Annals of Nuclear Cardiology Vol. 2 No. 1 99−105

FOCUS ISSUE: MBF QUANTIFICATION−REVIEW ARTICLE

Flow-Based Functional Assessment of Coronary Artery Disease by Myocardial Perfusion Positron Emission Tomography in the Era of Fractional Flow Reserve

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Received: March 22, 2016/Revised manuscript received: July 13, 2016/Accepted: July 13, 2016

Abstract

Myocardial perfusion positron emission tomography (PET) has long been regarded as a gold standard of myocardial blood flow (MBF) measurement. However, since randomized clinical trials showed the prognostic value of fractional flow reserve (FFR)-guided revascularization, FFR has rapidly become a new gold standard of functionally significant coronary artery disease (CAD). Despite the predominance of FFR in the management of stable CAD, FFR also has limitations. Overcoming hurdles by the lesion-specific MBF measurement by hybrid imaging and novel flow parameter can be a complimentary tool.

Keywords: Coronary artery disease, Fractional flow reserve, Myocardial blood flow, Positron emission tomography

Ann Nucl Cardiol 2016；2（1）：99-105

The revolutionary introduction of invasive coronary angiography (CAG) in 1959 (1) and elucidation of the relationship between anatomical stenosis severity and hyperemic flow (2) dramatically improved our understanding of coronary artery disease (CAD). Since then, anatomical stenosis severity has been used as an indicator for percutaneous coronary intervention (PCI). However, anatomical assessment of CAD is substantially variable among observers (3) and angiographically guided PCI did not always improve outcome in patients with stable CAD (4,5). Moreover, better prognosis of fractional flow reserve (FFR)-guided PCI was reported in two landmark clinical trials (6,7). In consequence, functional significance is considered as clinically more relevant than is anatomical stenosis severity for the treatment decision in stable CAD.

Myocardial perfusion positron emission tomography (PET) has long been regarded as a reliable tool for measurement of myocardial blood flow (MBF). Apparently, however, FFR has several advantages over PET-measured MBF, such as less dependence on hemodynamic changes, simplicity, relatively discrete and clear cutoff, lesion-specificity, and robust prognostic gain from FFR-guided PCI (8-10). As a result, despite that pressure cannot fully substitute flow, the current gold standard of functionally significant CAD is undoubtedly FFR. In this article, the challenges, strengths, and possible breakthrough of MBF measurement by myocardial perfusion PET are discussed from the perspectives of nuclear cardiology practitioners in so-called “the era of FFR”.

Definition and development of FFR

FFR is a fraction of the maximal achievable flow in the stenosed artery divided by the maximal achievable flow if the artery were to be normal (10,11). According to Ohm’s law, flow is derived by dividing pressure with resistance. The induction of maximal hyperemia decreases microvascular resistance nearly zero, making the denominator negligible. In addition, the venous pressure is also negligible in comparison with the pressure of the aorta and distal coronary artery. So, the FFR is simplified to the ratio of distal pressure to aortic pressure (12).

doi：10.17996/ANC.02.01.99

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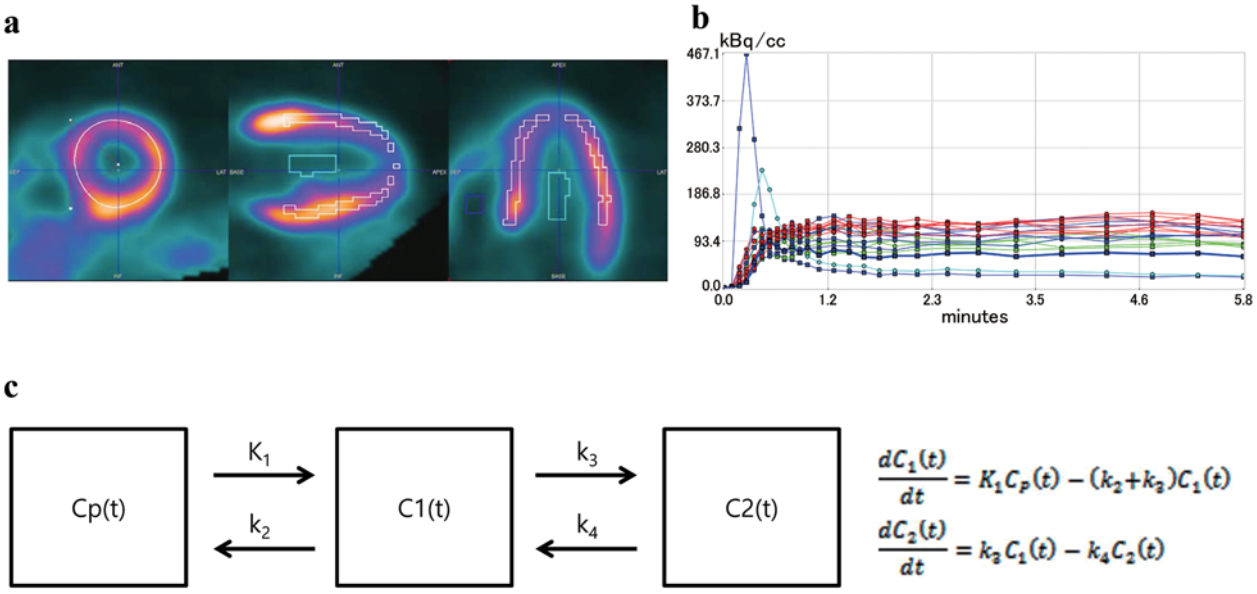

Fig. 1 Two-tissue three-compartment model of ^{13}N ammonia for measurement of myocardial blood flow (MBF)
Regions of interest are drawn in the myocardium and blood pools (a) to obtain time-activity curve of each compartment (b). The first-order rate constants of hypothetical compartments (c) are simultaneously estimated by time-activity curve fitting.
Cp (t), arterial input function; C1 (t), ^{13}N ammonia activity in the freely diffusible compartment; C2 (t), metabolically trapped ^{13}N ammonia activity; K1, MBF; k_2, MBF per volume of distribution; k_3, conversion rate of freely diffusible ^{13}N ammonia into metabolically bound ^{13}N glutamine; k4, clearance rate of ^{13}N activities from the bound to the free compartment.

The FFR cutoff ≤ 0. 75 was associated with inducible ischemia evidenced by stress testing (13). It was applied to the decision of deferral of PCI in the DEFER study (14) showing excellent prognosis in intermediate coronary stenosis with FFR >0.75. To improve sensitivity, the cutoff value of FFR was raised to 0.8 in FAME and FAME II trials (6,7), and PCI for arteries with FFR ≤0.8 showed better prognosis compared with angiographically guided PCI and optimal medical therapy. Although there is a substantial grey zone between 0.75 and 0.8, FFR ≤0.75 can be assumed with a certainty of 99% that this lesion in responsible for coronary ischemia and FFR >0.80 gives only 5% chance that inducible ischemia is present (15).

Based on the prognostic values, FFR has now become a gold standard of functionally significant stenosis triggering PCI. It was initially introduced as an invasive surrogate marker of relative severity of myocardial ischemia, and validated by comparison with PET-derived relative coronary flow reserve (CFR) (11). Ironically, however, novel flow-based functional assessment parameters measured by PET should be validated by comparison with FFR as a reference test these days (16,17).

FFR vs MBF

PET-measured MBF has shown excellent agreement with that measured by microsphere injection and invasive activity measurement (18-22). MBF can be measured by compartment modeling and estimation of rate constant values among tissue compartments (Fig. 1) (23). PET can measure MBF in an absolute volumetric term corrected for the myocardial mass (ml/min/g), which is not easily available in invasive measurements (24,25). Also, the measurement of MBF by PET is highly reproducible (26,27). Recently it was reported that even shorter acquisition time did not hamper the reproducibility of MBF measurement using ^{15}O water PET (28). However, MBF values can vary according to which tracers or methods are used (29,30). So, it is recommended that the same tracer, analytical method and software be used for follow-up or comparison of MBF results.

CFR is the ratio of hyperemic MBF to resting MBF, indicating the vasodilatory capacity of a vascular bed to hyperemic stimulation. Usually >2.0 is regarded as acceptably normal while many young and healthy adults show CFR values >4.0 (31). The prognostic value of CFR was repeatedly demonstrated previously (32-35). Especially, CFR showed additive prognostic value by substratification of cardiac event risk even within patients with normal relative perfusion scores (34). Moreover, Taqueti et al. (35) recently reported that the patients with low global CFR measured with ^{13}N ammonia PET showed significantly better outcome when revascularization was performed, especially bypass surgery.

For diagnosis of significant coronary stenosis, CFR showed additive diagnostic value to visual assessment of relative tracer uptake. Fiechter et al. (36) reported that among 73 consecutive

patients with available ^{13}N ammonia PET and CAG, combined interpretation with perfusion defect and low CFR (<2.0) significantly improved sensitivity in diagnosis of stenosis ≥ 50%. One-third of patients with normal visual perfusion were reclassified by adding CFR information. Notably, more recent data consistently showed that hyperemic MBF itself may be superior to CFR in the detection of significant coronary stenosis (16,17,37). For instance, Danad et al. (16) showed that hyperemic MBF measured by ^{15}O water PET was the most accurate parameter among resting MBF, hyperemic MBF, corrected and non-corrected CFR, for the detection of anatomically or functionally significant stenoses. However, there is no clear discrete cutoff of CFR or hyperemic MBF for detection and/or treatment decision of CAD. MBF or CFR by PET still lacks of prognostic data regarding the decision of PCI according to specific cutoff, which prevents PET from being widely used for clinical decision.

FFR remains unchanged by variable hemodynamic effects from heart rate, neuronal blockade, short-term elevations in left ventricular and coronary arterial systolic pressures, or resting flow (8,38). It is a simple derivation from pressure recordings which has an unequivocal normal value of 1.0 for every patient and every artery (11,15). In contrast to relative CFR, FFR does not need an adjacent normal artery or myocardial area as reference, being applicable to triple-vessel disease (8). A lesion-specific analysis is enabled by simultaneous angiographic information. And as well known, the prognostic values of FFR-guided PCI have been repeatedly demonstrated in randomized clinical trials as mentioned above (6,7,14,39).

On the other hand, MBF is affected by many extrinsic factors including age, sex, heart rate, blood pressure and myocardial oxygen consumption (40). As a result, the normal reference or ischemic cutoff values of MBF and CFR substantially differ among studies (16,31,36,41), making it difficult to interpret in individual patients. Due to a poor distinction between epicardial stenosis and microvascular disease (42), it is quite challenging to directly correlate MBF with a specific epicardial lesion. Even more, the widely used standardized myocardial segment model (43) is frequently inaccurate in prediction of diseased coronary branch (44-46); an area at risk can be mixed with adjacent normal areas or truncated by the crude, irrelevant segmentation.

Despite many shortcomings of MBF detailed above, FFR is not an ideal parameter ubiquitously available and myocardial perfusion PET should still be appreciated. First, because of the invasiveness and reimbursement problem, routine use of FFR is hardly available in the initial step of CAD management. Second, since the degree of pressure drop across a stenosis positively correlates with the amount of proximal flow (47), FFR can be falsely high in a low-flow setting and vice versa (48). In addition, if hyperemic response by adenosine is blunted by microvascular disease, FFR may underestimate the significance of stenosis (49, 50). Third, the myocardial function depends on flow rather than pressure (51). Fourth, FFR does not explain all clinically relevant coronary pathophysiology. FFR has repeatedly showed substantial discordance with CFR (49,52-55) and, microvascular disease is thought to be independent of epicardial stenosis (56) and undetectable by FFR. But CFR is also of prognostic value. Van de Hoef et al. (57) reported that among 157 patients with intermediate coronary stenoses, those with normal FFR but abnormal CFR showed significantly higher 1-year event rate, which persisted throughout 10 years of follow-up after deferral of PCI. However, when CFR was normal, the prognosis was similar between those with normal and abnormal FFR. So, normal FFR should be considered as a heterogeneous group of flow profiles, consistent with the substantially high event rate even in patients with FFR >0.8 in the FAME trial (6) and the fact that 60% of FFR-positive stenoses did not require PCI up to 2 years (39).

Future perspectives: lesion-specific MBF

Flow-based functional assessment is needed to fill the gap where the value of FFR is limited. Hybrid PET/computed tomography (CT) technique and resultant lesion-specific MBF measurement may give appropriate answers. It can accurately correlate myocardial perfusion abnormality to certain epicardial lesions (58-62). It will provide MBF values corrected for the specific myocardial mass which is at risk by certain stenosis. In addition, anatomical information of epicardial vascular path on CT can make it possible to measure MBF following it (Fig. 2), similar to the pull-back pressure recording technique for diffuse or tandem lesions (63).

But the instability of MBF by hemodynamic changes is still challenging. Resting MBF is highly correlating with heart rate and blood pressure, eventually affecting CFR. Correction for rate-pressure product is crude and does not consider all the extrinsic factors influencing resting MBF (64,65). Moreover, resting MBF or CFR does not linearly correlate with focal stenosis severity; diffuse atherosclerosis or microvascular disease often attenuates CFR even in the absence of significant focal stenosis (66). Instead, a novel relative flow parameter based on hyperemic MBF, which is independent of hemodynamic and microcirculatory confounding factors (67), should be introduced. Consistently, a recent report (17) used “relative flow reserve (RFR)”, the ratio of stenotic MBF to non-stenotic MBF as a surrogate of FFR, assumed that the microvascular resistance is same throughout whole myocardium. Although its diagnostic accuracy was only comparable to hyperemic MBF, lesion-specific measurement of RFR may improve it. Once a novel lesion-specific MBF parameter has

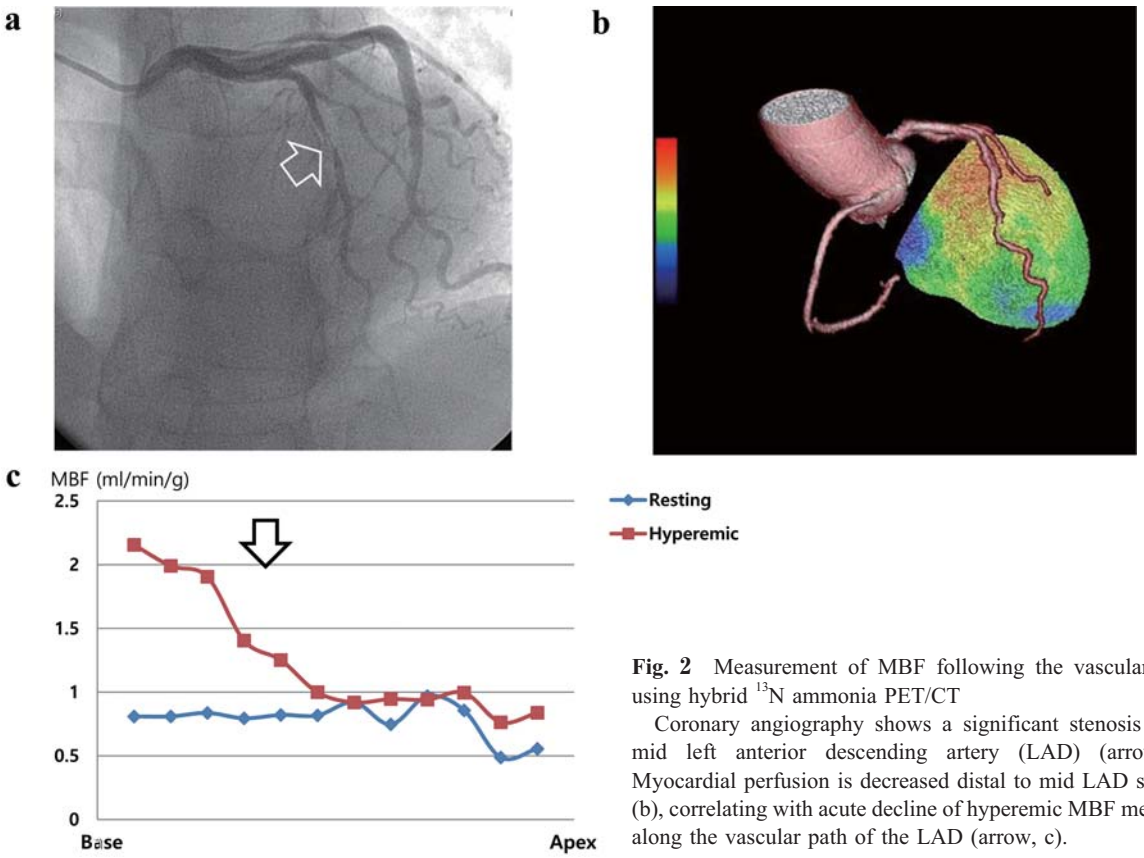

Fig. 2 Measurement of MBF following the vascular paths using hybrid ^{13}N ammonia PET/CT

Coronary angiography shows a significant stenosis in the mid left anterior descending artery (LAD) (arrow, a). Myocardial perfusion is decreased distal to mid LAD stenosis (b), correlating with acute decline of hyperemic MBF measured along the vascular path of the LAD (arrow, c).

been established, a clear cutoff below which patients benefit from PCI should be given. It needs clinical validation based on robust prognostic data from randomized clinical trials.

Although there are concerns about excessive radiation exposure by hybrid imaging, most clinically available myocardial perfusion PET agents generally have short half-lives and acceptably low radiation exposure (1.5-2.5 mSv) even by rest-stress studies (68). Also, the total radiation exposure from hybrid PET/CT did not reach 10 mSv without compromising image quality (69). The development and evolution of PET, CT scanners and/or softwares will further reduce radiation exposure from hybrid imaging.

Conclusion

Despite the predominance of FFR in the management of stable CAD, FFR also has limitations. The flow-based and lesion-specific CAD assessment by hybrid imaging technique will play a key role in clinical practice, although it is not ready to be applied to individual patients so far.

Acknowledgments

None

Sources of funding

This work was supported by a grant (A070001) from the Korea National Enterprise for Clinical Trials.

Conflicts of interest

The authors declare that they have no conflicts of interest to report.

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