With the widespread clinical use of angiography in the 70s of the last century, it became apparent that a sizeable proportion of patients referred for anginal symptoms had angiographically normal coronary arteries. These findings stimulated a hot debate among clinicians and scientists on the mechanisms and significance of this condition that seemed to be by far more frequent in women. For many years, there was uncertainty on the real significance of this condition that was often accompanied by electrocardiographic evidence of ischemia during stress.1 The situation began to unravel when myocardial perfusion studies demonstrated that many of these patients had evidence of abnormal perfusion. Cannon and Epstein2 introduced the term microvascular angina (MVA) for this patient population, in view of what appeared to be heightened sensitivity of the coronary microcirculation to vasoconstrictor stimuli associated with a limited microvascular vasodilator capacity. They proposed that dysfunction of small intramural prearteriolar coronary arteries might be the pathogenetic cause of this syndrome.

The term coronary microvascular dysfunction (CMD) was coined to provide an overarching definition that would encompass a large number of clinical scenarios characterized by evidence of a reduced coronary flow reserve (CFR) that could not be explained by an epicardial stenosis. It was also realized that CMD could coexist with coronary artery disease, providing an additional prognostic value.3

Diagnosis of MVA

MVA is fully acknowledged in the latest guidelines of the European Society of Cardiology on stable coronary artery disease although they do not provide a specific diagnostic algorithm.4 In the Figure, we propose a tentative diagnostic workup in patients presenting with suspected MVA. We think that stress echocardiography and gated single photon computed emission tomography can be used as the watershed technique in the quest for MVA. Indeed, a remarkable feature of MVA is the absence of detectable (using current equipment) wall motion abnormalities during stress despite reproduction of the anginal pain or ST segment depression. In the latter case, demonstration of a reduced CFR is necessary to confirm the diagnosis of MVA. There still uncertainty on what the lower limit of a normal CFR is although most groups agree that the cutoff should be between 2.0 and 2.5. If CFR is normal, it becomes important to rule out an increased susceptibility of the microcirculation to constrictor stimuli by performing an invasive acetylcholine test.5,6

Measurement of CFR

Both invasive (thermodilution catheter or Doppler flow wires) and noninvasive (transthoracic Doppler echocardiography or positron emission tomography) techniques can be used to measure CFR. As it is shown in our flowchart, the adoption of noninvasive techniques for measuring CFR avoids unnecessary invasive procedures. More recently, cardiovascular magnetic resonance (CMR) has emerged as an additional noninvasive tool to evaluate myocardial perfusion reserve.7 CMR studies of the coronary circulation exploit the first-pass kinetic of the T1-enhancing extracellular gadolinium–based contrast media. During the first pass, the contrast medium diffuses in the interstitial space from the microvasculature resulting in increased signal intensity proportional to the perfusion and blood volume of the tissue, size of extravascular compartment, and capillary permeability. In normal myocardium, the signal increases homogeneously during the first pass and is followed by contrast washout. A delayed signal increase and persistently hypointense regions indicate that the perfusion is reduced. The design of CMR perfusion pulse sequences is continuously improving spatial and temporal resolution, linearity between signal intensity and contrast agent concentration, and signal/noise ratio. The occurrence of image artifacts during stress (Dark Rim Artifact) mainly in the subendocardial at the margin of the left ventricular blood pool may represent a limiting factor in absolute quantification.

The Women’s Ischemia Syndrome Evaluation Study

Stress CMR perfusion has proven useful in women in the National Heart, Lung, and Blood Institute–sponsored Women’s Ischemia Syndrome Evaluation (WISE) study. Doyle et al8 investigated 100 women with symptoms of myocardial ischemia and no obstructive coronary artery disease in whom
myocardial perfusion was assessed semiquantitatively and was predictive of adverse events. In this issue of Circulation: Cardiovascular Imaging, Thomson et al expand these preliminary observations of the WISE study in a new female population with signs and symptoms of ischemia and no obstructive coronary artery disease. The main scope of this elegant study was to compare a CMR-derived index of CMD with coronary reactivity testing performed during angiography.

This study was carried out in 118 women with suspected CMD who had undergone coronary reactivity testing and in 21 asymptomatic reference subjects. Coronary reactivity testing included (1) abnormal endothelial function defined as a change in epicardial coronary artery diameter <0% in response to a maximum dose of acetylcholine; (2) CFR<2.5 in response to adenosine; (3) abnormal microvascular endothelial dysfunction, defined as an increase in coronary blood flow <50% in response to acetylcholine; and (4) abnormal nonendothelial function defined as a change in epicardial coronary artery diameter <20% in response to nitroglycerin. Semiquantitative analysis of CMR first-pass perfusion images was performed to determine myocardial perfusion reserve index (MPRI) with adenosine. Symptomatic women had significantly lower MPRI compared with controls, in line with previous findings, and a lower MPRI predicted abnormal coronary reactivity testing variables.

The principal merit of this investigation is that it provides a bridge between the invasive and noninvasive assessment of CMD. These 2 approaches provide similar but complementary information on the coronary microvasculature. In particular, a reduced MPRI confirms the diagnosis of CMD although a normal MPRI does not exclude the need to test for endothelium-dependent pathways. Thus, MPRI could be used to risk stratify patients with CMD noninvasively. Accordingly, the same authors have previously shown that cumulative event free survival was better in patients in the upper quartile of MPRI.

The main limitations of the study are that CMR data are analyzed only semiquantitatively and that, by design, the study population includes only women. In this regard, it is worth noting that similar prognostic data have been recently published by Murthy et al by positron emission tomography for the absolute quantification of myocardial blood flow and CFR in a population of >1200 individuals of both sexes. The results of the latter study demonstrate that CMD is highly prevalent among at-risk individuals and is associated with adverse outcomes regardless of sex. Further support to the fact that CMD caused by severe CMD is associated with a worse prognosis independently of sex is provided by the study of Jespersen et al.

In conclusion, noninvasive testing of the coronary circulation with measurement of perfusion reserve provides a valuable tool for the diagnostic workup of CMD. Although the WISE study is confined to women, there is growing evidence that CMD is not a women’s affair only, and therefore, it should not be underdiagnosed in men in the same way in which coronary artery disease was initially underdiagnosed in women.

**Disclosures**

Dr Camici acts as a consultant for Servier International. Dr Crea reports no conflicts.
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