FFR Guided Coronary Intervention In Intermediate Coronary Artery Disease: Acute and Intermediate Term Results

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Abstract: Background: Fractional Flow Reserve (FFR), a diagnostic test, is a physiological test to determine the functional significance of any stenosis in coronary artery. It is a pressure-derived ratio that estimates blood flow through a stenotic lesion at maximal hyperemia. FFR is objective measurement of stenosis in comparison to traditional visual interpretation of angiography. The objective of this study was to plan the treatment course of patients on the basis of FFR estimation in intermediate coronary artery disease and follow them up for the acute and intermediate term results. Material and Method: The study was performed on suitable identified patients of VS general Hospital, Ahmedabad. First, the diagnostic angiography was done. If angiography result showed intermediate lesion, FFR was measured with sensor wire and decision of management of the patient was taken according to the result of FFR. The results were compared with the results of management of patients by conventional angiography guidance. Results: When management of the patient was based on FFR result, event free survival rate was better with less number of major adverse cardiovascular events than traditional way of patient management based on angiography alone. Conclusion: It could be concluded that the addition of coronary physiological measurements like FFR complements traditional angiographic information and is essential for accurate clinical decision-making. It is cost-effective and prevents unnecessary Per-cutaneous Coronary Intervention (PCI). [Patel K Natl J Integr Res Med, 2020; 11(2):11-16]

Key Words: FFR, Angiography, Coronary Artery Disease, Physiological testing of coronary artery

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Introduction: During the past decade, the physiological assessment of coronary artery disease (CAD) has become increasingly important in both clinical and research applications. Angiography had long been considered as main-line invasive diagnostic test for ischemic heart disease. Although it gives relatively reliable information about patency of coronary arteries which provide blood supply to heart, it cannot be regarded as the best possible diagnostic test[1] because of the facts that it is based on visual impression of cardiologist which makes it subjective and it indicates anatomical defect in the artery and says very little about functional significance of any abnormality found.

Fractional flow reserve (FFR), a diagnostic test that addresses to both the drawbacks of angiography, is a physiological test to determine the functional significance of any stenosis in coronary artery objectively. It is a pressure-derived ratio that estimates blood flow through a stenotic lesion at maximal hyperemia. Importance of measuring FFR increases very much when result of angiography is not very clear indication for further course of management in the patient care[2] e.g. in intermediate coronary artery disease. In such cases, FFR gives reliable, objective and satisfactorily sufficient proof for further line of action. Measurements of FFR provides information complementary to the anatomic characterization of coronary disease obtained by angiographic examinations. Such physiological data acquired during the angiographic procedure can facilitate timely and more objective decision-making about therapy. [3, 4] Thus, the rationale for using coronary physiological measurement is to overcome the limitations of coronary angiography and provide the angiographer with an objective indicator of clinically relevant lesion significance.

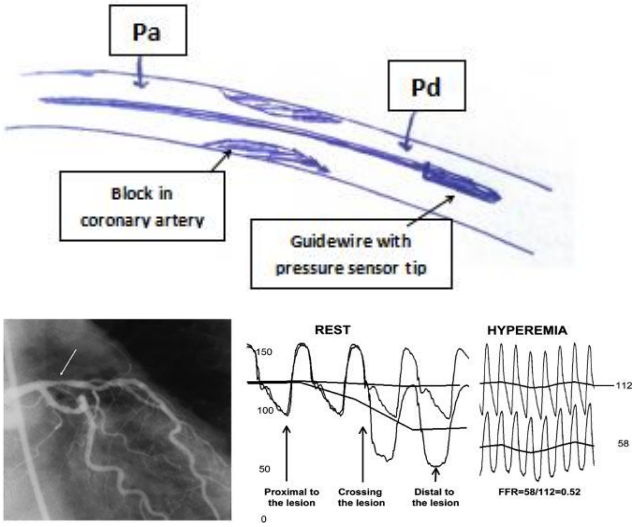
FFR And FFR Measurement: Myocardial perfusion pressure, normally the diastolic coronary pressure, equals aortic pressure minus the left ventricular diastolic pressure or central venous pressure. Across normal coronary arteries, aortic pressure is transmitted completely, without appreciable pressure loss even to the most distal regions. As noted earlier, the distal coronary pressure in arteries with an atherosclerotic narrowing is decreased in relationship to the degree of stenosis resistance. Pijls; et. al [5, 6] related the distal coronary pressure to the ischemic potential of a stenosis by calculating a value called the fractional flow reserve (FFR). By taking the ratio of the coronary pressure

measured distal to the stenosis to aortic pressure as the normal perfusion pressure (distal coronary pressure/aortic pressure) and obtaining these measurements when the microvascular resistance was minimal and assumed to be constant (i.e., at maximal hyperemia), the % of normal coronary flow, or a fraction of normal flow (i.e., FFR), can be calculated.The FFR signifies the maximum achievable myocardial blood flow in the presence of a coronary artery stenosis as a percentage of the maximum blood flow in the hypothetical case of a normal artery. [5, 6]

FFR can be easily calculated by a simplified ratio of pressures and expressed as

FFR = Pd/Pa

Pd = distal coronary pressure (distal to stenosis)
Pa = Mean aortic pressure



(Illustration of the measurement of FFR in a 77-year-old patient with an intermediate coronary lesion left anterior descending artery. Courtesy: N Pijls[6,7])

As shown in the figure, phasic and mean pressure signals are displayed as recorded by the guiding catheters and sensor-tip guidewire. At the left side of the pressure tracing, the pressure sensor is proximal to the stenosis with 2 identical pressures of the wire and guiding catheter. Distal pressure decreases as the pressure sensor crosses the stenosis. During maximal hyperemia (at the right side of the pressure tracing), the hyperemic distal pressure decreased to 58 mm Hg with aortic pressure of 112 mm Hg for an FFR of 0.52 (58/112). It means that by FFR measurement, in this case, it can be stated that maximal blood flow to the myocardium of the anterior wall of this patient is decreased to 52% of expected normal flow. The concept of FFR has been thoroughly examined in both experimental and clinical studies. [7, 8]

Unlike many parameters, FFR has a normal value of 1.0 for every patient and every coronary artery. A nonischemic threshold value has been prospectively confirmed [7] and was compared with noninvasive stress testing. [8,4]An FFR <0.75 is associated with inducible ischemia (specificity, 100%), whereas a value >0.80 indicates absence of inducible ischemia in the majority of patients (sensitivity, 90%). [3]

There have been some international research projects regarding effectiveness and implementation of such physiological parameters for patient care. Initial results have been very encouraging and they recommend implementation of such diagnostic tests in regular practice. This is a pilot study to check the results of Fractional Flow Reserve (FFR) on Indian population.

Objectives: To measure Fractional Flow Reserve (FFR) in the patients with intermediate coronary artery disease, determined by coronary angiography.To plan the treatment course on the basis of Fractional Flow Reserve (FFR) result.To check acute and intermediate term outcome of the patients with FFR guided management.To compare the outcome of the patients of the present study with that of the standard international studies.To find out prognostic value of FFR measurement.

Material and Methods: Ethical permission was sought from Institutional Review Board (IRB) of Smt. NHL Municipal Meddical College, Ahmedabad. Informed and written consent was taken from the patients enrolled in the study.

Study Area: The present study was undertaken at Department of Cardiology, Sheth Vadilal Sarabhai (VS) General Hospital, Paldi, Ahmedabad. Angiography and FFR measurement were taken place in Cath Lab. whereas patient/subject follow-up was monitored carefully during routine and regular follow-up OPD visits.

Study Population: Patients undergoing coronary artery angiography at VSGH as a part of diagnosis of ischemic heart disease.

Inclusion Criteria: Patients with intermediate coronary artery disease, determined by coronary

angiography (40% – 70% narrowing) [3], in the target coronary artery as single-vessel or a part of multivessels disease.All patients regardless of age and gender.All patients regardless of any co-morbidity.All patients regardless of any past history or family history of IHD.

Exclusion Criteria: Patients with either <40% narrowing or more >70% narrowing including complete block in the target coronary artery
Junctional stenosis (stenosis at branching site).

First, diagnostic angiography is done for the target lesion. After diagnostic angiography, if angiography result shows intermediate lesion, a sensor guidewire is passed through an angioplasty Y-connector attached to a diagnostic or guiding catheter. Heparin (40 to 60 U/kg IV) and nitroglycerin (100 to 200 µg IC) (to minimize vasomotion and measurement variability) are given several minutes before the measurements.

Pressure Measurements: FFR is calculated using a 175-or 300-cm-length,0.014-in-diameter pressure wire with a pressure sensor 30 mm from the tip. The wire is calibrated and introduced using standard interventional techniques, first placing the pressure sensor at the tip of the guide to equilibrate with the measured arterial pressure (Pa). The wire is then advanced so that the pressure sensor is 5 to 10 artery-diameters distal to the lesion in question in order to truly measure post-stenotic laminar flow.

For coronary pressure measurements, a pressure sensor is located 3 cm from the tip at the junction of the radioopaque and radiolucent portion of the wire. The pressure sensor therefore can be moved across a coronary artery stenosis and back again (showing a pressure drop) without recrossing the stenosis with the wire tip. An interface is available to record and analyze the pressure signals or to transfer the data to the regular catheterization laboratory physiological monitoring system.

Before inserting the guidewire into the patient, the sensorwire and guide catheter pressure signals are calibrated and zeroed. The patient is given heparin and nitroglycerin as noted earlier. The sensor-wire is then introduced and positioned at the tip of the guiding catheter where the guiding catheter and wire pressures are equalized. The wire is then advanced across the stenosis or to the most distal part of the coronary artery for serial lesions or diffuse disease measurement.

Next, a pharmacological hyperemic stimulus (adenosine or papaverine) is administered via an intracoronary route (through the guide catheter) or intravenously. The mean and phasic pressure signals are continuously recorded. At peak hyperemia, represented by the nadir or lowest distal pressure, the FFR is calculated as the ratio between the mean distal coronary pressure (measured by the pressure wire) and mean aortic pressure (measured by the guiding catheter).

FFR value <0.75 implies significance, with values between 0.75 and 0.80 considered a “gray zone.” In studies this value strongly correlates with noninvasive ischemia and post-intervention resolution of abnormal FFR also correlates with resolution of noninvasive ischemia. [7]

Results: No. of subject: 20; Male: 13; Female: 7

- Single vessel disease: 11
- Multi-vessel disease: 9
- Target lesion in LAD: 10; RCA: 5; LCX: 5
- No. of subjects with following co-morbidities
- Diabetes:6;Hypertension:12; Dyslipidemia: 8;
- Smoking: 8; High BMI:13; Previous history of IHD: 5
- FFR result: significant (PCI done at target lesion): 9
- FFR result: insignificant (no PCI done): 11
- Regular Follow-up: Monthly till 6 months
- No. of subjects with event free survival: 18
- No.of subjects with Major Adverse Cardiovascular Events (MACE): 2
  Death: 1
- Recurrence of symptoms with require-ment of Percutaneous Coronary intervention (PCI): 1

Discussion: Clinical Applications of Coronary Physiology:

Safety of Intracoronary Measurements: The clinical practice of using sensor-wire measurements with pharmacologically induced hyperemia has been applied in thousands of patients in the past decade and is generally considered safe. [10]

Ischemic Thresholds: An FFR <0.75 identified coronary stenoses in patients with inducible myocardial ischemia with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). [9]

Criteria Associated With Clinical Applications [3, 4]

Indication	FFR
Ischemia detection	<0.75
Deferred angioplasty	>0.80
End point of angioplasty	>0.90
End point of stenting	>0.90

The Intermediate Stenosis: The intermediate lesion, usually reported in the range of 40% to 70% narrowing, is the most frequently encountered stenosis in patients with CAD and has been associated with a large interobserver and intraobserver variability in the reported angiographic interpretation. When FFR is <0.75, the stenosis is considered to be hemodynamically significant and a PCI can be supported. If FFR is >0.80, the clinical benefit of PCI can be questioned. The FFR range 0.75 to 0.80 can be considered a gray zone in which clinical judgment must complement quantitative assessments in forming the final treatment decision. Although most studies identify a distinct threshold, this value varies slightly depending on multiple study designs and patient factors. For this reason, deferral of intervention can be confidently considered with FFR values >0.80. A number of studies [11, 12, 13, 14] have shown that for a given intermediate coronary stenosis and FFR >0.75, the combined risk for death or acute MI is only 1% per year with medical treatment alone.

Prognostic Value: Because of the limitations of the angiogram for precisely identifying luminal abnormalities, the angiographic criteria before and after balloon angioplasty are poor predictors of immediate and long-term prognosis. However, when coupled with a satisfactory angiographic result, coronary physiological indices were predictive of the short-term and long-term clinical outcomes after balloon angioplasty. [12, 15]

For the practice of stent implantation, FFR does not address adequacy of implantation but do provide prognostic information about the patient's long-term result. In a multicenter trial, Pijls et al [16] examined 750 patients with poststenting FFR data and found that the FFR immediately after stent implantation was an independent variable related to all MACE. The lowest MACE rates occurred in patients with the highest FFR values. FFR normalized (>0.95) in 36% of patients, a finding associated with an event rate of 5%.

For patients with FFRs between 0.90 and 0.95 (32% of patients), the event rate was 6%. In the 32% of patients with FFRs <0.90, event rates were 20%. In the 6% of patients with FFRs <0.80, the event rate was 30%. The use of FFR after stent implantation, although not routine, can provide insight into the patient's prognosis.

Limitations of Physiological Measurements: Several potential pitfalls and confounding conditions can complicate or produce erroneous coronary physiological measurements. The 3 most common major technical problems are guiding catheter obstruction to flow, poor zeroing/calibration, and signal drift. Additionally, for both pressure and flow measurements, suboptimal guide catheter engagement may result in inadequate delivery of bolus adenosine, producing submaximal hyperemia and thus limiting the accuracy of the FFR. An artificial difference between aortic and distal coronary pressures may appear because of a damped guiding catheter pressure signal (often in association with small caliber catheters caused by contrast media in the catheter) and can be recognized by the shape of the pressure waveform. Flushing the guiding catheter with saline will restore a reliable aortic pressure.

In summary, when used by trained operators, sensor-wire measurement is generally considered safe and valuable for the important clinical data obtained.

FAME Study: (FFR Vs Angiography in Multivessel Evaluation)The FAME study was a randomized, prospective, multi-center trial which enrolled 1,005 patients with multivessel coronary artery disease. It compared outcomes for patients whose treatment was guided by FFR to those whose treatment was guided only by angiography [17].

The 12-month results, published in the January 15, 2009 issue of the New England Journal of Medicine, demonstrated that instances of major adverse cardiovascular events (MACE), such as death, myocardial infarction[18] or repeat revascularization, were reduced significantly for patients whose treatment was guided by FFR

rather than by standard angiography alone [19 20]. Bootstrap simulation of results indicated that the FFR-guided strategy was cost-saving in 99.8%, and cost-effective in all 1,000 samples [19 20].

Conclusion: The present study summarizes that the addition of coronary physiological measurements like FFR complements traditional angiographic information and is essential for accurate clinical decision-making.It prevents unnecessary PCI. Major Adverse Cardio-vascular Events (MACE) within 6 months following FFR guided management among the patients in whom PCI wasn't undertaken on the basis of FFR, despite angiography guideline suggested so, is not more than the patients in whom PCI is performed because of traditional angiography guideline. In fact, in more than one multi-centric international trials MACE among 'FFR group' was found to be lower than 'Angiography group'. Number of days of hospital stay was reduced and Quality Adjusted Life Years (QALY) was significantly better among FFR group.

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