Review Article

Fractional Flow Reserve - A Review

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Abstract:

Percutaneous coronary intervention is being performed over the last 35 years. In this time span a remarkable advancement occurred in this field regarding skill & hardware. Its spectrum has also been widened starting from chronic stable angina to Acute coronary syndrome, single vessel disease to multivessel disease, simple to complex lesions including left main disease. The incidence and prevalence of Ischaemic heart disease (IHD) is also increasing. Number of studies has been conducted to decide how far this modality of treatment can change the morbidity and mortality of the IHD. Cardiologists are trying to detect the culprit lesions, treatment of which will be beneficial for the patient. Number of noninvasive and invasive modalities has been introduced to determine the functional significance of a coronary artery stenosis. Fractional flow reserve (FFR) is one of the relatively new methods in this field. We will discuss some of the basic aspects of FFR and its implications in different subsets of coronary artery disease.

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Introduction:

It is important to emphasize that in coronary artery disease, the most important factor related to outcome is the presence and extent of inducible ischemia.[1,2] A functionally significant stenosis generally causes anginal symptoms and is associated with impaired outcome. If a stenosis has no functional significance, it will not cause angina by definition, and the outcome of medical treatment is excellent with an infarction and a mortality rate of <1% per year.[3,4] Therefore, for decision making with respect to revascularization, it is of paramount importance to determine whether a stenosis is functionally significant.

Coronary angiography still plays a pivotal role in invasive imaging of the coronary arteries, but is of limited value in defining the functional significance of a coronary artery stenosis. Both exercise testing, technetium-99m Sestamibi Single Photon Emission Computed Tomography, and other classic noninvasive tests often indicate ischemia in patients with multivessel disease but fail to distinguish the specific ischemic territories and responsible stenoses. This has resulted in inappropriate stenting of functionally non-significant lesions, and in some cases, inappropriate deferral of PCI of significant lesions because they were deemed non-significant based on angiographic or non-invasive evaluation.[5]To complement angiography, Gould and colleagues developed coronary flow reserve (CFR) and relative CFR in the 1970s. By the early 1990s, fractional flow reserve (FFR) emerged as an important physiologic adjunct to coronary angiography for the assessment of intermediate lesions, directing multivessel percutaneous revascularization and guiding stent deployment.[6] Fractional flow reserve (FFR) is an accurate and lesion specific index to indicate whether a particular stenosis or coronary segment can be held responsible for ischemia.[7,8] It has been shown that deferring stenting in a FFR-negative stenosis (i.e., in the nonischemic zone) is safe, cost effective and associated with excellent long-term outcome.

Definition of FFR:

FFR is defined as the ratio of maximum blood flow in a stenotic artery to maximum blood flow if the same artery were normal. FFR is a ratio of 2 flows: the maximum myocardial flow in the stenotic territory divided by the maximum myocardial flow in the same territory in the normal case. Because flow is proportional to pressure, if resistance is minimal and constant (Ohm's Law), pressure can be used as a surrogate

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of flow during maximal hyperemia, which minimizes resistance. Thus ratio of the 2 flows is expressed as the ratio of 2 pressures, which can be easily measured by a pressure wire and the guiding catheter, respectively. Pressure in a normal coronary artery is equal to aortic pressure (Pa).Therefore, FFR equals Pd/Pa, where Pd is the distal coronary pressure across the stenosis and Pa is the aortic pressure, both measured at maximum coronary hyperemia.

FFR is linearly related to maximum blood flow and its normal value is 1.0, irrespective of the patient, artery, blood pressure, and so forth. FFR of 0.60 means that the maximum blood flows to the myocardial distribution of the respective artery only reaches 60% of what it would be if that artery were completely normal. An increase to 0.90 after stenting indicates that maximum blood supply has now increased by 50%.

Method:

FFR is measured during the process of Coronary Angiography, before and after Percutaneous Coronary Intervention (PCI). For FFR measurement usually coronary guiding catheters are used. During the procedure same anticoagulation protocol is maintained as it is in case of PCI. An activated coagulation time (ACT) of 250 sec is expected.

A special guidewire is needed for this purpose. These are 0.014 inch floppy tipped guidewire with a specific solid-state sensor mounted on it at the junction between the 3-cm-long radiopaque tip and the remainder of the wire. Two such systems exist: the PressureWire (St. Jude Medical Inc., Minneapolis, Minnesota and Uppsala, Sweden) and the PrimeWire (Volcano Inc., Rancho Cordova, California). These pressure wires are connected to an interface (Analyzer Express, St. Jude Medical Inc., Uppsala, Sweden or Combomap, Volcano Inc.), which will show FFR immediately. For FFR estimation it is essential to induce maximal vasodilation of the 2 compartments of the coronary circulation (epicardial or "conductance" arteries and the microvasculature or "resistance" arteries). Nitrate is used for epicardial coronary vasodilatation and intracoronary(IC)/ intravenous (IV) Adenosine or intracoronary Papaverine is used for microvascular circulation.

Before introducing the sensor into the vessel to be studied, the wire is placed at the tip of catheter. Intracoronary bolus of 200-µg nitrate is given. After at least 30 sac pressures are recorded by the sensor and by the guiding catheter and equalized (Pd/Pa =1). Then the wire is introduced into the coronary artery with the sensor distal to the index lesion. Then vasodialtors are to be given for microvascular dilatation. Pharmacologic agents most commonly used are adenosine, papaverine, and adenosine 2A agonists. The preferred and most used method is continuous intravenous administration of adenosine peripherally at 140 µg/kg/min. Maximal hyperemia is usually attained within 1 minute from the start of the infusion. Patients may complain of chest pain, tightness, and shortness of breath on adenosine infusion, which is transient, and can be minimized by warning the patient beforehand about these side effects. Alternatively, intracoronary adenosine infusion can also be used to induce hyperemia at a dose of 30 µg for the right coronary artery and 40 to 60 µg for the left coronary artery. Intracoronary adenosine induces hyperemia faster (within 10 seconds) than intravenous adenosine. Once an FFR value is obtained, adenosine is discontinued and its effect fades away in less than 10 seconds. Pressure is measured by both the catheter tip and the sensor of the pressure wire simultaneously and displayed in the monitor, which will also show the ratio of two pressures (FFR).

FFR has a number of unique characteristics that make this index particularly suitable for functional assessment of coronary stenoses and clinical decision making in the catheterization laboratory.

1. FFR has a theoretical normal value of 1 for every patient, artery, and myocardial bed. The lowest value found in individuals with strictly normal coronary arteries was 0.94.[9,10]
2. Stenoses with FFR <0.75 are almost invariably able to induce myocardial ischemia, whereas stenoses with FFR >0.80 are almost never associated with exercise-induced ischemia. This means that the gray zone for FFR (between 0.75 and 0.80) spans <10% of the entire range of FFR values.

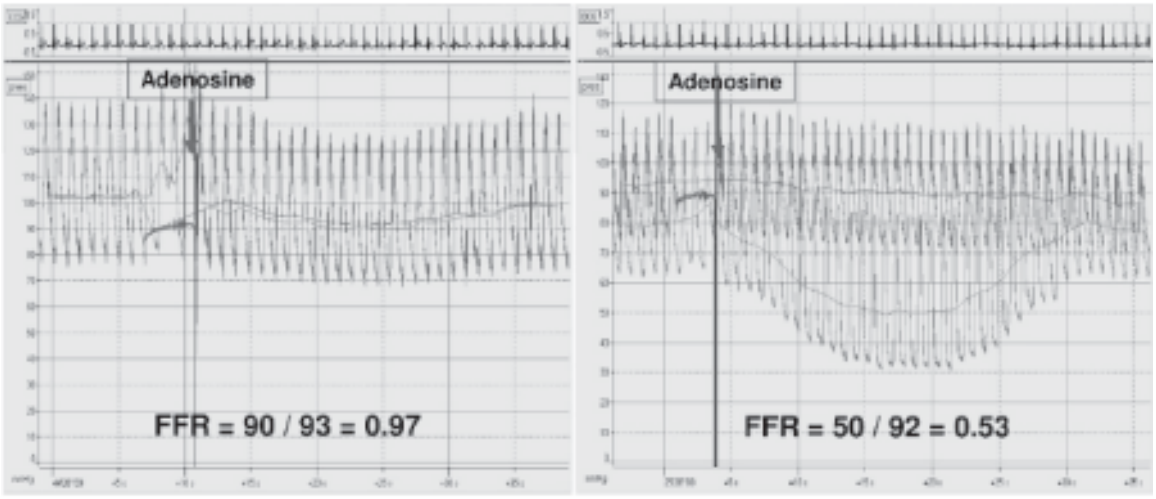

Fig.-1: *FFR in insignificant coronary artery stenosis (Left) and significant coronary artery stenosis (Right)*

Therefore, the practical lesson is that in a stenosis with FFR <0.75, revascularization is always justified (if technically feasible), whereas in a stenosis with FFR >0.80, revascularization can be safely deferred and optimal medical treatment is sufficient. Between 0.76 and 0.80, sound clinical judgment (taking into account the character of symptoms, results of noninvasive tests, if available, and whether a gradient is focal or diffuse) should balance the final decision.

3. In the catheterization laboratory, systemic pressure, heart rate, and left ventricular contractility are prone to change. In contrast to many other indices measured in the catheterization laboratory, changes in systemic hemodynamics do not influence the value of FFR in a given coronary stenosis.[11] In addition, FFR measurements are extremely reproducible.[12]

4. FFR takes into account the contribution of collaterals. Whether myocardial flow is provided antegradely by the epicardial artery or retrogradely through collaterals does not really matter for the myocardium. Distal coronary pressure during maximal hyperemia reflects both antegrade and retrograde flows according to their respective contribution.[4,13] This holds true for the stenoses supplied by collaterals but also for stenosed arteries providing collaterals to another more critically diseased vessel. For example, if an RCA with 60% stenosis supplies collaterals to LAD territory, the FFR in RCA will be low. After revascularization of LAD, the myocardial mass supplied by the RCA will be reduced and the FFR in RCA will be high.

5. FFR specifically relates the severity of the stenosis to the mass of tissue to be perfused. The larger the myocardial mass subtended by a vessel is, the larger the hyperemic flow, and in turn, the larger the gradient and the lower the FFR for a given stenosis. This explains why an angiographic stenosis of same magnitude gives different FFR in proximal and distal part of the same vessel.[14] It also means that the hemodynamic significance of a particular stenosis may change if the perfusion territory changes (as is the case after myocardial infarction [MI]).These changes are accounted for by FFR.

6. FFR has unequaled spatial resolution. The exact position of the sensor in the coronary tree can be monitored under fluoroscopy and documented angiographically. Pulling back the sensor under maximal hyperemia provides the operator an instantaneous assessment of the abnormal resistance of the arterial segment located between the guide catheter and the sensor. Although other functional tests reach a per-patient accuracy (exercise electrocardiography) or, at best, a

per-vessel accuracy (myocardial perfusion imaging or stress echocardiography/magnetic resonance imaging), FFR reaches a per-segment accuracy with a spatial resolution of a few millimeters.

FFR in angiographically intermediate stenoses:

Decision of revascularization of the coronary lesions with 50-70% stenosis is often difficult. Besides there is always inter observer and intra observer variability in the estimation of degree of coronary artery stenosis in coronary angiogram. It was shown that FFR has a much greater accuracy in distinguishing hemodynamically significant stenoses than exercise electrocardiography, myocardial perfusion scintigraphy, and stress echocardiography performed separately. FFR can indeed be considered as a true gold standard for decision making in this group of lesions.[15]

A number of registries have reported low adverse cardiac event rates at 1 to 2 years after deferral (better stated as nonperformance) of PCI in patients with moderate stenoses and nonischemic FFR. The DEFER (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses) study randomized 325 patients scheduled for PCI into 3 groups and reported the 5-year outcomes.[4] If FFR was ≥ 0.75, patients were randomly assigned to the **deferral** group (n = 91, medical therapy for CAD) or the PCI **performance** group (n= 90, PCI with stents). If FFR was ≤0.75, PCI was performed as planned, and patients were entered into the **reference** group (n = 144). Complete follow-up was obtained in 98% of patients. Overall, the event-free survival was not different between the deferred and performed groups (80% and 73%, respectively, p = 0.52), and both were significantly better than in the reference group (63%, p = 0.03). The composite rate of cardiac death and acute myocardial infarction in the deferred, performed, and reference groups was 3.3%, 7.9%, and 15.7%, respectively (p = 0.21 for deferred vs. performed and p = 0.003 for reference vs. both of the deferred and performed groups). The percentage of patients free from chest pain on follow-up was not different between the deferred and performed groups. The 5-year risk of cardiac death or myocardial infarction (MI) in patients with normal FFR is <1% per year and is not decreased by stenting. Treating patients guided by FFR is associated with a low event rate, comparable to event rates in patients with normal noninvasive testing.[16]

FFR in Multivessel disease:

Patients with multivessel disease actually represent a very heterogeneous population. Their anatomic features (number of lesions, location and respective degree of complexity) may vary tremendously. There is often a large discrepancy between the anatomic description and the actual physiologic severity of each stenosis. All these things make the decisions of revascularization a difficult one i.e. whether revascularization is to be done, what would be the better option surgery or PCI, in case of PCI which are the culprit vessels, in case of serial lesions in a vessel which is the culprit lesion etc. Tailoring the revascularization according to the functional significance of the stenoses rather than to their mere angiographic appearance decreased costs and avoided the need for surgical revascularization.[17] Recently, benefit of FFR-guided multivessel PCI has been proved in comparison to standard angiography in the large randomized, multicenter FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study.[3,18] It was demonstrated that all types of adverse events were decreased by 30% in the first year after PCI in multivessel disease, when guided by FFR. This was achieved at a lower cost and without prolonging the interventional procedure, whereas angina in FFR-guided patients was relieved at least as effectively.[3,19] After 2 years, the advantage of FFR guidance of PCI in multivessel disease even increased with respect to lower mortality and MI rates, whereas some catching up occurred with respect to repeat revascularization. Importantly, in this study, the progression of deferred lesions was excellent.

FFR in Left main disease:

The presence of a significant stenosis in the left main stem is of critical prognostic importance. Conversely, revascularization of a nonsignificant stenosis in the left main may lead to early occlusion of the conduits, especially when internal mammary arteries are used.[20] Noninvasive testing is often noncontributive.

Furthermore, the left main is among the most difficult segments to assess by angiography.[21] The reasons behind this are-

1. The interobserver variability is very large. In some study, the interobserver concordance was 52%.[22]
2. The catheter may overlap with the origin of the LAD and the LCx; in addition, spillover of contrast medium and incomplete mixing of blood and contrast medium in the proximal part of the LMCA may render the evaluation of an ostial lesion difficult.
3. The LMCA is generally short, and when present, atherosclerosis is often distributed diffusely so that a normal segment is lacking. This leads to an underestimation of the "reference" segment and thus to an underestimation of LMCA stenoses by both visual estimation and QCA.

Several studies have shown that FFR could be used safely in left main stenosis and that the decision not to operate on left main stenosis with FFR >0.80 is safe.[23,24] In one study 23% of patients had an LMCA stenosis <50% while the FFR was <0.80.[22] Courtis et al. studied 142 consecutive patients with intermediate left main coronary artery stenosis (42±13% diameter). Those patients with FFR >0.80 (n = 82) were treated medically; those patients with FFR ≤0.75 (n = 60) underwent CABG. MACE at 14 months' follow-up was 13% and 7%, respectively (p = 0.27). Cardiac death or MI was also similar (6% and 7%, p = 0.70).[25]

Given the critical prognostic importance of appropriate decision making in LMCA stenoses and the frequent underestimation of LMCA stenosis at angiography, FFR measurements should be obtained in patients with equivocal LMCA stenosis instead of "blindly" making the decision about revascularization based solely on angiography. Distinguishing the patients in whom surgery can safely be deferred and more important, those patients in whom CABG should not be denied might improve long-term survival in these patients.

Estimation of FFR often becomes difficult when there is involvement of LAD and LCX along with LM. In the presence of proximal mild to moderate LAD or LCX disease, LM FFR can be reliably measured with the pressure wire placed in the uninvolved epicardial artery.[26] For evaluation of ostial LMCA lesions, care must be taken to disengage the guiding catheter during FFR measurements to prevent pressure dampening and an artificial increase in the FFR measurement obtained.

FFR in Ostial lesions and bifurcation lesions:

Coronary angiography is regarded as the gold standard to evaluate coronary artery disease, but it has limitations in predicting the presence of myocardial ischemia in ostial lesions. Accurate angiographic assessment of ostial lesions is difficult due to vessel overlap, angulations and artifacts.[27] But evaluation of ostial lesion is clinically important as an MV(Main vessel) ostial lesion can cause ischemia in large myocardial territory, and MV and SB(side branch) ostial lesions usually require complex interventions. Percutaneous coronary intervention for coronary bifurcation lesions and ostial lesion remains technically challenging and clinical advantage of it is unclear. Rather such interventions may increase the subsequent risk of adverse clinical events.[28]

Intravascular Ultrasound (IVUS) has been used to evaluate ostial lesions. A MLA < 3.5 cm^2 is used to determine a significant lesion. Sensitivity, specificity, and positive and negative predictive values of MLA (3.5 mm^2) is 83%, 75%, 69% and 87% respectively. The low positive predictive value (69%) limits the use of IVUS in defining the presence of ischemia in these lesions. As the negative predictive value of MLA is more than 80% in ostial lesions, minimal lumen area (MLA) by IVUS seems to be more useful for excluding the presence of ischemia and deferring the revascularization than for defining the presence of ischemia.

FFR is the best way to define whether MV ostial lesions are significant and whether they need revascularization. For SB ostial lesions, the positive predictive value of all angiographic and IVUS parameters are < 50%. Appropriate angiographic and IVUS parameters to predict the functional significance of SB ostial lesions are difficult due to high variability of SB in vessel size, branching pattern and the amount of

supplying myocardium. As both the severity of a stenosis and the myocardial mass determine the presence of myocardial ischemia, these anatomical variations limit the value of angiographic and IVUS assessment of SB ostial lesions. In these cases FFR can play a good role in determining the functional significance of the lesions.[29-32] In fact in a FFR based study by Jung-Min Ahn et al showed that most side branch lesions do not have functional significance after stent implantation in the main vessel. They suggested that FFR measurements should be considered first to evaluate functional significance, when the operator intends to treat the jailed side branches supplying large regions of jeopardized myocardium or having a large vessel diameter. In this manner, unnecessary complex coronary procedures and their associated complications could be avoided.[30]

In bifurcation lesions, stenting the main branch and kissing balloon dilation of side branch should be done thereafter, only if FFR of the side branch is <0.75. If FFR of the side branch is >0.75, the outcome is excellent without further intervention.

FFR in diffuse disease:

Atherosclerosis in coronary arteries is often diffuse in nature and this can often not be clearly assessed from the angiogram.[34,35] In these patients, chest pain is often considered noncoronary because no single focal stenosis is found and the myocardial perfusion imaging is wrongly considered false positive.[36,37] This can be assessed by IVUS or OCT. The haemodynamic impact of diffuse disease can be demonstrated by performing a careful pull-back maneuver of the pressure sensor under steady-state maximal hyperemia which will show progressive decrease in coronary pressure and flow.

FFR in sequential stenosis

When several stenoses are present in the same artery, the concept and the clinical value of FFR are still valid to assess the effect of all stenoses together. However, it is important to realize in such cases that each of several stenoses will influence the FFR. The influence of the distal lesion on the proximal is more important than the reverse. Theoretically, the FFR can be calculated for each stenosis individually.[38] However, this is neither practical nor easy to perform. Practically, as for diffuse disease, a pull-back maneuver under maximal hyperemia is the best way to appreciate the exact location and physiologic significance of sequential stenoses and to guide the interventional procedure step-by-step. After the most severe stenosis (i.e., the stenosis with the largest gradient) has been stented, the pull-back recording can be repeated, and it can be decided whether and where a second stent should be placed.

FFR in PCI evaluation

An inverse relationship has been shown between post-PCI FFR and the restenosis rate.[39] After successful stenting, no noticeable hyperemic gradient should be present across a well-deployed stent.[40] Post-interventional FFR <0.95 increased the risk of MACE about sixfold compared with FFR > 0.95.[41] It is important to distinguish whether a persistent hyperaemic gradient is due to incomplete stent deployment, to abnormalities within the adjacent segments, or to diffuse disease more proximal or distal to the treated lesion. Such diffuse disease is often not apparent angiographically but may result in a significant pressure drop when blood flow is increased by stenting the most severe lesion. In case of doubt, intravascular ultrasound or optical coherence tomography is a better way to study stent deployment.

FFR in instent restenosis:

Many patients with previous revascularization undergo catheterization in order to rule out Instent restenosis (ISR). Many of them present nonspecific symptoms, and non-invasive tests are either inconclusive or not performed. A percentage diameter stenosis equal or superior to 50% in an angiography performed during the follow-up has been the criterion used to define ISR in most of the studies that have analyzed the long-term results of coronary stents. In clinical practice, the sole presence of angiographic restenosis frequently motivates new intervention in these patients without clear demonstration of myocardial ischaemia. Conservative management of moderate 40–70% in-stent restenotic lesions with FFR value ≥0.75 is safe avoiding unnecessary revascularizations based solely on the angiography.[42]

FFR and CABG Conduit Patency

Although most surgical recommendations for patients with multivessel disease are to bypass all lesions with >50% diameter narrowing, the patency rate of saphenous vein grafts on vessels with hemodynamically insignificant lesions has been questioned. Botman et al.[43] found that there was a 20% to 25% incidence of graft closure in 450 CABGs when placed on hemodynamically insignificantly stenosed arteries (preoperative FFR >0.80) at 1 year of follow-up. 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. FFR has significant implications for best long-term CABG outcomes.

FFR in Acute Coronary Syndrome:

In the acute phase of MI, FFR is neither reliable nor useful to assess the culprit lesions, and the electrocardiography trumps any other investigation. From 5 days after the infarction, FFR can be used as usual to indicate residual ischemia of the infarct-related or remote arteries. After MI, previously viable tissue is partially replaced by scar tissue. Therefore, the total mass of viable myocardium supplied by a given stenosis in an infarct-related artery will tend to decrease.[34] Assuming that the morphology of the stenosis remains identical, FFR must therefore increase. Recent data confirm that the hyperemic myocardial resistance in viable myocardium within the infarcted area remains normal. Viable myocardium should produce substantial hyperemia and an FFR <0.80, whereas nonviable myocardium will not respond to hyperemia and FFR will be high.[44]

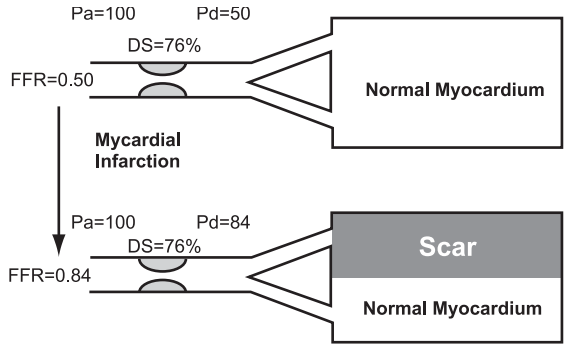

Fig.-2: *Change in FFR as the effect of MI*

In STEMI significant microvascular dysfunction develops in both culprit and nonculprit areas during the acute phase. Extensive ischemia in adjacent territories, vasoconstriction mediated by local neurohumoral reflexes, and elevated LVEDP are considered as possible underlying pathophysiologic mechanisms. Even the presence of subendocardial ischemia is sufficient to induce significant microvascular dysfunction remote to the ischemic territory. As microvascular dysfunction can influence the FFR result, a study was conducted to evaluate the reliability of fractional flow reserve (FFR) of nonculprit coronary stenoses during percutaneous coronary intervention (PCI) in acute myocardial infarction. It was found that the severity of nonculprit coronary artery stenoses can reliably be assessed by FFR. This allows a decision about the need for additional revascularization and contribute to a better risk stratification.[45]

In case of UA or NSTEMI with Multivessel disease when several stenoses are present, selection of the culprit lesion might be difficult. Often electrocardiography is helpful and indicates the lesion responsible for the acute ischemia, but sometimes it does not. In addition, even when the culprit lesion is known, doubt might arise about the ischemic potential of other concomitant lesions and the necessity to treat such lesions invasively. In FAME study, FFR guided multivessel PCI was done in patients with UA/ NSTEMI. It was found that FFR guided PCI is as effective UA/NSTEMI as it is in the setting of stable angina.[46]

The use of FFR to reduce cost in ACS patient management was reported by Leesar et al.[47] who randomized 70 patients with recent unstable angina or non–ST-segment elevation myocardial infarction with intermediate single vessel stenosis to 1 of 2 strategies: angiography followed by SPECT the next day or FFR-guided revascularization at the time of angiography. Compared with the SPECT strategy, the FFR-guided approach had a reduced hospital duration (11 ± 2 h vs. 49±5 h, p<0.001) and cost (U.S. $1,329± $44 vs. $2,113 ± $120, p <0.05), with no increase in procedure time, radiation exposure time, or clinical event rates at 1 year of follow-up.

FFR in female:
In a substudy of FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) impact of sex differences on FFR-guided percutaneous coronary intervention (PCI) was evaluated. FFR was measured in 1,329 lesions (1,028 in men and 301 in women).[48] The lesions were categorized into 50% to 70%, 71% to 90%, and 91% to 99% diameter stenosis by visual estimation. The proportion of functionally significant lesions (FFR ≤0.80) was lower in women than in men for lesions with 50% to 90% stenosis. In the 91% to 99% category, the proportion of patients with FFR ≤0.80 was not different between women and men. A possible explanation for this is woman has got more prevalence of micro vascular dysfunction, which played a role in this result. Another explanation is, women generally have smaller myocardial mass, a smaller myocardial perfusion territory will be subtended by a stenosed vessel and the flow across any given stenosis may be less, thereby requiring a more severe stenosis to be functionally significant.[49] However an FFR-guided PCI strategy is equally beneficial in women as it is in men. [48]

FFR mismatch- Angiographic FFR "mismatch" is defined as angiographic stenosis >50% and FFR ≥0.80, whereas "reverse mismatch" is defined as angiographic stenosis ≤50% and FFR < 0.80. Park et al conducted a study to find out the factors responsible for these phenomena.[50] For non-LMCA lesions, multivariate analysis identified the independent predictors for mismatch were older age, non-LAD lesions, the absence of plaque rupture, shorter lesion length, larger IVUS-MLA, smaller plaque burden, and greater angiographic minimal lumen diameter (MLD); independent predictors for reverse mismatch were younger age, LAD lesions, presence of plaque rupture, smaller IVUS-MLA, and larger plaque burden. For LMCA lesions, mismatches were associated with a larger IVUS-MLA, and reverse mismatches were associated with smoking, smaller IVUS-MLA, larger plaque burden, and the presence of plaque rupture. A larger amount of perfused myocardium subtended by a stenosis is associated with a higher probability that an angiographically intermediate coronary stenosis is functionally significant.[51]

FFR vs IVUS:
Because of the limitations of coronary angiography, adjunctive techniques to more accurately evaluate lesion severity are important in patients with intermediate coronary stenosis before percutaneous coronary intervention (PCI).IVUS is another device to decide which patients with 40- 70% stenosis in the coronary arteries should be subjected to revascularization. An intravascular ultrasound (IVUS) derived minimal lumen area (MLA) ≤4.0 mm^2, or minimal lumen diameter ≤1.8 mm is used an indication of revascularization. But IVUS-guided group undergo revascularization therapy significantly more often in comparison to FFR guided group (91.5% vs. 33.7%, $p < 0.001$). No significant difference is found in major adverse cardiac event rates between the 2 groups (3.6% in FFR-guided PCI vs. 3.2% in IVUS-guided PCI).[52]

Long term outcome of FFR guided PCI:
In one study 730 patients with a 30% to 70% isolated stenosis in the proximal LAD were subjected to FFR guided revascularization. FFR>80 was given medical treatment and FFR<80 was treated with PCI or CABG. 5 year event free survival was 89.7% and 68.5%, respectively ($p < 0.0001$). 5 year survival of the medically treated group was similar to an age- and sex-matched control population.[53]

Can we live without fractional flow reserve?
Fractional flow reserve measurement is not necessary in every interventional procedure. If a patient has typical chest pain, a positive non-invasive test and a single severe stenosis on the angiogram, stenting can be performed straightforwardly. But such simple cases are becoming rare and in an increasing number of patients in the catheterization laboratory, FFR becomes indispensable for good decision-making.

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

these reasons that the use of FFR in selecting lesions to be stented in multivessel disease is designated as an IA classification in the recent guidelines of the ESC.[55]

Pitfalls of FFR:

From the technical point of view, there are several pitfalls to watch when performing FFR measurement. The 2 most important pitfalls are submaximal hyperemia (underestimating the stenosis severity) and issues related to the guiding catheter. There are a number of physiologic reasons why FFR can be high despite an apparently tight stenosis like-

1. Physiologic explanations-
    - Small perfusion territory, old myocardial infarction, little viable tissue, small vessel
    - Abundant collaterals
    - Severe microvascular disease (rarely affecting FFR)
2. Interpretation explanations-
    - Other culprit lesion
    - Diffuse disease rather than focal stenosis (make pull-back recording)
3. Technical explanations-
    - Insufficient hyperemia (check system and solution or use other stimulus)
    - Guiding catheter–related pitfall (deep engagement, small ostium, side holes)
    - Electrical drift (pull sensor back to ostium to check and equalize)
    - Equalization with introducing needle and measurement without it
4. Actual false-negative FFR
    - Acute phase of ST-segment elevation myocardial infarction
    - Severe left ventricular hypertrophy
    - Exercise-induced spasm

Conclusion:

Coronary artery disease is being treated by PCI and CABG along with drug therapy. But along with their beneficial effects, these invasive treatment modalities have different short and long term complications. It is also expensive. So estimation functional significance of the coronary lesions is important before revascularization to decide when to use invasive treatment. FFR can detect the functional status of coronary artery stenosis in almost all subsets of patients. It should be used more frequently and effectively specially in multivessel coronary artery disease and in coronary artery disease with intermediate severity. Proper use of FFR will reduce unnecessary revascularization, unexpected complications and undue expenditure.

Conflict of Interest - None.

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