Value of FFR in clinical practice

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ABSTRACT

Fractional flow reserve is an important tool in the cardiac catheterization lab to assess the physiological significance of coronary lesions. This article discusses the basic concepts about FFR and its utility in clinical decision making.

1. Introduction

Coronary artery disease is a leading cause of death in developed countries and is increasingly being recognized in the developing countries like India. Over the last 40 years the decision to define the need for therapy and prognosis of coronary artery disease is based on anatomical description of extent of CAD as number of vessels affected by more than 50–70% stenosis.1 There is distinct shift in the guidelines for revascularization now to physiologically significant lesions rather than anatomically significant lesions based on data from studies employing the Fractional Flow Reserve (FFR) for clinical decision making.2–5 Therefore it is important to understand the basic concepts behind FFR and incorporate it into as tool to make clinical decisions in patients with CAD.

2. Normal coronary blood flow, Coronary flow reserve (CFR), Relative CFR(r-CFR) and Fractional flow reserve (FFR)

Under resting condition, the myocardium extracts the maximum amount of oxygen delivered by the blood and increase in myocardial oxygen demand is entirely met by changes in coronary perfusion. Coronary and myocardial blood flow is directly proportional to the coronary perfusion pressure (Aortic diastolic pressure–Left ventricular end diastolic pressure) and inversely proportional to the resistance offered by the coronary vessels at various levels. In normal coronary arteries epicardial vessels or conductance vessels (R1) offer negligible resistance to coronary perfusion and increase in coronary blood flow in response to increased myocardial oxygen demand (MVO2) is achieved by the dilation of the resistance vessels at pre-capillary (R2) and microvascular levels (R3). The factors responsible for the changes in vascular resistance and maintaining basal and maximal coronary blood flow are local metabolites (adenosine during ischemia), endothelial factors (NO) and neural tone.6

In normal heart conditions the ratio of maximum stress flow to rest coronary blood flow in absolute units is called coronary flow reserve (CFR) or absolute coronary flow reserve.7 As defined by PET, in normal volunteers the resting flow was 0.82 ± 0.06 cc/min/g, the maximum stress flow was 2.86 ± 1.29 cc/min/g and CFR was 3.55 ± 1.36.1 With development of significant stenotic lesion in the epicardial artery the micro-vascular resistance is decreased at basal conditions to maintain resting flow thereby borrowing from the flow reserve. Therefore in maximum stress conditions the hyperemic flow capacity is lowered and the ratio maximal
hyperemic to resting flow (CFR) is lowered. In the absence of significant epicardial stenosis, the diffuse arterial disease or damage to microvasculature may limit the maximal vasodilatory capacity and maximum achievable flow, thereby reducing CFR. In some PET imaging studies the maximum stress flow of <0.91 cc/min/g and absolute CFR of less than 1.74 were correlated with evidence of definite ischemia.7

In clinical practice Doppler flow wires and thermo-dilution techniques are used to determine CFR. It is helpful in assessing microvascular function but is highly dependent on hemodynamic conditions (aortic pressure/heart rate).

In contrast, relative CFR is independent of hemodynamic conditions. It describes the ratio of maximum hyperemic flow in the diseased artery to maximum flow in the adjacent normal arterial distribution.1 However, relative CFR is limited in its utility clinically as atherosclerosis is a diffuse process and affects multiple arterial segments. Therefore “normal” arterial segment is not truly normal. Both absolute CFR and relative CFR are flow derived measures affected by the severity of epicardial stenosis as well as the extent of disease in the microvasculature. In order to overcome these limitations, Pijls and De Bruyne developed the concept of Fractional Flow Reserve (FFR) - a pressure derived relative coronary flow reserve - to assess specifically epicardial coronary stenosis.8,9

In normal coronary arteries, the pressure in the distal segment of the coronary artery is the same as aortic pressure (origin of the artery). With development of progressive discrete epicardial stenosis there will be a pressure drop across the lesion in the resting or hyperemic state, depending on the severity of the arterial narrowing. In a basal resting state, in such a patient, the resting myocardial flow is maintained by continuous alteration in microvascular resistance distal to the stenosis. This constant auto-regulation creates a state of where the distal resistance and therefore the pressure gradient across the lesion is variable and nonlinear in relation to the coronary blood flow. By pharmacologically inducing maximal coronary microvascular vasodilatation (i.e. hyperemia), coronary resistance is lowered to a minimum steady state. In this condition, theoretically, the relationship between the coronary perfusion pressure and coronary blood flow is linear i.e. the maximum myocardial blood flow distal stenosis is proportional to perfusion pressure distal to discrete stenosis taking into account both antegrade and collateral flow. Therefore one can use pressure measurements across the lesion as a surrogate of flow.

In swine model with different levels of stenosis and aortic pressures, Pijls et al showed that in a state of maximum hyperemia (minimal constant resistance) and low central venous pressure (Pv), FFR (fraction of maximum normal flow: a relative CFR) is derived simply by ratio of mean pressure distal to the stenosis (Pd) over the mean aortic pressure (Pa), a theoretical pressure in the coronary artery in the absence of stenosis.8

\[ FFR = \frac{Q_{smax}}{Q_{Nmax}} = \frac{P_d}{P_a} \]

Qsmax: The maximal myocardial blood flow in a stenotic territory.

QNmax: The theoretical maximal myocardial blood flow in the same territory as Qsmax assuming the coronary artery was completely normal (i.e. absence of any stenosis).

We now have a relatively simple method of assessing the significance of discrete stenosis at any level in the arterial segment. In normal coronary artery the mean aortic pressure and distal coronary artery pressure will be the same. Therefore, FFR (Pd/Pa) will be 1. The FFR of 0.7 and 0.5 implies that the in the presence of stenosis the maximal achievable flow is reduced to 70% and 50% of normal maximal flow. Therefore lower the FFR value, more severe is the impairment in the maximal achievable flow and more likely it to cause ischemia below a threshold value. Similarly a change in FFR value from 0.6 to 0.9 will indicate 50% improvement in the maximal flow.

### Table 1 - Vasodilators for testing Fractional Flow Reserve.

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<thead>
<tr>
<th>Vasodilators for testing Fractional Flow Reserve</th>
<th>Dose</th>
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<tr>
<td><strong>Epicardial vasodilators:</strong></td>
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<td>Nitroglycerin: 200–400 µg IC, administer 30 s before 1st measurement</td>
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<tr>
<td><strong>Microvascular vasodilators:</strong></td>
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<tr>
<td>Adenosine or ATP: 40 µg/IC bolus in RCA, 80 µg IC bolus in LCA</td>
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<tr>
<td>Adenosine or ATP: 140 µg/kg/min IV (preferably through a central venous line)</td>
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<tr>
<td>Regadenoson (Rapiscan): 400 µg single bolus IC or peripheral IV</td>
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<tr>
<td>Papaverine: 10–12 mg in the RCA, 15–20 mg in the LCA</td>
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IC: Intracoronary, IV: Intravenously, RCA: Right Coronary Artery, LCA: Left Coronary Artery, ATP: Adenosine triphosphate.

### 3. Measurement of FFR in Cardiac Catheterization Laboratory

Currently there are three systems available for measurement of FFR in the catheterization laboratory: Radiwire system, St. Jude Medical; Volcano Pressure wire system; and the Navus catheter-ACIST RXi System (Bragco, MN, USA).

In both the Radiwire system and Volcano system, the pressure wire is a small caliber 0.014-inch PTCA wire that contains a pressure sensor at the junction of the distal radiopaque shapeable tip to radiolucent body of the wire. Initially after flushing the pressure wire loop with saline (placing the sensor in the fluid), both the guide catheter transducer and the pressure wire sensor are calibrated to zero. In the newer Radiwire system, the wire calibration is done automatically. After appropriate anticoagulation, the shaped pressure wire is introduced using the introducer needle through the Y connector and the sensor is advanced to the tip of the guide catheter. The introducer needle is removed. The pressures measured from the tip of the guide catheter (a fluid filled system) and from the pressure sensor are equalized electronically in the ascending aorta. After engagement of the coronary arterial segment to be studied with the guiding catheter, intracoronary nitroglycerin (200–400 µg) is administered. Subsequently, the pressure wire is advanced carefully across the coronary lesion, placing the sensor at least 3 cm distal to it. Baseline Pd/Pa is recorded after disengaging the guide catheter form the coronary ostium. Now a maximal hyperemic state is induced by any of the currently recommended vasodilatory agents (Table 1) and continuous recording of Pa, Pd and FFR is done.10,11 When the mean Pa and Pd pressures reach a steady
state the lowest recorded ratio of Pd/Pa is recorded as the FFR value for the arterial lesion studied. If one uses IV Adenosine or Regadenoson, the pressure sensor can be pulled back slowly along the length of the artery to the tip of the guide catheter to determine the pressure drops along the entire length of the artery. The pullback of pressure sensor into guide catheter also checks for any significant electronic drift which may have happened during the course of the recording, so that the value of FFR can be properly interpreted. Pullback allows the assessment of degree of pressure drops across serial multiple lesions. Intracoronary bolus injections do not allow for the continuous pullback.

In patients with multi-vessel disease, all arterial segments in questions can be studied for physiologic significance similarly and the mode of therapy can be determined based on physiologic extent of CAD. In case of serial lesions in the artery, the lesion producing the maximum pressure drop is treated first and FFR is repeated to determine the hemodynamic significance of the residual disease. In presence of diffuse arterial disease there may not be specific pressure drop but a gentle pressure change throughout the arterial segment indicating no need for revascularization.

**4. FFR cut-off points for ischemic potential**

The angiographic assessment of the degree of coronary stenosis has a significant intra and inter observer variability, especially in ostial, left main or bifurcation lesions. In addition for the same degree of stenosis, the length of the lesion, amount of viable myocardium supplied by the lesion, presence of diffuse disease distal to the lesion as well as collateral flow to other arterial segment, may all determine the physiologic significance of the lesion. Pijls et al correlated the FFR values measured at a later date to presence or absence of ischemia by multiple noninvasive modalities (nuclear imaging studies, dobutamine stress echocardiograms, and exercise stress testings) in the same group of patients. In the study, FFR value of <0.75 determined the presence of reversible ischemia with 93% accuracy (88% sensitivity, 100% specificity, 100% positive predictive value, 88% negative predictive value) for a single discrete stenosis. FFR values between 0.75 and 0.8 conferred a gray zone and an FFR >0.8 correlated with absence of ischemia on noninvasive testing.

This cut-off value of <0.75 (for treatment of patients with single vessel disease) was tested initially in DEFER study and subsequently validated in multiple studies including the ones for left main disease. The DEFER study showed that it was safe and preferable to avoid or defer stenting of the lesions with FFR>0.75. Such strategy was associated with lower risk of death and MI (less than 1% per year) than routine revascularization.

However in both FAME and FAME-2, patients with multi-vessel disease were judged to have ischemic potential if the FFR for the lesion was <0.8. The FAME study (using FFR > 0.8 defined as non-ischemic) showed that FFR-guided PCI strategy verses angiographic guided PCI resulted in deferral of PCI in almost 1/3 of the lesions and better 1 year clinical outcome (combined endpoint of death, myocardial infarction, and repeat revascularization at 1 year (FFR group 13.2% vs. Angiography group 18.3%, P = 0.02). Based on the results of these trials, the current coronary revascularization guidelines for stable ischemic heart disease recommend strict dichotomous cut-off value of less than 0.8 as appropriate for revascularization. However, no single value of a test should be used for clinical decision making as there is inherent variability in repeated measurements besides other clinical factors; physician’s clinical judgment should be taken into account for therapeutic strategies. As suggested by Petracco et al, a single FFR measurement of <0.75 or >0.85, can be used with confidence clinically to revascularize the lesion or to defer invasive therapy respectively. Single FFR value between 0.75 and 0.85 represents a gray zone requiring physician judgment for deciding the course of management.

**5. Key points**

- FFR is a single highly reliable and reproducible invasive method to assess the ischemia producing potential of a lesion with accuracy of more than 90%
- Currently a cutoff value of less than 0.8 is recommended for revascularization
- Useful in assessment of intermediate coronary lesions in stable ischemic heart disease (left main disease, bifurcation disease, ostial disease, serial lesions, diffuse disease, old MI, collateralized vessels)
- In ACS patients it can be used for non-culprit lesions and after 7 days in the culprit lesions (not reliable in the culprit vessels in acute stage)
- While performing FFR important to equalize pressure sensor at the tip of the guide catheter after removing the introduced needle
- Pressure sensor should be placed at least 3 cm distal to the lesion
- Although a number of resting indices (resting Pd/Pa, IFR etc) have been proposed, their diagnostic accuracy is around 80%. However if resting Pd/Pa is < 0.8 on maximal hyperemia, the FFR will be < 0.8. If one is evaluating a single focal stenosis one can use the baseline criteria for revascularization
- Hyperemia is essential to achieve a steady state of minimal microvascular resistance to correctly interpret lesion physiology in all lesions (single or serial or diffuse disease)
- For hyperemia IV adenosine or Regadenoson is better than IC bolus for steady state and continuous pullback to assess serial lesions
- Sometimes IV adenosine may not have adequate vasodilatory effect due to rapid peripheral metabolism. In such scenarios perform the response using incremental doses of IC adenosine bolus
- For multi-vessel evaluation, IV adenosine is preferred over Regadenoson because it has a longer lasting hemodynamic effect
- Regadenoson has significantly larger blood pressure lowering effect than IV adenosine (caution in patients with borderline blood pressures)
- Slight variations in FFR values seen with respirations but use the lowest value in steady state
- Pullback slowly along the entire length of the artery
- Pullback to guide catheter to identify if there is any significant electronic drift

**Conflicts of interest**

All authors have none to declare.

**REFERENCES**