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Fractional flow reserve: physiological bases, clinical applications and limitations

Fluxo fracionado de reserva do miocárdio: bases fisiológicas, aplicações clínicas e limitações

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ABSTRACT – Invasive physiological assessment of the coronary circulation has emerged in recent years as a valuable diagnostic approach in the management of patients with chronic coronary syndrome, overcoming important limitations such as evaluating function from the anatomy and the low spatial resolution associated with angiography or non-invasive tests. The value of hyperemic flow measurements to estimate the functional relevance of coronary stenoses is supported by many studies. The aim of this paper is to review the physiological bases, clinical applications and limitations of myocardial fractional flow reserve, the main index used in the invasive functional assessment of the coronary circulation.

Keywords: Fractional flow reserve; Myocardial ischemia; Coronary artery disease; Percutaneous coronary intervention

RESUMO – A avaliação fisiológica invasiva da circulação coronariana emergiu nos últimos anos como uma abordagem diagnóstica valiosa no manejo de pacientes com síndrome coronariana crônica, contornando limitações importantes como avaliar função a partir da anatomia e a baixa resolução espacial associada à angiografia ou testes não invasivos. O valor das medidas de fluxo hiperêmico para estimar a relevância funcional das estenoses coronárias é suportado por um grande número de estudos. O objetivo do presente artigo é rever as principais bases fisiológicas, aplicações clínicas e limitações do fluxo fracionado de reserva do miocárdio, o principal índice utilizado na avaliação funcional invasiva da circulação coronariana.

Descritores: Fluxo fracionado de reserva do miocárdio; Isquemia miocárdica; Doença da artéria coronariana; Intervenção coronária percutânea

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INTRODUCTION

It is well established that the presence of myocardial ischemia is one of the most important prognostic factors in patients with coronary artery disease (CAD).¹ This has been shown conclusively in some meta-analyses: the annual rate of cardiac death or acute myocardial infarction (MI) was approximately 0.5% after a normal perfusion scintigraphy or stress echo, as compared to more than 6% when one of these methods showed evidence of ischemia.^{1,2}

In practice, however, noninvasive tests are performed in a minority of patients sent for coronary angioplasty.^{3,4} Most percutaneous coronary interventions (PCI) are conducted based only on angiographic criteria, without prior assessment of the existence of ischemia.⁵ Notwithstanding its unquestionable merits, angiography shows already known limitations in estimating the real severity of coronary obstructions, particularly in the case of moderate stenoses.^{6,7} Therefore, the combination of perfect anatomical definition (angiography) together with functional information is indispensable to adequately define treatment strategy for patients with CAD.^{8,9}

This article aimed to review one of the main methods of invasive functional assessment of the coronary circulation: myocardial fractional flow reserve (FFR), which has been the most widely used method, with the longest follow-up (>20 years), since its validation by Nico Pijls, in 1993.¹⁰

DEFINITION

Fractional flow reserve is defined as the maximum blood flow to the myocardium in the presence of a given stenosis (or stenoses), divided by that same flow if there were no stenosis.¹¹ This index represents the fraction of normal maximum myocardial flow that could be achieved despite the presence of stenosis. Fractional flow reserve can be easily determined by dividing the mean pressure distal to the coronary lesion by the mean pressure in the aorta during maximal vasodilation (induced by intracoronary papaverine or adenosine or intravenous adenosine), as shown in table 1. Figure 1 shows the schematic representation of how to determine the FFR, and why a flow measurement can be inferred by dividing pressures, based on the hydraulic equation.

The value of FFR to ensure presence of myocardial ischemia has already been widely established.^{11,12} It is known that vessels presenting with FFR >0.80 can be safely treated conservatively, while an FFR ≤0.80 is a sign of myocardial ischemia. Patients in these cases could benefit from percutaneous or surgical revascularization procedures.¹³⁻¹⁵ However, it is important to note that FFR reflects a continuum of risk, and there is an inverse relation between FFR values and the risk of adverse clinical events, increasing the potential usefulness of FFR beyond just a binary index. This is supported by a large patient-level pooled meta-analysis,¹⁶ demonstrating clinical events increased as FFR decreased, and that revascularization showed greater net benefit for lower baseline FFR values. For the evaluation of FFR as a continuous variable across its spectrum of values, statistical modeling suggested the optimal FFR cut-off value to guide revascularization might be 0.67. This observation was corroborated by the registry IRIS-FFR (Interventional Cardiology Research In-cooperation Society Fractional Flow Reserve), which included >8,000 lesions, in which statistical modeling suggested that the optimal FFR threshold to predict cardiac death or MI was 0.64, and that only vessels with FFR ≤0.75 correlated with better clinical outcomes when treated.¹⁷

Table 1. Importance of epicardial and microvascular vasodilation during myocardial fractional flow reserve measurement

Epicardial vasodilation	
Isosorbide dinitrate: 200µg to 500µg IC bolus, at least 30 seconds before the first measurements	
Microvascular vasodilation	
Adenosine or ATP IC	60µg to 100µg in RCA and 150µg to 200µg in LCA
Papaverine IC	15mg in RCA and 20 mg in LCA
Nitroprussiate IC	0.6µg/kg bolus
Intravenous adenosine or ATP	140µg/kg/minute (in a central vein, e.g., femoral)
Side effects	
Adenosine, papaverine, and ATP	Bradycardia, hypotension, transient feeling of malaise (burning sensation) in the precordial region, and generalized warmth or flushing
Sodium nitroprussiate	Hypotension

IC: intracoronary; ATP: adenosine triphosphate; RCA: right coronary artery; LCA: left coronary artery.

Hydraulic equation

$$\Delta P = Q \times R$$

$$Q = \Delta P / R$$

$$FFR_{myo} = \frac{Q_{Stenosis}}{Q_{Normal}} = \frac{(P_d - P_v) / R_{myo}}{(P_A - P_v) / R_{myo}} = \frac{P_d}{P_A}$$

Source: Pijls NH, DeBruyne B. Coronary pressure. 2. ed. The Netherlands: Kluwer Academic Publ; 2000.¹⁹

P: pressure; Q: flow; R: resistance; $Q_{stenosis}$: flow in the coronary artery with stenosis; Q_{normal} : flow in the coronary artery in the absence of stenosis; P_d : mean distal pressure in the coronary artery; P_A : mean pressure in the aorta; R_{myo} : myocardial resistance.

Figure 1. Basis of fractional flow reserve calculation. Myocardial fractional flow reserve is calculated by dividing the mean distal coronary artery pressure by the mean aortic pressure during maximal hyperemia.

On the other hand, a retrospective, multicenter, population-based study, published in 2020,¹⁸ investigated whether adherence to FFR cut-off values (≤ 0.80 , ischemic or >0.80 , non-ischemic) to indicate or not PCI would be associated with better clinical outcomes. This study involved 9,106 patients and showed that doing PCI, compared with not doing it, was associated with lower rates of major adverse cardiac events (MACE) in ischemic lesions, and higher rates of MACE in non-ischemic lesions, which supports performing PCI according to FFR values.

In any case, the combination of angiography with physiological assessment of the lesion (FFR or other indices) emerges as the only complete strategy, since it combines anatomy, physiology and even the possibility of *ad hoc* treatment.

FRACTIONAL FLOW RESERVE MEASUREMENT

As a practical recommendation, it is preferable to use 6F or 7F guiding catheters, with no side holes to measure FFR. The guidewire used for FFR measurement has a specific sensor located 3cm from its tip, has a 0.014" diameter (0.36mm), and a soft tip like the one used in angioplasty procedures. Currently, the three main guidewires available on the market are the PressureWire™ X (Abbott, Chicago, Illinois, United States), the Verrata™ (Philips/Volcano, San Diego, California, United States), and the Comet™ (Boston Scientific, Marlborough, Massachusetts, United States). These guidewires are connected (by cable or WiFi) to a device that captures and analyzes the pressure signal, which is then converted into an electrical signal and displayed on the analyzer's screen. All of these devices measure both FFR and non-hyperemic indices (RFR, iFR, dPR), which will be the subject of another review.

As a practical recommendation, the step by step for FFR measurement follows below:

1. Administer intracoronary vasodilator (Table 1).
2. Wash and calibrate (zero) the guiding catheter and the pressurewire (PW).
3. Insert the PW until its sensor (3cm from the tip) coincides with the tip of the guiding catheter.
4. Equalize the pressures in the PW/guiding catheter after vigorously flushing the guiding catheter, removing remnants of contrast and blood.
5. Advance the PW to the distal bed of the coronary artery to be evaluated.
6. Administer adenosine IC or deep IV (doses on Table 1).
7. Record FFR measurement by performing, when indicated, the pullback curve (progressive and slow pullback of the guidewire from the distal coronary bed to the tip of the guiding catheter, which allows detailed assessment of the entire coronary segment to be studied, and is important in the evaluation of serial lesions and diffuse atherosclerotic disease).
8. Carefully check for the presence of drift at the end.

MAIN CAUSES OF ERROR IN THE MEASUREMENT OF THE FRACTIONAL FLOW RESERVE

The main errors to be avoided when measuring FFR are the following.^{19,20}

Table height

It is well known how important is the height of the transducer relative to the patient. It should be neither too high nor too low, ideally at the level of the patient's mid-axillary line. Otherwise, there may be artifacts, such as those shown in figure 2.

P_A: mean pressure in the aorta; P_d: mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 2. Most common errors in the measurement of the fractional flow reserve rate.

Insufficient hyperemia

In measuring FFR, adequate hyperemia is paramount.^{10,11} Whenever possible, the use of intravenous adenosine in a deep vein is recommended. The standard dose is 140 µg/kg/minute. Higher doses, according to a recent study,²¹ showed no advantage, and increased the incidence of side effects. Always remember that insufficient hyperemia underestimates the translesional gradient and overestimates FFR, thus underestimating the severity of the lesion.

Guiding catheter

Avoid engaging the guiding catheter into the coronary ostium (which leads to a ventricularization of the pressure tracings in the aorta, also known as damping) and guiding catheters with side holes (Figure 2). This can produce artifacts in aorta pressure tracings, in addition to preventing the administration of intracoronary hyperemic agents, since part of what is injected flows through the side holes.

Drift

It can be defined as a fluctuation in the pressure tracings, and occurs when equal pressure gradients are observed in diastole and systole, with the presence of parallel signals (Figure 2). When this happens, the sensor must be moved back to the tip of the guiding catheter, and pressures must be equalized again. If the defect persists, consider changing the PW.

Needle or guidewire introducer

The needle, used to introduce the PW through the Y-connector into the guide catheter, should be removed from this connector when equalizing pressures, and when measuring FFR. Otherwise, it may also produce artifacts in the pressure measurements.

Reverse gradient

In some cases, we can observe hydrostatic differences of the order of 3 mmHg to 7 mmHg between the aortic root and the distal coronary bed. This gradient disappears when the pullback maneuver is performed.

Failure in interpretation

We included this item as a possible error, because often the physician considers the physiological measurement incorrect and is actually failing to take into account some factors. For example, a high FFR in the presence of a severe coronary lesion may mean a small perfused area (vessel of little importance), old infarction compromising much of the viability of that area, abundant collateral circulation, or even an error in the angiographic interpretation of the lesion.

CLINICAL APPLICATIONS OF FRACTIONAL FLOW RESERVE

The main clinical application of FFR in CAD is to evaluate intermediate lesions, in different scenarios, such as: single- and multivessel disease, serial lesions, diffuse atherosclerotic disease, left main coronary artery (LMCA), ostial and bifurcation lesions, and non-culprit lesions in acute MI.

Single-vessel disease

The physiological assessment of CAD has become one of the cornerstones of decision-making for coronary artery revascularization. The main indication of FFR measurement is to assess the functional importance of moderate lesions, *i.e.*, obstructive lesions between 40% and 70% by visual estimation. Figure 3 shows how two angiographically similar stenoses can have completely distinct functional importance. In an initial series of 45 single-vessel CAD patients, with moderate stenoses on coronary angiography, it was shown that the FFR measurement has significantly superior accuracy for distinguishing lesions responsible for ischemia when compared with exercise testing, myocardial scintigraphy, or stress echocardiography.¹² All patients (n=21) in whom FFR was <0.75 showed signs of ischemia on one or more of the tests, whereas in 24 patients in whom FFR was ≥0.75, only three had any positive noninvasive test.

Another analysis of 250 patients (452 lesions) undergoing PCI after FFR measurement, showed poor correlation between intermediate lesions by angiography and FFR measurement ($\rho = -0.33$, $p < 0.0001$).⁹

The DEFER study (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis)¹³ demonstrated safety and efficacy of deferring PCI in stenoses with FFR ≥0.75. The group in which FFR values were ≥0.75 (91 patients) and PCI was deferred, showed a cardiac event-free survival of 89% compared with 83% ($p = 0.27$) in the PCI-performed group (90 patients). The 15-year follow-up of the DEFER study,²² performed in 92% of patients, showed consistent results, with similar combined rates of mortality or target vessel revascularization among the three groups. However, there was a lower rate of MI in the population whose treatment was deferred based on FFR compared to the other two groups (Perform and Reference; 2.2% *versus* 10% *versus* 12.5%; $p < 0.05$ for both comparisons).

Multivessel disease

The next major trial on FFR focused on its value in patients with multivessel disease, a clinical setting in which non-invasive functional testing does not always provide accurate information in deciding which stenoses should be considered for revascularization. Additionally, patients with multivessel CAD present as a very heterogeneous population. The anatomical characteristics of the lesions, their degree of complexity, and their functional importance can vary tremendously and have important implications

P_A : mean pressure in the aorta; P_d : mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 3. Fractional flow reserve in moderate lesions. Example of two patients with moderate lesions in the proximal third of the left anterior descending artery. Despite the angiographic similarity, the two lesions show distinct functional importance. While the lesion in A is responsible for ischemia and was treated by angioplasty with stent implantation, lesion B was only treated clinically, based on the fractional flow reserve measurement (>0.80).

for the revascularization strategy. Moreover, there is a great discrepancy between the anatomical description of the lesion and its actual importance. For example, a patient may be considered as having “triple-vessel disease” based on angiography, but actually has only two functionally significant stenoses. The opposite may also be true; a patient may have an apparently inconspicuous lesion in the LMCA and another important lesion in the right coronary artery. When FFR is evaluated, this LMCA lesion may actually be the most important.

Some preliminary studies involving the use of FFR in multivessel patients have been encouraging. In 2009, the FAME study (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention) was published.¹⁴ This study randomized 1,005 multivessel patients to be treated by angioplasty with drug-eluting stent implantation, stratifying them into two groups, Angiography Group (496), in which all lesions were treated based on angiographic criteria, and FFR Group (509), in which only lesions with $\text{FFR} \leq 0.80$ would be treated. The rate of MACE after the one-year period in the FFR Group was 30% lower than in the Angiography Group. Additionally, the cost of the procedure in the FFR Group was also significantly lower. Thus, the FAME study demonstrated the superiority

of FFR-guided PCI over angiography-guided PCI among patients with multivessel disease at 1 year. After 2-years follow-up,²³ the FAME study continued to show advantages for the FFR-based treated group, both with respect to death or MI rates, and incidence of MI alone. Even more interestingly, of the 513 lesions initially untreated because they had $\text{FFR} \geq 0.80$, only one (0.2%) was responsible for a late infarction and only 16 (3.2%) progressed over 2 years, requiring a revascularization procedure, extraordinarily low rates that attest the safety of conservative treatment based on FFR. Finally, even after 5 years of follow-up²⁴ the differences persisted, but lost statistical significance due to fewer patients at risk. The MACE rate in the two groups became similar ($p=0.31$), but the physiologic approach proved to be much more cost-effective, with significantly fewer stents implanted per patient ($p<0.0001$).

However, it was not yet known whether stable CAD patients treated with drug-eluting stents based on FFR would have superior clinical outcomes to those treated with optimal medical therapy (OMT) alone, even with evidence of ischemia. So, there was FAME II¹⁵ was published in 2012. This study randomized patients with $\text{FFR} \leq 0.80$ to be treated medically only (OMT Group) or medically plus PCI and drug-eluting stent implantation in the ischemic lesions

(PCI Group). Those patients in whom all lesions showed FFR >0.80 were allocated to a Registry Group, treated only with drugs (OMT). The primary endpoint was a composite of death, MI or urgent revascularization. Recruitment for this study was prematurely stopped at 1,220 patients (888 randomized and 332 in the registry group), because the event rate was significantly lower in the PCI Group compared to the OMT Group. This was mainly due to the lower rate of hospitalizations for emergency revascularization in the PCI Group, such as unstable angina or MI. The study authors concluded that in patients with stable CAD and at least one stenosis with FFR ≤ 0.80 , angioplasty followed by drug-eluting stent implantation associated with OMT, compared to OMT alone, resulted in lower rates of urgent revascularization in the PCI Group. Among functionally non-significant stenoses (Registry Group), OMT results in excellent clinical outcomes (composite event rate of 3%), regardless of the angiographic aspect of the lesions. The 5-year follow-up of this study²⁵ showed maintained results with a lower MACE rate in the PCI group compared with the OMT Group. This was mainly due to urgent revascularizations and composite events of death or MI, resulting from a lower rate of spontaneous MI in the PCI Group compared with the OMT Group.²⁶ There was no difference in the mortality or infarction rates between the groups, nor in the occurrence of MACE between the PCI Group and the Registry Group (OMT).

In conclusion, the FAME II trial demonstrated that FFR-guided PCI associated with OMT is superior to OMT alone in patients with at least one stenosis with FFR ≤ 0.80 . It is important to mention that the FAME II trial was launched shortly after the study COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation),²⁷ which demonstrated a lack of benefit of PCI over isolated OMT with respect to mortality and MI, in the long term. The COURAGE results were criticized for having included patients with mild myocardial ischemia. Recently, the ISCHEMIA study (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) showed that in patients with moderate or severe myocardial ischemia assessed by non-invasive tests, an invasive strategy with OMT offers no clinical benefit compared with isolated OMT, with respect to the primary composite endpoint at a median follow-up of 3.2 years.²⁸ Considering physiological assessment, it is not known whether the invasive strategy guided by physiology could have led to different outcomes,²⁶ because the decisions made in the invasive strategy were predominantly guided by angiography. Fractional flow reserve was used in only 20% of patients in the invasive arm, according to the protocol.

Figure 4 shows a typical case of invasive functional assessment of multivessel CAD by measuring the FFR.

P_A: mean pressure in the aorta; P_d: mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 4. Fractional flow reserve in multivessel coronary artery disease. Patient with unstable angina and angiography showing severe lesion in the great marginal branch of the circumflex artery (A), and two moderate lesions in the right coronary artery (B). Fractional flow reserve measurement confirmed severity of the circumflex artery lesion, but more importantly, showed that the right coronary artery lesions did not cause ischemia. The patient was treated with only one stent in the circumflex artery.

Serial lesions

Serial stenoses are broadly defined as two or more lesions separated by intervening angiographically normal segments. They reflect the diffuse nature of the coronary atherosclerotic disease, being frequently found in coronary angiograms. When there are many stenoses in the same vessel, non-invasive functional tests have limited spatial resolution to identify which stenosis is responsible for the localized ischemia. In this regard, invasive physiological assessment offers a practical advantage in unraveling the epicardial segments responsible for downstream flow reduction.

Nonetheless, it is imperative to understand that hyperemic flow velocity can be attenuated by stenoses of even moderate severity.²⁹ Therefore, even trivial stenoses or diffuse disease can confound hyperemic pressure assessments. The presence of a distal lesion decreases the hyperemic flow through the proximal lesion, changing its relative severity. On the other hand, the proximal lesion promotes hyperemic flow reduction in varying degrees, ultimately exaggerating the relative severity of the distal lesion. This flow interaction between serial lesions has been referred to as lesion crosstalk. In practical terms, the relation between mean distal pressure in the coronary artery and mean pressure in the aorta (P_d/P_A) ratio measured between two serial lesions is not the same as the FFR calculated for the same lesion after treatment of the distal stenosis.

De Bruyne et al.³⁰ developed theoretical equations from animal models, subsequently validated in humans by Pijls et al.,³¹ to predict the FFR of each stenosis in series, as if the other stenosis was not present. Dependent variables were the P_A , P_d , the pressure between the two lesions (P_m), and the coronary wedge pressure (P_w) under maximal hyperemia. The coronary wedge pressure represents the degree of myocardial flow composed of collaterals, and can only be obtained during balloon occlusion of the coronary vessel. This requires a commitment to PCI before making diagnosis, thus limiting the clinical application of such theoretical formulas.

In a study with 131 subjects from two large Korean centers, Kim et al.³² reported on the long-term outcomes of using FFR, measured by pullback pressure tracings to guide revascularization in patients with tandem lesions in a single coronary artery. According to their protocol, the lesion that caused the largest pressure step-up was treated first (primary target lesion). The second stenosis was only treated if the FFR of this lesion was significant after PCI of the first lesion. In 61% of lesions, revascularization was postponed based on FFR. There were no adverse events related to the deferred lesions, suggesting the safety of FFR pullback tracings to guide revascularization in patients with tandem lesions. Another study using *in vitro* computational flow dynamic models validated the FFR gradient (Δ FFR) across stenosis, during pressure wire pullback as a surrogate estimate for relative functional severity for each tandem lesion.³³ As a result, a practical approach for

evaluating serial lesions in the same vessel are as follows: after pressure equalization, advance the pressure wire into the target vessel, and position it in its most distal segment, distal to all serial stenoses; induce maximal hyperemia and record the lowest P_d/P_A ratio in the distal position; during maximal hyperemia pullback the pressure wire with a slow and steady pace, using bookmarks to identify each lesion in the pullback tracing; identify the lesion across which the maximum pressure gradient (FFR big delta) was recorded and treat it first; after stenting the first lesion, measure the FFR of the remaining lesion, and decide on the management of such lesion accordingly. Figure 5 illustrates this approach.

Diffuse atherosclerotic disease

Pathological and intravascular ultrasound studies have shown that when focal lesions are identified by angiography, atherosclerotic disease is often present in the other segments of the coronary circulation as well.^{34,35} On the other hand, the classical concept that the impact on maximum myocardial flow occurs due to the presence of stenoses greater than 50% could, at first analysis, erroneously suggest that diffuse atherosclerosis, not accompanied by focal obstructions, would not be able to cause a significant physiological repercussion.

Within this context, De Bruyne et al. observed a continuous pressure reduction along arteries with diffuse atherosclerotic disease, contrary to the pattern observed in normal coronaries, leading to a significant drop in flow reserve and consequent increased detection of ischemia by noninvasive methods.³⁶ The development of abnormal resistance in epicardial arteries affected by atherosclerosis would be the main mechanism related to this phenomenon.

Measurement of FFR must be carefully performed in this situation, with a more distal positioning of the guidewire, gradual pullback, preferably under continuous infusion of intravenous adenosine, and careful observation of the appearance of the curve until the return of equalization, identifying eventual pressure spots that could unmask more severely affected segments. In arteries with diffuse atherosclerotic disease, the progression of the P_d is slow and continuous, rendering the curve a typical "slope pattern" (Figure 6).

The addition of a motorized pullback (1mm/second) demonstrated a greater ability to discriminate between focal and diffuse disease, through accurate quantification of pressure drop by pressure pullback gradient (PPG) and functional extent of CAD, reclassifying the pattern observed by angiography in one third of the cases.³⁷

Revascularization in these cases, regardless of the modality, has a worse prognosis when compared to the treatment of focal lesions, and suboptimal FFR results are observed after PCI, especially with multiple stents in very long arterial segments (>50mm), as well as reduced late patency of surgical grafts.^{38,39}

P_A : mean pressure in the aorta; P_d : mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 5. Practical management of a patient with diffuse and serial lesions. Case of a patient with stable angina Canadian Cardiovascular Society III showing diffuse disease in the left anterior descending with a severe lesion in the mid-distal segment (A). Fractional flow reserve pullback was performed after stenting the mid-distal lesion, (B) showing a significant flow reduction in the distal left anterior descending (fractional flow reserve of 0.47), despite successful percutaneous coronary intervention of the angiographically severe lesion. Two pressure step-ups are seen proximal to the treated region (yellow arrows). The mid-left anterior descending lesion was treated with another stent implantation, (C) and fractional flow reserve reassessment still showed a significant flow reduction in the distal left anterior descending (fractional flow reserve of 0.71). Magnification of the proximal lesion step-up can be appreciated (yellow arrow). Only after stenting the proximal left anterior descending lesion (D), a non-ischemic flow was obtained in the distal left anterior descending (fractional flow reserve of 0.86). Note that only a slight pressure gradient is seen within the treated segment (green arrow), with the resolution of pressure loss within the other vascular segments. The treated regions in each step of the procedure are indicated in the fractional flow reserve pullback traces by vertical white lines.

P_A : mean pressure in the aorta; P_d : mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 6. Fractional flow reserve in diffuse atherosclerotic disease. A pullback curve in the left anterior descending artery during maximal hyperemia, demonstrated slow and continuous rise of intracoronary pressure (short arrows), a typical pattern of diffuse atherosclerotic disease (slope pattern).

Left main coronary artery

Significant LMCA stenosis has classically been defined by angiography as >50% luminal narrowing. Short arterial segment, diffuse disease, lack of a distinct normal reference, angulation, eccentricity, tortuosity, presence of overlapping branches, reverse tapering at the ostium, contrast streaming, and distortions caused by the catheter positioned in the ostium, challenge the assessment of LMCA lesion by angiography. As a result, significant inter-observer variability and weak correlation between angiographic diameter stenosis and FFR have been described.⁴⁰⁻⁴²

To date, there are no large-scale randomized trials comparing FFR- and angiography-guided revascularization of LMCA lesions. Table 2 presents prospective cohort studies, which evaluated the role of FFR-guided revascularization of LMCA lesions.⁴³

In practice, important caveats of FFR assessment of LMCA lesions need to be acknowledged. LMCA is usually accompanied by downstream disease in the left anterior descending (LAD) and left circumflex (LCx) arteries. In such cases, the downstream stenoses act in series together with the LMCA lesion. Therefore, the complex interdependence of altered flow dynamics by serial lesions affects the ability to interpret the relative contribution of each stenosis, which together, results in a reduced FFR at the distal vascular bed.

Isolated left main coronary artery lesion

Theoretically, the minimal resistance in a vascular bed is assumed to be independent of any upstream stenosis,⁴⁴ and the FFR of an isolated LMCA lesion should be identical, whether measured in the LCx or LAD. However, it is recommended to perform an FFR pullback from both the LAD and LCx branches, due to the possibility of angiographically unapparent downstream disease in such vessels, and the different myocardial mass at risk in both territories.

Left main coronary artery stenosis with concomitant lesion in one downstream vessel

In this scenario, the hyperemic flow crosstalk between serial lesions affects the FFR assessment of the LMCA lesion. The magnitude of influence of FFR in a downstream lesion on the LMCA depends on severity and proximity of the downstream lesion. While such interaction can theoretically affect flow through the unobstructed downstream branch, *in-vitro* studies have shown that measuring LMCA FFR, by placing the wire in the disease-free downstream vessel, can be a reliable method.^{45,46} A human validation was subsequently proposed by Fearon et al.⁴⁷ After PCI of the LAD, LCx, or both, in 25 patients, an intermediate LMCA stenosis was created with a deflated balloon. FFR was measured in the LAD and LCx before and after creating downstream stenosis by inflating an angioplasty

Table 2. Summary of studies assessing the potential role of fractional flow reserve to guide revascularization in patients with left main coronary artery disease

Author, year	n	Follow-up	Revascularization criteria	Main results
Bech et al., 2001	54	29±15 months	FFR<0.75	Uneventful survival of 76% in the OMT Group and 83% in the CABG Group
Jiménez-Navarro et al., 2004	27	26.2±12.1 months	FFR<0.75	3 events occurred. One patient with FFR(+) died during CABG and 2 patients with FFR (-) required CABG during follow-up
Suamaru et al., 2005	15	32.5±9.7 months	FFR<0.75	No deaths occurred. No symptoms in patients with FFR(-) who were maintained in OMT. Symptom improvement in most patients with FFR(+) submitted to revascularization
Legutko et al., 2005	38	2 years	FFR<0.75	2 (11%) fatal events in patients with FFR<0.75, who were revascularized. One (5%) patient with FFR>0.75 underwent elective revascularization due to LMCA lesion progression
Lindstaedt et al., 2006	51	29±16 months	FFR<0.75	The 4-year survival of 81% in FFR(+) patients submitted to revascularization, and 100% in FFR(-) patients kept in OMT 4-year uneventful survival was 66% 69% in the CABG and OMT Groups, respectively
Hamilos et al., 2009	213	5 years	FFR<0.80	At 5 years, there was no significant difference in mortality (89.8% versus 85.4%; p=0.48) and in the rate of patients free from events (74.2% versus 82.8%; p=0.5) between the group of patients with FFR(+) who received revascularization, and the group of patients with FFR(-) who were kept in OMT
Courtis et al., 2009	142	14±12 months	FFR<0.75-0.80	There were no significant differences between the groups for MACE, death, or myocardial infarction for those with FFR(+), revascularized and FFR(-) kept in OMT

Source: modified from Kayaert P, Coeman M, Gevaert S, De Pauw M, Haine S. Physiology-based revascularization of left main coronary artery disease. *J Interv Cardiol*. 2021;2021:4218769. <https://doi.org/10.1155/2021/4218769>.⁴³
FFR: fractional flow reserve; OMT: optimal medical therapy; CABG: coronary artery bypass grafting; LMCA: left main coronary artery; MACE: major adverse cardiac events.

balloon within the newly placed stent. The true LMCA FFR was significantly lower than the apparent FFR (0.81 *versus* 0.83; $p < 0.001$). This difference correlated with severity of downstream stenosis ($r = 0.35$; $p < 0.001$), and was interpreted as clinically insignificant and at the upper end of the natural test-retest variability of FFR. The authors concluded that in most cases, downstream disease in another branch does not have a clinically significant impact on LMCA FFR with the pressure wire positioned in the disease-free vessel, unless the FFR in the diseased branch is very low (FFR < 0.45); an FFR > 0.85 in the disease-free branch would mean that the LMCA lesion can be safely assumed to be functionally non-significant.⁴⁷ Although this approach is considered a currently acceptable solution for assessment of LMCA stenoses, together with significant lesion in one vessel downstream, care should be taken in interpreting such results, since the evidence derives from a very small population, or from *in vitro* studies, where stenoses were virtually and focally created. Thus, the true effect of diffuse

atheroma with its complex interaction on flow dynamics in humans cannot be completely derived from such studies. Figure 7 illustrates the management of a patient with intermediate LMCA stenosis in the presence of a significant downstream lesion.

Left main coronary artery with concomitant lesions in all downstream vessels

In the absence of a disease-free branch, serial lesion interplay is particularly challenging for the identification of the exact pressure gradient across the LMCA. Currently accepted practice dictates FFR pullback be performed from all downstream vessels towards the LMCA, and the pressure gradients along the epicardial vessels are mapped. Revascularization strategies should be decided not only based on the physiological information, but also on the demographic/clinical characteristics, clinical presentation, and anatomical and surgical risks, made by the Heart Team. If

FFR: fractional flow reserve; P_d : mean distal pressure in the coronary artery; P_a : mean pressure in the aorta.

Figure 7. Fractional flow reserve assessment of an intermediate left main coronary artery stenosis, in the presence of a significant downstream lesion. Case of a female patient presenting with stable angina Canadian Cardiovascular Society III. An intermediate (40% to 50%) stenosis in the left main coronary artery is followed by a severe (90%) lesion in the proximal left anterior descending (A). The left circumflex is unobstructed. The fractional flow reserve measurement in the distal left anterior descending pre-percutaneous coronary interventions revealed severe flow reduction (fractional flow reserve of 0.49). The pullback maneuver depicted a steep and focal gradient across the proximal left anterior descending stenosis (white arrow) (A₁). A spot fractional flow reserve measurement in the proximal left anterior descending, between the left main coronary artery lesion and the left anterior descending lesion, revealed a fractional flow reserve of 0.96 before percutaneous coronary interventions (A₂). Fractional flow reserve measurement in the mid-left circumflex pre-percutaneous coronary interventions was 0.81, in the presence of the severe left anterior descending lesion (A₃). After percutaneous coronary interventions of the proximal left anterior descending lesion (B), fractional flow reserve measurement in the distal left anterior descending was borderline (0.81), indicating a pressure recovery of 0.32 fractional flow reserve unit with the left anterior descending percutaneous coronary interventions (B₁). Interestingly, fractional flow reserve measurement in the proximal left anterior descending, between the left main coronary artery and left anterior descending stent (B₂), now revealed a reduction of 0.09 fractional flow reserve unit between the measurements taken before and after percutaneous coronary interventions of the left anterior descending lesion. This highlights the negative effect the severe left anterior descending lesion on the assessment of the left main coronary artery physiological significance. Fractional flow reserve measurement in the mid-left circumflex revealed a change in the opposite direction, with a gain of 0.03 fractional flow reserve units from pre- left anterior descending percutaneous coronary interventions (A₃) to after left anterior descending percutaneous coronary interventions (B₃), suggesting some flow steal from the left circumflex after the left anterior descending lesion has been treated and flow increased in that vessel.

PCI is the chosen revascularization modality, physiological evaluation can assist in the interventional strategies. If distinct lesions are present in the LMCA and downstream vessels, revascularization of the lesions that cause the greatest FFR delta is advised, followed by repeat FFR assessment of the remaining lesions.

Ostial and bifurcation lesions

Ostial lesions in the major vessels or at the origin of the side branches have distinct anatomical and physiological characteristics, related to the supplied myocardial mass, angulation, luminal-narrowing pattern, overlapping branches, or imaging artifacts, which impair the assessment of severity by angiography.⁴⁸ Even intravascular imaging modalities, such as intracoronary ultrasound and optical coherence tomography, which provide important complementary anatomic information, have limited accuracy in assessing the functional significance of these obstructions.⁴⁹ Within this scenario, FFR may represent a valuable tool and modify the strategy of percutaneous intervention.

Much of the clinical benefit of physiology-guided revascularization is related to the reduction of potential early or late complications from unnecessary interventions.⁵⁰ This is most evident in percutaneous bifurcation treatment, which is technically more complex and has a higher incidence of periprocedural infarction and adverse coronary events.⁵¹

Some technical aspects should be emphasized in the evaluation of ostial lesions, such as removal of the guiding catheter from the coronary ostium during equalization and measurement of pressures, handling it patiently together with the PW, to ensure reliable tracings and true information. One should also avoid intracoronary bolus of adenosine in these cases, since the catheter will be far from the vessel origin, giving preference to continuous intravenous infusion.

Fractional flow reserve can be useful in several stages of the intervention, such as planning the strategy and determining the functional significance of dubious lesions in the origins of side branches. During the procedure, FFR may assist in the decision to change the strategy from one to two stents, or even to approach jailed branches, highlighting the studies by Koo et al., which observed no significant physiological repercussion in most of these cases.⁵² It has also been shown that the need for stents in true bifurcations (Medina 1,1,1 and 0,1,1) has been reduced when FFR was systematically evaluated in side branches.⁵³

At the end of the procedure, presence of residual ischemia in the side branches after the kissing-balloon technique or stenting can be assessed, thus estimating the clinical prognosis.

Finally, it should be kept in mind that the total ischemic burden is more important in prognostic terms than the mere presence or absence of ischemia,⁵⁴ and that a side

P_A : mean pressure in the aorta; P_d : mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 8. Fractional flow reserve in ostial lesions. (A) Case of a male patient with stable angina Canadian Cardiovascular Society III and moderate left coronary ostial lesion. (B) When measuring fractional flow reserve in the left anterior descending artery, on the pullback curve, a focal gradient is noted at the site of the ostial lesion. Notice that during the measurement, the guiding catheter is slightly withdrawn from the ostium, so as not to cause damping of the curve. (C) The same measurement, this time in the left circumflex artery, shows almost the same gradient when crossing with the guidewire through the ostial lesion (yellow arrows). However, in the pullback curve, one can notice a moment in which the aortic pressure almost equals the pressure in the coronary (white circle). This indicates, at that instant, the guiding catheter probably engaged into the coronary ostium and had to be pulled back slightly.

branch with FFR <0.80 will not necessarily cause a significant clinical repercussion. This should be part of the decision-making about the treatment of bifurcations and ostial lesions, along with the potential risks and benefits of adding complexity to the percutaneous procedure. Figure 8 shows a case of ostial lesion of the LMCA and the particularities of FFR measurement.

Acute myocardial infarction

About 50% of patients with ST-segment elevation MI (STEMI) present with multivessel CAD,⁵⁵ and the approach of the non-culprit lesions is an important and current research topic. Should we approach non-culprit lesions based exclusively on the angiographic aspect? Or would a management based on the presence of ischemia, supported by invasive physiological assessment methods, be more rational? Next, we will discuss aspects related to the use of FFR in this scenario.

The presence of viable microcirculation is a mandatory condition to obtain maximum hyperemia, fundamental for FFR assessment. However, in an infarcted area, microcirculation dysfunction occurs to a greater or lesser degree. Thus, even culprit lesions that limit flow during an MI may present with false-negative results for FFR, due to myocardial stunning.⁵⁶ Replacement of viable myocardial tissue by scar tissue promotes attenuation of gradients, by decreasing flow reserve. Therefore, FFR assessments are not reliable in an MI culprit artery, with potential false-negative results. On the other hand, the evaluation of non-culprit lesions has potential indication to hyperemic indices.

If evaluated immediately after primary angioplasty, as in the study by Ntalianis et al., less than 2% of non-culprit lesions may have significant change in values, if a new evaluation is performed 35 days after MI.⁵⁷ We can conclude that the values observed in non-culprit lesions during the index event will remain unchanged after the acute phase. The disadvantage of performing FFR at the same time of a primary angioplasty refers to the use of a higher contrast volume, prolongation of the procedure time, in addition to situations that are not rare in this scenario, such as bradycardia and hypotension, which make it difficult to use adenosine to obtain maximum hyperemia.

A more rational strategy of performing FFR in a staged manner, about 2 to 3 days after angioplasty of the culprit artery, was tested in two studies in the setting of acute MI.^{58,59} In one of them, performing FFR in intermediate non-culprit lesions resulted in a lower revascularization rate, when compared with management based solely on angiography, making it evident that FFR-based revascularization of non-culprit lesions in MI reduces unnecessary stent implantation in non-ischemic lesions.⁵⁸ The DANAMI 3 PRIMULTI trial (Third Danish Study of Optimal Acute Treatment of Patients with STEMI: Primary PCI in Multivessel Disease)⁵⁹ demonstrated a decrease in the need for new revascularization, when FFR was used before

hospital discharge, in a staged fashion, 3.5 days after primary angioplasty, but with no decrease in mortality or nonfatal infarction.

The study COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients with Multivessel Disease)⁶⁰ demonstrated a benefit in the use of FFR, even in the acute phase, performed during primary angioplasty, with a decrease in the study composite endpoints, which included death, nonfatal acute MI, cerebrovascular events, and revascularization. Again, although significant, this benefit was directed more toward decreasing the need for revascularization.

Another more recent study, COMPLETE (Complete Revascularization with Multivessel PCI for Myocardial Infarction),⁶¹ used angiography (lesions $>50\%$) as the primary method for staged revascularization of non-culprit lesions, and also showed better outcome of revascularization when compared with the conservative strategy. It is thus established that complete revascularization of all significant lesions, in a staged fashion, in a patient with acute MI, should be the strategy of choice. However, whether to rely on FFR or angiographic severity to choose to treat non-culprit lesions in this setting remains an open question. The recently published study FLOWER-MI (FLOW Evaluation to Guide Revascularization in Multivessel ST-elevation Myocardial Infarction),⁶² compared patients with STEMI and multivessel disease to receive complete revascularization guided by FFR or angiography, and its primary endpoint was death from any cause, nonfatal MI, or unplanned hospitalization due to urgent revascularization. This study, which involved more than 1,000 patients, showed an FFR-guided revascularization strategy was not superior to that guided by angiography after one year of follow-up. However, the authors made it clear in their conclusions that, due to the wide confidence interval for the effect estimates, these findings do not allow for a conclusive interpretation. Perhaps the COMPLETE-2 study will fill this gap in clinical practice.⁶³

A recently published meta-analysis⁶⁴ involving the COMPARE ACUTE, DANAMI PRIMULTI, and FAME 2 studies, compared the difference in the rates of death or infarction over 3 years, between the FFR-guided angioplasty and optimal medical therapy groups. There was a 28% reduction in the incidence of acute MI or death in the FFR-guided angioplasty group, mainly due to a decreased incidence of acute MI. The authors demonstrated a number needed to treat (NNT) of 18 over 5 years to avoid the cumulative event (death or acute MI) and 20 to avoid an acute MI. In view of these results, the recently published Guidelines on Myocardial Revascularization of the European Society of Cardiology⁶⁵ placed the use of FFR for evaluation of non-culprit lesions during acute MI, as class IIA, level of evidence A.

Figure 9 demonstrates a case of FFR use in non-culprit lesions during a STEMI.

P_A: mean pressure in the aorta; P_d: mean distal pressure in the coronary artery; FFR: fractional flow reserve.

Figure 9. Assessment of fractional flow reserve in non-culprit lesions in myocardial infarction. A 52-year-old male patient presenting with ST-segment elevation myocardial infarction in inferior wall. (A) Angiographic and optical coherence tomography findings showing thrombotic culprit lesion in mid-third of right coronary artery. (B) Intermediate to significant lesion in the mid-third of the left anterior descending artery showing stable non-ischemic plaque by the fractional flow reserve. Left anterior descending artery was kept under medical treatment.

LIMITATIONS

The FFR should not be used (in the culprit vessel) in the first 7 days after acute MI^{19,66} due to the difficulty, in these cases, to obtain maximum hyperemia, although there are already studies showing its usefulness in the evaluation of non-culprit lesions during the acute event.^{59,60}

It should be used with caution in patients with significant left ventricular hypertrophy (LVH),¹⁹ myocardial bridge,⁶⁷ and in very tortuous and calcified vessels, the latter especially when the so-called accordion effect occurs, which can produce important artifacts in the pressure tracings.

In LVH, a recently published substudy of the DANAMI 3 PRIMULTI in patients with LVH, in whom FFR was measured,⁶⁸ showed no differences in its measurement between patients with and without LVH in the evaluated population (mild or moderate LVH), which led the authors to conclude that LVH did not modify the stenosis diameter and FFR of these lesions, nor did it correlate with the occurrence of clinical events.

Currently, in invasive functional assessment of myocardial bridges, several studies have tested the use of intravenous dobutamine for the measurement of FFR and d-FFR (FFR during diastole). One of these studies,⁶⁹ published in 2021, evaluated 60 symptomatic patients with myocardial bridge in the left anterior descending artery and systolic compression >50%. This study showed conventional FFR during IV adenosine or dobutamine infusion in these patients was similar, but d-FFR during dobutamine infusion was lower than that obtained with adenosine, and correla-

ted well with stress test-induced ischemia in this group of patients. The authors concluded the use of high-dose dobutamine with d-FFR measurement has a higher correlation with ischemia in these patients and should be used, something that still awaits further studies to prove.

FINAL CONSIDERATIONS

Introduction of FFR in clinical practice has changed paradigms in the diagnosis and treatment of CAD. It is a practical, simple, and robust way to evaluate the functional repercussion of this disease. Its performance is simple, fast, and safe. The clinical evolution of patients in whom revascularization was based on FFR is very encouraging, especially after the publication of the 15-year follow-up of the DEFER study,²² and the 5-year follow-up of the FAME studies.²⁴ Thus, FFR can be considered as the “card up the sleeve” of interventional cardiologists, their “pocket tool” to measure myocardial perfusion.

The Guidelines of the Brazilian Society of Cardiology⁷⁰ place as indication class I, level of evidence A, performance of FFR to identify hemodynamically significant coronary stenoses in patients with no evidence of significant ischemia by noninvasive methods, or in cases where these methods are inconclusive, unavailable, or discordant. After the publication of the FAME studies, the American College of Cardiology/American Heart Association,^{71,72} and the European Society of Cardiology⁶⁵ maintained the aforementioned indications for FFR, also as class I, level of evidence A.

In figure 10 we propose a practical algorithm for measuring FFR in CAD, depending on its clinical presentation.

FFR: fractional flow reserve; PCI: percutaneous coronary intervention; OMT: optimal medical treatment; MI: myocardial infarction.

Figure 10. Algorithm for measurement of myocardial fractional flow reserve in coronary artery disease.

More important than comparisons between hyperemic and other indices to know which is the best method, is to be aware of the importance of using physiology to analyze the real need for revascularization, never sticking to binary values just for decision-making, especially when facing challenges as in multivessel coronary artery disease.

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DECLARATION OF CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: FMS and DC; data collection: FMS, DGSFB, LBS, BC, JPM, AC, CNZ and DC; data interpretation: FMS; text writing: FMS, DGSFB, LBS, BC, JPM, AC, CNZ and DC; approval of the final version to be published: FMS.

REFERENCES

1. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol.* 2004;11(2):171-85. <https://doi.org/10.1016/j.nuclcard.2003.12.004>
2. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol.* 2007;49(2):227-37. <https://doi.org/10.1016/j.jacc.2006.08.048>
3. Sant'Anna FM, Sant'Anna FB, Couceiro SL, Pérez MA. Cardiac catheterization with normal coronary arteries: prevalence rate and analysis of predictor variables. *J Transcat Interv.* 2020;28:eA20190034. <https://doi.org/10.31160/JOTCI202028A20190034>
4. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA.* 2008; 300(15):1765-73. <https://doi.org/10.1001/jama.300.15.1765>
5. Topol EJ, Ellis SG, Cosgrove DM, Muller DW, Schork NJ, Schork MA, et al. Analysis of coronary angioplasty practice in the United States with an insurance-claims data base. *Circulation.* 1993;87(5):1489-97. <https://doi.org/10.1161/01.cir.87.5.1489>
6. Fischer JJ, Samady H, McPherson JA, Sarembock IJ, Powers ER, Gimple LW, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for

- native coronary narrowings of moderate severity. *Am J Cardiol.* 2002;90(3):210-5. [https://doi.org/10.1016/s0002-9149\(02\)02456-6](https://doi.org/10.1016/s0002-9149(02)02456-6)
7. Sant'Anna FM, da Silva ER, Batista LA, Brito MB, Ventura FM, Ferraz HA, et al. What is the angiography error when defining myocardial ischemia during percutaneous coronary interventions? *Arq Bras Cardiol.* 2008;91(3):162-7, 179-84. <https://doi.org/10.1590/s0066-782x2008001500007>
8. De Bruyne B, Sarma J. Fractional flow reserve: a review: invasive imaging. *Heart.* 2008;94(7):949-59. <https://doi.org/10.1136/hrt.2007.122838>
9. Sant'Anna FM, Silva EE, Batista LA, Ventura FM, Barrozo CA, Pijls NH. Influence of routine assessment of fractional flow reserve on decision making during coronary interventions. *Am J Cardiol.* 2007;99(4):504-8. <https://doi.org/10.1016/j.amjcard.2006.09.097>
10. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation.* 1993;87(4):1354-67. <https://doi.org/10.1161/01.cir.87.4.1354>
11. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation.* 1995;92(11):3183-93. <https://doi.org/10.1161/01.cir.92.11.3183>
12. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334(26):1703-8. <https://doi.org/10.1056/NEJM199606273342604>
13. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation.* 2001;103(24):2928-34. <https://doi.org/10.1161/01.cir.103.24.2928>
14. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, et al.; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360(3):213-24. <https://doi.org/10.1056/NEJMoa0807611>
15. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al.; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367(11):991-1001. <https://doi.org/10.1056/NEJMoa1205361>. Erratum in: *N Engl J Med.* 2012;367(18):1768. Mobius-Winckler, Sven [corrected to Möbius-Winkler, Sven].
16. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol.* 2014;64(16):1641-54. <https://doi.org/10.1016/j.jacc.2014.07.973>
17. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, et al.; IRIS-FFR Investigators†. Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation.* 2017;135(23):2241-51. <https://doi.org/10.1161/CIRCULATIONAHA.116.024433>
18. Sud M, Han L, Koh M, Austin PC, Farkouh ME, Ly HQ, et al. Association between adherence to fractional flow reserve treatment thresholds and major adverse cardiac events in patients with coronary artery disease. *JAMA.* 2020;324(23):2406-14. <https://doi.org/10.1001/jama.2020.22708>
19. Pijls NH, DeBruyne B. Coronary pressure. 2. ed. The Netherlands: Kluwer Academic Publ; 2000.
20. Jerabek S, Kovarnik T. Technical aspects and limitations of fractional flow reserve measurement. *Acta Cardiol.* 2019;74(1):9-16. <https://doi.org/10.1080/00015385.2018.1444951>
21. Sparv D, Götberg M, Harnek J, Persson T, Madsen Hardig B, Erlinge D. Assessment of increasing intravenous adenosine dose in fractional flow reserve. *BMC Cardiovasc Disord.* 2017;17(1):60. <https://doi.org/10.1186/s12872-016-0463-4>
22. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J.* 2015;36(45):3182-8. <https://doi.org/10.1093/eurheartj/ehv452>
23. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al.; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol.* 2010;56(3):177-84. <https://doi.org/10.1016/j.jacc.2010.04.012>
24. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engström T, et al.; FAME Study Investigators. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet.* 2015;386(10006):1853-60. [https://doi.org/10.1016/S0140-6736\(15\)00057-4](https://doi.org/10.1016/S0140-6736(15)00057-4)
25. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PA, et al.; FAME 2 Investigators. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med.* 2018;379(3):250-9. <https://doi.org/10.1056/NEJMoa1803538>
26. Kogame N, Ono M, Kawashima H, Tomaniak M, Hara H, Leipsic J, et al. The Impact of Coronary Physiology on Contemporary Clinical Decision Making. *JACC Cardiovasc Interv.* 2020;13(14):1617-38. <https://doi.org/10.1016/j.jcin.2020.04.040>
27. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007;356(15):1503-16. <https://doi.org/10.1056/NEJMoa070829>
28. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al.; ISCHEMIA Research Group. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med.* 2020;382(15):1395-407. <https://doi.org/10.1056/NEJMoa1915922>
29. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol.* 1974;34(1):48-55. [https://doi.org/10.1016/0002-9149\(74\)90092-7](https://doi.org/10.1016/0002-9149(74)90092-7)
30. De Bruyne B, Pijls NH, Heyndrickx GR, Hodeige D, Kirkeeide R, Gould KL. Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. *Circulation.* 2000;101(15):1840-7. <https://doi.org/10.1161/01.cir.101.15.1840>
31. Pijls NH, De Bruyne B, Bech GJ, Liistro F, Heyndrickx GR, Bonnier HJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation.* 2000 Nov 7;102(19):2371-7. <https://doi.org/10.1161/01.cir.102.19.2371>
32. Kim HL, Koo BK, Nam CW, Doh JH, Kim JH, Yang HM, et al. Clinical and physiological outcomes of fractional flow reserve-guided percutaneous coronary intervention in patients with serial stenoses within one coronary artery. *JACC Cardiovasc Interv.* 2012;5(10):1013-8. <https://doi.org/10.1016/j.jcin.2012.06.017>
33. Park SJ, Ahn JM, Pijls NH, De Bruyne B, Shim EB, Kim YT, Kang SJ, et al. Validation of functional state of coronary tandem lesions using computational flow dynamics. *Am J*

- Cardiol. 2012;110(11):1578-84. <https://doi.org/10.1016/j.amjcard.2012.07.023>
34. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987;316(22):1371-5. <https://doi.org/10.1056/NEJM198705283162204>
 35. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. *J Am Coll Cardiol.* 1995;25(7):1479-85. [https://doi.org/10.1016/0735-1097\(95\)00088-1](https://doi.org/10.1016/0735-1097(95)00088-1)
 36. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation.* 2001;104(20):2401-6. <https://doi.org/10.1161/hc4501.099316>
 37. Collet C, Sonck J, Vandelloo B, Mizukami T, Roosens B, Lochy S, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol.* 2019;74(14):1772-84. <https://doi.org/10.1016/j.jacc.2019.07.072>
 38. Baranauskas A, Peace A, Kibarskis A, Shannon J, Abraitis V, Bajoras V, et al. FFR result post PCI is suboptimal in long diffuse coronary artery disease. *EuroIntervention.* 2016;12(12):1473-80. <https://doi.org/10.4244/EIJ-D-15-00514>
 39. Shiono Y, Kubo T, Honda K, Katayama Y, Aoki H, Satogami K, et al. Impact of functional focal versus diffuse coronary artery disease on bypass graft patency. *Int J Cardiol.* 2016;222:16-21. <https://doi.org/10.1016/j.ijcard.2016.07.052>
 40. Puri R, Kapadia SR, Nicholls SJ, Harvey JE, Kataoka Y, Tuzcu EM. Optimizing outcomes during left main percutaneous coronary intervention with intravascular ultrasound and fractional flow reserve: the current state of evidence. *JACC Cardiovasc Interv.* 2012;5(7):697-707. <https://doi.org/10.1016/j.jcin.2012.02.018>
 41. Lindstaedt M, Spiecker M, Perings C, Lawo T, Yazar A, Holland-Letz T, et al. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? *Int J Cardiol.* 2007;120(2):254-61. <https://doi.org/10.1016/j.ijcard.2006.11.220>
 42. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J.* 2014;35(40):2831-8.
 43. Kayaert P, Coeman M, Gevaert S, De Pauw M, Haine S. Physiology-based revascularization of left main coronary artery disease. *J Interv Cardiol.* 2021;2021:4218769. <https://doi.org/10.1155/2021/4218769>
 44. Spaan JA, Piek JJ, Hoffman JI, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. *Circulation.* 2006;113(3):446-55. <https://doi.org/10.1161/CIRCULATIONAHA.105.587196>
 45. Yamamoto E, Saito N, Matsuo H, Kawase Y, Watanabe S, Bao B, et al. Prediction of the true fractional flow reserve of left main coronary artery stenosis with concomitant downstream stenoses: in vitro and in vivo experiments. *EuroIntervention.* 2016;11(11):e1249-56. <https://doi.org/10.4244/EIJV11I11A246>
 46. Yong AS, Daniels D, De Bruyne B, Kim HS, Ikeno F, Lyons J, et al. Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv.* 2013;6(2):161-5. <https://doi.org/10.1161/CIRCINTERVENTIONS.112.000104>
 47. Fearon WF, Yong AS, Lenders G, Toth GG, Dao C, Daniels DV, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. *JACC Cardiovasc Interv.* 2015;8(3):398-403. <https://doi.org/10.1016/j.jcin.2014.09.027>
 48. Ziaee A, Parham WA, Herrmann SC, Stewart RE, Lim MJ, Kern MJ. Lack of relation between imaging and physiology in ostial coronary artery narrowings. *Am J Cardiol.* 2004;93(11):1404-7, A9. <https://doi.org/10.1016/j.amjcard.2004.02.041>
 49. Koh JS, Koo BK, Kim JH, Yang HM, Park KW, Kang HJ, et al. Relationship between fractional flow reserve and angiographic and intravascular ultrasound parameters in ostial lesions: major epicardial vessel versus side branch ostial lesions. *JACC Cardiovasc Interv.* 2012;5(4):409-15. <https://doi.org/10.1016/j.jcin.2012.01.013>
 50. Lee JM, Koo BK, Kumsars I, Curzen N, Thondapu V, Barlis P, et al. Coronary fractional flow reserve in bifurcation stenoses: what have we learned? *EuroIntervention.* 2015;11 Suppl V:V59-63. <https://doi.org/10.4244/EIJV11SVA13>
 51. Lee DW, Cavender MA. Periprocedural Myocardial Infarction in Contemporary Practice. *Interv Cardiol Clin.* 2019;8(2):209-23. <https://doi.org/10.1016/j.iccl.2018.12.001>
 52. Koo BK, Kang HJ, Youn TJ, Chae IH, Choi DJ, Kim HS, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol.* 2005;46(4):633-7. <https://doi.org/10.1016/j.jacc.2005.04.054>
 53. Chen SL, Ye F, Zhang JJ, Xu T, Tian NL, Liu ZZ, et al. Randomized Comparison of FFR-Guided and Angiography-Guided Provisional Stenting of True Coronary Bifurcation Lesions: The DKCRUSH-VI Trial (Double Kissing Crush Versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions VI). *JACC Cardiovasc Interv.* 2015;8(4):536-46. <https://doi.org/10.1016/j.jcin.2014.12.221>
 54. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al.; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation.* 2008;117(10):1283-91. <https://doi.org/10.1161/CIRCULATIONAHA.107.743963>
 55. Muller DW, Topol EJ, Ellis SG, Sigmon KN, Lee K, Califf RM. Multivessel coronary artery disease: a key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. *Am Heart J.* 1991;121(4 Pt 1):1042-9. [https://doi.org/10.1016/0002-8703\(91\)90661-z](https://doi.org/10.1016/0002-8703(91)90661-z)
 56. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol.* 2012;59(12):1045-57. <https://doi.org/10.1016/j.jacc.2011.09.077>
 57. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv.* 2010;3(12):1274-81. <https://doi.org/10.1016/j.jcin.2010.08.025>
 58. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, et al.; FAMOUS-NSTEMI investigators. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J.* 2015;36(2):100-11. <https://doi.org/10.1093/eurheartj/ehu338>
 59. Engström T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, J, et al.; DANAMI-3-PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. *Lancet.* 2015;386(9994):665-71. [https://doi.org/10.1016/s0140-6736\(15\)60648-1](https://doi.org/10.1016/s0140-6736(15)60648-1)

60. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, et al.; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376(13):1234-44. <https://doi.org/10.1056/NEJMoa1701067>
61. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al.; COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019;381(15):1411-21. <https://doi.org/10.1056/NEJMoa1907775>
62. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, et al.; FLOWER-MI Study Investigators. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. *N Engl J Med*. 2021;385(4):297-308. <https://doi.org/10.1056/NEJMoa2104650>
63. Bossard M, Mehta SR. Complete or Incomplete Revascularization for ST-Segment Elevation Myocardial Infarction: The PRAMI Trial to COMPLETE. *Interv Cardiol Clin*. 2020;9(4):433-40. <https://doi.org/10.1016/j.iccl.2020.06.001>
64. Zimmermann FM, Omerovic E, Fournier S, Kelbæk H, Johnson NP, Rothenbühler M, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. *Eur Heart J*. 2019;40(2):180-6. <https://doi.org/10.1093/eurheartj/ehy812>
65. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al.; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87-165. <https://doi.org/10.1093/eurheartj/ehy394>. Erratum in: *Eur Heart J*. 2019;40(37):3096
66. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, et al. Fractional flow reserve in patients with prior myocardial infarction. *Circulation*. 2001;104(2):157-62. <https://doi.org/10.1161/01.cir.104.2.157>
67. Singh IM, Subbarao RA, Sadanandan S. Limitation of fractional flow reserve in evaluating coronary artery myocardial bridge. *J Invasive Cardiol*. 2008;20(5):E161-6. PMID: 18460720.
68. Sabbah M, Nepper-Christensen L, Lønborg J, Helqvist S, Køber L, Høfsten DE, et al. Fractional flow reserve-guided PCI in patients with and without left ventricular hypertrophy: a DANAMI-3-PRIMULTI substudy. *EuroIntervention*. 2020;16(7):584-90. <https://doi.org/10.4244/EIJ-D-19-00577>
69. Aleksandric SB, Djordjevic-Dikic AD, Dobric MR, Giga VL, Soldatovic IA, Vukcevic V, et al. Functional Assessment of Myocardial Bridging With Conventional and Diastolic Fractional Flow Reserve: Vasodilator Versus Inotropic Provocation. *J Am Heart Assoc*. 2021;10(13):e020597. <https://doi.org/10.1161/JAHA.120.020597>
70. Feres F, Costa R, Siqueira D, Costa JR Jr, Chamié D, Staico R, et al. Diretriz da Sociedade Brasileira de Cardiologia e da Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista sobre Intervenção Coronária Percutânea. *Arq Bras Card*. 2017;109(1). doi: <https://doi.org/10.5935/abc.20170111>
71. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69(17):2212-41. <https://doi.org/10.1016/j.jacc.2017.02.001>. Epub 2017 Mar 10. Erratum in: *J Am Coll Cardiol*. 2018;: PMID: 28291663.
72. Correction. *J Am Coll Cardiol*. 2018;71(19):2279-80. doi: <https://doi.org/10.1016/j.jacc.2018.03.453>. Erratum for: *J Am Coll Cardiol*. 2017;69(17):2212-41.