

# Estimating ischemic burden

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## Abstract

Ischemic heart disease is the leading cause of death worldwide. Selection of patients that would be good candidates for management by revascularization is challenging, with accurate identification and quantification of ischemic burden playing a critical role. Current approaches for imaging and quantification of ischemia at rest and after stress are discussed here, including myocardial perfusion imaging (both single-photon emission computed tomography and positron emission tomography [PET]), stress echocardiography, cardiac magnetic resonance (CMR) imaging, and computed tomography, each with their advantages and limitations. Thus far, CMR perfusion and PET have been most accurate, with cardiac PET considered the gold standard for quantifying myocardial blood flow and coronary flow reserve (CFR); there is evidence that measures of CFR improves risk assessment beyond that previously achieved and allows incorporation of measures of overall vascular health, including, for example, measures of effects of epicardial coronary stenoses, diffuse atherosclerosis and vessel remodeling, and microvascular dysfunction on myocardial perfusion. ■ *Heart Metab.* 2017;72:37-43

**Keywords:** coronary flow reserve (CFR); ischemic burden; multimodality cardiac imaging

Ischemic heart disease (IHD) remains the leading cause of death in the world. Although the role of anatomically guided early revascularization is firmly established in patients with acute coronary syndromes, its role in patients with stable IHD is more controversial. Indeed, in randomized controlled trials in patients with stable IHD, revascularization based on anatomic thresholds has not resulted in lower rates of adverse cardiovascular events than guideline-directed medical therapy<sup>1,2</sup> or fractional flow reserve-guided percutaneous intervention.<sup>3</sup> An alternative approach generated from observational<sup>4</sup> and post hoc<sup>5</sup> analyses proposes that there may be a threshold of inducible ischemia above which an early revascularization strategy could result in improved cardiovascular outcomes. This suggests that a binary approach based on the assessment

of the presence or absence of ischemia would be insufficient and that quantification of total ischemic burden is essential for selecting patients with stable IHD for revascularization.

## Noninvasive quantification of ischemic myocardium

### Radionuclide myocardial perfusion imaging

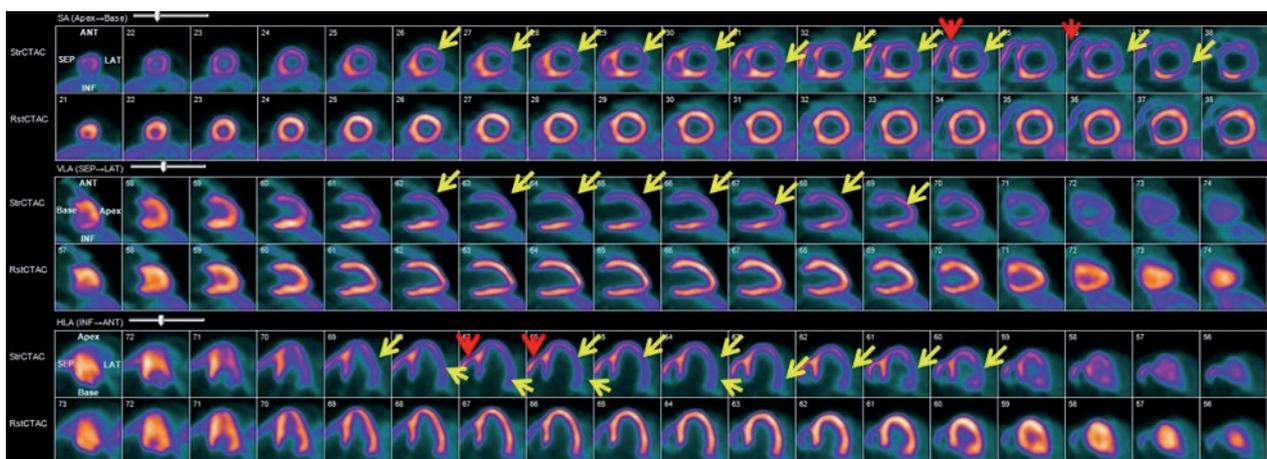
Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are the two nuclear medicine-based approaches for evaluation of ischemia by myocardial perfusion imaging (MPI). The basic principle of radionuclide MPI for detecting obstructive coronary stenosis and quantification of ischemic myocardium is based on the

### Abbreviations

**CCTA:** coronary computed tomography angiography; **CMR:** cardiac magnetic resonance; **CT:** computed tomography; **DeFACTO:** Determination of Fractional flow reserve by Anatomic Computed Tomographic angiography; **DISCOVER-FLOW:** Diagnosis of ISChemia-causing stenoses Obtained Via noninvasivE fRactional FLOW reserve; **FFRCT:** CT-based fractional flow reserve; **IHD:** ischemic heart disease; **LV:** left ventricular; **MPI:** myocardial perfusion imaging; **MRI:** magnetic resonance imaging; **NXT:** Analysis of Coronary Blood Flow Using Coronary CT Angiography: NeXt sTeps; **PET:** positron emission tomography; **SPECT:** single-photon emission computed tomography

ability of a radiotracer to identify a transient regional perfusion deficit in a myocardial region subtended by a coronary artery with a flow-limiting stenosis. A reversible perfusion defect is indicative of ischemia, whereas a fixed perfusion defect generally reflects scarred myocardium from previous infarction (Figure 1). Generally, myocardial perfusion defects during stress develop downstream from epicardial stenosis with greater than 50% luminal narrowing and become progressively more severe with increasing degree of stenosis. It is noteworthy that coronary stenoses of intermediate severity (eg, 50%-90%) associate with significant variability in the resulting maximal coronary blood flow, which in turns affects the presence and/or severity of regional perfusion defects.

Regional myocardial perfusion is usually assessed by semiquantitative visual analysis of the rest and stress images.<sup>6</sup> The segmental scores are then summed into global scores that reflect the total burden of ischemia and scar in the left ventricle. Objective quantitative image analysis is a helpful tool for a more accurate and reproducible estimation of total defect size and severity, and it is generally used in combination with semiquantitative visual analysis (Figure 2). The semiquantitative (visual) and quantitative scores of ischemia and scar are linearly related to the risk of adverse cardiovascular events and are useful in guiding patient management, especially in assessing the need for revascularization and the response to medical therapy. The presence of transient left ventricular (LV) dilation during stress imaging (so-called transient ischemic dilation or TID) is an ancillary marker of risk that reflects extensive subendocardial ischemia and often accompanies radionuclide MPI studies with extensive and severe perfusion abnormalities (Figure 1). It is often an important finding, particularly when it occurs in patients with no or only mild perfusion abnormalities, suggesting the presence of more extensive balanced subendocardial ischemia. The presence of this abnormality has often been shown to be a harbinger of increased risk.<sup>7,8</sup> Similarly, the presence of transient pulmonary radiotracer retention and right ventricular uptake during stress along with a drop in LV ejection fraction (LVEF) after stress (a sign of post-ischemic stunning) are also markers of multivessel LV ischemia (Figure 1).



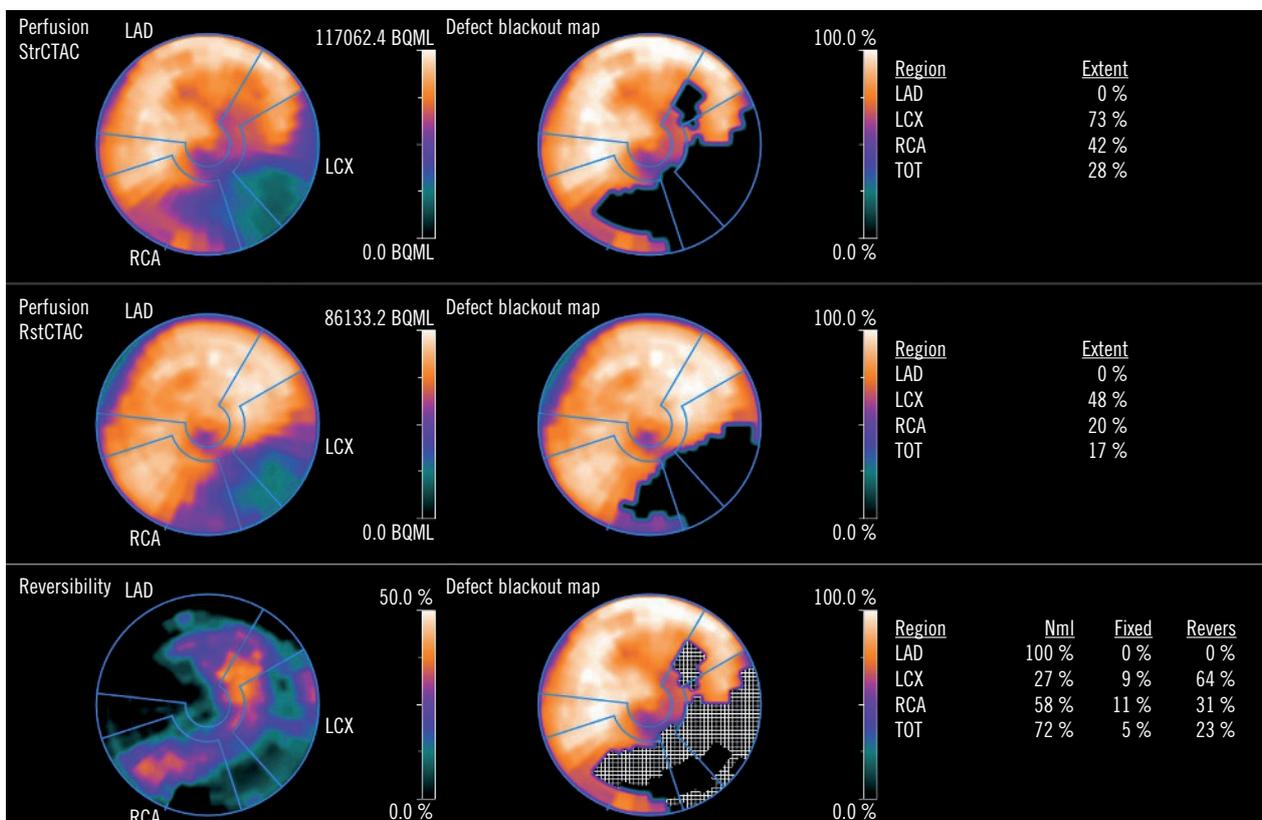
**Fig. 1** Rest-stress positron emission tomography in a 53-year-old woman with previous history of coronary artery bypass graft, showing large areas of severe stress-induced ischemia throughout the distribution of the left anterior descending artery and left circumflex artery (yellow arrows). In addition, on the stress images, there is transient ischemic dilation of the left ventricle and increased right ventricular uptake (red arrows).

**Abbreviations:** ANT, anterior; HLA, horizontal long-axis view; INF, inferior; LAT, lateral; RstCTAC, rest computed tomography attenuation correction; SA, short-axis view; SEP, septum; StrCTAC, stress computed tomography attenuation correction; VLA, verticle long-axis view.

## Echocardiography

The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening. Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional function of a previously abnormal segment might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia. The advantages of stress echocardiography over other stress imaging techniques include its widespread availability, no use of ionizing radiation, and relatively low cost. However, there are a number of limitations for stress echocardiography, including the following: (i) there are technical challenges associated with image acquisition at peak exercise because of exertional hyperpnea and cardiac excu-

sion; (ii) sensitivity may be limited by rapid recovery of wall motion abnormalities, which can be seen with mild ischemia, especially with one-vessel disease; (iii) detection of residual ischemia within an infarcted territory may be difficult because of an abnormality in resting wall motion; (iv) the technique for acquisition of echocardiographic data and analysis of images is highly operator dependent; and (v) complete images of good quality for viewing all myocardial segments are obtained in only 85% of patients. Newer techniques, including second harmonic imaging and the use of intravenous contrast agents improve image quality, but their effect on diagnostic accuracy has not been well documented. The use of intravenous contrast agents may also allow assessment of myocardial perfusion, although this is not approved or generally reimbursed, and data concerning the utility of contrast perfusion echocardiography are limited. As with radionuclide MPI, stress echocardiography is often used for risk stratification in patients with suspected or known IHD. A negative stress echocardiogram result is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely,



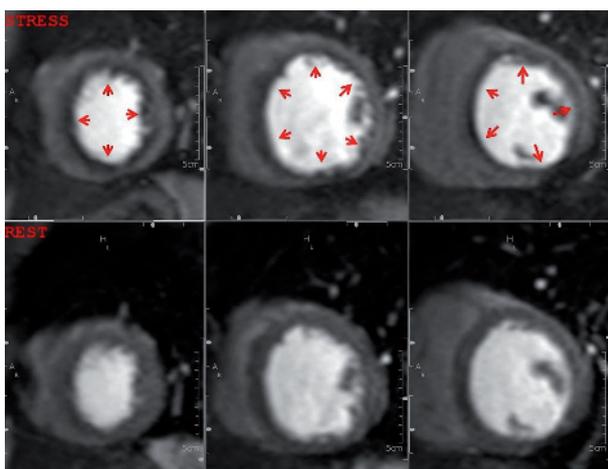
**Fig. 2** Polar map of a 72-year-old patient undergoing a rest-stress positron emission tomography, showing stress (top), rest (middle), and reversibility (bottom) plots. There is a medium-sized area of previous myocardial infarction, which involves 17% of the left ventricular mass in the distribution of the left circumflex territory, with a mild amount of residual stress-induced peri-infarct ischemia.

**Abbreviations:** LAD, left anterior descending artery; LCX, left circumflex artery; Nml, normal; RCA, right coronary artery; Revers, reversibility; RstCTAC, rest computed tomography attenuation correction; StrCTAC, stress computed tomography attenuation correction; TOT, total.

the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

### Cardiac magnetic resonance

The two approaches used with cardiac magnetic resonance (CMR) to evaluate patients with known or suspected IHD include the assessment of regional myocardial perfusion (the most common clinical approach) or wall motion at rest and during stress, the latter being analogous to stress echocardiography. Whereas treadmill or bicycle exercise stress CMR is practiced in a small number of specialized centers,<sup>9</sup> the logistics for stress magnetic resonance imaging (MRI) studies currently require the use of pharmacologic stress agents, including vasodilators or dobutamine. Myocardial perfusion is evaluated by injecting a bolus of a gadolinium-based contrast agent, followed by continuous data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Qualitative or quantitative analysis of rapidly acquired, sequential images (a "cine loop") obtained during the first pass of contrast into the myocardium can identify perfusion defects present at rest or under pharmacologically induced vasodilation. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium (*Figure 3*). Stress CMR perfusion has better diagnostic accuracy than stress echocardiography and SPECT, and comparable accuracy to that obtained by PET. Quan-

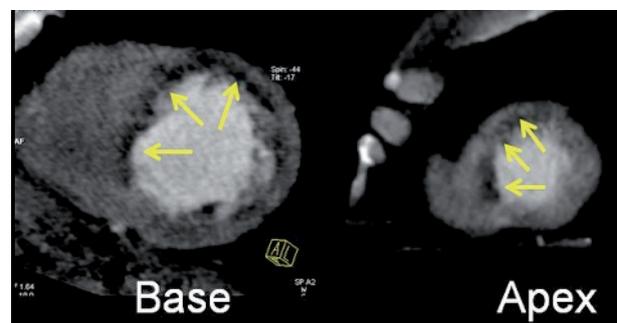


**Fig. 3** Vasodilator stress magnetic resonance (MR) myocardial perfusion study in a 69-year-old woman with exertional chest pain who was referred for ischemia assessment. Stress (top) and rest (bottom) first-pass perfusion images showing stress-induced first-pass perfusion defect in distribution of all three coronary vessels, including the left anterior descending coronary artery, the left circumflex artery, and the right coronary artery territory (red arrows).

tification of ischemic burden with CMR perfusion is more challenging than radionuclide MPI because of the limited sampling of the left ventricle, which is restricted to three short-axis slices. The addition of the information from late gadolinium enhancement imaging allows differentiation between hypoperfused (potentially ischemic) and infarcted myocardium. As with other imaging modalities, there is evidence that ischemia measurements derived from stress CMR studies also have prognostic value. In line with the nuclear and echocardiography literature, a normal result on CMR study is associated with a good prognosis. Conversely, the presence of new wall motion abnormalities, regional perfusion defects, the combination of wall motion abnormalities and perfusion defects, and the presence of late gadolinium enhancement are all predictors of adverse events.

### Computed tomography

Preliminary studies indicate that contrast-enhanced computed tomography (CT) might be useful to visualize myocardial perfusion, thereby enabling quantification of ischemic burden. As with stress perfusion MRI, this technique is based on acquiring CT images during the first pass of iodinated contrast into the myocardium. When the myocardium is visualized appropriately, areas of hypoenhancement correspond with perfusion defects (*Figure 4*). When seen under resting conditions, such defects represent areas of previous myocardial infarction, particularly if they are also associated with wall thinning or intramyocardial calcification. When CT images are acquired during administration of vasodilators, such as adenosine,



**Fig. 4** Vasodilator stress computed tomography (CT) perfusion images in a magnetic resonance (MR) myocardial perfusion study in a 58-year-old male. There is a large area of stress-induced subendocardial perfusion defect extending from the base to the apex of the anterior and septal walls, which is consistent with ischemia in the distribution of the left anterior descending artery territory (yellow arrows). Images courtesy of Dr. Joao Lima, Johns Hopkins University.

areas of inducible ischemia can be visualized. Limitations of this technique include motion-related and beam-hardening artifacts that can mimic areas of myocardial hypoenhancement. Although this technique remains experimental, the prospect of being able to perform a single scan that combines the anatomical information provided by coronary CT angiography (CCTA) with concomitant assessment of myocardial perfusion during pharmacologic stress is of potential clinical value. Recent relatively large clinical trials have shown that the technique is feasible and has reasonable diagnostic accuracy for identification of flow-limiting coronary stenoses.<sup>10</sup>

An alternative approach to the evaluation of flow-limiting stenosis is the use of CCTA data acquired at rest (without the use of adenosine-stimulated hyperemic challenge as is performed in the catheterization laboratory) to solve numerous fluid dynamics equations to noninvasively estimate lesion-specific fractional flow reserve (so-called  $FFR_{CT}$ ). Studies to date have shown only modest results with regard to the incremental value that the  $FFR_{CT}$  information adds to CCTA data. First, the DISCOVER-FLOW study (Diagnosis of ISChemia-causing stenoses Obtained Via

noninvasive fractional FLOW reserve) demonstrated that the addition of  $FFR_{CT}$  to CCTA did not improve the sensitivity for detection of lesions with an invasive FFR value under 0.8 (91% for CCTA alone versus 88% for CCTA +  $FFR_{CT}$ ) but did improve the specificity of CCTA alone from 40% to 82%. Next, the DeFACTO study (Determination of Fractional flow reserve by Anatomic Computed Tomographic angiography) similarly demonstrated that sensitivity for detection of stenoses with an invasive FFR value under 0.8 remained comparable for CCTA alone versus CCTA +  $FFR_{CT}$  (84% versus 90%), but specificity only marginally improved from 42% to 54%, and the study did not reach its prespecified primary end point for improving specificity. The most recent study, NXT (Analysis of Coronary Blood Flow Using Coronary CT Angiography: NeXt sTeps), showed a sensitivity of 94% versus 86% for CCTA alone versus CCTA +  $FFR_{CT}$  and specificity of 34% versus 79%, respectively. The NXT study is an encouraging improvement to CCTA alone, but essentially demonstrates an accuracy of  $FFR_{CT}$  now approaching SPECT or stress echocardiography, although potentially inferior (without direct comparison) to stress MRI or PET.

	Stress ECG	Nuclear SPECT	Nuclear PET	Stress echocardiogram	CCTA	Cardiac MRI perfusion
<b>Sensitivity</b>	++	86%	90%	80%	94%	84%
<b>Specificity</b>	++	74%	89%	86%	82%	85%
<b>Prognosis</b>	++	++++	++++	+++	+++	+++
<b>Radiation</b>	-	+++	+++	-	++	-
<b>Cost</b>	+	+++	++++	++	++++	++++
<b>Assessment of ischemic burden</b>	Cannot be assessed	Semiquantitative assessment with SSS and SDS; automated quantification with TPD and TID ratio	Semiquantitative and automated quantification similar to SPECT; MBF and CFR quantification	Semiquantitative assessment with wall motion score index and number of ischemic segments	$FFR_{CT}$ , Stress CTP	Qualitative assessment of number of segments involved with first-pass perfusion, semiquantitative assessment of myocardial signal intensity with first-pass perfusion, fully quantitative method to assess absolute MBF
<b>Future directions</b>	Incorporation of Ca score	MBF and CFR assessment, CTAC, low radiation dose protocol, stress only protocol	New radiotracers – to facilitate exercise PET and wider use without need for on-site cyclotron, increasing application of CFR	Myocardial perfusion, strain, single-beat 3D acquisition	Further validation of data with Stress CTP; wider availability of $FFR_{CT}$	Less laborious post processing involving quantitative and semiquantitative techniques; coronary plaque visualization

**Table 1** Summary of different noninvasive imaging modalities to assess for underlying ischemia.

**Abbreviations:** Ca, calcium; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; CTAC, computed tomography attenuation correction; ECG, electrocardiogram;  $FFR_{CT}$ , computed tomography-based fractional flow reserve; MBF, myocardial blood flow; PET, positron emission tomography; SDS, sum different score; SPECT, single-photon emission computed tomography; SSS, sum stress score; Stress CTP, stress computed tomography perfusion; TID, transient ischemic dilation; TPD, total perfusion defect.

Table 1 summarizes the different noninvasive imaging modalities to assess underlying ischemia. When interpreting this table, it is important to keep in mind that with any imaging modality, the diagnostic accuracy of the test is limited by posttest referral bias, which may increase the sensitivity and decrease the specificity of the test.

### Coronary flow reserve

Myocardial blood flow (in mL/min/g of myocardium) and coronary flow reserve (CFR; defined as the ratio between peak stress and rest myocardial blood flow) are important physiologic parameters that can be measured by routine postprocessing of myocardial perfusion PET and CMR images. However, cardiac PET is considered the gold standard for quantifying myocardial blood flow and CFR and shows excellent accuracy and reproducibility. Pathophysiologically, CFR estimates provide a measure of the integrated effects of epicardial coronary stenoses, diffuse atherosclerosis and vessel remodeling, and microvascular dysfunction on myocardial perfusion; as such, the value obtained is a more sensitive measure of myocardial ischemia. In the setting of increased oxygen demand, a reduced CFR can upset the supply-and-demand relationship and lead to myocardial ischemia, subclinical LV dysfunction (diastolic and systolic), symptoms, and death. These measurements of CFR have important diagnostic<sup>11-15</sup> and prognostic<sup>16-22</sup> implications in the evaluation and management<sup>20</sup> of the patients with known or suspected IHD.

Because quantitative measures of CFR integrate the fluid dynamic effects of atherosclerosis throughout the coronary arterial tree, including epicardial stenoses with early changes to endothelial and/or smooth muscle function, it may be a superior measure of overall vascular health, providing unique information about clinical risk. Five studies have demonstrated that PET measures of CFR improve cardiac risk assessment. In the largest of these studies,<sup>23</sup> CFR was prognostically important after adjusting for multiple factors, including LVEF at rest and conventional measures of ischemia. The lowest tertile of CFR had a hazard ratio of 5.6 and the middle tertile had a hazard ratio of 3.4. These results were confirmed by a similar study in a smaller cohort with a follow-up period of slightly more than a year.<sup>22</sup> As discussed, the noninvasive PET measure of CFR can improve

risk classification, especially among high-risk cohorts (eg, diabetics, non-ST-segment elevation myocardial infarction, in patients with chronic renal impairment, and in those with high coronary calcium scores).<sup>24-26</sup> Thus, assessment of CFR appears to permit a level of risk assessment beyond that achieved previously, with the potential for incorporation of vascular/endothelial status into routine patient investigations. Importantly, an abnormal CFR identified an increased risk of cardiac death even among those with normal scans by semiquantitative visual analysis. These findings suggest that coronary microvascular dysfunction is a widespread finding and that future work is needed to identify its putative role as a therapeutic target.

### Summary

Identification and quantification of ischemic burden plays a pivotal role in guiding patient management. There are several noninvasive imaging approaches for the quantification of ischemic myocardium, each with their own strengths and weaknesses. Stress CMR perfusion and PET are the most accurate techniques. The added advantage of PET is the routine assessment of quantitative myocardial blood flow and CFR, which are integrated into clinical workflow. There is emerging evidence suggesting that in comparison with conventional ischemia assessment, CFR—a more sensitive marker of ischemia—provides incremental risk stratification and the potential for more accurate selection of revascularization candidates. ■

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