REVIEW ARTICLE

Functional Assessment of Coronary Artery Disease by Myocardial Flow Reserve Versus Pressure-wire Based Assessment: A Systematic Review

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Abstract

Positron emission tomography (PET) permits the noninvasive quantification of myocardial blood flow (MBF). Myocardial flow reserve (MFR), calculated by dividing stress MBF by rest MBF is a reliable index for the functional information of coronary artery disease. A pressure-derived physiological index, such as fractional flow reserve (FFR) is also an important measurement. Both MFR and FFR values are used to evaluate coronary physiology; however, but they are not interchangeable because each test has certain discrepancies.

In this systematic review, we provide an overview of coronary physiology with PET compared to pressure-derived physiological indices.

Keywords: Coronary artery disease, Fractional flow reserve, Instantaneous wave-free ratio, Myocardial blood flow, Myocardial flow reserve, Positron emission tomography

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Assessment of the physiologic significance of stenosis and morphological stenosis is highlighted for the evaluation of coronary artery disease (CAD). There are several types of cardiovascular tests that lead to large variations in the choice of diagnostic modalities. Among them, myocardial perfusion imaging (MPI) using positron emission tomography (PET) permits both qualitative and quantitative assessments of patients with CAD. PET has a significantly higher diagnostic accuracy than single-photon emission computed tomography because of its higher spatial resolution (1). Dynamic or list-mode data collection has been used to quantify myocardial blood flow (MBF) in recent practical PET MPI studies (2). PET quantification allows assessment of the severity of physiological stenosis.

Ischemic heart disease is caused by oxygen deficiency due to an imbalance between demand and supply. The concept of physiological stenosis is essential for CAD assessment. Coronary revascularization guided by fractional flow reserve (FFR) is the current standard for the functional assessment of lesion severity in patients with CAD. Recently, resting pressure-derived index, such as the instantaneous wave-free ratio (iFR), has been used as alternative to FFR.

This article summarizes the physiologic basis for PET MPI compared to pressure-wire-based assessment, including FFR, which is one of the most established measures for identifying physiologically significant coronary stenoses.

PET

MPI has played an important role in the diagnosis and management of patients with known or possible CAD. PET is one of the most established noninvasive techniques for the assessment of blood flow to the myocardium. PET MPI provides clear evidence for the diagnosis and risk assessment of CAD (1). Dynamic first-pass perfusion PET imaging allows noninvasive quantification of MBF. Estimation of myocardial flow reserve (MFR), which is the ratio of stress/rest MBF, provides several advantages to assess CAD and microvascular dysfunction in addition to the conventional visual assessment.

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To compare the diagnostic performance of pressure-derived physiological indices, relative flow reserve (RFR) is sometimes evaluated as the ratio of stress MBF in target myocardial segments to that of reference myocardial segments (3).

Pressure-wire based assessment of physiological ischemia

FFR is a guide-wire-based procedure to measure blood pressure differences across coronary artery stenosis, which can be performed during cardiac catheterization to assess the indication for percutaneous coronary intervention (PCI). FFR is defined as the ratio of maximal flow achievable in the stenotic coronary artery relative to the maximal blood flow if the same coronary artery had no stenosis (4). Even if the degree of stenosis is similar, the state of ischemia measured by FFR differs depending on the lesion length, the existence of collateral flow, and the shape of the stenotic lesion (5, 6). Multiple clinical studies have shown that FFR values of less than 0. 75 to 0. 80 have high specificity for identifying ischemia, and 0.80 is the best-endorsed cutoff for deferral of PCI for functionally nonsignificant stenoses (7, 8). FFR-guided revascularization has been the gold standard for assessing the functional significance of epicardial coronary stenosis.

Recently, the instantaneous wave-free ratio (iFR) has been introduced as a promising alternative to FFR (4). iFR is performed using a pressure-sensitive catheter that is passed distal to the coronary stenosis to measure the pressure drop in a specific period called a wave-free period, but iFR is measured under resting conditions without the need for a hyperemic-inducing drug. Recent studies indicate that an iFR-guided strategy is non-inferior to an FFR-guided strategy for coronary revascularization in patients with CAD (9, 10).

Epicardial artery and microcirculation

The concept of physiological stenosis can be easily understood by distinguishing between the epicardial arteries (macrocirculation) and microcirculation. Both are blood vessels that supply oxygen and nutrients to cardiac myocytes (Figure 1). The epicardial arteries running on the surface of the myocardium, which is typically more than 500 μm in diameter, depicted on coronary angiography, hold less than 10% of the total myocardial blood volume (11). The remaining is assumed by microcirculation, which is difficult to reveal using conventional imaging techniques (12). Coronary microvascular networks play an important role in coronary vascular resistance in the myocardium. Both arteries consisting of macro- and microcirculation have the possibility of narrowing by atherosclerosis with plaque (Figure 2) (13). The loss of coronary autoregulation is also one of the causes of microcirculation dysfunction.

Systematic reviews comparing PET-derived flow indices

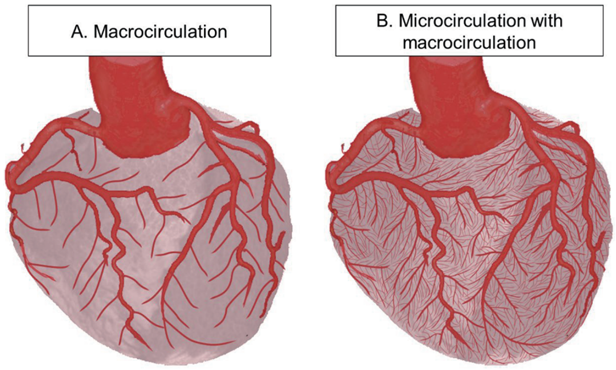

Figure 1 Schematic of macro- and microcirculation.
Although the boundary of each compartment is difficult to define anatomically, the coronary arterial system is composed of macro- and microcirculation. Macrocirculation is a proximal compartment represented by epicardial coronary arteries (A). The distal smaller compartment is microcirculation, which is represented by arterioles and capillaries (B).

and pressure-derived physiological indices are summarized in Table 1. The index obtained from PET and pressure-wire-based assessments tends to have a modest, not very high correlation. What are the reasons for the discrepancy between these physiological indices?

MFR is well known to be influenced not only by stenosis of the epicardial artery, but also by coronary microvascular dysfunction due to risk factors, such as diabetes, dyslipidemia, hypertension, renal dysfunction, obesity, and smoking (13, 14). Therefore, the MFR reflects the condition of the entire coronary arterial circulation without distinction between macro- and microcirculation. However, the results derived from pressure-wire-based assessments are lesion-based parameters, which do not represent information on the size of the perfused area exposed to ischemia due to stenosis, and it is thought that they do not reflect the microcirculatory condition (15). A recent study showed that FFR is slightly increased during the presentation of microcirculation dysfunction (16). Therefore, the correlation between pressure-wire-based parameters and PET-derived MFR and stress MBF was moderate. In the case of one- or two-vessel disease, it is worth pointing out that PET-derived RFR has been shown to have a higher correlation with FFR and iFR than MFR and stress MBF (Table 1) (Figure 3).

The role of physiological measurements of CAD

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that PCI did not reduce coronary events compared to optimal medical therapy (OMT) in patients with stable CAD, bringing into question the effectiveness of revascularization (30). In recent years, the ORBITA (percutaneous coronary intervention in stable angina) study has reported that PCI does not improve exercise time compared to placebo procedures in

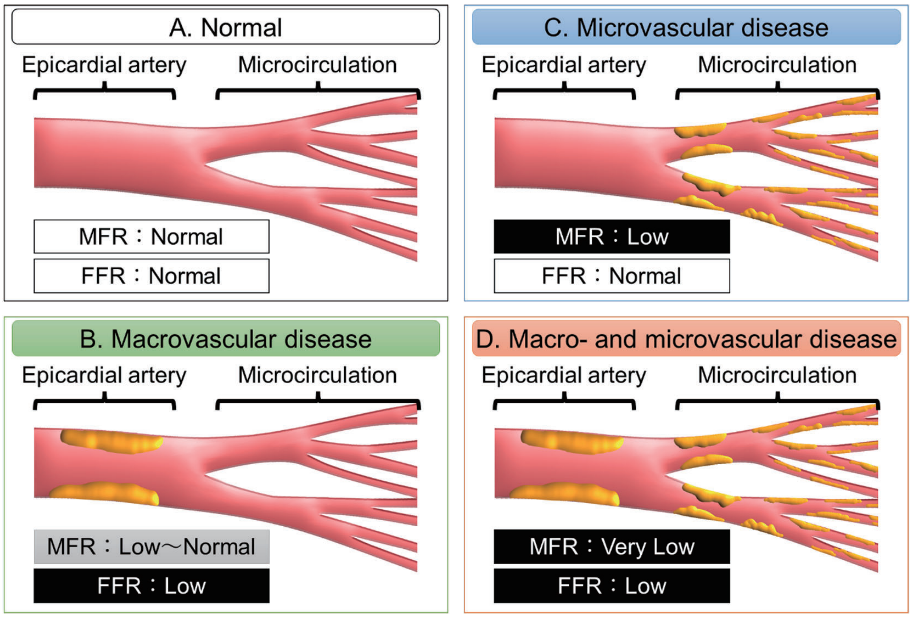

Figure 2 Shema of a combination of macro- and microcirculation.
Schema of normal (A), focal stenosis of an epicardial artery (B), microvascular disease (C), and both macro- and microvascular diseases (D) are displayed. Focal and diffuse epicardial coronary disease and coronary microvascular dysfunction have the potential to exist simultaneously. The expansion of focal and diffuse diseases reflect the MFR and FFR values.

Table 1 Relationship between PET-derived flow indices and pressure-derived physiologic indices in patients with CAD

Study	N	PET tracer	PET-derived indices			Pressure-derived indices		Correlation	
			Stress MBF (mL/g/min)	MFR (CFR)	RFR	FFR	iFR	MFR (CFR) vs. FFR	RFR vs. FFR
Dai N, et al. (17)	109	^{13}N-ammonia	–	2.3 ± 0.7	0.83 ± 0.11	0.83 ± 0.11	0.92 ± 0.12	–	0.786 Spearman's ρ
Bendix K, et al. (18)	25	^{15}O-water	2.49 ± 0.67 (Diseased vessels) 2.89 ± 0.65 (Refer ence vessels)	2.55 ± 0.60 (Diseased vessels) 3.02 ± 0.59 (Reference vessels)	–	0.68 ± 0.18 (Diseased vessels) 0.90 ± 0.08 (Refer ence vessels)	–	0.493 Pearson's r	–
Everaars H, et al. (19)	40	^{15}O-water	2.55 ± 0.9	3.0 ± 0.9	–	0.93 (0.84–0.97)	–	–	–
Driessen RS, et al. (20)	53	^{15}O-water	1.57 ± 0.59	2.02 ± 0.69	0.65 ± 0.18 (48 of 90 vascular territories)	0.61 ± 0.17 (61 of 90 vascular territories)	–	0.56 Pearson's r	0.76 Pearson's r
Chih S, et al. (21)	40 (only heart transplant patients)	^{82}Rb	1.95 ± 0.75	2.38 ± 0.82	–	–	–	–	0.28 Pearson's r
Kawaguchi N, et al. (22)	63	^{13}N-ammonia	Diseased vessels; 1.67 ± 0.54 Reference vessels; 2.19 ± 0.52	Diseased vessels; 1.85 ± 0.69 Reference vessels; 2.38 ± 0.69	–	–	–	0.32 Spearman's ρ	–
Lee JM, et al. (23) Hwang D, et al. (24)	115	^{13}N-ammonia	1.80 ± 0.43	2.13 ± 0.58	0.77 ± 0.09	0.81 (0.73–0.85)	0.92 (0.87–0.94)	0.400 Spearman's ρ	0.6830 Spearman's ρ
Lee JM, et al. (25)	56	^{13}N-ammonia	High iFR vessels; 1.94 ± 0.45 Low iFR vessels; 1.60 ± 0.33	High iFR vessels; 2.27 ± 0.50 Low iFR vessels; 1.76 ± 0.33	–	High iFR vessels; 0.77 (0.76–0.78) Low iFR vessels; 0.68 (0.61–0.73)	High iFR vessels; 0.92 (0.91–0.94) Low iFR vessels; 0.81 (0.71–0.87)	–	–
Lee JM, et al. (26)	130	^{13}N-ammonia	2.08 ± 0.55	2.25 ± 0.66	0.85 ± 0.11	0.84 ± 0.11; 0.85 (0.78–0.93)	–	0.38 Pearson's r	0.78 Pearson's r
Valenta I, et al. (27)	29	^{13}N-ammonia	Diseased vessels; 1.44 (1.23–1.72) Reference vessels; 1.60 (1.37–1.82)	Diseased vessels; 1.97 (1.71–2.36) Reference vessels; 2.23 (1.76–2.37)	–	–	–	0.50 Pearson's r	–
Peelukhana SV, et al. (28)	8	^{13}N-ammonia	1.85 ± 0.22	2.44 ± 0.11	–	0.79 ± 0.03	–	0.08 Spearman's ρ	–
De Bruyne B, et al. (29)	22	^{15}O-water	–	–	0.60 ± 0.26	0.61 ± 0.17	–	–	0.87 Pearson's r

Values are presented as the mean ± standard deviation or median (interquartile range).
CAD: coronary artery disease, CFR: coronary flow reserve, FFR: fractional flow reserve, iFR: instantaneous wave-free ratio, MBF: myocardial blood flow, MFR: myocardial flow reserve, PET: positron emission tomography, RFR: relative flow reserve.

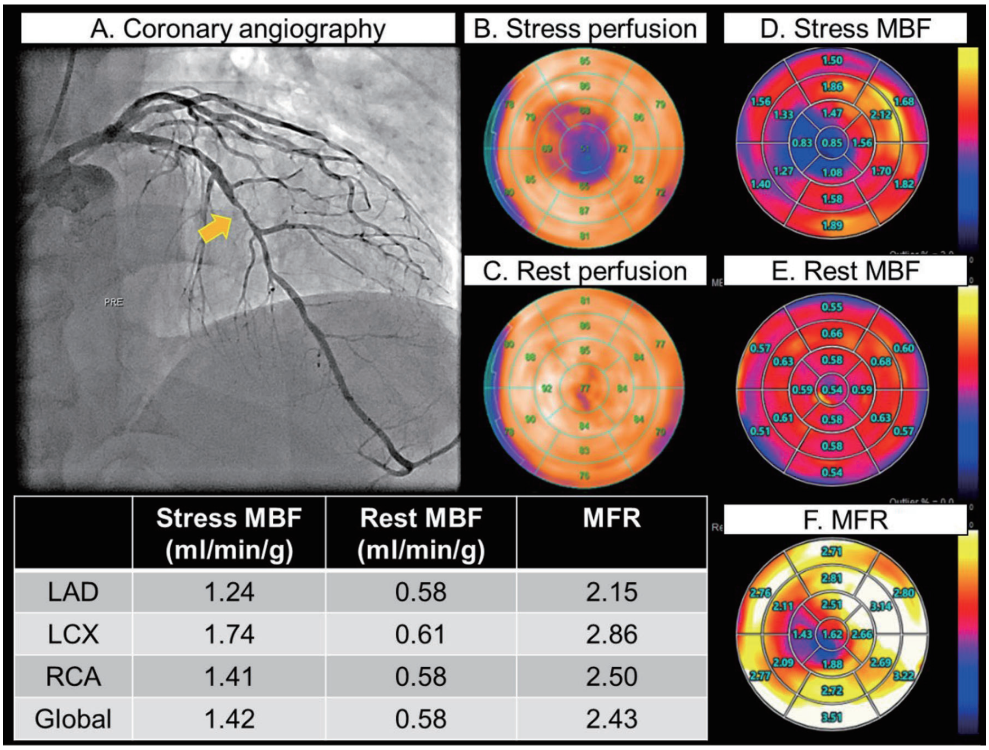

Figure 3 Representative case of macrovascular disease.

Angiography of the left coronary artery (LAD) (A), perfusion polar map of stress (B) and rest (C), rest (D), stress myocardial blood flow (MBF) (E), and myocardial blood flow (MFR) (F) by $^{13}N\text{-}NH_3$ PET (E) are shown. A man in his 70s had significant stenosis in the middle of the LAD (yellow arrow) with an FFR value of 0.48 and an iFR value of 0.50. Ischemia in the mid to distal LAD territory and reduced MFR in the LAD territory are seen on $^{13}N\text{-}NH_3$ PET.

patients with medically treated angina and severe coronary stenosis (31).

Meanwhile, the nuclear substudy of the COURAGE trial showed that significant ischemia reduction was observed in patients treated with PCI+OMT, and patients who achieved ≥5% ischemia reduction had a lower unadjusted risk for death or myocardial infarction, particularly if baseline ischemia is moderate to severe (32). The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 study showed that fractional FFR-guided PCI reduced events in patients with stable CAD compared to medical therapy. Therefore, functional ischemia diagnosis has become mandatory for medical fee calculations in Japan.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial was conducted under the hypothesis that early invasive treatment strategies reduce coronary events in patients with moderate or advanced ischemia compared to conservative treatment strategies managed with medical treatment (33). However, this trial showed that invasive treatment strategies did not reduce the risk of cardiac events, including cardiovascular death, myocardial infarction, hospitalization for unstable angina or heart failure, and resuscitation after cardiac arrest. The ISCHEMIA trial included patients with at least moderate ischemia on imaging tests or severe ischemia on exercise tests without imaging. Ischemia eligibility criteria by nuclear perfusion test are in cases where ischemic changes are qualitatively observed in 10% or more of the entire myocardium, and quantitative evaluations, such as MBF and MFR are not included in the analysis. PET is the most validated and quantitative approach for evaluating myocardial ischemia and coronary vasomotor function. Furthermore, there is growing evidence that PET-based stress MBF and MFR provide incremental prognostic value over the qualitative assessment of myocardial ischemia (34, 35). Taqueti et al. reported that coronary artery bypass grafting may be more effective for long-term prognosis in patients with significant CAD and reduced MFR (36), which may be partly explained by the significant increase in MFR after complete revascularization with coronary artery bypass grafting (37). Appropriate criteria for coronary revascularization for stable angina have been proposed, but based on the results of the ISCHEMIA study, assessing the physiologic significance of stenosis may help further subdivided indications.

Conclusion

Both PET and pressure-wire-based assessments, such as FFR, are used to evaluate the physiologic significance of stenosis, which is indispensable when considering the treatment of patients with CAD. PET is a modality that can reflect the entire vascular system, including epicardial and microvascular conditions. FFR can detect physiological ischemia of coronary artery lesions and provide information directly related to treatment. Each test has a certain degree of discrepancy. Myocardial ischemia associated with a microvascular disease or diffuse coronary atherosclerosis without significant epicardial stenosis will produce different results between PET and pressure-wire based indices.

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Conflicts of interest

Dr. Noriko Oyama-Manabe has consulted for Canon Medical Systems; she also received payment for lectures from Daiichi-Sankyo, GE Healthcare, Nihon Medi-Physics, Co., Ltd., and Canon Medical Systems.

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