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Fractional flow reserve: current evidence base in stable coronary artery disease

Ozan M. Demir, MBBS; Matt Ryan, MBBS; Haseeb Rahman, MBBChir; Divaka Perera, MA, MBBChir, MD

NIHR Biomedical Research Centre and British Heart Foundation Centre of Excellence, School of Cardiovascular Medicine and Sciences, St Thomas' Campus, King's College London, UK

Correspondence: Prof Divaka Perera, Cardiovascular Division, Rayne Institute, St Thomas' Hospital, London, SE1 7EH
E-mail: Divaka.Perera@kcl.ac.uk

Abstract

The development of fractional flow reserve (FFR) has revolutionized interventional cardiology, leading to a physiology-based instead of anatomy-based approach to coronary revascularization. There have been three landmark FFR trials: DEFER, FAME, and FAME-2. In the DEFER trial an FFR threshold of 0.75 was used to guide revascularization; subsequently, in the FAME and FAME-2 trials the FFR threshold was increased to 0.80. All these studies demonstrated that FFR-guided revascularization resulted in improved clinical outcomes with reduction in major cardiovascular events. However, in the FAME and FAME-2 trials this reduction in major cardiovascular events has principally been driven by difference in rates of urgent revascularization. The treatment thresholds for FFR have increased from initial derivation studies where the threshold was 0.75. This has been in an empirical bid to increase the sensitivity and negative predictive value, at the inevitable cost of specificity; potentially to the detriment of hard end points. Recently, resting indices have been proposed. However, despite much interest there remain some unresolved questions including the discordance with FFR that occurs in 20% of patients. In conclusion, there is overwhelming evidence for the use of FFR in guiding percutaneous coronary intervention in stable coronary artery disease, and it has become a reference surrogate measure of ischemia. However, outcome data are principally driven by rates of urgent revascularization. It may be that a lower threshold is required, as suggested by early studies, to demonstrate a mortality benefit for FFR-guided revascularization. ■
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Introduction

The development of fractional flow reserve (FFR) has revolutionized interventional cardiology, leading to a physiology-based instead of anatomy-based approach to coronary revascularization. The seminal work by Pijls et al in 1996 demonstrated that FFR is a surrogate for ischemia testing at the point of diagnostic angiography.[1] This led to a number of large randomized studies demonstrating that FFR-guided revascularization resulted in improved clinical outcomes for patients with coronary artery stenosis.[2,3] Recently, resting pressure-wire indices (avoiding hyperemia) have been developed and validated against

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FFR.[4,5] This review provides a comprehensive overview of the evidence base for FFR, its use in the context of different coronary artery disease (CAD) pattern, and the role of emerging resting indices.

Principles of fractional flow reserve

In 1993, Piljs et al described the theoretical basis for the calculation of coronary flow reserve from coronary pressure, namely that the ratio of distal coronary to aortic pressure during maximal hyperemia in a stenosed coronary artery was linearly and strongly correlated with flow in the diseased artery in relation to hypothetical flow in an entirely disease-free artery supplying the same myocardial territory.[6,7] This was a landmark step as pressure measurements are markedly easier to perform than coronary flow measurements in clinical practice. In 1996, the optimal FFR threshold for detecting ischemia was established as 0.75; at sensitivity of 88%, specificity 100%, positive predictive value 100%, negative predictive value 88%, and diagnostic accuracy of 93%.[1]

There have been three landmark FFR trials: DEFER,[8] FAME,[2] and FAME-2.[3] In the DEFER trial, patients with moderate coronary artery stenosis were divided into three groups: (i) patients with FFR >0.75 were randomly assigned to either defer group (n=91) where no percutaneous coronary intervention (PCI) was performed; (ii) or perform group (n=144) where PCI was performed; (iii) patients with FFR <0.75, reference group (n=144), underwent PCI. At 5 years, event-free survival was similar between the defer and perform groups (80% and 73%, respectively; *P*=0.52). Furthermore, the risk of myocardial infarction or cardiac death in patients with an FFR value ≥0.75 stenosis was <1% per year, and not decreased by stenting.[8] In the FAME trial, 1005 patients with multivessel CAD were randomized to FFR-guided or angiography-guided PCI.[2] FFR-guided PCI, with a higher threshold of ≤0.80 for PCI, resulted in a reduction in the per-patient number of stents (2.7±1.2 versus 1.9±1.3, *P*<0.001). At 1 year the composite MACE-orientated primary end point (death, nonfatal myocardial infarction, and repeat revascularization) was 18.3% in the angiography group and 13.2% in the FFR group (*P*=0.02). However, despite FAME demonstrating that an FFR-guided PCI results in better clinical outcomes, this was principally driven by the repeat revascularization.

In the FAME-2 open-label trial, patients in whom at least one stenosis was functionally significant (FFR≤0.80) were randomly assigned to FFR-guided PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone (medical-therapy group). In addition, patients in whom all stenoses had an FFR > 0.80 were entered into a registry; this represented approximately one third of patients enrolled in the study. The study was halted prematurely due to significant difference in the primary end point 4.3% in the PCI group versus 12.7% in the medical therapy alone group, *P*<0.001; this was mostly driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% versus 11.1%; *P*<0.001).[3] However, urgent revascularization was performed following diagnosis of unstable angina on clinical assessment alone in half these patients, without any cardiac enzyme or electrocardiogram abnormalities. Furthermore, neither the rate of death from any cause nor the rate of myocardial infarction differed significantly between the PCI group and the medical-therapy group. Nonetheless, at 5 years, the rate of the primary end point was lower in the PCI group than in the medical-therapy group (13.9% vs 27.0%, *P*<0.001). The difference was again driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group as compared with 21.1% of those in the medical-therapy group.[9]

Of note, whilst the FAME and FAME-2 trials have been positive, demonstrating significantly lower MACE rates, this has been principally driven by difference in rates of urgent revascularization. The treatment threshold for FFR has increased from initial derivation studies where the cutoff established was 0.75, to 0.80 in the FAME studies.[10] This has been in an empirical bid to increase the sensitivity and negative predictive value of both these indices, at the inevitable cost of specificity; potentially to the detriment of hard end points including mortality.[11] This has been further illustrated by the IRIS-FFR registry, which included >8000 lesions, suggesting the optimal FFR threshold cardiac death or myocardial infarction was 0.64.[12] At present, the COMFORTABLE prospective study is recruiting to investigate the superiority of medical therapy plus PCI over medical therapy alone in reducing major cardiovascular events in patients presenting with coronary stenosis with “gray zone” FFR values, between 0.75 and 0.80.[13]

Evidence for FFR in different lesions

Whilst the evidence base for FFR has been established, its utility in different CAD lesion subsets remains a topic of interest, especially as interventional cardiologists seek to physiologically assess increasingly complex patterns of CAD. The vast majority of the clinical outcome data for FFR have been derived from isolated lesions in single or multiple vessels. Herein, we outline role of FFR in serial stenoses and chronic total occlusions, both commonly encountered during diagnostic coronary angiography.

Serial stenoses

The clinical utility of FFR in vessels with multiple stenoses is hampered as one stenosis influences the FFR of the others and complicates the determination of FFR of each individual stenosis. However, studies have demonstrated that FFR may be measured accurately in serial stenoses. In a prospective study, 131 patients with serial intermediate stenoses, pullback pressure-wire to the ostium of the coronary artery under steady-state hyperemia was performed and the stenosis that caused the largest pressure step-up ("primary target lesion") was treated first. After PCI to the "primary target lesion" repeat FFR was performed, leading to further PCI in only 26 vessels (18.4%).[14] The primary limitation of this method is that, due to interplay between lesions, the operator may inadvertently perform PCI on the lesion that is actually less significant in the first instance. More recently, it has been demonstrated that this error is significantly improved using a mathematical correction model, incorporating routinely available pressure-wire pullback data.[15]

Chronic total occlusions

In patients with chronic total occlusion there is usually blood supply to that vessel distally via collateral vessels. In these circumstances, it is thought that assessment of FFR in the donor vessel may lead to erroneously positive FFR values. However, it is important to appreciate that FFR measurements remain valid but incorporate the effect of a given stenosis on both coronary territories supplied. Hence, if the chronic total occlusion is treated the FFR rises, due to reduction in the dependent myocardial volume. A recent study showed that FFR values increased from 0.78 to 0.81 (P=0.001) following treatment of the occluded vessel.[16]

Acute coronary syndromes

In the setting of acute coronary syndromes, assessment of the non-culprit vessel with FFR, performed at the time of intervention to the culprit vessel, is affected by abnormalities of epicardial vasomotor tone and microvascular tone. This phenomenon in the non-culprit vessel is transient. Hence, whilst it may be efficacious to perform FFR measurements in the acute setting, it is preferable that this is performed at a later setting to allow these physiological abnormalities to normalize.[17] Conversely, assessment of the culprit vessel with FFR in the setting of an acute coronary syndrome is not recommended, as there is sparsity of any robust data on the efficacy of FFR.[18]

Non-hyperemic physiological indices

Over the last decade there has been significant interest in the ratio of distal coronary to aortic pressure, at prespecified segments of the cardiac cycle, without the use of hyperemia. Instantaneous flow reserve (iFR), measured in the latter 75% of diastole, is the most commonly utilized resting index. Patients managed on the basis of a dichotomous iFR threshold of 0.89 were found to have equivalent rates of major adverse outcomes to those managed on the basis of a FFR threshold of 0.80 in two large RCTs: DEFINE-FLAIR [4] and iFR-SWEDE-HEART.[5] Recent ESC guidelines have made a class I recommendation for physiological assessment of coronary disease by either FFR or iFR when planning revascularization in stable CAD.[19] However, there remain some unresolved concerns about iFR, including the difficulty in ensuring a consistent resting state in patients undergoing invasive coronary assessment and the discordance in classification based on dichotomous FFR and iFR thresholds that occurs in 20% of patients.[20,21] Other resting coronary indices, such as whole-cycle Pd/Pa ratio or the Pd/Pa ratio at different phases of the cardiac cycle, have been shown to be very similar to iFR, both numerically and with respect to their agreement with FFR, with a diagnostic accuracy compared with FFR of 76% to 77% for resting indices including iFR.[21]

Conclusions

There is overwhelming evidence for the use of FFR in guiding PCI in stable coronary artery disease, and it remains the reference standard ischemia test. Despite this, uptake has been suboptimal. Whether the advent of practically simpler but potentially less accurate approximations of FFR might increase physiological assessment of CAD remains unclear. Furthermore, whether these indices can be applied to more complex patterns of disease needs systematic evaluation. Finally, the gray zone between deferral and treatment thresholds needs further exploration and is particularly pertinent in the face of mounting evidence that revascularization may be of limited prognostic benefit in stable CAD. ■

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