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Invasive functional testing

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Abstract

The concept of "significant" coronary stenosis has been revisited since the introduction of physiological measurements in the cardiac catheterisation laboratory. Invasive functional testing evaluates coronary physiology by recording blood pressure, flow or velocity and yields important information about the epicardial arteries and the respective myocardial territory. Numerous clinical studies have demonstrated the value of physiological testing in the assessment of challenging angiographic subsets, such as multivessel disease, bifurcation lesions and diffuse coronary atherosclerosis. In selected cases, deferral of revascularisation on the basis of functional indices can actually decrease adverse cardiac events. Furthermore, physiological measurements after angioplasty and stent implantation can be used to optimise the angiographic results and improve patient outcome. This review will discuss the basic concepts of functional testing in the catheterisation laboratory and its main applications for the interventional cardiologist.

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Introduction

Invasive coronary angiography (ICA) remains the current standard for the anatomical assessment of the coronary arteries and the diagnosis of coronary artery disease (CAD) in the catheterisation laboratory. Nonetheless, the quantification of a coronary stenosis by means of the two-dimensional silhouette of the contrast-filled vessel lumen is not always feasible, especially for complex or eccentric luminal shapes[1]. Moreover, the presence of diffuse coronary atherosclerosis can lead to unreliable ICA interpretation, because of the difficulty to identify the "normal" reference segments.

The physiological significance of atherosclerotic lesions, which is the most important prognostic factor in patients with known CAD[2], cannot be appreciated by conventional angiography. Patients with chronic stable angina can benefit from either percutaneous or surgical revascularisation, which is a well-established approach to relieve ischaemia-driven symptoms and improve prognosis by reducing cardiovascular morbidity and mortality[3]. Yet, it is often challenging to identify the stenosis responsible for myocardial ischaemia, especially in patients with multiple lesions of intermediate angiographic severity (namely 40% to 70% diameter narrowing).

Invasive functional testing based on measurements of pressure, flow, and/or velocity, has been introduced since the 1980s to provide valuable information complementary to the anatomic assessment and improve clinical decision-making. Previous studies have demonstrated that assessment by both invasive and non-invasive angiography correlate poorly with the haemodynamic significance of coronary stenoses, especially for intermediate severity lesions[4] (Figure 1), highlighting the need to integrate physiology into the daily routine of the catheterisation laboratory.

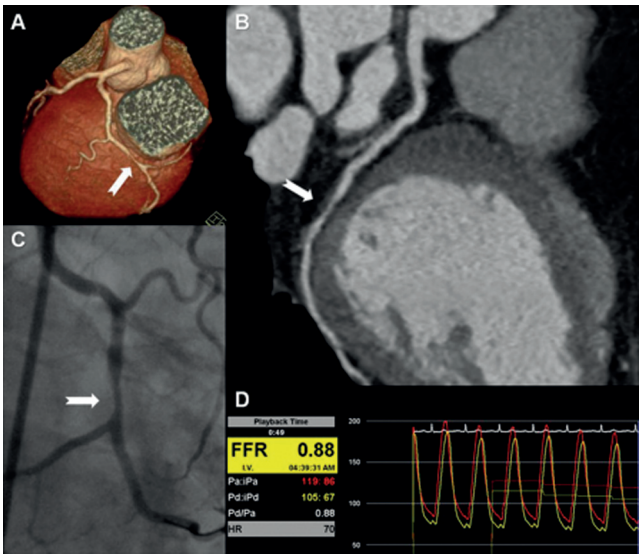

Figure 1. Comprehensive assessment of an intermediate coronary lesion with computed tomography coronary angiography (CTCA), invasive coronary angiography (ICA) and fractional flow reserve (FFR). A 51-year-old male patient presenting with coronary artery stenosis (arrows) in the left circumflex artery. A: volume-rendered image; B: curved multiplanar reconstruction; C: invasive coronary angiography. By visual assessment, the coronary lesion was estimated as moderate by ICA and as severe by CTCA. By quantitative analysis, the percent diameter stenosis was 50% by quantitative coronary angiography and 55% by quantitative CTCA. The FFR was 0.88; D: Based on the physiological assessment of this anatomically intermediate stenosis, percutaneous coronary intervention was deferred.

Physiology and coronary haemodynamic indices

The coronary circulation is characterised by the ability to adapt to myocardial metabolic needs. Normally, coronary blood flow increases automatically in response to an increase in myocardial oxygen demand, its overall resistance being controlled by small arteries and arterioles. Failure of the auto-regulatory capacity to maintain the balance between myocardial oxygen supply and demand results in myocardial ischaemia.

Resistance to blood flow in normal coronary arteries is negligible. The presence of an atherosclerotic stenosis and the energy dissipation due to frictional losses, turbulence and flow separation results in increased epicardial resistance[5]. As demonstrated by the work of Gould et al[6,7] on coronary physiology, resting coronary flow can be sustained by dilatation of the microcirculation distally to the stenosis up to the point of a critical reduction (>85%) of the vessel lumen. Conversely, under the influence of hyperaemic stimuli, the physiologic impact of a stenosis is more obvious, since the impairment of the maximal hyperaemic flow begins at approximately 50% lumen diameter narrowing.

Coronary flow reserve

The relative increase in coronary flow achieved with maximal vasodilation compared to basal coronary perfusion is denoted as coronary flow reserve (CFR) and measures the ability of the microcirculation to respond to a hyperaemic stimulus. Since the actual flow is difficult to be quantified, the coronary flow velocity reserve (CFVR) measured by intracoronary Doppler ultrasound represents CFR and is a reliable physiologic measurement of coronary flow (Figure 2). CFR is determined by measuring coronary or myocardial blood flow (velocity) both at rest (basal flow) and at maximal hyperaemia, which is achieved with intracoronary or intravenous infusion of a pharmacologic agent, such as adenosine

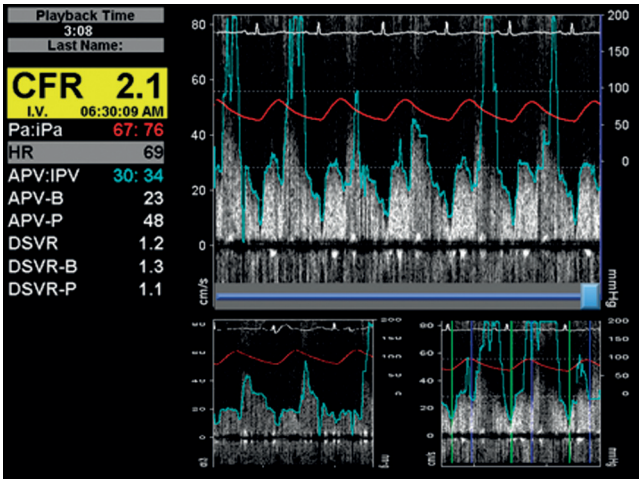

Figure 2. Measurement of the coronary flow reserve (CFR) by intracoronary Doppler ultrasound. The flow velocity signals are recorded at baseline (lower left) and maximal hyperaemia (lower right panel).

or papaverine. Absolute CFR is then expressed as the ratio of maximal hyperaemic to basal blood flow distal to the stenosis[7]. CFR reflects the combined capacity of the two major resistance components (the epicardial coronary artery and supplied vascular bed) to achieve maximal blood flow at hyperaemia. A normal CFR suggests that both components are normal; nonetheless, an abnormal CFR value does not necessarily mean that an epicardial obstruction is present, since the impairment of microvascular circulation due to hypertrophy, hypertension, diabetes or myocardial infarction also reduces CFR. The inability of CFR to indicate which component is affected, led to the introduction of relative CFR (rCFR)[7]. An additional measurement of CFR can be obtained in an adjacent non-diseased epicardial vessel and be used as reference value, under the assumption that microcirculation at the myocardial vascular bed is uniform and the basal flow in the two vessels is the same. The rCFR value is computed from the ratio of maximal flow in the target vessel to flow in the normal coronary artery ($rCFR=CFR_{target}/CFR_{normal}$). Obviously, rCFR is not useful either in patients with three-vessel coronary disease, who lack an appropriate reference vessel, or in patients with impaired microcirculation.

Fractional flow reserve

In the presence of an epicardial atherosclerotic stenosis, the aforementioned reduction of flow and energy loss result in a proportional loss of pressure and a translesional pressure gradient. Early clinical reports demonstrated that the pressure drop over a stenosis was highly predictive of myocardial perfusion defects on thallium scintigraphy[8]. The concept of fractional flow reserve (FFR) emerged as a pressure-derived index to assess the functional severity of epicardial stenosis in a simple and reproducible way. It is defined as the ratio of maximal blood flow in the presence of a coronary stenosis to the theoretical maximal flow in the absence of stenosis in the same vessel[9]. As demonstrated by Pijls et al[9] and De Bruyne et al[10], FFR can be derived simply by the ratio of the mean distal coronary pressure (Pd) to the aortic pressure (Pa) during maximal hyperaemia (Figure 3). The presumption of maximal coronary vasodilation is pivotal for the underlying theory; it allows the coronary resistances to be assumed minimal and constant, and thus the distal coronary pressure (Pd) to be considered proportional to the blood flow supplying the myocardium. Moreover, the distal coronary pressure in a normal coronary artery can be presumed equal to the aortic pressure (Pd≈Pa), since there is virtually no epicardial resistance, energy loss and flow reduction. As previous experiments have shown[9], FFR can be calculated individually for the myocardium, for the epicardial arteries and for the collaterals. The FFR presents some unique advantages compared to other physiologic indices: it is lesion-specific and has an unequivocal normal value of 1.0 for any patient, coronary artery and myocardial bed. Furthermore, because FFR is based on pressure measurements which can be acquired more easily, the reported reproducibility is high with variability ranging between 0-3%[11]. In addition, FFR seems to be independent from systemic haemodynamics, such as blood pressure, heart rate and left ventricular contractility[11].

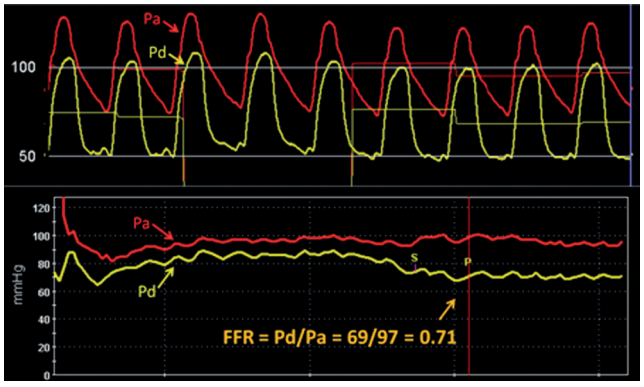

Figure 3. Example of fractional flow reserve (FFR) measurement at maximal hyperaemia as induced by intravenous infusion of adenosine. Pa: aortic pressure; Pd: distal pressure

Hyperaemic stenosis resistance

Despite the many advantages of FFR as an invasive physiological index, some components of its theory have come into question more recently, such as the assumption that myocardial resistance is constant at hyperaemia in stenotic and normal arteries. The variability in microvascular resistance is deemed to have an influence on invasive physiological indices[12]. The concept of measuring both pressure and flow signals emerged as an alternative for the comprehensive evaluation of both epicardial and microvascular resistance[13] (Figure 4). The hyperaemic stenosis resistance index (HSR) was introduced as the ratio of the hyperaemic trans-stenotic pressure gradient to the hyperaemic distal flow velocity and holds a better predictive value than FFR and CFR for the detection of inducible ischaemia in patients with discordant FFR and CFR measurements[14].

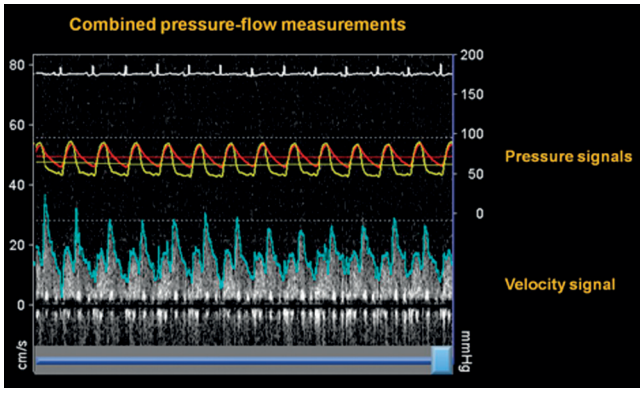

Figure 4. Combined single-wire pressure and flow velocity measurement at maximal hyperaemia. This patient had normal values for pressure (FFR=0.86) and flow (CFR=2.1), suggesting absence of myocardial ischaemia. FFR: Fractional Flow Reserve, CFR: Coronary Flow Reserve

Thresholds for ischaemia

The FFR normal value is 1 by definition; the thresholds of haemodynamic indices for identifying a coronary lesion of functional significance were derived from the strong correlation with myocardial perfusion imaging, such as single-photon emission

computed tomography (SPECT). The ischaemic cut-off values for FFR and CFR have been determined as <0.75 and <2.0 respectively, based on clinical validation by several studies comparing invasive physiological measurements with non-invasive stress testing, which have been summarised elsewhere[15]. An FFR of <0.75 has demonstrated excellent diagnostic performance to identify lesions related to reversible myocardial ischaemia, with an overall predictive accuracy of 93%[16]. Nonetheless, the cut-off values slightly differ among the studies, therefore FFR values ranging between 0.75-0.80 constitute a narrow "grey zone"; in such cases, decision making on the necessity of coronary intervention must be supported by patient-specific clinical assessment. Similarly, a CFR value <2.0 was correlated to inducible myocardial ischaemia with high predictive accuracy between 89 and 96%[15]. Regarding HSR, the available data for intermediate lesions show that HSR values >0.8 mmHg/cm/s have a sensitivity and specificity of 79% and 90% respectively and a predictive accuracy of 87% for the detection of reversible perfusion defects[17].

Invasive functional testing and different angiographic subsets

Assessment of intermediate stenosis

Coronary lesions of intermediate severity are the most common lesions in patients with CAD, yet they often pose the dilemma of whether to treat them or not. In this context, the aforementioned ischaemic thresholds for invasive functional testing can provide the interventionalist with useful information to select the patients who would benefit from percutaneous coronary intervention (PCI). Several studies have demonstrated that deferral of angioplasty of intermediate stenosis on the basis of haemodynamic indices is safe, reporting a low cardiac event rate at follow-up when FFR>0.75 or CFR>2.0[16,18-20]. The DEFER study documented the 5-year clinical outcome of PCI deferral based on FFR measurement[21]. A total of 325 stable angina patients planned for PCI of an intermediate stenosis were randomised into three groups. Patients with FFR >0.75 were randomly assigned to the deferral group (receiving medical therapy for CAD) or to the PCI performance group (treatment with bare-metal stents). If FFR was <0.75, patients underwent PCI as scheduled (reference group). At 5-year follow-up the event-free survival between the deferral and performance groups was similar (80% and 73%, respectively, p=0.52), whereas in the reference group it was significantly worse (63%, p=0.03). The composite rate of cardiac death and acute myocardial infarction (AMI) was substantially higher for the reference group (15.7%) than in the deferral and performance groups (3.3% and 7.9% respectively, p=0.003 for reference vs. both deferral and performance). Based on the 5-year outcome after FFR-guided PCI of an intermediate coronary stenosis, the authors concluded that among patients planned for intervention with an FFR>0.75, deferral holds no adverse prognostic value and the risk of cardiac death or AMI related to this lesion was approximately 1% per year and not reduced by stenting. Moreover, comparably low event rates (6%) for CFR use in assessment of intermediate stenosis were reported in a prospective, multicenter study[20]. SPECT was performed in 191 patients with stable angina and multivessel disease, planned for PCI of an angiographically severe coronary narrowing. CFR measurement was acquired distal to an intermediate lesion in a different artery and intervention for the intermediate lesion was deferred when SPECT was negative or CFR>2.0. At 1-year follow-up of the patients, major adverse cardiac events (MACE) related to the intermediate lesion were recorded. The investigators concluded that deferral of PCI of intermediate lesions in multivessel disease is safe when CFR>2.0 and that CFR could predict more reliably than SPECT future adverse events. Figures 1 and 5 demonstrate examples of patients with angiographically intermediate stenoses, for whom PCI was either deferred or performed respectively based on physiological measurements.

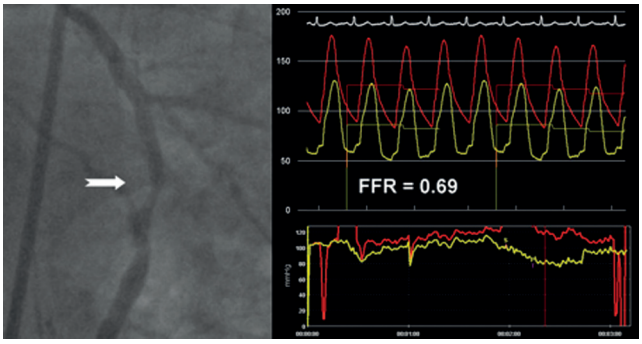

Figure 5. Example of patient with an angiographically intermediate stenosis (arrow) in the left circumflex artery. Percutaneous coronary intervention was performed on the basis of the Fractional Flow Reserve (FFR=0.69).

Multivessel disease and clinical decision-making

In the drug-eluting stents (DES) era, PCI is increasingly performed to treat CAD and relieve angina in more complex patient populations[22]. Assessing the complexity of multivessel disease by coronary angiography can be challenging, due to the large variation of anatomical features (number, location and severity of lesions); a patient may be classified as a "three vessel disease" case based on the angiographic data, but in reality have only two physiologically significant stenoses. Previous studies[20,23,24] suggest that invasive physiological indices allow a better risk stratification in this patient population than non-invasive testing, because the latter often lacks in accuracy to identify all ischaemic lesions, as a result of balanced ischaemia or masking of one hypoperfused area by another. In addition, single-centre studies demonstrated that PCI can be safely deferred in patients with multivessel CAD[25] and that FFR-guided PCI significantly decreases the number of vessels treated, the event rate, and the procedural cost[26]. These preliminary conclusions were confirmed by the FAME trial, a large multicentre, randomised study[27] with the objective to compare the FFR-guided to the angiography-guided PCI approach in patients with multivessel CAD. The angiograms of approximately 1,000 patients were evaluated by the investigators for the presence of angiographically significant lesions which were deemed to require stenting. The patients were then randomly assigned to either angiography- or FFR-guided

strategy. In the angiography-guided arm, patients received DES implantation as originally planned, whereas for patients assigned to the FFR-guided arm, first the FFR was measured in each diseased vessel and only if it was ≤0.80 the planned PCI was performed. The primary end point of the study was a composite of MACE including death, MI, and repeat revascularisation (CABG or PCI) and was documented at one year from randomisation. The results demonstrated clearly the superiority of the physiologically-guided approach. In the FFR-guided arm the number of implanted stents per patient was lower (1.9±1.3 vs. 2.7±1.2, P<0.001), as well as the procedural costs and length of hospital stay; in addition, the 1-year MACE rate was 13.2% , significantly lower than the 18.3% in the angiography-guided arm (P=0.02). Notably, the reduced endpoints in the FFR-guided arm were combined with a similarly high percentage of patients who were angina-free at 1 year (81% vs. 78% in the angiography-guided arm, P=0.20). The conclusions drawn from this randomised trial underscore once again the critical role of invasive functional testing for optimal decision-making and improvement of long-term clinical outcome.

Moreover, an FFR-based strategy in patients with multivessel disease can be useful for decision making on CABG performance, as demonstrated by Botman et al[28]. The study included 150 patients referred for CABG because of angiographic multivessel disease. FFR was measured in all diseased coronary arteries prior to CABG. Surgical revascularisation with bypass of all arteries was performed as planned only in patients with physiologically significant stenoses (FFR≤0.75) in three vessels or in two vessels involving the proximal LAD. Patients not eligible for CABG underwent PCI on the physiologically significant lesions. At 2-year follow-up, there was no difference observed in events rate, including repeat revascularisation (MACE rate 26% and 28% in the CABG and the PCI group, respectively). The number of angina-free patients was similar between the two groups (84% for CABG group and 82% for the PCI group). The authors concluded that, notwithstanding the presence of angiographic multivessel disease, selective PCI in patients with one or two physiologically significant lesions has a similar prognosis to CABG in those with three or more culprit lesions.

Assessment of left main lesions

Left main coronary artery (LMCA) lesions are a challenging angiographic subset, since they cannot always be reliably assessed by conventional angiography. Considering the poor long-term prognosis of significant LMCA disease, the accurate assessment of the LMCA lesions is paramount. Consequently, in routine clinical practice, ambiguous LMCA disease sometimes results in a dilemma as to which is the optimal therapeutic strategy for the patient. In this setting, existing data from several studies[29-31] suggest that FFR can facilitate decision making in dubious LMCA disease by identifying patients with physiologically significant lesions requiring surgical treatment. Bech and colleagues[29] examined 54 patients with equivocal LMCA coronary disease and reported that patients with an FFR of ≥0.75 can be deferred safely to a nonsurgical treatment approach. Those patients (44%) received medical therapy with PCI for concomitant lesions if needed; the patients with FFR<0.75 underwent surgical revascularisation. At 3-year follow-up, event-free survival was not different between the groups (76% in the medical group and 83% in the surgical group). These results were confirmed by other investigators who studied larger cohorts of patients with intermediate LMCA disease, strengthening the conclusion that physiological assessment by FFR can discriminate patients suitable for surgical revascularisation or medical therapy, ensuring excellent survival and low event rates[30,31].

Bifurcation and ostial lesions

Percutaneous intervention on bifurcation lesions is technically more challenging and is related to higher procedural failure and increased complication rates, mainly due to the occlusion of the side branch (SB). Moreover, long term prognosis bears a higher rate of late events caused by restenosis of the SB. Angiographic evaluation of coronary bifurcations is often difficult and not reliable, due to branch overlap and incomplete acquisition consisting in failure to discern the ostium of the SB. Quantitative coronary angiography (QCA) is plagued by the variant definition of the reference vessel diameter function at the SB ostium, having not yet been validated against a golden standard; overestimation of the SB reference diameter results in exaggerated percent diameter stenosis values.

An FFR-guided approach to evaluate the functional significance of "jailing" the SB after main vessel stenting was tested by Koo et al[32]; percent diameter stenosis values of apparently compromised SB ostia were correlated with respective FFR values. The authors concluded that the ostial lesions of the SBs are frequently overestimated by angiography. QCA-derived percent diameter stenosis measurements had a low positive predictive value for SB ischaemia, since less than one third of the angiographically severe lesions (≥75% diameter reduction) proved to be haemodynamically significant (FFR<0.75). Following up on this topic, Koo et al[33] documented the clinical outcome of FFR-guided PCI strategy for SB of bifurcation lesions. Coronary intervention on SB was performed in patients with FFR<0.75. At nine months, functional restenosis (FFR<0.75) rate was 8% for the FFR-guided group, with a similar clinical outcome to a control (angiography) group. Figure 6 demonstrates a bifurcation lesion assessment by FFR.

Functional assessment of serial stenoses and diffuse coronary atherosclerosis

The presence of tandem lesions within the same vessel results in a physiological interaction between them; the hyperaemic flow and pressure gradient through each stenosis is counteracted by the existence of the others. Consequently, one stenosis may confound the true impact of another more severe stenosis by restricting the potential maximum hyperaemia. Theoretically, the accurate measure of FFR for each sequential stenosis requires calculation of the coronary wedge pressure[34]. However, in clinical practice, the pressure pullback recording is used to identify the specific lesions that could benefit from coronary intervention[35]. Priority for treatment can be given to the stenosis with the largest gradient, and then new FFR measurements can be obtained to decide upon further treatment.

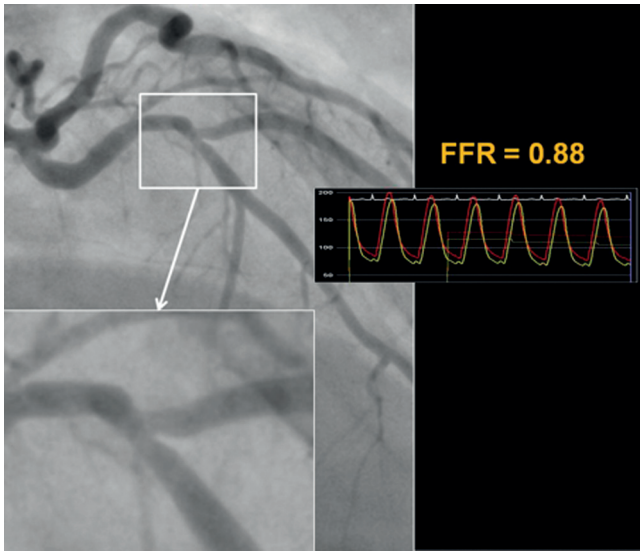

Figure 6. Physiological assessment of a coronary bifurcation. The fractional flow reserve (FFR) was 0.88 for the side branch (1st diagonal) and 0.89 for the main vessel (left anterior descending artery).

Similar is the concept for the assessment of diffuse and long lesions. In arteries with diffuse atherosclerotic disease, coronary blood pressure dissipates along the course of the artery, corresponding to an increase in epicardial resistance due to gradual diameter changes. De Bruyne et al[36] demonstrated that 8% of non-stenotic arteries in patients with disease in a different coronary artery, had an FFR value of <0.75, being indicative of ischaemia. Figure 7 shows patients' angiograms with diffuse coronary disease that differs in functional severity.

Physiological endpoints for percutaneous coronary interventions

Physiological indices have also been used to optimise the result after coronary interventions. The DEBATE (Doppler Endpoints Balloon Angioplasty Trial Europe) study evaluated the predictive value of Doppler flow velocity indices for the short- and long-term clinical outcomes after balloon angioplasty[37]. In patients with single-vessel disease, a CFR≥2.5 coupled with diameter stenosis ≤35% after angioplasty proved to have a favourable long-term outcome. Moreover, the DEBATE II trial which followed[38], concluded that physiologically guided balloon angioplasty had similar event-free survival rates at 1-year follow-up compared to coronary stenting (85.6% and 86.6%, respectively). However, stent implantation after a suboptimal angioplasty resulted in significantly improved outcome (MACE rate 10.7 vs. 26.7%, P=0.005). FFR can be used in a similar fashion to assess the result after balloon angioplasty. In a study by Bech et al[39], an FFR≥0.90 combined with a residual diameter stenosis ≤35% was associated with a significantly lower MACE-rate compared to the patients with suboptimal angiographic and/or functional result (12% vs. 41%, *P*=0.012).

In a multicentre trial, Pijls et al[40] concluded that post-stenting FFR measurement was an independent predictor of MACE. For patients with postprocedural normalised FFR (>0.95) the event-free survival was excellent with an event rate of 5%. Conversely, the patients with FFR<0.80, had the worse prognosis (30% event rate). In general, the lower the FFR, the more likely the patient would experience events at 6 months. These results indicate the potential role of invasive physiological measurements for guidance of coronary interventions.

Conclusions

Functional testing in the catheterisation laboratory is a valuable tool complementary to the coronary angiogram. This modality provides the interventionalist with data on intracoronary pressure, flow, and/or velocity, allowing for a haemodynamic appreciation of the coronary artery disease. In clinical practice, invasive physiological assessment when applied in the appropriate patient populations and addressing the right questions is associated with an improved prognosis.

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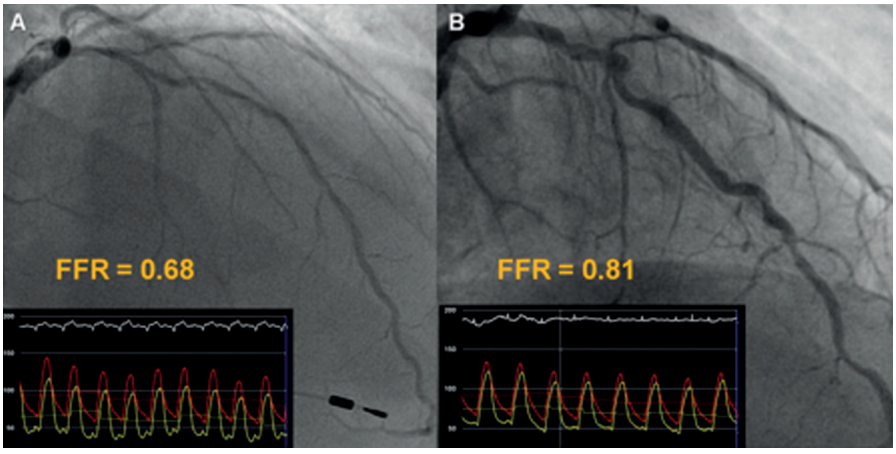

Figure 7. Angiographic and physiological data of 2 patients (panels A and B) with diffuse atherosclerosis in the left anterior descending coronary artery. FFR: Fractional Flow Reserve

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