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REVIEW

Fractional Flow Reserve-guided Percutaneous Coronary Intervention: Standing the Test of Time

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Abstract

Percutaneous coronary intervention (PCI) improves symptoms and prognosis in ischemia-inducing, functionally significant, coronary lesions. Use of fractional flow reserve allows physicians to investigate the ischemia-inducing potential of a specific lesion and can be used to guide coronary revascularization, especially in multivessel coronary artery disease. Fractional flow reserve-guided PCI has been extensively investigated. Results show that deferral of stenting in non-significant lesions is safe, whereas deferral of stenting in functionally significant lesions worsens outcome. FFR-guided PCI improves outcome in multivessel disease over angiography-guided PCI. Until recently, there was little known about the long-term outcome of FFR-guided revascularization and its validity in acute coronary syndromes. This review aims to address the new evidence regarding long-term appropriateness of FFR-guided PCI, the need for hyperemia to evaluate functional severity, and the use of FFR in acute coronary syndromes.

Keywords: coronary artery disease; percutaneous coronary intervention; fractional flow reserve

Introduction

In coronary artery disease as in health care in general, justification of any treatment, in this case percutaneous coronary intervention (PCI), should either be the relief of symptoms or improvement of prognosis. Coronary artery stenoses only induce symptoms and affect prognosis if they provoke myocardial ischemia, i.e. are functionally significant [1]. In such patients, PCI improves both symptoms and outcome [1, 2]. On the other hand, prognosis of non-ischemic stenoses, i.e. functionally non-significant stenoses, is excellent when treated medically and is not improved by PCI [3]. This review aims to go over new evidence regarding long-term appropriateness of FFR-guided PCI, the need for hyperemia to evaluate functional severity, and the use of FFR in acute coronary syndromes.

Limitations of Angiography-Guided PCI

Despite the knowledge that only revascularization of functionally significant lesions improves outcome, the majority of patients in current practice undergo cardiac catheterization without previous non-invasive assessment of the presence and extent of ischemia [4]. In these patients, justification of PCI used to be based upon visual estimation of lesion severity on the coronary angiogram. Coronary luminology however is misguiding due to several factors. Most importantly, the coronary angiogram

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depicts a distorted two-dimensional view of a three-dimensional lumen, and is confounded by vessel tortuosity and overlap of structures [5]. For these reasons, coronary angiography has a large inter-observer variability, and apparent lesion severity on the angiogram differs significantly from post-mortem histology [6, 7]. Moreover, the effects of diameter stenosis on coronary flow is dependent on more than just morphology. Morphology alone will simply never be sufficient to predict physiology, since it does not incorporate important determinants of maximal blood flow, such as myocardial mass and microvascular function. All these aforementioned factors result in regular misinterpretation of functional severity of coronary lesions on the angiogram [8]. To overcome the shortcomings of angiographic lesion assessment, the physiologic index fractional flow reserve (FFR) has emerged to assess the functional significance of coronary artery disease [9, 10]. Using FFR to guide revascularization, interventional cardiologists have finally been able to show improvement in outcome by PCI over medical therapy in stable coronary artery disease, due to more judicious stent placement, i.e. better selection of those lesions requiring PCI and those better treated medically [11].

Coronary Physiology: Historical Perspective

Shortly after the introduction of selective coronary angiography, laboratory studies demonstrated that coronary flow remains stable over a range of epicardial stenosis severities. In the majority of patients, only when the lumen is narrowed >85% coronary flow starts to decline [12, 13]. The importance of hyperemia to unmask the true ischemic potential of a certain lesion was already acknowledged at the birth of balloon angioplasty. In this perspective, coronary flow reserve (CFR), defined as maximal coronary blood flow divided by resting flow, was developed and measured using a Doppler wire. Although CFR is a valuable parameter to study coronary physiology, clinical use of CFR is restricted by the lack of an absolute normal value, moderate reproducibility in humans, and variation with blood pressure, contractility, and heart rate [14, 15]. Moreover, reflecting total coronary blood flow, CFR does not separate epicardial and microvascular disease, and cannot be considered truly lesion specific. From the early days of PCI on, interventional cardiologists have focused on pressure gradients across an epicardial lesion, measuring residual gradients after coronary angioplasty [16]. However, due to the size of catheters used at that time, overestimation of gradients restricted its clinical use. In addition, the importance of hyperemia was not yet recognized, and mere gradients were studied instead of pressure ratios. This all changed approximately two decades ago with the introduction of fractional flow reserve (FFR) and the development of a 0.014 coronary pressure wire [9, 10].

Fractional Flow Reserve

FFR is a lesion-specific pressure-derived index of functional severity, defined as the maximum myocardial blood flow in the presence of an epicardial stenosis compared with the maximum flow in the hypothetical absence of the stenosis (Figure 1). The rationale behind FFR is based on the fact that myocardial blood flow is equal to the myocardial perfusion pressure over the coronary circulation divided by the resistance. Using nitroglycerine and adenosine, epicardial and microvascular resistance is kept minimal and constant, resulting in a linear relationship between pressure and flow. In this way, pressure can be used to assess flow. In a healthy coronary artery, there is no pressure loss along its course, i.e. proximal and distal coronary pressures are equal. In a diseased vessel, there is pressure loss along its course, lowering the distal coronary pressure compared to the proximal coronary pressure. Thereby, under conditions of maximum hyperemia (and minimal and constant resistance), the proximal pressure serves as a representation of what the distal pressure would have been in the absence of the stenosis, and the distal coronary pressure serves as the actual myocardial perfusion pressure in the presence of the stenosis. By dividing the mean distal coronary pressure by the mean proximal coronary pressure, a ratio is calculated representing the fraction of normal maximum coronary flow reaching the myocardium behind the stenosis under investigation. FFR can be measured easily in the catheterization laboratory, and has

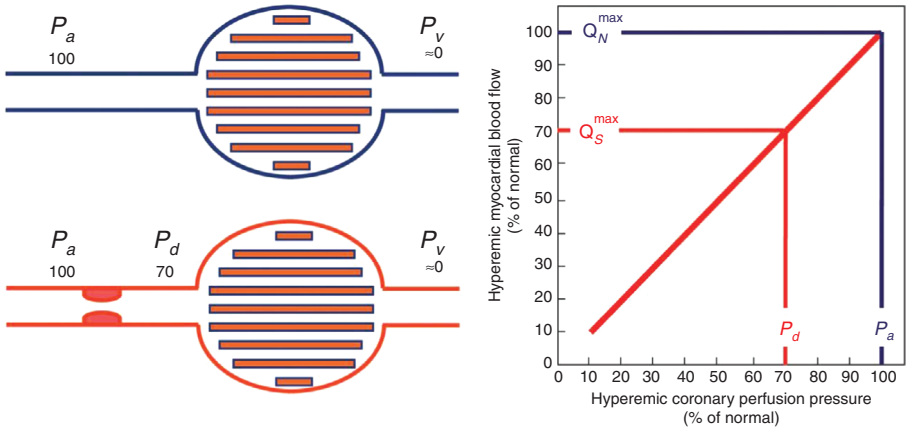

Figure 1 Concept of Fractional Flow Reserve.
During maximum vasodilatation in the coronary circulation, when there is no epicardial stenosis present (blue lines), the driving pressure P_a determines the normal maximal coronary blood flow (100%). When there is an epicardial lesion, responsible for a hyperemic pressure gradient of 30 mmHg (red lines), the driving pressure is no longer 100 mmHg, but 70 mmHg (Pd). Since there is a linear relationship between perfusion pressure and myocardial blood flow during maximum hyperemia, maximum myocardial blood flow is decreased to 70% of its normal value. Reproduced with permission [17].

proven to be safe and highly reproducible [18, 19]. When compared with angiography-guided PCI, the use of FFR does not prolong the procedure. Moreover, in contrast to other indices, it is independent of resting flow, heart rate, blood pressure, and left ventricular contractility [14]. FFR has been extensively validated, has a narrow grey zone and a normal value of 1.00, consistent for any patient and any lesion. FFR is the only functional stenosis index which has been validated against a true gold standard using a sequential Bayesian approach [20]. Numerous studies have shown FFR is able to predict outcome. Three large randomized trials have consecutively shown that deferral of stenting in non-significant lesions is safe and not improved by stenting while deferral of stenting in functionally significant lesions worsens outcome, and that FFR-guided PCI improves outcome in multivessel disease compared to angiography-guided PCI [11, 21, 22]. Recently, a large meta-analysis confirmed the hypothesis of a continuous relationship of FFR with clinical outcome [23]. FFR has been validated in numerous randomized trials in a variety of patient populations and lesion subsets, all corroborating the robustness of FFR. Besides the ability of FFR to determine whether or not a particular stenosis should be stented, FFR can also shift the complete treatment strategy towards medical therapy, coronary artery bypass grafting, or vice versa. Measurement of FFR results in a change of management strategy in patients presenting with stable coronary artery disease in about 25% [24]. The ongoing FAME 3 trial plans to randomize 1500 patients with angiographic three-vessel disease to undergo either CABG or FFR-guided PCI with contemporary stenting [25]. The hypothesis of that study is that FFR-guided PCI with contemporary stenting is non-inferior to CABG in these patients.

Long-Term Outcome of FFR-Guided PCI

Until recently, there was little known about long-term outcome of FFR-guided revascularization. There was concern about a possible so-called late catch-up phenomenon by progression of coronary artery disease in untreated functionally non-significant lesions. Concerns about plaque rupture have also played a major role in this discussion. The 5-year results of the DEFER study, randomizing functionally non-significant lesions to either medical treatment or revascularization, had already shown that the risk of cardiac death or acute myocardial infarction in functionally non-significant lesions (FFR≥0.75) was less than 1% per year and outcome was not improved by revascularization [26]. Moreover, as recently described, even after 15 years of follow-up, the prognosis of these functionally non- significant lesions in DEFER proved

to be excellent [3]. Revascularization of these lesions did not improve outcome in any way, and even resulted in a significant increase in myocardial infarction over 15 years when compared with medical therapy (Figure 2). In this longest follow-up of a randomized trial using FFR-guidance, there was no sign of the catch-up phenomenon mentioned above. The FAME study, randomizing patients with multivessel coronary artery disease to angiography-guided or FFR-guided PCI, consisted of a patient population with more severe and complex coronary artery disease, including acute coronary syndromes. Moreover, the patient population was roughly three times larger, and drug-eluting stents were used in this study. The recently published 5-year follow-up of this study showed that the benefit of FFR-guided PCI occurs in the first two years, whereafter the risks evolve in parallel (Figure 3) [27]. The benefit was not undone by an excess of late clinical events in the FFR-guided group. This was true over a wide range of endpoints, including major adverse cardiac events and its individual components. Altogether, these data corroborate earlier findings of benefit of revascularization in functionally significant lesions compared with the absence of such benefit in functionally non-significant lesions, and negate concerns about the long-term safety of FFR-guided PCI.

The Need for Hyperemia

The presence of maximum hyperemia is one of the most important prerequisites to measure FFR. In daily practice in the catheterization laboratory, several hyperemic stimuli can be used. The current gold standard is central venous infusion of adenosine at 140 µg/kg/min. Use of central venous infusion of adenosine is safe, well-investigated, and very reproducible [17, 28]. Its biggest advantage is the ability to create steady state coronary hyperemia, used to perform a pressure pullback recording in more complex coronary artery disease. Due to the need for central venous access, and the high price of adenosine in some countries, physicians sometimes use alternatives to central venous infusion of adenosine. Hyperemic alternatives consist of intracoronary injections of adenosine or papaverine, peripheral infusion of adenosine, or regadenoson. Although capable of inducing maximum coronary hyperemia, all alternatives have some specific disadvantages. Intracoronary adenosine acts too briefly to perform an accurate pullback recording. The hyperemic stimulus of papaverine has a longer plateau phase, but is sometimes accompanied by polymorphic ventricular tachycardia. Both intracoronary adenosine or papaverine are not reliable for investigating ostial lesions. Peripheral infusion of

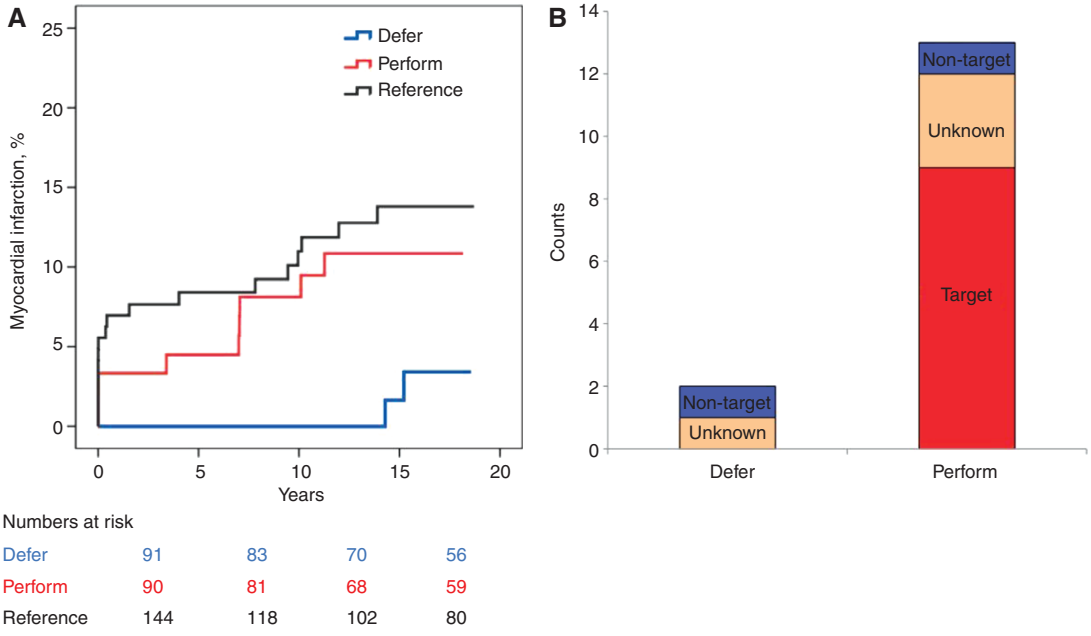

Figure 2 Kaplan-Meier curves of Myocardial Infarction in the DEFER Trial. Reproduced with permission [3].

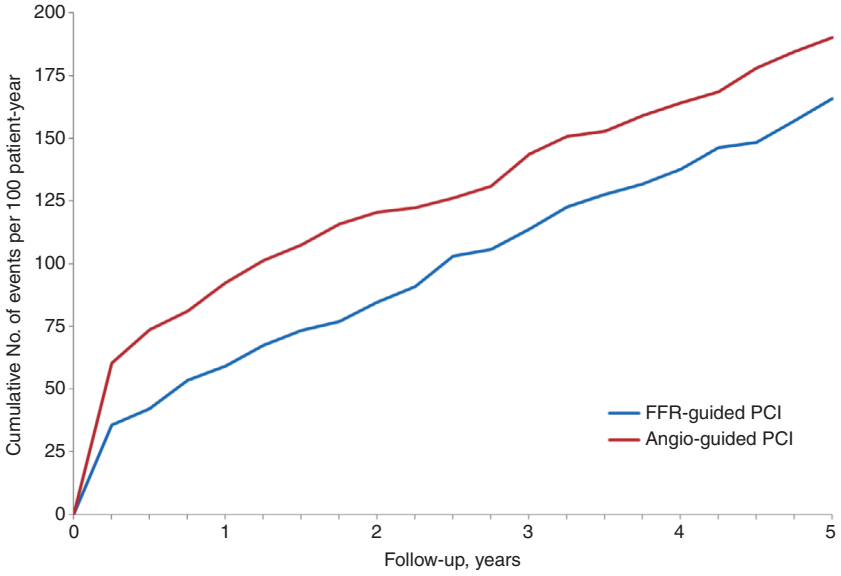

Figure 3 Cumulative Events Per 100 Patient-Years in the FAME Study.
Cumulative events of angiography-guided PCI versus FFR-guided PCI during 5-year follow-up are shown in this cumulative event-curve. Reproduced with permission [21].

adenosine has a slower onset of hyperemia and the depth of hyperemia is less reliable [28]. Regadenoson is a relatively new alternative hyperemic stimulus. The A2A-receptor selective, non-weight based hyperemic stimulus (400 µg) is known for its rapid onset and ease of use. Recent studies have proven the hyperemic effect of regadenoson to be equal to central venous infusion of adenosine, and regadenoson can be administered both centrally and peripherally [18, 29–32]. Its plateau phase can be variable. While regadenoson is a welcome addition to the hyperemic armamentarium in the catheterization laboratory, its use should be restricted to relatively simple, focal coronary artery disease. In more complex disease, where a pressure pullback recording or multiple measurements are necessary, central venous infusion of adenosine remains the gold standard to ensure steady-state hyperemia. In recent literature, there has been debate about the dosage of intracoronary adenosine. There were only few studies investigating intracoronary dosages of adenosine [28, 33, 34]. A recently performed extensive dose-response study investigated the hyperemic effect of intracoronary bolus injections of adenosine in the range from 4 to 500 µg. The suggested dose to be sure to reach maximum coronary hyperemia is 100 µg for the right coronary artery and 200 µg for the left coronary artery [35].

Resting Pressure Indices

While trying to simplify coronary physiologic measurements in the catheterization laboratory, some physicians have propagated to leave out maximum coronary hyperemia and rather rely upon resting indices such as distal to proximal pressure ratio at rest (Pd/Pa at rest) or the instantaneous wave-free ratio (iFR) [17, 36]. iFR uses wave intensity analysis to define a certain portion of diastole where myocardial resistance is allegedly low and constant, and Pd/Pa during this period would reflect FFR without the need of inducing hyperemia. Although an attractive alternative at first sight, in all studies investing Pd/Pa at rest and iFR compared with FFR, irrespective whether performed by proponents or opponents, accuracy never exceeds approximately 80% [17, 36–38]. Using a bolus of contrast injection as submaximum hyperemic stimulus, a middle way between avoiding a hyperemic stimuli and not wanting to accept suboptimal decision making was recently proposed [39]. This contrast-FFR showed better accuracy over pure resting indices, but reached an accuracy of 85% when compared with “true” FFR. While not as good as FFR, its use could be considered when use of adenosine in contraindicated, or not easily available. Overall, the more hyperemia, the more accurate the decision (Figure 4). The most appropriate

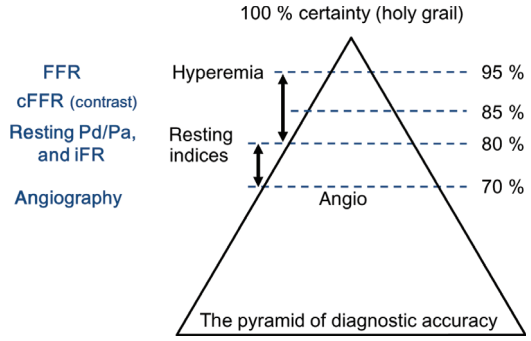

Figure 4 Pyramid of Diagnostic Accuracy.

decision and treatment is achievable in >95% of patients when using FFR. Any attempt to abandon maximum hyperemia to simplify the procedure, will inevitably result in a decrease in accuracy.

Fractional Flow Reserve in Acute Coronary Syndrome

The validity of FFR measurements in acute coronary syndrome (ACS) is often questioned. While the culprit stenosis is often easily identified by the electrocardiogram and angiogram, a relatively large part of these patients has multivessel coronary artery disease. In those non-culprit lesions, it is difficult to decide whether or not these lesions should be treated, and while incomplete revascularization is associated with worse prognosis, assessing inducible myocardial ischemia non-invasively in a patient with a recent acute coronary syndrome can be difficult. In the culprit vessel, reversible changes in microvascular function accompanying the acute phase of ACS might (temporarily) affect FFR accuracy. The extent of microvascular dysfunction is dependent on the amount and duration of ischemia, distal embolization, and filling pressures, among others. So, FFR should not be used in the culprit vessel in the acute setting of STEMI. The role of FFR in the culprit artery in NSTEMI is less clear and future research should prove its validity. Nevertheless, the clinical impact of these changes on FFR accuracy in non-culprit arteries is minimal. When comparing FFR values in non-culprit lesions in patients presenting with ACS at time of PCI with repeated FFR measurement 6 weeks later, there was no significant difference in functional significance [40]. These results were corroborated by the FAME trial, in which almost one third of the patients presented with unstable angina or NSTEMI, with an equal benefit of FFR-guided PCI. The FAMOUS-NSTEMI trial was the first trial studying FFR and focusing only on NSTEMI, randomizing patients to either angiography-guided or FFR-guided revascularization [41]. Measurement of FFR resulted in lower rates of coronary revascularization and changed the decision of the interventional cardiologist in approximately 20%. The DANAMI-3–PRIMULTI trial broadened the perspective to STEMI, proposing an approach with a second, staged procedure before discharge using FFR guidance for complete functional revascularization [42]. Compared with infarct-related artery revascularization only, complete functional revascularization by FFR significantly improved prognosis, mainly driven by fewer repeat revascularizations. All these recent data suggest an important role for FFR, also in the setting of acute coronary syndromes. FFR can provide an overview of functional lesion severity in the complete coronary tree, obtainable right at the time of first presentation with ACS or during a staged procedure before discharge.

Conclusions

Fractional flow reserve is the current standard of care to identify coronary lesions responsible for myocardial ischemia in the catheterization laboratory. It is easy, rapid, and safe, and can be measured ad hoc and followed by PCI immediately thereafter if needed. The index FFR has a firm scientific base and has been validated in numerous randomized trials and in a wide variety of clinical settings. FFR-guided revascularization improves both symptoms and outcome on short-term as well as on long-term.

Conflict of Interest

Disclosure: the corresponding author, Lokien X. van Nunen, acts as a consultant for Rapidscan Pharma Solutions.

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