterior descending flow. Echo-contrast agents can enhance the Doppler signal and led to improvement in measuring left anterior descending flow responses.

In conclusion, the present study highlights the importance of considering CMD as an explanation for chest discomfort or heart failure among both women and men without flow-limiting epicardial stenoses. In this setting, the link between CMD and adverse outcomes appears firmly established. Fortunately, many invasive and noninvasive techniques are available to evaluate coronary microvascular function. The possibility of CMD occurring in the presence of flow-limiting stenoses is also highly likely and warrants additional study relative to its contribution to symptoms and adverse outcomes. Identification of CMD will not only assist in counseling patients on prognosis but also has the potential to serve as a novel therapeutic target. Although microvascular spasm is gaining support as a potential mechanism responsible for CMD, the specific mechanism(s) responsible for CMD remains elusive and warrants continued study.

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