Fractional Flow Reserve: An Updated Review

Islam Y. Elgendy, MD; C. Richard Conti, MD, MACC; Anthony A. Bavry, MD, MPH

Department of Medicine (Elgendy), University of Florida College of Medicine, Gainesville, Florida;

Division of Cardiovascular Medicine (Conti, Bavry), University of Florida College of Medicine, Gainesville, Florida

Address for correspondence:

Anthony A. Bavry, MD, MPH,
Division of Cardiovascular Medicine,
University of Florida,
1600 SW Archer Road,
PO Box 100277,
Gainesville, FL 32610-0277
bavryaa@medicine.ufl.edu

ABSTRACT

Revascularization of ischemia-producing coronary lesions is widely used in the management of coronary artery disease. However, some coronary lesions appear significant on the conventional angiogram when they are truly non-flow limiting. For this reason, it is becoming increasingly important to determine the coronary physiology. Fractional flow reserve (FFR) has emerged as a useful tool to determine the lesions that require revascularization. Measurement of FFR during invasive coronary angiography now has a class IA indication from the European Society of Cardiology for identifying hemodynamically significant coronary lesions when noninvasive evidence of myocardial ischemia is unavailable. Current data on FFR can be broadly classified into studies that compare the diagnostic accuracy of FFR measurement compared with other noninvasive modalities and studies that test treatment strategies of patients with intermediate coronary stenoses using a threshold value for FFR and that have clinical outcomes as endpoints. In this review, we will discuss the concept of FFR, current evidence supporting its usage, and future perspectives.

Rationale for the Use of Fractional Flow Reserve

Revascularization of ischemia-producing coronary lesions with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery is recommended in the management of coronary artery disease (CAD).^{1–3} In clinical practice, patients often are referred for coronary angiography without prior noninvasive evaluation for ischemia. The decision to proceed with revascularization becomes particularly challenging when it comes to lesions with between 30% and 70% stenosis. Data indicate wide inter-observer variability in interpreting coronary angiography.^{4,5} Quantitative coronary angiography is a poor predictor of functional significance of coronary lesions (eg, a short, focal stenosis may not be as flow limiting as a long, moderate narrowing).⁶ In addition, appropriate interpretation of conventional angiography may be limited by vessel foreshortening, heavy calcifications, and side-branch overlap.

The Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis (DEFER) study investigators have shown that PCI plus optimal modern medical therapy for non-ischemia-producing lesions results in no additional benefit when compared with modern optimal medical therapy alone.⁷ Furthermore, bypass grafting in patients with nonischemic left-main CAD is associated with disease progression in the grafted coronary artery, and the surgery itself is not without risk.⁸ For these reasons,

assessment of coronary-artery physiology at the time of coronary angiography, using fractional flow reserve (FFR) to determine ischemia-producing lesions, has become widely acceptable in the past 2 decades.⁹ In this review, we will discuss the concept of FFR, the current evidence that supports its usage, and future directions.

What Is Fractional Flow Reserve and How Is It Measured?

Fractional flow reserve is defined as the ratio of maximal achievable blood flow in a coronary artery in the presence of a stenosis to the hypothetical maximal achievable blood flow in that same epicardial artery in the absence of the stenosis. It is derived from the ratio of the mean distal coronary artery pressure (Pd) to the mean aortic pressure (Pa) during the period of maximum hyperemia. Fractional flow reserve is calculated during this period when the Pd is at the nadir.^{9–12} Fractional flow reserve is not affected by changes in the hemodynamic conditions or microcirculation.¹³ The “normal” ratio is expected to be 1. For example, an FFR value of 0.80 means that the maximum blood flow in the myocardial distribution of the epicardial artery is 80% of what it would be if the artery were completely normal.

To measure FFR, the technique requires advancing a 0.014-inch wire with a pressure sensor to measure the pressure distal to the stenosis, across the intermediate stenotic lesion with the support of a guiding catheter in the target artery. An anticoagulant is recommended in an approach similar to a PCI procedure.

Maximal hyperemia is achieved by dilation of both the epicardial and microvascular arteries. Epicardial vasodilation is achieved by sublingual or intracoronary administration of nitroglycerine.^{11,12} Various pharmacological agents

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Figure 1. (A) An example of measuring a non-ischemia-producing coronary stenosis by fractional flow reserve (FFR = 0.90). Note the simultaneous aortic pressure (Pa) and distal coronary pressure (Pd) during rest and maximal hyperemia. FFR is calculated as the ratio of Pd/Pa during maximal hyperemia. (B) An ischemia-producing coronary stenosis with FFR of 0.60. Abbreviations: FFR, fractional flow reserve; Pa, mean aortic pressure; Pd, mean distal coronary artery pressure.

have been used to induce microvasculature vasodilation: adenosine, adenosine 5'-triphosphate, and papaverine.^{14–16} Some investigators consider intravenous adenosine at a rate of 140 µg/kg/min as the gold standard for induction of maximal hyperemia in complex cases (eg, multiple lesions or diffusely diseased arteries), as this achieves a lasting effect necessary for pullback recording.^{14,17} Intracoronary adenosine is usually reserved for single-vessel stenosis.¹⁴ A small study suggested that higher doses of intracoronary adenosine (up to 720 µg) were well tolerated and increased the sensitivity of FFR in detecting hemodynamically significant coronary stenoses.¹⁸ In addition, regadenoson, a selective A_{2A} adenosine receptor agent with a relatively safer profile,¹⁹ in a dose of 400-µg bolus, has shown promising results when compared with intravenous adenosine.²⁰

The Figure illustrates FFR recordings for both non-ischemic and ischemia-producing lesions during the period of maximal hyperemia.

It should be noted that in patients with left-ventricular hypertrophy, the muscle growth is usually greater than the vascular bed growth^{21,22}; however, FFR measurement in patients with left-ventricular hypertrophy appears to be reliable.²³ It is important to mention that FFR tests for inducible ischemia, which the patient might develop during stress or exercise. Fractional flow reserve also can determine resting ischemia; however, this usually will be clinically evident.

In our institution, patients who undergo a FFR-only procedure are discharged a minimum of 3 hours after the procedure, provided that no acute complications occurred. Patients are observed overnight if they underwent FFR-guided revascularization. A small retrospective study in France, enrolling 95 patients with 18 FFR procedures (the majority of the procedures used a transradial approach), showed that patients may be discharged safely 6 hours after an FFR-guided revascularization²⁴; however, this approach needs to be validated in a larger study.

The current data on FFR can be broadly categorized into 2 types: studies that compare FFR with other noninvasive modalities^{25,26} and studies that test treatment strategies of patients with intermediate coronary stenoses using a threshold value for FFR and that have clinical outcomes as endpoints.^{27–34}

What Fractional Flow Reserve Value Defines Ischemia?

There is no strict FFR value associated with myocardial ischemia; in fact, FFR has a well-defined cutoff with a narrow gray zone. Pijls et al demonstrated that an FFR value <0.75 was associated with reversible ischemia on noninvasive stress testing (exercise stress test, nuclear scan, and dobutamine stress echocardiogram) with 88% sensitivity, 100% specificity, 100% positive predictive value, 88% negative predictive value, and 93% accuracy.²⁵ The

DEFER study and other studies have used an FFR value of <0.75 as the cutoff for ischemia.^{7,27–33}

In contrast, an FFR value >0.80 has been shown to exclude an ischemia-producing lesions, with predictive value of $>95\%$.^{9,25,26} Thus, the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME)³⁴ and the FAME II³⁵ trials used an FFR value of ≤ 0.80 for defining ischemia. The Society for Cardiovascular Angiography and Interventions recommended a cutoff of ≤ 0.80 in their consensus statement in 2013.³⁶

Coronary stenoses can be arbitrarily classified into 3 groups on the basis of FFR values: (1) non-ischemic stenoses with FFR >0.80 , (2) ischemia-producing stenoses with FFR <0.75 , and (3) a gray zone with FFR values between 0.75 and 0.80. Deferral of revascularization of stenoses with FFR >0.80 appears to be safe.⁷ For stenoses with FFR <0.75 , revascularization is recommended.^{35,37}

Studies of stenoses with FFR 0.75 to 0.80 have shown conflicting outcome data.^{38,39} Petraco et al found that there is varying reproducibility of FFR values if the test is repeated within 10 minutes when the FFR value is 0.75 to 0.80. There is more variability if the FFR is close to 0.80.⁴⁰ Thus, clinical judgment is necessary for decision-making in patients with coronary stenosis and FFR values in this gray zone. This would include assessment of the adequacy of antiangina medications, results of noninvasive testing (if available), predicting the likelihood of successful revascularization of the stenosis, and perhaps even repeating the FFR measurement within 10 minutes.

Applications for Fractional Flow Reserve in Coronary Artery Disease

Single-Vessel Disease

The DEFER study has shown that patients with single-vessel stenosis and FFR >0.75 who did not undergo PCI had excellent outcomes. The risk of cardiac death or myocardial infarction (MI) related to the stenosis was $<1\%$ per year and was not reduced with PCI. In contrast, patients with single-vessel stenosis and FFR <0.75 are 5× more likely to experience cardiac death or MI within 5 years, despite undergoing revascularization.⁷

Deferral of revascularization for single-vessel stenoses according to the FFR value is safe regardless of the stenosis location. Muller et al showed that medical treatment of patients with proximal left anterior descending stenoses and FFR >0.80 had excellent 5-year outcomes.⁴¹

Even for patients with small coronary arteries (diameter <2.8 mm), FFR can safely determine stenoses that necessitate revascularization. In the Physiologic and Anatomical Evaluation Prior to and After Stent Implantation in Small Coronary Vessels (PHANTOM) trial, 60 patients with small coronary arteries underwent FFR. Fifty-six of the 60 patients had undergone intravascular ultrasound (IVUS). Patients were stratified according to FFR (<0.75 and >0.75). The group with FFR <0.75 underwent revascularization. At 1 year, there was no occurrence of MI or death in either group. In patients with FFR <0.75 , 24% underwent a repeat PCI, but only 2.6% of patients with FFR >0.75 underwent

revascularization. Overall, there was no correlation between FFR and IVUS.²⁹

In Table 1, we summarize the studies that evaluated the use of FFR in intermediate stenoses in non-left-main CAD.

Tandem Lesions

Tandem lesions are defined as 2 separate lesions with $>50\%$ stenosis each (with visual assessment on conventional angiography) in the same coronary artery, separated by an angiographically normal segment.^{42,43} Fractional flow reserve is measured by advancing the wire distally in the vessel, followed by adenosine administration; the pressure wire is slowly pulled back with continuous recording of the pressures.^{9,42,43}

Fractional flow reserve may be used to guide revascularization for tandem lesions using the same concept of FFR (comparing the distal coronary flow to the mean aortic pressure). If the FFR is <0.75 , Hirota et al suggested performing PCI for the stenosis that showed marked narrowing first and then repeating the FFR measurement. If the FFR remains <0.75 , the other stenosis was revascularized as well; in contrast, if the FFR value of the first lesion increased after PCI to >0.75 , then the second lesion was treated only medically.³⁰

Left-Main Coronary Artery Disease

Several studies have concluded that FFR is a valuable tool in determining ischemia due to left-main CAD. Table 2 summarizes the studies that evaluated the outcomes of patients with left-main CAD in which FFR was used to guide revascularization and medical management.

Multivessel Coronary Artery Disease

Although myocardial perfusion scintigraphy is considered the clinical reference standard for diagnosing ischemia, several studies showed that there is discordance of results compared with FFR values, especially in multivessel disease.^{44,45} This discordance can be explained by the phenomenon of balanced ischemia, in which the nuclear stress test appears normal as a result of flow limitation in all arteries in patients with multivessel CAD.

In the FAME trial, 1005 patients with multivessel CAD were randomly assigned to either angiographically guided PCI or PCI guided by FFR (if FFR was ≤ 0.80). The mean number of indicated lesions in the angiographically guided group was 2.7 ± 0.9 , vs 2.8 ± 1.0 in the FFR-guided group. The number of stents used per patient was significantly lower in the FFR-guided group (1.9 ± 1.3 vs 2.7 ± 1.2 , $P < 0.001$). The composite outcome of death, nonfatal MI, and urgent revascularization at 1 year was significantly lower in the FFR-guided group (13.2% vs 18.3%, $P = 0.02$).³⁴ The mean overall cost was significantly lower in the FFR-guided group (\$14 315 vs \$16 700, $P < 0.001$).⁴⁶ After 2 years, the composite endpoint continued to be significantly lower in the FFR-guided group; the rate of MI was 0.2% and the revascularization rate was 3.2%.⁴⁷ Based on the results of this study, measurement of FFR during invasive coronary angiography is a class IA indication from the European Society of Cardiology for identifying hemodynamically significant coronary lesions when noninvasive evidence of myocardial ischemia is unavailable.²

Table 1. Studies That Evaluated the Outcomes of FFR in Intermediate Lesions in Patients With Non–Left Main CAD

Author or Study	Single-Vessel or Multivessel CAD	Study Design	FFR Value Defining Ischemia	No. of Patients	Survival, %	Event-Free Survival, %	Follow-up, mo	Completeness of Follow-up, %
DEFER ⁷	Single	Randomized, prospective, multicenter	0.75	91/144	93/91	80/63	60	98
Bech et al ¹¹	Single	Retrospective, multicenter	0.75	100 (all patients were deferred)	98	90	18	NR
Misaka et al ²⁸	Both	Prospective, single center	0.75	29/15	100/100	93/87	53	100
PHANTOM ²⁹	NR	Prospective, multicenter	0.75	39/21	100/100	97/76	12	100
Hirota et al ³⁰	Both	Prospective, single center	0.75	26/46	100/100	92/87	18	100
Verna et al ³¹	Both	Prospective, single center	0.75	54/58	98/95	87/76	34	100
Legalery et al ³⁷	Both	Prospective, single center	0.80	237/99	99/100	94/93	12	99
Muller et al ⁴¹	Single (proximal LAD)	Prospective, single center	0.80	544/166	93/90	90/69	60	100
Hernández García et al ⁷²	Single	Prospective, single center	0.75	43 (all patients were deferred)	100	93	11	100
Rieber et al ⁷³	Both	Prospective, single center	0.75	59/48	100/88	89/58	12	96
Chamuleau et al ⁷⁴	Single	Prospective, single center	0.75	92/15	100/100	91/73	12	100
Rieber et al ⁷⁵	Both	Prospective, single center	0.75	56 (all patients were deferred)	91	71	60	100

CAD, coronary artery disease; DEFER, the Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis; FFR, fractional flow reserve; LAD, left anterior descending artery; NR, not reported; PHANTOM, Physiologic and Anatomical Evaluation Prior to and After Stent Implantation in Small Coronary Vessels.
Data are formatted as deferral group/revascularization group.

Table 2. Studies That Looked Into the Outcomes of Patients With Left-Main CAD in Which FFR Was Used to Guide Revascularization vs Medical Therapy

Author	Study Design	FFR Value Defining Ischemia	No. of Patients	Survival, %	Event-Free Survival, %	Follow-up, mo	Completeness of Follow-up, %
Hamilos et al ⁸	Prospective, single center	0.80	136/73	90/85	74/83	35	98
Bech et al ²⁷	Prospective, multicenter	0.75	24/30	100/100	76/83	29	100
Suemaru et al ³²	Prospective, single center	0.75	08/07	100/100	100/100	33	100
Jasti et al ³³	Prospective, single center	0.75	41/13	100/100	90/100	38	100
Courtis et al ⁷⁶	Prospective, single center	>0.80 medical treatment, <0.75 revascularization	82/60	96/95	84/98	14	100
Lindstaedt et al ⁷⁷	Prospective, single center	>0.80 medical treatment, <0.75 revascularization	24/27	100/81	69/66	29	100
Jiménez-Navarro et al ⁷⁸	Prospective, single center	0.75	20/7	90/71	80/71	26	100
Legutko et al ⁷⁹	Prospective, single center	0.75	20/18	100/89	90/89	24	100

Abbreviations: FFR, fractional flow reserve.
Data are formatted as deferral group/revascularization group.

Jailed Side-Branch Lesions

Treatment of bifurcation coronary lesions is challenging, and visual assessment of jailed side-branch stenosis is seldom accurate.^{48,49} Fractional flow reserve has been shown to be a feasible technique in managing these cases. Koo et al used FFR to assess the functional stenosis in 97 jailed side-branch lesions after stent deployment in the main branches. The side branches were ≥ 2 mm in diameter

and demonstrated a stenosis of $\geq 50\%$ on visual assessment. Seventy-three lesions had stenosis $>75\%$, but only 20 of these lesions had an FFR <0.75 .⁴⁹

Prediction of Coronary Artery Bypass Graft Conduit Patency

Bypass grafting of nonfunctional coronary stenosis is believed to enhance the graft closure, as the blood flow

favors the lower-resistance path in the native vessel rather than the vein graft with slower flow.⁵⁰ In a study that included 450 grafts with preoperative FFR >0.80 in the native vessel, the incidence of graft occlusion was 20% to 25%.⁵¹ Although the patients with occluded or patent grafts on the nonsignificant coronary lesion did not yet experience increased rates of angina or revascularization, the study points out that FFR has prognostic implications for graft patency in patients with multivessel CAD planned for CABG.

Acute Coronary Syndromes

Maximum hyperemia is a prerequisite for accurate FFR measurement. It has been proposed that hyperemia may be suboptimal in patients with a recent MI due to microvascular injury.⁵² However, more recent studies have shown that FFR can safely guide revascularization in nonculprit lesions in patients with unstable angina and non-ST-segment elevation MI (NSTEMI) without an increase in cost or duration of radiation exposure.^{53,54} Results from the FAME trial demonstrated that the benefit of FFR-guided PCI was similar in patients with unstable angina and NSTEMI vs stable CAD.⁵⁵ Fractional flow reserve is of great benefit in these situations due to the lack of noninvasive imaging prior to coronary angiography, unlike stable CAD. An ongoing multicenter randomized trial, Fractional Flow Reserve Versus Angiography in Guiding Management to Optimize Outcomes in Non-ST-Elevation Myocardial Infarction (FAMOUS-NSTEMI) is evaluating the feasibility of FFR measurement in NSTEMI and the influence of FFR disclosure on treatment decisions and health and economic outcomes.⁵⁶

In contrast, in the setting of ST-segment elevation MI (STEMI), the culprit lesion is identified during the primary PCI procedure with the electrocardiographic changes and findings during the coronary angiography. Nonculprit lesions with intermediate significance can be further evaluated with FFR usually after 4 days of the acute MI.⁵⁷

Frequency of Fractional Flow Reserve Usage

Current guidelines recommend FFR-guided revascularization when noninvasive stress tests are unavailable or nondiagnostic.^{1–3} Despite these recommendations, FFR is not as widely used as expected. In a study conducted in the Medicare population, FFR was used in <1% of the total number of patients undergoing coronary angiography in the period from 2005 to 2009.⁵⁸ Another study done in Europe showed that the rate of FFR usage was 6.3% of the total number of coronary angiograms.³⁷ These 2 studies were published prior to the FAME trials,^{34,35} which might explain the relatively low percentage of FFR usage in these studies.

Several reasons may explain the underusage of FFR. First, some cardiologists find it time-consuming and therefore make clinical decisions based solely on conventional angiography. Second, FFR is believed to increase the total cost of health care provided. In fact, Fearon et al performed a decision model looking into the long-term cost-effectiveness of measuring FFR in guiding revascularization for questionable coronary stenoses. They found that FFR-guided revascularization saved \$1795 per patient when compared with deferring revascularization and performing

a nuclear stress test, and saved \$3830 when compared with stenting the questionable stenoses.⁵⁹ More recently, an evaluation of FFR-guided revascularization from the FAME trial in patients with multivessel CAD demonstrated that this technology saves economic resources, as we pointed out earlier.⁴⁶

Finally, some cardiologists may prefer to perform PCI on borderline stenoses under a belief that it will stabilize plaques and reduce adverse events. The DEFER study reminded us that stenting non-ischemia-producing stenoses does not add any additional outcome benefit to the patient; furthermore, unnecessary stenting may actually be harmful.⁷

Modalities for Assessment of Intracoronary Anatomy

Fractional flow reserve aids in determining the physiological significance of coronary lesions, yet the use of FFR to evaluate post-PCI results is not well investigated. One multicenter study showed that a FFR >0.95 after stent deployment was associated with better outcomes at 6 months.⁶⁰ Intravascular ultrasound and optical coherence tomography (OCT) are 2 supplemental modalities that may be used as adjuncts to FFR for better anatomical delineation of coronary lesions and to assess stent deployment.³⁶

Intravascular ultrasound is a catheter-based technique that provides cross-sectional images to enable measurement of the luminal and vessel areas. It is simple to perform and has a very low rate of complications.⁶¹ Intravascular ultrasound has been shown to have good correlation with FFR in patients with left-main CAD³³; however, in non-left-main stenosis, IVUS has moderate correlation with FFR.⁶² The utility of IVUS measurements in correlating with ischemia in small vessels may be more limited.²⁹ The use of IVUS in guiding PCI for challenging interventions (eg, left main, bifurcation lesions) has been associated with reduced incidence of major adverse cardiac events, stent restenosis, and stent thrombosis.^{63,64}

Optical coherence tomography is an emerging invasive coronary-imaging modality that provides better resolution but less penetration power than IVUS, offering more precise evaluation of the vessel lumen and stent edge.^{36,65} Furthermore, OCT provides good assessment of the thickness of the fibrous cap, indicating potential plaque vulnerability. To date, there are no prospective studies that evaluated the outcomes of PCI-guided OCT; however, one multicenter retrospective study showed that the use of OCT in guiding PCI was associated with better outcomes.⁶⁶

In Table 3 and Table 4, we summarize the studies that correlated IVUS and OCT measurements with FFR.

How Can the Clinical Cardiologist Integrate Fractional Flow Reserve Into Daily Practice?

In the current era, an evidence-based approach is important to guide revascularization decisions, especially when functional assessment of a coronary stenosis is available. Although most studies favor the incorporation of FFR, it is worth mentioning that the clinical studies supporting FFR have some drawbacks (eg, the DEFER study enrolled a relatively small number of patients, and the design of the FAME and FAME II trials render them susceptible to

Table 3. Studies That Correlate Between IVUS Measurements and FFR

Author	Study Design	No. of Patients	No. of Lesions	Follow-up, mo	FFR Value Defining Ischemia	IVUS MLD, mm	Sensitivity, %	Specificity, %	IVUS MLA, mm	Sensitivity, %	Specificity, %	Survival, %	Event-Free Survival, %
Left-main CAD													
Jasti et al ³²	Prospective, single center	41/14	55	38	0.75	2.8	93	98	5.9	93	95	100/90	100/90
Kang et al ⁸⁰	Cross-sectional	55	55	NR	0.80	NR	NR	NR	4.8	89	83	NR	NR
					0.75	NR	NR	NR	4.1	95	83		
Non-left-main CAD													
Waksman et al ⁶²	Prospective, multicenter	350	367	NR	0.80	NR	NR	NR	3.07	64	65	NR	NR
Takagi et al ⁸¹	Cross-sectional	42	51	NR	0.75	NR	NR	NR	3.0	83	92	NR	NR
Briguori et al ⁸²	Cross-sectional	43	53	NR	0.75	1.8	100	66	4.0	92	56	NR	NR </body>

Abbreviations: CAD, coronary artery disease; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MLD, minimal lumen area; MLA, minimal lumen diameter; NR, not reported. Data are formatted as deferral group/revascularization group.

Table 4. Studies That Correlate Between OCT Measurements and FFR

Author	Study Design	No. of Patients	No. of Lesions	Follow-up, mo	FFR Value Defining Ischemia	OCT MLD, mm	Sensitivity, %	Specificity, %	IVUS MLD, mm	Sensitivity, %	Specificity, %	OCT MLA, mm	Sensitivity, %	Specificity, %
Gonzalo et al ⁸³	Cross-sectional	56	61	NR	0.80	2.0	82	63	2.4	67	65	NR	NR	NR
Shiono et al ⁸⁴	Cross-sectional	59	62	NR	0.75	1.4	90	81	NR	NR	NR	1.9	94	77

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound; MLD, minimal lumen area; MLA, minimal lumen diameter; NR, not reported; OCT, optical coherence tomography. Data are formatted as deferral group/revascularization group.

selection bias, as most of the included patients had less complex CAD).

In addition, in clinical practice many factors may influence the decision of whether to perform revascularization, including patient preference, compliance with medication, bleeding tendency, the complexity of the coronary lesion, and various other factors that may lead to a decision that disagrees with the FFR result.

Moreover, FFR measurement may be suboptimal in cases of submaximal hyperemia or an ostial coronary lesion that causes pressure damping and reduces maximal blood flow.²¹ Despite these possible pitfalls in FFR measurement that may be considered by the physician and affect the clinical decision, the majority of FFR results in most clinical scenarios represent the true physiological significance of the lesion and should therefore guide coronary intervention.

Future Perspectives

As has been demonstrated, there is strong evidence supporting the use of FFR in assessing intermediate coronary stenoses in guiding revascularization decisions, yet several areas warrant future studies.

The current gold standard for induction of microvasculature hyperemia is intravenous adenosine infusion through a central venous catheter, although it is not commonly used because it requires a central line placement. High doses of intracoronary adenosine and regadenoson have shown promising results.^{18,20} Whether any of these agents may replace intravenous adenosine needs to be further validated, as both studies were performed in a single center and included a small number of single-vessel intermediate stenoses. More recently, instantaneous wave-free ratio (iFR), which records the coronary pressure during the diastolic period when the microvascular resistance is steady, recently has been introduced to replace the use of hyperemia-inducing agents.⁶⁷ Coronary-stenosis measurement with iFR has been shown to be equivalent to FFR.⁶⁸ An ongoing study for evaluation of nonculprit lesions using iFR in acute coronary syndrome, the Diastolic Pressure Gradient for Patients With Acute Coronary Syndrome: Evaluation of Non Culprit Lesions (FORECAST), has shown promising results so far.

The best approach for management of lesions with FFR 0.75 to 0.80 is unknown. Clinical judgment incorporating all of the pertinent facts about the patient's condition should be used for clinical decision-making, and repeating the FFR measurement within 10 minutes can be considered in these cases.

The investigators of the FAME trial are planning to conduct the FAME-3 trial, which will compare FFR-guided PCI to CABG in patients with multivessel CAD. FAME-3 is a trial designed to merge the concepts of the FAME and Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) trials.

As mentioned earlier, an ongoing trial is evaluating the use of FFR to guide revascularization in NSTEMI; it will be interesting to know whether FFR can rule out unnecessary interventions. Additionally, evaluation of FFR as a promised modality to guide outcomes after PCI requires further exploration.

The frequency of FFR usage is underreported; studies need to address whether FFR is appropriately used or not in decision-making for questionable stenoses.

Noninvasive FFR assessment using cardiac computed tomography (FFR_{CT}) is another promising modality for coronary physiology assessment. Two multicenter prospective studies, Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW) and the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO), have shown that noninvasive evaluation of FFR with computed tomography is fairly accurate and sensitive when compared with invasive FFR measurement.^{69,70} Data from the DISCOVER-FLOW study showed that a strategy of using FFR_{CT} to guide the selection of patients for invasive coronary angiography and PCI might reduce costs and improve clinical outcomes in patients with suspected CAD.⁷¹ Whether this novel noninvasive modality may replace invasive FFR measurement in the future requires further investigation.

Conclusion

Using FFR, coronary stenoses can be classified into 3 groups based on physiologic assessment during coronary angiography: ischemia-producing stenoses (FFR <0.75), non-ischemia-producing stenoses (FFR >0.80), and the gray zone (FFR 0.75–0.80). Fractional flow reserve can safely guide revascularization in single-vessel, left-main, and multivessel CAD, and in nonculprit lesions during acute coronary syndrome. Fractional flow reserve has shown to result in better clinical and economical outcomes compared with conventional angiography. Although FFR is a useful tool, it is not widely used.

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