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Review

Functional assessment of coronary stenosis: an overview of available techniques. is quantitative flow ratio a step to the future?

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Abstract

Introduction: The assessment of coronary lesions severity has always been a relevant topic in the management of the patient undergoing coronary angiography. Fractional flow reserve (FFR) has been introduced as an objective index to determine the significance of a coronary stenosis with a positive impact on clinical outcomes has been demonstrated for FFR-guided coronary interventions. However, several technical drawbacks have been pointed out in clinical practice limiting the diffusion of FFR worldwide. To exceed these limits, other indices and the quantitative flow ratio (QFR) have been recently developed and tested in clinical studies.

Areas covered: This review aims to provide a brief overview of functional assessment of coronary stenosis and a particular attention to the QFR, to its validation and application studies for its potential applicability in clinical practice. QFR through a computational fluid dynamics (CFD) analysis, proved to be useful in discriminating functionally significant stenosis, with an excellent correlation with FFR values, and considerable advantages in terms of acquisition time and costs.

Expert Opinion/Commentary: QFR is an innovative angiographic-based technique that uses modern software for three-dimensional vessel reconstruction, and flow models calculation. The significant technical benefits reported in the management of patients with intermediate coronary stenosis, make it a modern, effective and usable tool.

Key words

myocardial ischemia, coronary physiology, quantitative flow ratio, coronary artery disease, coronary angiography, percutaneous coronary intervention, 3D-angiography, fractional flow ratio

1. Introduction

Coronary artery disease (CAD) represents one of the main causes of morbidity and mortality worldwide (1,2). In the last decades, newer diagnostic and therapeutic techniques have certainly provided an essential contribution to CAD management, significantly improving patients' outcomes. Percutaneous coronary intervention (PCI) is nowadays one of the most common invasive procedure performed worldwide, providing a survival benefit in acute coronary syndromes patients and symptom relief in stable patients with significant stenosis and proven myocardial ischemia (3–8). However, the decision of whether to perform PCI in intermediate lesions is difficult, as both physician visual assessment (PVA) and quantitative coronary analysis (QCA) have shown poor correlation with functional stenosis severity. In this contest, functional evaluation of coronary stenosis has progressively assumed a crucial role (9), and the use of Fractional Flow Reserve (FFR) allowed improving the decision making in patients with intermediate coronary stenosis. To date, in the 2013 European Society of Cardiology (ESC) on Stable Coronary Artery Disease, FFR-guided PCI has a class I A recommendation to identify haemodynamically relevant coronary lesions in stable patients when evidence of ischaemia is not available, and class IIa A recommendation to manage PCI in patients with multivessel disease (MVD) (10), these indications are recently strengthened by the 2018 ESC / EACTS Guidelines on myocardial revascularization that place the FFR in class IA as well as the iFR (3). In addition to the FFR, in the last few years, several invasive and non-invasive tests emerged for the anatomic and functional evaluation of coronary stenosis severity. The development of X ray-related diagnostic and angiographic techniques has sought to find an alternative tool for the functional assessment of coronary stenosis. The Coronary Computed Tomographic Angiography (CCTA) has shown a high diagnostic performance for the detection of coronary lesions causing ischemia (11). Afterward, functional assessment of coronary stenosis was studied using three-dimensional quantitative coronary angiography (3D-QCA) and blood flow simulation (12), and the combined use of 3D-QCA and Thrombolysis In Myocardial Infarction (TIMI) frame count have been used to obtain FFR-derived calculation (13). This less-invasive technique, called Quantitative Flow Ratio (QFR), uses 3 different flow simulation models: fixed-flow QFR [fQFR], contrast-flow QFR [cQFR]), adenosine-flow QFR [aQFR], allowing the discrimination between functionally significant non-significant stenosis. The definition of this as a less invasive technique is more

correct than a non-invasive technique because the patients to whom it can be applied are patients who are nevertheless subjected to coronary angiography. Thus, it is a less invasive technique compared to other functional indices such as FFR and iFR that require a pressure wire.

2. Coronary artery stenosis: assessment and functional significance

Coronary stenosis, generally due to an atheromatous thickening or plaque of the artery wall, limits the flow gradient in maximum vasodilation conditions and significantly alters the coronary flow control systems. At rest, coronary microcirculation responds with vasodilatation to compensate the pressure drop downstream the stenosis, but often it is not able to further expand if necessary (i.e., for an increased flow and oxygen demand) (14,15). Significant coronary stenosis is described by the 2017 American College of Cardiology and American Heart Association (ACC/AHA) Appropriate Use Criteria for revascularization for patients with stable Heart Disease (16) as a 70% or more luminal diameter reduction by visual assessment. However, it has been documented that, the relationship between quantitative stenosis severity on coronary angiography and the level of functional flow limitation is weak (17,18), and increasing clinical data have confirmed that a simple percentage description of the stenotic coronary does not characterize the full physiological impact on its perfused myocardium (19)(20).

2.1 Angiography and its evolution

Selective coronary angiography is the gold-standard for the diagnosis of CAD (21), and remains the accepted imaging method for the study of the coronary tree, despite the development of other non-invasive imaging techniques, such as computed tomography (CT) and cardiac magnetic resonance (CMR) (19). Before 1958, it was thought that any procedure that involved injecting contrast into the coronary arteries could be dangerous or even fatal. Thanks to the work of Mason Sones, coronary angiography was born and evolved (22), creating the conditions for the development of percutaneous revascularization (3,10,23). For a long time, the PVA remained the only method available to assess stenosis severity. However, this quick method has a marked inter- and intra-observer variability, providing consistent limitations (24,25), and reporting substantially higher readings of stenosis severity than QCA (26). Since the

1980s, investigators have developed and implemented methods of quantitative coronary angiography (QCA) analysis using automated or semi-automated edge recognition (27). QCA is based on contrast coronary angiography that obtains parameters that quantify the significance of coronary stenosis empirically (28) and, differently from PVA, has a good inter- and intra-observer reproducibility (29). Initially, the software was designed for "single-vessel" 2D-QCA, and its use in bifurcation lesions resulted biased for the detection of vessel outline at the ostium site. Subsequently, a software suitable for bifurcations was developed making this technique applicable also in complex vessel anatomies (30,31).

However, the use of 2D-QCA to analyze three-dimensional structure implies several critical limitations, for example coronary segments can overlap, and vessel tortuosity and lesion eccentricity may result in distortions and/or errors in the diagnosis of severe stenosis; thus, using 2D-angiographic images, many of the concerns of traditional angiography persists (29). To overcome these issues, novel imaging techniques have been developed, including rotational angiography and 3D-modeling techniques, that use 2 or more angiographic projections to analyze vessels anatomy and create a 3D-model (32). Several studies tried to standardize the procedures for the acquisition of images for 3D reconstruction as much as possible (33,34). 3D-coronary modeling showed to be a more precise tool for the evaluation of the lengths of coronary segments than standard QCA (35). 3D-quantitative coronary angiography (3D-QCA) exploits multiple images obtained from conventional coronary angiography to reconstruct three-dimensional views by a proper algorithm, and it could theoretically be able to evaluate stenosis and predict lesions producing ischemia more accurately because it examines and measures lesions from 3-dimensional views.

This tool has been validated in different populations (36), and demonstrated an excellent correlation with intracoronary imaging techniques in the evaluation of stenosis severity and length (37), finding clinical applications in the decision-making for the treatment of significant lesions.

The development of 3D-QCA allows a more correct anatomical valuation of coronary stenosis, but the discordance between anatomical severity and the functional significance persists (19).

2.2 Fractional flow reserve

Fractional Flow Reserve (FFR) is the ratio between the average pressures downstream and upstream the stenosis during maximum hyperemia conditions and represents the fraction of coronary flow preserved despite the presence of luminal stenosis calculated as FFR = Pd/Pa, where Pd is the pressure downstream the stenosis and Pa aortic pressure.

FFR is an invasively measured parameter that can reliably assess the aptitude of a lesion to induce myocardial ischemia (38), measuring the trans-stenotic pressure gradient directly to obtain the trans-stenotic flow indirectly (39). This method is based on the physiological principle that in a general condition of hyperemia, a proportionality exists between pressure and flow (18,40).

Although several drugs, administered by intracoronary (i.c.) or intravenous (e.v.) route, can be used to induce maximal hyperemia (i.e., adenosine, sodium nitroprusside, nicorandil, nitrate, and papaverine) (41–43), currently e.v. adenosine is considered the gold-standard for the technique (9,44).

A value of FFR = 1 represents a condition of normality (injury-free vessel), whereas values <1 can indicate the presence of an atherosclerotic lesion. According to the main studies (9,38,45,46) showing the clinical efficacy of FFR, the reference cut-off to determine the significance of stenosis is 0.80. A lesion with values >0.80 is to be considered not hemodynamically significant; a lesion associated with a value <0.80 is to be considered hemodynamically significant (9,45).

Several studies have validated the FFR, showing that the combination of anatomical evaluation of the coronary arteries lumen with a functional assessment by FFR guidance is crucial to adapt the treatment of patients with CAD (18,47,48). The first randomized trial that established the efficacy and safety of the FFR-guided PCI was DEFER study (49,50) that shows defer PCI in patients with stable coronary artery disease and normal FFR value is safe, and the clinical outcome of patients is favorable. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study has been shown that a strategy of FFR-guided treatment in patients with MVD is associated with more favorable long-term outcomes (51). The results in favor of the FFR-guided PCI strategy are also confirmed in the 5-year follow-up study (52) with a reduction of Major Adverse Cardiac Event (MACE) in the FFR-guided group compared to

angiography-guided group, and number of stents located per patient was considerably higher in the angiography-guided group.

The FAME 2 study is a randomized trial investigating patients with CAD assessed with angiography that could be treated with PCI (46). Patients with at least one functionally significant stenosis (FFR<0.80) were randomized to PCI + optimal medical therapy (OMT) or medical therapy alone, while patients with non-functionally significant stenosis were enrolled and treated with medical treatment only. The study was interrupted due to a significant increase in the risk of MACE in patients randomized to OMT to those randomized to PCI + OMT, as the incidence of the primary end-point was 12.7% and 4.3% respectively (p <0.001). Also in the 5-year follow up the results were overlapping, an initial FFR-guided PCI strategy was related with a lower rate of the primary composite end point of death, myocardial infarction, or urgent revascularization than OMT alone (53).

In the FAMOUS-NSTEMI study (54), in patients with non-ST-elevation myocardial infarction , FFR use resulted in a change in the treatment plan in more than 20% of cases, and the overall number of revascularization was reduced. At 1-year follow-up, there were no differences in outcomes (MACE) between the randomized groups, showing the feasibility and clinical utility of a functional approach in these patients. This strategy can reduce the number of inappropriate revascularizations and maximize the benefit of PCI as shown in a study in which the stenosis which resulted in the most pressure drop was treated first and then the functional evaluation was repeated: no events related to deferred injuries suggesting that the strategy of FFR-guided revascularization was safe (55) (56).

2.3 Instantaneous wave-free ratio

The instantaneous wave-free ratio (iFR) is the ratio of pressure and flow in the latter 75% of diastole based on the wave intensity analysis (WIA) with its assumed wave-free period. This technique uses a pressure wire, and samples intracoronary pressure during the diastolic “wave-free” period (WFP), a period in the cardiac cycle when microvascular resistance is already constant and minimal, therefore it does not require adenosine administration (57–59).

In the VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice (VERIFY) study (58), and in the VERIFY 2 Study (60) the results affirmed that there was no diagnostic advantage to utilizing an iFR-guided revascularization strategy compared with FFR. This initial studies did not give the expected results, probably because the number of patients was not sufficient. The most important results derived from the iFR-SWEDEHEART (61) and the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) studies (62) that aimed to investigate whether iFR was non-inferior to FFR concerning clinical outcomes between patients who have an indication for assessment of coronary artery stenosis (63,64). The iFR-SWEDEHEART study showed that there was no difference respect to the rate of MACE at 12 months in patients with stable angina or an acute coronary syndrome, with iFR-guided revascularization strategy compared with an FFR-guided revascularization strategy. In the same direction were the results of the DEFINE-FLAIR study (62). Also, in this case, coronary revascularization guided by iFR was non-inferior to revascularization guided by FFR concerning the risk of MACE at 1 year. However, based on these results, iFR stands as a safe tool and usable for intracoronary functional assessment when the administration of adenosine is not desirable (Table 1).

Lately, with the new 2018 ESC / EACTS Guidelines on myocardial revascularization the iFR received recognition as being recommended in class IA as at the FFR for the study of intermediate stenosis. (3)

2.4 Resting full-cycle ratio

Resting full-cycle ratio (RFR) is a novel non-hyperemic index of coronary stenosis severity measuring the ratio of the pressure at the point of lowest resting diastolic pressure (Pd) compared to aortic pressure (Pa) through the cardiac cycle. It measures the pressure difference in the cardiac cycle and does not require an ECG and regardless of timing within the cardiac cycle. A minimum of four, but preferentially five, consecutive heart cycles were needed to determine the RFR (65).

It's different from iFR because it is measured during a precise section of diastole, the "wave-free period" where it is supposed that coronary flow is maximal and resistance minimized.

The "VALIDATE-RFR" (Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio) study aimed to confirm the reliability of the RFR (65). It's a retrospective study and the primary endpoint was the agreement between RFR and iFR. RFR was retrospectively measured in 651 waveforms in which iFR was measured using a proprietary Philips/Volcano wire, and it demonstrated a good correlation with iFR (R^2=0.99, p<0.001). The diagnostic accuracy was 97.4%, sensitivity 98.2%, specificity 96.9%, positive predictive value 94.5% and negative predictive value 99.0%, thus showing itself as a new and equivalent tool to iFR.

3. Quantitative Flow Ratio (QFR): fractional flow reserve by 3D-angiography

As discussed above, coronary angiography has several important limits in determining the severity of intermediate coronary stenosis. The measurement of FFR selectively in all the lesions considered as angiographically significant allows identifying those lesions able to induce myocardial ischemia. Indeed, this approach permits a redefinition of the coronary pathology from the morphological level to the functional level. The QFR method combines a 3D reconstruction of the target vessel, based on two angiographic projections and the contrast flow velocity to compute the "FFR value" without the need for pressure and/or flow wires. The QFR stands as mediation between the physiological and angiographic evaluation of coronary stenosis. Two studies, in particular, have laid the groundwork for this, the DISCOVER-FLOW (Diagnosis of ISChemia-Causing Stenoses Obtained Via NoninvasivE FRactional FLOW Reserve) and VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) studies (66).

In the DISCOVER-FLOW study, computational fluid dynamics (CFD) analysis has been applied to coronary computed tomographic angiography (CCTA) data to predict FFR (11) and, the addition of FFR to CCTA has shown to improve clinical decision-making, and demonstrated a good correlation with the invasive measurement of FFR.

The VIRTU-1 study aimed to develop a computer model that could accurately predict myocardial fractional flow reserve (FFR) from angiographic images deriving from rotational coronary angiography. Virtual fractional flow reserve (vFFR) and measured fractional flow reserve (mFFR) values were closely correlated (66).

Tu et al. (13) investigated a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. They used 3D-QCA, and the mean volumetric flow rate at hyperemia was calculated using TIMI frame count combined with 3D-QCA proving that computation of FFR-QCA is an innovative system that allows assessing the functional significance of intermediate coronary stenoses. In particular, 77 vessels in 68 patients have been analyzed, while the testing group comprised 22 vessels in 20 patients. They found a good correlation ($r = 0.81$; $p < 0.001$) and agreement between FFR-QCA and FFR. Applying FFR cutoff value of ≤ 0.80, all coronary vessels with intermediate stenosis resulted in a higher area under the curve (0.93 [95% CI: 0.86 to 0.99]) than did MLA (0.73 [95% CI: 0.61 to 0.85]. FFR-QCA upgraded the diagnostic performance of coronary angiography, with 88% accuracy, 78% sensitivity, 93% specificity, 82% positive predictive value, and 91% negative predictive value.

FFR-QCA was more accurate than FFR-CT (13), probably because image resolution in X-ray angiography is greater than coronary computed tomography angiography and for the evaluation of the downstream microcirculation. Furthermore, FFR-CT is influenced by calcified coronary heart disease and heart rhythm (13). CT-FFR is indicated for low-intermediate risk patient screening, in whom a delay in the results is not an issue and it is manly used to avoid further stress tests and unnecessary invasive procedures. FFR-QCA method of calculating the severity of intermediate stenoses appears a safe and cost-saving tool during diagnostic angiography.

On these assumptions is based the prospective multicenter FAVOR Pilot Trial study (Functional Assessment by Various Flow Reconstructions) (67), that defined this new tool as quantitative flow ratio (QFR). The FAVOR study aimed to track the best way to use this technology, investigating offline computation of QFR as paralleled with conventional pressure wire-based FFR.

Computation of QFR is possible online and offline, using a software package (QAngio XA 3D, Medis Medical Imaging System, Leiden, the Netherlands), currently the only software available.

As discussed above, the CFD is applied and this allows the calculation of the index by an algorithm.

First, for the computation of QFR, is necessary to acquire two diagnostic angiographic projections, at least 25° apart, allowing 3D reconstruction **(Figure 1).** The reliability of this angio based 3D model is critical for QFR assessment. Tu et al. (68) demonstrated a very close correlation with both IVUS and OCT (r= 0.8 and

0.89, respectively). Starting from the assumption that the flow moves across the stenosis, and follows the fluid-dynamic rules, the mass flow rate along the selected vessel can be established by the mean flow velocity and the reference sizing from 3D-QCA. In particular CFD quadratic mathematical algorithm instead of fully developed Navier-Stokes equation was applied, thanks to its faster computation time without loss of accuracy. Moreover with this model the side branches reconstruction was not necessary anymore. Frame rate count was calculated in both angiographic views to obtain patient specific hyperemic flow velocity estimation during contrast injection and adenosine administration. A detailed description of equation and assumptions used for QFR calculation have been previously described (67), and are depicted in **Figure 2**. Three different computations were executed with different mean hyperemic flow velocities: fixed-flow QFR [fQFR], contrast-flow QFR [cQFR]), adenosine-flow QFR [aQFR] **(Table 2).**

All three models were compared with the FFR value measured by the pressure wire. Good correlations with standard FFR were observed for fQFR ($r = 0.69$ [$p < 0.001$]); cQFR ($r = 0.77$ [$p < 0.001$]); and aQFR ($r = 0.72$ [$p < 0.001$]). The diagnostic accuracy of all approaches for predicting an FFR of ≤ 0.80 was good, particularly for cQFR and aQFR models (86% and 87% respectively).

cQFR improved the diagnostic performance of coronary angiography, with a sensitivity of 74%, specificity of 91%, positive predictive value of 80%, negative predictive value of 88% (67). With cQFR value >0.90 or $\leq$ 0.70, all stenoses were considered appropriately as compared with FFR with the cutoff value of 0.80 **(Figure 3)**.

The cQFR calculation without pharmacologic hyperemia induction, enhanced the diagnostic accuracy related to fQFR and aQFR but not further improve its FFR estimation, partly explained by submaximal hyperemia induction from contrast (69). This provides an even lower cost in the context of an already more economically favorable technique compared to the FFR. Data coming from another smaller study confirm this trend in the reliability of this new tool (70).

The FAVOR II China study was the first trial with adequate power to measure the diagnostic accuracy of QFR (71). The primary end-point was the diagnostic accuracy of online QFR (≤0.8 or >0.8) to identify functional coronary stenosis using FFR (≤0.8 or >0.8) as the reference standard. 308 patients were consecutively enrolled at 5 centers. Online analysis vessel-level QFR had a diagnostic accuracy of 92.7%,

and offline analysis vessel-level QFR had a high diagnostic accuracy of 93.3%. The FAVOR II Europe and Japan study shows QFR superior sensitivity and specificity for detection of functional significant lesions in comparison with 2D-QCA using FFR as the reference standard (72). In a total population of 329 patients enrolled in 11 centers, data from 274 patients were analyzed. The sensitivity and specificity of QFR were both 88%, the positive predictive value with FFR as reference was 78% and the negative predictive value was 94%. Another datum coming from the study, and that should not be underestimated amongst the advantages of the QFR, concerns the times of obtaining the result. Indeed, the comparison between QFR and FFR showed a significant difference in times that resulted of 4.8 min (IQR 3.5-6.0) and 7.0 min (IQR 5.0-10.0), respectively ($p<0.001$) (72).

Afterward, the WIFI II study (Wire-Free Functional Imaging II) aimed to evaluate the feasibility and performance of QFR (73). It was a predefined substudy to the Dan-NICAD study (Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease) that analyzed 362 consecutive patients with suspected CAD on CCTA with an indication to ICA. FFR was performed in 292 lesions from 191 patients, and QFR was calculated from blinded observers in 240 lesions. In this case, the median QFR was 0.84 (IQR, 0.77–0.89) and the QFR computation showed a correlation of $r=0.70$ ($P<0.0001$), and precision with a mean difference of 0.01±0.08 ($P=0.08$) with FFR. The QFR computation accuracy was 83% with 66 true positives, 132 true negatives, 20 false positives, 22 false negatives and it improved when eliminating cases with FFR values in the range of 0.77 to 0.83 (83%–87%; $P=0.002$) around the diagnostic cut point. The QFR limits to performance specificity and sensitivity >90% were 0.78 and 0.87 respectively, while >95% accuracy were 0.71 and 0.90.

Regarding the times, Yazaki et al. give us information: in their study, the average time to calculate QFR was 266 s (IQR, 181 - 332 s), including time for 2 optimal angiographic acquisition and complete the QFR calculation (74) **(Table 3).**

3.1 QFR in non-standard clinical scenario

Asserted its reliability, safety, and economy, the QFR computation has been then applied in different patient settings.

Emori et al. (75) have experienced the QFR for assessing myocardial ischemia in prior myocardial infarction. It is a retrospective, single centre study that analyzed 75 prior MI-related coronary arteries in 75 patients. They used FFR and only 2 different flow models: (1) fixed-flow QFR (fQFR) and (2) contrast-flow QFR (cQFR) and highlighted no difference in fQFR, cQFR and FFR correlation between the prior-MI-related and non-prior-MI-related coronary arteries. fQFR resulted reduced as compared with FFR in prior-MI-related coronary arteries. This could be explained because it is based on anatomic information obtained from 3D-QCA and then may not consider the vital myocardium. The value of cQFR vs. FFR was significantly lower in prior-MI-related coronary arteries compared with non-prior-MI-related arteries, with the vital myocardium insufficiently taken into account by the TIMI frame count analysis.

In a recent study, Spitalieri et al. (76) investigated different aspects of QFR in 3 patient cohorts: a) the reproducibility and agreement of QFR values of nonculprit lesions (NCLs) in ST-segment elevation myocardial infarction (STEMI) patients that received FFR assessment of NCLs; b) diagnostic accuracy of QFR vs FFR in NLCs in STEMI patients with multivessel disease; c) the long-term clinical outcomes of NCLs according to QFR result in STEMI with multivessel disease. Compared to these three points, they found a good reproducibility of QFR computation, an excellent diagnostic accuracy with standard FFR measurement as a reference, and the potential prognostic value using the functional SYNTAX score (FSS).

Indeed, patients with incomplete revascularization have a 2.3-fold increase in the risk of patient-oriented cardiac events, while patients with complete functional revascularization had a long-term outcome similar to those obtaining complete revascularization (76).

The Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation (HAWKEYE - NCT02811796) is currently investigating the use of QFR after stent implantation in about 600 patients. This trial will assess the relationship between QFR value and adverse events and will evaluate the best QFR value able to discriminate the cumulative occurrence of adverse events. In the study, STEMI patients are also included as an independent cohort to obtain preliminary results. This approach will allow extending the horizon of functional assessment in the revascularized patient, a territory not much explored for invasive assessment with FFR / iFR.

3.2 Why operators need a new tool to assess intermediate stenosis?

The disparity between the angiographic and functional evaluation of the stenosis and the consequent classification of the patients in single-, two-, or three-vessel disease was confirmed by the validation studies of FFR (39,42,44).

Despite the demonstrated benefits of physiology-based revascularization, to date the reference techniques for the evaluation of intermediate coronary stenosis are still rarely used. FFR has clinical guideline recommendations, but its application in coronary catheter laboratories worldwide remains low (77). Indeed, although the use of FFR has grown every year in the last decade (78), this varies significantly across countries and centers, ranging from 3% to 30% of the total volume of PCI (77–79). The poor penetration of the FFR in daily practice is probably due to the costs, equipment and operator choice. An international survey with 495 participants on interventional strategy analyzed 4421 lesions showing that in most cases the participants relied only on angiographic appearance that was discordant in 47% with the known FFR. This confirms that visual assessment continues to dominate the treatment decisions for intermediate stenosis, with a significant gap between recommendations and practice. The iFR, exceeding the administration of adenosine and eliminating the side effects and reducing costs, did not further shift the use of physiology-based guidance (77).

The Evolving Routine Standards of FFR Use (ERIS) study (79) is an investigator-driven, nationwide, prospective, cross-sectional study involving 76 Italian centers that have the aim to describe the current use of invasive coronary physiology assessment and recognize the causes for its little use in daily practice. Also in this case, the main reason for not using physiology assessment was the operator's confidence that clinical and angiographic data alone were sufficient.

In this context, the use of the QFR could increase because it has several advantages: it is a less-invasive technique, which costs little, can be calculated offline, and is closer to the operators' approach. Hence, QFR can represent a valid and handy option in the cath-lab, leading to more appropriate revascularizations.

4. Conclusions

Angiographic evaluation of coronary stenosis has proved to be poorly performing, and although the evolution of angiography has led to the development of techniques such as QCA, this is not adequate especially for intermediate stenosis assessment. For the evaluation of the significance of coronary stenosis, FFR is considered the reference technique having robust validation and outcome data and being recommended by the guidelines for myocardial revascularization, leading to revascularization only in the case of significant stenosis. Further angiographic developments up to 3D-QCA that allows a three-dimensional reconstruction of the coronary vessel, using principles of flow models and TIMI frame count, the QFR was developed. QFR computation, and its three different models (fQFR, cQFR and aQFR), showed good reproducibility and good correlation with FFR. Furthermore, quantifying vessel dimensions, this is useful for the fast computation of FFR adding anatomical details for optimal stent sizing if subsequent revascularization is planned.

QFR appears as a safe and cost-reducing diagnostic modality improving the utilization of functional guided decision making, having the advantage of not using the pressure wire and using less drugs, reduction in procedure time and risk for the patient.

5. Expert commentary

The assessment of intermediate coronary stenosis is still an open question. The limitations to the coronary flow imposed by atherosclerosis are mainly related to geometry, severity, length, rigidity and vasomotility of stenosis. These parameters, unfortunately, cannot be assessed by the “view” of the operator, and also the development of techniques (such as QCA) resulted not adequate. One of the main problems of angiography is that it is a two-dimensional representation of three-dimensional structures. Evidence suggest the superiority of a functional study of intermediate lesions, showing that the insertion of the pressure wire in the diagnostic path of the patient allows to pursue therapeutic appropriateness, reach an accurate diagnosis, and improve outcomes, avoiding adverse events associated with improperly implanted stents. In a subgroup of the FAME study, the SYNTAX score (SS) was compared with a SYNTAX FFR guided score, defined as "functional SYNTAX score" (FSS), resulting only from the lesions with an FFR ≤0.80, in

predicting 1-year major adverse events (80). Interestingly, calculating the FSS for each patient, the 32% was moved to a low-risk group with better accuracy for major adverse events compared to the SS. This strategy can reduce the number of inappropriate revascularizations and maximize the benefit of PCI as shown in a study in which the stenosis which resulted in the most pressure drop was treated first and then the functional evaluation was repeated: no events related to deferred injuries suggesting that the strategy of FFR-guided revascularization was safe (55) (56).

The key weaknesses in daily clinical management are represented by the poor use and penetrance of physiology evaluation techniques. The use of the FFR is the gold standard, and it has progressively increased over the years, in parallel with the availability of scientific data to support its usefulness and its cost-effectiveness but nowadays is still underused. The reasons are different, but among all the belief of the operator in the angiography assessment stenosis emerges. The iFR seemed to increase the use of the functional evaluation being more manageable, without adenosine administration and with shorter times compared to FFR, but this has not improved its use in recent years.

The QFR exploiting the angiographic evolution with three-dimensional reconstruction of the vessel and dynamic fluid computations is able to discriminate significant lesions from non-significant lesions. It uses 3 different flow simulation models: fixed-flow QFR [fQFR], contrast-flow QFR [cQFR]), adenosine-flow QFR [aQFR]. Some argue that QFR is a redundant tool, having FFR and iFR a large amount of patients enrolled in validation and outcomes studies. But QFR exceeds the limits of FFR and iFR, showing an excellent correlation with FFR values in the assessment of intermediate stenosis, reporting technical advantages such as time and costs reduction, not requiring the use of an intracoronary pressure wire. QFR is used in high-risk patients not as a screening test to decide whether the patient needs the angiography or not, but once the indication to coronary angiography is established, to define if the found lesion needs to be treated or not. While demonstrating an excellent technical performance, the QFR does not have outcomes studies yet, a factor that penalizes it as compared with the reference techniques. Currently, a trial is underway to evaluate this aspect: the FAVOR III China (NCT NCT03656848). It is a prospective, multicenter, randomized, clinical trial comparing the clinical outcome and cost-effectiveness of the two strategies, QFR-guided PCI versus standard angiography-guided PCI, in evaluation of patients with CAD.

However, the important technical advantages reported in the management of patients with coronary heart disease and intermediate stenosis, make it a modern, effective and usable tool.

6. Five-year view

The techniques available in the laboratory of hemodynamics are constantly evolving, and the progress of the last 20 years is the testimony. QFR is an innovative angiographic-based technique that uses modern software for three-dimensional vessel reconstruction, and flow models calculation. The combination of past and present makes it a familiar and contemporary technique at the same time. The advantages offered regarding less-invasiveness, offline analysis, and reduction of time and costs, open the way for an ever-increasing use. Currently underused, in the next 5 years it could be one of the main tools for the evaluation of intermediate stenosis. Moreover, the ongoing studies in the evaluation of patients who have been already revascularized can favor its use in a field that is not very applicable for FFR and iFR.

Key issues

- Percutaneous coronary intervention (PCI) is currently the most common invasive procedure performed providing a survival benefit in acute and chronic coronary artery disease (CAD). The assessment of coronary lesions severity by physician during invasive coronary angiography has been proved unsatisfactory to discriminate between functionally significant and non-significant coronary stenosis.
- Fractional Flow Reserve (FFR) studies the stenosis during maximum hyperemia conditions (with adenosine administration), with a pressure wire estimanting the aptitude of a lesion to induce myocardial ischemia. Currently, this has guidelines recommendations for the management of intermediate coronary stenosis. The instantaneous wave-free ratio (iFR) uses a pressure wire but it does not need adenosine administration. Despite the scientific evidence has shown benefits in revascularization based on functional assessment, FFR and iFR are still poorly used in clinical practice.

- Quantitative Flow Ratio (QFR) uses 3D vessel reconstruction from 2 orthogonal angiographic images and computational fluid dynamics analysis. It allows rapid computation of FFR pullbacks from 3D-QCA, and provides 3 different flow models: fixed-flow QFR [fQFR], contrast-flow QFR [cQFR]), adenosine-flow QFR [aQFR].
- QFR proved to be useful in discriminating functionally significant stenosis, demonstrating an excellent correlation with FFR values, and considerable advantages in terms of acquisition time and costs (i.e., not requiring the use of an intracoronary pressure wire).

  New fields of application are opening up for this technique, also in the assessment of non-culprit lesions and in post-stenting evaluation.

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Figure and table legends

Figure 1. 3D reconstruction of Left anterior descending artery (LAD) from two 2D angiographic view of at least 25° apart.

Figure 2: Fast computational QFR algorithm and its main assumptions.

Figure 3. QFR vs. FFR for coronary stenosis assessment**.** (A) 2D-QCA of LAD vessel. (B) 3D-QCA C) QFR value for LAD: the upper diagram shows the 3D model maximum and minimum diameter. The red line represents the ideal reference vessel diameter. The lower plot is the virtual pressure pullback. Each drop represents the singular lesion functional weight.
ADO i.c.= intracoronary adenosine. LAD= left anterior descending. FFR= fractional flow reserve. QCA= Quantitative coronary angiography. QFR= quantitative flow ratio.

Table 1. Main validation and outcome studies of FFR and iFR.
CAD= coronary artery disease. iFR= instantaneous wave-free ratio. FFR= Fractional Flow Reserve. MACE= Major Adverse Cardiac Event. NSTEMI= Non ST Elevation Myocardial Infarction. Pts= patients

Table 2. Three different QFR computations in three different flow models.
aQFR= adenosine Quantitative Flow Ratio. cQFR= contrast Quantitative Flow Ratio. fQFR= fixed Quantitative Flow Ratio. HFV =hyperemic flow velocity. i.v.= intravenous

Table 3. Main features, strengths and limitations of FFR, iFR, and QFR.
aQFR= adenosine Quantitative Flow Ratio. cQFR= contrast Quantitative Flow Ratio.
iFR= instantaneous wave-free ratio. FFR= Fractional Flow Reserve. Pa= aortic pressure. Pd= pressure measured downstream the stenosis. QFR= Quantitative Flow Ratio.

Study	*FFR/iFR*	*Sample size*	*Study design*	*Population*	*Primary Endpoint*	*Outocomes*
Bech et al.[49] DEFER study	FFR	325 pts	Prospective, randomized study	Stable CAD	No adverse cardiac events during 24 months of follow-up.	No beneficial treating with PCI a nonischemic lesion (FFR <0.75)
Tonino et al. [51] FAME	FFR	1005 pts	Prospective, randomized study	Multivessel disease	Composite endpoint (death, MI, and repeat revascularization) at 1 year follow up	Lower rate of the composite endpoint in the FFR-guided group vs. angiography-guided group (FFR<0.80)
De Bruyne et al. [46] FAME 2	FFR	888 pts	Prospective, randomized study	Stable CAD	Composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization	FFR-guided PCI + (OMT) vs. OMT alone decreased the rate of urgent revascularization (FFR<0.80)
Layland et al. [54] FAMOUS NSTEMI	FFR	350 pts	Prospective, randomized study	NSTEMI patients	The between-group difference in the proportion of patients allocated to medical management.	Angiography-guided management had higher rates of coronary revascularization vs. FFR-guided management. (FFR<0.80)
Berry et al. [58] VERIFY	iFR	200 pts	Observational study	Patients undergoing FFR assessment for standard clinical indications	Comparison of FFR vs. iFR for assessment of coronary artery stenosis severity in routine practice	iFR correlates poorly with FFR (iFR <0.80)
Hennigan et al. [60] VERIFY 2	iFR	197 pts	Single-center prospective study	Angiographically intermediate coronary stenoses in which FFR measurement was clinically indicated	The level of agreement of iFR versus Pd/Pa using binary cutoff values in reference to FFR ≤0.80.	Binary cutoff values for iFR and Pd/Pa result in misclassification of 1 in 5 lesions (iFR< 0.90)
Jeremias et al. [59] RESOLVE	iFR	1768 pts	Multicenter, non - randomized,	Coronary artery disease undergoing	Evaluate the level of diagnostic	iFR and Pd/Pa compared with FFR demonstrated an

			retrospective study	physiological lesion assessment by FFR	accuracy of iFR and Pd/Pa compared with FFR	overall accuracy of ~80% for both (iFR <0.90)
Götberg et al. [61] iFR-SWEDEHEART	iFR	2037 pts	Prospective, randomized study	Patients with stable angina pectoris or acute coronary syndrome	Noninferiority iFR compared FFR. The rate of a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization	iFR-guided revascularization strategy was non-inferior to an FFR-guided revascularization strategy with respect to the rate of MACE at 12 months (iFR<0.89)
Davies et al. [62] DEFINE-FLAIR	iFR	2492 pts	Prospective, randomized study	CAD with at least one intermediate stenosis in a native artery	1-year risk of MACE, which was a composite of death, nonfatal myocardial infarction, or unplanned revascularization.	Coronary revascularization guided by iFR was noninferior to revascularization guided by FFR concerning the risk of MACE at 1-year (iFR<0.89)

Table 1. Main validation and outcome studies of FFR and iFR.
CAD= coronary artery disease. iFR= instantaneous wave-free ratio. FFR= Fractional Flow Reserve. MACE= Major Adverse Cardiac Event. NSTEMI= Non ST Elevation Myocardial Infarction. Pts= patients

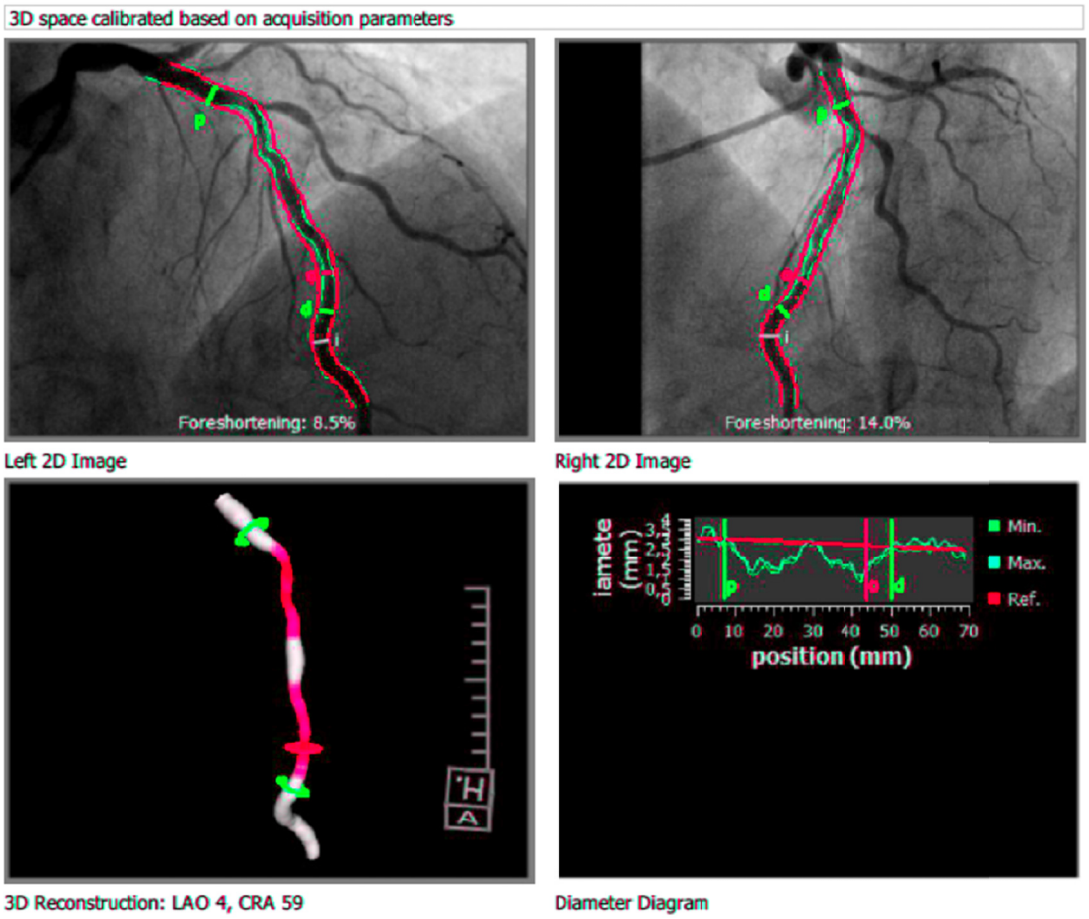
	fQFR	**cQFR**	**aQFR**
Complete name	Fixed Quantitative Flow Ratio	Contrast Quantitative Flow Ratio	Adenosine Quantitative Flow Ratio
3D-QCA reconstruction	3D model reconstruction from 2 angiographic projections with angles ≥ 25º apart, acquired by monoplane or biplane systems.	3D model reconstruction from 2 angiographic projections with angles ≥ 25º apart, acquired by monoplane or biplane systems.	3D model reconstruction from 2 angiographic projections with angles ≥ 25º apart, acquired by monoplane or biplane systems.
Flow velocities	A ***fixed*** empiric HFV of 0.35 m/s that was derived from previous FFR studies was used for computation.	Frame count analysis is performed, ***without*** pharmacologically induced hyperemia, to derived the HFV.	Frame count analysis is performed ***during hyperemia***, induced by i.v. administration of adenosine.
Correlation with FFR	r= 0.69	r= 0.77	r=0.72
Diagnostic accuracy for identifying an FFR of ≤0.80	80%	86%	87%

Table 2. Three different QFR computations in three different flow models.
aQFR= adenosine Quantitative Flow Ratio. cQFR= contrast Quantitative Flow Ratio. fQFR= fixed Quantitative Flow Ratio. HFV =hyperemic flow velocity. i.v.= intravenous

	FFR	iFR	QFR
Indication	Intermediate coronary stenosis assessment.	Intermediate coronary stenosis assessment.	Intermediate coronary stenosis assessment.
Guidelines recommendations	Class IA[10]	Class IA[3]	-
Pressure wire use	Yes [18]	Yes [57]	No [70]
Hyperemia	Needed [18]	Not needed [57,58,60]	Needed for aQFR [70]
3D-reconstruction	No	No	Yes
Cut-off value for ischemia	<0.80 [10,50]	<0.89[64]	<0.80 [73,74]
Hemodynamic principles	$Pd_{Hyperemia}/Pa_{Hyperemia}$ [18,40]	$Pd_{wave\text{-}free\ period}/Pa_{wave\text{-}free\ period}$ [57]	Fluid dynamic equations, emulating hyperaemic flow velocity [69]
Strengths	Currently, the gold standard for coronary lesions assessment. Evidence from outcome studies.	Adenosine not required. Supported by outcome studies.	Non-invasive. Cheap. Not requiring pressure wire. No need for adenosine (cQFR only). Faster than FFR and iFR.
Limits	Invasive. Expensive. Use of pressure wire and adenosine.	Invasive. Expensive. Use of pressure wire.	No outcome studies are available.

Table 3. Main features, strengths and limitations of FFR, iFR, and QFR.
aQFR= adenosine Quantitative Flow Ratio. cQFR= contrast Quantitative Flow Ratio.
iFR= instantaneous wave-free ratio. FFR= Fractional Flow Reserve. Pa= aortic pressure. Pd= pressure measured downstream the stenosis. QFR= Quantitative Flow Ratio.

Figure1



Left 2D Image

Right 2D Image

3D Reconstruction: LAO 4, CRA 59

Diameter Diagram

Figure2

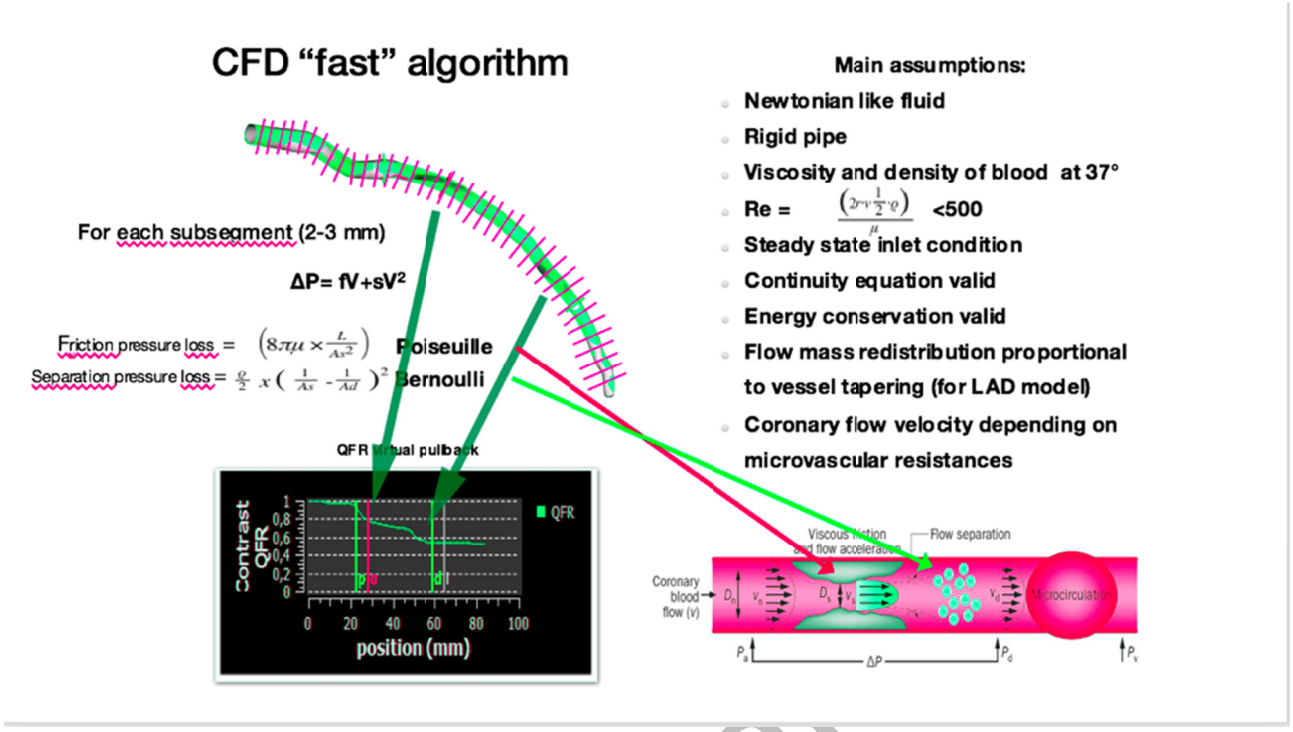


Figure3