Frontiers in cardiovascular medicine

Functional assessment of coronary stenoses: can we live without it?

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When selecting coronary stenoses for interventional treatment, assessment of reversible ischaemia is paramount from a symptomatic as well as prognostic point of view. Fractional flow reserve (FFR) is now considered the gold standard for invasive assessment of ischaemia. By measuring FFR in the catheterization laboratory, one can accurately identify which lesions should be stented resulting in improved patient outcome in most elective clinical and angiographic conditions. Recently, in the European Society of Cardiology guidelines on coronary revascularization, FFR was upgraded to an IA classification in multivessel percutaneous coronary intervention. In this review paper, the rationale for routine measurement of FFR will be reviewed and studies supporting its integration into everyday practice will be highlighted.

Keywords
Fractional flow reserve • Coronary artery stenosis • Pressure wire • Functional assessment

Rationale of percutaneous coronary intervention

In general, the goal and justification of any treatment in health care are either to relieve a patient’s symptoms (i.e. to improve quality of life) or to increase longevity (i.e. to improve outcome and prognosis). When translating this principle to coronary artery disease and the role of percutaneous coronary intervention (PCI), we have to recognize that stenting of a coronary stenosis is justified if that stenosis is responsible for symptoms, adverse outcome, or a combination of both. This is the key issue in selecting those lesions to be revascularized. And although this sounds quite simple and logical, it is neglected too often.

Numerous studies have demonstrated the correlation between the presence of myocardial ischaemia and symptoms. Moreover, the greater the degree of myocardial ischaemia, the worse the outcome. In deciding whether or not to perform PCI, the key aspect is determining whether a particular stenosis is responsible for reversible ischaemia, i.e. ischaemia when sufficiently stressed. Those coronary stenoses which are associated with inducible ischaemia are also called functionally significant stenoses or haemodynamically significant stenoses. Unfortunately, non-invasive imaging techniques, as well as coronary angiography, are flawed approaches and lack the accuracy to reliably identify ischaemia-producing lesions, particularly in patients with multivessel coronary artery disease. This has resulted in inappropriate stenting of functionally non-significant lesions, and in some cases, inappropriate deferral of PCI of significant lesions because they were deemed non-significant based on angiographic or non-invasive evaluation.1

Since the first introduction of PCI by Andreas Grunzig in 1977, it has been disappointing for interventional cardiologists not to be able to show that PCI improves survival.2 However, it should be realized that previous studies comparing PCI to medical therapy have been limited by the above-mentioned inappropriate selection of those lesions which truly benefit from stenting, thereby negatively affecting outcome parameters for the PCI groups in such studies. One can hypothesize that better selection of lesions requiring PCI will lead to more complete resolution of ischaemia and improved survival.

Importance of ischaemia

To better clarify the key issue reviewed in this paper, let us divide coronary lesions into those which are responsible for inducible ischaemia (functionally significant stenoses) and those which are not (functionally non-significant stenoses).

A functionally significant stenosis generally causes symptoms (angina pectoris), which are more effectively relieved by PCI as compared with medical therapy.1,4–7

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For example, in the DEFER trial, patients with ischaemic lesions (indicated by FFR < 0.75) underwent PCI and were followed for more than 5 years. At baseline, 90% of these patients had clear angina pectoris whereas 5 years after stenting, 80% of these patients remained completely free of symptoms. Also, in the recently published SYNTAX and FAME trials, 80% of PCI-treated patients were completely free of angina at a follow-up of 2 years. In contrast, only 50% of medically treated patients in the COURAGE trial were free of angina at 1 year, even though the coronary disease in those patients was less extensive.

Furthermore, it has been suggested that if ischaemia is clearly present, stenting is also beneficial with respect to preventing death and myocardial infarction. In a subgroup of the patients in the COURAGE trial with proven ischaemia by MIBI Spect, the annual rate of death and myocardial infarction was ~3% if treated by stenting and 6% if treated by medical therapy only. Similar data have been observed in several other large trials, including the DEFER and FAME trials. Also, in a recent study using nuclear stress testing a correlation was demonstrated between the extent of inducible ischaemia and outcome. Therefore, stenting a functionally significant stenosis is extremely effective in relieving angina pectoris and potentially improves outcome.

What about a functionally non-significant stenosis?

A functionally non-significant stenosis does not cause any complaints or symptoms by definition, so from the symptomatic point of view there is no reason to stent such a stenosis. And what about prognosis and longevity in such case? In the DEFER study, non-significant stenoses [as indicated by a fractional flow reserve (FFR) >0.75] were randomized to be treated either medically or by stenting. After a follow-up of 5 years, the prognosis of those lesions treated medically was excellent with a mortality and myocardial infarction rate that was <1% per year and was not improved by stenting. In the FFR-guided arm of the FAME study, lesions with an FFR < 0.80 were stented, while PCI was deferred in lesions with FFR > 0.80. After a follow-up of 2 years, outcome of the deferred lesions was excellent with medical treatment with a <1% rate of myocardial infarction or death.

Similar data were obtained in a slightly different way by the IVUS-based PROSPECT trial. In that study, the outcome of non-significant lesions by IVUS was excellent. The 1% death or myocardial infarction rate per year for medically treated non-ischaemic lesions is better than the outcome of stented lesions where the average rate of death or MI is ~2–3% per year.

Therefore, at this point it will be clear that functionally significant lesions need to be revascularized when technically feasible whereas it makes no sense to stent non-ischaemic lesions.

Consequently, the main issue in treating coronary artery disease by PCI is to distinguish those lesions which are responsible for ischaemia from those which are not. Because many of today’s patients have multivessel disease, the question is often not if the patient needs to be stented but where the stent(s) should be placed and how many. So, the key is how to identify lesions responsible for ischaemia. The most accurate and practical way of doing that is by measuring FFR.

Fractional flow reserve

Fractional flow reserve is defined as the ratio of maximum blood flow in a stenotic artery to maximum blood flow in the same artery in the case that artery would be completely normal. Stated in another way, maximum flow in the presence of the stenosis is expressed as a fraction of maximum flow in the hypothetical case that the epicardial artery would be completely normal. It may be clear that FFR is a ratio of two flows: the maximum myocardial flow in the stenotic territory divided by the maximum myocardial flow in the same territory in the normal case. The ratio of the two flows is expressed as the ratio of two pressures, which can be easily measured by a pressure wire and the guiding catheter, respectively, provided that maximum coronary and myocardial flow is present. So, FFR equals \( \frac{P_d}{P_a} \), where \( P_d \) is distal coronary pressure across the stenosis and \( P_a \) is aortic pressure, both measured at maximum coronary hyperemia. The concept of FFR is explained in Figure 1.

FFR has a direct clinical equivalent: FFR of 0.60 means that the maximum blood flow (and oxygen supply) to the myocardial distribution of the respective artery only reaches 60% of what it would be if that artery were completely normal. An increase to 0.90 after stenting indicates that maximum blood supply has now increased by 50%.

So, FFR is linearly related to maximum blood flow and its normal value is 1.0, irrespective of the patient, artery, blood pressure, etc. Also collateral flow is accounted for by FFR and measurement of coronary occlusion pressure during balloon stent placement enables quantitative assessment of collateral blood flow with prognostic implications. For further details about the mathematical aspects and derivation of FFR, we refer to the literature.

Practical aspects and features of fractional flow reserve

Measurement of FFR is a relatively easy and straightforward technique in the catheterization laboratory and can be performed both during diagnostic and interventional procedures. Generally, guiding catheters are used because they make steering of wires and other manipulations easier. Measurement is performed by a so-called pressure guidewire (PressureWire, St Jude Medical Systems, Uppsala, Sweden and SmartWire, Volcano Inc., Rancho Cordova, CA, USA). The pressure sensor is located 3 cm from the tip of the wire and the handling characteristics are almost similar to most standard angioplasty guidewires. Before introducing the sensor into the vessel to be studied, the pressures recorded by the sensor and the guiding catheter are equalized.

The pressure wire is connected to an interface (Analyzer or Combomap) which offers the possibility to record the pressure tracings and show FFR immediately. Recently, a ‘wireless’ pressure wire has been introduced (Aeris Wire, St Jude Medical Systems, Inc.). This wire does not need to be connected to an interface and the signals are transmitted wirelessly to the regular cath lab monitor. Anticoagulation is used as in every routine PCI procedure and nitroglycerin should be administered beforehand to maximally dilate the epicardial vessel.
Adequate hyperaemia, paramount for the determination of FFR, can be induced in several ways (Table 1). Without maximum hyperaemia, FFR is overestimated and stenosis severity underestimated with the risk of leaving an ischaemic stenosis untreated.

To have full benefit of coronary pressure measurements, in most patients pressure pullback recordings during steady-state hyperaemia should be performed and for that purpose use of intravenous adenosine administration by a central venous sheath is the most convenient and reliable method for inducing hyperaemia. Such pressure pullback recording enables haemodynamic analysis of all abnormalities along the length of the coronary

**Table 1 Hyperaemic stimuli for state-of-the-art fractional flow reserve measurement**

<table>
<thead>
<tr>
<th>Vasodilating Method</th>
<th>Amount</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardial vasodilation</td>
<td>Isosorbide dinitrate: at least 200 μg ic bolus, at least 30 s before the first measurements</td>
<td></td>
</tr>
<tr>
<td>Microvascular vasodilation</td>
<td>Adenosine or ATP ic</td>
<td></td>
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<tr>
<td></td>
<td>At least 40 μg ic bolus in RCA, 40–80 μg in LCA</td>
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<tr>
<td></td>
<td>Papaverine ic</td>
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<td></td>
<td>10–12 mg in the RCA, 15–20 mg in the LCA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenosine or ATP iv</td>
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<tr>
<td></td>
<td>140 μg/kg/min (preferably through a central venous, e.g. femoral line)</td>
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**Figure 1** Concept of fractional flow reserve. When no epicardial stenosis is present (black lines) the driving pressure $P_a$ determines a normal (100%) maximal myocardial blood flow. In case of stenosis responsible for a hyperaemic pressure gradient of 30 mmHg (red lines), the driving pressure will no longer be 100 mmHg but 70 mmHg ($P_d$). Since the relationship between driving pressure and myocardial blood flow is linear during maximal hyperaemia, myocardial blood flow will only reach 70% of its normal value. This numerical example shows how a ratio of two pressure ($P_d/P_a$) corresponds to a ratio of two flows ($Q_{max}^S/Q_{max}^N$). It also illustrates how important it is to induce maximal hyperaemia.

**Figure 2** Threshold values of fractional flow reserve for discriminating inducible or reversible ischaemia associated with a particular stenosis.

Adequate hyperaemia, paramount for the determination of FFR, can be induced in several ways (Table 1). Without maximum hyperaemia, FFR is overestimated and stenosis severity underestimated with the risk of leaving an ischaemic stenosis untreated.

To have full benefit of coronary pressure measurements, in most patients pressure pullback recordings during steady-state hyperaemia should be performed and for that purpose use of intravenous adenosine administration by a central venous sheath is the most convenient and reliable method for inducing hyperaemia. Such pressure pullback recording enables haemodynamic analysis of all abnormalities along the length of the coronary artery with an unsurpassed resolution. The technique of coronary pressure measurement is easy to learn and after having performed 10 or 20 procedures, it can be mastered by any experienced interventionalist.

Fractional flow reserve has some specific features that make it particularly useful for identifying the presence or absence of inducible ischaemia: unlike other methodologies, it has an unequivocal normal value of 1 for every patient and every artery; it includes the contribution of collaterals; it accounts for the extent of the perfusion territory; it is not influenced by haemodynamic perturbations; and it has an unequaled spatial resolution. These specific features
are also discussed extensively in the literature, including in Chapter 8 of the ESC Textbook of Cardiovascular Medicine.15–19

Because of these unique features of FFR, there is a narrow cut-off value discriminating ischaemic stenoses (Figure 2). If FFR is \( \leq 0.75 \) for a particular stenosis, it can be assumed with a certainty of 99% that this lesion is responsible for coronary ischaemia and therefore stenting such a lesion is justified if it is technically feasible. If, on the other hand, FFR is \( > 0.80 \), there is a \( <5\% \) chance that inducible ischaemia is present.

In the grey zone, between 0.76 and 0.80, decision making should be based upon sound clinical judgement, typicality of complaints, presence of other test results, and technical issues related to the measurements. For example, if a focal pressure drop of 20 mmHg is present in a vessel with an FFR of 0.78, it is more attractive to place a stent than if the pressure drop is very gradual along the entire coronary artery.

FFR in fact is the only index of ischaemia which has been validated vs. a true gold standard, using a so-called prospective, multitest Bayesian approach.14 Over the last years, many studies have been performed in a variety of patient populations (left main disease, diabetics, multivessel disease, previous MI) examining the accuracy of FFR, and in all these studies, the best cut-off value was found to be between 0.76 and 0.79.1,16,18–21

Only in a few clinical situations FFR should not be used, especially not in the culprit vessel of a patient in the acute phase of an ST segment elevation myocardial infarction, where it can be unreliable and fortunately is not necessary because the electrocardiogram and coronary angiogram typically guide PCI.16,19 Some other limitations are discussed later in this review.

Advantages of fractional flow reserve above other invasive and non-invasive methods

The shortcomings of anatomic methods for evaluating the functional severity of a coronary stenosis have been recognized for many years. Apart from technical issues related to image acquisition (e.g. in coronary angiography), a similar angiographic stenosis in a similar coronary artery can have a completely different functional meaning depending on the extent of the perfusion territory, presence of collaterals, etc. Furthermore, using absolute morphologic criteria like minimum luminal diameter or cross-sectional area is limited by the absence of a normal reference value. A stenosis with a cross-sectional area of, e.g. 4 mm² has a completely different meaning in the mid-part of a coronary artery of a 50 kg short lady compared with the proximal part of a coronary artery of a 100 kg tall man.

When comparing FFR with non-invasive functional testing, like exercise-testing and MIBI-Spect, some essential differences should be noted. Besides the fact that regular exercise-testing is often not possible due to physical limitations of the patient, pre-existing ECG abnormalities, insufficient increase of heart rate and the fact that MIBI-Spect in multivessel disease only indicates the multivessel disease correctly in the minority of patients,22 there is another fundamental difference between the three methodologies.

Exercise-testing, even if performed under optimum conditions, indicates ischaemia per patient. MIBI-Spect indicates ischaemia per perfusion territory. FFR indicates ischaemia per stenosis or per particular segment of the coronary artery. This is illustrated in Figure 3 where three different angiographic conditions all result in the same perfusion defect on MIBI-Spect but a more accurate per segment analysis with a high spatial resolution is necessary to determine if stenting is useful and technically feasible.

There are also some practical issues favouring use of FFR. It is completely within the hands of the cardiologist. The methodology can be performed immediately on the table during angiography and the intervention, if indicated, can than be performed immediately without loss of time, extra expenses or the need for an additional catheterization. In fact, if a patient has chest pain and a moderate or high likelihood of coronary artery disease, such a patient can be planned for angiography combined with FFR measurement and immediately treated if indicated and technically feasible.

Fractional flow reserve and outcome

Over the last 10 years, favourable outcomes when using FFR for selecting and treating patients with PCI have been reported in many subsets of patients. Initially, FFR was used to decide upon the need for revascularization in patients with an intermediate coronary artery stenosis.8,14 This issue was investigated in the DEFER study which clearly showed the advantage of using FFR in intermediate stenosis. Next, FFR was extended to almost all different types of subsets of patients, including left main coronary artery disease, diabetes mellitus, complex multivessel disease, ostial stenosis, diffuse disease, etc.1,12,18,20,21,23,24

In all of these subsets, favourable results were reported. A recent large study by Hamilos et al.20 studied a consecutive cohort of more than 4000 patients, 247 of whom had equivocal left main disease and subsequent FFR measurement and who were followed for a period of up to 12 years. Angiography proved to be unreliable in these patients for establishing the presence of a functionally significant stenosis. Treatment was based upon the FFR measurements and those patients with an FFR \( >0.80 \) were treated medically whereas those with FFR \( <0.80 \) underwent (mostly surgically) revascularization. After an average follow-up of 5 years, survival in the deferred patients based on FFR measurements was 95% compared with 93% in the surgical group. Major adverse cardiac event (MACE) rate was not significantly different, although at the end of the follow-up, revascularization was more common in the deferred group due to progression of the initial disease. This study confirmed a number of smaller previous studies which all yielded similar good results.25,26

In patients with multivessel disease, often it is not clear which lesions are responsible for ischaemia and should be revascularized. A number of retrospective studies suggested favourable outcome using FFR.27,28 More recently, three large prospective, randomized studies have been performed to examine the best possible treatment of patients with multivessel coronary artery disease. In these studies, the respective value of optimum medical treatment
only, PCI in addition to medical treatment, and coronary artery bypass surgery were investigated.

These studies were the COURAGE study, SYNTAX study, and FAME study. In the COURAGE study, optimum medical treatment alone was compared with PCI in addition to medical treatment in patients with multivessel disease and moderately severe coronary disease. In most patients bare metal stents were used. In the SYNTAX-3VD study, standard angiographic-guided PCI with drug-eluting stents was compared with bypass surgery in patients with multivessel CAD. The degree of disease was more severe than in the COURAGE trial. In the FAME study, patients with two- or three vessel disease but excluding left main stenosis, were randomized to standard angiography-guided PCI with drug-eluting stents or to FFR-guided multivessel PCI with drug-eluting stents. The SYNTAX-3VD and FAME study had more liberal inclusion criteria than the COURAGE study, including unstable patients and NSTEMI as well as decreased LV function. In the FAME study, also patients with previous PCI were included.

Although the baseline characteristics of the studies were slightly different (with the angiographically most complex disease in SYNTAX and least complex disease in COURAGE), 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 MACE was significantly reduced by routine measurement of FFR, but also the mortality and occurrence of myocardial infarction. Importantly, no heterogeneity was observed between different subgroups (diabetes, unstable angina, or previous PCI) with respect to these favourable results after FFR-guided PCI in the FAME study. (Figure 4). In Figure 5 one can hypothesize that if compared directly in the same population, multivessel PCI guided by FFR would be superior to optimum medical treatment in the COURAGE trial and comparable to coronary artery bypass graft surgery in the SYNTAX-3VD trial. Of course, direct comparison to confirm such hypothesis is mandatory and newer stents with improved characteristics compared with Cypher, Taxus, and Endeavour stents as used in the SYNTAX and FAME studies could modify these standpoints.

Moreover, one can hypothesize that by incorporation FFR into the evaluation of patients with multivessel CAD, the indications for performing PCI will expand. This was investigated recently in a substudy of the FAME trial looking at the impact of FFR on the SYNTAX score. The SYNTAX score was calculated in all of the patients in FAME randomized to FFR guidance. A ‘Functional SYNTAX Score’ was then calculated by eliminating all of the angiographic lesions in which the FFR was >0.80. It was shown that the Functional SYNTAX score moved roughly one-third of the patients from a higher-risk tertile to a lower-tertile and that it better predicted major adverse events, compared with the classic SYNTAX score. This could have important implications on what treatment strategy, coronary artery bypass grafting or PCI, we choose for our patients with multivessel CAD.

Finally, one can wonder why the outcome after FFR-guided PCI is so good compared with standard, angiography-guided PCI, despite the use of less stents. This can be understood by reflecting about the combined mortality and myocardial infarction rate associated with ischaemic and non-ischaemic stenoses in general and after PCI (Figure 6). As outlined above, the event rate is <1% per year for a functionally non-significant stenosis, if treated appropriately by
medication7–9,11 between 5 and 10% per year for a functionally significant stenosis, if only treated by medication6,12 and ≏3% per year for a stented lesion, no matter whether it was functionally significant or not.4,7,12

This means that stenting a functionally significant stenosis improves outcome but stenting a functionally non-significant stenosis worsens outcome, because of both the short-term effect on periprocedural myocardial infarction and/or stent thrombosis and the long-term increased risk of restenosis and stent thrombosis.

Both FFR-guided and angiography-guided PCI will effectively relieve ischaemia, but the positive influence on reducing mortality and myocardial infarction by stenting the ischaemic stenoses is reduced in the angiography-guided PCI group because of ’collateral damage’ resulting from intervening on functionally non-significant lesions as well.

Can we live without fractional flow reserve?

Fractional flow reserve measurement is not necessary in every interventional procedure. If a patient has typical chest pain, a positive non-invasive test and a single severe stenosis on the angiogram, stenting can be performed straightforwardly. But such simple cases are becoming rare and in an increasing number of patients in the catheterization laboratory, FFR becomes indispensable for good decision-making.

Nevertheless, despite overwhelming data demonstrating that standard angiography is insufficient to judge about the functional significance of lesions, still quite a number of operators continue to base their decision upon angiography solely.

In that respect, it is interesting to look at a study performed by Sant’Anna FM et al. in which lesion significance was assessed from angiograms in 195 consecutive patients with multivessel disease by
three experienced operators. Next, FFR was measured in all arteries and those results were used for actual decision making. This resulted in a change of strategy in 34% of the lesions corresponding with 54% of the patients.

In the FAME study, a change in strategy was made after measurement of FFR in ≏35% of all stenoses. The relation between FFR and angiography is presented in Figure 7 for the patients in the FFR-guided cohort in the FAME study. It shows that for lesions with an angiographic severity between 50 and 70%, roughly 40% are causing ischaemia and for lesions between 70 and 90%, 20% are not. Only in the most severe lesions, can it be safely assumed by angiography that the lesion is indeed causing reversible ischaemia. In summary, selecting lesions to be stented on basis of the angiogram in multivessel disease is inaccurate and not supported by published literature. Therefore, it should be strongly discouraged. Finally, using FFR to decide upon revascularization in multivessel disease, saves contrast, is cost-saving, and does not appreciably prolong the interventional procedure.

It is for these reasons that the use of FFR in selecting lesions to be stented in multivessel disease is designated as an IA classification in the recent guidelines of the ESC.

Figure 6 Schematic explanation why fractional flow reserve-guided percutaneous coronary intervention decreases rate of death and myocardial infarction. The hypothetical patient in this figure has four angiographically significant stenoses, two of them are also functionally significant (i.e. causing reversible ischaemia; yellow circles). The intrinsic risk of such ischaemic stenosis to die or experience myocardial infarction is at least 5% per stenosis per year (see text). The intrinsic risk for the non-ischaemic lesions (green circles), on the contrary, is ≏1% per year. By stenting a stenosis (whether or not being functionally significant) the risk of death or myocardial infarction is ≏3% per year. Stenting all four lesions based upon angiography, eliminates ischaemia very effectively and relieves angina pectoris. The risk to die or experience MI, however, is decreased for two of the lesions but increased for the other two. The benefit in terms of survival by stenting the ischaemic lesions is annihilated by ‘collateral damage’ by unnecessary stenting of the other two lesions. By fractional flow reserve-guided percutaneous coronary intervention, ischaemia and angina pectoris is eliminated as effectively, but also the net chance for death or MI is decreased by 30–35%.

Figure 7 Angiographic severity vs. functional severity of coronary artery stenoses. Box-and-Whisker plot showing the fractional flow reserve values of the lesions in the categories of 50–70, 71–90, and 91–99% diameter stenosis as visually estimated on the basis of the coronary angiogram (from Sant’Ann FM et al., with permission).
Some specific situations and limitations of fractional flow reserve

There are some specific clinical or angiographic conditions where the measurement of FFR is highly beneficial but where its interpretation should be clarified, like serial stenosis, diffuse disease, and bypass grafts. In addition, there are several pitfalls related to FFR measurement and a few clinical situations where it is not reliable and should not be applied (Table 2). The most important of these is acute ST-elevation myocardial infarction (STEMI). During primary PCI for acute myocardial infarction, the combination of the symptoms, ECG and angiogram, indicates the culprit lesion in the majority of cases and is sufficient to guide intervention. In addition, thrombus embolization, myocardial stunning, and acute ischaemic microvascular dysfunction, make achieving complete microvascular vasodilation unlikely. Therefore, FFR measurement of the culprit vessel is not indicated in the setting of acute STEMI. In contrast, once reversible microvascular dysfunction has resolved (likely after 5 days), FFR can be applied as in routine practice. The finding that FFR can be applied during primary PCI to resolve (likely after 5 days), FFR can be applied as in routine practice. In contrast, once reversible microvascular dysfunction has resolved (likely after 5 days), FFR can be applied as in routine practice. 16 The finding that FFR can be applied during primary PCI to assess the haemodynamic severity of lesions in a non-culprit vessel was shown recently. 13 A few other conditions where FFR should be interpreted with caution are myocardial bridging and exercise-induced spasm. 33

Also in case of severely elevated right heart pressure, theoretically it can be expected that such pressure has to be taken into account in calculating FFR.

A specific situation to discuss is the patient after bypass surgery. In the case of a totally occluded native coronary artery and FFR measurement through the bypass, FFR can be interpreted straightforward. However, in the case of an open native artery and an open graft, high FFR distal to the anastomosis does not distinguish between sufficient graft function, sufficient native artery function, or both. Fortunately, for clinical decision-making that is not a real problem because no intervention is needed in such case. If FFR distal to the anastomosis is in the ischaemic range, it means that both the graft and the native artery are functionally insufficient to provide adequate perfusion of the distal myocardium and intervention is indicated. Technical considerations will guide then the operator whether the graft or the native artery will be stented.

Another situation where FFR is extremely useful but where difficulties with interpretation might occur, is the patient with multiple lesions within one coronary artery or with focal stenosis superimposed upon diffuse disease. In that situation, due to severe limitation of blood flow by one stenosis, the gradient across another stenosis (or within the complete artery in case of diffuse disease) can be masked. In such patients, the pressure pullback recording is especially helpful. At first, by means of FFR measurement in the very distal part of the artery, the summed effect of all lesions is assessed and makes clear if treatment is indicated or not. Thereafter, the pullback recording at maximum hyperaemia (where intravenous adenosine is mandatory) reveals the different gradients within the artery and if focal step-ups are present, stenting can be performed. Generally, the most severe lesion is treated first whereafter the gradient across another lesion is unmasked. In the case of multiple focal gradients of similar magnitude, the most distal one will be stented first because of technical reasons. By repeating the pressure pullback recording, the physiological significance and interaction between lesions can be made clear step-by-step and treatment be followed beautifully until a satisfactory result is obtained. An example of such a patient with two focal stenoses in the right coronary artery, superimposed upon diffuse disease, is presented in Figure 8.

In the case of a severe lesion with a collateral-dependent myocardium and a moderate lesion in the donor artery, coronary steal might occur during intravenous adenosine induced hyperaemia. If that is the case, an intracoronary hyperaemic stimulus is preferable.

Finally, in case of severe microvascular disease it can be argued that FFR will be higher than expected and underestimates epicardial stenosis severity. In that case, FFR expresses maximum flow as a ratio to maximum flow without the epicardial stenosis but still not normal because of the microvascular disease. In that case, however, FFR still indicates to what degree epicardial flow can be restored by stenting and in no validation study so far, the applicability of FFR was affected in this respect. Most likely, this small effect is accounted for by the generally accepted upper limit of the grey zone of 0.80 instead of the traditional cut-off point of 0.75.

From the technical point of view, there are several pitfalls to beware of when performing FFR measurement. The two most important pitfalls are submaximal hyperaemia (underestimating the

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Table 2 Reasons of non-ischaemic fractional flow reserve despite an apparently tight stenosis

| Physiological explanations |  |
|----------------------------|  |
| Stenosis haemodynamically non significant despite angiographic appearance |  |
| Small perfusion territory, old myocardial infarction, little viable tissue, small vessel |  |
| Abundant collaterals |  |
| Severe microvascular disease (rarely affecting FFR) |  |
| Mean arterial pressure < 60 mmHg, outside autoregulatory range (give volume expansion) |  |

| Interpretation explanations |  |
|----------------------------|  |
| Other culprit lesion |  |
| Diffuse disease rather than focal stenosis (make pull-back recording) |  |
| Chest pain of non-cardiac origin |  |
| Open bypass graft or open native artery |  |

| Technical explanations |  |
|------------------------|  |
| Insufficient hyperemia (check system and solution; or use other stimulus) |  |
| Guiding catheter related pitfall (deep engagement, small ostium, sideholes) |  |
| Electrical drift (pull sensor back to ostium to check and equalize) |  |
| Equalization without and measurement with introducer needle |  |
| Actual false-negative FFR |  |
| Acute phase of ST elevation myocardial infarction |  |
| Severe left ventricular hypertrophy |  |
| Exercise-induced spasm |  |
stenosis severity) and guiding catheter issues. Such situations can be easily recognized and avoided, once the operator has some experience with FFR.18,19

Recently, a newer hyperaemic stimulus has been proposed in a preliminary study, i.e. regadenoson in a dosage of 400 μg administered as a single bolus in a peripheral vein and resulting in a few minutes of maximum hyperaemia very closely to intravenous adenosine in administered in a central vein.34,35 This would combine the advantage of easy administration with the possibility of making a pullback recording. Further validation studies are mandatory in this field.

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.

**Conclusion: Why cannot we live without it?**

Today, there is ample evidence that stenting ischaemic stenoses result in effective and durable relief of angina pectoris and improves outcome. In contrast, stenting non-ischaemic stenoses worsen outcome and is not cost-effective. Therefore, the functional assessment of a coronary stenosis to establish whether the stenosis is responsible for ischaemia provides indispensable information necessary to perform optimal PCI.

Fractional flow reserve provides this functional information and its measurement can be performed easily, rapidly, and safely in the catheterization laboratory during diagnostic angiography and can

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**Figure 8** Right coronary artery in middle-aged patient, with two focal stenoses in the proximal and mid-part of the artery, superimposed on diffuse disease (A). The corresponding pressure recording is shown on the right-hand side. The sensor is located at the crux of the Right coronary artery, hyperaemia is induced by central venous adenosine infusion (140 μg/kg/min), and the hyperaemic pressure pullback recording is made. Fractional flow reserve of the artery, summing all abnormalities together, is 0.34. A large focal pressure drop occurs when pulling back the sensor across the distal stenosis (asterisk) and only a small gradient of 5 mmHg is present across the proximal lesion (arrow). In B, a stent has been placed in the distal stenosis and fractional flow reserve has increased to 0.74. When the pressure pullback recording is repeated, no gradient is present anymore across the stent, but the proximal gradient has increased to 22 mmHg (arrow), of which part is due to the proximal stenosis and part to the diffuse disease. In panel C a second stent has been placed and at the final pressure pullback recording, no focal gradients are noticeable anymore but only a gradient of 10 mmHg through the coronary artery, due to the diffuse disease. Although fractional flow reserve has not normalized, the value of 0.87 is amply in the non-ischaemic range and this is the best possible result in this artery.
be followed immediately by PCI if necessary. By systematic use of FFR in a wide variety of clinical and angiographic conditions, PCI can be made more effective and better treatment than it was before. FFR strongly supports the developing paradigm of function-
alone complete revascularization, i.e. stenting ischaemic lesions and medical treatment of non-ischaemic ones. It is hard, if not impossible, to live without!

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References

2. Gruentzig AR, Senning A, Siegenthaler WE. Non-operative dilatation of coronary
6. Davies RF, Goldberg AD, Fornam S. Asymptomatic Cardiac Ischemia Pilot (ACIP) study-two year follow-up, outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037–2043.
12. Wijns W, Kjol PH. on behalf of the Joint Task Force on Myocardial Revasculari-

zation of the European Society of Cardiology (ESC) and the European Association of Cardiac-Thoracic Surgery (EACTS). Guidelines on myocardial revasculari-

13. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after per-
18. Pijls NHJ. Optimum guidance of complex PCI by coronary pressure measure-

20. Hamilos M, Muller O, Cuisset T, Ntalansis A, Chouvarakis G, Sarno G et al. Long-