FFR, iFR, and Other Resting Indices: Pressure-Wire Based Assessment of Ischemia

Reviewing current wire-based indices and evidence supporting their use.

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It is well known that apparent significant coronary stenosis on angiography sometimes does not cause significant ischemia, and vice versa. Thus, the importance of functional assessment of coronary stenosis based on coronary physiology has been increasingly recognized. Since the introduction of fractional flow reserve (FFR) more than 25 years ago, FFR-guided revascularization has become the current standard of care for functional assessment of lesion severity in patients with coronary artery disease (CAD). More recently, the instantaneous wave-free ratio (iFR) and other resting pressure–derived indices that do not require hyperemia have emerged as alternatives to FFR. This article summarizes the concepts of FFR, iFR, and other resting indices and the current evidence supporting their use.

CONCEPT AND FEATURES OF FFR

FFR is a pressure wire–based index used during coronary angiography to assess the potential of coronary stenosis to induce myocardial ischemia. FFR is defined as the ratio of myocardial blood flow in the coronary artery in the presence of epicardial stenosis compared with the

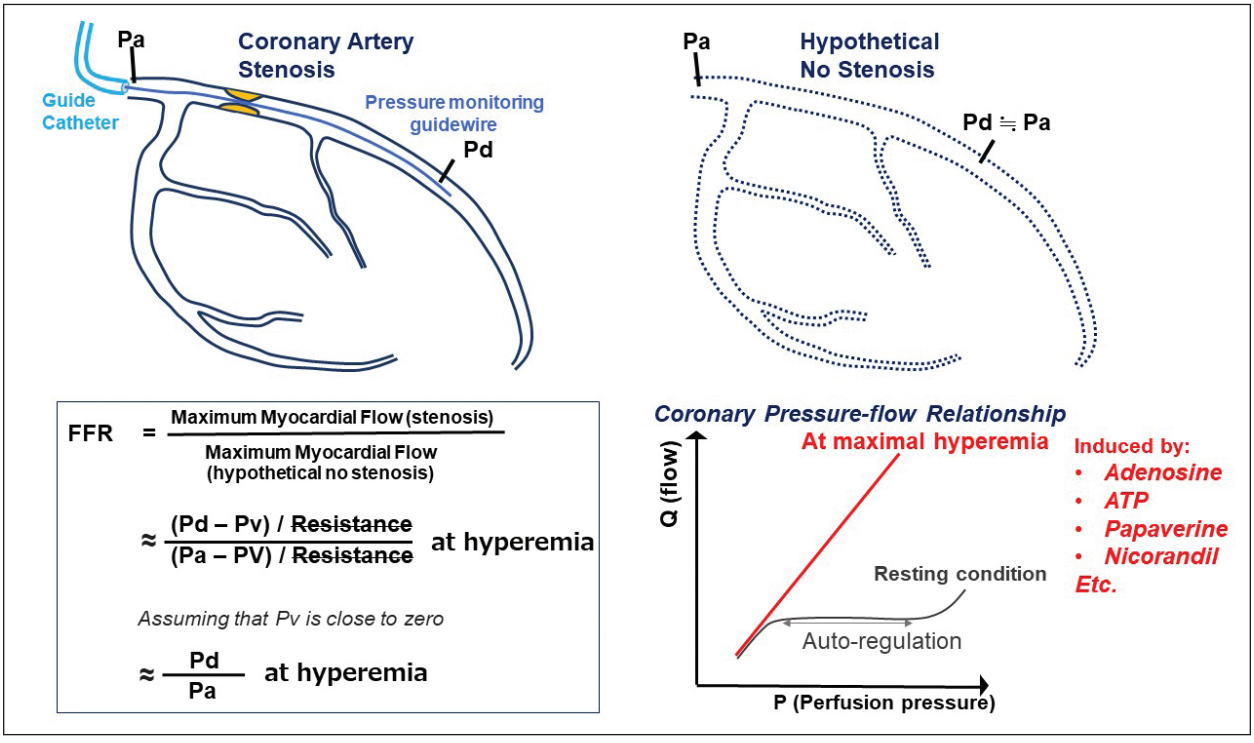

Figure 1. An overview of the concept of FFR. ATP, adenosine 5' triphosphate; Pv, central venous pressure.

TABLE 1. FFR AND iFR PIVOTAL TRIALS

	DEFER[10-12]	FAME[4,13-15]	FAME2[5,16,17]	iFR-SWEDEHEART[18]	DEFINE-FLAIR[19]
N	325	1,005	1,220	2,037	2,492
Enrollment year	1997-1998	2006-2007	2010-2012	2014-2015	2014-2015
Patient	Stable patients referred for elective PCI	Stable angina, unstable angina, or NSTEMI	Stable or stabilized patients with angina or silent ischemia	Stable angina, unstable angina, or NSTEMI (nonculprit)	Stable angina or ACS (nonculprit lesion)
Lesion	A single de novo stenosis (> 50% DS)	Multivessel disease (> 50% DS)	Single- or multivessel disease (> 50% DS)	Single- or multivessel disease (40%-80% DS)	Single- or multivessel disease (40%-70% DS)
Primary comparison	Deferral of PCI (n = 91) vs performance of PCI (n = 90) in patients with FFR ≥ 0.75	FFR-guided (n = 509) vs angiography-guided PCI (n = 496)	FFR-guided PCI plus MT (n = 447) vs MT alone (n = 441) in patients with a lesion with an FFR ≤ 0.8	FFR-guided (n = 1,018) vs iFR-guided revascularization (n = 1,019)	FFR-guided (n = 1,250) vs iFR-guided revascularization (n = 1,242)
Primary endpoint	Death, MI, repeat revascularization at 2 years	Death, MI, or repeat revascularization at 1 year	Death, MI, or urgent revascularization at 2 years	Death, MI, or unplanned revascularization at 1 year (noninferiority)	Death, MI, or unplanned revascularization at 1 year (noninferiority)
Findings	Similar event-free survival between the deferral and performance groups (89% vs 83%) at 2 years	Lower events in the FFR-guided PCI (13.2% vs 18.3%; *P* = .02) at 1 year	Lower rate of primary endpoints in the PCI (8.1% vs 19.5%; *P* < .001) at 2 years	Similar event rate between FFR vs iFR guidance (6.1% vs 6.7%; *P* = .53; *P* = .007 for noninferiority)	Similar event rate between FFR vs iFR guidance (7% vs 6.8%; *P* = .78; *P* < .001 for noninferiority)
Long-term follow-up	5 and 15 years	5 years	5 years	Ongoing	Ongoing

Abbreviations: ACS, acute coronary syndrome; DS, diameter stenosis; iFR, instantaneous wave-free ratio; FFR, fractional flow reserve; MI, myocardial infarction; MT, medical therapy; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

flow in the same vessel in the theoretical absence of stenosis.[1] Because of the linear relation between perfusion pressure and coronary blood flow during hyperemia, this ratio of maximum flows can be represented by the ratio of perfusion pressures: distal coronary artery pressure (Pd) divided by aortic pressure (Pa), under the assumption that venous pressure is close to zero. With this methodology, Pa is measured by a guiding catheter and Pd by a pressure-monitoring guidewire (Figure 1).

FFR was first validated in a prospective, multitesting Bayesian approach where an FFR threshold value of 0.75 was identified to be associated with evidence of myocardial ischemia on noninvasive stress tests with high sensitivity and specificity.[2] Multiple subsequent studies performed by numerous groups have shown that FFR values < 0.75 to 0.80 have very high specificity for identifying ischemia based on a variety of noninvasive imaging studies.[3] If the FFR value is > 0.80, it is unlikely that the interrogated vessel or lesion is responsible for significant ischemia; FFR < 0.75 indicates that significant ischemia is likely inducible in the interrogated vessel. Currently, 0.80 is the best-endorsed cutoff to defer percutaneous coronary intervention (PCI) in clinical practice, as determined after validation in multiple prospective randomized trials with this threshold.[4,5] Importantly, however, ischemia does not exist as a dichotomous state but as a graded continuum that can be measured by FFR on a per-vessel basis.[6] FFR demonstrates a continuous and independent inverse relationship with the risk of adverse outcomes, which are modifiable by revascularization or medication (ie, the lower the FFR value, the greater the benefit from revascularization).[6-9]

FFR PIVOTAL TRIALS

The usefulness of FFR-guided PCI is supported by robust clinical outcomes data. Three landmark, multicenter, randomized trials have tested the hypothesis of an FFR-based approach to guide revascularization in CAD, playing a very important role in establishing evidence of FFR (Table 1).[4,5,10-19]

The DEFER Trial

The DEFER trial included a total of 325 patients who were referred for percutaneous transluminal coronary angioplasty (PTCA) of an angiographically intermediate stenosis and ultimately showed that deferral of PTCA for functionally nonsignificant stenoses (FFR ≥ 0.75) was safe and comparable to revascularization of such stenoses with respect to outcome and symptoms at 2 and 5 years.[10,11] At up to 5 years, there was no difference in mortality, myocardial infarction (MI), or revascularization related to the deferred lesions.[11] Long-term follow-up of 15 years has shown that the favorable outcomes of PTCA deferral of functionally nonsignificant stenosis continued, without signs of late "catch-up" phenomenon.[12]

The FAME Trial

The FAME trial enrolled 1,005 patients with angiographic multivessel CAD amenable for PCI and presenting with stable angina, unstable angina, or non–ST-segment elevation myocardial infarction (< 5 days after the infarction).[4] Patients were randomly assigned to either FFR-guided or angiography-guided PCI. In the FFR-guided arm, only lesions with an FFR ≤ 0.80 were treated with PCI, whereas in the angiography-guided arm, all stenoses with a ≥ 50% diameter were treated with PCI. The FFR-guided PCI strategy demonstrated a lower rate of the primary endpoint, defined as a composite of death, MI, or repeat revascularization at 1 year (13.2% vs 18.3%; $P < .02$). In addition, the rate of death and MI was significantly reduced in the FFR-guided PCI (7.3% vs 11.1%; $P = .04$).[4] Subsequently, the 2-year results of FAME revealed a persistent reduction in the composite of death, MI, and repeat revascularization (17.9% vs 22.4%; $P = .08$). Additionally, the hard endpoints of death and MI remained significantly lower in the FFR-guided PCI patients (8.4% vs 12.9%; $P = .02$) at up to 2 years.[13] The 5-year follow-up of the FAME trial showed that the absolute difference in cardiac events persists, although is not significant because of the smaller number of patients at risk.[14] Overall, the FAME trial confirmed the long-term safety of FFR-guided PCI in patients with multivessel disease, with a lower number of stented arteries and less resource use.[14,15]

The FAME2 Trial

The FAME2 trial enrolled patients with stable angina or silent ischemia and one-, two-, or three-vessel disease. Patients who had at least one stenosis with an FFR ≤ 0.80 were randomized to FFR-guided PCI plus the best available medical therapy (PCI group, n = 447) or best available medical therapy alone (medical therapy group, n = 441).[5] Across all lesions, patients with an FFR > 0.80 were not randomized (n = 332), and 50% of these patients (n = 166) were followed-up in a registry. The rate of the primary endpoint—a composite of death, nonfatal MI, or urgent revascularization within 2 years—was significantly lower in the PCI group than in the medical therapy group (8.1% vs 19.5%; $P < .001$), primarily driven by a lower rate of urgent revascularization in the PCI group (4% vs 16.3%; $P < .001$).[5] This advantage of FFR-guided PCI compared with medical therapy alone continued at 3 and 5 years, although there was no significant difference in the rate of the primary endpoint between the PCI group versus the registry cohort at 5 years.[16] It is worth noting that a lower incidence of spontaneous MI was observed in the PCI group compared with the medical therapy group at 5 years.[16] Regarding symptom relief, patients in the FFR-guided PCI group reported significantly less angina up to 3 years after randomization compared with patients assigned to the medical therapy group. However, this difference was no longer significant at 5 years, by which time 51% of the patients initially assigned to the medical therapy group had undergone revascularization.[16]

In addition, the cost-effectiveness analysis of the FAME2 trial showed that at 3 years, the incremental cost-effectiveness ratio of PCI guided by FFR was approximately $1,600/quality-adjusted life-year (QALY) and was below a willingness-to-pay threshold of $50,000/QALY in 85% of the 10,000 bootstrap replications based on Medicare reimbursement rates, suggesting that FFR-guided PCI is economically attractive compared with medical therapy alone.[17]

CLINICAL GUIDELINES ENDORSING FFR FOR CLINICAL PRACTICE

With a growing body of evidence supporting FFR-guided revascularization, international guidelines now recommend FFR for guiding revascularization strategies. The latest American College of Cardiology Foundation/American Heart Association guidelines have given a class Ia recommendation for revascularization of functionally significant stenoses and a class IIa recommendation for using FFR to assess intermediate stenoses.[20,21] The European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines have

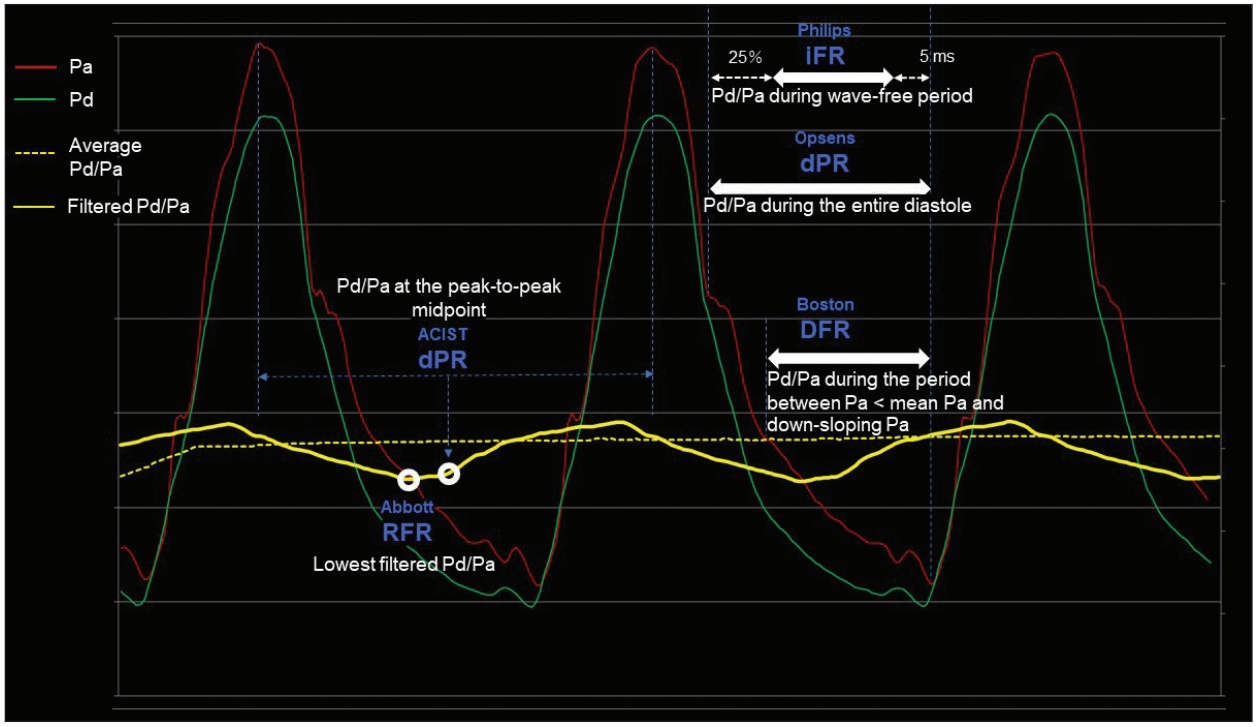

Figure 2. NHPRs and where in the cardiac cycle they are calculated. DFR, diastolic hyperemia-free ratio; dPR, diastolic pressure ratio; RFR, resting full-cycle ratio.

given a class Ia recommendation for assessment of the hemodynamic relevance of intermediate-grade stenosis when evidence of ischemia is not available.[22] Further, large-scale, real-world data support that performing PCI guided by FFR is associated with better outcomes (even reduction of death or MI) in patients with CAD.[23,24]

INSTANTANEOUS WAVE-FREE RATIO

Recently, iFR was introduced as a nonhyperemic alternative to FFR. This index is calculated as the ratio of resting Pd to aortic Pa over a specific period in late diastole (the so-called "wave-free period") during which intracoronary resistance is reportedly constant and "minimal." However, the resistance during the wave-free period without hyperemia is generally higher than the average resistance during the entire cardiac cycle in hyperemia.[25] Therefore, there is discordance between iFR and FFR. When using FFR as a reference standard, iFR achieved an accuracy of approximately 80%.[26,27] Nonetheless, there are potential advantages of iFR compared with FFR, such as independence from hyperemic medications (resulting in increased patient comfort) and reduced procedural time and costs.

As seen in Table 1, two recent large-scale randomized trials have shown comparable results between FFR- and iFR-guided revascularization strategies in patients with intermediate-grade stenoses.[18,19] In both trials, revascularization was indicated if FFR was ≤ 0.80 or iFR was ≤ 0.89. iFR-guided revascularization was proven to be noninferior to FFR-guided revascularization for adverse cardiovascular events at 1-year follow-up of both trials, leading to iFR being included in the European guidelines as equivalent to FFR.[22] In both trials, fewer revascularization procedures were performed in the iFR-guided strategy than in the FFR-guided strategy, without a clear initial difference in terms of short-term clinical outcomes. Long-term clinical outcomes data are awaited to determine the safety of higher rates of revascularization deferral by iFR given that recent randomized trials have observed a higher rate of nonprocedural MI with the conservative strategy at 5 years.[16,28]

NOVEL RESTING NONHYPEREMIC PRESSURE RATIOS

More recently, several wire-based nonhyperemic pressure ratios (NHPRs) other than iFR have been developed. These novel indices measure the ratio of Pd to Pa but differ on the phase of the cardiac cycle where measurement takes place, as shown in Figure 2 and summarized in Table 2. Essentially, the diagnostic accuracy of these novel NHPRs is almost identical to iFR. In addition, retrospective studies have shown com-

TABLE 2. FFR, RESTING Pd/Pa, AND OTHER NHPRs

Pressure Index	Company	Hyperemia	Cutoff	Calculation of the Index
FFR	All	Required	≤ 0.80	Average Pd/Pa during the entire cardiac cycle at hyperemia (typically averaged over 3 beats)
Resting Pd/Pa	All	NHPR	≤ 0.91	Average Pd/Pa during the entire cardiac cycle (typically averaged over 3 beats)
RFR	Abbott	NHPR	≤ 0.89	Instant lowest filtered Pd/Pa ratio during the entire cardiac cycle (over 5 beats)
iFR	Philips	NHPR	≤ 0.89	Average Pd/Pa during wave-free period (over 5 beats)
DFR	Boston Scientific Corporation	NHPR	≤ 0.89	Average Pd/Pa during the period between Pa < mean Pa and down-sloping Pa (over 5 beats)
dPR	Acist	NHPR	≤ 0.89	Instant Pd/Pa at the peak-to-peak midpoint (over 5 beats)
	Opsens Medical	NHPR	≤ 0.89	Average Pd/Pa during the entire diastole (over 5 beats)

Abbreviations: DFR, diastolic hyperemia-free ratio; dPR, diastolic pressure ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NHPR, nonhyperemic pressure ratio; Pa, aortic pressure; Pd, distal coronary artery pressure; RFR, resting full-cycle ratio.

parable prognostic performance among NHPRs and iFR, although this has not been prospectively validated.[29-32] These studies suggest that novel NHPRs and iFR could be applied clinically in a similar fashion.

CONCLUSIONS

The primary goal when treating patients with CAD should be to relieve symptoms and improve their quality of life and clinical outcomes. This is best accomplished by identifying and relieving the stenoses that are responsible for myocardial ischemia and/or are at high risk for future adverse events. FFR is a simple and validated method for achieving this goal in the catheterization laboratory. Although more prospective data are needed, iFR and novel NHPRs may contribute to further adoption of wire-based physiologic assessment. We anticipate that as coronary physiologic assessment is used more, patients with CAD will more likely receive better treatment. ■

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