REVIEW

Fractional flow reserve: Concepts, applications and use in France in 2010

Mesure de la réserve coronaire : concept, indications et utilisation en France en 2010

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Received 24 August 2010; received in revised form 18 October 2010; accepted 19 October 2010
Available online 25 November 2010

Summary Fractional flow reserve (FFR) is emerging as a useful clinical tool for assessing the functional significance of coronary atherosclerosis. As opposed to anatomical approaches, physiological measurements (particularly pressure-derived FFR) assess the function of the coronary circulation and offer the possibility of ‘ad hoc’ treatment. The use of FFR is still limited in France because there is no financial support. The present review will focus on coronary pressure-derived FFR.

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MOTS CLÉS
Réserve coronaire ; Angiographie ; Intervention coronaire percutanée ; Revascularisation

Abbreviations: CABG, coronary artery bypass graft; CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microvascular resistance; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; Pd, distal coronary arterial pressure; Pv, coronary venous pressure; R, resistance of the coronary microvascular compartment; Tmn, mean transit time.

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doi:10.1016/j.acvd.2010.10.006
Introduction
The goal of any treatment is to improve patients’ prognosis and/or symptoms. Accordingly, the goal of any diagnostic tool is to guide decision-making, to apply optimal treatment to individual patients. Any diagnostic tool not fulfilling these requirements should not be used in patients. FFR is emerging as a useful technique for the assessment of coronary artery stenosis. FFR evaluates the functional significance of coronary artery stenosis and helps interventional cardiologists with ‘on the spot’ decision-making [1,2]. This is especially relevant when a coronary angiogram shows mild-to-moderate coronary atheroma. The usefulness of FFR is also further clinically validated in complex bifurcation lesions, ostial stenoses, multivessel disease and left main stenoses [3]. As opposed to anatomical approaches, physiological measurements (particularly pressure-derived FFR) assess the function of the coronary circulation and offer the possibility of ‘ad hoc’ treatment [4]. The use of this tool is still limited in France because there is no financial support. The present review will focus on coronary pressure-derived FFR.

Coronary circulation
To comprehend the concept of FFR, the coronary circulation can be viewed as a two-compartment model. The first compartment consists of large epicardial vessels (> 400 microns), which are also referred to as ‘conductance vessels’ because they have minimal resistance to blood flow. Therefore, the pressure in the distal part of a healthy human coronary artery should be equal to central aortic pressure. The second compartment consists of arteries smaller than 400 microns, or ‘resistive vessels’ (Fig. 1). Myocardial flow is controlled predominantly by resistive vessels.

Physiological indices of the coronary circulation
In the next few paragraphs, we will discuss some of the relevant indices of coronary physiology that can be used to estimate coronary circulatory function as a guide to clinical decision-making. FFR is the best validated of all these physiological indices. In the first part of this section, we will briefly describe the other indices before focusing on FFR.

Coronary flow reserve
CFR is defined as the ratio of hyperaemic blood flow (Qmax) to resting myocardial blood flow (Qrest) (i.e., CFR = Qmax/Qrest). The normal value for CFR is still not well defined and normal values differ from study to study [5,6]. There is some consensus of opinion, however, suggesting that a value >4 should be considered as normal, which means that microvascular resistance can decrease by a factor of 4 [7]. As absolute myocardial flow is not easy to determine, surrogate markers of flow are commonly used, such as flow velocities assessed by the Doppler Wire (FloWire, Volcano Inc., Rancho Cordova, CA, USA) or Tmn assessed by the PressureWire (Saint Jude Medical Systems Inc., Uppsala, Sweden). Regardless of the method used to measure CFR, this technique has several limitations: resting flow is highly variable; there is considerable spatial heterogeneity of flow velocity distal to an epicardial stenosis; hyperaemic flow is directly dependent on systemic blood pressure; the hyperaemic and resting measurements are performed simultaneously not successively; and CFR is not specific for an epicardial stenosis, as the CFR value depends on both epicardial vessels and microcirculation. When CFR is low, it is impossible to distinguish whether this value is related to an epicardial artery stenosis alone, microcirculatory dysfunction alone or a combination of both. Owing to these limitations, CFR is not used routinely in clinical practice to assess the haemodynamic significance of a coronary stenosis and has limited value in clinical decision-making.

Index of microvascular resistance
The resistance of a vascular system is defined as the ratio of the pressure gradient divided by the flow across that particular system. Accordingly, the resistance of the coronary microvascular compartment is equal to the ratio (Pd−Pv)/Q, where Pd is distal coronary arterial pressure and Pv is coronary venous pressure or right atrial pressure. In the coronary circulation, Pv is often almost negligible. Fearon et al. [8] introduced the concept of IMR, considering that the Tmn during maximal hyperaemia is inversely proportional to hyperaemic flow.

Therefore, during maximal hyperaemia, IMR = Pd/1/Tmn = Pd × Tmn. IMR is specific for the microcirculation and is simple to obtain, as Pd and Tmn can be obtained simultaneously with the PressureWire. This technique has been well validated in animals and was recently used in the setting of acute coronary syndromes to predict clinical outcomes and assess the effect of treatment [5,7–12]. Nevertheless,
Fractional flow reserve

FFR is the ratio of maximal myocardial blood flow depending on a stenotic artery to maximal myocardial blood flow if that same artery were to be normal. In other words, it is a fraction of the maximal normal flow, assuming that these measurements are obtained when the microvasculature resistance is minimal and constant (maximal hyperaemia) [1,2].

FFR represents the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis. If FFR is 0.60, it means that maximal myocardial blood flow reaches only 60% of its normal value. Conversely, FFR provides the interventionist with the exact extent to which optimal stenting of the epicardial stenosis will increase maximal myocardial blood flow. An FFR of 0.60 implies that stenting the focal stenosis responsible for this abnormal FFR should bring FFR to 1.0, which represents an increase in maximal myocardial blood flow of 67%. In addition, FFR excludes the confounding influence of the microcirculation, changes in haemodynamics or contractility [1,13].

FFR is a ratio of two flows. It has been shown, however, that this ratio of two flows can be derived from two pressures, provided they are both measured during maximal hyperaemia. The theoretical explanation of this relationship between hyperaemic flows and hyperaemic pressures is displayed in Fig. 2.

Fractional flow reserve: practicalities

Catheters

The use of diagnostic catheters is technically feasible [14]. However, due to the higher levels of friction hampering wire manipulation, the smaller internal calibre prejudicing pressure measurements and the inability to perform ad hoc PCI using diagnostic catheters, the use of guiding catheters is recommended.

Wires

Two pressure wire systems are available on the market for measuring intracoronary pressure, namely the PressureWire (Saint Jude Medical Systems Inc., Uppsala, Sweden) and the Volcano WaveWire (Volcano Inc., Rancho Cordova, CA, USA). The sensor is located 30 mm from the tip, at the junction between the radiopaque and radiolucent portions. The last generations of these 0.014 inch wires have similar handling characteristics to most standard angioplasty guide wires.

Hyperaemia

To measure FFR, it is absolutely essential to achieve maximal vasodilatation of the two vascular compartments of the coronary circulation, namely the conductance arteries (epicardial) and the resistance arteries (microvasculature). The pharmacological agents most often used to induce hyperaemia are listed in Table 1 [15—17]. A bolus of 200 mg isosorbide dinitrate (or any other form of intracoronary nitrate) abolishes any form of vasoconstriction.

IMR is a novel index that needs further validation in clinical studies.
The presence of a significant stenosis in the LMCA is of critical prognostic importance and often determines the type of treatment [13]. Therefore, the evaluation of haemodynamic severity is essential and non-invasive testing is often non-contributive [4]. As mentioned before, the potential of coronary angiography to evaluate the haemodynamic severity of a stenosis is limited, especially in the LMCA [21]. In addition, there are significant interobserver variations in the assessment of LMCA lesions [22]. There may be several reasons for the discrepancy between angiographic and haemodynamic assessments of LMCA stenoses: the catheter may overlap with the origin of the left anterior descending and the left circumflex arteries, and spillover of contrast medium and incomplete mixing of blood and contrast medium in the proximal part of the L. MCA may render the evaluation of an ostial lesion difficult; the LMCA is generally short and, when present, atherosclerosis is often distributed diffusely, so that a normal segment is lacking, which leads to an underestimation of the ‘reference’ segment and thus to an underestimation of LMCA stenoses by both visual estimation and quantitative coronary angiography; the myocardial mass that depends on the LMCA is large, so the amount of blood that flows through it is great, and substantial trans-stenotic flow, in turn, induces large pressure gradients, especially during hyperaemia [23]. Finally, revascularization strategies based solely upon an angiogram are often inappropriate in patients with an LMCA stenosis.

FFR can identify LMCA stenosis responsible for ischaemia. Several studies showed that an FFR-guided strategy for equivocal LMCA lesions is safe and related to a favourable clinical outcome [23–27]. Hamilos et al. assessed the long-term clinical outcome of 213 patients with an angiographically equivocal LMCA stenosis in whom the revascularization strategy was based on FFR. When FFR was ≥ 0.80, patients were treated medically (n = 138) and when FFR was < 0.80, a CABG was performed (n = 75). The 5-year survival and event-free survival rates were similar in both groups, supporting the use of FFR in patients with LMCA disease [23].

Multivessel disease

Patients with ‘multivessel disease’ actually represent a very heterogeneous population. In these patients, FFR measurement has a major implication for the mode of revascularization strategy (PCI vs CABG). Furthermore, determining which lesion(s) warrant stenting and which do not can be difficult in these patients, when using
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Figure 3. Fractional flow reserve (FFR) in intermediate lesion. A) Intermediate stenosis of the middle left anterior descending estimated at 45% by quantitative coronary angiography. B) Typical example of simultaneous aortic pressure (Pa) and distal coronary pressure (Pd) recordings at rest and during maximal steady state hyperaemia, as induced by an intracoronary bolus of adenosine. Soon after starting the infusion, the decrease in distal pressure is preceded by a transient increase in aortic pressure.

non-invasive imaging modalities. For example, myocardial perfusion scintigraphy is limited in its ability to accurately localize lesions responsible for ischaemia in these patients [21,28]. Preliminary FFR-guided revascularization strategies in patients with multivessel disease were very encouraging [4]. A recent randomized multicentre study (FAME: FFR versus Angiography for Multivessel Evaluation) in 1000 patients showed that routine measurement of FFR during PCI with drug-eluting stents in patients with multivessel disease reduced the rate of the composite end-point of death, myocardial infarction, re-PCI and CABG at 1 year by approximately 30% and reduced mortality and myocardial infarction at 1 year by approximately 35%, compared with current angiography-guided strategy. Moreover, the FFR-guided strategy reduces the number of stents used, decreases the amount of contrast agent used, does not prolong the procedure and is cost saving [29,30].

Myocardial infarction

After a myocardial infarction, previously viable tissue is partially replaced by scar tissue. Therefore, the total mass of functional myocardium supplied by a given stenosis in an infarct-related artery will tend to decrease [31]. By definition, hyperaemic flow and thus hyperaemic 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 myocardial infarction. It simply illustrates the relationship that exists between 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 Fig. 4. Recent data have confirmed that the hyperaemic myocardial resistance in viable myocardium within the infarcted area remains normal.
This further supports the application of the established FFR cut-off value in the setting of partially infarcted territories. Earlier data had suggested that microvascular function was abnormal in regions remote from a recent myocardial infarction [33,34]. However, more recent work, taking into account distal coronary pressure, indicates that hyperaemic resistance is normal in these remote segments [35]. These data support the use of FFR to evaluate stenoses remote from a recent myocardial infarction.

**Bifurcation lesions**

Bifurcation lesions are particularly difficult to assess angiographically because of the overlap orientation relative to parent branch and radiological artefacts. Data supporting the use of FFR in guiding PCI for bifurcation lesions are limited. Two recent studies by Koo et al. demonstrated: that after stenting, the ostium of the side branch often looks 'pinched' but is often overestimated by angiography (measurement of FFR identifies a minority of lesions that are functionally significant) [36]; and a favourable outcome for FFR-guided side branch PCI strategy for bifurcation lesions. Indeed, when kissing balloon dilation was performed only in ostial stenoses with an FFR < 0.75, the FFR at 6 months was > 0.75 in 95% of all cases [37].

**Coronary artery bypass graft lesions**

In theory, the assessment of stenosis severity in CABGs by FFR should not be different from FFR assessment of native vessels. At present, there are no clinical outcome data available regarding the use of FFR in graft stenosis. Therefore, FFR should be used with caution in bypass graft stenosis. Nevertheless, in patients requiring CABG for multivessel revascularization, angiographic lesions of uncertain significance would benefit from FFR, providing prognostic information regarding potential of future bypass graft patency. Botman et al. showed that the rate of occlusion was approximately three times higher when the bypass was placed on a native artery with a haemodynamically non-significant stenosis [38]. This study suggested that FFR could have serious implications for best long-term CABG outcomes.

**Post stenting**

Angiography alone is not a precise technique for detecting local areas of incomplete stent expansion [39]. In 40–70% of stents that appear well deployed by angiography, intravascular ultrasound imaging reveals a region of the stent that is underexpanded compared with the remainder of the stent and with the reference segments [40,41]. Intravascular ultrasound is the gold standard for assessing optimum stent deployment and its results are well correlated with the FFR. FFR has the advantage of being easier to use but its results are more controversial. In a small single-centre study evaluating coil stents, an FFR ≥ 0.94 was identified as the appropriate threshold defining optimal stent deployment [42]. This finding has not been evaluated in a broader trial with current generation stents.

**Practical tips and tricks**

**Be consistent in your fractional flow reserve-based decisions**

It is important to be consistent in decision-making regarding FFR. Traditionally, cardiologists have been trained to assess coronary stenosis by angiogram, and the use of FFR requires a change in mindset. If, after measuring an FFR of 0.9, you would decide to perform a PCI anyway or, conversely, if after measuring an FFR of 0.7 you would decide to leave a stenosis in a vessel supplying a large territory, then it is better not to perform the test at all. In addition, inconsistencies in decision-making will weaken the enthusiasm of catheterization laboratory personnel and decrease the operator’s credibility (keep in mind: ‘pressure never lies’).

**Be careful with the sensor**

Take care with the sensor that is located at the junction between the radiopaque and radiolucent part of the wire.

**Thin introducer needles**

Use thin introducer needles—but not if there is significant backflow. The valve of the Y-connector should be tightly closed.

**Equalization is essential**

The aortic pressure transducer should be positioned at a height 5 cm below the patient’s sternum, which is estimated to be the location of the aortic root. After calibration of aortic pressure and the microchip of the PressureWire, the PressureWire is advanced into the proximal part of the target artery, located at the tip of the guide, in order to equalize both pressures electronically. After a long procedure, differences may sometimes occur between aortic and coronary pressures. Morphology of the distal pressure can cause the difference between true pressure gradient (ventricularized) and drift (exactly the same morphology).
Avoid side-holes catheters

With side-holes catheters, the guiding pressure will result in a pressure ‘somewhere in between’ coronary and aortic pressure (side holes and end hole). Intracoronary administration of drugs is unreliable.

Recognize ‘whipping’ of the wire

When the guide-wire sensor hits the coronary wall, an increase in the pressure signal can be seen. Pull back (or advance) the wire a few millimetres.

French register of fractional flow reserve

Every year in France 260,000 coronary angiograms are performed; however, measurement of FFR is conducted in only 2000 cases (< 1%). A national registry (R3F Register) was established in March 2008 to evaluate the use of FFR in France. So far, 1051 patients have been included in 25 centres. Follow-up is scheduled at 1, 6 and 12 months. Objectives of this registry are to evaluate: the use of FFR in France (indications, etc.); FFR-guided revascularization strategies (compared with current angiography guided strategy); and to report cost effectiveness.

Financial register: where is it?

At present, there is no financial support for the use of FFR in France. Discussions are underway with the Ministry of Health and should reach an agreement regarding reimbursement soon. FFR has demonstrated favourable outcomes in patients with intermediate single-vessel stenoses, complex bifurcation and ostial branch stenoses, multivessel coronary artery disease, and left main stenoses. Furthermore, one of the major arguments in favour of FFR use is a reduction in cost [30,43,44]. In patients with an intermediate coronary lesion and no prior functional evaluation, measuring FFR can lead to significant cost savings. Indeed, a 10—14% reduction in cost was achieved compared with a strategy of systematic PCI in patients with single- or multivessel coronary artery disease, and left main stenoses. Furthermore, one of the major arguments in favour of FFR use is a reduction in cost [30,43,44]. In patients with an intermediate coronary lesion and no prior functional evaluation, measuring FFR can lead to significant cost savings. Indeed, a 10—14% reduction in cost was achieved compared with a strategy of systematic PCI in patients with single- or multivessel disease, and 39% compared with performing coronary angioplasty. Circulation 1993;87:1354—67.

Conflict of interest statement

None.

Acknowledgements

Dr Puymirat was supported by a grant from the French Federation of Cardiology.

References


Conclusion

The use of invasive coronary physiology in the catheterization laboratory is increasingly common. FFR introduces a new concept for patients with suspected or known coronary artery disease, as it combines physiological information, anatomical information and the possibility of immediate revascularization, if needed. With minimal experience, the technique of FFR measurement is simple and safe. Clinical outcome data from patients in whom the revascularization strategy has been based on FFR measurements are very encouraging. The current clinical evidence for FFR should encourage cardiologists in France to use this tool in the catheterization laboratory.


