Fractional flow reserve and complex coronary pathologic conditions

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Fractional flow reserve (FFR) is a well-validated index for assessing the physiologic significance of a coronary stenosis in most clinical conditions encountered in today’s catheterisation laboratory. The aim of this paper is to provide a short overview of the theoretical background of the coronary pressure-derived FFR index and its clinical applicability in guiding complex coronary intervention procedures.

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KEYWORDS
Fractional flow reserve; Pressure-sensing guidewire; Vasodilator; Hyperaemia

Introduction

Coronary angiography is limited in its ability to determine the physiologic significance of coronary stenoses. As a result, intracoronary physiologic measurement of myocardial fractional flow reserve (FFR) was introduced and has proven to be a reliable method for determining the functional severity of coronary stenosis. Using a pressure-sensing guidewire, distal pressure can now be easily assessed and FFR can be calculated from the ratio of mean distal coronary artery pressure to mean aortic pressure during maximal hyperaemia. In a landmark study, Pijls and colleagues showed that a cutoff value of 0.75 reliably detects ischaemia-producing lesions for patients with moderate coronary stenosis and chest pain of uncertain origin, with a sensitivity of 88%, specificity of 100%, and diagnostic accuracy of 93%. A FFR of less than 0.75 is functionally significant and has been found to correlate well with the presence of ischaemia as measured by noninvasive testing modalities such as perfusion scintigraphy, stress echocardiography, and bicycle exercise testing.

Retrospective and prospective work from the DEFER study suggested that deferral of intervention in patients with chest pain referred for angioplasty of an intermediate stenosis with a FFR of more than 0.75 is safe and results in an excellent clinical outcome. Moreover, it has been shown that a high FFR value after balloon angioplasty or stenting is associated with a favourable long-term outcome.

In addition to assisting clinical decision-making about the need for intervention and evaluating the results of coronary intervention procedures, the coronary pressure-derived FFR index is also helpful in monitoring and guiding some complex pathologic conditions.

Concept and features of FFR

The concept of coronary pressure-derived FFR has been extensively studied and clinically validated. Fig. 1 shows a schematic illustration of the FFR concept. Under maximum arteriolar vasodilatation, the resistance imposed by the myocardial bed is minimal and blood flow is proportional to driving pressure. In the absence of stenosis, the driving pressure over the myocardium is 100 mmHg at maximum vasodilatation. However, the presence of stenosis results in a hyperaemic gradient of 40 mmHg, thus the overall maximum driving pressure falls to only 60 mmHg. This implies that the maximum amount of blood flow in this stenotic artery is only 60% of normal maximum flow in the absence of stenosis and, by
and is highly reproducible. Also, as a normal reference blood pressure, heart rate, or myocardial contractility measurement of FFR is independent of changes in systemic pressure to aortic pressure during maximal hyperaemia. Since central venous pressure is the central venous pressure, all measured at maximum hyperaemia. The achievement of maximal arteriolar vasodilatation is critical to obtaining an accurate and reliable FFR value. If maximal vasodilatation is not achieved, the pressure gradient across a lesion will be smaller than expected and FFR will be overestimated. Consequently, the severity of the lesion will be underestimated. Several hyperaemic stimulants, delivered either through IC injection or as a continuous IV infusion, have been used for this purpose, including adenosine, adenosine 5′-triphosphate (ATP), papaverine, and dobutamine. Practically speaking, a desirable hyperaemic stimulant should fulfil the following criteria: rapid onset of action, short duration of action, low cost, lack of significant side effects, and stable steady state. In view of the high safety profile, low cost, and ease of use, ATP or adenosine administered IC are the agents most commonly used for FFR assessment. The study conducted by De Bruyne et al. showed that, at a sufficient dose, ATP, adenosine, and papaverine all induce maximal hyperaemia, but contrast medium does not. Furthermore, the study also suggested that, IC ATP or adenosine (20–40 µg) administration induces a degree of hyperaemia similar to IC administration of 20 mg papaverine. However, only IC papaverine and IV ATP or adenosine are able to induce a complete, true steady-state hyperaemia for a pressure pull-back manoeuvre, which clearly demonstrates the exact location and severity of the stenosis in assessing arteries with long and diffuse disease or multiple lesions. Even though the standard protocol for IC adenosine or ATP administration recommends doses of 15–20 µg in the right coronary artery (RCA) and 18–24 µg in the left coronary artery (LCA), there is evidence suggesting that for some patients higher doses may be needed to

**Pharmacological vasodilator**

The theoretical value for FFR of a normal coronary artery is 1.0, regardless of vessel or patient. The measurement of FFR is independent of changes in systemic blood pressure, heart rate, or myocardial contractility and is highly reproducible. Also, as a normal reference vessel is not required, the concept of FFR can also be applied to patients with multivessel disease.

**Instrumentation**

The use of an infusion catheter is not recommended for coronary pressure measurement, as unpredictable and significant overestimation of the pressure gradient may occur, resulting in underestimated FFR readings. At present, two FDA-approved pressure wire systems are available: Pressure Analyser (RADI Medical Systems, Uppsala, Sweden) and WaveMap (Volcano Therapeutics Inc., Rancho Cordova, USA). These systems both use .014-in. wire with a pressure sensor located 3 cm proximal to the wire tip, which can be used as a primary angioplasty guidewire. Even though 6F or 7F guiding catheters are recommended for FFR measurement, a recent study by Legahey et al. has demonstrated that FFR measurement can also be safely performed through a conventional 4F diagnostic catheter. Intracoronary nitroglycerin and heparin are first administered according to the standard protocol. Afterwards, the pressure-sensing guidewire is zeroed, introduced into the guiding catheter and advanced to its tip. At this point, the equality of the pressures recorded from both pressure-sensing guidewire and guiding catheters is verified. The pressure-sensing guidewire is then further advanced and positioned at least 2 cm beyond the stenosis. The aortic pressure and distal coronary pressure are measured continuously by the guiding catheter and pressure-sensing guidewire. After the pressures stabilise, maximum coronary hyperaemia is induced by either intracoronary (IC) bolus administration or through continuous intravenous (IV) infusion of a vasodilator agent, and FFR is then calculated.

![Fig. 1 Simplified schematic of the coronary artery and its dependent myocardial vascular bed illustrating the concept of FFR. In the absence of stenosis, the driving pressure over the myocardium is 100 mmHg at maximum vasodilation. However, the presence of stenosis results in a gradient of 40 mmHg and the overall maximum driving pressure falls to 60 mmHg. This implies that the maximum amount of blood flow in this stenotic artery is 60% of normal maximum flow in the absence of stenosis and, by definition, FFR is 0.6. The maximum coronary hyperaemia.](image-url)
ensure maximal hyperaemia. A study by Murtagh et al. suggested that a single high dose of 42 μg of IC adenosine was sufficient to induce maximum hyperaemia in both the RCA and LCA in the patients they studied. For patients with FFR in the grey range of 0.75–0.80, a higher dose is recommended to ensure maximal hyperaemia.

**FFR and complex coronary intervention**

**Multivessel coronary disease**

Coronary pressure-derived FFR measurement is very useful in identifying patients with multivessel disease who might benefit from catheter-based treatment instead of surgical revascularisation. If acceptable physiologic assessment criteria are met for all the lesions, catheter-based treatment or coronary bypass surgery can be safely deferred and medical treatment, which is safer and may eventually result in a better outcome, should be used instead.

For patients with multivessel coronary disease, it is important to know which particular lesion is physiologically significant and responsible for reversible ischaemia. With the help of FFR measurement, it is now possible to identify one or more culprit lesions in this type of patients so that catheter-based treatment of culprit lesions can be performed. Studies conducted by Chamuleau et al. showed that FFR is more useful than single-photon emission computed tomography for clinical decision-making and risk stratification in patients with multivessel disease.

**Left main coronary artery (LMCA) disease**

Recently, FFR measurements have been used to assist decision-making in patients with intermediate LMCA disease, in order to determine whether or not bypass surgery should be performed. If the FFR measurement in a case of intermediate LMCA disease is greater than 0.75, coronary bypass surgery is not needed and a safer medical treatment approach can be used instead. Studies conducted by Bech et al. on 54 patients with equivocal LMCA disease demonstrated that coronary pressure-derived FFR is a lesion-specific index to quantify reversible ischaemia caused by LMCA disease, and that deferral of surgical treatment is safe if the FFR value is greater than 0.75. In the 54 patients they studied, medical instead of surgical treatment was used in 24 patients with FFRs greater than 0.75, while coronary bypass surgery was performed in the rest of the patients, who had FFR values less than 0.75. Mean follow-up was 29 months. The survival rates of the patients in the medical treatment and surgical groups were 100% and 97%, respectively. The event-free survival was 76% in the medical treatment group and 83% in the surgical group. No death or acute myocardial infarction occurred in any of the deferred patients.

**Diffuse and long lesions**

In order to quantify lesion severity in a diffusely affected coronary vessel, a pressure pull-back curve is needed. This can be done by withdrawing the pressure-sensing guidewire from a distal to a proximal position very slowly during a steady-state maximum hyperaemia induced by IV ATP or adenosine. This curve represents the pressure gradient over the entire length of the vessel, and clearly demonstrates the exact location and severity of the lesion. This so-called pull-back curve is extremely useful in guiding spot-stenting in a vessel with long and diffuse lesions.

**Tandem lesions**

In the case of tandem lesions, the haemodynamic significance of each individual lesion is influenced by the presence of the other lesion. The FFR of each individual lesion cannot be calculated by the simple classical equation \( \frac{P_d}{P_a} \) as for a single lesion. To obtain accurate FFR measurements in arteries with tandem lesions, a more complex approach must be used. De Bruyne and colleagues have developed equations (Fig. 2) for predicting the FFR of each individual lesion separately in the case of tandem lesions, and these equations have been validated successfully in animals and humans.

**Transplant vasculopathy**

Cardiac allograft vasculopathy (CAV) is the major cause of mortality and morbidity after the first year of heart transplantation. Even though several treatment options are available, such as percutaneous coronary intervention (PCI), repeat cardiac transplantation, and coronary artery bypass grafting, the long-term results are poor.

\[
P_{a} \quad P_{m} \quad P_{d} \quad P_{v}
\]

\[
\text{FFR(A) pred} = \frac{P_{d} - (P_{m}/P_{a})P_{w}}{P_{a} - P_{m} + P_{d} - P_{w}}
\]

\[
\text{FFR(B) pred} = \frac{(P_{a} - P_{m})/(P_{m} - P_{d})}{P_{a} - P_{m} - P_{w}}
\]

Where

- \( P_{a} \) is mean aortic pressure
- \( P_{m} \) is coronary pressure between two lesions
- \( P_{d} \) is coronary pressure distal to the second lesion
- \( P_{w} \) is coronary wedge pressure (distal coronary pressure during balloon occlusion)

**Fig. 2** Simplified schematic illustrating an epicardial vessel with two stenoses. The proximal lesion is A, the distal lesion is B, and the FFR associated with each lesion is indicated by FFR(A)\(_{\text{pred}}\) and FFR(B)\(_{\text{pred}}\). \( P_{a} \) is recorded by the guiding catheter. \( P_{m} \) is the pressure between lesion A and lesion B recorded by the pressure guidewire. \( P_{d} \) is the pressure distal to lesion B measured by a second pressure guidewire. \( P_{w} \) is the distal coronary pressure measured by the pressure guidewire during balloon occlusion, which means that PTCA of at least one lesion should be performed. All pressures are obtained at maximum coronary hyperaemia. \( P_{v} \) is the central venous pressure, which is usually close to zero and thus negligible.
Techniques that can be used as tools for online decision-making to either justify intervention procedures on unstable CAV patients or to avoid unnecessary intervention in stable CAV patients would clearly benefit interventional cardiologists. Casella et al. reported a case in which FFR measurement was used to guide and monitor the results of coronary balloon angioplasty on a CAV patient and the results seem very promising. In addition, a recent study by Fearon et al. on 53 cardiac transplant patients further suggested that the use of physiologic assessment techniques is feasible for screening asymptomatic cardiac transplant recipients for angiographically unapparent transplant arteriopathy. However, more studies on the feasibility and safety of this pressure-derived measurement technique in heart transplant patients are needed.

Myocardial infarction (MI)

Previous studies have demonstrated that FFR measurement is a useful method for physiologic and functional evaluation of coronary artery stenosis in vessels without previous MI. In the case of prior MI, two concerns remain: (1) the mass of viable myocardium is smaller; and (2) impairment of resistance vessels might blunt pharmacologically induced maximal hyperaemia. However, as both the decrease of viable myocardium and impairment of coronary resistance vessels are matched in the infarcted area, FFR is still a reliable indicator for predicting inducible ischaemia, even if the angiographic image of a stenosis might be more severe.

In the acute phase of MI, FFR measurement should not be used due to serious microvascular impairment and treatment should be guided by the clinical symptoms and ECG. Pressure measurements are useful only after the artery has stabilised.

Recently, the reliability of applying FFR measurement in the study of patients with previous MI has attracted the attention of several researchers. Claeyss et al. provide data that FFR is minimally affected (+5%) in patients with severely impaired microvascular function and may still be applied to patients with recent MI. De Bruyne and colleagues have demonstrated that FFR assessment criteria are also valid in detecting reversible ischaemia in patients at least 6 days after an MI. Even although there is a “grey area” of FFR measurements of 0.72–0.8, an FFR value of 0.75 is still applicable and reliable for distinguishing patients with positive from patients with negative myocardial scintigraphy, with a sensitivity of 82% and specificity of 87% in the case of prior MI. Another study conducted by Usui et al., comparing FFR and thallium-201 myocardial imaging also showed that pressure-derived FFR is reliable in assessing coronary artery stenosis in patients with previous MI, with a sensitivity of 79% and specificity of 79%.

Unstable angina

The 0.75 cutoff value of FFR was assessed in patients with stable angina. For patients with unstable angina, it is commonly believed that maximal hyperaemic flow can be lower than in patients with stable angina. Consequently, the 0.75 cutoff value of FFR might not be valid in these patients and the appropriate value needs to be determined. However, a recent study by Leesar et al. of patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) further demonstrated that the FFR assessment criteria are also valid in this patient group. A decision-making strategy based on the 0.75 cutoff is superior to a more conservative approach based on stress perfusion scintigraphy (SPS). FFR reduces the duration and, therefore, the cost of hospitalisation compared with SPS. These benefits are not associated with a longer procedure time, radiation exposure, or clinical event rate.

Summary

In this era of expensive drug-eluting stents, a cost-effective strategy may include the determination of the haemodynamics of a stenosis in the catheterisation laboratory before stenting, especially in the management of patients with multivessel disease. It is important to know which lesions should be stented and which might be left alone. Some lesions that are deemed to be “haemodynamically nonsignificant” may actually be significant and should be revascularised. Haemodynamic studies can reduce the number of stents used and overall medical expenditures.

The main drawback of FFR measurements occurs in the presence of microvascular disease, as this index does not take into consideration the contribution of abnormal microvasculature. The ideal means of assessing patients with microvascular disease is a combination of coronary flow reserve (CFR) and FFR measurements. A low FFR and CFR indicate significant epicardial disease, whereas a high FFR and low CFR indicate significant microvascular disease. Recent technological advances have made available a new pressure wire equipped with both pressure and temperature sensors. The pressure sensor measures FFR and the temperature sensor allows calculation of CFR by the thermodilution method. For practical decision-making in the catheterisation laboratory, however, FFR alone is usually sufficient.

In summary, the coronary pressure-derived FFR index is reliable for evaluating lesion-specific physiologic stenosis severity. It is a valuable tool for decision-making in patients with complex coronary disease, especially for determining which lesions should be treated and which not, and identifying patients who may benefit from mechanical revascularisation.

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