Fractional flow reserve (FFR) has become an increasingly important index for decision making with respect to revascularization of coronary artery stenosis. It is the gold standard to indicate whether a particular stenosis is responsible for inducible ischemia and it is generally accepted that a stenosis with an ischemic value of FFR is responsible for angina pectoris and a worse outcome, and should be revascularized, whereas lesions with a non-ischemic FFR have a more favorable prognosis and can better be treated medically. In this review paper, the background, concept and clinical application of FFR are discussed from a practical point of view. On top of that, some in-depth considerations are given with respect to further possibilities of FFR for examining the coronary circulation, including separate assessment of coronary, myocardial, and collateral blood flows. Finally, a word of caution is given with respect to using resting pressure indexes, which seem attractive because they avoid the need for hyperemia, but negatively affect the accuracy of the measurements. This review can be read as an overview of the state-of-the-art of FFR and as a guide to further reading. (Circ J 2013; 77: 561–569)

Key Words: Coronary artery disease; Coronary circulation; Fractional flow reserve; Resting pressure indexes

In patients with coronary artery disease (CAD), the most important factor with respect to both symptoms and outcome is the presence and extent of inducible ischemia. If a particular stenosis is associated with inducible ischemia, generally it causes symptoms. And the more extensive the inducible ischemia, the worse the outcome.

It has become increasingly clear that revascularization, either by percutaneous coronary intervention (PCI) or by coronary artery bypass surgery (CABG), is the superior treatment in these patients to relieve symptoms and is much more effective than medical treatment. Also with respect to outcome (ie, decreasing the chance of premature death or myocardial infarction [MI]), revascularization of ischemia-associated lesions is useful.

However, if a coronary stenosis is not associated with inducible ischemia (“non-ischemic stenosis”), prognosis is more favorable and medical treatment is indicated and most likely better than mechanical revascularization.

Therefore, the key issue in the treatment of CAD is to discriminate those stenoses that are associated with inducible ischemia from those that are not.

In the case of 1-vessel CAD, typical complaints and a positive non-invasive test, the decision to revascularize is easy. But unfortunately, at present the majority of our patients have multivessel disease with multiple focal stenoses and often focal stenosis superimposed on diffuse disease.

Discriminating those lesions that are causing ischemia and would benefit from stenting or bypass surgery can be difficult. Coronary angiography is a flawed approach to discriminating such lesions.

Fractional flow reserve (FFR), based upon hyperemic coronary pressure measurements, has been shown to be the most accurate methodology for discriminating which lesions are associated with ischemia or not. Initially, FFR was used to assess intermediate lesions, but now it has been proven to be useful in almost every clinical and angiographic condition, with the exception of ST-segment elevation MI (STEMI).

FFR can be easily measured during coronary angiography and if indicated, PCI can be performed within the same session. It is a simple methodology using a coronary pressure wire and an adequate hyperemic stimulus, and takes only a little time.

In this review, I will briefly discuss the principles of FFR measurement, its clinical applications, and the influence on patient outcome.

Concept and Features of FFR

The basic concept of FFR is presented in Figure 1. Although at rest, it is extremely difficult to assess coronary blood flow from coronary pressure as a result of autoregulation in the coronary circulation, during maximum hyperemia a linear relation exists between perfusion pressure and blood flow. Therefore, hyperemic perfusion in a myocardial territory is proportional to perfusion pressure because the resistance is minimal and therefore constant.

FFR is defined as maximum myocardial blood flow in a stenotic territory, divided by normal maximum blood flow in
of maximum flows can be represented by the ratio of perfusion pressures, being distal coronary pressure at hyperemia divided by aortic pressure under the assumption that venous pressure is close to zero. With this methodology, aortic pressure is measured by the guiding catheter and distal coronary pressure by a pressure monitoring guidewire (Aeris wire or Certus wire, St. Jude Medical, Minneapolis, MN, USA; or Smart wire, Volcano Inc, Rancho Cordova, CA, USA).

FFR has a number of unique features that make it very easy to use and for decision making in clinical practice. First, unlike a number of other indexes, there is an unequivocal normal value of 1.0 for every patient and every coronary artery. Second, FFR has been shown to be independent of changes in blood pressure, heart rate, and contractility. Third, FFR measurements are extremely reproducible, unmatched by any other methodology in cardiology. Fourth, the concept of FFR can be extended to calculate separately myocardial, coronary, and collateral perfusion (to be discussed later). Fifth, by performing a so-called hyperemic pressure-pullback recording, detailed spatial information can be obtained about the distribution of all abnormalities along the coronary tree. FFR is unequalled in this respect. Sixth, there is sharp discrimination by FFR between ischemic and non-ischemic lesions. FFR ≥ 0.80 excludes inducible ischemia by a particular stenosis with an accuracy of 95% and FFR < 0.75 indicates inducible ischemia in almost 100% of lesions, thereby justifying PCI if technically feasible. FFR has been validated vs. a true gold standard in an prospective multitesting Bayesian approach and is the only physiologic index that has ever been validated in such a robust way.

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Fractional Flow Reserve

At the end of the procedure, FFR can be measured again to observe the rate of improvement after stent placement. Because FFR is linearly related to maximum blood flow, a pre-PCI value of FFR of 0.6 increasing to 0.9 after stenting, for example, indicates that myocardial blood flow has been improved by 150%, reflecting improvement in the functional capacity of the patient.

At the end of the procedure, the pressure wire is pulled back until the sensor is close to the tip of the guiding catheter and it can be verified that no drift has occurred.

For further details of the practical set-up, refer to the literature.\textsuperscript{11,12,15,16} An example of a procedure in which FFR is measured is shown in Figure 3.

**Maximal Hyperemia**

Maximal hyperemia is essential for adequate FFR measurement.\textsuperscript{7,9,11,12} If maximal hyperemia is not present, the distal coronary pressure will not decrease as much as it could and the value measured for FFR will be too high, thereby underestimating stenosis severity.

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\textsuperscript{11} Lastly, FFR has been shown to improve outcome, decrease death and MI rate, and to be cost-effective (discussed later).\textsuperscript{14}

**Practical Set-up and Recommendations**

To measure FFR requires only minor adaptations to be made compared with regular angiography or PCI. Generally, a 6F guiding catheter is used because the lumen of such a catheter is large and smooth and easily accommodates advancement of a pressure guidewire. The pressure wire is advanced as a normal guidewire and equalized at the tip of the guiding catheter to make sure that equal pressures are recorded at that point. The pressure wire is then further advanced, across the stenosis and placed in the distal part of the coronary artery whereafter an adequate hyperemic stimulus is given and the FFR measurements can be made. To analyze the complete course of the coronary artery, a pressure-pullback recording can be made.

In the case where PCI is indicated, based on FFR <0.80, the procedure can be performed as usual, using the pressure wire as a regular guidewire. During balloon inflation, coronary wedge pressure can be measured, providing information about collateral blood flow. If necessary, the pressure wire can be used for other techniques like an OCT or IVUS catheter in the usual way.

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**Figure 3.** Example of fractional flow reserve (FFR) measurement in an ambiguous, moderate proximal left anterior descending (LAD) artery stenosis. \textit{(Lower left)} Pressures are equalized when the pressure sensor is at the tip of the guiding catheter (the red and green signals are superimposed). \textit{(Upper right)} The sensor is in the distal LAD, resting pressures are measured, followed by induction of maximum hyperemia induced by central venous infusion of adenosine 140μg·kg\textsuperscript{-1}·min\textsuperscript{-1}. At steady-state hyperemia, the sensor is pulled back slowly under fluoroscopic guidance, which clearly indicates either a gradual decline of pressure along the LAD (ie, diffuse disease) or a sudden pressure drop at the site of the angiographic lesion (ie, focal disease; \textit{Right lower}). The FFR of the LAD was 0.66 and the vessel was successfully stented whereafter FFR increased to 0.91.
It should be emphasized that both the epicardial coronary artery and the arteriolar system and microcirculation should be fully dilated. As with every state-of-the-art catheterization, 200–300 μg of nitroglycerin is administered every 30 min to avoid coronary vasoconstriction and guarantee epicardial vasodilation. Next, there are a number of practical ways of inducing arteriolar and microvascular hyperemia by several drugs administered by several routes.15–16

Intracoronary papaverine is cheap and creates maximum hyperemia for approximately 30–60 s, but has the disadvantage of inducing arrhythmias in some patients. Intracoronary adenosine or ATP creates hyperemia for a few seconds only and can be used in patients with 1-vessel disease and no other abnormalities. It does not allow for performance of a pressure-pullback recording. Intravenous administration of adenosine (particularly by the central venous route) is the gold standard for creating hyperemia, acts within 1 min, creates a steady-state level of maximum hyperemia and is safe. The disadvantage is an unpleasant feeling in the chest or the throat of the patient (which is harmless and that should be emphasized). Intravenous adenosine is contraindicated in cases of severe asthma. ATP can be used as an equivalent to adenosine (similar dosage). In the experience of the Catharina Hospital in the Netherlands, adenosine in doses of 10–12 mg in the RCA, 15–20 mg in the LCA were used in 98% and only 2 serious adverse events were observed (ie, in 0.02% [2 out of more than 11,000 patients undergoing FFR measurements, in Japan, often 8 mg is used in the RCA and 12 mg in the LCA). ATP, adenosine triphosphate; IC, intracoronary; IV, intravenously; LCA, left coronary artery; RCA, right coronary artery.

The different hyperemic drugs and their actions are summarized in Table 1 and for further discussion refer to the literature.15–18

### Clinical Applications of FFR

Initially, FFR was used to investigate the functional significance of intermediate lesions,4 over time it has been validated as useful in most clinical and angiographic conditions encountered in the catheterization laboratory. FFR has been well validated in multivessel disease, left main disease, ostial lesions, tandem lesions, diffuse disease, unstable angina pectoris and non-STEMI. In all these conditions, especially those with most complex angiography, the importance of the pressure-pullback recording can hardly be overestimated.11,12 To perform such a pullback recording, the pressure wire is put into the distal part of the coronary artery, steady-state hyperemia is induced (mostly by IV adenosine, but in the future a bolus injection of regadenoson might be an alternative) and under fluoroscopy the pressure wire is slowly pulled back, thereby recording the pressure decline along the artery. In this way, focal stenosis (with a sudden drop in pressure) and diffuse disease (with a gradual pressure drop) can be distinguished (Figure 3). Based upon such a pressure-pullback recording, it is easy to determine if stenting is indicated, technically feasible, and beneficial for the patient. As a rule of thumb, if the FFR of the complete artery is <0.80 (ischemic threshold), it can be deduced from the pressure-pullback recording where stents should be placed.

Also in cases of coronary bypass, pressure measurement can be useful. In the case of an occluded native artery, FFR is measured through the bypass and interpreted as usual. In the case of an open native artery and open bypass, interpretation is slightly less straightforward but still adequate for decision making.19

### Deep Dive Into the Concept of FFR

So far, only so-called myocardial FFR (also sometimes abbreviated as FFR\textsubscript{myo} in the literature) has been discussed. From the clinical point of view, FFR\textsubscript{myo} is the most important parameter because it indicates that particular fraction of normal maximum myocardial blood flow being maintained despite the presence of the epicardial stenosis. However, using coronary pressure measurements it is also possible to distinguish separately the contribution of coronary blood flow and collateral blood flow to myocardial blood flow.7,8 Those 2 parameters are called FFR\textsubscript{cor} and FFR\textsubscript{coll}, respectively. As a matter of fact, FFR\textsubscript{myo} = FFR\textsubscript{cor} + FFR\textsubscript{coll}.

The last parameter, FFR\textsubscript{coll}, has also been called CFiP (collateral flow index by pressure) in the literature.20 In fact, by

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<th>Table 1. Hyperemic Stimuli for State-of-the-Art Measurement of Fractional Flow Reserve</th>
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<td><strong>Epicardial vasodilatation</strong></td>
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<td><strong>Microvascular vasodilatation</strong></td>
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<td>Papaverine IC*: 10–12 mg in the RCA, 15–20 mg in the LCA</td>
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<td>Adenosine or ATP IV: 140 μg·kg(^{-1})·min(^{-1}) (preferably through a central venous eg, femoral line)</td>
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<td>Regadenoson (Rapiscan): In central or peripheral vein irrespective of bodyweight) A number of studies with this new drug are in the pipeline. First results are promising.</td>
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\*In Japan, often 8 mg is used in the RCA and 12 mg in the LCA.

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<th>Table 2. Deep Dive Into the Concept of Fractional Flow Reserve: Calculation of Coronary, Myocardial, and Collateral Blood Flows</th>
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<tr>
<td>Maximum recruitable collateral flow at coronary occlusion</td>
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<tr>
<td>(P_v - P_r)</td>
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<tr>
<td>Coronary fractional flow reserve</td>
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<tr>
<td>Myocardial fractional flow reserve</td>
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<td>Fractional collateral reserve</td>
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measuring coronary pressure during PCI (and by also recording the coronary wedge pressure), all these different flows can be calculated during a coronary intervention. Complete equations for these different parameters are summarized in Table 2. For further reading about this interesting physiologic method, refer to the literature.\(^7,9,21\)\(^\text{22}\) (For further reading the standard textbook “Coronary pressure”\(^21\) has been translated into Japanese by Dr T. Akasaka and Dr K. Takajama.\(^22\))

**FFR and Clinical Outcome**

As mentioned before, in CAD the most important factor with respect to improving symptoms and better outcome (prolonging life or avoiding MI) is the presence and extent of inducible ischemia. It has been clearly shown in the past that for a non-ischemic lesion, stenting does not make sense. Such non-ischemic stenosis, by definition, does not cause angina pectoris and has an excellent outcome with medical treatment, with rates of death and MI of less than 1%/year, not further reduced by stenting.\(^2,4\)\(^,5\)\(^,23\)\(^,24\)

On the other hand, if a stenosis is associated with inducible ischemia, generally it causes angina pectoris and is associated with a higher chance for death and MI in the future.\(^23,25\) In the Flow Reserve Versus Angiography for Multivessel Evaluation

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**Figure 4.** (A) Survival free from major adverse coronary events (MACE) in the FAME study and (B) cumulative death, acute myocardial infarction (AMI), and non-ST elevation MI rates in FAME-2 study (for further explanation see text). OMT, optimum medical treatment; PCI, percutaneous coronary intervention. (Reprinted with permission.)
(FAME) study, it has been clearly shown that guiding PCI by FFR in multivessel CAD results in a superior outcome compared with standard angiography-guided PCI.\textsuperscript{2,23} In the FAME study, systematically applying FFR measurement and using it as the basis for deciding where and whether to stent decreased the rates of death, MI, and repeat revascularization all by approximately 30–35\% after 1 year (Figure 4A). In the second year, the advantage in terms of avoiding death and MI was even more pronounced, although a small catch-up of repeat PCI was observed in the FFR-guided group.\textsuperscript{23} Besides that, guidance of multivessel PCI by FFR resulted in a shorter hospital stay, use of less contrast agent, less radiation and was also cheaper in absolute terms.\textsuperscript{14} The duration of the procedure was not significantly prolonged by measuring FFR in a systematic way.\textsuperscript{2}

Finally, functional improvement after FFR-guided PCI was at least as good as after angiographically-guided PCI and approximately 80\% of all patients were completely free of anginal complaints after 2 years, underlining the superiority of PCI to relieve anginal complaints in patients with proven ischemia.\textsuperscript{23}

Recently, the results of the FAME II have been published, also showing that FFR-guided PCI is superior to optimum medical treatment (OMT) alone in relieving angina and improving outcome.\textsuperscript{24} The endpoint in the FAME II study was the combination of death, MI, and acute coronary syndromes with urgent PCI (Figure 4B). The study was stopped prematurely because the last component of the primary endpoint occurred 8-fold more often in the OMT group than in the PCI group. Of these urgent cases of PCI, half of the patients had positive enzymes (non-STEMI) or transient ECG changes and if the analysis was confined to patients with death, STEMI, non-STEMI, and ECG-proven unstable angina, there was a highly significant advantage for FFR-guided PCI compared with OMT.\textsuperscript{24}

Finally, the outcome of FFR-guided PCI in multivessel disease yielded major adverse cardiac event rates comparable with the CABG group in the SYNTAX trial.\textsuperscript{25} Therefore, the FAME III trial is planned to compare FFR-guided PCI in 3-vessel disease with CABG.

The common denominator of the DEFER and FAME studies is that PCI guided by FFR for selection of the arteries and lesions to be treated results in a superior outcome compared with angiography-guided PCI, is superior to OMT, and is possibly as effective as CABG in 3-vessel disease. FFR supports the concept of functional complete revascularization (ie, stenting of ischemic lesions and medical treatment of the non-ischemic ones).\textsuperscript{2,23}

**Is Hyperemia Essential? A Critical Word About Resting Indexes**

Grunzig et al\textsuperscript{26} recognized the importance of coronary pressure measurement and were aware that measuring resting pressure...
Fractional Flow Reserve

Figure 6. (A) In the Resolve registry, a poor correlation was found between resting pressure indexes (iFR and P/Pa at rest) and fractional flow reserve (FFR). Only if iFR was <0.82 (as in 24% of the 1,539 patients) or if the resting Pd/Pa was <0.80 (as in 33% of the patients), could hyperemia be omitted to achieve a 95% certainty of making the correct decision whether or not to revascularize. In other words, when using Pd/Pa at rest, hyperemia is not necessary in 33% of patients and when using iFR, hyperemia is not necessary in 24% of patients to confirm the presence of inducible ischemia. (Reproduced with permission.) (B) ROC curves for the different resting indexes (i.e., trans-stenotic gradient at rest, resting Pd/Pa over the complete heart cycle, and iFR), which all perform equally poor when compared with hyperemic indexes. (Reproduced with permission.)

The index iFRhyp was formerly defined as FFRdiast by Abe et al.9 ROC, receiver-operating characteristic.
emia is at least 250% lower than diastolic resistance at any point during rest. It has been well documented in many animal studies that resistance during the complete heart cycle in hyperemia and not be influenced by adenosine infusion. This assumption is not true for a particular part of diastole will be as low as the average resistance or iFR, the latter being the resting gradient during a particular part of diastole). It was claimed initially that this iFR index would be numerically identical to FFR, but shortly thereafter the claim was withdrawn as quickly as it was introduced. The assumption of iFR is that the resistance during a particular part of diastole will be as low as the average resistance during the complete heart cycle in hyperemia and not be influenced by adenosine infusion. This assumption is not true and it has been well documented in many animal studies that average resistance in healthy coronary arteries during hyperemia is at least 250% lower than diastolic resistance at any point during rest. Furthermore, iFR is calculated as an average value (and not instantaneous as the name suggests) and is strongly influenced by hyperemia. It is neither instantaneous nor hyperemia-free. As well as it is almost impossible in a catheterization laboratory to achieve a true resting condition and it is never clear to what extent some hyperemia is present, values measured for iFR are highly variable in clinical practice. It has been well documented in several recently published studies and in a large registry that, if a 95% certainty of making the right decision is requested, relying solely on iFR (and removing a hyperemic stimulus) leads to the correct decision in only 25% of all patients, whereas Pd/ Pa at rest would be reliable for that purpose in 33% of all patients. In the literature advocating the use of iFR, investigators suggest being satisfied with an accuracy of only 90% or, even worse, 80%. But if 80% accuracy of making the right decision to stent or not to stent is sufficient, we could rely just as well on angiography and coronary pressure measurement would never be necessary.

Therefore, I consider that, having at our disposal an index such as FFR with an accuracy of 95% for making the correct decision, it is unacceptable to accept less and to abandon hyperemia. Finally, as a matter of fact, in the case of Pd/ Pa at rest <0.80, it is clear that FFR will be also <0.80 and in such a patient hyperemia is not necessary to confirm that ischemia is present. But by inducing hyperemia and measuring FFR, one knows at least if FFR is, for example, 0.55 or 0.75 and one can more accurately estimate the rate of improvement after stenting with post-stent PCI of 0.90, for example, as any good interventionalist likes to do.

Conclusions

In today’s practice with many patients with multiple stenoses and often complex CAD, coronary pressure measurement and FFR are both useful methods for better decision making in the catheterization laboratory and for guiding coronary revascularization. FFR results in more accurate selection of lesions and patients who benefit from revascularization from those who will not. Systematic use of FFR in appropriate situations results in direct benefit for the patient by reducing symptoms and avoiding adverse events such as death, MI, or acute coronary syndromes.

Apart from that, it is an interesting methodology that gives insights into coronary physiology and our understanding of what is truly happening in the coronary circulation in both health and disease.

FFR supports the concept of functionally complete revascularization, that is, revascularization of ischemic lesions and medical treatment of non-ischemic ones.

References


