FOCUS ISSUE: MBF QUANTIFICATION—REVIEW ARTICLE

Clinical Application of Myocardial Blood Flow Quantification in CAD Patients

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Abstract

With the introduction of the concurrent myocardial blood flow (MBF) quantification in ml/g/min with positron emission tomography/computed tomography (PET/CT) assessment of myocardial perfusion in clinical routine, the scope of conventional scintigraphic myocardial perfusion imaging now expands from the identification of the most advanced and culprit CAD lesion, as signified by the stress-induced regional myocardial perfusion defect, also to less severe but flow-limiting stenoses in multivessel CAD. Thus, by adding regional MBFs determined at rest and during vasomotor stress with the resulting myocardial flow reserve (MFR=MBF during stress/MBF at rest) to conventional myocardial perfusion PET/CT, a comprehensive identification and characterization of flow-limiting effects of multivessel CAD has become feasible. The non-specific nature of the hyperemic MBF increase and MFR, however, necessitates an evaluation and interpretation of regional hyperemic MBFs in the appropriate context with coronary morphology, microvascular function, and wall motion analysis in patients with CAD. Such a diagnostic approach may foster a more individualized and image-guided decision making process towards coronary revascularization procedures in patients with complex multivessel CAD that, however, remains to be tested in clinical outcome studies.

Keywords: CAD, Left ventricular wall motion, Multivessel disease, Myocardial blood flow, Myocardial flow reserve, Positron emission tomography

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With the advent of positron emission tomography/computed tomography (PET/CT) assessment of myocardial perfusion in concert with myocardial blood flow (MBF) quantification in ml/g/min a comprehensive and non-invasive characterization from subclinical to clinically-manifest stages of the CAD process has become possible (1-6), that carries important diagnostic and prognostic information (7-12). Clinically, PET/CT-determined MBFs and MFR may be applied to evaluate the presence of microvascular dysfunction as potential source of persistent anginal symptoms or so called syndrome X in patients with or without cardiovascular risk factors or with hypertropic obstructive cardiomyopathy (13-17). In patients with syndrome X and pronounced microvascular dysfunction ranolazine, a late Na current inhibitor, may be installed leading to improved anginal symptoms and microvascular function as increases in MFR demonstrate (18). Given the central role of coronary circulatory dysfunction in the initiation and development of the atherosclerotic process, an improvement or even normalization of hyperemic MBFs and MFR by preventive medical treatment, such as angiotensin-converting enzyme inhibitors or ARBs (19, 20), beta-hydroxymethylglutaryl coenzyme A reductase inhibitors (21), hormone replacement therapy in post-menopausal women (22), insulin-sensitizing thiazolidinedione in insulin-resistant individuals (23), euglycemic control in diabetes (24), physical exercise (25) or gastric bypass induced weight loss (26-28), has emerged as a potential therapeutic strategy for individualizing the prevention of the CAD process and its atherothrombotic sequelae (3). In this direction, initial findings in the assessment of peripheral vascular function emphasize...
that a normalization thereof by standard preventive medical intervention may indeed result an improved cardiovascular outcome as compared to those with without normalization of vascular function (29, 30). Since different regulatory mechanisms of the coronary and peripheral microcirculations in the diseased and normal vascular states apply, extrapolations between findings in the two vascular beds may be misleading (31, 32). Of note, coronary circulatory dysfunction has widely been realized as a useful integrating index of the overall stress burden by various cardiovascular risk factors on the arterial wall, taking into account the cumulative risk of cardiovascular risk factors and as yet unknown variables and genetic predispositions (15, 31). If this holds true, then a marked improvement or normalization of coronary circulatory function in cardiovascular risk individuals should also counterbalance the manifestation and/or progression of a CAD process and improve cardiovascular outcome. Such consideration is also supported by a recent investigation with PET/CT flow measurements in type 2 diabetes mellitus patients (24). Currently more of clinical interest, however, is the application of hyperemic MBF and MFR in patients with advanced multivessel CAD (6), as it expands the scope of conventional scintigraphic myocardial perfusion imaging from the identification of the most advanced and culprit CAD lesion, as signified by the stress-induced regional myocardial perfusion defect, also to less severe but flow-limiting stenosis in multivessel CAD (3, 6). This review strives to provide a framework of various diagnostic scenarios of PET/CT-determined myocardial perfusion and flow quantification in the detection and characterization of clinically manifest CAD (Table 1).

### Stenosis, ischemia and hyperemic MBFs

Pioneer investigations by Gould et al. (33-36), that were expanded and confirmed by subsequent clinical studies (37-39), demonstrated that hyperemic MBFs during pharmacologic vasodilation commonly decreased when a lesion exceeded 50% of luminal diameter (37-40). Despite this well described relationship between CAD lesions and MFR, individual hyperemic flows may underlie a substantial variety owing to different degree of adaptive vasodilation of the coronary microcirculation to compensate for downstream, flow-limiting effects of epicardial CAD lesions and/or the presence of collateral flow (16, 41, 42). In this respect, relatively maintained regional hyperemic MBF or MFR may through physical exercise or preventive medical care like in the “clinical outcomes utilizing revascularization and aggressive drug evaluation” (COURAGE) trial or the development of collateral flow indeed counterbalance the manifestation of stress-induced myocardial ischemia (43). This again provides some rationale for the observed relatively low prevalence of only about 30% of myocardial ischemia in the presence of epicardial narrowing ≥70% stenosis. As regards reductions of hyperemic MBFs, they may be related to adverse effects of cardiovascular risk factors induced increases in oxidative stress burden and inflammation within the coronary arteriolar wall in the absence of any CAD (31, 46, 47). Consequently, the relatively low specificity of reductions in hyperemic MBFs alone cannot certainly signify obstructive and flow-limiting CAD in multivessel CAD. It is important to consider that with increasing severity of CAD induced epicardial narrowing, the vascular resistances shift from the microcirculation to the site of epicardial stenosis as the adaptive vasodilation becomes exhausted (Fig. 1) (34-36, 48). In patients with multivessel

### Table 1 | Scope of PET/CT-determined hyperemic MBF and MFR

<table>
<thead>
<tr>
<th>Targeted Population</th>
<th>Role of MBF Estimation</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>1. Subclinical CAD</td>
<td>Reduced hyperemic MBF</td>
<td>Homogenous radiotracer uptake but reduced hyperemic MBF</td>
</tr>
<tr>
<td>2. Subclinical and clinically-manifest CAD</td>
<td>Incremental predictive value of reduced hyperemic MBF and/or MFR on cardiovascular outcome</td>
<td>Homogenous or regional reduction in radiotracer uptake associated with reduced hyperemic MBF</td>
</tr>
<tr>
<td>3. Patients with syndrome X or recurrent chest pain in non-obstructive CAD</td>
<td>Assessment of microvascular disease</td>
<td>Homogenous radiotracer uptake but reduced hyperemic MBF</td>
</tr>
<tr>
<td>4. CAD detection in advanced obesity</td>
<td>Assessment of macro- and microvascular disease</td>
<td>Optimal image quality of perfusion studies as compared to other imaging modalities</td>
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<tr>
<td>5. Identification of each flow-limiting epicardial lesion in multivessel CAD</td>
<td>Evaluation of hemodynamic significance of epicardial lesion ≥70% stenosis</td>
<td>Reduced regional hyperemic MBF and MFR</td>
</tr>
<tr>
<td>6. Detection of diffuse ischemia owing to significant left main stem and/or three vessel CAD</td>
<td>Unravelling diffuse ischemia despite homogenous radiotracer uptake</td>
<td>Globally reduced hyperemic MBFs*</td>
</tr>
</tbody>
</table>

*Effects of diffuse myocardial ischemia should be confirmed by a peak stress transient cavity dilation of the left ventricle during maximal vasomotor stress on gated PET images.

CAD: coronary artery disease; CT: computed tomography; MBF: myocardial blood flow; MFR: myocardial flow reserve; PET: positron emission tomography.
CAD, reductions in hyperemic MBFs therefore need to be interpreted in conjunction with coronary morphology for an appropriate interpretation of myocardial perfusion and regional MFR values (3, 6). A recent consensus paper reported by Gould et al. (4) has put forth the contention that for a CAD stenosis exceeding 70%, reductions in MFR < 1.7 can be considered to be widely related to stenosis induced epicardial resistance to hyperemic flow increases. The combined use of the severity of coronary lesions and MFR therefore may overcome the non-specificity of the MFR but necessitates further information of the presence of CAD and severity of focal stenosis (3). In clinical practice this means that a stress-induced regional myocardial perfusion defect commonly signifies the most advanced and thus the “culprit lesion” in multivessel CAD, while a reduction of the MFR of less than 1.7 subtended to a stenosis of intermediate severity identifies flow-hampering effects even when no regional perfusion defect is noted (Fig. 2) (6). The application of abnormal MFR to identify flow-hampering effects of CAD lesions is supported by several invasive validation studies measuring the post-stenotic coronary flow velocity reserve in CAD patients with stress-induced myocardial perfusion defects in the corresponding region on scintigraphic myocardial perfusion images (6). As regards $^{13}$N-ammonia PET/CT-determined optimal threshold for hyperemic MBFs, it has been reported to be 1.85 ml/g/min in a total of 27 patients with known or suspected CAD and in 21 normal individuals (Table 2) (49). In view of previous invasive investigations with intracoronary Doppler flow measurements of flow velocities (50-52), the threshold of MFR is commonly defined as 2.0 for both $^{13}$N-ammonia and $^{82}$Rubidium (1). Conversely, as regards $^{82}$Rubidium PET flow measurements, Johnson et al. (53), suggested of an optimal cutoff level of hyperemic MBF of 0.98 ml/g/min with an AUC=0.98 and a MFR of 1.74 with an AUC=0.91, respectively, to accurately identify myocardial ischemia in a large number of 1674 patients. Another positron-emitting flow tracer, that is increasingly used in a few centers in Europe not only for research but also clinically, is $^{15}$O-
for which thresholds have been well defined with 2.3 ml/g/min for hyperemic MBF and 2.50 for the MFR, respectively (Table 2) (54, 55). As the clinical use of these thresholds for PET-determined hyperemic MBFs and/or MFR affords the assessment of the functional significance of each CAD lesion (4), it may aid in the clinical decision making process to tailor coronary revascularization option with PCTA, CABG, or hybrid interventions in these patients with multivessel disease (Fig. 3). Nevertheless, reductions in hyperemic MBFs may not only result from advanced and thus flow-limiting CAD lesions but also from microvascular dysfunction or both that leads to a relatively low specificity of the hyperemic MBF in CAD detection and characterization (56, 57). For this reason, the interpretation of hyperemic

<table>
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<tr>
<th>Coronary Territory</th>
<th>Rest MBF (ml/g/min)</th>
<th>Stress MBF (ml/g/min)</th>
<th>MFR (Stress/Rest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>1.09</td>
<td>1.31</td>
<td>1.20</td>
</tr>
<tr>
<td>LCx</td>
<td>1.10</td>
<td>1.55</td>
<td>1.41</td>
</tr>
<tr>
<td>RCA</td>
<td>1.22</td>
<td>1.65</td>
<td>1.35</td>
</tr>
</tbody>
</table>

MBF: myocardial blood flow; MFR: myocardial flow reserve. LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.
MBFs and/or MFR in multivessel CAD needs to be performed in the appropriate context with coronary morphology, microvascular function, and wall motion analysis in these patients (3, 6). Whether such an individualized coronary revascularization strategy with the aid of PET-measured MBFs, however, may also result into an improved or equivalent cardiovascular outcome as compared to standard CABG in patients with multivessel CAD remains to be seen clinically.

The diagnostic challenge: diffuse ischemia

The evaluation of myocardial perfusion is based on the evaluation of the “relative” radiotracer uptake of the left ventricle to identify regions with relative lower radiotracer uptake or perfusion defect as compared to the remaining regions. While the most advanced CAD lesion in multivessel disease is likely to cause a relative decrease in regional radiotracer or perfusion deficit, the remaining remote regions may still have a homogenous uptake of the radiotracer despite the presence of less severe or stenosis of intermediate severity. Thus, conventional stress-rest myocardial scintigraphy commonly identifies the presence of clinically-manifest CAD by denoting stress-induced regional ischemia in the territory subtended to the culprit lesions, while remaining and less severe flow-limiting stenosis may be missed. In the presence of significant left main stenosis and/or advanced three vessel disease, “balanced” reductions of hyperemic MBFs or diffuse ischemia may be actually missed. As hyperemic MBFs are reduced widely homogeneously, the entire left ventricle may remain without any detectable regional difference in radiotracer uptake and diffuse ischemia may be missed (58). For example, only in 10% (14/143) of patients with demonstrated left main disease (≥50% stenosis) and ≥70% stenosis of the right coronary artery or three vessel disease with ≥70% epicardial narrowing in each major vessel on invasive coronary angiography, stress-induced regional ischemia was indeed identified (59). Adding regional wall motion abnormalities on post-stress gated SPECT to findings of stress-rest myocardial perfusion imaging, the identification of three-vessel CAD increased but only to 25% (59). Conversely, in another investigation in 101 patients without prior myocardial infarction or coronary revascularization, who underwent gated exercise or adenosine stress-Technetium sestamibi SPECT myocardial perfusion imaging, the diagnostic accuracy of gated scintigraphic myocardial perfusion imaging in the detection of with significant left main CAD (≥50% diameter stenosis) was evaluated (60). Interestingly, when evaluating myocardial perfusion images, high-risk feature with moderate to severe perfusion defects (>10% myocardium at stress), it was observed in up to 59%. The combined analysis of abnormal perfusion and wall motion on post-stress gated SPECT, however, increased the detection of high-risk individuals to 83% (60). In order to further optimize the identification of significant left main and/or advanced three vessels disease induced diffuse ischemia, the concurrent calculation of hyperemic MBF and MFR and wall motion analysis with gated PET/CT may be of unique advantage.

Given the presence of diffuse ischemia, decreases in hyperemic MBFs and MFR in all three major coronary artery vascular territories of the LAD, LCx, and RCA should be detected (Fig. 4). On the other hand, as several studies have demonstrated, pronounced and diffuse decreases of hyperemic MBFs and/or MFR may also be related microvascular dysfunction rather than to significant left main lesion and/or three-vessel disease. As stress-induced diffuse ischemia should lead to global myocardial stunning of the left ventricle associated with a “peak” stress transient ischemic cavity dilation (TID) on gated PET images, the presence of TID at peak stress should be included to identify diffuse ischemia owing to significant left main disease and/or advanced three vessel CAD (61, 62). Of note, Naya et al. (56) reported more recently that PET determined normal hyperemic MBFs has a high negative predictive value of 97% in excluding high risk CAD on coronary angiography (Fig. 5). In addition, the assessment of the left ventricular (LV) ejection reserve (Δ LVEF=stress LVEF-rest LVEF) adds further most valuable information for the exclusion of significant left main and/or three-vessel CAD. In this direction, a LVEF reserve of more than+5% had a positive predictive value of only 41% but a negative predictive value of 97%. The combination of normal hyperemic MBFs with a normal to high LVEF reserve, therefore, reliably excludes the presence of significant left main and/or three-vessel disease (Fig. 4-5) (56, 62). Overall, the assessment of hyperemic MBFs, MFR, LVEF at “peak”

Table 2

<table>
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<tr>
<th>Hyperemic MBF</th>
<th>131N-Ammonia (1.8 ml/g/min)</th>
<th>18Rubidium (0.98 ml/g/min)</th>
<th>15O-Water (2.3 ml/g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFR</td>
<td>2.0*</td>
<td>1.74</td>
<td>2.5</td>
</tr>
<tr>
<td>Reference (s)</td>
<td>(49)</td>
<td>(53)</td>
<td>(54,55)</td>
</tr>
</tbody>
</table>

*Commonly accepted threshold as defined by invasive investigations (6,50-52). MBF: myocardial blood flow; MFR: myocardial flow reserve.
stress as well as the LVEF reserve afford a differentiation between significant left main and/or three vessel CAD induced diffuse ischemia, its exclusion, and the presence of predominantly microvascular dysfunction that, however, should be further confirmed in more large-scale clinical investigations.

In individuals with normal stress-rest myocardial perfusion images, the quantification of hyperemic MBF and MFR may unmask microvascular dysfunction as functional precursor of CAD that may reinforce lifestyle-changes and/or preventive medical care. A stress-induced regional perfusion defect, however, signifies the "culprit" or most advanced CAD lesion. In this respect, adding hyperemic MBF and MFR may signify flow-limiting effects of lesions >70% diameter but less severe than observed for the culprit lesions and with normal radiotracer-uptake. (Reproduced with kind permission from reference (6)).

Regarding specifically cardiac PET practice in Japan (65), 13N-ammonia PET perfusion studies were performed in 2,172 cases for CAD in 2012, reflecting only 0.13% of any PET studies. With recent advances in PET technology and introduction of hyperemic MBF and MFR in clinical practice for the identification and characterization of complex and multivessel CAD (1, 6, 66), a further increase in cardiac PET perfusion studies is to be expected.

Conclusions

The concurrent ability of PET/CT to quantify myocardial perfusion, MBF and LVEF at peak stress expands the field of conventional myocardial perfusion imaging from the classical CAD detection to an optimized identification and characterization of the extent and severity of ischemia in multivessel disease. Furthermore, such analytic approach allows the differentiation between diffuse ischemia owing to significant left main lesion and/or three vessel CAD, its exclusion, and the presence of predominantly microvascular dysfunction in cardiovascular risk individuals with normal left ventricular function. In heart failure patients, however, PET/CT-determined normal hyperemic MBFs widely exclude the presence of high-risk CAD. Conversely, decreases in hyperemic MBFs may not differentiate between diffuse ischemia and microvascular dysfunction as myocardial...
A 38 year-old women with arterial hypertension and dyslipidemia complained of effort-induced chest pain. (a) Invasive coronary angiography demonstrates a proximal narrowing of \( \approx 50\% \) of the left main (LM) vessel. Furthermore, there is a 30% stenosis in the mid left anterior descending artery (LAD) after the first diagonal branch, whereas a \( \approx 40\% \) narrowing of the left circumflex artery (LCx) proximal to the second marginal branch noted. (b) The right coronary artery (RCA) system is are free of CAD. (c) The patient was referred for \(^{13}\)N-ammonia myocardial perfusion and flow PET/CT to evaluate the hemodynamic significance of the LM lesion. Regadenoson-stress and rest \(^{13}\)N-ammonia PET/CT images in corresponding short-axis (top), vertical long-axis (middle), and horizontal long-axis (bottom) slices demonstrate a widely homogenous and, thus, normal radiotracer-uptake of the left ventricle. (d) Corresponding display of myocardial perfusion on polar map and in 3D. (e) Regional myocardial blood flow quantification (MBF) and myocardial flow reserve (MFR) calculation with \(^{13}\)N-ammonia PET/CT and tracer kinetic modeling. The summarized quantitative data denote reduced hyperemic MBFs (<1.85 ml/g/min) and myocardial flow reserve (MFR <2.0) in the LAD-, LCx-, and RCA-distribution, respectively. (Abbreviations: Str = stress, Rst = rest, LV = left ventricle, and RV = right ventricle). (f) Since on gated PET left-ventricular wall motion is normal associated with a left-ventricular ejection fraction (LVEF) of 77% at rest and also at peak stress, respectively, diffuse myocardial ischemia potentially related to the left main lesion can be excluded. In the absence of a global hypokinesis during peak-stress without a drop in LVEF during stress from rest, the pronounced decreases in hyperemic MBFs and MFR in all three major coronary territories do not represent diffuse myocardial ischemia but rather reflect cardiovascular risk factors caused microvascular dysfunction. (Reproduced with kind permission from reference (1)).
stunning may not manifest in a further decrease in left ventricular function due to cardioprotective effects of ischemic conditioning. In such cases, non-invasive or invasive coronary angiography may be considered in order not to miss the presence of high-risk CAD. Taken together, the concurrent evaluation of myocardial perfusion, MBF, and left ventricular function at peak stress with positron-emitting flow tracers and PET/CT may translate into a clinical tool aiding to individualize and guide the decision-making process for interventional, surgical, or hybrid coronary revascularization procedures in complex and multivessel CAD in the near future.

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References


