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REVIEW ARTICLE

The Role of Coronary Physiology in Contemporary Percutaneous Coronary Interventions

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Abstract: Invasive assessment of coronary physiology has radically changed the paradigm of myocardial revascularization in patients with coronary artery disease. Despite the prognostic improvement associated with ischemia-driven revascularization strategy, functional assessment of angiographic intermediate epicardial stenosis remains largely underused in clinical practice. Multiple tools have been developed or are under development in order to reduce the invasiveness, cost, and extra procedural time associated with the invasive assessment of coronary physiology. Besides epicardial stenosis, a growing body of evidence highlights the role of coronary microcirculation in regulating coronary flow with consequent pathophysiological and clinical and prognostic implications. Adequate assessment of coronary microcirculation function and integrity has then become another component of the decision-making algorithm for optimal diagnosis and treatment of coronary syndromes.

This review aims at providing a comprehensive description of tools and techniques currently available in the catheterization laboratory to obtain a thorough and complete functional assessment of the entire coronary tree (both for the epicardial and microvascular compartments).

Keywords: Coronary physiology, myocardial revascularization, functional assessment, percutaneous coronary intervention, ischemic heart disease, microvascular dysfunction.

1. INTRODUCTION

The study of coronary physiology refers to the assessment of laws and mechanisms regulating coronary circulation with the ultimate practical clinical application of identifying myocardial ischemia secondary to an anatomical and/or functional impairment of either the epicardial and/or of the microvascular compartment. The measurement and/or the development of indices and parameters of coronary physiology have been clinically validated over the last two decades, proving to be highly valuable in guiding and optimising myocardial revascularization. The present review aims to provide a compendium of the available evidence about concepts of coronary physiology applied in clinical practice within the Catheterization Laboratory (Figs. **1** and **2**).

1.1. Overview on the Development and Validation of Major Indices of Coronary Physiology for the Assessment of the Coronary Epicardial Segment

1.1.1. Fractional Flow Reserve

One of the main concepts in the assessment of coronary physiology comes from the landmark studies by Lance Gould and colleagues, who firstly demonstrated in the animal model the relationship between the degree of diameter stenosis induced by a micromanometer occluder and the reduction of maximal achievable coronary flow (expressed as Coronary Flow Reserve (CFR)) [1]. However, it soon became evident that the correlation between anatomy and function was suboptimal and not accurate enough to be the sole method to guide revascularization in clinical practice [2].

The first explanation for this discrepancy between the anatomical degree of stenosis and coronary flow reduction, relied on the substantial difference between animal models where "exact" coronary stenosis was obtained through the application of calipers on the artery and clinical studies in man where the percentage of diameter stenosis was determined on a coronary angiogram image, that may be ambiguous due to the poor spatial resolution and due to the "two-dimensional" nature of the technique. Besides the degree of stenosis, lesion length, plaque composition and location, the presence of diffuse atherosclerosis represents all elements to be taken into account since all contribute to defining the functional impact of coronary stenosis.

Due to these limitations, there has been early interest in developing techniques and tools to allow a more direct assessment of changes in coronary flow secondary to progression of coronary atherosclerosis with the ultimate aim to better identify myocardial ischaemia and guide indication for revascularization.

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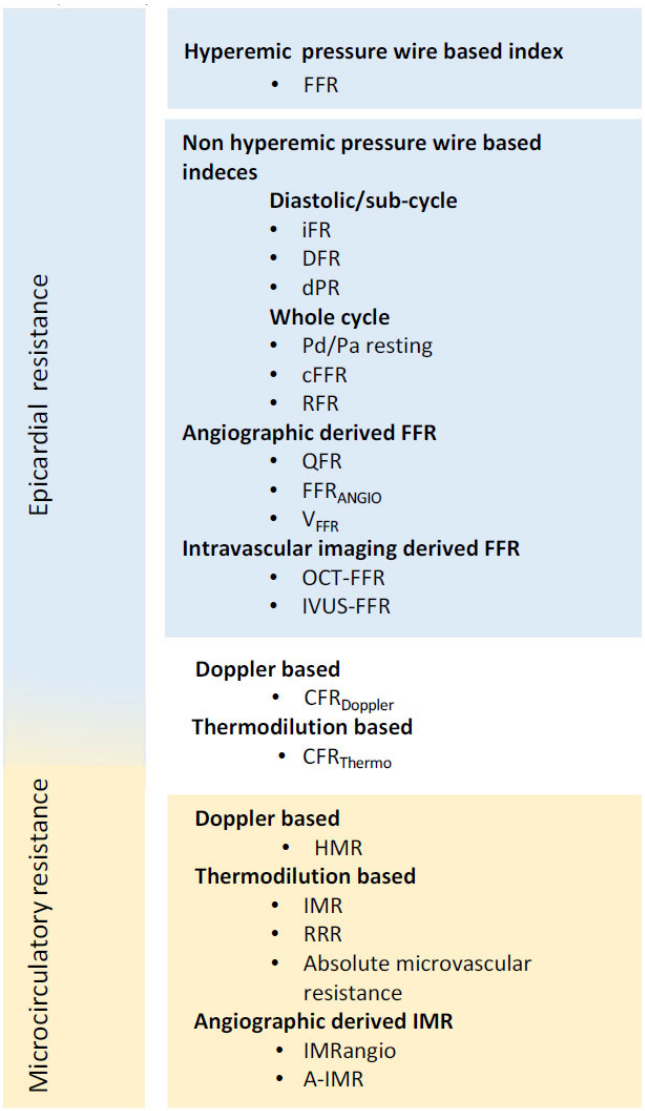


Fig. (1). Tools for the assessment of epicardial and microvascular resistance in the Catheterization laboratory.
Abbreviations: CFR, Coronary Flow Reserve; cFFR, contrast FFR; DFR, diastolic hyperaemia-free ratio; dPR, diastolic pressure ratio; FFR, Fractional Flow Reserve; FFRangio angiography-derived FFR; HMR hyperaemic microvascular resistance index; iFR, instantaneous wave-free ratio; IMR, Index of Microcirculatory Resistance; IMRangio, angiography-derived index of microcirculatory resistance; A-IMR, Angio-based Index of Microcirculatory Resistance, IVUS-FFR, Intravascular Ultrasound derived FFR; OCT-FFR, Optical Coherence Tomography derived FFR; Pa, aortic pressure; Pd, distal pressure; QFR, Quantitative Flow Ratio; RFR, Resting Full-cycle Ratio; RRR, Resistive Reserve Ratio; vFFR, virtual FFR. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The first attempt to implement coronary physiology assessment in the clinical practice was right at the time of the first percutaneous coronary intervention (PCI) in 1977 by Gruentzig, who firstly described a translesional pressure gradient. The first balloon catheter presented a dedicated internal lumen to allow measurement of coronary pressure across the stenosis. This allowed to report a correlation between the reduction in angiographic stenosis and the pressure gradient across the stenosis following angioplasty [3].

In the early 1990's, a new miniaturized, solid-state sensor mounted on a 0.014"-inch guidewire ("pressure-wire") became available, enabling reliable coronary pressure measurements across given coronary stenosis [4]. The pivotal work by Pijls and De Bruyne focused on the ratio of aortic and distal coronary pressures during hyperaemia, thus introducing an index defined as fractional flow reserve (FFR) [5, 6]. FFR was defined as the maximum achievable myocardial blood flow in the presence of coronary artery stenosis expressed as a percentage of the maximum blood flow in the absence of the stenosis under investigation. Direct measurement of coronary flow was (and still remains) methodologically and logistically complex. However, the work by Pjils *et al.* showed that when microcirculatory resistance is minimal and constant (such as during maximal hyperaemia), the coronary flow becomes proportional to pressure. Since pressure is easily measurable thanks to pressure-wire adoption, then FFR (ratio of flows) can be calculated as a ratio of two driving pressures across the stenosis during maximal hyperaemia.

$$FFR = \frac{P_d - P_v}{P_a - P_v}$$

Where P_d represents the coronary pressure distal to the stenosis; P_a, the aortic pressure, and P_v the mean right atrial pressure (venous pressure), since right atrial pressure is usually low and trending to zero in the majority of cases, the calculation of FFR in clinical practice can be simplified as the ratio of mean distal coronary pressure and mean aortic pressure at maximum hyperaemia [7].

$$FFR = \frac{P_d}{P_a}$$

After the publication of the theoretical principles, the method was then validated using a prospective multi-testing Bayesian approach, and an FFR threshold value of 0.75 was identified to be associated with evidence of myocardial ischaemia on non-invasive stress tests, high sensitivity and specificity [8]. During the following 15 years, three multicenter, randomized, landmark trials have tested the hypothesis of an FFR-based approach to guide revascularization in Coronary Artery Disease (CAD), as summarised in Table **1**. The Percutaneous Coronary Intervention of Functionally Non-significant Stenosis (DEFER) trial included 325 patients scheduled for PCI of intermediate stenosis and showed that deferral of PCI on functionally non-significant stenosis (FFR $\geq$ 0.75) was associated with a favourable outcome without signs of late 'catch-up' phenomenon up to fifteen-year follow-up [9, 10]. The Fractional Flow Reserve *Versus* Angiography for Multivessel Evaluation (FAME I) trial included 1005 patients with multivessel coronary artery disease and demonstrated that FFR-guided PCI using a cut-off value of 0.80 significantly reduced the rate of the com-

posite endpoint of death, non-fatal myocardial infarction (MI), and repeat revascularization compared to an angiography-guided approach, up to five-year follow-up (relative risk 0,91, 95% confidence interval (CI): 0,75-1,10; p=0,31) [11-13]. The Fractional Flow Reserve *Versus* Angiography for Multivessel Evaluation 2 (FAME II) trial included 888 patients with stable CAD, who had at least one stenosis in a major coronary artery with an FFR ≤ 0.80 who were randomly assigned to an FFR-guided PCI strategy plus optimal medical therapy *versus* optimal medical therapy alone. The enrolment of the study was halted prematurely because of an excess of urgent revascularization events in the medical therapy alone group [14], and the advantage of FFR-guided PCI over medical therapy alone was maintained at 3 and 5 years [15, 16].

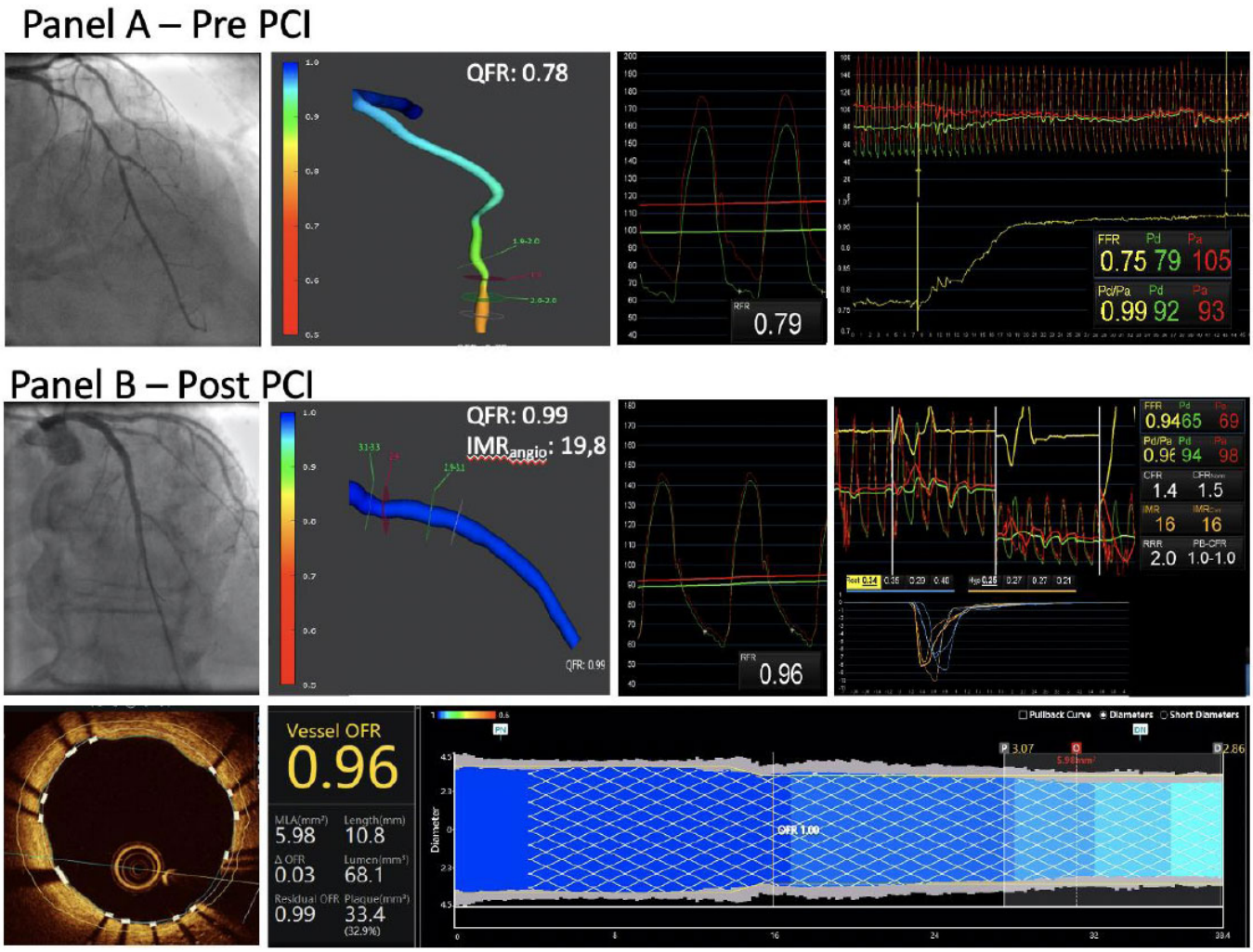


Fig. (2). Explanatory case of comprehensive physiological assessment of both the epicardial and microvascular resistance obtained by different complementary tools in the catheterization laboratory.

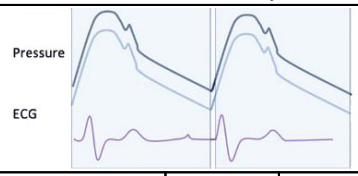
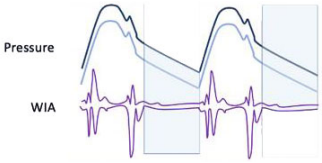
In Panel A from left to right is represented the physiological assessment of an angiographic intermediate stenosis on the mid segment of the LAD with different approaches; 3D quantitative coronary analysis and subsequent QFR computation was 0,78); Resting full cycle ratio (RFR), a non-hyperaemic full cycle pressure-wire based index, was 0,79; hyperemic FFR pull-back confirmed a significant step up located in the mid segment of LAD.

In Panel B the previous measurements were repeated after PCI: QFR was 0.99, RFR was 0.96 and FFR was 0.96 suggesting non-significant residual ischemia. Optical coherence tomography of the LAD was performed in order to assess the post stenting result and the computed optical flow ratio (OFR) derived from 3-dimensional reconstructed artery was 0.96.

Microvascular assessment was also performed after PCI measured by thermodilution and derived from angiography: Coronary Flow Reserve (CFRthermo) was 1,4; Index of microcirculatory resistance (IMR) was 16 and RRR was 2. Based on QFR computation IMRangio was 19,8.

Abbreviations: LAD, Left Descending anterior artery; QFR, Quantitative Flow Ratio; RFR, Resting Full cycle Ratio; FFR, Fractional Flow Reserve; PCI, Percutaneous Coronary Intervention; OFR; Optical Flow Ratio; CFR, Coronary Flow Reserve, IMR_{angio}, angiography derived index of microcirculatory resistance. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Comparison between FFR and iFR and milestone validating studies.

FFR				iFR			
Pressure Wire Based							
Hyperaemic Index				Non Hyperaemic Index			
Whole Cycle				Diastolic Wave-free Period			
 $FFR = \frac{P_d}{P_a}$				 $iFR = \frac{P_d}{P_a}$			
Trial	n° Patients; Clinical Syndrome	FFR Cut-off	Main Finding	Trial	n° Patients; Clinical Syndrome	iFR cut-off	Main Finding
DEFER trial	325; stable CAD	0,75	Safety of deferral PCI in intermediate stenosis up to 15 yr.	DEFINE-FLAIR	2,492; stable CAD and ACS	0,89	Non inferiority compared to FFR in terms of MACE at 1 yr
FAME I	1,005; MVD	0,80	FRR-guided revascularization superior to angio-guided PCI in terms con MACE up to 5 yr	iFR SWEDEHEART	2,037; stable CAD and ACS	0,89	Non inferiority compared to FFR in terms of MACE at 1 yr
FAME II	888; stable CAD	0,80	FRR guided-PCI superior to medical therapy alone in presence of FFR < 0,80				

Abbreviations: CAD, coronary artery disease; FFR Fractional Flow Reserve; iFR, instantaneous Wave-Free Ratio; ECG, Electrocardiogram; MACE, Major Adverse Cardiac Events; PCI, Percutaneous Coronary Intervention; Pa, aortic Pressure; Pd, distal Pressure; yr, years; WIA, Wave Intensity Analysis. DEFER, Percutaneous Coronary Intervention of Functionally Non significant Stenosis (9); FAME I, Fractional Flow Reserve *Versus* Angiography for Multivessel Evaluation (12); FAME II, Fractional Flow Reserve *Versus* Angiography for Multivessel Evaluation 2 (15);DEFINE-FLAIR, Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (41); iFR SWEDEHEART, Evaluation of iFR *vs* FFR in Stable Angina or Acute Coronary Syndrome (42).

Even though FFR was initially interpreted as a binary index with a fixed cut-off validated against non-invasive stress tests, studies that followed have revealed that FFR behaves as a continuous variable that enables to grade the severity of myocardial ischemia, tracking the risk of adverse outcomes. In a study-level and patient-level meta-analysis including up to 9173 patients, Johnson *et al.* showed that the risk of a clinical event was inversely proportional to the value of the FFR [17]. Moreover, the authors showed that FFR can represent a post-revascularization target to achieve [17]. At near normal (high) FFR values, event rates are the lowest, and the risk of revascularization, either with PCI or CABG, offers no net benefit or even harm. In contrast, at lower FFR values, event rate increases, and revascularization provides growing benefits. Similar findings were confirmed by Barbato *et al.* in a prespecified subanalysis of the FAME II trial and by Ahn *et al.* in the Interventional Cardiology Research In-cooperation Society Fractional Flow Reserve (IRIS-FFR) registry) [18, 19]. Nishi *et al.* found that even the benefit of PCI in terms of improvement of quality of life, measured by the assessed by the European Quality of Life–5 Dimensions index, was related to the FFR value [20]. Notably, quality of life improved significantly after PCI in each abnormal FFR tertile, whereas it did not change in the reference group (FFR>0.80). The subgroup of patients in the lowest FFR tertile had the greatest improvement in the quality of life at 1 month (P<0.001) after revascularization [20].

In recent years, real-world studies have further confirmed the advantages of FFR-guided revascularization in clinical practice and also across different cohorts of high-risk patients, frequently excluded or underrepresented in previous clinical trials.

Diabetic patients have an acknowledged higher cardiovascular risk compared to non-diabetic patients [21, 22], nevertheless only a relatively small proportion of diabetic patients have been included in the landmark trials on FFR (11.3% in DEFER, 24.7% in FAME and 27.0% in FAME 2) [10, 11, 14]. Due to the high prevalence of microvascular dysfunction in the diabetic population, concerns about the achievement of maximal hyperaemia have indeed cast doubts on the reliability of FFR in this cohort [23]. Despite this theoretical consideration, a large cross-sectional study including 1983 patients, of whom 701 diabetics, has recently encouraged the use of FFR even in this cohort [24]. Data from the PRIME-FFR (POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French Study of FFR Integrated Multicenter Registries–Implementation of FFR in Routine Practice]) joint international prospective study have shown that routine use of FFR was associated with a reclassification of clinical management in a significant proportion of cases compared to angiography guided strategy and a treatment plan guided by FFR was associated with good clinical outcome in diabetic patients [24].

Chronic Kidney Disease (CKD) is another vastly underrepresented population in large trials (2.2% in FAME 2, rate not reported in DEFER and FAME) [13]. Similar to diabetic patients, CKD increases cardiovascular risk and impairs microcirculation. Even though no prospective randomized data are available on this cohort of patients, Alkhalil *et al.* have

shown that the risk of myocardial infarction and urgent revascularization were comparable in patients undergoing physiology assessment and stratified according to their renal function status [25].

The role of FFR has been proven to be effective also in patients with reduced ejection fraction. Despite the calculation of FFR in the presence of systolic dysfunction should theoretically take into account mean right atrial pressure (Pv), Toth *et al.* have shown that its measurement has a negligible clinical impact even in the presence of markedly increase values, making the simplified FFR (hyperaemic P_d/P_a) reliable also in this cohort of patients [26]. Despite the lack of prospective data, an FFR-guided revascularization strategy is associated with lower rates of death (hazard ratio (HR) 0.64, 95% CI: 0.51–0.81; $p < 0.001$) and major adverse cardiovascular and cerebrovascular events at 5 years (HR 0.81, 95% CI 0.67–0.97; $p = 0.019$) compared with the angiography-guided strategy in a patient with reduced ejection fraction [27].

Based on contemporary evidence, the European Society of Cardiology guidelines recommend a physiology-guided assessment to guide myocardial revascularization in patients with stable angina symptoms lacking a pre-angiogram non-invasive ischaemia-test (Class of recommendation I, Level of evidence A), or in those with multivessel disease (Class of recommendation IIa, Level of evidence B) [28]. The latest American College of Cardiology/American Heart Association guidelines have given a Class IA recommendation for revascularization of functionally significant coronary stenosis, and a Class IIA recommendation for the use of FFR to assess angiographic intermediate coronary stenosis [29, 30].

However, despite these recommendations and the accumulating amount of evidence supporting physiology-guided revascularization over angiographic guidance alone, FFR remains underused in routine clinical practice worldwide. The rate of FFR utilization in the real-world setting ranges from 3% to 30%, depending on geographical areas, countries and operators [31-35]. A recently published retrospective study collecting data from 17989 patients with stable CAD and angiographically intermediate stenoses reported a low yet increasing uptake of FFR in clinical practice from 2009 to 2019, going from 14.8% to 18.5% among cases with intermediate lesions, and from 44% to 75% across all cases undergoing PCI [36]. Reasons explaining the slow uptake of FFR in clinical practice include the operator's confidence in angiographic data, increased procedural time and costs related to pressure-wire adoption, lack of reimbursement and patient's discomfort or symptoms associated with the infusion of adenosine necessary to achieve hyperaemia [37]. However, a web-based survey has shown that even after removing all logistical barriers, operators only selected FFR in 21% of cases and made an angiographic-guided decision in 71% [38]. In order to facilitate the diffusion of coronary physiology guidance in clinical practice, new lines of research have started to investigate and develop novel indices with the ultimate aim of simplifying the functional assessment of coronary stenosis.

1.1.2. Non-hyperaemic Pressure-wire-based Indices

1.1.2.1. Instantaneous Wave-free Ratio

The landscape of physiologic assessment of coronary ischemia has been enriched over recent years by the introduction of instantaneous wave-free ratio (iFR), which is an invasive, resting (non-hyperaemic/adenosine-free) index. iFR is defined as the instantaneous pressure ratio of distal coronary and aortic pressures (Pd/Pa) measured during the so-called "wave-free" period in resting conditions. Based on wave intensity analysis theory applied to coronary circulation, a wave-free period has been identified as a time window within the cardiac cycle occurring in diastole, when intracoronary pressure and coronary flow decline together in a linear fashion and when microvascular resistances are stable and minimal [39]. This corresponds to a phase of the cardiac cycle with an absence of expansion and/or compression waves typically associated with heart contraction and relaxation. The potential advantage of iFR over FFR assessment is its independence from hyperaemic medications, with consequent increased patient comfort, and reduced procedural time and costs, as summarised in Table **1**. In addition, the iFR-software (SyncVision, Philips/Volcano, Amsterdam, the Netherlands) allows real-time integration with coronary angiogram with co-registration of the iFR values onto the angiogram during pullback [40].

The clinical value of iFR has been well demonstrated by the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) and iFR SWEDEHEART (Evaluation of iFR *vs* FFR in Stable Angina or Acute Coronary Syndrome) trials [41, 42]. The DEFINE-FLAIR randomized 2,492 patients with stable angina or an acute coronary syndrome (ACS) and with intermediate coronary stenosis to iFR-guided revascularization (using a cut-off value of 0.89) and to FFR-guided revascularization (using a cut-off value of 0.80). iFR guidance was showed to be non-inferior to FFR in terms of the rate of the composite endpoint of death from any cause, non-fatal MI, or unplanned revascularization at 1 year. Similar results were observed in the iFR SWEDEHEART trial randomising 2,037 patients to an iFR-guided revascularization strategy compared to an FFR-guided revascularization strategy. Both studies highlighted that the rate of adverse procedural signs and symptoms was lower, and the procedural time was shorter with iFR than with FFR. A pooled patient-level meta-analysis including per-protocol population (n = 4,486) of the DEFINE-FLAIR and iFR-SWEDEHEART confirmed that deferral of revascularization is equally safe with both iFR and FFR, with a low rate of major adverse cardiovascular events (MACE) of about 4% [43]. Although the non-inferiority of iFR compared to FFR, up to 20% of lesions present discordant values between the two metrics (Fig. **3**). The prospective multicenter CONTRAST study comparing iFR and FFR in 466 patients, found a negative discordance (FFR+/iFR-) in 69 (11.8%) patients and a positive discordance (FFR-/iFR+) in 52 (8.9%) patients [44]. On multivariate regression, stenosis location (left main or proximal left anterior descending) (OR: 3.30[1.68;6.47]), more severe degree of

stenosis (OR: 1.77[1.35;2.30]), younger age (OR: 0.93 [0.90;0.97]), and slower heart rate (OR: 0.59[0.42;0.75]) were predictors of a negative discordance between FFR and iFR. Absence of a beta-blocker (OR: 0.41 [0.22;0.78]), older age (OR: 1.04[1.00;1.07]), and less severe degree of stenosis (OR: 0.69[0.53;0.89]) were predictors of a positive discordance [44]. What is the long-term clinical outcome of patients with discordant iFR and FFR remains still unclear and clinical management is also debated.

1.1.2.2. Novel Non-hyperaemic Pressure-wire-based Indices

Besides iFR, a number of novel non-hyperaemic pressure-wire-based indices have been developed. All these novel indices measure the ratio between distal coronary pressure and aortic pressure but differ on the phase of the cardiac cycle in which measurement takes place so that they can be grouped in phase-specific indices, *versus* whole-cycle indices, as shown in Table **2** [45]. A brief description of each index will be presented below, but it is important to consider that all the current non-hyperaemic pressure ratios have less validation than FFR, having all been tested in relatively small-sized non-inferiority studies enrolling relatively low-risk cohorts of patients.

1.1.2.3. Phase Specific Indices

Diastolic hyperaemia-free ratio (DFR, Boston Scientific, Marlborough, MA) provides a resting index derived from the average Pd/Pa during the period that occurs when instantaneous Pa is less than the mean Pa, and there is a down-sloping Pa. The resultant value is based on a 5-beat average. The proposed ischemic cut-off for DFR is ≤0.89.

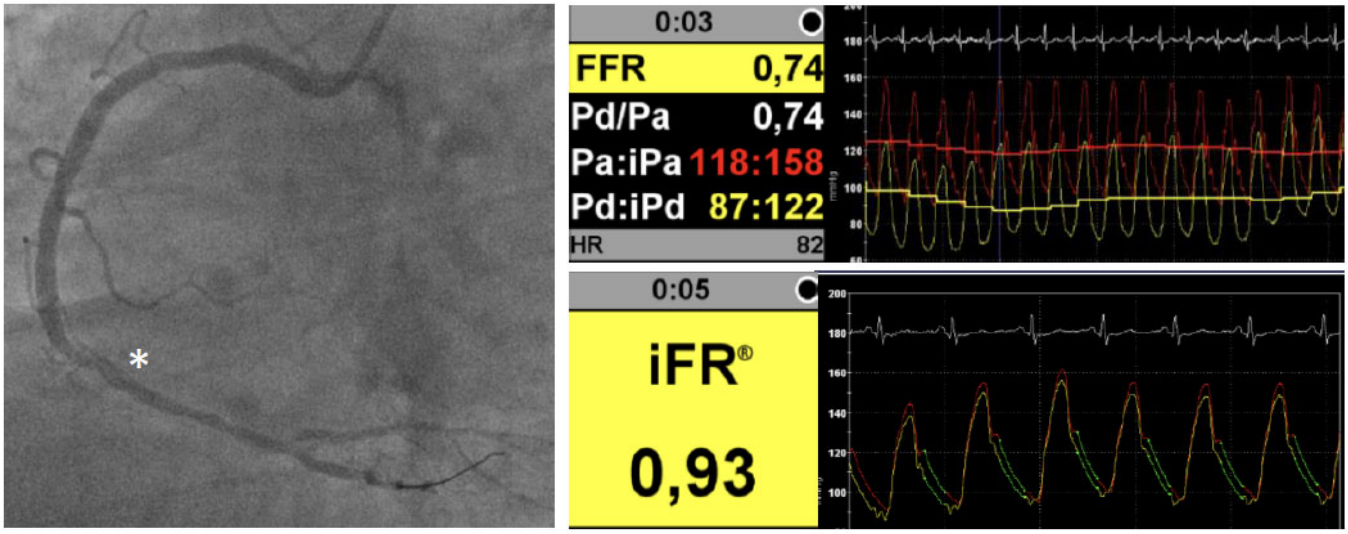


Fig. (3). Case example of disagreement between iFR and FFR.
Coronary angiogram of a 55-year old gentleman presenting with stable angina, showing a moderate lesion on the distal segment of the right coronary artery (asterisk). Invasive pressure-wire assessment was performed both in resting condition using iFR and hyperaemia using FFR. Discordant values were obtained: iFR was 0,93, above the ischemic threshold; FFR was 0,74, suggesting myocardial ischemia. Based on clinical presentation, angioplasty was performed. During follow-up, no further recurrence of symptoms was reported.
Abbreviations: iFR, instantaneous wave Free Ratio; FFR, Fractional Flow Reserve. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Novel adenosine-free, pressure wire-based indices.

-	-	Cut-off	Non Hyperaemic	Procedural Time	Patient Disconfort	Randomized Control Trial
Phase specific	iFR	0,89	Yes	Low	Low	Yes
	dFR	0,89	Yes	Low	Low	No
	dPR	0,89	Yes	Low	Low	No
Whole cycle	Pd/Pa resting	0,92	Yes	Low	Low	No
	cFFR	0,84 – 0,88	No	Low	Low	No
	RFR	0,89	Yes	Low	Low	No

Abbreviations: cFFR, contrast FFR; DFR, Diastolic hyperaemia-Free Ratio; dPR, diastolic Pressure Ratio; iFR, instantaneous wave-Free Ratio; Pa, aortic Pressure; Pd, distal Pressure; RFR, Resting Full-cycle Ratio.

Diastolic Pressure Ratio (dPR) equals the resting ratio of mean diastolic pressure distal to the stenosis to the mean diastolic aortic pressure. When using iFR as the reference standard, dPR has been shown to have numerical equivalence [46].

1.1.2.4. Whole Cardiac Cycle Indices

Resting Pd/Pa ratio is calculated over the entire cardiac cycle and equals the ratio of the mean (non-instantaneous) Pd and Pa over the entire cardiac cycle. Although the lack of a unique and validated ischemic threshold, a cut-off of 0.92 for resting Pd/Pa has most often been considered in clinical studies [47].

Contrast FFR (cFFR) is the lowest mean (non-instantaneous) Pd/Pa value obtained after intracoronary injection of a standard dose of radiographic contrast medium. RINASCI (Rapid Injection of Contrast Medium *vs.* Nitroprusside or Adenosine in Intermediate Coronary Ste-noses), MEMENTO-FFR (The Multi-Center Evaluation of the Accuracy of the Contrast Medium Induced Pd/Pa Ratio in Predicting FFR), and CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) studies clearly reported the ability of cFFR to predicting FFR values in intermediate coronary stenosis [48-50]. A cut-off of 0.83 for cFFR has been proposed for the best prediction of FFR. Furthermore, at a cut-off of 0.83, cFFR was more accurate than resting Pd/Pa (cut-off of 0.92) and iFR (cut-off of 0.90) in predicting FFR. In a retrospective cohort of 488 patients who underwent FFR guided revascularization, Leone *et al.* have recently reported good accuracy between cFFR and FFR. In the rare case of discordance, there was no significant difference in terms of outcomes up to a 2-year follow-up. Interestingly, patients with FFR > 0.80 and cFFR ≤ 0.85 showed a higher rate of target vessel revascularization compared to the group with FFR > 0.80 and cFFR > 0.85 (5.7% *vs* 16.0%; p = 0.027 [51].

Resting full-cycle ratio (RFR) seeks the lowest instantaneous Pd/Pa ratio within the entire cardiac cycle. A minimum of five consecutive heart cycles is needed to determine the RFR. The RFR index was derived and validated for the first time in the retrospective VALIDATE-RFR study with an optimal RFR cut-off of 0.89 to predict a positive FFR [52]. RFR was highly correlated to iFR (R^2=0.99, P<0.001), with a diagnostic accuracy of 97.4%, sensitivity of 98.2%, specificity of 96.9%, positive predictive value of 94.5%, negative predictive value of 99.0%.

1.1.3. Angiography Derived Indices

Another step into the simplification of physiological assessment has been the development of angiography-based indices, which estimate FFR using computational flow-dynamics techniques or simplified mathematical algorithms applied to three-dimensional modelling of the target vessel derived from standard coronary angiogram images, as summarised in Fig. **(1)**. Angiography-based indices allow coronary physiology assessment without the use of intracoronary wires and can potentially reduce costs, risks and procedural time compared to pressure-wire-based techniques. Different software solutions have been developed and validated against invasive FFR, including Quantitative Flow Ratio (QFR), Vessel Fractional Flow Reserve (vFFR) and Fractional Flow Reserve Derived From Coronary Angiography (FFR_{angio}).

QFR (QangioXA-3D prototype, Medis, Leiden, the Netherlands) is an angiography-based index that applies mathematical algorithms to a three-dimensional model of the vessel derived from two angiographic views and uses thrombolysis in myocardial infarction (TIMI) frame count as the surrogate marker of coronary blood flow to derive the trans-lesional pressure ratio (Fig. **4**) [53-56]. The prospective, observational, multicenter FAVOR Pilot Study (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis), compared QFR and FFR in 84 vessels in 73 patients, demonstrating a superior diagnostic accuracy compared to 3-dimensional quantitative coronary angiography in predicting the functional significance of stenosis (using FFR as a reference) [53]. Moreover, contrast-flow derived QFR (cQFR) showed similar diagnostic accuracy to QFR during adenosine infusion (aQFR), thus allowing to consider adenosine-free QFR (namely cQFR) as a valid and more user-friendly alternative [53]. The preliminary data of the FAVOR pilot study were further expanded in the FAVOR II E-J (Functional Assessment by Various Flow Reconstructions II Europe□Japan) study [54], in the FAVOR II China (Functional Assessment by Various Flow Reconstructions II China) [55]. A meta-analysis of these three studies has confirmed the good accuracy of QFR in predicting FFR [56]. For the first time, the FAVOR III Europe-Japan study will compare the outcome between a QFR-based strategy *versus* an FFR-based strategy in patients with stable angina pectoris or need for evaluation of non-culprit lesions after acute myocardial infarction (MI) (Clinical Trial: NCT03729739).

vFFR (Pie Medical Imaging, Maastricht, the Netherlands) builds a 3D reconstruction of a coronary artery based on 2 standard X-ray angiograms and assesses the pressure drop across the stenosis allowing to determine the vessel FFR value by using the invasively measured aortic root pressure (Fig. **5**). CAAS-vFFR has been validated by the FAST (Fast Assessment of STenosis Severity) study, an observational, single-center cohort study that enrolled 100 patients presenting with stable angina or non-ST-segment elevation MI and shown good correlation with invasive FFR (r=0,89, p < 0,001) [57]. The results were confirmed by the FAST I extended study, in which the authors increased the population up to 303 patients [58].

FFR_{angio} (CathWorks Ltd., Kfar Saba, Israel) allows a reconstruction of the entire coronary artery tree using two or three single plane angiographic views and the mean aortic pressure to calculate a virtual FFR mapping of the 3D-model. Based on a mathematical algorithm, the coronary arterial network is modeled as an electrical circuit with each segment acting as a resistor, the vessel resistance is estimated based on its length and diameter and each vessel's contribu-

tion to flow is based on its impact on overall resistance depending on the arrangement [59]. FFR_{angio} has been validated in a multi-center study enrolling 201 patients and that has showed a good correlation with invasive FFR (r=0,80, p < 0,001) [59].

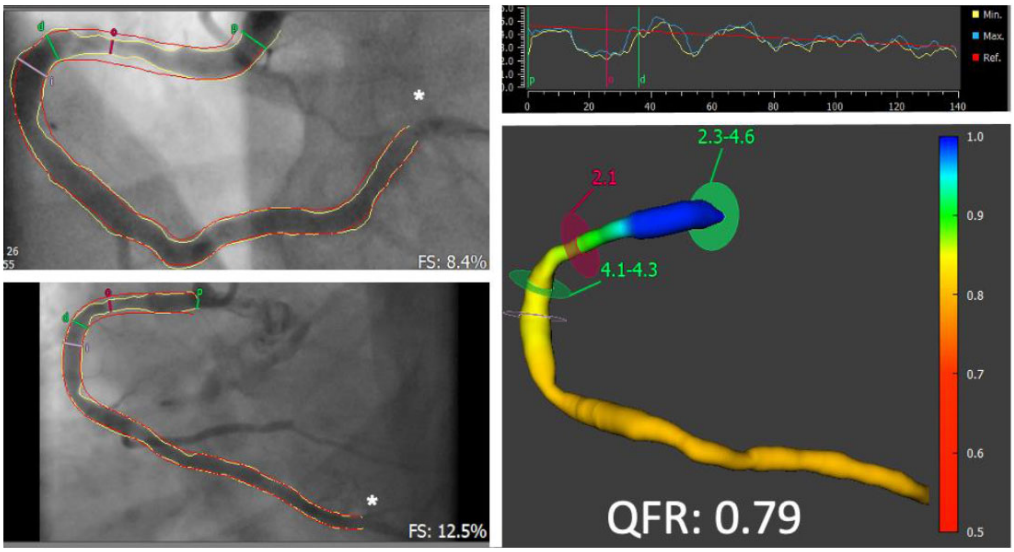


Fig. (4). Case example of Quantitative Flow Ratio (QFR). Coronary angiography shows a diffuse disease on the right coronary artery. FFR measured by pressure wire at asterisk was 0,75. Three-dimensional reconstruction of coronary artery and computation of QFR was 0,79.
Abbreviations: FFR, fractional flow reserve; FS indicates foreshortening; QFR, quantitative flow ratio. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

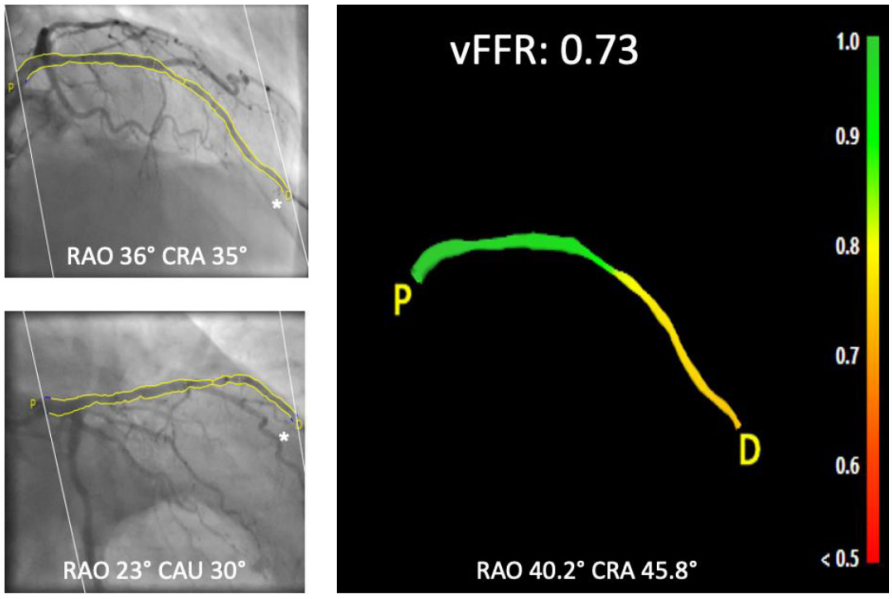


Fig. (5). Case example of vessel fractional flow reserve (vFFR). Coronary angiography shows a left anterior descending lesion. FFR measured by pressure wire at asterisk was 0.72. Three-dimensional reconstruction of coronary artery and computation of vFFR, using 2 angiographic projection with at least 30 degrees apart and invasively measured aortic root pressure showed a value of 0.73.
Abbreviations: FFR, fractional flow reserve; vFFR, vessel fractional flow reserve; CRA indicates cranial, CAU indicates caudal, RAO, right anterior oblique; and RAO, right anterior oblique. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The development of angiography-based physiology software has the potential to routinely offer functional data together with coronary anatomy limiting invasiveness. However, at present, the adoption of this software is still mainly available for research, but clinical trials are ongoing to ascertain their suitability in guiding clinical decision-making.

1.1.4. Intracoronary Imaging Derived Indices

These methods rely on computational flow dynamic applied to a three-dimensional model of the target vessel obtained from intra coronary imaging modalities, both Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT), to ultimately derive the functional assessment of the target coronary stenosis.

The application of computational flow dynamics to intracoronary imaging may overcome the main limitations of angiographic-based indices. High vessel tortuosity, vessel overlapping on a selected angiographic view, or presence of ostial lesions are all elements affecting the feasibility and reliability of angiography-derived indices.

One of the upcoming solutions for OCT-based FFR, under the acronym of OFR (Optical Flow Ratio; OctPlus, Pulse Medical Imaging Technology, Shanghai, China), has been recently validated against pressure wire FFR. In the optical flow ratio, the lumen contour is automatically delineated from the OCT image pullback, and a 3D reconstruction of the coronary lumen is performed (Fig. **6**). The optical flow ratio has showed high diagnostic accuracy (92%) in predicting FFR ≤ 0.80 in 212 vessels from 181 patients [60] . Optical flow ratio computation required only 55±23 seconds with low interobserver and interobserver variability (0.00±0.02 and 0.00±0.03, respectively) [61].

UFR (Ultrasonic Flow Ratio, IvusPlus prototype, Pulse Medical Imaging Technology, Shanghai, China) has been recently described as a novel method to compute FFR using IVUS image pullback. Vessel segmentation is derived from IVUS image using an automatic artificial intelligence-based algorithm; applying a validated computational FFR method based on fluid dynamic equations, UFR value is obtained. UFR showed strong correlation with FFR (r=0.87; P<0.001) and high diagnostic accuracy (92%, (95% CI: 87–96) in predicting FFR ≤ 0.80 in 167 vessels from 94 patients [62]. Median UFR analysis time was 102 seconds (interquartile range, 87–122 with low interobserver and interobserver variability (0.00±0.02 and 0.00±0.03, respectively) [62].

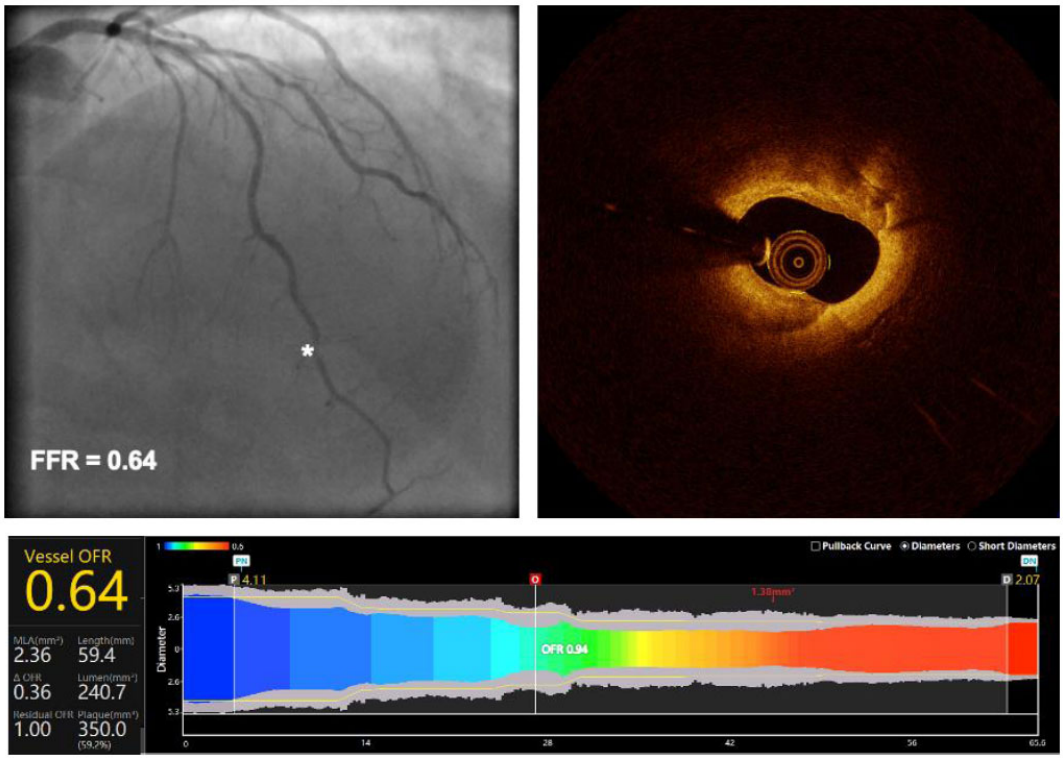


Fig. (6). Case example of optical flow ratio (OFR). Coronary angiography shows a left anterior descending lesion with a minimal lumen area (MLA) by OCT of 2.36 mm2. FFR measured by pressure wire at asterisk was 0,64. The computed optical flow ratio (OFR) value was 0,64, which was color-coded and superimposed on the 3-dimensional reconstructed artery (OctPlus v. 2.0, Pulse medical imaging technology.
Abbreviations: FFR, Fractional Flow Reserve; MLA, Minimal Lumen Area; OCT, Optical Coherence Tomography; OFR, Optical Flow Ratio. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

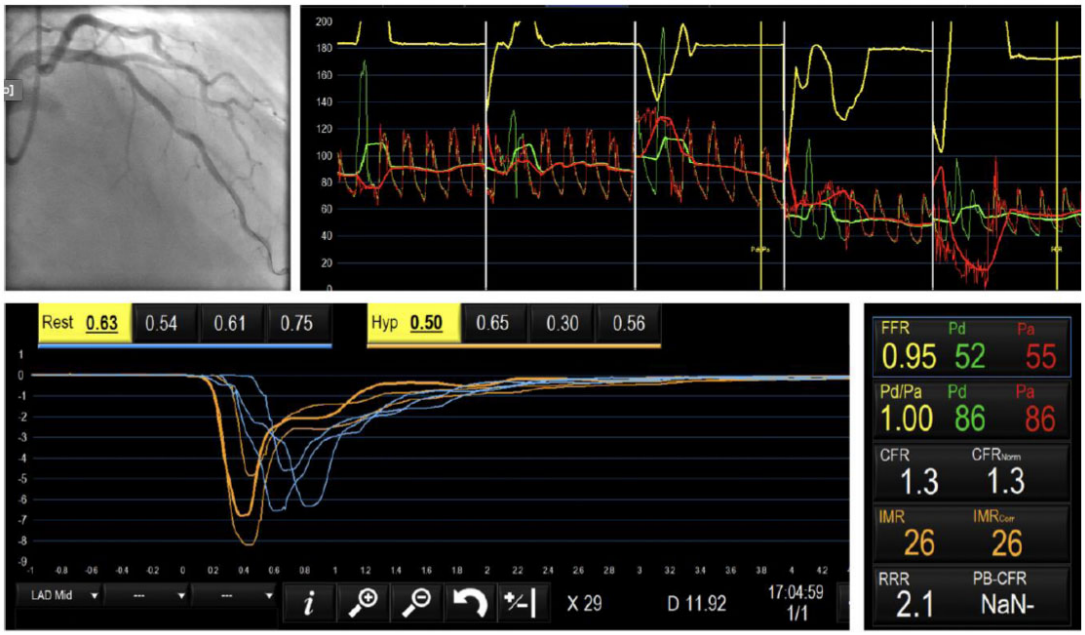


Fig. (7). Physiological assessment of microvascular resistance.
Explanatory case showing a comprehensive assessment of coronary physiology in a 55-year old lady complaining of chest pain.
Coronary angiogram revealed the presence of mild disease on the left anterior descending artery. Functional assessment of epicardial resistance assessed by FFR was inside normal range (FFR: 0.95). The assessment of microvascular compartment, performed using a pressure wire coupled with thermodilution, demonstrated the presence of increase microvascular resistance (IMR: 26, RRR 2.1) and a reduction of CFR (CFR 1.3). Microvascular angina was diagnosed, and appropriate therapy was started.
Abbreviations: CFR, Coronary Flow Reserve; FFR, Fractional Flow Reserve; IMR, Index of Microcirculatory Resistance; RRR, Resistive Reserve Ratio. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The integration of intracoronary imaging with physiological assessment appears certainly promising with likely improved accuracy of predicting adverse events outcome, especially in high-risk patients. Both OCT and IVUS imaging can indeed identify high-risk plaques, that may not necessarily be associated with inducible ischaemia at the time of assessment. The results of the COMBINE OCT-FFR trial, which enrolled 500 diabetic patients, has recently demonstrated that despite the lack of ischaemia, confirmed by a negative FFR assessment, the presence of thin cap fibroatheroma identified by OCT was a strong predictor of target-lesion-related MACE at 1.5-year follow up [63, 64]. On the other hand, the Prospective observational study using multimodality imaging (PROSPECT II) trial has recently demonstrated the ability of IVUS combined with near-infrared spectroscopy to identify plaques prone to future rupture and clinical events in 3629 untreated non-culprit lesions of patients with MI [65]. The integration of coronary physiology with intracoronary imaging and the possibility to directly derive the index of myocardial ischaemia from intravascular imaging techniques, may elucidate the complex relationship between the functional significance of stenosis and the anatomical morphology of the plaque offering the ultimate benefit of improving the prediction of future events, especially in patients with the high cardiovascular risk profile.

2. DEVELOPMENT AND VALIDATION OF INDICES OF CORONARY PHYSIOLOGY FOR THE ASSESSMENT OF CORONARY MICROCIRCULATION

Coronary microvasculature refers to the segment of coronary circulation with a vessel diameter less than 500 μm. Over the last years, coronary microcirculation has been identified as a key component of coronary physiology assessment and to be as important as the epicardial segment. An increasing body of evidence supports the role of assessment of coronary microvascular status in the clinical practice with the option of optimising medical and device-based therapies in clinical settings featured by a high degree of microvascular dysfunction or injury (such as ST-Elevation Myocardial Infarction (STEMI) or myocardial ischemia but no evidence of obstructive coronary artery disease (INOCA)).

Coronary Microvascular assessment is gaining more attention as a diagnostic tool and as a gatekeeper of therapeutic strategies in patients with INOCA [66-68]. According to the recently published ESC Guidelines for the diagnosis and management of chronic coronary syndromes, guidewire-based measurement of CFR and/or microcirculatory resistance should be considered (IIA recommendation) in patients with persistent symptoms of angina and with coronary arteries that are either angiographically normal or have moderate non-flow limiting stenoses (FFR > 0.80, iFR >0.90) [69] (Fig. **7**).

The role of microvascular assessment in this setting has been recently confirmed by the CORonary MICrovascular Angina (CorMicA) trial in which 151 patients with INOCA have been randomized to medical therapy guided by invasive assessment or standard care (sham procedure) (70). The intervention resulted in a mean improvement of 11.7 U in the Seattle Angina Questionnaire summary score at 6 months (95% CI: 5.0 to 18.4; p = 0.001) and led to improvements in the mean quality-of-life score (Seattle Angina Questionnaire, quality of life index 0.10 U; 95% CI: 0.01 to 0.18; p = 0.024) and visual analogue score (14.5 U; 95% CI: 7.8 to 21.3; p < 0.001) [70].

Accumulating evidence support the role of coronary microvascular as an important prognostic factor in patients with ST-Elevation Myocardial Infarction (STEMI). The extent of microvascular injury and dysfunction in the infarct-related artery territory could aid a thorough and objective risk stratification allowing triaging of additional and/or novel therapies on top of Primary Percutaneous Coronary Intervention (PPCI) [71-74].

3. TOOLS FOR THE ASSESSMENT OF CORONARY MICROCIRCULATION IN THE CATHETERIZATION LABORATORY

Due to technical and methodological constraints, *in vivo* and invasive assessment of the microcirculation in man remains primarily functional. The invasive techniques available in the catheterization laboratories for the functional assessment of microvascular resistance are still based on the implementation of a pressure wire and can be grouped into two main categories: Doppler-based techniques and thermodilution techniques.

4. INTRACORONARY DOPPLER-BASED TECHNIQUES

Doppler-based techniques are all derived from the application of Doppler-flow guidewire (FlowWire, Volcano). This is a 0.014" steerable guidewire with a tip-mounted 12 MHz ultrasound transducer that transmits and receives pulse-wave ultrasound signal generated by a piezoelectric transmitter [75]. Coronary flow velocity or Average Peak Velocity (APV) can then be measured at both resting conditions and after induction of hyperaemia. Notably, Doppler wire does not measure flow but the velocity of red cells flowing into the vessel. Assuming that luminal cross-section stays constant (Flow = Cross-section Area * Velocity), velocity becomes a surrogate of actual coronary flow [76]. The latest generation of Doppler flow wire (ComboWire, Volcano) also presents a pressure transducer 3 cm from the distal tip allowing simultaneous measurement of distal coronary flow velocity and distal coronary pressure. Two main parameters for the assessment of microvascular status can be derived by applying Doppler wire: 1) Doppler-derived Coronary Flow Reserve ($CFR_{Doppler}$), 2) Hyperaemic microvascular resistance index (HMR).

4.1. Doppler-derived Coronary Flow Reserve

Coronary flow reserve (CFR) is defined as the ratio between maximal and resting coronary blood flow. CFR evaluates the capacity of the whole coronary circulation to provide an increase in flow in response to increased metabolic demand. CFR takes into account both the epicardial and microvascular compartment, and it does not allow discrimination between these two components. A CFR value less than 2-2.5 is conventionally considered abnormal. Invasive CFR can be measured using intracoronary Doppler as the ratio between average peak velocity (APV) during hyperaemia and at rest:

$$CFR_{Doppler} = \frac{avarage\ peak\ velocity_{Hyperaemia}}{avarage\ peak\ velocity_{Rest}}$$

Even though a viable tool, $CFR_{Doppler}$ has several limitations when applied for the assessment of microvascular resistances. Firstly, since based on the measurement of resting APV, it is affected by baseline hemodynamic conditions, including arterial pressure and heart rate [77]. More importantly, $CFR_{Doppler}$ reflects the condition of the whole coronary tree, and for this reason, it is affected by the presence of residual epicardial disease offering only an indirect evaluation of coronary microvasculature.

4.2. Hyperaemic Microvascular Resistance Index (HMR)

To overcome $CFR_{Doppler}$ limitations when assessing specifically the microvascular compartment, the concept of hyperaemic microvascular resistance (HMR) has been introduced. HMR is defined as the ratio between distal coronary pressure and Doppler-derived average peak flow velocity during hyperaemia. HMR is expressed in mmHg/cm/s.

$$HMR = \frac{P_d}{Flow} = \frac{P_d}{Avarage\ peak\ velocity_{Hyperaemia}}$$

Hyperaemic microvascular resistance has been shown to be significantly related to the extent of infarct size, infarct transmurality [78] and long-term left ventricular remodelling [79] with a predictive power superior to $CFR_{Doppler}$. A direct correlation between post PCI elevated HMR and actual microvascular injury assessed by cardiac magnetic resonance (cMRI) has been described by Teunissen *et al*. with a cut-off of 2.5 mmHg/cm/sec presenting the best diagnostic accuracy. Notably, an elevated HMR was also related to a decreased myocardial flow in the culprit region, measured by H2 [15] O positron emission tomography [66]. De Waard *et al.* have reported an association between elevated post-procedural HMR (using a threshold of 3.0 mm Hg/cm/sec) and long-term clinical events, with HMR presenting a superior diagnostic accuracy compared to CFR [80]. The amount of data collected for HMR, however, remains still limited and for this reason, it is still most applied as a research tool.

5. THERMODILUTION-BASED TECHNIQUES

In 2001, De Bruyne *et al.*, introduced a new invasive method for the assessment of coronary microvascular func-

tion based on the principle of thermodilution. By using a temperature-sensor wire, the authors demonstrated that the mean transit time, defined as the time elapsed for the intracoronary temperature to drop to a minimum value and to rise back to the baseline value after the intracoronary injection of 3-5 mL of room temperature saline was inversely proportional to coronary flow [81, 82].

$$Coronary\ flow\ \approx \frac{1}{transit\ time}$$

Three main parameters based on the application of thermodilution have been developed to assess the microvascular status: 1) Thermodilution-derived Coronary Flow Reserve (CFR_{thermo}), 2) Index of microcirculatory resistance (IMR), 3) Absolute microvascular resistance.

5.1. Thermodilution-derived Coronary Flow Reserve

CFR_{thermo} can be calculated as the ratio between the mean transient time at rest and during hyperaemia.

$$CFR_{Thermodilution} = \frac{mean\ transient\ time_{Rest}}{mean\ transient\ time_{Hyperaemia}}$$

Barbato et. al validated CFR_{thermo} in 34 patients, demonstrating a good correlation with $CFR_{Doppler}$ r=0.79, P<0.0001) [83]. Even though $CFR_{Doppler}$ remains a more accurate index, as demonstrated by a significantly higher correlation with PET-derived CFR ($t = 4.9$; $df = 95$; $p < 0.001$) [84], however, obtaining high-quality Doppler analysis is technically challenging even in the hands of an expert operator, making CFR_{thermo} (and in general thermodilution-derived techniques) a more user-friendly tool for wider application in clinical practice. Post-procedural CFR_{thermo} has been demonstrated to predict function regional left ventricular recovery after MI [85]. Similarly, Cuculi *et al.* have shown that a lower CFR_{thermo} after PCI was associated with the occurrence of microvascular obstruction (MVO) on cMRI [86]. Interestingly, a persistent low CFR_{thermo} after 24 hours from revascularization procedure was shown to be associated with a higher degree of MVO and intramyocardial haemorrhage on cMRI and with a lower ejection fraction and with a lower degree of myocardial salvage at 6-month follow up [87]. When it comes to the assessment of the coronary microcirculation, CFR remains, however, a non-microvascular-specific index, been affected by the concomitant presence of disease in the epicardial segment and by resting haemodynamics [77].

5.2. Index of Microcirculatory Resistance

The Index of Microcirculatory Resistance (IMR) has been introduced in 2003 by Fearon *et al.* and provides a quantitative measure of minimal coronary microvascular resistance. As hyperaemic mean transit time is inversely correlated to absolute flow, in accordance with Ohm's law, IMR is defined as the distal coronary pressure multiplied by the mean transit time of a 3-5 ml bolus of room-temperature saline during maximal hyperaemia, achieved with intravenous adenosine infusion [88].

$$IMR = \frac{P_d}{Flow} = \frac{P_d}{\frac{1}{mean\ transient\ time_{Hyperaemia}}}$$

$$= P_d * mean\ transient\ time_{Hyperaemia}$$

IMR may be expressed as mmHg x s, or it can be reported in units. The present formula can be applied in the absence of significant coronary artery stenosis, when the collateral flow is negligible. However, in the presence of epicardial stenosis, IMR calculation would require incorporation of the coronary wedge pressure (P_w) measurement during balloon dilation limiting its feasibility in clinical practice.

$$IMR = P_a * mean\ transient\ time_{Hyperaemia} * \frac{P_d - P_w}{P_a - P_w}$$

Notably, at least in STEMI patients, De Maria *et al.* have shown a good correlation between measured pre-stenting IMR and pre-stenting coronary wedge pressure corrected-IMR (R: 0.95, $p < 0.001$). The former slightly overestimates coronary wedge pressure corrected-IMR by a degree of roughly 10%, meaning that the overestimation becomes significant for very elevated values of IMR, with limited practical implications [71]. Nevertheless, Yong *et al.* has proposed a revised formula to derive IMR in the presence of coronary artery stenosis, which does not require coronary wedge pressure [89].

$$IMR = P_a * mean\ transient\ time_{Hyperaemia} * \left(1.35 * \frac{P_d}{P_a}\right) - 0.32$$

A large body of evidence has confirmed that IMR is not influenced by systemic haemodynamic and is highly reproducible [83, 90, 91]. An IMR value ≤ 23 has been identified as an indicator of normal microvascular resistance based on subjects with or without evidence of atherosclerosis on coronary angiogram, or with minimal or no risk factors and normal stress tests [92, 93]. IMR at the completion of PPCI has been associated with the extent of MVO (rho=0.29, p=0.002) and infarct size both in the acute phase after STEMI (rho=0.21, p=0.03) and at the 6-months follow-up (rho=0.43, p=0.001) [94]. Importantly, in STEMI patients, post-PCI IMR ≥ 40 units are associated with a higher risk of mortality and readmission for heart failure (odds ratio, 4.36; 95% CI, 2.10-9.06; P<0.001) [95] and has good accuracy in predicting major in-hospital cardiac complications after PPCI (area under the curve 0.90; 95% CI, 0.85–0.93) [96].

5.3. Resistive Reserve Ratio (RRR)

The Resistive Reserve Ratio (RRR) is another index recently proposed and derived as the ratio between basal and hyperaemic microcirculatory resistance, and it describes the ability of the coronary microcirculation to dilate in response to a vasodilator agent, such as adenosine. RRR is calculated as the ratio between baseline to hyperaemic microcirculatory resistance as follows:

$$RRR = \frac{BMR}{IMR} = \frac{Baseline\ microcirculatory\ resistance}{Hyperaemic\ microcirculatory\ resistance}$$

RRR can be calculated by recording both distal pressure and transit times at rest and during hyperaemia. In the T-TIME trial (Trial of Low-Dose Adjunctive Alteplase During Primary PCI), which included 144 patients with STEMI, low RRR was associated with MVO extent (coefficient, −0.60 [95% CI, −0.97 to −0.23]; P=0.002), presence of myocardial haemorrhage (OR, 0.34 [95% CI, 0.15–0.75]; P=0.008), and larger infarct size (coefficient, −3.41 [95% CI, −6.76 to −0.06]; P=0.046) [97]. In addition, Scarsini *et al.* showed that post-PPCI impaired RRR was a main independent predictor of infarct size extension at 6 months [98].

5.4. Absolute coronary flow

In 2007, Aarnoudse *et al.* introduced a new technique based on the principle of thermodilution under continuous infusion of saline to directly measure absolute coronary flow and absolute myocardial resistance [99]. Using a suitable infusion catheter and a 0.014-inch temperature-sensor-tipped guidewire, absolute coronary blood flow can be calculated from the known infusion rate of saline (Qi), the temperature of the infused saline (Ti), and the temperature of blood mixed with saline distally to the infusion site (T) [99]. During steady-state hyperaemia, Q can be calculated as follows:

$$Absolute\ Flow = Q_i * \left(\frac{T_i}{T}\right) * 1{,}08$$

where 1.08 relates to the difference between the specific heats and densities of blood and saline.

Depending on the infusion rate of the saline, different grades of hyperaemic response can be achieved. Although the mechanisms are not fully understood, the saline infusion could determine hyperaemia by inducing transient hypoxia due to the replacement of oxygenated blood and by stimulating endothelial paracrine pathways [100]. More recently, in the animal model, it has been described that continuous thermodilution-mediated hyperaemia is related neither with the temperature nor with the composition of the infusion, nor with the function of the epicardial endothelium. It has instead proposed that vibrations of the epicardial wall exerted by the infused saline through the side-ports of the dedicated continuous-thermodilution microcatheter could be responsible for triggering microvascular dilation specifically in the territory depending on the stimulated epicardial artery [101]. Gallinoro *et al.* have recently shown that using an infusion rate of 8 to 10 mL/min, a stable thermodilution signal can be obtained without increasing flow as compared to baseline allowing the measurement of resting absolute coronary blood [102]. In contrast, an infusion of saline at a rate of 20 mL/min induces stable maximal hyperaemia allowing the measurement of hyperaemic absolute coronary blood [103]. Notably, continuous thermodilution allows the achievement of maximal hyperaemia without adenosine. The measurement of both hyperaemic and resting absolute coronary flow allows the calculation of CFR by continuous thermodilution. Moreover, in accordance with Ohm's Law, absolute microvascular resistance can then be calculated as the ratio between the distal pressure and the absolute coronary flow.

$$Absolute\ microvacular\ resistance = \frac{P_d}{Absolute\ Flow}$$

The measurement of both hyperaemic and resting absolute microvascular resistance allows the calculation of microvascular resistance reserve. The safety and feasibility of absolute microvascular resistance have recently been tested in patients with MI showing a correlation with IMR [104].

Absolute flow and resistance are still research tools, and few limitations should be taken into account. Absolute flow and resistance are linearly related to myocardial mass, which is markedly variable between vascular territories and individuals. As a result, absolute flow measurements present a large interindividual variability and a normal range cannot be provided since the subtended myocardial mass remains unknown [105]. The concepts of coronary flow reserve and microvascular resistance reserve obtained by "normalizing" hyperaemic with resting absolute measurements could overcome the present limitations allowing easier application in clinical practice. The feasibility of CFR measurement by continuous thermodilution has been recently demonstrated by Gutirrez-Barrios *et al.*, who have demonstrated a good correlation with CFR obtained by thermodilution with saline boluses (r = 0.76; p <0.001) [106].

6. ANGIOGRAPHIC-BASED TECHNIQUE

The development of thermodilution-based techniques has allowed to overcome the technical limitations of Doppler-derived measurements, making the assessment of microcirculation user-friendly and still accurate. However, the adoption of these pressure-wire-based techniques for microvascular assessment in clinical practice remains very low due to the increase of procedural costs and time, as well as a small risk of complications related to intracoronary wiring. In order to overcome these limitations, novel angiography-based indices are becoming available to assess coronary microcirculation based on computational flow dynamics to model the coronary artery.

De Maria *et al.* have recently developed and validated the angiography-derived index of microcirculatory resistance (IMR_{angio}) as a novel and pressure-wire-free index (an example is reported in Fig. (**2**)). IMR_{angio} has been derived starting from the formula for calculation of IMR, using information derived from coronary angiography [107]. Distal pressure (Pd) has been estimated from the aortic pressure and the QFR of the vessel, while the ratio between the number of frames (Nframes) for contrast dye to travel, during hyperaemia, from the guiding catheter to a distal reference divided by the acquisition frame rate (fps), used as a surrogate of the transit time. In this way, the formula becomes:

$$IMR_{angio} = P_{a\ (Hyperaemia)}\ x\ QFR\ x\ \frac{Nframes_{Hyperaemia}}{fps}$$

IMR_{angio} has been validated in a cohort of 45 STEMI patients treated with PPCI, showing that a good correlation with pressure-wire-derived IMR (ρ: 0.85, $p < 0.001$). Moreover, post-PPCI IMR_{angio} presented an area under the curve of 0.81 (CI95% 0.65–0.97, $p < 0.001$) for the prediction of microvascular obstruction at the cMRI [107]. A similar approach has been applied by Tebaldi *et al.* who developed the angio-based index of microcirculatory resistance (A-IMR) [108]. The formula for the calculation of the A-IMR in the presence of coronary artery stenosis is as follows:

$$A - IMR = P_a \, x \, \frac{vessel\ length}{flow\ velocity} \, x \, [(1.35 \, x \, cQFR) - 0.32]$$

where Pa is the aortic pressure during catheterization, QFR can be calculated based on two angiograms and the ratio between vessel length and flow velocity is an expression of transit time. In a cohort of 44 patients with stable coronary artery disease the A-IMR has shown good correlation with invasive IMR (Pearson correlation = 0.32, R2 = 0.098, $p = 0.03$) [108].

The application of computational fluid dynamic to coronary angiogram seems a promising approach, allowing the evaluation of both the epicardial and microvascular compartment. This approach could overcome the limitations of pressure-wire-based measurements, facilitating a larger adoption of functional assessment of the coronary circulation in the clinical practice, as intended by the current guidelines. Notably, both IMR_{angio} and A-IMR have been developed only in small cohorts of patients, and future studies are warranted to elucidate the diagnostic and prognostic accuracy of such techniques in a larger population.

CONCLUSION

The assessment of coronary physiology plays a fundamental role in the evaluation of both epicardial and microvascular compartments. Although FFR has radically changed the management of coronary artery disease, and although it remains the gold standard technique for the assessment of the epicardial segment, it must be acknowledged that, unfortunately, its adoption is still not ubiquitous in clinical practice. For this reason, alternative tools have been developed or are under development in order to overcome some of the technical challenges that FFR assessment imposes. It must be acknowledged that the diagnostic accuracy of these alternative approaches remains slightly inferior to the gold standard (FFR) against which they are validated, but they could still have the merit to facilitate a larger adoption of functional assessment of the coronary circulation in the clinical practice.

At the same time, significant progresses have been made in tools and indices for the functional assessment of the coronary microvascular compartment with the option of optimising medical and device-based therapies in clinical entities (such as STEMI or INOCA) where coronary microvascular injury and/or dysfunction play a crucial pathophysiological and prognostic role.

In the upcoming years, it is possible to anticipate that the assessment of coronary physiology will always become more comprehensive, taking into account both the epicardial and the microvascular compartments, and it will be integrated with other imaging modalities, including angiography (co-registration) and intracoronary imaging.

This will provide the unique ability of combining functional and morphological assessment of coronary atheroma with the ultimate aim of achieving 1) accurate diagnosis of myocardial ischaemia in the culprit territory, 2) imaging-based optimized results of percutaneous revascularization, and 3) imaging-derived plaque characterization of non-culprit atheromas. This is anticipated to lead to a significant improvement in future clinical outcomes, thanks to a likely reduction of both target and non-target lesion-related future cardiovascular events.

LIST OF ABBREVIATIONS

A-IMR	=	Angio-based Index of Microcirculatory Resistance
ACS	=	Acute Coronary Syndrome
APV	=	Average Peak Velocity
CAD	=	Coronary Artery Disease
cFFR	=	contrast Fractional Flow Reserve
CFR	=	Coronary Flow Reserve
CFR_{thermo}	=	thermodilution-derived Coronary Flow Reserve
$CFR_{Doppler}$	=	Doppler-derived Coronary Flow Reserve
DFR	=	Diastolic hyperaemia-Free Ratio
dPR	=	diastolic Pressure Ratio
FFR	=	Fraction Flow Reserve
FFRangio	=	Fractional Flow Reserve derived from coronary angiography
iFR	=	instantaneous wave Free Ratio
HMR	=	Hyperaemic Microvascular Resistance index
IMR	=	Index of Microvascular Resistance
IMR_{angio}	=	angiography-derived Index of Microcirculatory Resistance
INOCA	=	Ischemia with Non-obstructive Coronary Artery
IVUS	=	Intravascular Ultrasound
MACE	=	Major Adverse Cardiovascular Events
MI	=	Myocardial Infarction
MVO	=	Microvascular Obstruction
MVD	=	Multivessel Disease

Pd/Pa = Pressure ratio of distal coronary and aortic pressures

OCT = Optical Coherence Tomography

OFR = Optical Flow Ratio

PCI = Percutaneous Coronary Intervention

PPCI = Primary Percutaneous Coronary Intervention

QFR = Quantitative Flow Ratio

RFR = Resting Full-cycle Ratio

RRR = Resistive Reserve Ratio

STEMI = ST Segment Elevation Myocardial Infarction

vFFR = vessel Fraction Flow Reserve

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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