FRACTIONAL FLOW RESERVE (FFR)

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Abstract: FFR is a form of coronary artery measurement that provides valuable information about the functional significance of coronary artery blockade. It works on a simple hemodynamic principle that the more severe the blockade, the more would be the pressure drop beyond the blockade. Depending upon the amount of pressure changes, objective calculation of blood flow changes can also be calculated which can provide the objective base to take decision in the management of a coronary artery disease patient, i.e. whether to go for angioplasty or manage the patient medically. The following review article shades some light on the topic.

Key words: FFR, Cardiac Physiology, Angiography, Coronary artery disease

Abbreviation: FFR = Fractional Flow Reserve, CAD = Coronary artery disease, MACE = Major adverse cardio-vascular events, PCI = Percutaneous coronary intervention

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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 alone cannot fully characterize the clinical significance of coronary stenosis. [1] [2] Coronary angiography produces a silhouette image and cannot identify intraluminal detail or provide the angiographer with information about the characteristics of the blood flow. Furthermore, accurate identification of both normal and diseased vessel segments is complicated by diffuse disease as well as by angiographic artifacts of contrast streaming, image foreshortening, and calcification. Bifurcation or ostial lesion locations may be obscured by overlapping branch segments.

Even with numerous angiographic angulations to reveal the lesion in its best view, the physiological significance of a coronary stenosis, especially for an intermediately severe luminal narrowing (approximately 40% to 70% diameter narrowing), cannot be accurately determined.

Like stress testing, measurements of coronary pressure and flow provide information complementary to the anatomic characterization of coronary disease obtained by both angiographic and intravascular ultrasound examinations. Such physiological data acquired during the angiographic procedure can facilitate timely and more objective decision-making about therapy [3] [4]. Thus, coronary physiological measurement overcomes the limitations of coronary angiography and provides the angiographer with an objective indicator of clinically relevant lesion significance.

What is FFR? And FFR measurement

Myocardial perfusion 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. 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).

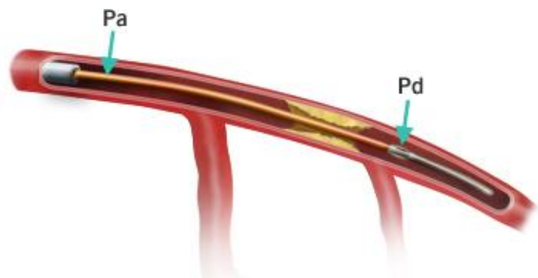
The FFR signifies the maximum achievable myocardial blood flow in the presence of a coronary artery stenosis as a percentage of the maximum blood flow in the hypothetical case of a completely normal artery. [5] [6]

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
An example of FFR measurement is shown in Figure.

$$\text{FFR} = \frac{\text{Distal Coronary Pressure (Pd)}}{\text{Proximal Coronary Pressure (Pa)}}$$

(During Maximum Hyperemia)



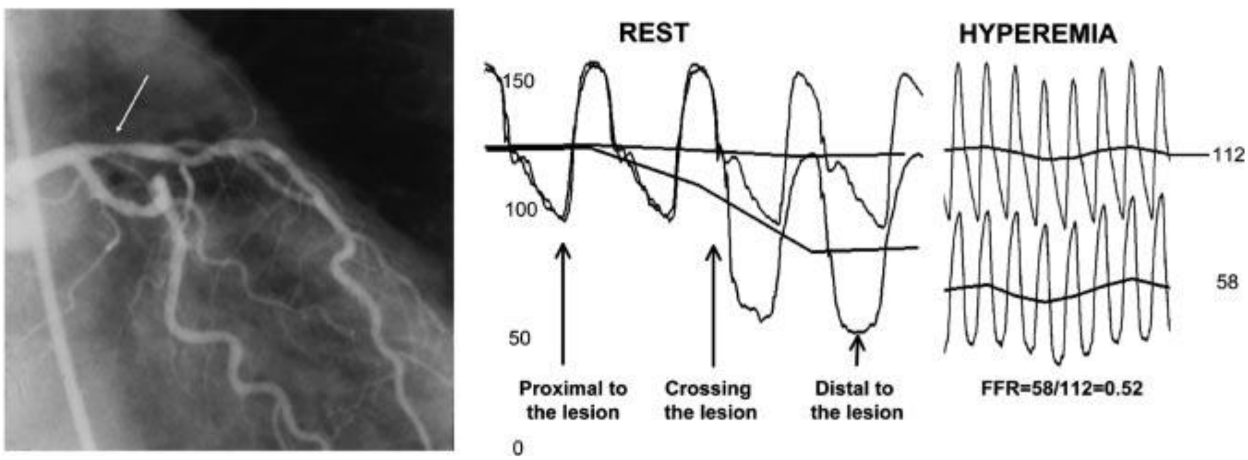


Illustration of the measurement of FFR in a 77-year-old patient with an intermediate coronary lesion left anterior descending artery. Courtesy: N Pijls

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. 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]

Features of FFR Measurements

- Nonischemic threshold range 0.75– 0.80
- Normal value of 1.0
- Specific to epicardial lesions

- Linear relation with relative maximum blood flow
- Independent of hemodynamic alterations
- Value that accounts for total myocardial blood flow, including collaterals
- High reproducibility

Method

A pharmacological hyperemic stimulus 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)

Discussion

Clinical Applications of Coronary Physiology

Ischemic Thresholds of Coronary Physiological Measurements

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)

Prognostic Value

When coupled with a satisfactory angiographic result, coronary physiological indices were predictive of the short-term and long-term clinical outcomes after balloon angioplasty. (10) (11)

For the practice of stent implantation, FFR does not address adequacy of implantation but do provide prognostic information about the patient’s long-term results. In a multicenter trial, Pijls et al (12) 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.

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, the technique for sensor-wire pressure and flow measurements is identical to angioplasty guidewire placement. The induction of maximal hyperemia with intracoronary or intravenous adenosine is important for obtaining accurate data. 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 landmark FAME (Fractional Flow Reserve (FFR) vs. Angiography in Multivessel Evaluation) study demonstrated improved outcomes for patients with multivessel coronary artery disease whose treatment was guided by FFR rather than by standard angiography alone.

The primary endpoint of the FAME study, MACE at 1 year, occurred in 13.2% of those in the FFR-guided arm and 18.3% of those in the angio-guided arm (p=0.02).

Quality Adjusted Life Years (QALY) were significantly greater in the FFR-guided arm (0.882 vs 0.850, for a difference of 0.032, 95% CI 0.010 – 0.056, p<0.05).

Bootstrap simulation indicated that the FFR-guided strategy was cost-saving in 99.8%, and cost-effective in all 1000 samples [13] [14].

The American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines upgraded the level of evidence for FFR from a "B" (At least fair scientific evidence suggests that the benefits of the clinical service outweighs the potential risks) to an "A" (Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks) because of new research conducted to determine its efficacy.

Result of FAME-2

At the end of 2 years, it had been concluded beyond any reasonable doubt that FFR guided coronary artery intervention has got distinct advantage over angiography guided intervention [15].

So, enrolment of new cases has been stopped stating that it is now unethical to enroll anybody in angiography group [15].

The FAME study showed that in patients with multivessel CAD, favorable outcome after routine measurement of FFR during PCI as compared with the standard strategy of PCI guided by angiography alone is maintained at 2-year follow-up.

Routine measurement of FFR probably improved outcomes by allowing more judicious use of stents and equal relief of ischemia. Performing PCI of all angiographic stenoses, regardless of their ischemic potential, diminishes the benefit of relieving ischemia by exposing the patient to additional stent-related risk, whereas PCI of ischemic stenoses only (FFR ≤0.80) is beneficial because the risk of stent thrombosis or restenosis is outweighed by the significant reduction in the risk of ischemic events without stent placement. Thus, by systematically measuring FFR, the benefit of PCI can be maximized by accurately discriminating the lesions for which revascularization will provide the most benefit.

Conclusion:

The best clinical practice suggests 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 PCI.

Major Adverse Cardio-vascular Events (MACE) 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.

It could be recommended that FFR should be made a routine physiological investigation in cardiac catheterization laboratory.

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Disclosure: No conflicts of interest, financial, or otherwise are declared by authors