Carried away with the flow to maintain the reserve

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Ischemia is an important factor in determining the outcome of patients with coronary artery disease (CAD). In patients with multi-vessel disease, it may become challenging to determine which lesion is inducing ischemia, requiring an intervention.

Until recently, invasive coronary angiography (ICA) was the gold standard, guiding intervention in patients with multi-vessel CAD. However, ICA may overestimate or underestimate lesions' functional significance. This is most common in the moderate stenosis range, where anatomical evaluation has a high interobserver variability even among experienced invasive cardiologists. Although coronary revascularization is at times performed based on the degree of stenosis alone, it has been demonstrated that intervention does not significantly decrease the risk of death or myocardial infarction in patients with stable CAD. Intervention based on the presence or absence of inducible ischemia is associated with improved outcome. In the presence of moderate or severe ischemia, revascularization is preferred, whereas in patients with mild ischemia, revascularization was associated with increased mortality; therefore, medical therapy is preferred.

In the normal coronary artery, vasodilation leads to an approximately fourfold increase in flow rate. With progressive coronary stenosis, rest flow remains normal until the vessel is narrowed by 80-85%. However, reduced coronary flow reserve occurs at approximately 40-50% degree of stenosis. [1] The hemodynamic significance of a coronary artery stenosis has crucial importance in the management of CAD. The FAME trial showed that only 35% of coronary artery stenosis in the range of 50-70% was functionally significant, as measured by fractional flow reserve (FFR).[2-4] FFR-guided angioplasty was associated with improved clinical outcome, a significant reduction in death, myocardial infarction and repeat revascularization, and a significant reduction in the use of stents and amount of contrast agent when compared to angiography-guided percutaneous coronary angioplasty (PCI). Hence, ischemia-driven treatment resulted in improved prognosis, reduced complication rate, and was cost effective. In patients with microvascular dysfunction and in patients with diabetes, kidney disease, hypertension, hypertrophic cardiomyopathy, and severe aortic valve stenosis who are at risk for the development of microvascular dysfunction FFR can be falsely elevated, underestimating coronary artery stenosis.[5]

Myocardial perfusion imaging (MPI) is commonly used to determine the presence or absence of ischemia and to guide intervention. However, MPI is a relative perfusion imaging technique. It may underestimate disease extent and severity, limiting its ability to diagnose multi-vessel CAD and diffuse microvascular disease.

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When positive, MPI may show only the territories supplied by the most severe coronary stenosis. In addition, MPI is limited in providing accurate diagnosis when inferior/lateral walls are involved because of the anatomical variability in blood supply to these territories.

Coronary computed tomography fractional flow reserve (CT-FFR) was recently introduced for the assessment of flow reserve, using CTA images and computational fluid dynamics (CFD) to estimate virtual FFR values.[6] It is, however, expensive and time consuming and can only be performed in specialized centers.

While invasive FFR has been used for years, it was validated for the use in humans by positron emission tomography (PET) measurements of myocardial flow reserve (MFR). A linear correlation was demonstrated between pressure-derived FFR and PET-derived MFR.[7] Flow quantification using PET is well established as the gold standard for myocardial flow measurements and has been clinically applied for almost 2 decades for diagnosis, risk stratification, and patient management. Large studies showed that PET-derived MFR has an added diagnostic value and an independent prognostic value to that of relative MPI.[8-10] Other studies showed that absolute PET quantification of hyperemic MBF is superior to relative radiotracer uptake for the identification of hemodynamically significant CAD.[11]

PET has known advantages over MPI single photon emission computed tomography (SPECT), including superior temporal resolution and intrinsic attenuation correction. It enables accurate delineation of radiotracer kinetics and accurate quantitation of myocardial blood flow over a wide range of flow and various radiotracers. It is, however, expensive, requires short-lived radiotracers, and is much less abundant than SPECT. Conventional SPECT technology with low count sensitivity and poor temporal resolution is limited in dynamic collection of data for the quantification of the rapid changes in the concentration of radiopharmaceuticals. The development of the novel solid-state cameras with increased detector sensitivity and increased temporal resolution enables to overcome some of these limitations and to perform list-mode acquisition and multi-frame dynamic reconstruction. Another limitation is the SPECT radiotracers with a relatively low extraction fraction, reaching a plateau in high flow rates, and therefore not ideal for quantitative assessment. Specific corrections are required to enable accurate quantitative assessment of dynamic SPECT studies.[12-15] Numerous studies have demonstrated the feasibility and added value of SPECT absolute myocardial blood flow and flow reserve, both in animals and in humans, including comparison of dynamic ^{99m}Tc-sestamibi CZT-SPECT to ^{15}O-water as well as N^{13}NH3 PET with good correlation of MBF and MFR and high diagnostic value. There was an overestimation of MBF obtained from CZT-SPECT with no attenuation correction.[16] Good correlations were also reported between SPECT myocardial flow reserve with ICA and FFR.[12-15]

In the current issue of the *Journal of Nuclear Cardiology*, Ferenczi et al[17] put another brick into the pavement and emphasize the invaluable underutilized SPECT-derived myocardial flow quantification as well as the need for further investigation and improvement. The authors compared the findings of visually analyzed MPI- and SPECT-derived stress and rest MBF and MFR in a group of 155 patients, 80 with known CAD and 75 patients with no documented CAD. Patients had MPI with list-mode dynamic data collection for myocardial flow quantification. There was no significant difference in the baseline characteristics in both groups. All patients with no documented CAD and 37 patients with documented CAD had a negative MPI. The remaining 43 patients had fixed perfusion abnormalities and 20/43 had evidence of inducible ischemia. The results of this study are in line with results of previous studies of PET- and SPECT-derived myocardial flow and reflect the prognostic impact of absolute myocardial blood flow and flow reserve. Patients with known CAD had significantly lower stress MBF and MFR compared to non-CAD patients (1.49 $mL \cdot g^{-1} \cdot min$ and 2.12, compared to 1.95 $mL \cdot g^{-1} \cdot min$ and 2.61, respectively). There was no significant difference in rest MBF between the two groups. Additional data were provided on risk assessment. Abnormal stress MBF and MFR in patients with documented CAD were associated with the worse prognosis when compared to the control group. The risk of CAD increased by 3.22 for every unit decrease in stress MBF.[15] This is in agreement with the pathophysiology of CAD and is due to the inability of atherosclerotic arteries to dilate and to increase the flow during stress.

The authors have reported reduced stress MBF and reduced MFR in all 3 territories in patients with documented CAD. Anatomical correlation is not available to ascertain the underlying etiology, whether obstructive CAD or microvascular disease attributed to endothelial dysfunction. The latter may precede the development of obstructive CAD.

MFR is an index of the entire circulation, from the epicardial coronary arteries down to the microcirculation. Therefore, MFR is an excellent tool to evaluate patients with increased risk for the development of microvascular dysfunction.[18] In the present work, significantly reduced stress and rest MBF but not MFR were observed in patients with diabetes. Lower MFR was noted in women. These are likely attributed to

endothelial and microvascular dysfunction.[15] The variability noted in MBF and MFR values in the control group, with similar baseline characteristic to the CAD group, could be explained by early endothelial changes in these patients who are at risk for microvascular dysfunction.[19]

Both stress and rest MBF were reduced in patients with ''necrotic lesions,'' leading to normal MFR and consistent with a previous myocardial infarction and scar.[15] As expected, MFR was reduced in ischemic territories compared to normal territories. Interestingly, there was no significant difference in MFR of ischemic and necrotic territories. The authors have not discussed this finding, uniquely reported in present work. There is no straightforward physiological explanation for that observation and further assessment is needed to clarify the underlying etiology. No significant difference was observed in rest MBF between the CAD and non-CAD patients, despite the presence of scar in 43 patients with CAD.[17]. This observation raises the question whether increased flow in territories adjacent to the scar may cause this phenomenon and warrants further investigation.

Similar to previous publications, lower MBF values were noted in the inferior wall, while MFR was not affected. This is likely due to attenuation artifact with similar effect on the stress and rest MBF. MFR can differentiate between a true perfusion defect in the inferior wall and diaphragmatic attenuation. This finding emphasizes the need for attenuation correction to enable accurate SPECT flow quantitation.

The results of the study by Ferenzi et al. are promising and support the current knowledge on the value of MPI and specifically quantitative MPI for the assessment of the hemodynamic significance of CAD. This study also opens the door for further investigation of conflicting findings. Comparison with morphological findings and additional functional testing such as FFR or PET MFR is warranted.

In the post-ISCHEMIA trial era, noninvasive patient management is preferred, based on the presence or absence of ischemia and on the amount of ischemia. SPECT MBF and MFR are available, but are still underutilized. It is time for SPECT-derived MBF and MFR to be a part of the clinical assessment for ischemia. The well-established benefit of flow measurements will increase the diagnostic accuracy of MPI and will raise the confidence of reporting physicians. At present, MFR can be obtained in all MPI studies performed on any CZT camera, even without attenuation correction that affects stress and rest MBF equally. More studies are needed before SPECT-derived MBF can be applied clinically. SPECT-derived MBF and MFR in special populations such as diabetics, patients with significantly increased BMI, and patients with heart failure, with either reduced or preserved left ventricular ejection fraction also need to be further evaluated to establish the prognostic role of this technique.

When interpreting SPECT-derived absolute MBF and MFR, physicians should be aware of differences in normal reference values and cutoffs between vendors of CZT scanners and dedicated software packages. The use of attenuation correction is expected to improve the accuracy of SPECT-derived measurements and should be explored. The suboptimal extraction fraction of the available SPECT radiotracers compared to the PET radiotracers is another limitation and available corrections, already offered by some vendors, should be improved to optimize the quantitative accuracy of SPECT. Standardization of the acquisition and processing protocols is required and could be achieved by large multi-center trials. These will enable to establish appropriate cutoff values and more accurate SPECT quantitation and will facilitate the implementation into routine clinical practice.

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