Treating patients with coronary artery disease (CAD) frequently requires assessment of myocardial ischemia before recommending coronary revascularization. Common clinical practice is to challenge the coronary blood supply, that is, provoke myocardial ischemia by employing any one of several outpatient stress tests. The adequacy of coronary blood flow and freedom from ischemia are indicated by the responses to exercise or pharmacologic stimulation observing the associated electrocardiographic changes, deficits of myocardial perfusion, or failure of the left ventricle to thicken or shorten on echocardiography. In a similar fashion and for similar reasons, the ischemic potential of a stenosis can be assessed in the cardiac catheterization laboratory at the time of angiography using sensor-tipped angioplasty guidewires to measure coronary blood flow and pressure across stenotic artery segments. The adoption of invasive coronary physiologic lesion assessment before percutaneous coronary intervention (PCI) has become routine in many catheterization laboratories. Indeed, in the last decade, numerous studies have demonstrated favorable outcomes for revascularization decisions based on in-lab coronary physiology in patients with intermediate single-vessel stenoses, bifurcation and ostial branch stenoses, multivessel CAD, and left main stenoses. The use of coronary physiology in the laboratory has been identified as a class Ila recommendation for patients in whom the clinical presentation and supporting data (ie, angiograms, stress tests) are too inconclusive to make an objective decision regarding treatment. The following discussion reviews selected pertinent concepts and studies of the more complex applications of translesional pressure measurements for optimal patient outcomes.

RATIONALE FOR IN-LAB CORONARY PHYSIOLOGY

The rationale for use of physiologic lesion assessment at the time of angiography is the necessity to overcome the limitation of the angiographic display of a stenosis. Coronary angiography produces 2-dimensional silhouette images of the 3-dimensional vascular lumen. Customarily in clinical practice, the angiographic stenosis severity is visually assessed as a percent diameter reduction from the ratio of the stenosis “minimal” lumen diameter to the adjacent “normal” reference segment diameter, often in a single projection (Fig. 1A). The accuracy of this value depends on the observer’s objective skills but also is limited by the inability to identify both “diseased” and “normal” vessel segments, particularly in the setting of diffuse CAD. The correlation between minimal lumen diameter and area with hemodynamic lesion significance is poor. To proceed with revascularization one must know the hemodynamic significance of a lesion and, more importantly, that coronary angiography cannot identify the accurate hemodynamic significance of many coronary stenoses, particularly those between...
30% and 80% diameter stenosis. This limitation has been documented repeatedly by poor correlation to the variety of stress-testing modalities employed in patients with CAD. Moreover, even sophisticated imaging, such as densitometry, rotational angiography, multidetector-row computed tomographic angiography, or 3-dimensional reconstruction, does not reliably reflect the physiologic significance of a given lesion.

CORONARY HEMODYNAMICS

Coronary flow through a normal epicardial artery encounters near zero resistance. As atherosclerosis develops, the altered laminar flow properties as well as obstructing topographic features of a stenosis produce resistance to flow, which is translated as pressure loss due to energy loss (overcoming resistance to flow). The morphologic features of coronary stenosis (ie, shape, length, angulations) responsible for increasing epicardial resistance ultimately limit blood flow and produce angina. Most of these features cannot be accurately discerned from the angiogram. Unlike intravascular ultrasound (IVUS) and computed tomographic angiography, angiography does not provide vascular wall detail sufficient to characterize plaque size, length, and eccentricity.

Moreover, an eccentric angiographic lumen produces conflicting degrees of diameter narrowing when viewed from different radiographic angulations, and introduces uncertainty related to lumen size and its relationship to coronary blood flow. Furthermore, stenosis length and reference vessel diameter play a significant role in the genesis of the pressure gradient across a given stenotic segment. A long moderate narrowing can be as or more hemodynamically significant than a short, focal severe narrowing (Fig. 2). Angiographic images often include contrast streaming, branch overlap, vessel foreshortening, calcifications, and ostial origins, which further limit the observer’s assessment of the stenosis. Given the limitations of the angiogram, the true value of translesional pressure measurements is the incorporation all unknown factors producing resistance and yielding the net distal pressure, to determine the ischemic potential and significance to the patient.

**Computation of Pressure-Derived Fractional Flow Reserve**

Fractional Flow Reserve (FFR) is derived from the relationship between pressure, flow, and resistance in a coronary artery and corresponding myocardial region. The goal of FFR is to provide
a measurement of the flow (Q) in the stenotic artery as a percentage of normal flow through the same artery in the theoretical absence of the stenosis. FFR is a ratio of flow derived from a ratio of coronary and aortic pressure.\textsuperscript{2} The first assumption in the derivation of FFR is that pressure in a normal coronary artery is equal to aortic pressure. The normal left anterior descending artery (LAD) coronary artery pressure is aortic pressure (Pa).

Thus, resistance to flow, \( R = \frac{Q}{P} \) (P, pressure);

\[
Q_s = \frac{P_d}{R_d} \quad \text{and} \quad Q_n = \frac{P_a}{R_a}
\]

where \( Q_s \) is stenotic artery flow, \( Q_n \) is normal artery flow, \( P_d \) is distal coronary pressure, \( P_a \) is aortic pressure, and \( R_d, R_a \) are the resistances in the myocardial bed beyond the stenosis.

\[
\text{FFR} = \frac{Q_s}{Q_n} = \frac{(P_d/R_d)}{(P_a/R_a)}
\]

\( R_d = R_a \) at maximal hyperemia (ie, minimal and fixed resistance), and these are cancelled from the equation.

Hence, \( \text{FFR} = \frac{P_d}{P_a} \), during maximal hyperemia

The full derivation of the FFR calculation also employs venous pressure, \( P_v \), and describes FFR of the collateral circulation using coronary occlusion wedge pressure, \( P_w \), which can be found elsewhere.\textsuperscript{2} \textbf{Box 1} provides a brief derivation of the 3 most commonly used physiologic parameters measured in the cath lab. FFR is distinguished from direct measurement maximal ratios of coronary blood flow (ie, coronary flow reserve [CFR], the ratio of hyperemic to basal blood flow) in several ways. FFR has a single normal value of 1 because FFR uses aortic pressure as the standard comparator. Recall that epicardial resistance to flow is negligible in the absence of disease. \( P_a \) is transmitted completely to the distal artery, making both the numerator and denominator the same value in a normal artery.\textsuperscript{16} An FFR value of 0.75 means that the stenotic vessel only provides 75\% of the normal expected flow in the theoretical absence of the stenosis. FFR is also specific for
the resistance of only the epicardial stenosis. Its derivation excludes the confounding influences of the microcirculation, changes in hemodynamics or contractility. Unlike CFR, FFR is minimally influenced by changes in hemodynamics or other conditions known to alter baseline or maximal hyperemic myocardial blood flow.

MEASUREMENT TECHNIQUE

The methods of translesional pressure measurement have been previously reviewed in detail. In brief, following diagnostic angiography in the catheterization laboratory and using a technique identical to that of angioplasty, a 0.014-in pressure sensor angioplasty guidewire is inserted through a guiding catheter and into the target artery. Before crossing the stenosis, the sensor wire’s pressure signal is matched to the aortic (guide catheter) pressure. The pressure wire is then advanced across the lesion. Coronary hyperemia is then induced, usually with intravenous or intracoronary adenosine, though papaverine, adenosine triphosphate, or selective adenosine 2A agonists has been used as well. The pressure distal to the stenosis (Pd) and aortic pressure (Pa) are continuously recorded. FFR is then calculated as Pd/Pa at maximal hyperemia, the nadir of Pd. An example of FFR is shown on Fig. 3A, B. It is important to recognize technical artifacts such as guide catheter clamping that would produce a false-negative FFR (see Fig. 3C). Box 2 is a partial list of reasons why one might encounter a false-negative FFR result.

To assess multiple, sequential lesions or diffuse CAD, the pressure wire is pulled back continuously from the distal to proximal vessel segments during hyperemia induced by an intravenous infusion of adenosine. The pressure pullback curve can demonstrate either an abrupt change in distal pressure across a focal narrowing or the gradual pressure recovery of diffuse disease without focal obstructions.

RADIATION, PROCEDURE TIME, AND CONTRAST USE FOR FFR

FFR may increase the radiation dose, procedural time, and contrast medium after a diagnostic coronary angiogram. Ntalianis and colleagues measured radiation dose (mSv), procedural time (minutes), and contrast medium (mL) in 200 patients (mean age 66 ± 10 years) undergoing diagnostic coronary angiography. FFR was measured in at least one intermediate coronary artery stenosis; 296 stenoses (1.5 ± 0.7 stenoses per patient) were assessed. Hyperemia was achieved by intracoronary (n = 180) or intravenous (n = 20) adenosine. The additional mean radiation dose, procedural time, and contrast medium

Box 1
Coronary physiologic measurements in the cath lab

Fractional Flow Reserve, FFR

Derivation: \( FFR = \frac{Q_{\text{sten}}}{Q_{\text{normal}}} \) at maximal hyperemia. \( Q \) = flow, \( \text{sten} \) = stenotic artery, \( \text{normal} \) = theoretical same artery without stenosis

\[
\begin{align*}
Q_{\text{sten}} &= P_{\text{sten}}/\text{Resistance}_{\text{sten}} \\
Q_{\text{normal}} &= P_{\text{aorta}}/\text{Resistance}_{\text{sten}}, \text{then} \\
Q_{\text{sten}}/Q_{\text{normal}} &= P_{\text{sten}}/P_{\text{aorta}}
\end{align*}
\]

Hence \( FFR = \frac{P_{\text{distal to stenosis}}}{P_{\text{aorta}}} \)

[complete derivation includes venous pressure \( P_v \) as \( FFR = P_{\text{distal to stenosis}} - P_v/P_{\text{aorta}} - P_v \), see Ref.]

Features: nonischemic threshold range > (0.75–0.80), normal value of 1.0 for every artery and every patient, epicardial lesion specific, linear relation with relative maximum blood flow, independent of hemodynamic alterations, value that accounts for total myocardial blood flow including collaterals, highly reproducible, high spatial resolution (pressure pull-back recording)

Coronary Flow Velocity Reserve, CFVR

Derivation: \( \text{CFVR} = \frac{Q_{\text{hyperemia}}}{Q_{\text{base}}}. Q = \text{Velocity if cross-sectional area unchanged during hyperemia}

Features: Nonischemic threshold range of CFR >2.0, CFR in nonobstructed vessels assesses microvascular integrity, useful for studies of coronary endothelial function, accurate estimation of volumetric flow when vessel cross-sectional area available

Combined Pressure and Flow Velocity measurements: eg, hyperemic stenosis resistance (HSR)

Derivation:

\( \text{HSR} = \frac{P_{\text{aorta}}}{Q_{\text{hyperemic}}} - \frac{P_{\text{distal to stenosis}}}{Q_{\text{hyperemic}}} \)

Features: Separate assessment of stenosis and microvascular resistances, allows construction of pressure-flow curves (assessment of compliant lesions, hemodynamic gain after PCI)

For stenosis resistance index: Nonischemic threshold values less than 0.8 mm Hg/cm/s; normal value of 0; lesion specific, highly reproducible, high sensitivity; useful in cases of discordance between CFR and FFR

needed to obtain FFR as a percentage of the entire procedure were 30% ± 16% (median 4 mSv, range 2.4–6.7 mSv), 26% ± 13% (median 9 minutes, range 7–13 minutes), and 31% ± 16% (median 50 mL, range 30–90 mL), respectively. The procedural time was slightly longer with intravenous adenosine (median 11 minutes vs 9 minutes, \(P = .04\)). There was no difference between intravenous and intracoronary adenosine for radiation or contrast dosages (Fig. 4). There was no difference between intravenous and intracoronary adenosine. When FFR was measured in 3 or more lesions, radiation dose, procedural time, and contrast medium increased. The minimal increases in radiation dose, procedural time, and contrast medium were low compared with IVUS or angioscopy. The clinical value of FFR measurements is worth the small additional radiation and procedure time involved.

**FFR THRESHOLD OF ISCHEMIA**

FFR values of less than 0.75 are associated with abnormal stress testing results in numerous comparative studies.\(^2\) FFR values greater than 0.80 are associated with negative ischemic results with a predictive accuracy of 95%. Because of variations in testing techniques and patient subgroups, a small zone of FFR uncertainty (0.75–0.80) with regard to stress testing exists. FFR values falling within the gray zone require additional clinical context for decision making. Given the variances of sensitivity, specificity, positive and negative predictive accuracy among patients, and types of stress testing, it is not surprising that, unlike the initial validation study comparing FFR to 3 different stress tests in the same patient before and after PCI,\(^1\) meta-analysis showed only modest concordance of

---

**Fig. 3.** (A) Hemodynamic tracings used to calculate pressure-derived fractional flow reserve (FFR). A mild resting gradient is shown by the difference in the mean aortic and coronary pressures (Pa, Pd), which increases during increasing flow or hyperemia. The hyperemic blood flow signal after adenosine is shown under the yellow shaded band. Coronary vasodilatory reserve, CVR is 2.2 and FFR 0.78. Intracoronary adenosine is indicated by the vertical black arrow. (B) Display screen showing FFR pressure signals. Red pressure signal is aortic pressure (Pa) and yellow signal is distal coronary pressure (Pd). In this example, FFR is 0.85. (C) Example of pressure signals acquired with deep-seated guide catheter. Guide pressure damping results in matched distal coronary pressure and false-negative FFR value.
FFR with noninvasive imaging tests. The selection of a clinical "gold standard" of ischemia is a significant limitation for all modalities used to correlate ischemic symptoms with coronary anatomy. The false-positive and false-negative test results of stress studies in patients with multivessel CAD are problematic to use as any single test as a gold standard. However, given the validation study for single-vessel disease by Pijls and colleagues,1 in contrast to noninvasive tests, FFR is a more vessel-specific index of the ischemic potential of a lesion. Table 1 is a summary of important validation studies of FFR.

**Box 2**

**Reasons for a false-negative FFR**

<table>
<thead>
<tr>
<th>Physiologic Explanations</th>
<th>Interpretable Explanations</th>
<th>Technical Explanations</th>
<th>Actual False-Negative FFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis hemodynamically nonsignificant despite angiographic appearance</td>
<td>Other culprit lesion</td>
<td>Insufficient hyperemia</td>
<td>Acute phase of ST elevation myocardial infarction</td>
</tr>
<tr>
<td>Small perfusion territory, old myocardial infarction (MI), little viable tissue, small vessel</td>
<td>Diffuse disease not focal stenosis</td>
<td>Guiding catheter related pitfall (deep engagement, small ostium, side holes)</td>
<td>Severe left ventricular hypertrophy</td>
</tr>
<tr>
<td>Abundant collaterals</td>
<td>Chest pain of noncardiac origin</td>
<td>Electrical drift</td>
<td>Exercise-induced spasm</td>
</tr>
<tr>
<td>Severe microvascular disease (rarely affecting FFR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Hyperemic change in pressure across a stenosis divided by the hyperemic distal velocity, HSR, may have better predictive value than FFR for detecting noninvasive ischemia.23

**VALIDATION OF MAGNETIC RESONANCE IMAGING PERFUSION WITH FFR**

Validation of magnetic resonance myocardial perfusion imaging (MRMPI) to detect reversible myocardial ischemia using FFR was reported by Watkins and colleagues. The previous studies have generally used quantitative coronary angiography as the standard to assess the accuracy of MRMPI, despite the weak relationship that exists between stenosis severity and functional significance. To address this limitation of prior validation studies, Watkins and colleagues studied 103 patients undergoing evaluation of angina with MRMPI with stress imaging using intravenous adenosine (140 μg/kg/min), and first-pass 0.1 mmol/kg gadolinium bolus imaging technique to FFR performed within 1 week of MRMPI. Perfusion defects were identified in 121 of 300 coronary artery segments (40%), of which 110 had an FFR less than 0.75; 168 of 179 normally perfused segments had an FFR greater than 0.75. The sensitivity and specificity of MRMPI for the detection of functionally significant coronary stenoses were 91% and 94%, respectively, with positive and negative predictive values of 91% and 94%. It appears that MRMPI can detect functionally significant coronary heart disease with high sensitivity, specificity, and positive and negative predictive values using FFR as the standard.

Melikian and colleagues reported on the correlation between ischemic myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) with FFR in patients with multivessel coronary disease. Sixty-seven patients (201 vascular territories) with angiographic 2- or 3-vessel coronary disease prospectively underwent MPI (rest/stress adenosine), and FFR in each vessel was measured within 2 weeks. In 42% of patients, MPI and FFR detected identical ischemic territories (mean number of territories 0.9 ± 0.8 for both; P = 1.00). In the remaining 36% MPI underestimated (mean number of territories;MPI: 0.46 ± 0.6, FFR: 2.0 ± 0.6; P<.001) and in 22% overestimated (mean number of territories; MPI: 1.9 ± 0.8, FFR: 0.5 ± 0.8; P<.001) the number of ischemic territories in comparison with FFR. There was poor concordance in detecting myocardial ischemia on both a per-patient (κ = 0.14 [95% confidence interval: −0.10−0.39]) and per-vessel (κ = 0.28 [95% confidence interval: 0.15−0.42]) basis. In this study there was poor concordance...
of MPI with FFR. MPI tends to under- or overestimate the functional significance of angiographic compared with FFR in patients with multivessel disease.

**Fig. 4.** (A) Additional amount of radiation (A), procedure time (B), and contrast medium (C) needed to perform FFR as a percentage of diagnostic and PCI procedure. (B) Incremental additional radiation (A), procedure time (B), and contrast medium (C) needed for 1-, 2-, and 3-vessel FFR. *(From Ntalianis A, Trana C, Muller O, et al. Effective radiation dose, time, and contrast medium to measure fractional flow reserve. J Am Coll Cardiol Interv 2010;3:821–7; with permission.)*

### Table 1

**FFR and noninvasive stress test results**

<table>
<thead>
<tr>
<th>Index</th>
<th>References</th>
<th>Refs.#</th>
<th>N</th>
<th>Ischemic Test</th>
<th>BCV</th>
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<td>X-ECG</td>
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<td>X-ECG/SPECT</td>
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<td>Pijls</td>
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<td>Abe</td>
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<td>SPECT</td>
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<td>SPECT</td>
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<tr>
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<td>SPECT</td>
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<td>DeBruyne</td>
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<td>57</td>
<td>MIBI-SPECT post MI</td>
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<td>SPECT</td>
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<td>87</td>
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</table>

**Abbreviations:** Acc%, percent accuracy; BCV, best cut-off value (defined as the value with the highest sum of sensitivity and specificity); DSE, dobutamine stress echocardiography; N, number; SPECT, single-photon emission tomography; X-ECG, exercise electrocardiography.

measurement of FFR. FFR is designed for physiologic epicardial lesion assessment. IVUS is designed to assess coronary lesion and vessel anatomy and morphology. IVUS is highly accurate for vessel sizing and for confirming stent expansion and strut apposition. The clinician’s first question should be “does this lesion limit blood flow and produce ischemia?” If the answer is yes, the stenting is indicated. If the answer is no, then stenting is of no value and introduces unnecessary risk and cost.

There are several IVUS studies that have compared FFR to IVUS measurements such as minimal lumen area (MLA). Tagaki and colleagues found that most MLA values of less than 4 mm² were associated with an FFR of less than 0.75 (Fig. 5), although several patients had nonischemic FFR. The reason for this variance is that resistance to flow is based on several different anatomic factors (entrance angle, length, MLA, eccentricity) of which MLA is only one. A 4-mm² MLA may limit flow in a large proximal vessel segments but will not impair flow in a smaller segment of the same artery. Moreover, for left main assessment, unlike FFR, the IVUS threshold for treatment or no treatment changes. There are several IVUS MLAs reported to be the cut-off value, ranging from 5.9 to 7.0 mm² for treatment decisions. Most IVUS thresholds are derived from clinical outcomes, with different areas from different studies. This variable IVUS “gold standard” is understandable, based on what is known about using only one dimension of a complex stenosis, with or without including the reference vessel segment dimensions. The loss of pressure across a stenosis can be computed from the simplified Bernoulli principle, which includes not only the stenosis area but also the length of the narrowing. $\Delta P = \frac{1}{A_s} \cdot V^2$, where $\Delta P$ is the pressure drop across a stenosis, $A_s$ is the minimal cross-sectional stenosis area (MCSa), and $V$ is blood flow velocity through the tube. Moreover, unlike IVUS, FFR is not only lesion-specific but also incorporates the variable myocardial blood flow across the stenosis supplying the specific myocardial

![Fig. 5. Correlation between FFR and quantitative coronary angiography and IVUS measurements. (A), FFR vs minimum lumen diameter (MLD) by quantitative coronary angiography (QCA), (B), percent diameter, (C), minimum lumen area (MLA) by IVUS, (D), area stenosis by IVUS. (From Takagi A, Tsurumi Y, Ishii Y, et al. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis. Relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. Circulation 1999;100:250–5; with permission.)](image-url)
bed. For example, a 70% stenosis in a vessel subtending a small diagonal or a previously infarcted mid-anterior descending territory will have less physiologic impact than an identical lesion in a mid-anterior descending subtending a normal anterior wall region because of the significantly higher flow requirements. Iqbal and colleagues demonstrated the dramatic change in the LAD FFR after recanalization of an occluded right coronary artery which was previously supplied by the LAD collateral flow (Fig 6). Thus, the FFR will be lower, even though the stenosis dimensions are identical.

The area of a normal 2.5-mm vessel is 4.9 mm². Thus, a stenosis with MLA of 4 mm² (a 28% area stenosis) in this vessel should not be considered obstructive or in need of PCI. Functionally significant coronary lesions must be greater than 50% diameter stenosis (approximately 75% area stenosis). A coronary narrowing with MLA of 4.0 mm² in a 3.0-mm vessel (area of 7.1 mm²) yields a 44% area stenosis, again questionably associated with ischemia. However, deferring PCI in a lesion with an IVUS-defined MLA greater than 4 mm² is associated with excellent clinical outcome. Several studies demonstrated the poor relationship between FFR and IVUS minimal lesion area ($r^2$ between 0.4 and 0.6).

Most recently, Nam and colleagues evaluated the long-term clinical outcomes of two strategies of PCI, comparing an FFR-guided PCI strategy with IVUS-guided PCI for intermediate coronary lesions in 167 consecutive patients (FFR-guided, 83 lesions vs IVUS-guided, 94 lesions). Cut-off

![Figure 6](image_url)

**Fig. 6.** (A) (Upper panels) (a) Left coronary angiogram demonstrating a moderate-to-severe stenosis in the mid LAD (arrow). Collateral connections from the septal branches of the LAD can be seen (white arrows). (b) Right coronary angiogram demonstrating a chronic total occlusion of the right coronary artery (RCA). (c) Late filling of posterior descending artery from retrograde filling (white arrowheads) following left coronary injection. (Lower panel) FFR of LAD at this time is 0.72. (B) The RCA was then approached and successfully recanalized. (Upper panels) (a) LAD lesion unchanged angiographically. (b) RCA is now patent after stenting. (c) Collaterals are no longer visible. (Lower panel) Repeat FFR of LAD is now 0.84, above the ischemic threshold. (C) Illustration of changes in supply bed influencing FFR after RCA recanalization. Because the supply bed of the LAD is markedly reduced after RCA recanalization, the FFR increased from 0.72 to 0.84, demonstrating role of flow on FFR-related ischemic potential. (From Iqbal MB, Shah N, Khan M, et al. Reduction in myocardial perfusion territory and its effect on the physiological severity of a coronary stenosis. Circ Cardiovasc Interv 2010;3:89–90; with permission.)
Fig. 6. (continued)
The value for FFR-guided PCI was 0.80, and for IVUS-guided PCI was a minimal lumen cross-sectional area of 4.0 mm². The initial percent diameter stenosis and lesion length were similar in both groups (51% ± 8% and 24 ± 12 mm in the FFR group vs 52% ± 8% and 24 ± 13 mm in the IVUS group, respectively). However, the IVUS-guided group underwent stenting significantly more often (91.5% vs 33.7%, P < .001) with no significant difference in rates of major adverse cardiac events (MACE) between the two groups (3.6% vs 3.2% in FFR-guided and IVUS-guided PCI, respectively) (Fig. 7). Independent predictors for performing intervention were guiding device: FFR versus IVUS (relative risk [RR]: 0.02); artery location: LAD versus non-LAD disease (RR: 5.60); and multi- versus single-vessel disease (RR: 3.28). Although both FFR- and IVUS-guided PCI strategies for intermediate CAD were associated with favorable outcomes, the FFR-guided PCI reduces the need for revascularization of many of these lesions. The health care economic implications of this comparison are self evident.

CLINICAL APPLICATIONS OF FFR FOR DIFFICULT ANGIOGRAPHIC SUBSETS

Intermediate Lesions and the Patient with Multivessel CAD

Many patients may have multivessel CAD with at least one obviously severe lesion and others that are intermediate-narrowed (30%–80%). Using FFR for revascularization decisions for such lesions has demonstrated excellent long-term results. The DEFER study randomized 325 patients scheduled for PCI into 3 groups and reported the 5-year outcomes. Patients were randomly assigned to the deferral group (n = 91), if FFR was 0.75 or greater, with continued medical therapy or the PCI performance group (n = 90, PCI with stents). If FFR was less than 0.75, PCI was performed as planned and patients were entered into the reference group (n = 144). Overall, the event-free survival was not different between the deferred and performed group (80% and 73% respectively, P = .52), and both were significantly better than in the reference group (63%, P = .03). The composite rate of cardiac death and acute MI in the deferred, performed, and reference groups was 3.3%, 7.9%, and 15.7%, respectively (P = .21 for deferred vs performed and P = .003 for reference vs both of the deferred and performed groups) (Fig. 8). The percentage of patients free from chest pain on follow-up was not different between the deferred and performed groups. The 5-year risk of cardiac death or MI in patients with normal FFR is less than 1% per year and was not decreased by stenting. Treating patients with intermediate lesions assisted by FFR is associated with a low event rate, comparable to event rates in patients with normal noninvasive testing. Similar outcomes for deferment of lesions with FFR greater than 0.80 is also reported in patients undergoing multivessel revascularization guided by FFR.7,34,35

**FFR-Guided Multivessel PCI**

One of the large confounders in the assessment and management of patients with multivessel disease is the uncertainty of ischemia related to a specific lesion. It is now known that not all multivessel angiographic CAD is physiologically equivalent CAD. This counterintuitive phenomenon has been demonstrated by Tonino and colleagues, who assessed FFR in all 3 vessels in patients with multivessel CAD. Before FFR measurements, at the time of randomization into the study, of the total 1329 lesions that were successfully assessed by the FFR, angiographic lesions were grouped by severity into 3 categories: 50% to 70% (47% of all lesions), 71% to 90% (39% of all lesions), and 91% to 99% (15% of all lesions) diameter stenosis by visual assessment. In the category 50% to 70% stenosis, 35% were functionally significant (FFR <0.80) and 65% were not (FFR >0.80)
In the category 71% to 90% stenosis, 80% were functionally significant and 20% were not. In the category 91% to 99% stenosis, 96% were functionally significant. Of all 509 patients with angiographically defined multivessel disease, only 235 (46%) had functional multivessel disease (>2 coronary arteries with an FFR <0.80). This analysis demonstrated that angiography continues to be inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR, not only in the 50% to 70% angiographic severity category but also in the 70% to 90% category. The reduction in the number of vessels that are physiologically significant has an impact on selection of patients for the different available revascularization options.

Both nonrandomized and prospective randomized studies demonstrated the benefit of FFR guidance in patients with multivessel CAD. Berger and colleagues showed a reduction in MACE in 102 patients with multivessel CAD with planned PCI of at least 2 vessels. In 113 coronary arteries with baseline FFR of 0.57 ± 0.13, PCI was performed and in 127 coronary arteries with an FFR greater than 0.75 (FFR 0.86 ± 0.06), PCI was not performed. Overall, MACE occurred in 9% of patients after 12 months and 13% after 36 months. In the nontreated vessels, 8 (6.3%) MACE were reported whereas 14 (12.3%) MACE were related to one of the initially PCI-treated coronary arteries. Similarly, FFR-guided PCI (FFR-PCI) was compared with angiographically guided PCI (Angio-PCI) in 137 patients with multivessel CAD. Compared with the FFR-PCI group, there were more vessels per patient treated in the Angio-PCI group (2.27 ± 0.50 vs 1.12 ± 0.30 vessels) at a higher cost ($3167 ± $1194 vs $2572 ± $934, respectively; P<.001). The 30-month Kaplan-Meier event-free survival was significantly higher in the FFR-PCI group than in the Angio-PCI group (89% vs 59%, P<.01).

The largest prospective randomized, multicenter trial showing the benefit of this approach was the FAME trial. Tonino and colleagues compared a physiologically guided PCI approach (FFR-PCI) with a conventional angiographically guided PCI (Angio-PCI) in patients with multivessel CAD. Twenty centers in Europe and the United States randomly assigned 1005 patients with multivessel CAD undergoing PCI with drug-eluting stents to one of the two strategies. Operators selected all indicated lesions in advance of randomization for stenting by visual angiographic appearance (>50% diameter stenosis). For the FFR-PCI group, all lesions had FFR measurements and were only stented if the FFR was less than 0.80. Of the 1005 patients, 496 were assigned to the Angio-PCI and 509 were assigned to the FFR-PCI. Clinical characteristics and angiographic findings were similar in both groups. The Syntax (Synergy between PCI with Taxus and Cardiac Surgery) scores for gauging risk in multivessel disease involvement were identical at 14.5, indicating low- to intermediate-risk patients.

Despite identifying in advance 3 angiographically indicated lesions per patient for stenting, compared with the Angio-PCI group the FFR-PCI group used fewer stents per patient (1.9 ± 1.3 vs 2.7 ± 1.2, P<.001), less contrast medium (272 mL vs 302 mL, P<.001), had lower procedure cost ($5332 vs $6007, P<.001), and shorter hospital stay (3.4 vs 3.7 days, P = .05). More importantly, at 1 year follow-up the FFR-PCI group had fewer MACE (13.2% vs 18.4%, P = .02), fewer
Fig. 9. (A) Angiographic severity versus functional severity of coronary artery stenoses by stenosis category. (B) Proportions of functionally diseased coronary arteries in patients with angiographic upper 3- or lower 2-vessel disease. (From Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the fame study, fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010;55:2816–21; with permission.)
Fig. 10. (A) Two-year outcome of stenoses in FFR group initially deferred on basis of FFR >0.80. Numbers of late myocardial infarction and repeat revascularization of the stenoses in the FFR group initially deferred from stenting on the basis of FFR >0.80, and in stenoses in the FFR group that were stented because of FFR 0.80. (B) Percentage of patients treated by angiography-guided strategy (red bars) and fractional flow reserve (FFR)-guided strategy (blue bars) who were completely free from angina at baseline, and at 1- and 2-year follow-up. CABG, coronary artery bypass grafting; MACE, major adverse cardiac event. (From Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177–84; with permission.)
Fig. 11. (A) Distribution of baseline angiographic and hemodynamic variables. (B) Proportion of patients achieving post-stent FFR $\geq$ 0.90 according to baseline FFR and stent diameter. (C) Incidence of MACE rates according to SD and baseline FFR. (From Samady H, McDaniel M, Velledar E, et al. Baseline fractional flow reserve and stent diameter predict optimal post-stent fractional flow reserve and major adverse cardiac events after bare-metal stent deployment. J Am Coll Cardiol Interv 2009;2:357–63; with permission.)
combined death or MI (7.3% vs 11%, \(P = .04\)), and a lower total number of MACE including death, MI, and repeat revascularization (coronary artery bypass grafting [CABG] or PCI) (76 vs 113, \(P = .02\)) than the Anglo-PCI group. The 2-year rates of mortality or MI from the FAME study\(^7\) were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group (\(P = .02\)). Rates of PCI or coronary artery bypass surgery were 12.7% and 10.6%, respectively (\(P = .30\)). Combined rates of death, nonfatal MI, and revascularization were 22.4% and 17.9%, respectively (\(P = .08\)) (Fig. 10). For lesions deferred on the basis of FFR greater than 0.80, the rate of MI was 0.2% and the rate of revascularization was 3.2% after 2 years. Routine measurement of FFR in patients with multivessel CAD undergoing PCI with drug-eluting stents significantly reduces mortality and MI at 2 years when compared with standard angiography-guided PCI.

The precise mechanisms of reduced end points in the FFR-guided arm of FAME are not known, but are likely associated with fewer implanted stents having fewer procedure-related early (eg, side branch occlusion, additional troponin release) and late stent complications (eg, subacute thrombosis, restenosis). This study is a substantial clinical validation of the preceding FFR outcome studies in single- and multivessel-disease patients from single centers, and has important implications for managing CAD patients by integrating physiology for best long-term results.

**FFR and outcome of stenting**

Samady and colleagues\(^37\) reported on the use of FFR to predict post-stent MACE after bare metal stent (BMS) in 586 patients from the multicenter post-BMS FFR registry. Multivariable logistic regression models were used to identify clinical, angiographic, and hemodynamic variables associated with post-stent FFR of 0.90 or greater and 6-month MACE. Baseline FFR and stent diameter were predictive of post-stent FFR greater than 0.90. Lower FFR (odds ratio [OR]: 7.8); smaller stent diameter (OR: 3.7 per millimeter); longer stent length (OR: 1.0 per millimeter); and larger minimal luminal diameter (OR: 2.2 per millimeter) were predictors of MACE. In patients receiving 3-mm diameter stents, baseline FFR greater than 0.70 yielded significantly higher likelihood of achieving post-stent FFR greater than 0.90 than baseline FFR 0.70 or less (77% vs 63%, \(P < .05\)); and in patients receiving stents of diameter less than 3 mm, baseline FFR less than 0.50 was associated with higher MACE than FFR 0.50 to 0.70 and FFR greater than 0.70 (40% vs 15% vs 13%, \(P < .05\)) (Fig. 11). These variables may allow selection of patients who will have excellent results with BMS.

**Assessment of Left Main Stenosis**

Correct clinical assessment left main stem CAD lesions is of critical importance to patients facing possible CABG surgery or medical therapy. On the basis of angiographic information alone, this evaluation often cannot be done reliably. FFR can support decision making in equivocal left main disease. In prospective single-center studies, Bech and colleagues\(^9\) and others (Table 2) found that consecutive patients with intermediate left main coronary artery stenosis (42% ± 13% diameter) and FFR greater than 0.80 did as well when treated medically as those patients with FFR of less than 0.75 who underwent CABG. MACE at 14 months follow-up was 13% and 7%, respectively (\(P = .27\)); cardiac death or MI was also similar (6% and 7%, \(P = .70\)).

In a larger multicenter prospective trial, Hamilos and colleagues\(^10\) examined FFR in 213 patients with an angiographically equivocal left main coronary artery stenosis, When FFR was greater than 0.80, patients were treated medically or another stenosis was treated by coronary angioplasty (nonsurgical group; \(n = 138\)). When FFR was less than 0.80, CABG was performed (surgical group; \(n = 75\)). The 5-year survival estimates were 89.8% in the nonsurgical group and 85.4% in the surgical group (\(P = .48\)). The 5-year event-free survival estimates were 74.2% and 82.8% in the nonsurgical and surgical groups, respectively (\(P = .50\)) (Fig. 12). Percent diameter stenosis at quantitative coronary angiography correlated significantly with FFR (\(r = 0.38, P < .001\)), but a very large scatter was observed. In 23% of patients with a diameter stenosis greater than 50%, the left main coronary artery stenosis was hemodynamically significant by FFR. In patients with equivocal stenosis of the left main coronary artery, angiography does not correlate with functional significance. Erroneous individual decision making about the need for revascularization may occur that relies on angiography alone (see Table 2). The role of IVUS should be carefully evaluated because of the unaccounted anatomic factors involved.\(^\text{10}\) The favorable outcomes suggest that FFR should be assessed in equivocal left main patients before finalizing a revascularization decision.

**Ostial Lesion and Side Branch Assessment**

Ostial narrowings of side branches or newly produced narrowing in side branches within stents (called “jailed” branches) are difficult to assess by angiography because of the overlapping
<table>
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<th>Study</th>
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<th>FFR Threshold</th>
<th>N</th>
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<th>MACE</th>
<th>Death</th>
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<td>62</td>
<td>0.75 surg 0.80 med</td>
<td>142</td>
<td>82 (58%)</td>
<td>13%</td>
<td>3 (3.6%)</td>
<td>60 (42%)</td>
<td>7%</td>
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Data from Lokhandwala J, Hodgson JB. Assessing intermediate left main lesions with IVUS or FFR. How intravascular ultrasound and fractional flow reserve can be used in this challenging subset. Cardiac Interventions Today 2009. p. 47–58.
orientation relative to the parent branch, stent struts across the branch, and image foreshortening. Koo and colleagues\textsuperscript{5,38} compared FFR with quantitative coronary angiography in 97 jailed side branch lesions (vessel size >2.0 mm, percent stenosis >50% by visual estimation) after stent implantation. No lesion with less than 75% stenosis had FFR less than 0.75. Among 73 lesions with 75% or more stenosis, only 20 lesions (27%) were functionally significant. Koo and colleagues\textsuperscript{38} also reported the 9-month outcome of FFR-guided side branch PCI strategy for bifurcation lesions. Of 91 patients, side branch intervention was performed in 26 of 28 patients with FFR less than 0.75. In this subgroup FFR increased to greater than 0.75 despite residual stenosis of 69% \pm 10%. At 9 months, functional restenosis was 8% (5/65) with no difference in events compared with 110 side branches treated by angiography alone (4.6\% vs 3.7\%, $P = .7$) (Fig. 13). Measurement of FFR for ostial and side branch assessment identifies the minority of lesions that are functionally significant.

Koo and colleagues\textsuperscript{39} also evaluated the anatomic physiology of the bifurcation lesion to identify the predictors of functionally significant
jailed side branch lesions in 77 patients from 8 centers. Main branch IVUS was performed before and after main branch stenting and FFR was measured in the jailed side branch. The vessel volume index of both the proximal and distal main branch was increased after stent implantation. The plaque volume index decreased in the proximal main branch (9.1 ± 3.0 to 8.4 ± 2.4 mm³/mm, \( P = .001 \)) implicating plaque shift, but not in the distal main branch (5.4 ± 1.8 to 5.3 ± 1.7 mm³/mm, \( P = .227 \)), implicating carina shift to account for the change in vessel size (n = 56). The mean side branch FFR was 0.71 ± 0.20 (n = 68) with 43% of lesions being functionally significant. Pre-intervention percent diameter side branch stenosis and the main branch minimum lumen diameter distal to the side branch ostium were independent predictors of functionally significant side branch jailing. In patients with 75% or more stenosis and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the side branch, no difference in post-stent angiographic and IVUS parameters was found between side branch lesions with and without functional significance. Both plaque shift from the main branch and carina shift contribute to a side branch ostial lesion after main branch stent implantation. Anatomic evaluation does not reliably predict the functional significance of a jailed side branch stenosis.

**Saphenous Vein Graft Assessment**

Considerations regarding use of FFR in assessing lesions in the saphenous vein graft (SVG) involve two questions. First, is there a difference in FFR when assessing a lesion in an SVG, and second, what is the fate of the conduit when placed on a vessel for a lesion which is not physiologically significant?

With regard to assessing a lesion in an SVG, there are 3 sources of coronary blood flow to the distal myocardial region: epicardial, conduit flow, and collateral flow. After CABG surgery, the bypass conduit should act in a similar fashion to the native low resistance epicardial vessel supplying the myocardial bed. The assessment of a stenosis in a CABG conduit
is must include consideration of the competing flow (and pressure) from (1) the native and conduit vessels; (2) the collateral flow induced from long-standing native coronary occlusion; and (3) the potential for microvascular abnormalities caused by ischemic fibrosis and scarring, preexisting or bypass surgery related MI, or chronic low flow ischemia. In the most uncomplicated situation of an occluded native vessel with minimal distal collateral supply, the theory of FFR should apply just as much to a lesion in an SVG to the right coronary artery feeding a normal myocardial bed as a lesion in the native right coronary. For more complex situations, the FFR of less than 0.08 will reflect the summed responses of the 3 supply sources and yield a net FFR indicating potential ischemia in that region, and vice versa.

With regard to the fate of SVG conduits implanted distal to hemodynamically insignificant lesions, bypass surgeons and cardiologists have recognized that late patency is reduced and native CAD in that vessel can be accelerated. Although most surgical consultations recommend bypassing all lesions with greater than 50% diameter narrowing in patients with multivessel disease, the patency rate of saphenous vein grafts on vessels with hemodynamically nonsignificant lesions has rarely been questioned. Botman and colleagues found that there was a 20% to 25% incidence of graft closure in 450 coronary artery bypass grafts when placed on nonhemodynamically significantly stenosed arteries (preoperative FFR >0.80) at 1-year follow-up (Fig. 14). While the precise mechanisms of graft closure remain under study, it is postulated that coronary blood flow favors the lower resistance path through the native (relatively) nonobstructed arteries rather than vein grafts, with slower or competitive graph flow promoting premature graft closure. In patients requiring CABG for multivessel revascularization, angiographic lesions of uncertain significance would benefit by FFR, providing prognostic information regarding potential of future bypass graft patency. FFR has serious implications for the best long-term CABG outcomes.

Acute Coronary Syndrome

The pathophysiology of the infarct-related artery and bed after MI is complex. Because of the dynamic nature of patients with acute coronary syndrome (ACS), particularly MI, the predictive ability of FFR has some theoretical limitations. In ACS the microvascular bed in the infarct zone may not have uniform, constant, or minimal resistance. The stenosis may also evolve as thrombus and vasoconstriction may abate. FFR measurements are not meaningful when angiographic reperfusion (ie, TIMI 3 flow) not been achieved in the artery. FFR has limited use in the infarct-related artery in the first 24 to 48 hours. However, FFR is has value in lesion assessment in the recovery phase of MI and in the assessment of lesions in the remote noninfarct-related vessels.

To address the utility of measurements days after MI, DeBruyne and colleagues compared SPECT MPI and FFR obtained before and after PCI in 57 MI patients more than 6 days (mean 20 days) prior to evaluation. Patients with positive SPECT before PCI had a significantly lower FFR than patients with negative SPECT (0.52 ± 0.18

![Fig. 14.](image-url)
0.67 ± 0.16; \( P = .0079 \)), but a significantly higher left ventricular ejection fraction (63% ± 10% vs 52% ± 10%; \( P = .0009 \)) despite a similar percent diameter stenosis (67% ± 13% vs 68% ± 16%; \( P \) not significant). The sensitivity and specificity of FFR of less than 0.75 to detect a defect on SPECT were 82% and 87%, respectively. When only truly positive and negative SPECT imaging was considered, the corresponding values were 87% and 100% (\( P < .001 \)). The best FFR cut-off for determining peri-infarct ischemia was 0.78. Of note, a significant inverse correlation was found between left ventricular ejection fraction and FFR (\( r = 0.29, P = .049 \)), suggesting a relationship between FFR and the mass of viable myocardium. In a similar study, McClish and colleagues found that FFR values were the same in 43 vessels subtending recent infarct beds 4 days after MI compared with 25 control vessels, matched by lesion length and minimal luminal diameter, in patients without infarcts (0.67 ± 17 vs 0.68 ± 17, \( P \) not significant). Samady and colleagues compared FFR with SPECT and myocardial contrast echo (MCE) in 48 patients 3.7 ± 1.3 days after infarction. To identify true reversibility, follow-up SPECT was performed 11 weeks after PCI. The sensitivity, specificity, and concordance of FFR of 0.75 or less for detecting true reversibility on SPECT were 88%, 93%, and 91% (chi-square \( P < .001 \)), and for detecting reversibility on MCE were 90%, 100%, and 93% (chi-square \( P < .001 \)), respectively (Fig. 15). The optimal FFR value for discriminating inducible ischemia on noninvasive imaging was also 0.78, similar to DeBruyne and colleagues.

To predict left ventricular function recovery after ST-segment elevation myocardial infarction (STEMI), Fearon and colleagues found that patients with preserved IMR after primary angioplasty may have greater recovery of regional ventricular function after primary angioplasty for

Fig. 15. (A) Concordance between FFR and SPECT (DP-stress paired with rest imaging). (B) Concordance between FFR and MCE. (C) Sensitivity and specificity curves of fractional flow reserve for detecting reversibility of combined noninvasive testing in ACS patients. (C, From Samady H, Lepper W, Powers ER, et al. Fractional flow reserve of infarct-related arteries identifies reversible defects on noninvasive myocardial perfusion imaging early after myocardial infarction. J Am Coll Cardiol 2006;47:2187–93; with permission.)
STEMI. In addition to providing prognostic information in this important patient subset, IMR may potentially be used in selecting patients with relatively preserved postinfarct microvasculature that might most benefit from regional delivery of regenerative cell therapies.

For patients with non-STEMI, Leesar and colleagues\textsuperscript{45} randomized 70 patients with recent unstable angina or non-STEMI with intermediate single-vessel stenosis to one of two strategies: angiography followed by SPECT the next day or FFR-guided revascularization at the time of angiography. Compared with the SPECT strategy, the FFR-guided approach had a reduced hospital duration (11 ± 2 hours vs 49 ± 5 hours, \( P < .001 \)) and cost ($1329 ± $44 vs $2113 ± $120, \( P < .05 \)), with no increase in procedure time, radiation exposure time, or clinical event rates at 1-year follow-up. Similarly, Potvin and colleagues\textsuperscript{46} evaluated 201 consecutive patients (62\% with unstable angina or MI), in whom revascularization was guided by FFR. At 11 ± 6 months of follow-up, cardiac events occurred in 20 patients (10\%), and no significant differences were observed between patients with unstable angina or MI and those with stable angina (9\% vs 13\%, \( P = .44 \)). Finally, Fischer and colleagues\textsuperscript{47} found similar MACE rates at 12 months in patients with \((n = 35)\) and without \((n = 85)\) ACS in whom revascularization was guided by FFR (15\% vs 9\%, \( P \) not significant).

### Serial (Multiple) Lesions in a Single Vessel

When more than one discrete stenosis is present in the same vessel, the hyperemic flow and pressure gradient through the first one will be attenuated by the presence of the second one, and

\[
\text{FFR(A)}_{\text{pred}} = \frac{P_d - [(P_m/P_a) \times P_w]}{(P_a - P_m) + (P_d - P_w)}
\]

*Note:* Max Flow (a) changes after resistance (b) is reduced.

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**Fig. 16.** (A) Illustration of serial lesions in epicardial vessel. Note: Max Flow (a) changes after resistance (b) is reduced. (B) Calculation of FFR predicted for serial lesion individually. (C) Comparison of predicted and measured FFR in serial lesions. (C, From Pijls NH, De Bruyne B, Bech GJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. Circulation 2000;102:2371–77; with permission.)
Fig. 17. (A) Example of pull-back pressure recording in a patient with serial lesions. Multiple LAD lesions were seen on angiography in a patient with positive stress test for anterior ischemia. Upper and lower left panels are cine angiographic frames showing the 4 lesions. (Lower right) the translesional pressure ratio (Pd/Pa) at rest across all lesions was 0.86 but FFR, which summed the 4 lesions, was 0.73.
Fig. 17. (B) (Upper panels) Cine frames of wire positions before and after pull-back of pressure wire. Pressure pull-back shown in lower panel identified step-up of gradient at lesion 3 only. (C) Cine frame of LAD after stenting of lesion 3 with a final FFR across all lesions of 0.88.
vice versa (Fig. 16). One stenosis will mask the true effect on its serial counterpart by limiting the achievable maximum hyperemia. This fluid dynamic interaction between two serial stenoses depends on the sequence, severity, and distance between the lesions as well as the flow rate. When the distance between two lesions is greater than 6 times the vessel diameter, the stenoses generally behave independently and the overall pressure gradient is the sum of the individual pressure losses at any given flow rate.48

When addressing two stenoses in series, equations have been derived to predict the FFR (FFRpred) of each stenosis separately (ie, as if the other one were removed) using arterial pressure (P_a), pressure between the two stenoses (P_m), distal coronary pressure (P_d), and coronary occlusive pressure (P_w). FFRapp (ratio of the pressure just distal to that just proximal to each stenosis) and FFRtrue (ratio of the pressures distal and proximal to each stenosis but after removal of the other one) have been compared in instrumented dogs48 and in patients.49 FFRtrue was more overestimated by FFRapp than by FFRpred. It was clearly demonstrated that the interaction between two stenoses is such that the FFR of each lesion separately cannot be calculated by the equation for isolated stenoses applied to each separately, but can be predicted by more complete equations taking into account P_a, P_m, P_d, and P_w.

Although calculation of the exact FFR of each lesion separately is possible, it remains academic. In clinical practice, the use of the pressure pull-back recording is particularly well suited to identify the several regions of a vessel with large pressure gradients that may benefit by treatment. The one stenosis with the largest gradient can be treated first, and the FFR can be remeasured for the remaining stenoses to determine the need for further treatment (Fig. 17).

**Diffuse Coronary Disease**

A diffusely diseased atherosclerotic coronary artery can be viewed as a series of branching units diverting and gradually distributing flow along the longitudinally narrowing conduit length. The perfusion pressure gradually diminishes along the artery. In this artery, CFR is reduced but is unassociated with a focal stenotic pressure loss. Thus mechanical therapy directed at a presumed “culprit” plaque to reverse such abnormal physiology would be ineffective in restoring normal coronary perfusion. Using FFRmyo during continuous pressure wire pull-back from a distal to proximal location, the impact of a specific area of angiographic narrowing can be examined and the presence of diffuse atherosclerosis can be documented.50 Diffuse atherosclerosis, rather than a focal narrowing, is characterized by a continuous and gradual pressure recovery without localized abrupt increase in pressure related to an isolated region. De Bruyne and colleagues51 have demonstrated the influence of diffuse atherosclerosis that often remains invisible at angiography. FFRmyo measurements were obtained from 37 arteries in 10 individuals without atherosclerosis (group I) and from 106 nonstenotic arteries in 62 patients with angiographic stenoses in another coronary artery (group II). In group I, the pressure gradient between aorta and distal coronary artery was minimal at rest (1 ± 1 mm Hg) and during maximal hyperemia (3 ± 3 mm Hg). Corresponding values were significantly larger in group II (5 ± 4 mm Hg and 10 ± 8 mm Hg, respectively; both P<.001). The FFRmyo was near unity (0.97 ± 0.02; range, 0.92–1) in group I, indicating no resistance to flow in truly normal coronary arteries, but it was significantly lower (0.89 ± 0.08; range, 0.69–1) in group II, indicating a higher resistance to flow (Fig 18). This resistance to flow contributes to myocardial ischemia and has consequences for decision making during PCI.

![Fig. 18](Graphs of individual values of FFR in normal arteries and in atherosclerotic coronary arteries without focal stenosis on arteriogram. The upper dashed line indicates the lowest value of FFR in normal coronary arteries. The lower dashed line indicates the 0.75 threshold level. (Reproduced from De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but “normal” coronary angiography. Circulation 2001;104:2401–6; with permission.)
The pressure pull-back recording at maximum hyperemia will provide the necessary information to decide if and where stent implantation may be useful (see Fig. 17). The location of a focal pressure drop superimposed on the diffuse disease can be identified as an appropriate location for treatment.

**FFR AND THE COLLATERAL CIRCULATION**

The collateral circulation can be described by intracoronary pressure and flow relationships. Ipsilateral collateral flow and contralateral arterial responses have been described in numerous studies using both pressure and flow to provide new information regarding mechanisms, function, and clinical significance of collateral flow in patients. To improve the conventional angiographic assessment of collateral supply, FFR of the collateral flow employs the use of coronary occlusion wedge pressure. FFR collateral greater than 0.25–0.30 is associated with good collateralization and often nonischemic evaluations of provocative outpatient ischemia.

**SUMMARY**

FFR is considered as one of the standards for functional assessment of CAD, acting as a single-vessel stress test within the cardiac cath lab environment.

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**Box 3**

**Current role of physiologic measurements in the cath lab**

**PCI Guideline Recommended Uses**

1. Assessment of the effects of intermediate coronary stenoses (30%–70% luminal narrowing) in patients with anginal symptoms. Coronary pressure or Doppler velocimetry may also be useful as an alternative to performing noninvasive functional testing (eg, when the functional study is absent or ambiguous) to determine whether an intervention is warranted (Class IIa, *Level of Evidence: B*).
2. Assessing the success of PCI in restoring flow reserve and to predict the risk of restenosis (Class IIb, *Level of Evidence: C*).
3. Evaluating patients with anginal symptoms without an apparent angiographic culprit lesion (Class IIb, *Level of Evidence: C*).
4. Routine assessment of the severity of angiographic disease in patients with a positive, unequivocal noninvasive functional study is not recommended (Class III, *Level of Evidence: C*).

**Applications of FFR Under Study**:  
1. Determination of one or more culprit stenoses (either serially or in separate vessels) in patients with multivessel disease.
2. Evaluation of ostial or distal left main and ostial right lesions, especially when these regions cannot be well visualized by angiography.
4. Determination of significance of focal treatable region in vessel with diffuse CAD.
5. Determination of prognosis after stent deployment.
6. Assessment of stenosis in patients with previous (nonacute, >6 days) MI.
8. Assessment of the collateral circulation.

**Applications of Coronary Doppler Flow Under Study**

1. Assessment of microcirculation.
2. Endothelial function testing.
3. Myocardial viability in acute MI.

**Applications of Combined Coronary Pressure and Doppler Flow Velocity Under Study**

1. Assessment of intermediate stenosis.
2. Assessment of the microcirculation.
3. Identification of lesion compliance (change of pressure-velocity relationship).

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Although the cost of the physiologic information translates into an operational expense for the catheterization laboratory, the data identify significant overall savings to the health care system and a substantial clinical benefit to the patient.

FFR use in the cath lab has steadily grown over the past decade and, given the strong case for favorable outcomes in a variety of common and complex anatomic subset, FFR has evident clinical value for decision making in the laboratory. Box 3 lists the current role of physiology for decision making in the laboratory. FFR technology has overcome the hurdles of cumbersome setup time and concerns regarding accurate hemodynamics. Physiologic data acquired during the angiographic procedure can facilitate timely, as well as clinically and economically sound decision making to direct revascularization options for best patient outcomes.

REFERENCES


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