Medical progress

Current status of assessment of fractional flow reserve

FANG Yi-min, Grisana Grootenhuijs-Triyasut, Pieter A. Doevendans and Yolande Appelman

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Coronary angiography presently remains the main method for the diagnosis and instruction of epicardial coronary disease. However, precise characterization of the significance for any given stenosis is limited by the inability to identify intermediate coronary lesions responsible for ischemia. In clinical practice, in addition to the assessment of the anatomical details of vessel narrowing, a more precise assessment of the impediment to coronary blood flow has become extremely important. At present, several physiological parameters have been introduced to improve discrimination in functional coronary lesion severity during cardiac catheterization. Of these parameters, myocardial fractional flow reserve (FFR) has been the most frequently used and is being increasingly applied to assess the functional significance of intermediate lesions. FFR can provide important information, both for decision making in diagnostic angiography and for monitoring and evaluating coronary interventions.

FFR is the ratio of maximum hyperemic blood flow in the presence of a coronary artery stenosis to the normal hyperemic blood flow in the same vessel in case of the absence of stenosis, FFR=Pd/Pa.1-7 (Pa is the mean aortic pressure measured with the guiding catheter, Pd is the pressure measured from the pressure-sensing guide wire distal from the stenosis and Pv is the central venous pressure, all measured at maximum coronary hyperemia). Although the complete formula for measuring FFR uses venous pressure, generally it can be neglected unless there are clinical indications that venous pressure is markedly elevated, or specific studies of collateral blood flow are anticipated. Therefore, FFR can be expressed as the ratio of the maximum hyperemic mean distal coronary artery pressure and the aortic pressure, i.e. FFR=Pd/Pa.1,5

In a normal artery without stenosis, FFR has an unequivocal value of 1.0. This index is relatively independent of changes in systemic blood pressure, heart rate and myocardial contractility. The established threshold value of FFR is <0.75, which implies that the stenosis is considered significant and shows a good agreement with exercise electrocardiogram, dobutamine stress echocardiography and stress perfusion scintigraphy.

METHODS

After the insertion of a sheath in the femoral artery, a 6-7F guiding catheter without side holes is introduced to the coronary ostium. After the intracoronary administration of 100–200 µg nitroglycerin, 0.3556-mm (0.014-inch) pressure guide wire is advanced to the tip of the guiding catheter, where the pressure measured through the guiding catheter and the pressure measured with the guide wire are verified as being equal. The pressure wire is then advanced into the coronary artery across the stenosis to the most distal part of the vessel, while the tip of pressure guide wire is free within the vessel lumen and not against the vessel wall. The aortic pressure and distal coronary pressure are measured simultaneously in a maximum hyperemic state induced by a vasodilator agent either intracoronary (IC) bolus administration or continuous intravenous (IV) infusion, and FFR is then determined.

The pharmacologic vasodilator stimuli include adenosine, adenosine 5′-triphosphate (ATP), papaverine, nitroprusside or dobutamine. Due to the rapid onset and short duration of action, cost effectiveness, high safety profile, simplicity and facility, steady state, the most widely used pharmacologic agent to induce coronary hyperemia for FFR measurement is adenosine. Because the distal coronary artery pressure is influenced by both epicardial stenosis and distal resistance, maximal hyperemia is a key determinant for FFR measurement in a fixed epicardial stenosis. Less than maximal vasodilation would overestimate the FFR, which might result in an underestimation of stenosis severity and lead to erroneous clinical decisions in patients with intermediate stenosis. The regularly recommended dosage for intracoronary adenosine bolus injection is 15–30 µg for the right coronary artery (RCA) and 20–40 µg for the left coronary artery (LCA), intravenous adenosine infusion dosage is 140 µg·kg⁻¹·min⁻¹.
APPLICATION

Intermediate coronary stenosis (40%–70%)

FFR assessment is an accurate diagnostic method for determining the physiological significance of an intermediate coronary lesion and distinguishes ischemia-producing lesions from those that do not. It has been shown that patients with an FFR of >0.75, deferral of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) are safe and result in an excellent clinical outcome. Deferral of unnecessary coronary revascularization of non flow-limiting stenoses by pressure measurements may reduce procedural costs and the need for repeated revascularization. Therefore, only patients with an FFR of <0.75, which regards as indicative of a functionally important stenosis, need a PCI or CABG. A recent study by Verna et al demonstrated that unnecessary PCI may be saved in more than half of individual coronary stenoses and there was not a nonlinear correlation between FFR and quantitative coronary angiography (QCA). The risk of major adverse cardiac events (MACE) and target vessel revascularization (TVR) in patients with FFR >0.75 and deferral of PCI was lower than the risk associated with PCI. In their study on 112 patients with 175 stenoses including 71 multivessel coronary artery disease patients (MVD) (63%) and 30 patients (27%) with unstable symptoms, based on the results of FFR, PCI was deferred in 67 stenoses in 54 patients (FFR >0.75, group I). In the remaining 58 patients (group II) with 108 diseased vessels, PCI was performed in one or more functionally significant stenoses (FFR <0.75) and deferred in nonsignificant stenoses (FFR >0.75). During a median period of 34 months follow-up, MACE occurred in 12.9% of group I patients and in 24.1% of group II patients, TVR was required in 5% of the stenoses untreated based on FFR result in both groups and in 12.6% of stenoses that underwent PCI.

Multivessel coronary artery disease (MVD)

In patients with MVD, it is attractive to have techniques to determine which particular culprit lesion is physiologically significant and is responsible for reversible ischemia. Since FFR is a reliable and lesion-specific index of stenosis severity, it is possible to identify one or more culprit lesions in such patients, when PCI or CABG can be avoided and performed, even if initially planned on the basis of visual assessment by the angiogram. Wongpraparut et al analyzed 137 patients (312 vessels) with MVD to compare FFR-guided PCI (PCI of stenosis with an FFR <0.75) to conventional PCI (PCI was performed by visual estimation of the stenosis). In the FFR-guided PCI group (57 patients with 128 stenoses), PCI was performed in 48 patients (53 stenoses). In the conventional PCI group (80 patients with 184 stenoses), all patients underwent PCI. The average number of stenoses per patient that underwent PCI and the cost of the procedure were significantly higher in the conventional PCI group compared to the FFR-guided PCI group (2.27±0.50 vs 1.12±0.30 stenoses and 3167±1194 dollars vs 2572±934 dollars, respectively; P <0.001). During a 30-month follow-up period, FFR-guided PCI significantly reduced the number of TVR and MACE (5% vs 23% and 8% vs 27%, respectively; P <0.01), increased event-free survival estimate (89% vs 59%, P <0.01). Nevertheless, the optimal revascularization strategy (PCI or CABG) remains a problem for patients with MVD. Botman et al compared the long-term outcomes of patients with MVD undergoing selective PCI of only hemodynamically significant lesions (FFR <0.75) to patients undergoing CABG of all stenoses. One hundred and fifty patients with MVD (381 coronary arteries) referred for CABG. If the FFR was <0.75 in three vessels or if the FFR was <0.75 in two vessels including the proximal left anterior descending artery (LAD), CABG was performed (CABG group). If only one or two vessels were physiologically significant (not including the proximal LAD), PCI of those lesions was performed (PCI group). Of the 150 patients, there were 87 patients who fulfilled the criteria for CABG and 63 patients for PCI. At 2-year follow-up, no differences were found in the number of MACE including death, acute myocardial infarction (AMI), repeat revascularization and anginal status. Recently, a large multicenter, randomized trial (FAME study) by Tonino et al demonstrated that routine FFR measurement of all lesions in patients with MVD significantly reduced MACE at 1 year when only PCI with drug-eluting stents was performed in lesions with FFR <0.80. One thousand and five patients with MVD were randomly assigned to undergo PCI guided by angiography alone or guided by FFR measurements in addition to coronary angiography. The number of stents used per patient was 2.7±1.2 and 1.9±1.3, respectively (P <0.001). The 1-year event rate and percentage of patients free from angina were 18.3% and 78%, respectively in the angiography group, 13.2% and 81% in the FFR-guided PCI group, respectively (P=0.02 and P=0.20). This trial confirmed that the use of FFR measurement was useful, safe and seemed cost-effective.

Diffuse and serial diseased lesions

Diffuse disease, multiple sequential stenoses or plaques are commonly present and an objective selection of the most appropriate stenosis to be dilated out of several in sequence is an important interventional decision. FFR measurement is extremely useful in guiding spot-stenting in a vessel with long and diffuse lesions by performing the pressure pullback maneuver. It is known that coronary atherosclerosis is a diffuse process and QCA does not always reflect this. De Bruyne et al obtained FFR in 37 arteries in 10 individuals without atherosclerosis (group I) and in 106 nonstenotic arteries in 62 patients with arteriographic stenoses in another coronary artery (group II). In group I, the pressure gradient between aorta and distal coronary artery was minimal at rest (1±1 mmHg) and during maximal hyperemia (3±3 mmHg), corresponding values were significantly higher in group II (5±4 mmHg and 10±8 mmHg, respectively; both P
The FFR was near unity (0.97±0.02) in group I, but it was significantly lower (0.89±0.08) in group II. In 8% of arteries in group II, FFR was <0.75, the threshold for inducible ischemia. Accordingly, using pressure pull-back recording at maximum hyperemia can provide the necessary information to decide if and where stenting is useful. The location of a focal pressure drop superimposed on the diffuse disease can be identified as appropriate location for treatment. On the other hand, the decline of pressure along the vessel might be so diffuse that interventional treatment is not possible, multivessel/lesion stenting can be avoided and medical treatment or CABG is recommended. Sant'Anna et al described a patient with stable angina and a severe lesion in LAD. The FFR was 0.37 during maximum hyperemia. After stent implantation, the FFR was only 0.75 despite the excellent angiographic result. When the pressure wire was slowly drawn back from the distal portion of LAD to its proximal portion, a continuous and gradual increase in intracoronary pressure was noted, but was not observed in the stent and the patient was asymptomatic.

For patients with multiple sequential stenoses or diffuse coronary artery disease in the same vessel, a stepwise or more gradual decrease in pressure along the artery can be expected during maximum hyperemia. These longitudinal pressure changes can be measured by positioning the pressure wire distal in the coronary artery and pulling it back slowly to the ostium during sustained myocardial hyperemia with vasodilating stimulus persistently given intravenously. In this instance, the hyperemic flow and pressure gradient through the first one will be influenced by the presence of the second one and vice versa. One stenosis will mask the true effect of its serial counterpart by limiting the ability to achieve maximum hyperemia. The fluid dynamic interaction between two serial stenoses depends on the sequence, severity, and distance between the lesions as well as the flow rate. When the distance between two lesions is greater than six times the vessel diameter, they generally behave independently and the overall pressure gradient is the sum of the individual pressure losses at any given flow rate. The precise clinical assessment of each lesion by FFR separately is possible but remains academic as the coronary wedge pressure (during artery occlusion) is needed to perform these calculations. In clinical practice, the stenosis with the largest gradient can be treated first and FFR can be remeasured for the remaining stenosis to determine the need for further treatment.

**Bifurcation lesions**

Assessment of severity of coronary stenosis and PCI in bifurcation lesion remains one of the most challenging lesion subsets in PCI. Treatment of this lesion is associated with low procedural success and high complication and restenosis rates. Angiographic assessment of the severity of bifurcation lesions is hampered by the inherent limitations of angiography, especially overlap of adjacent vessels, angulation, and foreshortening of the origin of the side branch. Therefore, it is still not clear which side branches should be treated after stent implantation of the main branch lesion and how to assess the functional significance of these lesions. Koo et al investigated 97 jailed side branch lesions (vessel size >2.0 mm, percent stenosis >50% by visual estimation) after stent implantation at main branches and found that mean FFR was 0.94±0.04 and 0.8±0.11 at the main branches and jailed side branches, respectively. There was a negative correlation between the percent stenosis and FFR (r=0.41, P <0.001). However, no lesion with <75% stenosis had FFR <0.75. Among 73 lesions with ≥75% stenosis, only 20 lesions were functionally significant. Thus, most of the lesions involving the jailed side branch might not have functional significance and do not require PCI. The use of FFR in the assessment of bifurcation lesions might prevent unnecessary interventions in lesions that are not functionally restrictive. The need for revascularization of the side branch in bifurcation lesions can be guided by hemodynamic parameters as determined by FFR.

**Left main coronary artery stenosis (LMCS)**

In view of the shortcoming of angiography and the limitation of QCA analysis, the angiographic assessment of LMCS may often be particularly difficult and unreliable and may not correlate with its functional significance. Furthermore, autopsy reports have shown many LMCS were mildly diseased, but were often reported as significantly stenosed by angiography. It has been established that withdrawal from intervention in patients with isolated borderline LMCS with FFR ≥0.75 is safe and associated with favourable clinical outcomes. A study by Jasti et al demonstrated that when decision-making about revascularization was based on physiological data, a significant number of patients (37 patients in 55 patients) can be spared from unnecessary CABG or PCI, and that in patients with an ambiguous LMCS, a decision based on an FFR cut point of 0.75 to proceed with revascularization or medical therapy was associated with excellent 38-month survival and event-free survival rates. Lindstaedt et al observed 51 patients with intermediate LMCS (40%–80%). If FFR was <0.75 along the LM, CABG was recommended, if FFR was >0.80, medical treatment or PCI elsewhere in the coronary tree was chosen. After mean follow-up of (29±16) months, estimated survival and event-free survival were 81% and 66% respectively in the CABG and in the non CABG 100% and 69% respectively.

**Evaluating the results of implanted stents**

The restenosis rates after implanting a bare-metal stent (BMS) or a drug-eluting stent (DES) are 20%–40% and 5%–10%, respectively and it is probably higher in complex coronary lesions. Because normal epicardial coronary arteries provide no resistance to blood flow, optimum coronary stenting should at least result in the disappearance of any hyperemic pressure drop within the treated coronary segment. FFR has been proposed for
the assessment of optimal stent deployment while QCA alone is not a precise technique to detect local areas of incomplete stent expansion.29 A recent study in 119 patients performed by Klauss et al26 has shown that a post-interventional FFR >0.95 was a significant and independent predictor for developing adverse cardiac events (death, MI, TVR) and post-interventional FFR <0.95 increased the risk of adverse outcome about sixfold compared to FFR ≥0.95 during a follow-up of 6 months. In addition, Pijls et al27 demonstrated in a study with 750 patients and apparently satisfactory stent implantation (residual diameter stenosis <10% by visual estimation) that FFR was a strong independent predictor of outcome at 6 months; the higher the post-stenting FFR, the lower the MACE. For patients with a post-stenting FFR >0.95, the MACE was 4.9%; for values between 0.90 and 0.95, it was 6.2%; for values between 0.80 and 0.90, it was 20.3%; and for post-stenting FFR <0.80, the MACE was 29.5% (P <0.001).

**In-stent restenosis (ISR)**

The main limitation of implanting stents is ISR and the optimal treatment strategy of ISR remains unclear. Although some treatments (cutting balloon angioplasty, vascular brachytherapy, DES) have been used, ISR is still not eliminated and is expensive to treat. Therefore, it is clinically important to identify patients with a favourable clinical outcome, who are not expected to obtain further benefit from additional interventional treatment. The best way is to prevent unnecessary treatment in a patient with a nonsignificant ISR. The use of FFR >0.75 in these patients with moderate or intermediate ISR can safely avoid new complex and expensive unnecessary TVR based solely on QCA and results in a better clinical outcome. Krüger et al27 studied 42 patients with intermediate ISR (40%–70%) and found that FFR averaged 0.77±0.15 and was <0.75 in 20 patients. In the 22 stented patients with an FFR >0.75, no MACE occurred related to the stented lesion in the subsequent 6 months. Another study by Lopez-Palop et al20 also demonstrated that QCA was of no value in discriminating functional significance of ISR <70% measured by visual assessment. In their study on 25 lesions in 26 patients with angiographically intermediate ISR (40%–70%), an FFR value >0.75 was obtained in 41 lesions (63%), 21 of them with stenosis ≥50%. The co-efficient of correlation between parameters of QCA and FFR value was <0.5, furthermore, no events related to the non-treated lesions were observed.

**LIMITATION**

**Dosages and approach**

Induction of maximal hyperemia is a prerequisite for a reliable estimation of FFR, but the optimal dosing to achieve maximal vasodilation is still unclear.10,29 A lot of studies showed that recommended standard dose of adenosine was usually sufficient to cause maximal hyperemia in both the RCA and LCA systems. However, for some patients especially in patients with FFR in the borderline range of 0.75–0.80, a higher dose of adenosine was needed to ensure maximal hyperemia, otherwise lesion severity would be underestimated and subsequent treatment would be inappropriate. Casella et al20 demonstrated that high doses of IC adenosine up to 150 µg were needed to ensure maximal hyperemia in some patients, and such high doses were safe and associated with few adverse systemic effects compared with the standard dose.

Many data indicated that intracoronary bolus injection was equivalent to intravenous infusion for determination of FFR in a large majority of patients, however, studies have demonstrated that IC adenosine was sometimes inadequate for the induction of maximal hyperemia and a repeated higher IC adenosine may be helpful.31,32 Intravenous infusion requires a large venous access, a large amount of adenosine and a longer procedure time. With IC adenosine, the duration of the hyperemic state is sometimes too short for a pressure pullback maneuver and it is not recommended in ostial stenosis.33 Koo et al10 demonstrated that intracoronary infusion 180–240 µg/min of adenosine was also a safe and effective method of inducing maximal hyperemia for FFR measurement.

**Grey zone of the ischemic threshold (FFR value 0.75–0.80)**

The FFR range of 0.75 to 0.80 is commonly considered to be the “grey zone” in which clinical judgement must complement quantitative assessments in forming the final treatment decision. Still a small number of patients with an FFR between 0.75 and 0.80 have proven inducible ischemia.34 Hence, deferral of PCI may be unjustified for some patients. In fact, similar mean FFR values have been reported in studies that used the cut-off values of 0.80 rather than 0.75 to defer coronary revascularization.23,35 Previous studies have suggested that deferring coronary revascularization in moderate coronary lesions with FFR values in the “grey zone” might be associated with a higher rate of cardiac events. Legalery et al35 reported a cardiac event rate of 21% at 1-year follow-up in a group of 34 patients who did not undergo revascularization on the basis of FFR values between 0.75 and 0.79. Also, Chamuleau et al36 identified an FFR value of 0.79 as the best cut-off point to predict cardiac events during follow-up. Therefore, it may be of clinical importance in some patients, when FFR is 0.75–0.80, and a change of 0.05 reclassifies the lesion from amenable for conservative therapy to a lesion which should be treated invasively.4,30 Rzeczuch et al37 have demonstrated that an increase of the intracoronary adenosine dose from 30 to 60 µg was well tolerated and caused further decrease in the FFR values in 36 patients with 53 moderate coronary lesions. The mean value of FFR30 was significantly higher than FFR60 (0.854± 0.152 vs 0.836±0.162, P <0.001). In 29 (54.7%) evaluated lesions, FFR30 values were higher than FFR60; in 12
(22.6%) measurements the difference exceeded 0.02, and in 8 (15%) cases exceeded 0.05. Thus, the use of a standard dose of adenosine may artificially increase the FFR value and cause erroneous selection for conservative therapy. Barbato et al37 discovered that if FFR was between 0.75 and 0.80, administration of adrenergic blockade (phenolamine and urapidil, especially latter) dropped the value of FFR from above 0.75 to below this threshold value in some patients. Another study by Aarnoudse et al38 showed that in 15 patients who did not have microvascular disease, no differences in hyperemic response to adenosine were noted, whether or not α-blockade (3 mg of intracoronary infusion phenolamine) was given before adenosine administration. In another 15 patients who had microvascular disease, some increases in hyperemic response were observed after administration of phenolamine and FFR levels decreased from 0.74 to 0.70 using intracoronary adenosine (P=0.003) and from 0.75 to 0.72 using intravenous adenosine (P=0.04). Therefore, in selected patients who have clear microvascular dysfunction and in which FFR is in the grey zone (0.75 to 0.80), additional intracoronary administration of phenolamine can be used to ensure the presence of truly maximum hyperemia.

Myocardial infarction (MI) and microvascular disease

In the absence of a stenosis and collaterals, the myocardial flow is equal to coronary flow. In the case of a stenosis with collaterals, however, myocardial flow is not equal to coronary flow but increasingly exceeds coronary flow due to the collateral flow.39 More recent studies have suggested that microvascular resistance paradoxically increases with increasing stenosis severity.40-42 The presence of previous MI may blunt the maximal hyperemic response, which has been attributed to infarct-related microvascular dysfunction. As the coronary blood flow in AMI patients with microvascular damage is restricted, the pressure drop across the stenosis during hyperemia may be smaller than expected. However, although the effects of microvascular dysfunction on FFR in MI patients remain undetermined, microvascular dysfunction is likely to restrict coronary flow dynamics.39,43 In such cases, the FFR may not accurately reflect the degree of coronary lesion severity and underestimate it. FFR can be influenced by several factors including time after the onset of MI, myocardial stunning or hibernation, severity of the stenosis, infarct size and the presence of collateral blood flow. Tamita et al43 compared 33 AMI patients within 12 hours to 15 patients with stable angina pectoris. Assessment of the 48 lesions by means of intravascular ultrasound (IVUS) and FFR measurements after successfully stenting showed that post-interventional FFR was higher in AMI compared with angina pectoris patients (0.95±0.04 vs 0.90±0.04; P=0.002), although there were no significant differences in IVUS. AMI patients were assigned to two subgroups based on their post-procedural Thrombolysis on Myocardial Infarction (TIMI) flow grade (23 patients with TIMI 3 and 10 with TIMI 2). There were no differences in IVUS between the AMI subgroups, while FFR was higher in the patients with TIMI 2 compared to those with TIMI 3 (0.98±0.02 vs 0.93±0.05; P=0.017). Tani et al39 also discovered two patients after AMI with related wall ischemia by single-photon emission computed tomography (SPECT), one with a 73% coronary stenosis in RCA and one with 68% coronary stenosis in LAD. The FFR was 0.89 and 0.87, respectively. Therefore, FFR measurements in the residual stenosis of the culprit lesion after MI must be interpreted with caution. However, Samady et al44 studied 48 patients after MI (3.7±1.3) days and compared the relationship of FFR with myocardial contrast echocardiography (MCE) and SPECT. The optimal FFR value for discriminating inducible ischemia on noninvasive imaging was 0.78. This finding demonstrated that FFR of the infarct-related artery accurately identified reversibility on noninvasive imaging early after MI and supported the utility of FFR early after MI. Another recent study by Fischer et al45 showed that deferral of revascularization based on FFR ≥0.75 in patients with acute coronary syndromes (ACS) and moderate coronary stenoses was associated with acceptable and low event rates at 1 year. In their study, revascularization was deferred in 120 lesions (111 patients) with FFR ≥0.75. ACS was present in 35 patients (40 lesions). The 35 patients with ACS consisted of three patients (four lesions) with unstable angina, 11 patients (13 lesions) with recent (within 7 days) ST segment elevation MI and 21 patients (23 lesions) with non-ST segment elevation MI. Among the 35 patients with ACS, there were 3 deaths, 1 MI, and 6 TVR, among the 76 patients without ACS, there were 5 deaths, 1 MI, and 7 TVR (P <0.05, respectively).

CONCLUSIONS

FFR has offered a new and convenient method for choosing PCI or CABG versus conservative treatment. Furthermore, it can be used to evaluate and predict the result of PCI in single vessel disease, MVD and LMCS. The value of FFR has been demonstrated by many experimental and clinical studies, but still requires further investigation to determine its overall significance, particularly in diffuse and complex lesions and after MI. However, most of the former studies with FFR were performed in patients with bare metal stents, and it needs further investigation to demonstrate if these results of the application and value of FFR can be extrapolated to patients with drug-eluting stents.

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