FOCUS ISSUE: MBF QUANTIFICATION－REVIEW ARTICLE

Clinical Application of Myocardial Blood Flow Quantification in CAD Patients

Thomas H. Schindler, MD, Wael Marashdeh, MD and Lilja Solnes, MD

Received: March 8, 2016/Revised manuscript received: April 1, 2016/Accepted: April 1, 2016

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 stenosis 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, Myocardial ischemia, Positron emission tomography

Ann Nucl Cardiol 2016；2（1）：84-93

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 improvment 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 thiazolodinedione 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 atherothombotic sequelae (3). In this direction, initial findings in the assessment of peripheral vascular function emphasize

doi：10.17996/ANC.02.01.84

Thomas H. Schindler, Wael Marashdeh, Lilja Solnes
Department of Radiology School of Medicine, Division of Nuclear Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
E-mail: tschind3@jhmi.edu

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

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

*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.

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 ≥50% (44, 45). 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

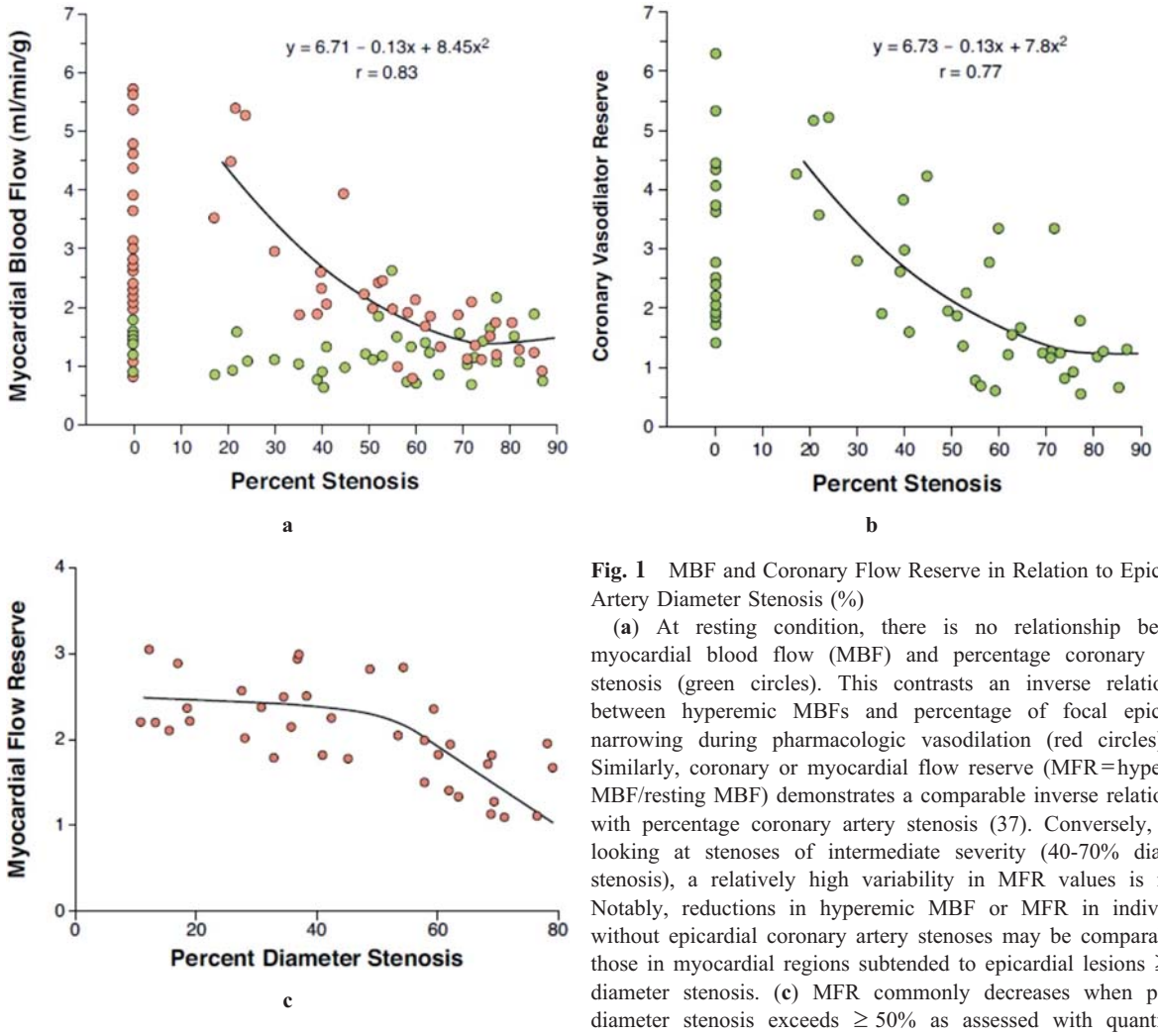
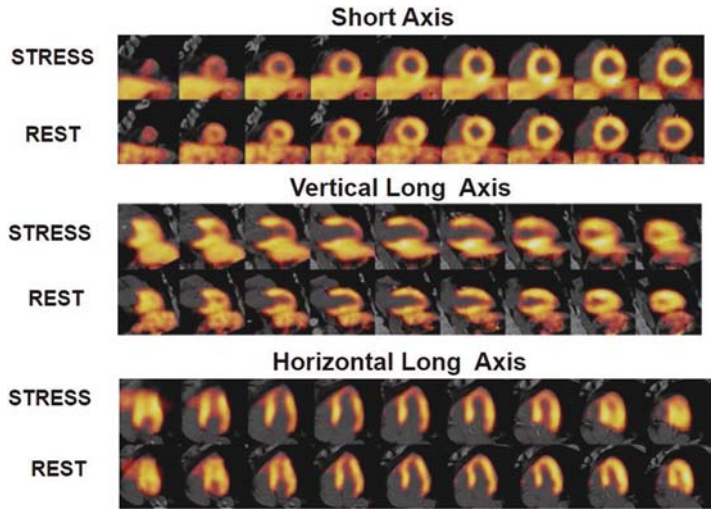


Fig. 1 MBF and Coronary Flow Reserve in Relation to Epicardial Artery Diameter Stenosis (%)

(**a**) At resting condition, there is no relationship between myocardial blood flow (MBF) and percentage coronary artery stenosis (green circles). This contrasts an inverse relationship between hyperemic MBFs and percentage of focal epicardial narrowing during pharmacologic vasodilation (red circles). (**b**) Similarly, coronary or myocardial flow reserve (MFR＝hyperemic MBF/resting MBF) demonstrates a comparable inverse relationship with percentage coronary artery stenosis (37). Conversely, when looking at stenoses of intermediate severity (40-70% diameter stenosis), a relatively high variability in MFR values is noted. Notably, reductions in hyperemic MBF or MFR in individuals without epicardial coronary artery stenoses may be comparable to those in myocardial regions subtended to epicardial lesions ≥50% diameter stenosis. (**c**) MFR commonly decreases when percent diameter stenosis exceeds ≥ 50% as assessed with quantitative coronary angiography (correlation coefficient r＝0.77, root mean square error ＝ 0.37, $p < 0.00001$) (37). (Reproduced with kind permission from reference (39)).

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-



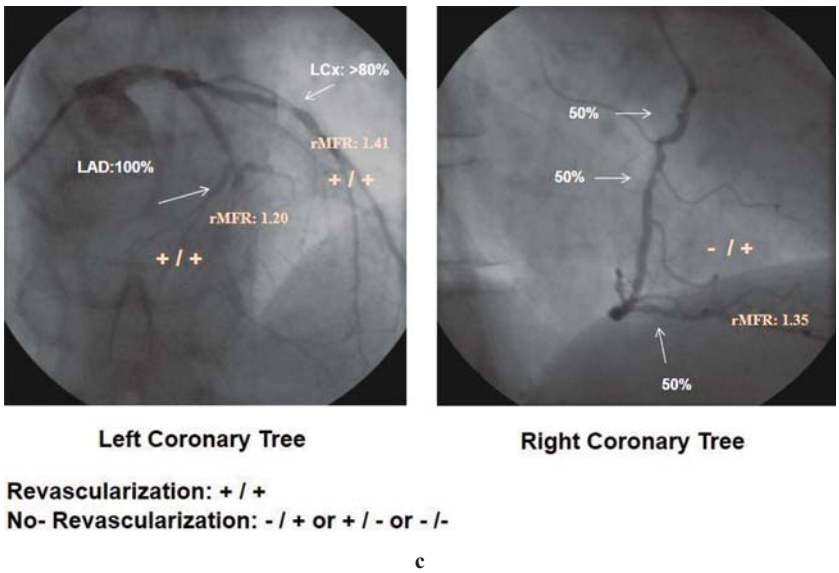
a

PET/CT and MBF quantification with radiotracer ^{13}N-Ammonia

Coronary Territory	Rest MBF (ml/g/min)	Stress MBF (ml/g/min)	MFR (Stress/Rest)
LAD	1. 09	1. 31	1. 20
LCx	1. 10	1. 55	1. 41
RCA	1. 22	1. 65	1. 35

MBF: myocardial blood flow; MFR: myocardial flow reserve. LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

b



c

Fig. 2 ^{13}N-ammonia PET/CT-Determined Perfusion and MBF in Multivessel CAD

A 61-year-old patient with arterial hypertension and type 2 diabetes mellitus presented with progressive shortness of breath and atypical chest pain. (**a**) On stress ^{13}N-ammonia perfusion images, a moderate decrease in radiotracer uptake of the mid-to-distal anterior, anteroseptal, and apical regions of the left ventricle can be observed, that becomes reversible on the rest images to signify ischemia in the LAD distribution. ^{13}N-ammonia uptake, however, is widely preserved in the lateral and inferior regions. (**b**) Quantification of MBFs demonstrates globally reduced MFR with a regional MFR of 1.20 in the LAD- , 1.41 in the LCx-, and 1.35 in the RCA-distribution, respectively. (**c**) Invasive coronary angiography demonstrates significant three vessel disease with proximal occlusion of the LAD, 80% stenosis in the proximal segments of the LCX (left panel), and sequential 50% to 60% lesions in the RCA (right panel). When defining flow-limiting CAD with epicardial stenosis >70% and MFR <1.7 (criteria: +/+), then apart from the proximal LAD occlusion, the LCx lesion of less and intermediate severity (≈80%) is also appreciated as hemodynamic significant despite normal radiotracer uptake. As regards the RCA, only one criteria applies. While regional MFR is markedly reduced with 1.35, the serial lesions of 50% do not reach the threshold of > 70% diameter stenosis (criteria: -/+). Thus, the marked decrease in MFR in the RCA distribution may predominantly reflect microvascular dysfunction and not hemodynamically obstructive CAD. (Reproduced with kind permission from references (3,6)).

water 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 2 Thresholds of different PET-Radiotracers to define Normal versus Abnormal Hyperemic MBF and MFR

	^{13}N-Ammonia	^{82}Rubidium	^{15}O-Water
Hyperemic MBF	1.8 ml/g/min	0.98 ml/g/min	2.3 ml/g/min
MFR	2.0*	1.74	2.5
Reference (s)	(49)	(53)	(54,55)

*Commonly accepted threshold as defined by invasive investigations (6,50-52).
MBF: myocardial blood flow; MFR: myocardial flow reserve.

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 ^{99m}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 (ΔLVEF＝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"

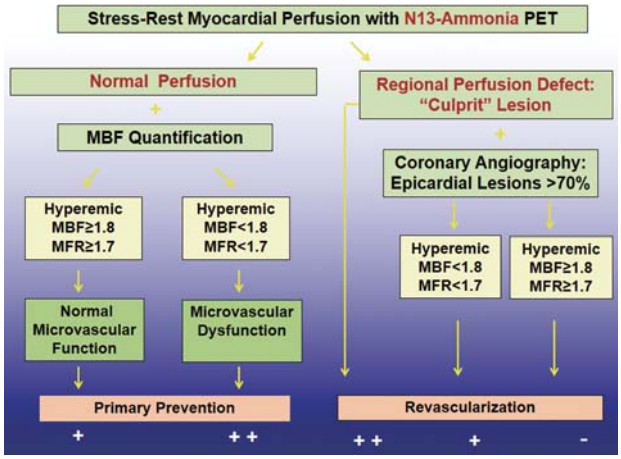


Fig. 3 Algorithm for the Integration of ^{13}N-ammonia PET/CT Perfusion Images and MBFs in Multivessel CAD

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)).

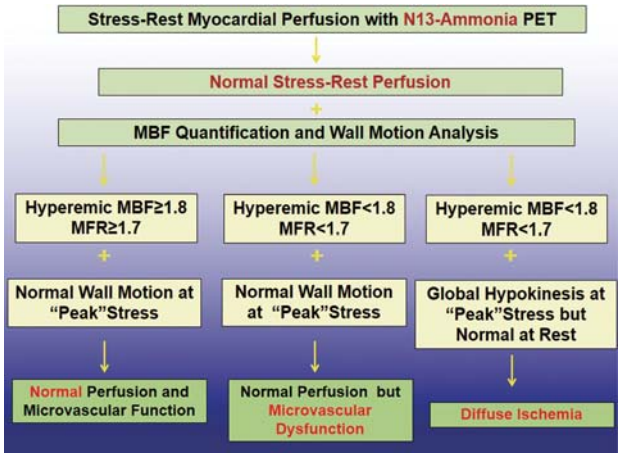


Fig. 4 Algorithm for the Integration of ^{13}N-ammonia PET/CT Perfusion Images, MBF, and Wall Motion Analysis for Differentiation between Microvascular Dysfunction and Diffuse Ischemia

Evaluating hyperemic MBFs in conjunction with wall motion analysis at "peak" stress enables the differentiation between predominant microvascular dysfunction and diffuse myocardial ischemia caused to significant left main and/or three vessel CAD. Balanced reductions in hyperemic MBFs and normal wall motion of the left ventricle at peak stress argues for the presence of predominantly microvascular disease but not diffuse ischemia, while diffuse reductions in hyperemic MBFs associated with transient ischemic cavity dilation (TID) of the left ventricle during vasomotor stress on gated PET images indicates the presence of diffuse ischemia. (Reproduced with kind permission from reference (3)).

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 ischemic cardiomyopathy patients with pre-existing low left ventricular function, the latter outlined scenario may not be applicable any more. Ischemic preconditioning of the heart portends a certain cardioprotection that strives to counterbalance a further worsening of left ventricular function related to repeat episodes of myocardial ischemia (63, 64). As a consequence, even in the presence of diffuse ischemia a minor or even no further decrease in global left ventricular function may occur. The absence of a significant drop in LVEF during peak stress from baseline in cardiomyopathy patients excludes a definite differentiation between diffuse ischemia or pronounced microvascular dysfunction as both conditions are associated with reduced hyperemic MBFs (Fig. 6). In such cases with normal stress-rest myocardial perfusion and reduced hyperemic MBFs, non-invasive or invasive coronary angiography may be of added value to identify the presence of left-main and/or three vessel CAD otherwise missed by PET perfusion and flow quantification. On the other hand, normal hyperemic MBFs commonly exclude high-risk CAD in patients with cardiomyopathy, as recent investigations from Naya et al. (56) emphasize, and further diagnostic work up with coronary angiography may not ensue any more.

Regarding specifically cardiac PET practice in Japan (65), *^{13}N-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 disease, 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

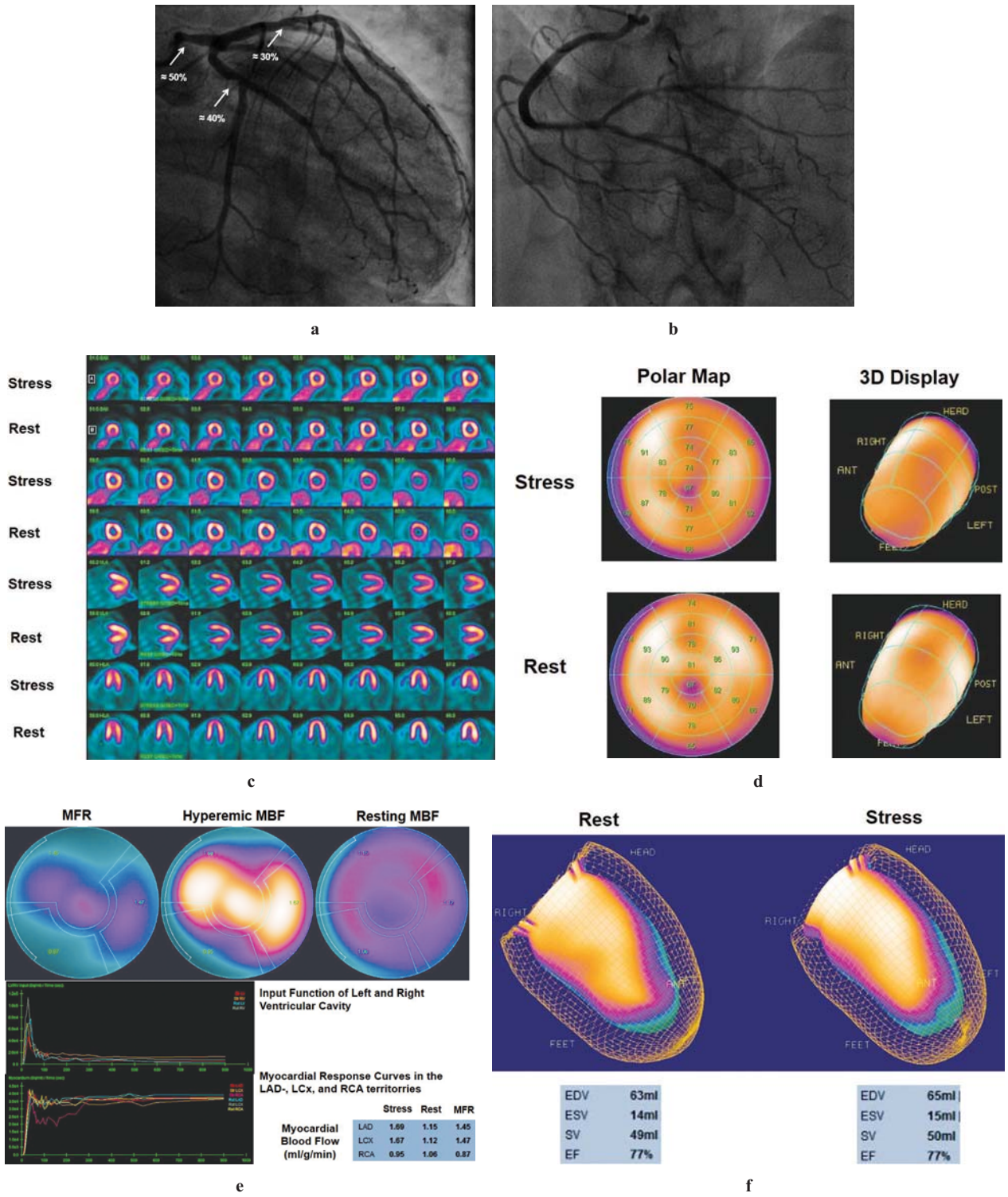


Fig. 5 ^{13}N-ammonia PET/CT-determined Perfusion, MBF, and Wall Motion with Left Main Stem Disease

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 ≈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 ≈40% narrowing of the left circumflex artery (LCx) proximal to the second marginal branch noted. (**b**) The right coronary artery (RCA) sytem is are free of CAD. (**c**) The patient was referred for ^{13}N-ammoniamyocardial 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)).

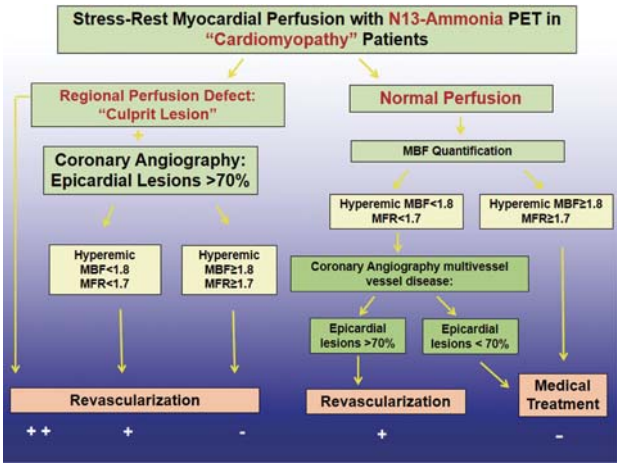


Fig. 6 Algorithm for the Integration of ^{13}N-ammonia PET/CT Perfusion Images, hyperemic MBFs and MFR in Individuals with Cardiomyopathy

In patients without cardiomyopathy or normal left-ventricular function, a stress-induced regional perfusion defect identifies the "culprit" or most advanced CAD lesion. In addition, reduced hyperemic MBF and MFR may signify flow-limiting effects of lesions >70 % diameter stenosis in patients with ischemic cardiomyopathy. Normal perfusion imaging, however, may not rule out diffuse ischemia due to significant left main and/or three vessel disease. While normal hyperemic MBFs and MFRs may widely excludes high risk CAD, reductions in hyperemic MBFs may be seen as non-specific. Abnormal hyperemic MBFs may suggest diffuse microvascular function or diffuse ischemia in these cardiomyopathy patients. In this setting, the additional wall motion analysis of the left ventricle at peak stress is not likely to be of much help as left-ventricular function is severely reduced in most patients and a further significant drop in left-ventricular ejection fraction is not to be expected due to ischemic conditioning or cardioprotective effects. Thus, given normal perfusion but abnormal hyperemic MBFs in cardiomyopathy patients, invasive or non-invasive coronary angiography may be considered to triage these high risk patients to coronary revascularization procedures or medical treatment alone. (Reproduced with kind permission from reference (6)).

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.

Acknowledgments

This article was supported by a departmental fund from Johns Hopkins University, Baltimore, Maryland (No. 175470). Some sections of the manuscript are similar to sections of an extensive review of cardiac PET by Schindler TH et al. (6)

Sources of funding

None

Conflict of interest

No potential conflict of interest exists and all sources of funding for the work are acknowledged as follows. Departmental fund (no. 175470) from Johns Hopkins University, Baltimore, MD, USA.

Reprint requests and correspondence:
Thomas Hellmut Schindler, MD
Johns Hopkins University, School of Medicine, Division of Nuclear Medicine, Cardiovascular Nuclear Medicine Department of Radiology and Radiological Science SOM, JHOC 3225, 601 N. Caroline Street, USA-Baltimore, MD, 21287
E-mail: tschind3@jhmi.edu

References

1. Schindler TH. Positron-emitting myocardial blood flow tracers and clinical potential. Prog Cardiovasc Dis. 2015; 57: 588-606.
2. Schindler TH, Dilsizian V. PET-determined hyperemic myocardial blood flow: further progress to clinical application. J Am Coll Cardiol. 2014; 64: 1476-8.
3. Schindler TH, Schelbert HR, Quercioli A, et al. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. JACC Cardiovasc Imaging. 2010; 3: 623-40.
4. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013; 62: 1639-53.
5. Schindler TH, Quercioli A, Valenta I, et al. Quantitative Assessment of Myocardial Blood Flow-Clinical and Research Applications. Semin Nucl Med. 2014; 44: 274-93.
6. Schindler TH. Myocardial blood flow: Putting it into clinical perspective. J Nucl Cardiol. 2015 Dec 28. [Epub ahead of print].
7. Schindler TH, Nitzsche EU, Schelbert HR, et al. Positron emission tomography-measured abnormal responses of myocardial blood flow to sympathetic stimulation are associated with the risk of developing cardiovascular events. J Am Coll Cardiol. 2005; 45: 1505-12.
8. Herzog BA, Husmann L, Valenta I, et al. Long-term prognostic value of ^{13}N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol. 2009; 54: 150-6.
9. Ziadi MC, Dekemp RA, Williams KA, et al. Impaired

myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. J Am Coll Cardiol. 2011; 58: 740-8.
10. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation. 2012; 126: 1858-68.
11. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation. 2011; 124: 2215-24.
12. Murthy VL, Naya M, Foster CR, et al. Coronary vascular dysfunction and prognosis in patients with chronic kidney disease. JACC Cardiovasc Imaging. 2012; 5: 1025-34.
13. Marinescu MA, Loffler AI, Ouellette M, et al. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. JACC Cardiovasc Imaging. 2015; 8: 210-20.
14. Recio-Mayoral A, Rimoldi OE, Camici PG, et al. Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. JACC Cardiovasc Imaging. 2013; 6: 660-7.
15. Schindler TH, Zhang XL, Vincenti G, et al. Role of PET in the evaluation and understanding of coronary physiology. J Nucl Cardiol. 2007; 14: 589-603.
16. Pries AR, Badimon L, Bugiardini R, et al. Coronary vascular regulation, remodelling, and collateralization: mechanisms and clinical implications on behalf of the working group on coronary pathophysiology and microcirculation. Eur Heart J 2015; 36: 3134-46.
17. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J. 2014; 35: 1101-11.
18. Bairey Merz CN, Handberg EM, Shufelt CL, et al. A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. Eur Heart J. 2015 Nov 27. pii: ehv647. [Epub ahead of print] Review.
19. Naya M, Tsukamoto T, Morita K, et al. Olmesartan, but not amlodipine, improves endothelium-dependent coronary dilation in hypertensive patients. J Am Coll Cardiol. 2007; 50: 1144-9.
20. Mancini GB, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. Circulation. 1996; 94: 258-65.
21. Baller D, Notohamiprodjo G, Gleichmann U, et al. Improvement in coronary flow reserve determined by positron emission tomography after 6 months of cholesterol-lowering therapy in patients with early stages of coronary atherosclerosis. Circulation. 1999; 99: 2871-5.
22. Schindler TH, Campisi R, Dorsey D, et al. Effect of hormone replacement therapy on vasomotor function of the coronary microcirculation in post-menopausal women with medically treated cardiovascular risk factors. Eur Heart J. 2009; 30: 978-86.
23. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med 2004; 140: 700-8.
24. Schindler TH, Cadenas J, Facta AD, et al. Improvement in coronary endothelial function is independently associated with a slowed progression of coronary artery calcification in type 2 diabetes mellitus. Eur Heart J. 2009; 30: 3064-73.
25. Czernin J, Barnard RJ, Sun KT, et al. Effect of short-term cardiovascular conditioning and low-fat diet on myocardial blood flow and flow reserve. Circulation. 1995; 92: 197-204.
26. Quercioli A, Montecucco F, Pataky Z, et al. Improvement in coronary circulatory function in morbidly obese individuals after gastric bypass-induced weight loss: relation to alterations in endocannabinoids and adipocytokines. Eur Heart J. 2013; 34: 2063-73.
27. Quercioli A, Pataky Z, Montecucco F, et al. Coronary vasomotor control in obesity and morbid obesity: contrasting flow responses with endocannabinoids, leptin, and inflammation. JACC Cardiovasc Imaging. 2012; 5: 805-15.
28. Quercioli A, Pataky Z, Vincenti G, et al. Elevated endocannabinoid plasma levels are associated with coronary circulatory dysfunction in obesity. Eur Heart J. 2011; 32: 1369-78.
29. Fichtlscherer S, Breuer S, Zeiher AM. Prognostic value of systemic endothelial dysfunction in patients with acute coronary syndromes: further evidence for the existence of the “vulnerable”patient. Circulation. 2004; 110: 1926-32.
30. Modena MG, Bonetti L, Coppi F, et al. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol. 2002; 40: 505-10.
31. Drexler H. Endothelial dysfunction: clinical implications. Prog Cardiovasc Dis. 1997; 39: 287-324.
32. Valenta I, Landmesser U, Schindler TH. Vascular function of the peripheral and coronary circulation: worthwhile to assess their relation? J Nucl Cardiol. 2011; 18: 201-3.
33. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. J Am Coll Cardiol. 1990; 15: 459-74.
34. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol. 1974; 34: 48-55.
35. Gould KL, Lipscomb K, Calvert C. Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. Circulation. 1975; 51: 1085-94.
36. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol. 1974; 33: 87-94.
37. Uren NG, Melin JA, De Bruyne B, et al. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med. 1994; 330: 1782-8.
38. Di Carli M, Czernin J, Hoh CK, et al. Relation among stenosis severity, myocardial blood flow, and flow reserve in patients with coronary artery disease. Circulation. 1995; 91: 1944-51.
39. Krivokapich J, Czernin J, Schelbert HR. Dobutamine positron emission tomography: absolute quantitation of rest and dobutamine myocardial blood flow and correlation with cardiac work and percent diameter stenosis in patients with and without coronary artery disease. J Am Coll Cardiol. 1996; 28: 565-72.
40. Demer LL, Gould KL, Goldstein RA, et al. Assessment of coronary artery disease severity by positron emission

tomography. Comparison with quantitative arteriography in 193 patients. Circulation. 1989; 79: 825-35.
41. Meier P, Gloekler S, Zbinden R, et al. Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. Circulation. 2007; 116: 975-83.
42. Seiler C, Stoller M, Pitt B, et al. The human coronary collateral circulation: development and clinical importance. Eur Heart J. 2013; 34: 2674-82.
43. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008; 117: 1283-91.
44. Di Carli MF, Hachamovitch R. New technology for noninvasive evaluation of coronary artery disease. Circulation. 2007; 115: 1464-80.
45. Sato A, Hiroe M, Tamura M, et al. Quantitative measures of coronary stenosis severity by 64-Slice CT angiography and relation to physiologic significance of perfusion in nonobese patients: comparison with stress myocardial perfusion imaging. J Nucl Med. 2008; 49: 564-72.
46. Schindler TH, Nitzsche EU, Munzel T, et al. Coronary vasoregulation in patients with various risk factors in response to cold pressor testing: contrasting myocardial blood flow responses to short- and long-term vitamin C administration. J Am Coll Cardiol. 2003; 42: 814-22.
47. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003; 23: 168-75.
48. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. I. Physiologic basis and experimental validation. Am J Cardiol. 1978; 41: 267-78.
49. Hajjiri MM, Leavitt MB, Zheng H, et al. Comparison of positron emission tomography measurement of adenosine-stimulated absolute myocardial blood flow versus relative myocardial tracer content for physiological assessment of coronary artery stenosis severity and location. JACC Cardiovasc Imaging. 2009; 2: 751-8.
50. Chamuleau SA, Tio RA, de Cock CC, et al. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. J Am Coll Cardiol. 2002; 39: 852-8.
51. Ferrari M, Schnell B, Werner GS, at al. Safety of deferring angioplasty in patients with normal coronary flow velocity reserve. J Am Coll Cardiol. 1999; 33: 82-7.
52. Kern MJ, Donohue TJ, Aguirre FV, et al. Clinical outcome of deferring angioplasty in patients with normal translesional pressure-flow velocity measurements. J Am Coll Cardiol. 1995; 25: 178-87.
53. Johnson NP, Gould KL. Physiological basis for angina and ST-segment change PET-verified thresholds of quantitative stress myocardial perfusion and coronary flow reserve. JACC Cardiovasc Imaging. 2011; 4: 990-8.
54. Danad I, Raijmakers PG, Harms HJ, et al. Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: a [^{15}O] H_2O PET study. Eur Heart J. 2014; 35: 2094-105.
55. Danad I, Uusitalo V, Kero T, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease. J Am Coll Cardiol. 2014; 64: 1464-75.
56. Naya M, Murthy VL, Taqueti VR, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. J Nucl Med. 2014; 55: 248-55.
57. Valenta I, Quercioli A, Schindler TH. Diagnostic Value of PET-Measured Longitudinal Flow Gradient for the Identification of Coronary Artery Disease. JACC Cardiovasc Imaging. 2014; 7: 387-96.
58. Beller GA. Underestimation of coronary artery disease with SPECT perfusion imaging. J Nucl Cardiol. 2008; 15: 151-3.
59. Lima RS, Watson DD, Goode AR, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. J Am Coll Cardiol. 2003; 42: 64-70.
60. Berman DS, Kang X, Slomka PJ, et al. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. J Nucl Cardiol. 2007; 14: 521-8.
61. Dorbala S, Hachamovitch R, Curillova Z, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. JACC Cardiovasc Imaging. 2009; 2: 846-54.
62. Dorbala S, Vangala D, Sampson U, et al. Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: a ^{82}Rb PET/CT study. J Nucl Med. 2007; 48: 349-58.
63. Thielmann M, Kottenberg E, Kleinbongard P, et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. Lancet. 2013; 382: 597-604.
64. Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. Lancet. 2013; 381: 166-75.
65. Yoshinaga K. Current Japanese Ministry of Health, Labor, and Welfare Approval of Cardiac Positron Emission Tomography. Ann Nucl Cardiol. 2015; 1 (1): 106-7.
66. Bengel FM. Leaving relativity behind: quantitative clinical perfusion imaging. J Am Coll Cardiol. 2011; 58: 749-51.