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Invasive functional assessment of moderate coronary artery stenoses,

State of the art and a glimpse to the future

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Abstract

Physiological assessment of moderate coronary lesions is routine practice in the majority of cardiac catheterization laboratories. This is performed using dedicated devices (pressure wires or microcatheters) that allow the measurement of pressure derived physiological indices, for example fractional flow reserve (FFR). FFR has Class I indication with level of evidence A according to the most recent European Guidelines on myocardial revascularization for the assessment of angiographically moderate coronary lesions. In this review we aim to: 1) summarize the theoretical basis of the FFR; 2) provide an overview of vasodilators used for FFR evaluation; 3) summarize the scientific evidence supporting FFR; and 4) to provide insights into the introduction and application of iFR, as a further tool for physiologically assessment of moderate coronary stenoses.

Key words: Myocardial Ischemia; Coronary Revascularization; Physiological Assessment of Coronary Lesion;

Introduction

The aim of coronary revascularization is relief from myocardial ischemia, this has been demonstrated to have a positive impact on patients prognosis and quality of life. [1]

As such, coronary revascularization has to be driven by proven ischemia to be actually effective. Despite this statement, the "oculo-stenotic" reflex (i.e. the "eye-balling" evaluation of coronary stenoses) is still a widely utilized approach, even though detection of ischemia represents a safer approach as it reduces the number of unnecessary revascularization. According to robust evidence, angiography-guided revascularization may not result in improved clinical outcomes, compared to optimal medical therapy [2].

Myocardial ischemia can be detected either non-invasively (treadmill test, stress echocardiogram, nuclear perfusion scan and stress magnetic resonance) or invasively by measuring fractional flow reserve (FFR) [4]. FFR is the ratio of maximum blood flow in a stenotic coronary artery to maximum blood flow if the same artery were completely normal. The physiological threshold for ischemia is 0.80: coronary stenosis above this limit have very good prognosis at 5 years, and medical therapy is as effective as percutaneous coronary intervention (PCI) [3, 4]. For lesions with a FFR ≤0.80, PCI is superior to optimal medical therapy in reducing unplanned revascularization and angina [3]. The European Society of Cardiology Myocardial Revascularization Guidelines considers functional stenosis evaluation by FFR measurement a class I A tool, when a non-invasive ischemia test is unavailable or inconclusive and several devices are nowadays available (Table 1)

Table 1: Currently Available FFR Systems.

	Technology
Volcano/Philips (Eindhoven, the Netherlands)	Piezoelectric wire
St. Jude/Abbott (Minneapolis, Minnesota)	Piezoelectric wire
Boston Scientific (Natick, Massachusetts)	Fiber optic wire sensor
Opsens (Quebec, Ontario, Canada)	Fiber optic wire sensor
ACIST (Minneapolis, Minnesota)	Fiber optic microcatheter

Elements of physiology and coronary circulation physiopathology

The coronary circulation can be divided in three components. The first is represented by the large epicardial arteries (diameter > 500 μm), the so called "conduction vessels", offering in normal conditions minimal resistance to the flow. For this reason, they

account for 10% of total coronary circulation resistance, with unaltered pressure along these vessels. The second is formed by extra myocardial pre-arterioles, with a diameter between 100 and 500 μm. The last component is formed by arterioles (with a diameter under 100 μm) and capillaries. Together, the second and the third components are the so called "microcirculation", responsible for over 90% of coronary flow resistance. For this reason, the microcirculation plays a fundamental role regulating coronary flow via resistance changes [5, 6].

Coronary flow regulation

Coronary resistance is regulated by several factors: metabolic, endothelial, humoral, autoregulation mechanisms, myogenic and neurogenic control, and extravascular compression [7].

Coronary flow is maximal during the diastolic phase primarily due to extravascular compression.

In normal conditions, the oxygen demand of the myocardium and the coronary flow are perfectly balanced. Considering that the oxygen extraction of the myocardium at rest is already maximal, the increased oxygen demand may be satisfied only by reduction in coronary resistance and subsequent increase in flow, the so-called "active hyperemia". Under normal physiological conditions, the main factor that increases coronary flow is adenosine derived from adenosine-triphosphates pathway (ATP). Adenosine is a coronary vasodilatator, together with nitroxide, prostaglandins, myocardial oxygen and carbonyl concentration [7].

Coronary perfusion and coronary perfusion pressure are related to pressure gradient between coronary arteries and left ventricular diastolic pressure. With low coronary pressure (40-50 mmHg), the diastolic flow is minimum, especially in subendocardium, due the major extravascular tissue compression. This feature explains the subendocardial ischaemia susceptibility [8]. Ischaemia is defined as the imbalance between oxygen demand and supply.

Oxygen myocardial demand factors

In the aerobic myocardial metabolism (with a strict relation between oxygen demand and metabolism), the main factors affecting oxygen demand are: heart rate, contractility, ventricular filling pressure, and afterload.

Coronary blood flow regulation is complex and incorporates several factors: metabolic control (mainly via ADP release and oxygen tension), autoregulation (factors released by myocardial interstitium), extravascular compressive forces, and diastolic phase in cardiac cycle, humoral factors, and neural control.

Correlation between stenosis, flow and coronary resistance

Flow-limiting atherosclerosis mechanisms are mainly: 1) Stenosis severity/length; 2) Vessel rigidity; 3) Reduced vasomotility; 4) Thrombosis.

Flow resistance is mainly related to minimal luminal diameter (MLD): i.e. the translesional pressure drop is inversely related to the MLD fourth power. This explains why a minimal MLD change may have bigger consequences in case of stenosis [9].

Flow resistance may be counterbalanced by arteriolar dilatation: in this manner, basal coronary flow is conserved until 85% stenosis. This mechanism explains why simple stenosis quantification is not a reliable method to assess flow reduction. Under circumstances where there is increased oxygen demand, compensation is reduced with 30-45% stenosis, while it is absent once there is a 90% stenosis.

Collateral circulation

Following coronary occlusion flow occurs via collateral vessels, connections between epicardial arteries (diameter 20-200 μm). Under normal conditions with patent vessels, collaterals are closed, due to pressure drop absence. On the other hand, when there is vessel closure, collaterals start working, with subsequent arteriogenesis.

Ischemia per se is not a crucial determining factor for collateral formation, but usually collaterals development requires at least 70% stenosis [10].

In chronic conditions, collaterals may satisfy oxygen demand increase, up to 50% of maximal flow.

In this setting, two mechanisms play a relevant role: arteriogenesis (pre-existing collaterals recruitment) and angiogenesis (new vessel development) [10].

Donor vessel FFR measurement may be affected by collateral circulation: in the presence of a Chronic Total Occlusion (CTO) and collateralization, donor vessel flow is increased, supplying the occluded vessel territory. For this reason, FFR measurement across donor stenosis is decreased.

After CTO reopening, collateral flow decrease and donor vessel FFR increase, as a consequence of flow reduction across the donor vessel lesion.

Fractional Flow Reserve and coronary circulation

Coronary flow is mainly autoregulated by the microcirculation (diameter < 400 μm). When there is maximal hyperemia/vasodilation, the microcirculation resistance is minimal and fixed, the coronary autoregulation is suppressed, and the coronary flow is directly proportional to blood pressure [10].

Under these conditions, the pressure drop across the lesion is derived by the stenosis length, lumen cross-sectional area and blood flow velocity.

The Fractional Flow Reserve (FFR), intended as the ratio of maximal hyperemic flow on a stenotic artery to hyperemic flow that would exist if the same vessel was normal, is unaffected by the changes in hemodynamic conditions, including heart rate, blood pressure or myocardial contractility and represents the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis.

Fractional Flow Reserve theoretical basis

Gould described the relation between the severity of coronary flow restriction, resting and maximal coronary blood flow, and regional flow more than 40 years ago, in an experimental setting [11]. Interestingly, the clinical application started in the late 90's. The theoretical basis of FFR is based on Ohm's law for the

electrical resistance that defines the relation between conduit resistance (R), current intensity (I) and potential difference as R=V/I.

Applying this law to hydrodynamics, considering as R the flow resistance, I as the flow across the stenosis and V the pressure gradient across the same lesion, while assuming a minimal and constant resistance (R) at maximal hyperemia, pressure may be considered as an acceptable flow equivalent.

In other words, considering the proximal to stenosis pressure (Pa) equivalent to the aortic pressure, FFR may be derived by the ratio between the distal pressure (Pd) and the aortic pressure (Pa) during maximal hyperemia, or FFR=Pd/Pa, assuming it as equivalent to $\mathbf{FFR = Q_{stenosis} / Q_{normal}}$, where Q means the flow rate.

The previous formula derives from the following:

$$\mathbf{FFR= [(Pd-Pa)/R_{mio}] / [(PA-Pa)/R_{mio}]}$$

Considering **Pd** as the pressure after the stenosis, **Pa** the right atrial pressure, **PA** the aortic pressure; and Rmio the myocardial resistance.

Pa is not considered in clinical practice, considering the low and relatively constant value.

$\mathbf{R_{mio}}$ during maximal hyperemia is a constant.

So, by approximation, the final formula is **FFR= Pd / Pa**.

Maximal hyperemia induction to evaluate the fractional flow reserve

Maximal hyperemia is an essential condition in the stenosis functional assessment. Hyperemia induction is sometimes considered as expensive and complex, but it has been demonstrated to be safe, cheap and easy [12].

Several drugs are used to cause hyperemia. The most commonly used, perhaps the gold-standard, is the adenosine (Table 2).

Table 2: Hyperemic agents for FFR Measurements. AMP = adenosine monophosphate; ATP = adenosine triphosphate; AV = atrioventricular; IC = intracoronary; VT = ventricular tachycardia; IV = intravenous.

	Effect	Peak Effect	Side-effects
IV adenosine	Activates A2A adenosine receptors, which increases cyclic AMP production	90-120 sec	AV block (transient), bronchospasm, hypotension, chest pain, shortness of breath
IC adenosine	Same as above	10-20 sec	Same as the IV adenosine
ATP	Precursor of adenosine	90-120 sec	Same as adenosine
IC nicorandil	ATP-sensitive potassium channel opener causing potent coronary vasodilation of both epicardial and resistance vessels.	20-30 sec	No significant side effects
IV dobutamine	Positive inotropic and hronotropic effects; enhancing myocardial blood flow through metabolic vasodilation.	Very prolonged and variable	Tachycardia
IC nitroprussiade	Relaxes smooth muscle cells and preferentially vasodilates coronary microcirculation;	>120 sec	Transient hypotension
IC papaverine	Inhibits phosphodiesterase, causing elevation of cyclic AMP levels;	30-60 sec	Transient QT-interval prolongation, rarely torsades de pointes and VT
IC regadenoson	Selective A2A adenosine receptor binder	unknown	No side effects associated with A1, A2B and A3A receptors binding

Adenosine

Adenosine is natural nucleoside produced by myocardiocytes, by adenosine-triphosphate (ATP) dephosphorylation. ATP is produced during increased metabolic activity or during ischemia.

Adenosine causes intramyocardial arteries dilatation binding A2 receptor on vessel muscular cells membrane. Adenosine may be administered by intracoronary or intravenous route. [13]

Intracoronary bolus is the most widely adopted method of administration. Although a unique dose for both the left and right coronary is still debated, recent data has shown that coronary flow increases until 600mcg of adenosine is administered without an increase in side effects, while having the same sensitivity and specificity of 140mcg, which is deemed to be the minimum dose [13]. The intracoronary administration is obviously unable to reach a stable hyperemia, thus, the measurement must be performed at the "peak" hyperemia: currently available software can do this measurement automatically, thus reducing the risk of inappropriate results.

Adenosine administered intravenously, perhaps the "gold standard" method of administration, should be given at a dose of 140μg/Kg/min [12, 13]. Resultant hyperemia is stable and starts 90 seconds after infusion. Side effect of intravenous adenosine includes hypotension, chest pain, and shortness of breath, atrio-ventricular block and flushing. These effects are directly link to the drug infusion, and they are not ischemia consequence. The most common hemodynamic effect of adenosine is a 10-20% drop in systemic pressure and reflex tachycardia (counterbalanced by the intrinsic adenosine bradycardic effect).

Some substances, as metilxantine or caffeine, binding A2a receptors, may impede hyperemic effect. For this reason, even if there are not clear data regarding FFR false negative after caffeine and aminophylline intake, caffeine is not recommended in the 24 hours before the test. Theoretically, femoral vein is usually recommended for the infusion; however, there is some evidence on the safety and efficacy of adenosine infusion via peripheral vein [12, 13].

For patients who have multiple FFR measurements, in view of venous flow modulation during breathing, the lowest value should be considered.

Regarding adenosine preparation, the best choice is to use a 200 mg adenosine dilution in 100 ml of saline. The infusion has to be done via volumetric automatic pump. On the other hand, 30 mg adenosine/10 mL solution is also available, but with greater costs, for a direct infusion; 6 mg in 2 ml vials (i.e. 3mg/ml) are also available (Krenosin™, Sanofi-Aventis).

Regarding intracoronary injection of Adenosine, most utilized method of administration, the maximal effect is reached after 10 seconds and it lasts for 20 seconds. This is an easier approach, with less systemic collateral effects. However, the optimal dose of intracoronary adenosine is still a matter of debate. Recent evidence has demonstrated that 600 μg dose has the same sensitivity of intravenous adenosine. The suggested approach is to inject incremental adenosine doses (from 60 μg to 600 μg), switching to intravenous infusion in case of atrioventricular block or grey zone results. When doing so, it is crucial to avoid side-hole catheters and to give intracoronary nitrates before Adenosine to obtain the maximal vasodilatation of the epicardial vessels. Of note, the adenosine injection has to be fast and complete, in order to avoid a long "blind" pressure period [14].

Other hyperemia inductors

Papaverine

Intracoronary papaverine causes maximal coronary vasodilatation; the effect is maximum after 20 seconds and it lasts for at least 40 seconds. The recommended dose is 12-16 mg in the right coronary and 16-20 mg in the left coronary system. Despite evidence supporting its efficacy, papaverine use is limited due to its proarrhythmic effect (mediated by QT prolongation). While using papaverine, hypokalemia correction is mandatory, and class I and III anti-arrhythmic drugs need to be avoided. Moreover, with contrast medium injection, crystallization may occur. On the other hand, papaverine effect lasts up to 5 minutes; therefore, several FFR measurements (and pullbacks) are possible. For these reasons, Papaverine is used when adenosine is contraindicated [15].

Sodium Nitroprusside

Sodium nitroprusside acts on arterial and venous smooth muscle cells, probably via sympathetic activation, by stimulating nitroxide release. Sodium nitroprusside has been used for treatment of no reflow phenomenon, but with 0.6 μg/Kg it has adenosine-like specificity and sensitivity when used for assessment of FFR. The main side-effect is transient systemic hypotension, but myocardial hyperemia is 25% longer than with adenosine. [16] It is used when adenosine is contraindication.

Others

ATP has short half life due fast degradation to ADP, AMP and adenosine. Despite the main ATP effect been related to adenosine production, direct binding to adenosine or purine receptors is also possible. With intracoronary ATP dose between 15 and 50 μg, the vasodilatator effect is similar to 10 mg papaverine, without any systemic hemodynamic or electrocardiographic effect.

In addition, pharmacological researchers have attempted to identify new molecules such as regadenoson, a safe and fast A2A receptor binder that does not have the side effects associated with adenosine, related to A1, A2B and A3A receptors binding; whether these pharmacological features can give to regadenoson a safer and more reliable application than adenosine is still a matter of debate [17]

Evidence and clinical trials

The 2014 European Society of Cardiology (ESC) Myocardial Revascularization Guidelines gave recommendation Class IA to FFR for coronary stenosis evaluation in cases where ischemia had not been proven by another modality. [4] This indication is based on robust evidence from several trials demonstrating that: 1) FFR guided PCI is a safe approach, and that 2) FFR guided PCI has a significant advantage compared with "angiography" guided PCI. From a clinical perspective, the use of a threshold is extremely helpful and reproducible to guide management, however, it is crucial to consider that the risk associated with any FFR value

is a continuum: as such, the lower the FFR value, the greater the severity of ischemia [4]. Theoretically, patients with very low FFR will have the greatest benefit from revascularization, whereas patients with a normal FFR will have no benefit at all or even potential harm.

FFR to defer unnecessary PCI

The DEFER trial demonstrated the safety of deferring PCI according to a FFR value > 0.75 [12]. In 325 patients, stenoses with an FFR > 0.75 were randomized to either PCI (Perform Group) or medical treatment (Defer Group). In addition, all patients with an FRR <0.75 had PCI (Reference Group). At 15 years follow up, free from MACE survival was similar between the Defer and Perform group, but was worse in the Reference group. These results suggest that rates of mortality and myocardial infarction in patients with negative FFR is low, and that these are not reduced by PCI. The FFR cut off has been recently updated to 0.8, as having the best combination of sensitivity and specificity as demonstrated by ROC curve analysis [13].

Multivessel coronary disease

Multivessel patients represent a wide and heterogenous population, with relevant discrepancy between anatomical and functional data. FFR guided PCI has been demonstrated to be associated with a better outcomes.

The FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) [13] trial was the first randomized trial evaluating FFR guided PCI. The authors randomized 1005 patients with multivessel coronary artery disease to FFR guided PCI (FFR cut-off: 0.80) vs anatomically guided PCI. One year major adverse cardiovascular event (MACE) rates were lower in FFR guided PCI (13.2% vs.18.3%, p = 0.02). There was no significant difference between the groups in rates of freedom from angina (78% vs 81%, p = 0.20).

In the FAME-2 Trial 1222 patients with FFR values ≤ 0.80 were randomized to either PCI or medical therapy [18]. The trial was prematurely stopped due to increased primary end point event rates in the medical group (4,3% in the PCI group and 12,7% in the medical therapy alone group, (HR PCI = 0.32, 95% C I = 0,19-0,53, P <0.001). The main factor for this was higher rates of unplanned revascularization in the medical therapy group (1.6% in the PCI group vs 11.1% in the medical group; HR = 0.13, 95% CI 0,06-0,30, P <0.001). However, in view of the limitations of this trial (mean follow-up of 7 months and no demonstrated cardiovascular death or myocardial infarction benefit, excluding the periprocedural events) more data is needed. Last but not least, the confounding effect of dual antiplatelet therapy in the PCI arm.

In subgroup analysis of FAME, "anatomical" Syntax score (SS) was compared with a "functional, FFR guided" Syntax score (FSS) in terms of one year events rate prediction. [19] Patients were divided accordingly to SS tertiles. After FSS evaluation, 32% of patients has been reallocated in a lower SS tertile, with a better event rate prediction.

FFR in Acute Coronary Syndromes (ACS)

In the 1005 FAME patients, 328 patients have been randomized with a diagnosis of Non-ST Elevation ACS (NSTEACS). Even in this high risk group, non culprit FFR guided PCI has been related to adverse events rate reduction (5,1% vs 3,7%, p = 0.92) [20]. These results have been confirmed by other studies. The FAMOUS-NSEMI trial published recently also demonstrated this in patients with NSTEMI and at least one coronary stenosis who were randomized to angiographic guided vs FFR guided PCI. In almost 20% of stenosis, the indication was changed from PCI to medical therapy alone, with similar 1 years follow up event rate. [21] Of note, the trial had several limits: the inclusion of centers with limited FFR experience, and the high delay between NSTEMI diagnosis and coronary angiography (mean 72 hours, revealing a not so acute population). A recently published trial by Smits et al, demonstrated efficacy and safety of FFR in non-culprit lesion assessment during STEMI setting. At 12 months follow up, FFR assessment during STEMI reduced unplanned revascularization occurrence [22].

FFR in previous myocardial infarction

In patients with previous myocardial infarction, the amount of viable myocardium is reduced and replaced by necrotic tissue, thus hyperemic flow is reduced resulting in higher FFR values [12, 13].

FFR, left main disease and downstream stenosis

Non-invasive tests in left main disease may have high false negative rate, especially with concomitant significant disease in the right coronary artery. Moreover, perfusion defects may be diffuse, resulting in poor detection of ischemia due to 'balanced ischemia'. In this context, FFR has showed good efficacy and safety. Daniels et al. tested an in vitro model for left main FFR assessment with and without concomitant downstream stenosis in the anterior descending (LAD) or circumflex (Cx) stenosis, without significant difference in left main stenosis detection sensitivity (Left main and LAD/Cx stenosis: 0.76 ± 0.06, Left main isolated lesion: 0.76 ± 0.05, p = 0.124) [23].

Fearon et al evaluated in 25 patients the impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease, creating a temporary stenosis inflating a balloon in a recent implanted stent (in anterior descending or circumflex). Therefore, the study gave two FFR left main measurements: the "true" (without downstream stenosis) and "apparent" (with artificial downstream stenosis). There was no significant difference between the true and apparent FFR values for patients with intermediate left main coronary artery disease. In addition, an apparent FFR over 0.85 was related to true FFR over >0.80, avoiding a reclassification of stenosis severity [24].

In series stenosis

In patients with series stenoses, FFR measurements have clinically been demonstrated to be valid. Although, theoretically FFR calculation is based on single lesion assessment, in clinical practice a "pull back" measurement can be performed easily by pulling back the pressure wire during maximal hyperemia from distal to proximal lesion [24].

Bifurcation lesions

Koo et al. evaluated the utility of FFR measurements in jailed side branches after main branch stenting. This showed that there was a correlation between the percentage of stenosis and FFR values whereby no lesion with <75% stenosis that had FFR <0.75. Of note, Chen et al, in the DKCRUSH-VI Trial compared outcomes of FFR-guided and angiography-guided provisional side-branch stenting for true coronary bifurcation lesions. In this trial, angiographic and FFR guidance of provisional side branch stenting of true coronary bifurcation lesions provided similar 1-year clinical outcomes [25].

Post PCI FFR

Post PCI FFR data remains sparse. Inverse relation has been observed between post PCI FFR and restenosis rate. The aim of PCI is to achieve an FFR value of 1 however several factors can cause lower values including stent malapposition and diffuse distal disease.

A recent meta analysis by Rimac et al. of 105 studies, showed that higher post-PCI FFR values were associated with reduced rates of repeat intervention (P<0.0001) and MACE (P=0.0013). A post-PCI FFR ≥0.90 was associated with significantly lower risk of repeat PCI (odds ratio 0.43, 95% CI 0.34-0.56, p < .0001) and MACE (odds ratio 0.71, 95% CI 0.59-0.85, p = .0003) [26].

iFR: the diastolic trans-stenotic pressure gradient.

The Instantaneous wave-free ratio (iFR) has been introduced in order to overcome the limitation of the drug-induced hyperemia [27]. iFR is an instantaneous diastolic trans-stenotic pressure gradient, measured in the "wave free" period, when resistances are stable and minimal (Figure 1).

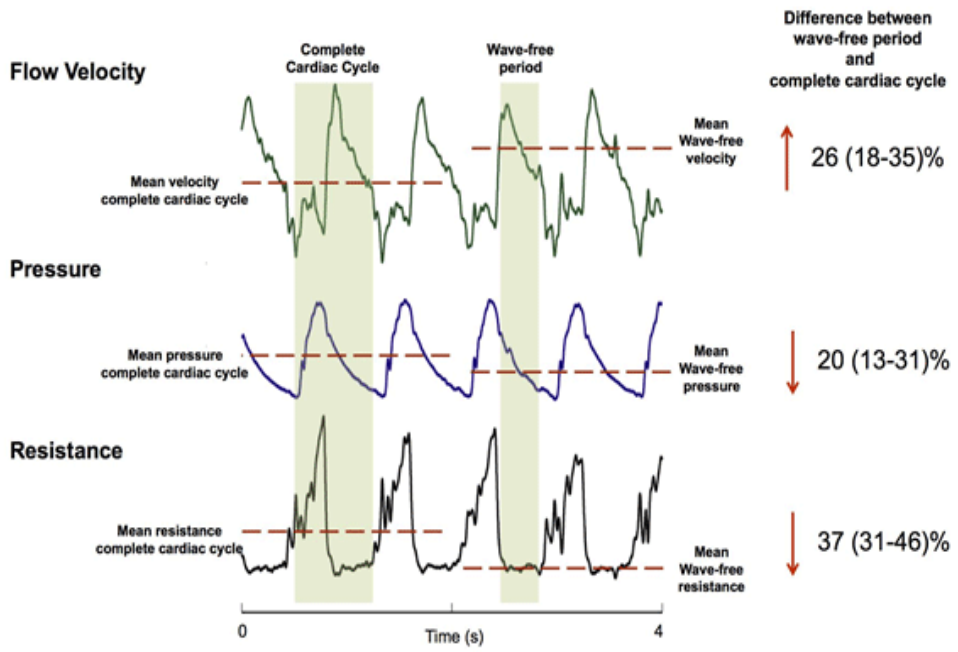

Figure 1: Pattern of coronary blood flow velocity, resistance and pressure during the Cardiac Cycle and the "wave-free" period

The formula is: **iFR= Pd (wfp) / Pa (wfp),** where Pd is the distal pressure, Pa is the pressure proximal to the lesion and wfp is "wave-free period".

The wave free period is the part of cardiac cycle without new pressure wave front generation and with minimal microvascular resistance. This is the reason why iFR measurements do not require administration of vasodilators. Several studies have demonstrated a good correlation between iFR and FFR (more than 90%, with r between 0,79 and 0,90 depending on the distribution of stenoses), with some discordance around the cut off (the so called "gray zone") [28,29].

This discrepancy may be due to:

1) Different adenosine response
2) FFR been derived by mean pressures, iFR by "beat by beat" measurement
3) Wave free period resistances may be higher than those after adenosine.

For these reasons, Petraco et al proposed a hybrid iFR-FFR strategy: iFR measurement within the high predictive range and for iFR values between 0.86 and 0.93 (the "gray zone"), an FFR measurement is indicated. Recent evidence about iFR safety and reliability are available in multivessel disease.

Two recent large trials by Gotberg et al (SWEDEHEART) [30] and Davies et al (DEFINE-FLAIR)[31] randomised 4,529 patients to either FFR or iFR guided PCI. At one year follow up, iFR-guided revascularization strategy was non-inferior to an FFR-guided revascularization strategy with respect to the rate

of MACE (myocardial infarction, target-lesion revascularization, restenosis, and stent thrombosis) using an iFR threshold of ≤0.89.

There have been criticisms regarding these trials comparing iFR and FFR. Firstly, the wide non-inferiority limit: in the SWEDEHEART trial it has been set a 3.2% (hazard ratio 1.4) and 3.4% in DEFINE-FLAIR. Secondly, in the recent iFR trials the number of lesion per patient was less than 1.56 while in the FAME trial it was > 2.8. Thirdly, the low PCI rate in the trial populations: in the FAME trial PCI occurrence was almost 60%, this was around 50% in both SWEDEHEART and DEFINE-FLAIR. These elements suggest a lower risk population, in which a non-inferiority evaluation may be overestimated. Moreover, several doubts are present regarding FFR accuracy measurement in iFR trials, primarily due to concerns regarding administration of low dose of intracoronary adenosine. Nonetheless, we believe that iFR will definitely assume a growing role in the assessment of moderate coronary stenosis, as a consequence of its easiness of application and the availability of the scout modality (Figure 2). Of note, several additional resting indices will soon be ready for the clinical application [32]

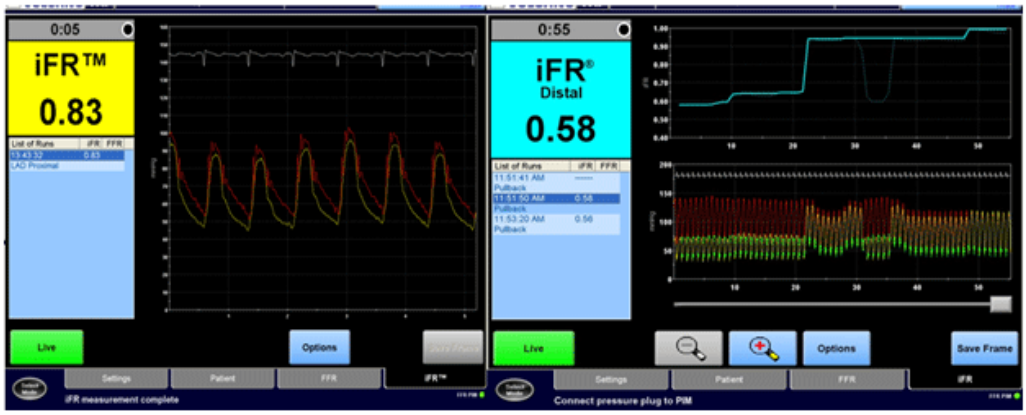

Figure 2: : **Left Panel:** example of iFR measurement; Right Panel: example of iFR scout measurement

By calculating the stenosis-specific relationship between the pressure drop across a stenosis and the flow velocity through it, other evaluations are possible: BSR (stenosis resistance calculated during basal conditions), and the HSR (pressure drop across the stenosis divided by distal coronary flow velocity under hyperaemic conditions). Both recently demonstrated equivalent diagnostic accuracy for inducible myocardial ischaemia compared with current clinical standards, including FFR. [33]

The formulas are:

BSR= (mean P_{aorta} - mean P_{distal})/APV (during basal conditions)

HSR= (mean P_{aorta} - mean P_{distal})/APV (during hyperemia)

Where APV means Average Peak Flow Velocity distal to the coronary lesion

Since the pressure drop across a stenosis and distal flow velocity change in the same direction with altered coronary flow through the stenosis, the stenosis resistance index is less affected by the magnitude of flow at which it is calculated. For this reason, HSR basal measurement may be a useful tool, although a large "clinical" study is needed to provide further evidence [34].

Beyond invasive FFR: the "virtual" reality

Contemporary research is providing not only new parameters to measure, but also new manner to measure relatively "old" parameters as FFR. Thanks to computational fluid dynamics and CT scan progresses, the virtual FFR has been introduced. DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive FFR) was the first major published trial of vFFRCT, it showed 87% accuracy with invasive FFR. Similar data came out from the Heart Flow NXT trial (Heart Flow Analysis of Coronary Blood Flow Using CT Angiography [35]. At the current time, vFFR helps reduce CT false positives, but it still has suboptimal accuracy to represent a real alternative to invasive FFR.

Coronary absolute flow

Recently, two parameters have been introduced: the coronary absolute flow and the minimal microvascular resistance. By means of a side-holes microcatheter, an intracoronary saline infusion is given (to reach maximal vasodilatory effect); then, two thermistors wires can measure the flow by thermodilution [36]. The minimal microvascular resistance can be also calculated.[37]

At the moment, there is no clinical application, but in the future these parameters could be of interest to assess microcirculation disease.

Conclusions

Assessment of coronary artery stenosis is a fascinating field that incorporates physics (fluid mechanics), physiology, interventional techniques, radiology and general cardiology.

After more than 2 decades of experience and despite the availability of several FFR Systems (Table 1), iFR has probably reached a level of evidence to be fairly considered a valid alternative, and newer parameters are under investigation. Computed Tomography FFR, on the other hand, is making encouraging progresses towards being a reliable non-invasive tool [38].

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