The Prevalence of Microvascular Dysfunction,
Its Role Among Men, and Links with Adverse Outcomes:
Non-Invasive Imaging Reveals the Tip of the Iceberg

Running title: Petersen et al.; Prevalence of microvascular dysfunction

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Considerable evidence has accumulated to counter older concepts of a categorical definition of ischemic heart disease (IHD) as simply the presence or absence of a flow-limiting stenosis. Revised concepts increasingly recognize IHD 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 myocardium.

Although not visualized by angiography, the coronary microcirculation may be indirectly assessed from the speed of radiographic contrast movement as the corrected TIMI frame count. This simple, objective, continuous index is accurate, reproducible, highly correlated with Doppler blood flow measurements, and provides information for risk stratification.\textsuperscript{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. Non-invasive methods, such as positron emission tomography (PET), Doppler echocardiography, and gadolinium perfusion cardiac magnetic resonance imaging, are also 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).\textsuperscript{4,5} We and others have identified that symptomatic patients with non-obstructive CAD may have an elevated risk of adverse outcomes compared with cohorts without symptoms and/or signs of IHD.\textsuperscript{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.\textsuperscript{6} About
45-60% of such patients have coronary vascular dysregulation (endothelial and/or non-endothelial dependent macro- or microvascular dysfunction) capable of causing ischemia with provocative testing.\textsuperscript{4,7} Numerous reports have linked coronary vascular dysregulation, usually referred to as coronary microvascular dysfunction (CMD), with adverse clinical outcomes.\textsuperscript{8-10} But these data have mostly been derived from cohorts of women. Indeed the finding from the NHLBI Women’s Ischemic Syndrome Evaluation (WISE) that CMD predicted adverse outcomes\textsuperscript{9} has been termed a “milestone” in furthering our understanding of IHD among women.\textsuperscript{11} This finding has resulted in multiple attempts to link CMD with female reproductive hormones and other female-specific issues, with variable results.

Yet the role of CMD among men has been open to question since relatively few studies included large numbers of men. In the current issue of \textit{Circulation}, Murthy et al. report investigations of the prevalence and prognosis of CMD among women and men referred for evaluation of suspected CAD.\textsuperscript{12} Patients were assessed with whole-body PETcomputed tomography and studies were analyzed semi-quantitatively 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), 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 (e.g. coronary calcification), CFR remained significantly associated with adverse outcomes. The adjusted hazard decreased about 20% for every 10% increase in CFR. These new data confirm and extend the authors’ prior 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 as this field lacks evidence-based data to inform patient management. Future study is also necessary to determine if CMD significantly strengthens the prediction of adverse outcomes beyond that provided by traditional risk models, such as the Framingham risk score.

While the prevalence and associated adverse prognosis of CMD in those patients with a normal perfusion scan included in this cohort is impressive, the true prevalence of CMD is likely to be even higher. Patients with perfusion defects were excluded from the current study, as 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 have had CMD.

The high prevalence of CMD is noteworthy as CMD likely contributes not only to chest discomfort but also to ischemia-related left-ventricular (LV) 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 LV 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 LV diastolic dysfunction and this likely
contributes to the symptoms of patients with heart failure with preserved EF (HFpEF).\textsuperscript{15}

Similarly, in the Murthy et al. study, patients with a CFR <2.0 were two times more likely to have a heart failure hospitalization versus those with a CFR \geq 2.0. Thus CMD is a potentially important therapeutic target for the growing population of patients with HFpEF.

Because of its high prevalence and associated adverse prognosis, it is important to consider testing for CMD in patients with chest discomfort and/or LV dysfunction of unclear etiology. The investigators used a well-validated method to determine absolute myocardial blood flow reserve with PET.\textsuperscript{16, 17} Their study design exemplified the importance of considering absolute and/or regional measures of flow as compared to relative distribution of flow. While 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. Change in blood flow velocity in response to intra-coronary adenosine is used to determine CFR, and change in coronary flow and coronary cross sectional area in response to intra-coronary acetylcholine are used to define endothelial-dependent vascular function.\textsuperscript{18} But as 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.\textsuperscript{7}

In addition to the PET techniques described by these investigators, there are other non-invasive 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 (LAD) coronary that can be used to determine CFR after
hyperemia.\textsuperscript{19} Doppler echo–derived measures of CFR have been shown to correlate significantly with invasive measures of CFR.\textsuperscript{20} 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 LAD flow in all of the patients. Studies have reported that as few as 34\% and as many as 96\% of patients included in various cohorts have had successful evaluation of LAD flow.\textsuperscript{19} Echo-contrast agents can enhance the Doppler signal and have led to improvement in measuring LAD flow responses.\textsuperscript{20}

In conclusion, the present study highlights the importance of considering CMD as an explanation for chest discomfort and/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 non-invasive 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 one potential possibility\textsuperscript{4}, the specific mechanism(s) responsible for CMD remain elusive and warrant continued study.

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