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EDITORIAL

Fractional flow reserve: Current applications and overview of the available data

Matteo Tebaldi, Gianluca Campo, Simone Biscaglia

Matteo Tebaldi, Gianluca Campo, Simone Biscaglia, Cardiovascular Institute, Azienda Ospedaliera Universitaria S. Anna, Cona, 44100 Ferrara, Italy

Gianluca Campo, LTTA Center, 44100 Ferrara, Italy

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Correspondence to: Matteo Tebaldi, MD, Cardiovascular Institute, Azienda Ospedaliera Universitaria S. Anna, Via Mortara 66, Cona, 44120 Ferrara, Italy. tblmtt@unife.it
Telephone: +39-532-237227
Fax: +39-532-236593

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Abstract

Flow fractional reserve (FFR) allows to evaluate the functional significance of coronary artery lesions, through the ratio of the mean coronary artery pressure after the stenosis to the mean aortic pressure during maximum hyperemia. The actual widely accepted cut-off value is 0.80. Below this value a coronary lesion is considered significant and therefore it requires invasive revascularization. Several studies [in particular Fractional Flow Reserve *vs* Angiography for Multivessel Evaluation 1 (FAME-1) and FAME-2] have shown the relationship between FFR measurement and hard end-points (death, myocardial infarction, and urgent revascularization). Consequently, FFR evaluation represents the cornerstone in the decision-making in intermediate coronary lesions. Recent studies paved the way for further applications of FFR evaluation in complex and tricky clinical settings. In this paper, we perform an overview of the data regarding contemporary application of FFR. In particular, we review the use of FFR in: left main intermediate stenoses, serial stenoses, evaluation after stenting, guidance in coronary artery bypass surgery, and acute coronary syndrome. All the data presented in our overview confirm the essential role of FFR assessment in the daily clinical practice. The shift from "operator-dependent" to "FFR-dependent" evaluation in intermediate coronary artery stenosis is of paramount importance in order to improve the prognosis of our patients, through the discrimination of the functional role of every single coronary stenosis.

Key words: Intermediate coronary lesion; Fractional flow reserve; Coronary artery bypass surgery; Left main; Acute coronary syndrome; Serial stenoses

Core tip: Fractional flow reserve (FFR) evaluation is well validated in intermediate coronary lesions. Still, there are several clinical settings in which its use is debated. In this paper, we perform an overview on the available data regarding FFR and complex clinical settings, as left main intermediate stenoses, serial stenoses, evaluation after stenting, guidance in coronary artery bypass surgery, and acute coronary syndromes.

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INTRODUCTION

Fractional flow reserve (FFR) is an objective method to assess the functional significance of coronary artery lesions. FFR is defined as the ratio of maximal achievable blood flow in coronary artery to the hypothetical maximal achievable blood flow in the same artery in the absence of stenosis. It is derived from the ratio of the mean distal coronary artery pressure to the mean aortic pressure during the period of maximum hyperemia. Initial studies suggested that the cut-off value of 0.75 was reliable in the identification of ischemia-producing lesions. Afterwards, several outcome studies[1,2] validated the cut-off value of 0.80, which is actually widely accepted.

CLINICAL STUDIES

The randomized clinical trial FFR to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenoses (DEFER) first evaluated the clinical benefit of FFR-guided revascularization. This study enrolled 325 patients with intermediate coronary stenosis. Patients with FFR value < 0.75 underwent percutaneous coronary intervention (PCI) (reference group, n = 144), whereas patients with an FFR value $\geqslant$ 0.75 were randomly allocated to PCI (perform group, n = 90) *vs* medical therapy (DEFER group, n = 91). At a median follow-up of 5 years, the prognosis of "non-ischemic" stenosis (FFR $\geqslant$ 0.75) was excellent even without the placement of a stent[3,4]. In the Fractional Flow Reserve *vs* Angiography for Multivessel Evaluation (FAME) study, 1005 patients with multivessel coronary artery disease were randomly assigned to PCI with drug-eluting stents guided by angiography alone or guided by FFR. Patients randomized to receive PCI, underwent stenting of all lesions; whereas those randomized to receive a functional assessment of coronary stenosis by FFR, underwent PCI only if FFR value was $\leqslant$ 0.80. The study showed a statistically significant reduction of the primary end point at 1 year (a composite of death, MI and repeat revascularization) in favor of the procedure guided by FFR (P = 0.02)[5]. In the subsequent FAME-2 trial, patients with stable coronary artery disease and at least one stenosis with FFR $\leqslant$ 0.80, were randomly allocated to medical therapy alone or to medical therapy plus PCI. The trial was stopped prematurely due to a highly significant difference in the incidence of the primary endpoint (a composite of death, myocardial infarction, and urgent revascularization) in favor of FFR-guided PCI, entirely driven by lower incidence of urgent revascularization. There were no statistically significant differences with regard to death or MI between the two groups[2,6]. In summary, FAME-2 showed that FFR-guided angioplasty reduces the incidence of urgent revascularization when compared to medical therapy.

FFR AND LEFT MAIN

In a study published in 2009, Hamilos *et al*[7] randomized 213 patients with angiographically equivocal left main coronary artery stenosis. All patients underwent FFR evaluation on left main. When the value was $\geqslant$ 0.80, patients were treated with medical therapy alone (non surgical group), while when FFR was < 0.80, coronary artery bypass grafting was performed (surgical group). The follow-up performed at 5 years did not demonstrate statistically significant differences between the two groups of patients, with regard to survival and event-free survival. Percent diameter stenosis at quantitative coronary angiography correlated significantly with FFR (r = -0.38, P < 0.001), but a very large scatter was observed. An important evidence emerging from this analysis is that 23% of lesions judged less than 50% at angiographic analysis, resulted critical after FFR evaluation. It follows that in left main intermediate lesions, angiography alone is unable to determine whether a stenosis is critical or not, tending to underestimate its functional significance. In this very important scenario, FFR plays a central role in the decision-making. In a worthy editorial by Kern[8], the author investigated a particularly complicated angiographic scenario, where stenosis in the left main (LM) is associated with a stenosis of the left anterior descending (LAD). In clinical practice, the sum of FFR across both lesions (LM + LAD) determines the need to treat, while the pressure pullback recording determines which lesion needs to be treated. In fact, the lesion with the largest pressure drop (ΔP, not FFR) is treated first. Then, FFR evaluation is repeated across the remaining lesion in order to decide whether even the second lesion needs to be treated. Such a method can be used to assess serial LM - LAD disease, but this approach engenders a downside: acceptance of stenting an unprotected LM after LAD treatment, if FFR remains < 0.80. In this particular case, both anatomical and physiopathological variables can determine a high number of errors. In order to overcome these limitations, intravascular ultrasound is frequently used to assess the minimum luminal area in the LM. Although a minimal luminal area > 6 mm^2 is an oft-quoted threshold, it represents a conservative approximation of true physiology, best indicating a lack of functional significance rather than a minimal luminal area < 6 mm^2 being an indication to treat[8,9].

FFR AND SERIAL STENOSES

Kim *et al*[10] investigated the treatment of intermediate coronary stenoses in series on the same coronary artery

using FFR pullback pressure tracings. If FFR result was < 0.80, the stenosis with the largest pressure step-up was treated with stenting first. Subsequently, the patients were divided into two groups (FFR < 0.8 *vs* FFR > 0.8), according to FFR value after PCI. There were no events related to deferral of lesion treatment. The evaluation by conventional FFR of a single coronary artery stenosis in a vessel where there are several intermediate lesions, is underestimated ("apparent FFR"). Indeed, in this scenario, the assessment with FFR tends to ignore the real contribution of each stenosis to the ischemic burden. The real value of the FFR ("true FFR") can be calculated only after the treatment of the lesion which gave the largest pressure step-up using FFR pullback pressure tracings or by using a more complex method described by De Bruyne *et al*[11] which also considers the coronary wedge pressure[11,12]. In conclusion, FFR-guided revascularization strategy using pullback pressure tracing in serial stenoses is safe and effective[10].

FFR AFTER STENT

In a study published in 2011, Nam *et al*[13] assessed the impact of FFR value after stent on MACE (myocardial infarction, death, ischemia-driven target vessel revascularization) at one year. Patients were divided into two groups according to the value of FFR detected after PCI (FFR < 90: low-FFR group; FFR > 90: high-FFR group). The study showed a statistically significant MACE reduction in the high-FFR group; for that reason the 0.90 value it is considered the cut-off reference to obtain after PCI.

FFR AND CORONARY ARTERY BYPASS SURGERY

Myocardial revascularization is recommended when a large territory of reversible myocardial ischemia is present. Of note, patients undergoing cardiac surgery usually have a very complex coronary anatomy. In such situation, non-invasive functional testing has shown many limitations. On the contrary, as described previously, FFR is safe and accurate even in patients with multivessel disease with multiple stenosis. The usefulness of FFR in patients undergoing coronary artery bypass surgery was confirmed by the results of a registry by Toth *et al*[14]. In this registry, authors evaluated patients with at least one intermediate coronary stenosis. These patients were divided into two groups: the angiography-guided group, in which patients underwent coronary artery bypass graft surgery (CABG) solely on the basis of coronary angiography; and the FFR-guided group, in which patients underwent CABG if FFR was ⩽ 0.80, and were treated conservatively if FFR was > 0.80. The registry showed that FFR-guided coronary artery bypass graft surgery was associated with a lower number of graft anastomoses, a lower rate of on-pump surgery and a lower rate of angina in the absence of an increase of events during follow-up[14].

FFR AND ACUTE CORONARY SYNDROME

During the acute phase of acute coronary syndrome (ACS), we deal with a non-permanent microvascular dysfunction, which both changes during hours and is affected by multiple factors (embolization, changes in filling pressures, duration and intensity of ischaemia, changes in systemic or local vasoconstrictors, *etc.*)[15]. The microvascular dysfunction is a key aspect for the evaluation with FFR: a reduced ability to respond to vasodilation through adenosine by the microcirculation, may cause an underestimation of coronary stenosis. At present, the main study evaluating the relationship between FFR and outcome in ACS patients is the FAMOUS-NSTEMI trial[16]. In this trial, 350 patients with no ST-segment elevation MI were enrolled. The evaluation using FFR resulted in a reduction of patients undergoing PCI without increase of events at 1 year follow-up.

CONCLUSION

All available studies suggest that FFR assessment should be considered an essential tool in daily clinical practice. Therefore, the operator-dependent evaluation of intermediate stenosis should now represent just an old memory in the history of interventional cardiology. FFR value permits to better discriminate the functional role of intermediate stenosis significantly improving the prognosis of our patients.

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