Coronary physiology in the catheterization laboratory

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Introduction: Coronary artery disease remains (CAD) a major cause of morbidity and mortality worldwide. However, the mortality rates of CAD have declined over the past decades, mainly due to improvements in the treatment of acute coronary syndromes, therapies for heart failure or revascularization for chronic angina, but also because of awareness-raising and prevention strategies.

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The high metabolic demands of the myocardium are met through an elaborate vascular network, which includes the large epicardial coronary arteries (over 500 μm in diameter) and smaller vessels – such as extramyocardial prearterioles, arterioles (<100 μm) and capillaries – that form the coronary microcirculation, the main regulator of flow. The myocardial vascular supply (Figure 1) is complex not only from an anatomical point of view, but also from a physiological perspective, with coronary regulatory mechanisms and microvascular dysfunction playing an important role in the pathophysiology of ischemic heart disease.

Angina and myocardial ischaemia usually occur because of flow-limiting epicardial fixed stenosis, but they may also occur in the setting of normal epicardial coronary arteries due to endothelial dysfunction and subsequent microvascular disease. A coronary angiogram assesses the extent of coronary disease severity, but its visual interpretation may be subjective and it has acknowledged limitations in intermediate, eccentric or diffuse coronary stenosis, thus making therapeutic decisions challenging and potentially inaccurate in such clinical scenarios.

There are several methods for assessing coronary physiology in the catheterization laboratory, which provide evaluation of coronary blood flow, functional significance of a coronary stenosis and/or microvascular dysfunction. Guidewire-based measurements of coronary blood pressure, flow velocity, temperature or resistance, integrated in various parameters, allow the assessment of coronary physiology.

FRACTIONAL FLOW RESERVE

The angiographic aspect of an atherosclerotic lumen does not accurately reflect the physiologic impact on hemodynamics, as the angiographic image is a 2-dimen-

Figure 1. Coronary vascular compartments. Pa – aortic/proximal pressure; Pd – distal pressure; Pv – venous pressure; FFR – fractional flow reserve; IMR – index of myocardial resistance; CFR – coronary flow reserve.

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ional representation of a 3-dimensional lesion. Therefore, eccentric lesions, calcifications, branch overlap and ostial lesions additionally contribute to the unreliability of angiographic interpretation. Studies have shown that angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR, not only in the 50% to 70% category, but also in the 70% to 90% angiographic severity category.

Fractional flow reserve (FFR) is a parameter that measures pressure differences across an epicardial stenosis in order to establish if the stenosis is flow-limiting and consequently responsible for myocardial ischaemia. It is defined as the ratio between the maximal achievable blood flow in a diseased vessel and the maximal flow in the hypothetical absence of the stenosis. In a state of maximal hyperaemia, the microvascular resistance is minimal and the pressures obtained proximally and distally to a coronary stenosis can be considered proportional to blood flow. Venous pressure is disregarded in clinical practice, so the simplified equation for FFR is: \( FFR = \frac{Pd}{Pa} \) (\( Pd \)=pressure distal to the stenosis, \( Pa \)=aortic pressure, recorded at the tip of the guiding catheter). A special coronary 0.014 guidewire with a pressure sensor usually 3 cm from its tip is inserted distally from the target stenosis. The blood pressure is simultaneously recorded in the aorta and distally, in the target coronary, and an FFR value is provided (Figure 2). Hyperaemia is usually achieved with adenosine, but other drugs may be used (papaverine, nitroprusside, regadenoson), with reproducible measurements.

The theoretical value of FFR in a normal coronary artery is 1, as there should be no pressure drop along a normal vessel. A cutoff value of 0.75 predicts inducible ischaemia, but since most studies have used the cutoff of 0.8 for deferral of angioplasty, the current European and American guidelines for revascularization recommend coronary intervention for stenosis with FFR <0.8 FFR is a reproducible, feasible parameter, minimally modified by the baseline status of the patient. However, in patients with sequential lesions, pressure pullback recording during stable hyperaemia is mandatory in order to identify the culprit lesion. FFR is not recommended in the setting of an acute coronary syndrome, since the patient’s microcirculation might be severely damaged and thus it might compromise the response to adenosine.

Trials showed the benefits of using FFR measurement to guide revascularization with better outcomes and reduced costs compared to angiography-guided revascularization alone. The first randomized trial of FFR-guided percutaneous coronary intervention (PCI), the DEFER trial, randomly assigned patients with intermediate lesions and FFR >0.75 to PCI (Perform group) or deferral of PCI (Defer group), while patients with FFR<0.75 underwent PCI (Reference group). The 2 and 5-year follow-up showed that event-free survival did not differ between the Defer and Perform groups, but it was significantly worse in the Reference group. There was no difference between the Defer and Perform group in terms of recurrence of angina. The 15-year follow-up is further proof that the deferral of PCI of functionally nonsignificant lesions is safe, while PCI for such lesions does not improve outcome. The DEFER trial proves that in patients with stable CAD, the most important prognostic factor of a coronary stenosis is its functional significance indicated by a FFR<0.75; in such patients, outcome is worse than in patients with nonsignificant stenosis (FFR >0.75), even when treated by PCI.

The FAME trial enrolled 1005 patients with multivessel disease and randomly assigned them to angiography-guided PCI and FFR-guided PCI. In the former group, all lesions were treated with DES, while in the latter group, PCI was performed only for lesions with FFR <0.80. At 1 year, the FFR-guided PCI group had lower rates of MACE (13.2% vs 18.3%, \( p=0.02 \)) and lower rates of combined death and MI (7.3% vs 11%, \( p=0.04 \)) when compared to the angiography-guided PCI group. The 2-year follow-up showed similar benefits of FFR-guided PCI. The 5-year follow-up showed similar rates of MACE between the two groups, but this clinical outcome was achieved with less stents and less resource use in the FFR-guided PCI group.

The FAME 2 trial compared FFR-guided PCI plus optimal medical therapy (OMT) with OMT alone in

![Figure 2. FFR – console screenshot. Red wave: aortic/proximal pressure. Yellow wave: distal pressure, FFR value of 0.77.](image-url)
patients with functionally significant stenosis (FFR <0.80). The study was stopped prematurely because of the significant difference in the rates of death, MI and urgent revascularization (4.3% in the FFR group vs 12.7% in the OMT group, p<0.001)\(^{19,20}\).

FAMOUS-NSTEMI was a prospective, randomized trial that included 350 NSTEMI patients with at least one coronary stenosis >30%, who were assigned randomly to either the FFR-guided group, where FFR <0.80 was an indication for revascularization by PCI or CABG, as appropriate, or the angiography-guided group, where FFR measurements were not disclosed and the decision of revascularization was made according to visual assessment of the lesion. At 12 months, there were no significant differences in health outcomes and quality of life between the groups\(^ {21}\). However, a recent study showed that deferring PCI in patients with NSTEMI and culprit lesions with FFR >0.75 is associated with significantly worse outcomes\(^ {22}\), which brings into question the long-term safety of assessing the physiology of an acute lesion and of using the same threshold as for stable CAD. The FAMOUS-NSTEMI trial proved that FFR measurement in NSTEMI patients is safe and feasible, but further studies are needed to assess the prognostic significance and cost-effectiveness of a FFR-guided management in such a clinical setting.

A recent multicenter study, PRIMULTI, enrolled 627 patients with STEMI and a significant nonculprit lesion; all culprit lesions were treated, while nonculprit lesions were randomized to angiography-guided or FFR-guided revascularization. At 1 year, cardiac death and repeated revascularization were lower in the FFR-guided group, while there were no significant differences among hospitalizations for recurrent angina\(^ {23}\). The preliminary results of a recent similar study showed that in patients with STEMI and FFR-guided complete revascularization of non-culprit lesions the rate of MACE was lower than in patients with STEMI treated for the infarct-related artery only, mainly because of a reduction in repeated revascularization\(^ {24}\).

CABG is the current recommendation for patients with complex 3-vessel disease\(^ {25}\). The investigators of FAME 3, an ongoing multicenter, randomized trial, hypothesized that the inferiority of PCI in 3-vessel disease might be explained by the use of older types of stents and the lack of FFR-guidance of PCI. Therefore, the trial will investigate whether FFR-guided PCI with new-generation stents is noninferior to CABG in patients with 3-vessel disease, not including left main stenosis\(^ {26}\).

FFR is a well established and essential tool to guide the elective revascularization of intermediate lesions, as it provides specific information regarding their functional significance. Revascularization offers a greater absolute benefit for more severe FFR values\(^ {27}\). An FFR-guided revascularization significantly reduces MACE and increases freedom from angina when compared to an angiographic – based strategy.

**INSTANTANEOUS WAVE-FREE RATIO**

The instantaneous wave-free ratio (iFR) is a logical follow-up of the FFR. Like FFR, it determines whether an epicardial coronary stenosis leads to a drop in pressure that is significant. The iFR precludes the need for hyperaemia, one of the most common pitfalls of FFR. After an analysis of coronary pressure and velocity measurements, Sen et al. identified a wave-free period during diastole in which the resistance is both minimal and constant\(^ {28}\). This wave-free period starts 25% into diastole and ends 5 ms before the end. It can be used to calculate the ratio between the distal and proximal pressures (iFR = Pd/Pa) without the need of hyperaemia (Figure 3). An iFR measurement is made by using a normal pressure wire connected to a machine with dedicated software. It is a highly reproducible measurement with excellent spatial resolution, used with ease to perform a coronary pullback tracing, in order to distinguish between diffuse atherosclerotic disease and focal stenosis.

The iFR usually has a cut-off value of 0.90, which is used to predict with a diagnostic accuracy of 80% the FFR value of 0.80\(^ {29}\). Usually a grey zone of 0.86–0.93 is used in order to establish the need of further hyperaemia measurements and FFR determination\(^ {30,31}\). The grey-zone setting provides two thirds of patients with functionally significant stenosis (FFR <0.80). The study was stopped prematurely because of the significant difference in the rates of death, MI and urgent revascularization (4.3% in the FFR group vs 12.7% in the OMT group, p<0.001)\(^ {19,20}\).

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**Figure 3.** iFR – console screenshot. Re wave: aortic/proximal pressure. Yellow wave: distal pressure; Green wave: wave-free period.
a hyperaemia – free functional measurement while maintaining an excellent correlation with the FFR.

Recently, two high volume clinical trials that prove the non-inferiority of the iFR method to the FFR regarding hard clinical outcomes were published. DEFINE – FLAIR was a 2492 patient multicenter, randomized, clinical trial that compared iFR and FFR – guided PCI in patients with intermediate – severity lesions. The composite primary endpoint of all-cause death, nonfatal MI or unplanned revascularization occurred in 6.8% in the iFR group and 7.8% in the FFR group (95% CI 0.68–1.33, P=0.78). In the iFR group, the procedural signs and symptoms were reported in 3.1% (39 patients) as compared to the 30.8% (385 patients) in the FFR group (p<0.001)32.

The iFR – SWEDHEART STUDY consists of 2037 patients with an indication for a physiologically guided assessment of a coronary lesion randomized to either iFR or FFR guided PCI. The primary endpoint occurred in 6.7% of the patients in the iFR group and in 6.1% in the FFR group, meeting the noninferiority margin (p = 0.007 for noninferiority)33.

CORONARY FLOW RESERVE

The coronary flow reserve (CFR) expresses the capacity of the entire coronary vascular bed to respond to an increase in oxygen demand with a corresponding increase in blood flow through vasodilation. CFR represents the ratio between total coronary blood flow at maximal hyperaemia and at baseline. In normal subjects CFR is usually over 3 and a cutoff value of 2 is generally accepted in clinical practice for the detection of inducible ischaemia34. CFR can be assessed non-invasively using transthoracic Doppler echocardiography, myocardial contrast echocardiography, PET, cardiac magnetic resonance; each test has its own limitations in terms of availability, accuracy, costs and potential risks. Coronary flow at rest and under maximal hyperaemia can also be assessed invasively during coronary angiogram, through either Doppler-velocity assessment or thermodilution method35. A special coronary 0.014” guidewire with a 12–15 MHz piezoelectric ultrasound transducer in its tip is advanced usually until the mid segment of the target coronary artery and oriented away from the vessel wall. A base value is first recorded, and then, the second value during maximal hyperaemia, is obtained. Hyperaemia is usually achieved with adenosine, administered either intravenously or by a single intracoronary bolus, but several other drugs (papaverine, nitroglycerin, nitroprusside) can be used (Table 1). The most common side effects associated with CFR measurement are those related to adenosine administration (bradycardia, hypotension, bronchoconstriction, flushing, dyspnea), the drug being contraindicated in patients with persistent bronchospasm.

The role of CFR measurement lies in the assessment of global coronary vascular function (both epicardial vessels and microcirculation), in unraveling the total burden of myocardial ischaemia36 and in the diagnosis of microvascular angina (in the setting of chest pain with normal coronary angiogram and CFR less than 2). Trials regarding the prognostic value of non-invasive CFR have been conducted and they showed that CFR less than 2 was a independent predictor for major adverse cardiac events (MACE)37,38 and that higher CFR was associated with better outcome in patients with normal perfusion imaging39,40. A non-randomized study with a longer follow-up period (up to 5.4±2.2 years) showed not only that CFR is an independent predictor of MACE, but also that, in patients with normal perfusion, a low CFR allowed further prediction of high annual event rates41. This predictive power was maintained during the first 3 years of follow-up; afterwards, the survival curves converged. A recent study showed that reduced CFR was associated with adverse outcomes independently of the angiographic severity of coronary disease, and that it may affect the outcomes of revascularization: patients with low CFR who underwent coronary artery bypass grafting, but

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not percutaneous coronary intervention, had event rates similar to those with normal CFR).

While all these trials were based on non-invasive PET assessment of CFR, one previous study showed that a low invasive CFR (assessed by intracoronary Doppler) was an independent predictor of poor long-term outcome in patients with angina and normal or mildly diseased coronary arteries.

CFR has several limitations in clinical practice. Invasive measurement of CFR is expensive, time consuming and it has potentially serious adverse effects. An abnormal CFR does not help differentiate between epicardial and microvascular disease, as this parameter assesses the function of the whole coronary vascular bed and the cohesive effects of epicardial stenosis, vessel remodeling, microvascular dysfunction on myocardial perfusion. Any disturbances in the coronary blood flow at rest (such as tachycardia, abnormal coronary perfusion pressure, vasoactive drugs or hormones, left ventricular hypertrophy) will alter the ratio of hyperemic to baseline flow, potentially leading to a falsely abnormal CFR.

**INDEX OF MICROVASCULAR RESISTANCE**

The scenario of a patient with normal FFR and low CFR is generally attributed to microvascular dysfunction; however, this setting can also be explained by diffuse atherosclerotic disease or altered baseline coronary flow. For such cases, parameters evaluating the function of the microcirculation have been developed. The index of microvascular resistance (IMR) is a measure of coronary microvascular function, it was first described in 2003 and it is calculated as the ratio between distal coronary pressure recorded under maximal hyperaemia and coronary blood flow, or, using the simplified equation, as the product between coronary pressure and the mean transit time of a 3 ml bolus of saline during hyperaemia. An IMR higher than 25 is considered abnormal, expressing microvascular dysfunction. Measurement of IMR is specific for the microvasculature, reproducible and independent of haemodynamic variations and myocardial contractility. However, in the setting of associated significant epicardial stenosis, collateral blood supply may be substantial and IMR should be measured taking into account the coronary wedge pressure and venous pressure or it can be easier estimated using the myocardial fractional flow reserve: IMR=mean proximal coronary pressure - mean transit time x (1.34 x FFRmyo - 0.32).

Besides having a role in the diagnostic of microvascular angina, the IMR is also a predictor of myocardial damage in the setting of an acute STEMI. Two small-sample studies showed that the IMR measured during primary PCI is an independent predictor of infarct size and severity assessed by contrast-enhanced cardiac magnetic resonance at 2 days and at 3 months and it is also a predictor of recovery of left ventricular function based on the percent change in wall motion score at 3-month follow-up. A recent prospective, multicenter study, which enrolled 253 patients, showed that the IMR measured at the time of primary PCI for STEMI predicted long-term clinical outcomes such as death and hospitalization for heart failure, with the cutoff >40 being associated with a higher rate of cardiac adverse events (hazard ratio [HR]=3.95, p=0.028 for death, HR=2.1, p=0.034 for death or rehospitalization for heart failure). The study limitations include the relatively small number of adverse events (11 deaths, 24 hospitalizations) and the lack of data regarding the extent of coronary disease. The main clinical implication of such findings is that the IMR may be a useful method for identifying high-risk patients who would benefit most from novel therapies targeting microvascular recovery, such as intracoronary streptokinase or transplant of autologous stem cells. Nevertheless, further studies are needed to establish whether patients with a high IMR need particular therapeutic interventions to improve outcome.

Susceptibility to periprocedural MI is related to procedural aspects or lesion complexity (plaque burden assessed by intravascular ultrasound or thin cap fibroatheroma assessed by optical coherence tomography), but coronary microvascular dysfunction may also play a role in predisposing a patient to periprocedural MI. In a study of 50 patients undergoing elective PCI for a single lesion of the left anterior descending artery, pre-procedural IMR >27 was associated with a 23-fold risk of developing periprocedural MI (sensitivity=80%, specificity=85%, p=0.003), showing that impaired microcirculation before PCI determines susceptibility for periprocedural MI independent of lesion characteristics and that such patients might benefit from adjunctive risk-reduction strategies. The main limitation of the study is the inclusion only of left anterior descending artery lesions; further studies are needed to define IMR cutoffs for other territories.

**ABSOLUTE CORONARY BLOOD FLOW**

The latest method of characterizing the coronary physiology is the measurement of the absolute co-
Coronary blood flow and microvascular resistance. It is performed by continuous thermodilution with saline administered via a special microcatheter with four-side holes in order to obtain an optimal mixing of the indicator with blood. A pressure-temperature sensor-tipped wire is advanced in the distal vessel. With the aid of a dedicated software, the coronary absolute hyperemic blood flow measured in ml/min is obtained and also the microvascular resistance measured in dyne*s*cm⁻⁵. The technology is available at the moment only for research.

CONCLUSIONS

Despite the low prevalence of invasive physiologic assessment in clinical practice, comprehensive evaluation of both macro- and microvasculature systems enhances the patients’ outcomes. Coronary physiologic measurement overcomes the limitations of coronary angiography, as it integrates the atherosclerotic burden with its haemodynamic impact.

For patients with acute coronary syndromes, coronary physiology has the potential to improve the treatment of the culprit lesion, but further studies are needed. For stable patients and for acute non-culprit lesions, coronary physiology assessment allows functional quantification of the ischaemic burden of the coronary bed and thus guides the therapeutic decision. Physiology of both microvascular disease and diffuse atherosclerosis needs to be further explored, as the coexistence of these entities with focal stenoses may lead to failure of a local mechanical intervention to change the long-term outcome of the disease.

Standards of coronary physiologic assessment are constantly evolving and they will continue to be explored, in order to fully comprehend the mechanisms of endothelial dysfunction, microvascular disease or vulnerable coronary lesions. Although physiology testing in the catheterization laboratory means supplemental time, costs and potential side effects, it provides a substantial clinical benefit for the patient and thus savings to the health care system. Newer methods, like the iFR and absolute coronary blood flow and microvascular resistance, not only make the physiology assessment safer and quicker, but also open new ways for research. Understanding coronary physiology in patients with CAD complements the anatomical information provided by angiography and assists the physician in decision-making and improving long-term outcomes.

Conflict of interest: none declared.

References


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