Major progress has been made in the development and clinical application of dynamic imaging and tracer kinetic models to accurately measure absolute blood flow and coronary flow reserve (CFR) using quantitative positron emission tomography (PET) myocardial perfusion imaging (MPI) in patients with known or suspected coronary artery disease (CAD). Assessing CFR provides significantly greater separation of low- and high-risk subsets of patients compared with conventional single photon emission tomography or PET, imaging in which only relative tracer uptake is evaluated after exercise or pharmacological stress. Certainly, the traditional semiquantitative techniques used for many years for conventional single photon emission tomography and PET MPI have provided valuable diagnostic and prognostic information, particularly when extensive focal defects are identified on poststress images, which normalize on resting studies. In addition, the annual cardiac death or infarction rate is reported to be quite low (<1.0%) in patients undergoing stress MPI as derived from a pooled analysis of the literature. Nevertheless, multivessel disease is underestimated by using semiquantitative analysis of relative tracer uptake, and some patients with extensive 3-vessel disease or left main disease have normal or low-risk scintigraphic findings. This is attributable to what is often referred to as balanced ischemia, characterized by a rather uniform diminution in tracer activity throughout the myocardium. No one area of the left ventricle has a higher myocardial blood flow than other areas, so when a perfusion tracer such as Tc-99m sestamibi or Rb-82 is injected at peak vasodilator stress, no relative focal defects are identified. Occasionally, a single defect region associated with transient ischemic dilation of the left ventricle is observed in such patients with extensive epicardial CAD and balanced ischemia. This is attributed to extensive subendocardial hypoperfusion encompassing >1 coronary supply region. Another indication that multivessel or left main CAD may be present without extensive defects is presence of multiple wall motion abnormalities on single photon emission tomography or PET scans.

Additionally, diffuse microvascular dysfunction can be the sole cause of symptoms suggestive of myocardial ischemia or can be associated with large vessel epicardial CAD. Diffuse microvascular dysfunction can also be the substrate for a normal perfusion scan with vasodilator stress. This finding is more prevalent in patients with diabetes mellitus, as is the higher prevalence of nonobstructive CAD and endothelial dysfunction compared with nondiabetics. Endothelial dysfunction may be related to diffuse nonobstructive coronary atherosclerosis. Maya et al found that 38% of vessels with nonobstructive plaques had an abnormal regional CFR of <2.0. Vascular and endothelial dysfunction may be contributing factors to the higher annual cardiac event rate in diabetic compared with nondiabetic patients with normal perfusion scans. Subjects with high coronary calcium scores may have abnormal CFR without focal ischemia, reflecting the presence of nonobstructive coronary atherosclerosis. Liga et al reported that the presence of coronary calcium without focal significant coronary stenoses reduced CFR to a mean of 1.91, compared with 2.13 for normal coronary vessels and 1.63 for vessels with ≥50% stenoses. Patients with type 2 diabetes mellitus and high coronary calcium scores have been shown to have a high prevalence of abnormal MPI studies. Vascular inflammation is more prevalent in patients with diabetes mellitus and patients with metabolic syndrome than patients with normal glucose tolerance. This is suggestive of more inflamed atherosclerotic plaques. Vascular inflammation by biomarker criteria was associated with abnormal CFR in asymptomatic individuals with no focal perfusion defects on MPI.

In this issue of Circulation, Murthy et al quantified CFR in a large number of patients who underwent vasodilator Rb-82 PET imaging for clinical indications. It is a sequel to a study reported in the same group of 2783 patients in a previous publication by this group. In the earlier report, CFR was found to be an independent predictor of cardiac death and provided incremental risk stratification over clinical and gated PET scan variables. In the present study, diabetic and nondiabetic patients were compared. The majority of patients had symptoms of either chest pain or dyspnea. They were followed for a median of 1.4 years after imaging for the primary end point of cardiac death. As expected, the annualized rate of cardiac death increased with increasing extent and severity of perfusion defects, and was higher for diabetics than nondiabetics who had either normal scans, 1% to 9% defects, or ≥10% defects. This finding of an increased cardiac event rate in diabetic versus nondiabetic patients at
any severity of scan abnormality has been previously reported.\textsuperscript{7} What was striking in the study by Murthy et al\textsuperscript{18} was the incremental prognostic value in diabetic and nondiabetic patients of CFR after adjustment for clinical risk, presence of retinopathy, nephropathy, rest left ventricular ejection fraction, left ventricular ejection fraction reserve, and extent of ischemia and scar as identified by standard PET assessment. The fully-adjusted hazard ratio for an abnormal CFR for cardiac death was 3.2 and 4.9 for diabetic and nondiabetic patients, respectively. Quantitative estimation of CFR was able to improve risk stratification in more than half of both diabetic and nondiabetic patients who were at intermediate risk based on clinical risk variables and the conventional stress imaging findings. Diabetic patients without known CAD with abnormal CFR experienced a rate of cardiac death comparable with, and possibly higher than, that observed for nondiabetic patients with known CAD. In contrast, diabetic patients without known CAD and normal CFR had a very low rate of cardiac death during follow-up, which was comparable with nondiabetic patients without known CAD. Interestingly, among the diabetic patients without apparent ischemia or scar on conventional PET MPI, more than one-third (37\%) had abnormal CFR with an annual cardiac mortality rate of 3.5\%. This is >8 times higher mortality than seen in the diabetic patients with a normal PET MPI and normal CFR, which was 0.4\% annually. It is this subgroup of diabetic patients without inducible focal defects or scar but with abnormal CFR that surely contributes to the increased cardiac event rate seen in diabetic versus nondiabetic patients with normal scans. As mentioned above, such diabetic patients appear to have either diffuse CAD (obstructive or nonobstructive), endothelial dysfunction, microvascular dysfunction, or a combination of these abnormalities. Conversely, as the authors imply, diabetic patients with normal PET scans and normal CFR should perhaps not be classified as being equivalent to CAD patients, because they have an excellent prognosis, which is no different from that of nondiabetic patients with normal PET scans and normal CFR.

Murthy et al\textsuperscript{18} also found that for diabetic patients with \(\geq 10\%\) ischemia, those with impaired CFR had a 9.0\% annual unadjusted cardiac mortality rate compared with 3.4\% for those with \(\geq 10\%\) ischemia but preserved CFR. This finding suggests that even for patients exhibiting what would be considered a high-risk conventional PET scan with \(\geq 10\%\) ischemia, further risk stratification into very high risk versus lesser risk can be achieved. It may be that those with marked ischemia and impaired CFR have a higher prevalence of multivessel CAD or diffuse nonobstructive/microvascular disease, putting them in an even higher risk category for cardiac death. Such patients would benefit from coronary angiography. This might also be the case for patients with lesser degrees of ischemia and abnormal CFR. It is interesting that in the study by Murthy et al\textsuperscript{18} the mortality rate was similar for diabetic patients with 1\% to 9\% ischemia and impaired CFR (8.6\% per year) and diabetic patients with \(\geq 10\%\) ischemia and impaired CFR (9.0\% per year). These observations again highlight the benefit of measuring CFR for additional refining of risk.

Other groups have reported similar benefit of quantitative measurements of myocardial blood flow at rest and with vasodilator stress for assessing prognosis. Herzog et al\textsuperscript{20} found that in patients with normal perfusion on N-13-ammonia PET scans, an abnormal CFR was independently associated with a higher cardiac death rate over 3 years compared with normal CFR. The annual event rate was 6-fold higher in those with normal perfusion and abnormal CFR. Kajander et al\textsuperscript{21} using absolute quantification of myocardial perfusion with O-15-water and adenosine PET imaging, found a substantial increased detection rate of multivessel CAD compared with relative assessment of perfusion. All but 1 of 24 patients with angiographic multivessel disease were identified by abnormal quantitative blood flow. Ziadi et al\textsuperscript{22} using Rb-82 PET found that CFR provided significant incremental prognostic value over the summed stress score derived from conventional PET. As seen in the other studies, patients with low-risk (SSS <4) conventional PET scans and abnormal CFR (<2.0) had an intermediate cardiac event rate between those with low-risk scans and normal CFR and those with abnormal scans (SSS \(\geq 4\)) and abnormal CFR (<2.0). Fukushima et al\textsuperscript{23} performed rest–stress dipyridamole PET MPI in 275 patients with known or suspected CAD and found that CFR below the median was predictive of an adverse outcome in patients with normal perfusion as well as those with focal defects.

One issue that has to be confronted when CFR measurement becomes an integral part of a PET MPI study in patients with suspected CAD relates to determining the mechanism(s) of globally reduced CFR in the absence of focal perfusion defects. Such a finding could reflect balanced ischemia from severe multivessel CAD and high-grade epicardial stenoses, or diffuse nonobstructive CAD, or microvascular dysfunction. As mentioned previously, some patients (eg, diabetic) with a global decrease in CFR will have a combination of these pathophysiologic abnormalities. This is the situation where selective use of coronary CT angiography (CCTA) could be helpful. Because most cardiac PET centers use hybrid PET-CT cameras, it would be easy to perform noninvasive CCTA to detect those patients with balanced ischemia resulting from multivessel epicardial CAD as the cause of impaired CFR. Similarly, nonobstructive CAD can be identified with CCTA, which would lead to more aggressive medical therapy than if totally normal epicardial coronary arteries were observed. In the latter situation, microvascular dysfunction would be judged the cause of the decreased CFR. It might be the case that an excessive number of CCTA procedures would be performed if abnormal CFR was related primarily to presence of abnormal risk factors such as dyslipidemia, hypertension, smoking, and obesity and not to presence of CAD. This could be the case in nondiabetic patients with a low pretest likelihood of CAD based on age, gender, and atypical symptoms.

What has yet to be ascertained is whether outcomes of patients can be influenced by knowledge of CFR measurements. For example, if patients with type 2 diabetes mellitus and normal MPI scans with normal CFR are not aggressively treated with lipid-lowering drugs, as if they were a CAD equivalent, will they have similar outcomes as nondiabetic
patients with normal scans and normal CFR? Should patients with a mild focal reversible defect in the inferior wall, but abnormal CFR involving a major portion of the rest of the myocardium, undergo CCTA or be referred for invasive coronary angiography? In this situation, extent of CAD may have been underestimated by the conventional MPI study evaluating only relative uptake of the tracer. Or, the impaired CFR could reflect nonobstructive disease in the other 2 coronary vessels. The third explanation for the reduced CFR is presence of microvascular dysfunction with no major plaques in the other coronary arteries. Another question is whether just a quantitative stress-only scan with absolute stress flow measurements should be performed first in patients referred for MPI. If it shows normal stress flows in all myocardial regions, then no resting study is necessary. Another question relates to whether medical treatment effects on CFR have prognostic significance. For example, if CFR is improved with medical therapy, are outcomes better than if CFR is not increased? Should CCTA be the first test in a symptomatic patient with suspected CAD? If the study is entirely normal with no coronary plaques seen, is the prognosis as good as seen in those patients with normal perfusion scans and normal CFR? Microvascular disease would presumably not be identified if CCTA was the first test performed. What about the value of exercise stress? For example, should an exercise treadmill test be the first test performed in low- to intermediate-risk patients? Clearly, patients who achieve ≥10 METs without ischemic ST depression have a very low prevalence of ischemia on MPI and an excellent prognosis.24,25 Because many patients may require both an MPI study and a CCTA, can the total radiation dose to the patient be acceptable? Cost also becomes an issue if multimodality imaging is performed in a large percentage of patients with a reduced CFR. Finally, what is the cutoff for normal versus abnormal CFR? It seems to differ somewhat in each study. Would it be better to classify patients into tertiles of CFR and evaluate this parameter as a continuous variable rather than normal or abnormal with a specific cutoff value (eg, <2.0 versus ≥2.0)? The study by Murthy et al18 had only a 1.4-year follow-up, and it has yet to be ascertained whether the low cardiac event rate in diabetic patients with normal versus abnormal CFR and no perfusion defects is sustained over a longer follow-up time period.

In conclusion, the studies by Murthy et al,18,19 as well as those reported from other groups and summarized above, provide important data pertinent to the incremental prognostic value of noninvasively measuring coronary flow reserve by PET to achieve better risk stratification in patients with suspected or known CAD. This quantitative approach may be of greatest value in further risk stratifying diabetic patients. As MPI becomes more quantitative, the value of the technique for risk assessment becomes greater. We look forward to more of these types of studies to better understand how to use CFR information for clinical decision making.

Disclosures

None.

References


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Enhanced Risk Stratification With Noninvasive Measurement of Coronary Flow Reserve Using Positron Emission Tomography

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