People with ischemic symptoms who have no angiographically obstructive coronary artery disease (CAD) are at increased risk for major adverse cardiovascular outcomes (death, myocardial infarction, stroke, and heart failure) as compared with the general population. Previous investigation, much of it originating from the National Heart, Lung, and Blood Institute–funded Women’s Ischemia Syndrome Evaluation (WISE) study, has demonstrated objective vascular abnormalities in subsets of patients with ischemic symptoms and without obstructive CAD, that is, with microvascular coronary disease. For example, invasive measurement of coronary flow reserve was abnormal in 47% of such patients, and acetylcholine induced a ≥50% reduction in blood flow in 50% and vasospasm in 5%. Stress imaging using any available technique demonstrates inducible ischemia in a subset of patients with symptoms and without obstructive CAD, and these patients typically have worse outcomes than those without ischemia.

Increased risk of heart failure with microvascular coronary disease is of interest for several reasons. Peripheral endothelial dysfunction has been identified in patients with heart failure with preserved ejection fraction and is a risk factor for adverse outcomes in patients with heart failure with preserved ejection fraction, which may suggest a link between microvascular disease, diastolic dysfunction, and heart failure. Ranolazine has been shown to reduce angina in patients with microvascular coronary disease and to improve left ventricular end-diastolic pressure in patients with heart failure with preserved ejection fraction, which may suggest a link between microvascular disease, diastolic dysfunction, and heart failure. Ranolazine has been shown to reduce angina in patients with microvascular coronary disease and to improve left ventricular end-diastolic pressure in patients with heart failure with preserved ejection fraction (albeit without an effect on dP/dt). Diastolic dysfunction occurs early in the ischemic cascade. It is, therefore, reasonable to hypothesize that diastolic dysfunction is a mediator of increased risk of events, particularly heart failure, among patients with microvascular coronary disease.

In this issue of Circulation: Cardiovascular Imaging, Nelson et al. report the use of cardiac MRI (CMR) to evaluate diastolic function in 20 women with ischemic symptoms and preserved left ventricular ejection fraction and without obstructive CAD or history of advanced heart failure. CMR-derived measurements of systolic and diastolic function were compared between these patients and 15 healthy women matched for age and body size. The authors identified multiple abnormalities in diastolic function using tissue tagging analysis, a CMR technique that provides quantitative assessment of myocardial deformation throughout the cardiac cycle. Specifically, patients had lower diastolic circumferential strain rate, lower peak rate of left ventricular untwisting, and longer time to peak filling rate and peak ventricular untwisting rate, as well as a trend toward longer time to peak diastolic circumferential strain rate. However, there was no difference between patients and controls in peak ventricular filling rate (ie, an expected equivalent to mitral E-wave velocity). Parameters that are often included in echocardiographic analysis of diastolic function, such as mitral annular velocities and Tei index, were not evaluated in this study. It is notable that differences in diastolic function were not because of left ventricular hypertrophy; left ventricular mass was normal and similar between patients and controls, despite the presence of hypertension in 12 of the 20 patients. Systolic parameters including ejection fraction, circumferential strain, and systolic circumferential strain rate were similar between patients and controls. Although the MRI regional motion measurements were confined to circumferential components in this analysis, longitudinal motion may also be altered in diastolic dysfunction, to a degree that may differ from the circumferential components. The authors reported that there were no discrete regions of abnormal late gadolinium identified in the patients. However, this does not preclude the possible existence of diffuse fibrosis that could have contributed to increased myocardial passive stiffness. Diffuse fibrosis might not be visually apparent without more quantitative assessments, such as through MRI measurements of the contrast agent partition coefficient.

It is likely that many of the patients in this study had microvascular coronary disease, based on previous research, though the authors do not report detailed characterization of microvascular disease in this cohort. Patients in the current study did have lower myocardial perfusion reserve index (MPRI) compared with controls. MPRI is a CMR-based, semiquantitative measurement of myocardial perfusion in response to adenosine stress, which has excellent diagnostic accuracy for obstructive CAD as determined by fractional flow reserve. MPRI has been used to document microvascular disease in patients with ischemic symptoms and no obstructive CAD, although this is somewhat controversial. MPRI is more widely available than quantitative perfusion methods but is not as accurate, at least for the detection of ischemia because of obstructive CAD. There was no correlation between MPRI and diastolic function in
the study by Nelson et al., which would tend to refute the notion that ischemia was the direct cause of diastolic dysfunction; this may relate to the small sample size. Also, the authors did not mention the possible presence of greater relative ischemia in the subendocardial region, which, if present, may have been partially obscured by the use of total wall thickness measurements in the determination of MPRI (although the frequent presence of dark rim artifacts in this region can make analysis difficult).

The finding of objective abnormalities of diastolic function in patients with ischemic symptoms and no obstructive CAD, though limited by factors mentioned earlier, is thought-provoking and does raise interesting questions for further investigation about the relationship between microvascular disease and diastolic dysfunction in patients with cardiac syndrome X and the potential to predict risk of events using noninvasive testing.

Disclosures
Dr Hochman discloses the following consultant/advisory relationship, title—Glaxo Smith Kline; role—National Coordinator for the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial and Steering Committee member for the Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52 Trial. The other authors report no conflicts.

References

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