

EDITORIAL COMMENT

PET-Determined Hyperemic Myocardial Blood Flow

Further Progress to Clinical Application*

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Positron emission tomography (PET) has evolved as a mainstay to identify and characterize the coronary artery disease (CAD) process (1). The concurrent ability of PET with radio-tracer kinetic modeling to determine myocardial blood flow (MBF) at rest and during vasomotor stress enables the calculation of regional myocardial flow reserve (MFR) as an adjunct to the visual interpretation of myocardial perfusion studies. Adding quantification of hyperemic MBF and MFR by PET imaging to the visual analysis of myocardial perfusion identifies reduced coronary vasodilator capacity as a functional precursor of the CAD process and measures its response to preventive medical intervention, improves detection and quantification of the extent and severity of the burden of CAD, and potentially assesses the flow-limiting effect of single lesions in multivessel CAD (1).

SEE PAGE 1464

In this issue of the *Journal*, Danad et al. (2) report optimal cutoff values of [¹⁵O]H₂O PET-determined hyperemic MBF and MFR of 2.3 and 2.50 ml/g/min, respectively, in a clinical cohort of 330 patients with flow-limiting coronary artery stenosis as evidenced by invasively measured fractional flow reserve (FFR). Quantitative [¹⁵O]H₂O PET-derived MBF data provided an accuracy of 85% for detecting flow-limiting CAD as defined by an abnormal FFR.

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Hyperemic MBF proved more accurate than MFR in detecting flow-limiting stenoses on both per-patient and per-vessel analysis. Of all patients with FFR-defined, functionally limiting stenosis, only 13% were missed by quantitative hyperemic MBF. Moreover, a normal [¹⁵O]H₂O PET hyperemic MBF of >2.3 ml/g/min excluded the presence of flow-limiting stenosis with a high negative predictive value (90% per patient and 95% per vessel).

Although [¹⁵O]H₂O PET-derived cutoff values are encouraging, it remains uncertain how these thresholds for hyperemic flows using [¹⁵O]H₂O compare with other flow tracers, such as ¹³N-ammonia and ⁸²rubidium, for accurate diagnosis of CAD (1,3).

As for the reported optimal cutoff values of PET-determined hyperemic MBF and MFR with [¹⁵O]H₂O, it remains uncertain whether stenotic flow-limiting effects contribute mildly, moderately, or severely to a regional reduction in hyperemic MBF. This is because reduced coronary vasodilator capacity in patients with CAD is not merely a consequence of flow-limiting effects of any epicardial stenosis but also is related to cardiovascular risk factor-induced microvascular dysfunction (1).

The evaluation and interpretation of hyperemic MBF and MFR with PET therefore needs to be set in the clinical context with coronary anatomy and/or microvascular dysfunction in patients with cardiovascular risk and/or CAD (1). It has been suggested that for an epicardial stenosis ≥70%, reductions in MFR <1.7 can be assumed to account, at least in part, for increases in focal epicardial resistance using PET with ¹³N-ammonia or ⁸²rubidium as a myocardial flow tracer (4). Additional help may also come from PET-measured longitudinal hyperemic MBF decreases from the base to the apex of the heart (5). This diagnostic approach may provide more specific information on epicardial resistance

than conventional MFR (5,6) but requires further investigation.

CONCORDANCE AND DISCORDANCE BETWEEN MFR AND FFR. The strength of the investigation by Danad et al. (2) lies in the use of invasively measured FFR as reference for the [^{15}O]H $_2$ O PET-determined cutoff values of hyperemic MBF and MFR in the identification of hemodynamically (not just morphologically) significant CAD. Larger discordance between invasively measured FFR and PET-derived MFR has been reported (7). Such discordance can be attributed to diffuse CAD and/or microvascular dysfunction that lowers MFR without reduced FFR or a localized pressure gradient commonly seen in patients with CAD who have cardiovascular risk factors, such as diabetes mellitus and arterial hypertension. Conversely, vascular territories with coronary stenosis and reduced FFR (representing a localized pressure gradient across the lesion) may have preserved MFR on PET. This would reflect adequate hyperemic compensatory flow increases in resistance vessels and/or the development of collaterals to the distal perfusion bed (4). The presence of moderate to severe stages of microvascular dysfunction may in fact prevent submaximal or maximal hyperemic flow increases during pharmacological vasodilation of the coronary arteriolar vessels, such that FFR measurements may not fully reflect the potential functional, downstream effect of focal coronary lesions on hyperemic flow and may even be within “normal” range. This may also be partly reflected by a gray zone of FFR measurements ranging between 0.75 and 0.85 (8). Within this range, FFR measurement certainty may decrease to <80%. Thus, FFR and MFR provide distinctly different information regarding coronary pathophysiology, but these flow parameters complement each other in specific clinical scenarios (4).

THE POTENTIAL FOR “STRESS-ONLY” HYPEREMIC PET MYOCARDIAL BLOOD FLOW STUDIES. Measuring rest MBF in conjunction with vasodilator stress MBF and computing MFR (which equals the ratio of MBF during hyperemia to MBF at rest) offers a potential advantage; if a percentage error is made (e.g., in the arterial input function at rest) and the same error is made during hyperemia, the errors will cancel out (9). Therefore, when computing MFR, any systematic underestimate or overestimate of errors may not necessarily matter, provided the same percentage error is made both at rest and during hyperemia (10). The observations by Danad et al., however, also signify an impact of age and sex on the diagnostic accuracy of quantitative [^{15}O]H $_2$ O MBF measurements. Resting MBF is commonly higher with

increasing age (linked to an age-related increase of baseline myocardial work), which may lead to lower MFR values (11,12). Although sex did not appear to affect hyperemic MBF, resting MBF was higher in female subjects even after correction for myocardial workload. This difference may be related, at least in part, to effects of estrogens on vascular tone in women with CAD and/or sex-dependent lipid profile alterations (1). Given that hyperemic MBF was more accurate than MFR for the overall detection of flow-limiting coronary artery stenoses and less affected by the higher resting MBF in female and older subjects, stress-only PET determination of hyperemic MBF may be an alternative to MFR.

Higher predictive accuracy of hyperemic MBF over MFR for identifying hemodynamically significant CAD has also been shown with ^{13}N -ammonia PET (13). Notably, in patients older than 70 years of age, hyperemic MBF appears to be lower (11,12). Apart from evidence of deficient neuroendocrine regulation of the cardiovascular system with advancing age, a diminished effect of exogenous applied adenosine on vascular smooth muscle cell relaxation of the coronary arteriolar vessels may account for these reductions in hyperemic MBF in elderly patients (11). As for sex, the authors observed that sensitivity and the positive predictive value were lower in women than in men, which again was balanced by a higher specificity and negative predictive value in the detection of CAD. Because sex does not appear to affect hyperemic MBF, the observed higher diagnostic accuracy of [^{15}O]H $_2$ O PET in the detection of flow-limiting CAD in women than in men most likely is related to a lower prevalence of CAD in women, as the authors state. Consequently, given recent publications and public policies on reducing radiation exposure and controlling ever-growing diagnostic costs, single, stress-only PET determination of hyperemic MBF with [^{15}O]H $_2$ O (2) or ^{13}N -ammonia (13) may be a potential solution.

CONCLUSIONS. PET-derived hyperemic MBF and MFR show promise for noninvasively detecting flow-limiting, functionally relevant coronary artery stenosis (2). Despite proven prognostic importance in published reports, such absolute MBF values have rarely been used clinically, but that may change with the advent of several Food and Drug Administration-approved quantitative software packages. The higher diagnostic accuracy of stress-only hyperemic MBF over MFR, when compared with FFR and invasive coronary angiography, may be a welcome option in an era demanding reduced costs and radiation exposure. The latter may serve as the noninvasive “gatekeeper” to limit unnecessary cardiac catheterization while

accurately determining which patients would benefit from diagnostic coronary angiography and subsequent revascularization. Similar to the prospectively conducted multicenter studies with FFR, whether PET-guided hyperemic MBF and MFR parameters will also translate into improved clinical and patient outcomes after revascularization is a laudable goal to pursue.

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