Functional Measurement of Coronary Stenosis
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Coronary angiography still plays a pivotal role in invasive imaging of the coronary arteries. Despite rapid developments in noninvasive imaging, the temporal and spatial resolution of coronary angiography is unsurpassed and will remain the road map for cardiologic interventionalists and cardiac surgeons for performing revascularization. Nevertheless, it has been recognized for many years that coronary angiography is of limited value in defining the functional significance of a coronary artery stenosis. In this respect, functionally significant means hemodynamically significant or associated with inducible ischemia in case of stress.

It is important to emphasize that in coronary artery disease, the most important factor related to outcome is the presence and extent of inducible ischemia (1,2). A functionally significant stenosis generally causes anginal symptoms and is associated with impaired outcome. Therefore, functionally significant stenoses should be revascularized, if technically possible (3–5). On the other hand, if a stenosis has no functional significance, it will not cause angina by definition, and the outcome of medical treatment is excellent with an infarction and a mortality rate of <1% per year (5,6). Therefore, for decision making in the interventional catheterization laboratory with respect to revascularization, it is of paramount importance to determine whether a stenosis is inducing reversible ischemia—in other words, to assess whether a stenosis is functionally significant.

Although in many patients with single-vessel disease, noninvasive testing is a suitable methodology to determine the potentially ischemic nature of a stenosis, in multivessel disease, it is often very difficult to judge which of several lesions are functionally significant (associated with reversible ischemia) and should be stented, and, vice versa, which stenoses could better be left alone and treated medically (6,7). Both exercise testing, technetium-99m sestamibi single-photon emission computed tomography, and other classic noninvasive tests often indicate ischemia in patients with multivessel disease but fail to distinguish the specific ischemic territories and responsible stenoses. In addition, findings on technetium-99m sestamibi single-photon emission computed tomography may even be normal in multivessel disease because of balanced ischemia.

Fractional flow reserve (FFR) is an accurate and lesion-specific index to indicate whether a particular stenosis or coronary segment can be held responsible for ischemia (8,9). It has been shown that deferring stenting in a FFR-negative stenosis (i.e., in the nonischemic zone) is safe and associated with excellent long-term outcome. It has also been shown that revascularization of a FFR-positive stenosis (i.e., in the ischemic zone) is associated with significant decrease in ischemia and an improved outcome (3,6,8).

For those reasons, it is helpful in decision making in the interventional laboratory to measure FFR for guidance of coronary interventions, especially if it is unclear whether a stenosis causes ischemia. In this state-of-the-art paper, FFR and its practical application in the catheterization laboratory for functional measurement of coronary artery stenosis are discussed.

**Definition of FFR**

FFR is defined as the ratio of maximum blood flow in a stenotic artery to maximum blood flow if the same artery...
Concept of Fractional Flow Reserve Measurements

The possibility of distinguishing coronary and collateral blood flow contributions to myocardial blood flow, we refer to the literature (8–10).

**Practical Aspects of FFR Measurements**

**Catheters.** Generally, guiding catheters are used when measuring FFR. The use of diagnostic catheters is technically feasible. However, due to higher levels of friction hampering wire manipulation, the smaller internal caliber interfering with pressure measurements, and the inability to perform an ad hoc percutaneous coronary intervention (PCI) by using diagnostic catheters, the use of guiding catheters is recommended.

**Wires.** Measuring intracoronary pressure requires the use of a specific solid-state sensor mounted on a floppy-tipped guidewire. Two such systems exist: the PressureWire (St. Jude Medical Inc., Minneapolis, Minnesota and Uppsala, Sweden) and the PrimeWire (Volcano Inc., Rancho Cordova, California). In both wires, the sensor is located at the junction between the 3-cm-long radiopaque tip and the remainder of the wire. The last generations of these 0.014-inch wires have excellent handling characteristics, although slightly inferior to most standard angioplasty guidewires. Before introducing the sensor into the vessel to be studied, the pressures recorded by the sensor and by the guiding catheter should be equalized.

The pressure wire has to be connected to an interface (Analyzer Express, St. Jude Medical Inc., Uppsala, Sweden or Combomap, Volcano Inc.), which offers the possibility of recording the registrations and showing FFR immediately.

Recent developments in hardware and software have further facilitated the use of pressure wires and integration in the regular catheterization laboratory setup (wireless...
Aeris wire, St. Jude Medical Inc. and Integrated 5S Cath Lab System, Volcano Inc.).

**Anticoagulation.** As soon as any device is advanced into the coronary tree, the use of the same anticoagulation regimens as routinely used during a PCI is recommended: heparin adjusted to weight, validated by a monitored activated coagulation time of at least 250 s, or a fixed number of units per time and/or body weight, in accordance with the local routine.

**Hyperemic stimuli.** FFR, by definition, represents an index of maximum blood flow. Therefore, it is essential to induce maximal vasodilation of the 2 compartments of the coronary circulation (epicardial or “conductance” arteries and the microvasculature or “resistance” arteries). The pharmacologic options for inducing hyperemia are summarized in Table 1 (10,11).

A 200-μg bolus of isosorbide dinitrate (or any other form of intracoronary nitrate) allows the abolition of any form of epicardial vasoconstriction and should be administered as usual before any manipulation in the coronary artery.

Microvascular vasodilation is equally paramount for the calculation of FFR. Gauging pressure differences at rest does not offer a definitive measure: It cannot be emphasized strongly enough that there is no such thing as a baseline FFR. As a matter of fact, if the \( P_d/P_a \) ratio at baseline is in the ischemic zone, it may only further decrease at hyperemia and the decision to revascularize can already be made. Even when the resting pressure gradient is large, inducing hyperemia is recommended because it allows the evaluation of the residual resistance reserve and ability to quantify the improvement after treatment. An example of a typical coronary pressure tracing during the administration of intravenous adenosine is shown in Figure 2.

### Special Features of FFR

FFR has a number of unique characteristics that make this index particularly suitable for functional assessment of coronary stenoses and clinical decision making in the catheterization laboratory.

**FFR HAS A THEORETICAL NORMAL VALUE OF 1 FOR EVERY PATIENT, ARTERY, AND MYOCARDIAL BED.** An unequivocally normal value is easy to refer to but is generally rare in clinical medicine. So, this is a unique advantage of FFR. Because in a normal epicardial coronary artery there is virtually no decrease in pressure, not even during maximal

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**Table 1**

<table>
<thead>
<tr>
<th>Hyperemic Stimuli for State-of-the-Art FFR Measurement</th>
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<tr>
<td><strong>Epicardial vasodilation</strong></td>
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<td>Isosorbide dinitrate</td>
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<tr>
<td><strong>Microvascular vasodilation</strong></td>
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<tr>
<td>Adenosine or ATP ic</td>
</tr>
<tr>
<td>Papaverine ic</td>
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<tr>
<td>Adenosine or ATP iv</td>
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ATP = adenosine triphosphate; FFR = fractional flow reserve; ic = intracoronary; iv = intravenously; LCA = left coronary artery; RCA = right coronary artery.

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**Figure 2**

Maximum Hyperemia Induced by Intravenous Adenosine

Typical example of simultaneous aortic pressure \( P_a \) and distal coronary pressure \( P_d \) recordings at rest and during maximal steady-state hyperemia as induced by an intravenous (i.v.) infusion of adenosine. Fractional flow reserve (FFR) is simply calculated as the ratio of \( P_d \) and \( P_a \) during steady-state maximum hyperemia.
hyperemia (12), it is obvious that $P_e/P_a$ will equal or be very close to unity. This means that normal epicardial arteries do not contribute to the total resistance to coronary blood flow. The lowest value found in individuals with strictly normal coronary arteries ($n = 65$) was 0.94 (12,13). Yet it is important to realize that in normal-looking coronary arteries in patients with proven atherosclerosis elsewhere, the epicardial coronary arteries may contribute to total resistance to coronary blood flow even though there is no discrete stenosis visible on the angiogram. In $\sim 50\%$ of these arteries, FFR is lower than the lowest value found in normal individuals. In approximately $10\%$ of atherosclerotic arteries, FFR will even be lower than the ischemic threshold (12). Practically speaking, this finding implies that myocardial ischemia might be present in atherosclerotic patients in the absence of discrete stenoses.

**FFR Has a Well-Defined Cutoff Value with a Narrow Gray Zone Between 0.75 and 0.80.** Cutoff or threshold values are values that distinguish ischemic from nonischemic levels for a given measurement. To enable adequate clinical decision making in individual patients, it is essential that any level of uncertainty be reduced to a minimum. Stenoses with FFR $<0.75$ are almost invariably able to induce myocardial ischemia, whereas stenoses with FFR $>0.80$ are almost never associated with exercise-induced ischemia. This means that the gray zone for FFR (between 0.75 and 0.80) spans $<10\%$ of the entire range of FFR values.

FFR in fact is the only index of ischemia that has been validated compared with a true gold standard in a so-called prospective multitesting Bayesian approach (14). During the past years, many studies have been performed examining the gray zone, and in all these studies, invariably a best cutoff value between 0.75 and 0.80 was found in many subsets of patients including left main coronary artery disease, diabetes, multivessel disease, and previous infarction.

Therefore, the practical lesson is that in a stenosis with FFR $\leq 0.75$, stenting is always justified (if technically feasible), whereas in a stenosis with FFR $>0.80$, stenting can be safely deferred and optimal medical treatment is sufficient. Between 0.76 and 0.80, sound clinical judgment (taking into account the character of symptoms, results of noninvasive tests if available, and whether a gradient is focal or diffuse) should balance the final decision.

**FFR Is Not Influenced by Systemic Hemodynamics.** In the catheterization laboratory, systemic pressure, heart rate, and left ventricular contractility are prone to change. In contrast to many other indices measured in the catheterization laboratory, changes in systemic hemodynamics do not influence the value of FFR in a given coronary stenosis (15). In addition, FFR measurements are extremely reproducible (16). This is due not only to the fact that aortic and distal coronary pressures are measured simultaneously, but also to the capability of the microvasculature to repeatedly vasodilate to exactly the same extent. These characteristics contribute to the accuracy of the method and to the trust in its value for clinical decision making.

**FFR Takes into Account the Contribution of Collaterals.** Whether myocardial flow is provided antegrade by the epicardial artery or retrogradely through collaterals does not really matter for the myocardium. Distal coronary pressure during maximal hyperemia reflects both antegrade and retrograde flows according to their respective contribution (6,13). This holds true for the stenoses supplied by collaterals but also for stenosed arteries providing collaterals to another more critically diseased vessel.

**FFR Specifically Relates the Severity of the Stenosis to the Mass of Tissue to Be Perfused: Normalization for Perfusion Area.** The larger the myocardial mass subtended by a vessel is, the larger the hyperemic flow, and in turn, the larger the gradient and the lower the FFR for a given stenosis. This explains why a stenosis with a minimal cross-sectional area of 4 mm² has totally different hemodynamic significance in the proximal left anterior descending artery (LAD) versus the second marginal branch, as recently demonstrated by Iqbal et al. (17). It also means that the hemodynamic significance of a particular stenosis may change if the perfusion territory changes (as is the case after myocardial infarction [MI]). These changes are accounted for by FFR.

**FFR Has Unequaled Spatial Resolution.** The exact position of the sensor in the coronary tree can be monitored under fluoroscopy and documented angiographically. Pulling back the sensor under maximal hyperemia provides the operator an instantaneous assessment of the abnormal resistance of the arterial segment located between the guide catheter and the sensor. Although other functional tests reach a per-patient accuracy (exercise electrocardiography) or, at best, a per-vessel accuracy (myocardial perfusion imaging or stress echocardiography/magnetic resonance imaging), FFR reaches a per-segment accuracy with a spatial resolution of a few millimeters.

**FFR in Different Patient Subsets**

**FFR in angiographically intermediate stenoses.** One of the standard indications for FFR is the precise assessment of the functional consequences of a given coronary stenosis with unclear hemodynamic significance (14). In a study of 45 patients with angiographically dubious stenoses, it was shown that FFR has a much greater accuracy in distinguishing hemodynamically significant stenoses than exercise electrocardiography, myocardial perfusion scintigraphy, and stress echocardiography performed separately. This was shown using a so-called sequential Bayesian approach, proving that FFR can indeed be considered as a true gold standard (14).

Furthermore, results of different noninvasive tests are often contradictory, which renders appropriate clinical decision making difficult. In addition, the clinical outcome of patients in whom PCI is deferred because FFR indicated no
hemodynamically significant stenosis is very favorable. In such population, the risk of cardiac death or MI is approximately 1% per year, and this risk is not decreased by PCI (6). These results strongly support the use of FFR measurements as a guide for decision making about the need for revascularization in intermediate lesions. Figure 3 illustrates how 2 angiographically similar stenoses may have a completely different hemodynamic severity. One of them should be revascularized, and the other should not. Based solely on the angiogram, the decision should be identical in both cases, which would lead to an inappropriate interventional decision in 1 of these patients.

**FFR in left main coronary artery stenosis.** The presence of a significant stenosis in the left main stem is of critical prognostic importance (18). Conversely, revascularization of a nonsignificant stenosis in the left main may lead to early occlusion of the conduits, especially when internal mammary arteries are used (19). Furthermore, the left main is among the most difficult segments to assess by angiography (20). Noninvasive testing is often noncontributive in patients with a left main stenosis. Perfusion defects are often seen in only 1 vascular territory, especially when the right coronary artery is significantly diseased (21). In addition, tracer uptake may be reduced in all vascular territories (balanced ischemia), giving rise to studies with false-negative results (22). Several studies have shown that FFR could be used safely in left main stenosis and that the decision not to operate on left main stenosis with FFR >0.80 is safe (23,24). In addition, angiographic assessments of left main lesions with FFR <0.80 were no different from those with FFR >0.80, further reinforcing the importance of physiologic parameters in case of doubt. Therefore, patients with an intermediate left main stenosis deserve physiologic assessment before blindly making a decision about the need for revascularization. Two examples shown in Figure 4 illustrate how FFR measurements in the left main did drastically influence the type of treatment in these patients.

Left main disease is rarely isolated. When tight stenoses are present in the LAD or in the LCx the presence of these lesions will tend to increase the FFR measured across the left main. The influence of a LAD/left circumflex coronary...
artery (LCx) lesion on the FFR value of the left main will depend on the severity of this distal stenosis but, even more, on the vascular territory supplied by this distal stenosis. For example, if the distal stenosis is in the proximal LAD, its presence will markedly affect the stenosis in the left main. If the distal stenosis is located in a small second marginal branch, its influence on the left main stenosis will be minimal. Nevertheless, even in the presence of other stenoses in addition to left main coronary artery stenosis, the distal FFR value indicates to what degree maximum perfusion of the different left coronary artery territories is decreased. In a recent prospective study by Hamilos et al. (24), an excellent outcome of FFR-guided revascularization was found in 213 consecutive patients with equivocal left main coronary artery disease, whether or not in conjunction with LAD or LCx stenosis.

**Figure 4** Example of 2 Patients in Whom FFR Measurements in an Intermediate Ostial Left Main Stenosis Changed the Therapeutic Strategy

The first (upper panel) represents a 67-year-old man with massive mitral regurgitation who was assessed for minimally invasive (port access) mitral valvuloplasty. The coronary angiogram showed an intermediate ostial left main stenosis. The fractional flow reserve (FFR) of the left main stenosis was 0.69. Accordingly, this patient underwent conventional coronary artery bypass graft surgery and mitral valvuloplasty via a median sternotomy. The second (lower panel) represents an 89-year-old man with critical aortic stenosis referred for aortic valve replacement and bypass surgery because of the presence of an ostial left main stenosis. FFR of the left main stem was 0.83. According, only a percutaneous aortic valve implantation was performed. Abbreviations as in Figure 1.

FFR in multivessel disease. Patients with multivessel disease actually represent a very heterogeneous population. Their anatomic features (number of lesions, location, and respective degree of complexity) may vary tremendously and have major implications for the revascularization strategy. Moreover, there is often a large discrepancy between the anatomic description and the actual physiologic severity of each stenosis. For example, a patient may have 3-vessel disease based on the angiogram, but actually have only 2 hemodynamically significant stenoses. Conversely, a patient can angiographically be considered as having 1-vessel disease of the right coronary artery but actually have a hemodynamically significant stenosis of the left main. Figure 5 shows a typical example of a patient in whom the right coronary artery and the LCx are critically narrowed and in whom the mid LAD shows a mild stenosis. Myocardial perfusion imaging showed a reversible perfusion defect in the inferolateral segments and a normal flow distribution in the segments supplied by the LAD. In contrast, FFR shows that all 3 vessels are significantly narrowed but to a different
extent. By nuclear scintigraphy, the significant defect in the anterior wall is masked by the more severe defects in the other areas. This has a major implication with regard to revascularization. FFR-guided revascularization strategies in patients with multivessel disease were very encouraging (25–27). Tailoring the revascularization according to the functional significance of the stenoses rather than to their mere angiographic appearance decreased costs and avoided the need for surgical revascularization (25). Recently, incontrovertible proof of the benefit of FFR-guided multivessel PCI compared with standard angiography was provided in the randomized, multicenter FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study (5,28). In that study, it was demonstrated that all types of adverse events were decreased by 30% in the first year after PCI in multivessel disease, when guided by FFR. This was achieved at a lower cost and without prolonging the interventional procedure, whereas angina in FFR-guided patients was relieved at least as effectively (5,29), as is outlined in further detail in the following. After 2 years, the advantage of FFR guidance of PCI in multivessel disease even increased with respect to lower mortality and MI rates, whereas some catching up occurred with respect to repeat revascularization. Importantly, in this study, the progression of deferred lesions was excellent. Only 1 late MI occurred on a previously deferred lesion (0.2%) and 16 late PCIs were performed (3.2%) (5).

**Figure 5**  A 69-Year-Old Man With Severe Angina

Myocardial perfusion imaging showed a reversible defect in the inferolateral segments. From the angiogram, it is obvious that the right coronary artery (RCA) and the left circumflex artery (LCx) are significantly narrowed (no pressure measurements are needed). However, the mid left descending artery (LAD) stenosis, considered nonsignificant on the angiogram, appears to be hemodynamically significant. This LAD stenosis was undetected by myocardial perfusion imaging because the uptake of tracer is markedly worse in the LCx territory than in the LAD territory. Abbreviations as in Figure 2.
FFR after MI. After a MI, previously viable tissue is partially replaced by scar tissue. Therefore, the total mass of viable myocardium supplied by a given stenosis in an infarct-related artery will tend to decrease (30). By definition, hyperemic flow and thus hyperemic gradient will both decrease as well. Assuming that the morphology of the stenosis remains identical, FFR must therefore increase. This does not mean that FFR underestimates lesion severity after MI. It simply illustrates the relationship that exists among flow, pressure gradient, and myocardial mass and conversely illustrates that the mere morphology of a stenotic segment does not necessarily reflect its functional importance. This principle is illustrated in Figure 6. Recent data confirm that the hyperemic myocardial resistance in viable myocardium within the infarcted area remains normal (31). This further supports the application of the established FFR cutoff value in the setting of partially infarcted territories. In the acute phase of MI, FFR is neither reliable nor useful to assess the culprit lesions, and the electrocardiography trumps any other investigation. From 5 days after the infarction, FFR can be used as usual to indicate residual ischemia of the infarct-related or remote arteries. Earlier data had suggested that microvascular function would be abnormal in regions remote from a recent MI (32,33). However, more recent work taking into account distal coronary pressure indicates that hyperemic resistance is normal in those remote segments (34). These data support the use of FFR to evaluate stenoses remote from a recent MI.

FFR in diffuse disease. Histopathology studies and, more recently, intravascular ultrasound and optical coherence tomography have shown that atherosclerosis is diffuse in nature. The presence of diffuse disease is often associated with a progressive decrease in coronary pressure and flow, and this can often not be clearly assessed from the angiogram (12,35). In contrast, this decrease in pressure correlates with the total atherosclerotic burden (35). In approximately 10% of patients, this abnormal epicardial resistance may be responsible for reversible myocardial ischemia. In these patients, chest pain is often considered noncoronary because no single focal stenosis is found, and the myocardial perfusion imaging is wrongly considered false positive (36,37). Such diffuse disease and its hemodynamic impact should always be kept in mind when performing functional measurements. In a large multicenter registry of 750 patients, FFR was obtained after technically successful stenting. A post-PCI FFR value of <0.9 was still present in almost one third of patients (despite the absence of a gradient across the stent), reflecting diffuse disease, and was associated with a poor clinical outcome (38). The only way to demonstrate the hemodynamic impact of diffuse disease is to perform a careful pull-back maneuver of the pressure sensor under steady-state maximal hyperemia (Fig. 7).

FFR in sequential stenoses. When several stenoses are present in the same artery, the concept and the clinical value of FFR are still valid to assess the effect of all stenoses together. However, it is important to realize in such cases that each of several stenoses will influence hyperemic blood flow and therefore FFR across the other one. The influence of the distal lesion on the proximal is more important than the reverse. Theoretically, the FFR can be calculated for each stenosis individually (39). However, this is neither practical nor easy to perform and therefore of little use in the catheterization laboratory. Practically, as for diffuse disease, a pull-back maneuver under maximal hyperemia is the best way to appreciate the exact location and physiologic significance of sequential stenoses and to guide the interventional procedure step-by-step (Fig. 7). After the most severe stenosis (i.e., the stenosis with the largest gradient) has been stented, the pull-back recording can be repeated, and it can be decided whether and where a second stent should be placed.

FFR in bifurcation lesions. Overlapping of vessel segments and radiographic artifacts render bifurcation stenoses particularly difficult to evaluate on angiography, whereas PCI of bifurcations is often more challenging than for regular stenoses. The principle of FFR-guided PCI applies in bifurcation lesions even though clinical outcome data are currently limited. Two recent studies by Koo et al. (40,41) used FFR in the setting of bifurcation stenting. The results of these studies can be summarized as follows: 1) after stenting the main branch, the ostium of the side branch often looks pinched. Yet such stenoses are grossly overestimated by angiography: few of these ostial lesions with a stenosis diameter <75% were found to have FFR <0.75; and 2) when kissing balloon dilation was performed only in ostial stenoses with FFR <0.75, the FFR at 6 months was >0.75 in 95% of cases. These studies favor an approach in bifurcation lesions of stenting the main branch and kissing balloon dilation thereafter only if FFR of the side branch is <0.75. If FFR of the side branch is >0.75, the outcome is excellent without further intervention.
Optimizing Treatment in Multivessel Coronary Disease and Consequences of the FAME Study

In the past years, 3 large studies were conducted to examine the best possible treatment of patients with multivessel coronary artery disease. In these studies, the respective value of optimal medical treatment only, PCI in addition to medical treatment, and coronary bypass surgery were investigated (5,28,42,43).

These studies were the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study, SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) study, and FAME study (5,28,42,43). In the COURAGE study, optimal medical treatment only and PCI in addition to medical treatment were investigated in patients with multivessel disease and moderately severe coronary disease. In most patients, bare metal stents were used. In the SYNTAX–3-Vessel Disease (3VD) study, only patients with 3-vessel disease were included, and only drug-eluting stents were used. The degree of disease was more severe than that in the COURAGE trial, and in these patients, standard angiography-guided PCI with drug-eluting stents only was compared with bypass surgery. In the FAME study, also in patients with mainly 3-vessel disease but excluding left main stenosis, standard angiography-guided PCI with drug-eluting stents was compared with FFR-guided multivessel PCI with drug-eluting stents. The SYNTAX–3VD and FAME studies had broader inclusion criteria, including unstable patients and non–ST-segment elevation MI, and decreased left ventricular function, and...
the FAME study also included patients who had undergone a previous PCI.

The most important results of these 3 studies are presented in Figure 8. Although the baseline characteristics of the studies were slightly different (with the angiographically most complex disease in the SYNTAX study and least complex disease in the COURAGE study), it can be seen that outcome was comparable in all studies for standard angiography-guided PCI, whereas FFR-guided PCI improved outcome significantly. Not only the total number of major adverse cardiac events was significantly reduced by routine measurement of FFR as well as mortality and occurrence of MI. From Figure 8, it can be hypothesized that multivessel PCI guided by FFR is superior to optimal medical treatment and yields results comparable to those of coronary artery bypass graft surgery in many patients.

Therefore, it may be hypothesized that the indications for performing PCI will be further extended when guided by FFR measurements and that more patients, previously treated by medical treatment alone or by coronary artery bypass graft surgery, can be better candidates for sophisticated PCI-guided by FFR measurements. Adding functional data to the SYNTAX score to stratify patients with multivessel disease to either coronary artery bypass graft surgery or PCI, as recently suggested, is also an interesting development (44). Further prospective, randomized trials are mandatory (and ongoing) to investigate these hypotheses.

Finally, one can wonder why outcome after FFR-guided PCI is so good compared with standard angiography-guided PCI, despite the use of fewer stents.

This can be understood from considering the combined mortality and MI rate associated with ischemic and non-ischemic stenoses in general and with stents (Fig. 9). From many studies it is known that such an event rate is <1% per year for a functionally nonsignificant stenosis if treated appropriately by medication (5, 6, 42, 44), between 5% and 10% per year for a functionally significant stenosis if only treated by medication (4, 45), and approximately 3% per year for a stented lesion whether it was functionally significant or not (4, 5, 45).

This means that stenting a functionally significant stenosis improves outcome, but stenting a functionally nonsignificant stenosis worsens outcome.

Both FFR-guided PCI and angiography-guided PCI eliminate all ischemic lesions very effectively and therefore have a similar positive effect on relief of angina pectoris.
Table 2 Reasons for Nonischemic FFR Despite Apparently Tight Stenosis

<table>
<thead>
<tr>
<th>Physiologic explanations</th>
<th>Interpretation explanations</th>
<th>Technical explanations</th>
<th>Actual false-negative FFR</th>
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<tr>
<td>Stenosis hemodynamically nonsignificant despite angiographic appearance</td>
<td>Other culprit lesion</td>
<td>Insufficient hyperemia (check system and solution or use other stimulus)</td>
<td>Acute phase of ST-segment elevation myocardial infarction</td>
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<tr>
<td>Small perfusion territory, old myocardial infarction, little viable tissue, small vessel</td>
<td>Diffuse disease rather than focal stenosis (make pull-back recording)</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 (pull sensor back to ostium to check and equalize)</td>
<td>Exercise-induced spasm</td>
</tr>
<tr>
<td>Severe microvascular disease (rarely affecting FFR)</td>
<td></td>
<td>Equalization with introducing needle and measurement without it</td>
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If, however, indiscriminate stenting is performed based on the angiogram, the positive influence on reducing the mortality and MI rate by stenting of ischemic stenoses is eradicated by inadvertent stenting of the nonischemic stenoses. Such unintended damage is prevented by FFR guidance.

Based on the results of studies such as DEFER and FAME, use of FFR in multivessel PCI has been upgraded recently in the European Society of Cardiology guidelines to a class IA classification (46).

**FFR Post-Intervention**

The use of FFR to evaluate the results of PCI is less well investigated. An inverse relationship has been shown between post-PCI FFR and the restenosis rate (38). After successful stenting, no noticeable hyperemic gradient should be present across a well-deployed stent (47). The opposite is not always true, and in case of doubt, intravascular ultrasound or optical coherence tomography is a better way to study stent deployment.

Finally, the hyperemic pressure pull-back recording is an informative tool for analyzing the extent and significance of residual disease proximal or distal to the stent.

**Limitations and Pitfalls of FFR**

There are several pitfalls related to FFR measurement and a few clinical situations in which it is not reliable and should not be applied. The most important of these is acute ST-segment elevation MI. During primary PCI for acute MI, the combination of the symptoms, electrocardiogram, and angiogram makes it mostly possible to determine the culprit lesion in the majority of cases. In addition, thrombus embolization, myocardial stunning, acute ischemic microvascular dysfunction, and other factors make reaching complete microvascular vasodilation unlikely.

Therefore, FFR measurement makes no sense in the setting of acute ST-segment elevation MI. When a several days have passed (usually 5 days are considered sufficient), FFR can be applied as in routine practice. The question of whether FFR can be applied during primary PCI to assess the hemodynamic severity of remote lesions has recently been answered (34).

From the technical point of view, there are several pitfalls to watch when performing FFR measurement. The 2 most important pitfalls are submaximal hyperemia (underestimating the stenosis severity) and issues related to the guiding catheter. A large guiding catheter may interfere with maximum blood flow and a guiding catheter with side holes may influence proximal coronary pressure and interfere with intracoronary administration of adenosine. Such situations can be easily recognized and avoided once the operator has some experience with FFR. For a more in-depth discussion of pitfalls, we refer the reader to several excellent overviews in the literature (36,48).

Finally, there are a number of physiologic reasons why FFR can be high despite an apparently tight stenosis. This is further clarified in Table 2.

**Conclusions**

FFR is an indispensable tool in the state-of-the-art catheterization laboratory to support decision making in revascularization in almost all elective clinical and angiographic conditions. With modern equipment, as is available today, measurement can be easily, rapidly, and safely performed, and the methodology is cost-effective, if not cost-saving. FFR strongly supports the developing paradigm of functional complete revascularization (i.e., stenting of ischemic stenoses and medical treatment of nonischemic ones). By systematic use of FFR in equivocal stenosis and multivessel disease, PCI can be made an even more effective and better treatment than it is currently.

**References**

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**Key Words:** fractional flow reserve  myocardial ischemia  percutaneous coronary intervention  revascularization.