Fractional Flow Reserve in Contemporary Clinical Practice

Baskaran Chandrasekar*

Abstract

Percutaneous coronary intervention, guided by angiography, is a well established method of treatment of patients with severe coronary artery disease. However, in patients with intermediate severity lesions, the functional significance of the lesions must be ascertained to avoid unnecessary treatment of non-significant lesions while ensuring treatment of significant lesions. The functional significance of these lesions cannot be assessed by angiography, but can be readily determined by measuring the fractional flow reserve in the artery of interest. Compelling current evidence argues for the use of fractional flow reserve-guided revascularization in these patients.

Keywords

Intermediate stenosis; Multivessel disease; Revascularization

Abbreviations: FFR: Fractional Flow Reserve; PCI: Percutaneous Coronary Intervention; DEFER Study: Deferral versus Performance of PTCA in Patients without Documented Ischemia Study; FAME Study: Fractional Flow Reserve versus Angiography for Multivessel Evaluation Study; IVUS: Intracoronar Ultrasound

Introduction

Coronary angiography has been considered the gold standard for assessment of lesion severity in coronary artery disease. However, the limitation of angiography for functionally assessing the significance and severity of coronary stenosis has long been known, with both overestimation and underestimation of lesion severity being recognized [1]. Suboptimal assessment of severity and, therefore, the significance of a lesion to cause ischemia could lead to unwarrented revascularization procedures. There exists a need for assessing the physiological significance of a stenosis to help decide whether the stenosis requires to be treated or not.

Myocardial perfusion imaging has been used for evaluation of ischemia in patients with multivessel coronary artery disease [2]. However, myocardial perfusion imaging as compared to fractional flow reserve (FFR), underestimates significance of stenoses in multivessel disease, and thus may not be reliable to guide treatment in patients [3,4].

FFR is an invasive, yet safe method to assess the physiological significance of a lesion (Table 1). It can be performed during a coronary angiography procedure.

Definition

FFR is defined as the maximally achievable flow in a coronary artery in the presence of a stenosis, divided by the maximum flow expected in the same distribution in the absence of a stenosis [5]. In clinical practice, it is derived as the ratio of the mean aortic pressure and the mean distal coronary pressure during a state of maximal hyperemia. Mean aortic pressure is recorded by a dedicated pressure wire (0.014” coronary wire) placed at the distal tip of the guiding catheter, and distal coronary pressure is recorded by advancing the pressure wire distally beyond the lesion of interest.

Theoretically, normal FFR is equal to 1. An FFR <0.75 [6] or <0.8 [7] has been considered indicative of a functionally significant stenosis.

Maximal hyperemia

Adenosine is used in the vast majority of patients to achieve maximal hyperemia, although papavarine has also been used to induce maximal hyperemia.

In most patients, intracoronary bolus or intravenous infusion routes of administration of adenosine have had equivalent efficacy [8]. Intravenous infusion achieves a steady state of hyperemia which is of importance in the evaluation of patients with multiple lesions in a single artery. Intravenous infusion route is also recommended in patients with left main disease. However, the intravenous route requires a much higher dose of adenosine, as well as the insertion of a central venous line, usually a femoral vein. With percutaneous coronary intervention (PCI) being increasingly performed by radial technique, an additional femoral venous line would be a discomfort to the patient. Recently, it has been shown that intravenous infusion can also be administered by a forearm vein [9]. The recommended dose for intravenous infusion of adenosine is 140 µg/kg per min, and for intracoronary bolus is at least 30 µg for right coronary artery and 40 µg for left coronary artery [10]. Recently, in a small study, a single intravenous bolus of regadenoson (a selective adenosine A2A receptor agonist) was found to have comparable efficacy to standard dose of adenosine intravenous infusion [11].

Randomized trials

Two landmark randomized controlled trials have demonstrated the usefulness of FFR in guiding revascularization strategy as compared to angiography alone, in patients with coronary artery disease. In the DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) study, PCI of functionally significant intermediate lesions as guided by FFR was associated with higher event-free survival up to 5 years compared to angiographically-guided strategy [6,12]. The DEFER study also demonstrated that in patients with functionally nonsignificant stenosis, performing PCI did not improve clinical outcome compared to conservative management. The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study has shown that, the incidence of major adverse cardiac events is reduced in patients with multivessel disease undergoing PCI of only functionally significant lesions determined by FFR [7]. Long term economic benefits of FFR-guided strategy have also been documented [13].

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Optimal medical therapy alone has been proposed as an effective alternative to optimal medical therapy plus PCI in stable coronary artery disease [14]. However, recently it has been shown that in patients with stable coronary artery disease, using FFR as a guide to perform PCI in addition to best medical therapy, led to a better outcome as compared to best medical therapy alone [15].

**FFR in diffuse disease**

FFR may be of help in the functional evaluation of vessels that do not have stenosis, but show diffuse disease. One study reported that 8% of nonstenotic arteries with diffuse atherosclerosis demonstrated functionally significant ischemia by FFR evaluation [16]. Functionally significant diffusely diseased segments could be considered for revascularization.

**FFR post stent implantation**

Stent expansion may be inadequate even after a successful angiographic appearance, thereby requiring additional investigation such as intravascular ultrasound (IVUS) for optimal stent expansion [17]. Optimal stent expansion can also be assessed by measuring the FFR post procedure. The degree of post stent FFR has been shown to be a strong predictor of major adverse cardiac events [10]. A post stent FFR >0.95 was associated with the lowest event rate, with the event rate increasing with decreasing FFR.

**FFR for jailed side branch**

Bifurcation lesion stenting is relatively common in current interventional practice, forming nearly 14% of PCI performed. Following implantation of stent in the main vessel, there exists likelihood for the ostium of the side branch to be narrowed or jailed, which when significant, is a predictor of adverse outcome following PCI. Angiography can lead to overestimation or underestimation of the severity of jailed side branch compared to FFR, in the assessment of functional significance [18]. Performing side branch intervention only when the FFR is functionally significant has been demonstrated to be a safe and effective strategy during bifurcation stenting [19].

**FFR in multilesional single vessel disease**

FFR is also useful in guiding PCI strategy in patients with multiple lesions in the same artery [20]. Briefly, following a functionally significant FFR measurement, a pressure pull back is performed with the pressure wire in the coronary artery of interest under maximal hyperemia. The lesion showing the largest pressure step-up is stented first. FFR is then repeated, and stenting of additional lesions are performed if functionally significant (Figure 1).

![Figure 1: Suggested algorithm for FFR-guided revascularization in patients undergoing coronary angiography. FFR = fractional flow reserve, PCI = percutaneous coronary intervention, MVD = Multivessel disease, SVD = single vessel disease.](image-url)

**Figure 1: Suggested algorithm for FFR-guided revascularization in patients undergoing coronary angiography.**

### Table 1: Utility of Fractional Flow Reserve.

<table>
<thead>
<tr>
<th>Condition</th>
<th>FFR Post Stent Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivessel disease</td>
<td>PCI</td>
</tr>
<tr>
<td>Diffuse disease</td>
<td>No PCI</td>
</tr>
<tr>
<td>Post stent implantation</td>
<td>PCI</td>
</tr>
<tr>
<td>Jailed side branch</td>
<td>No PCI</td>
</tr>
<tr>
<td>Multilesional single vessel disease</td>
<td>PCI</td>
</tr>
<tr>
<td>Left main disease</td>
<td>No PCI</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>PCI</td>
</tr>
</tbody>
</table>

**FFR in small vessel disease**

Patients undergoing PCI of small vessels are at a higher risk of restenosis [23]. Thus, it is important to optimize revascularization strategies in this sub group of patients. Using FFR as opposed to angiography to guide drug-eluting stent implantation in these patients, leads to a significantly lower incidence of complications such as non-fatal myocardial infarction and target vessel revascularization; and, the major adverse cardiac event rate is reduced by nearly 50% [24].

**FFR Vs IVUS in intermediate stenoses**

Both FFR and IVUS have been used in the assessment of significance of intermediate lesions. Although IVUS has a high negative predictive value in excluding functionally significant stenosis when the minimal lumen area is ≥2.4 sq mm, it has a low specificity to diagnose a functionally significant stenosis when the minimal lumen area is <2.4 sq mm [25]. Compared to IVUS, FFR significantly reduces the need for PCI in patients with intermediate stenosis, with comparable long term clinical outcomes [26]. In the setting of left main disease, IVUS appears to have a distinct advantage over FFR, as noted above.
FFR “gray zone”

FFR values between 0.75 and 0.8 are considered a gray zone [27] which may present difficulties in decision-making regarding revascularization. One small study has suggested that PCI can be safely deferred in patients with FFR in the gray zone [28]. However, FFR in the gray zone has been shown to be dose dependent. More than 30% of patients with FFR >0.75 with 15 μg intracoronary bolus of adenosine, achieved significant FFR values of <0.75 with incremental doses of up to 210 μg [29]. A recent study has demonstrated that there exists substantial variability in the measurement of FFR in the gray zone with repeated tests, leading to the possibility that revascularization recommendation could change with a second measurement performed 10 min later [30].

Conclusion

FFR is a valuable complimentary tool to angiography for guiding revascularization in patients with intermediate lesion severity. Such an approach optimizes the need for stent implantation, with favorable long term clinical outcome and, potential cost savings.

References


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