Coronary Physiology Assessment for the Diagnosis and Treatment of Coronary Artery Disease

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KEYWORDS

• Percutaneous coronary intervention • Physiologic assessment • FFR • IFR • QFR

KEY POINTS

- Percutaneous coronary intervention is a well-established treatment option in patients with coronary artery disease. Survival benefit has been demonstrated, however, only by treating coronary lesions responsible for myocardial ischemia.
- Fractional flow reserve (FFR) is the gold standard for the analysis of lesion severity. Its use is limited, however, by reimbursement (not available in some countries, such as Italy) and the need for adenosine, which adds time, complexity, and potential side effects to the procedure.
- Nonhyperemic instantaneous wave-free ratio (iFR)-guided revascularization showed safety and effectiveness with respect to adverse events at 12-month. Newer tools, such as resting full-cycle ratio, diastolic hyperemia-free ratio (DFR), and the diastolic pressure ratio (dPR), showed good accuracy compared with FFR and iFR.
- Less invasive quantitative flow ratio (QFR) enables FFR computation from 3-dimensional quantitative coronary angiography and thrombolysis in myocardial infarction frame counting. Data showed a good performance of QFR with an excellent agreement and correlation with FFR.
- Nowadays, simple physiologic assessment of coronary stenosis is essential for interventional cardiologists. The use of any of these tools needs to be implemented to improve patient care.

INTRODUCTION

Coronary artery disease (CAD) and its consequences remain the leading causes of premature death and lifelong disability in most countries.[1] The main issue in treating CAD by percutaneous coronary intervention (PCI) is to distinguish lesions that are responsible for ischemia from those that are not. Although stenting functionally significant coronary lesions provides survival benefit and relief of symptoms, no benefit has been shown in treating nonfunctionally significant lesions.[2,3] So, demonstration of myocardial ischemia is the key aspect to decide whether or not PCI has to be performed.

Angiographic assessment of disease severity is weakened numerous limitations, because both physician visual assessment and quantitative

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coronary analysis (QCA) have shown poor correlation with functional stenosis severity. For these reasons, invasive functional assessment must be available and used before revascularization in patients with a high likelihood of CAD undergoing early angiography or when noninvasive functional imaging tests either are not available or are inconclusive.[4]

Intracoronary transgradient pressure measurement through fractional flow reserve (FFR) has become the gold standard for the assessment of lesion severity.[5] FFR measurement, however, requires adenosine administration to induce hyperemia, which limits its use in clinical practice. Thus, interest has been focused on indices derived from resting gradient alone, not requiring hyperemia, such as distal coronary pressure–to–aortic pressure (Pd/Pa), the Pd/Pa measured during contrast-induced hyperemia (cFFR) or instantaneous wave-free ratio (iFR), and resting full-cycle ratio (RFR). Both hyperemic and nonhyperemic indices, however, require invasive pressure guide wire utilization. More recently, the less invasive quantitative flow ratio (QFR) has emerged as a new tool to assess the functional significance of coronary lesions, showing excellent correlation with FFR.

The aim of this review is to provide a comprehensive overview of existing evidence regarding the physiologic assessment of coronary lesions and highlight newly available options in the field.

IMPORTANCE OF ISCHEMIA AND RATIONALE FOR PERCUTANEOUS CORONARY INTERVENTION

Coronary stenosis are defined as functionally significant if they are resposible for inducible myocardial ischemia. Several studies demonstrated that the presence of ischemia correlates with adverse clinical outcomes[6] and that the greater the extent of jeopardized myocardium, the higher the risk of death or myocardial infarction (MI).

Correct identification of functionally significant coronary lesions is of paramount is mandatory to properly pose indication for revascularization. In patients with non–functionally significant coronary stenosis, no benefits have been demonstrated compared with optimal medical therapy, even at 15-year follow-up.[2,3]

It has been shown that revascularization with PCI of ischemic lesions allows relief of symptoms more effectively than medical therapy alone.[7] The 5-year follow-up of the Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis (DEFER) trial[8] showed that stenting ischemia-producing lesions (FFR <0.75) improves symptoms. At baseline, 90% of patients had angina, whereas at 5-year follow-up after stenting, 72% of patients were free from symptoms. Similarly, the Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention (FAME)[9] study showed that 80% of patients were free from angina 2 years after stenting.

Recently the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial[10,11] questioned the role of PCI in reducing the rate of cardiac death and MI. The trial randomized more than 5000 patients with demonstrated obstructive CAD (at coronary computed tomography) and moderate to severe ischemia (>10% in physiologic tests; nuclear imaging was used most frequently) to percutaneous or surgical revascularization versus optimal medical therapy. No difference in the primary composite endpoint of cardiovascular death, MI, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest was noticed between the 2 strategies. The trial initially was designed, however, to include objective endpoints, such as cardiovascular death and MI, but then was changed to a composite endpoint to accrue more events. Cardiovascular death or MI did not differ over the 4 years, but the curves initially higher in the invasive group crossed at approximately 2 years and were lower in the invasive group at 2 years. Total MI rate did not differ between groups, but the invasive group had significantly higher rate of periprocedural MI and lower rate of spontaneous MI. It has been shown that spontaneous MIs not related to the PCI are independent predictors of mortality whereas periprocedural MIs are not related to the prognosis.[12] Moreover, the trial findings were sensitive to the definition of MI adopted. The quality-of-life outcomes analysis also reported significant improvement in angina control and quality of life with the invasive strategy in patients symptomatic at baseline.

FRACTIONAL FLOW RESERVE

FFR is defined as the ratio between the maximal blood flow in a coronary artery with a stenotic lesion and the maximal blood flow in the same artery if the stenosis would not be present. The ratio of these 2 flows is expressed as ratio between 2 pressures. FFR is calculated as the ratio between the Pd and the Pa at maximum blood flow. The derived Pd/Pa represents the relative fraction of total flow across the stenosis. FFR can be measured by coronary guidewires equipped with a pressure sensor located near the tip. Hyperemia

is required for FFR calculation and it can be obtained minimizing microvascular resistance through adenosine administration by either continuous intravenous infusion (140 μg/kg/min) or intracoronary bolus (right coronary artery 50–100 μg, left coronary artery 100–200 μg). Although associated with potential drawbacks, intravenous administration enables achieving a more consistent hyperemic effect, which allows a pressure pull back during steady-state hyperemia for the hemodynamic analysis of all abnormalities along the length of the coronary artery.[13] In normal coronary arteries, the expected FFR value is 1.0, meaning the absence of obstacles to the coronary flow. In diseased coronary arteries, an FFR value below the threshold of 0.80 indicates hemodynamically significant stenoses, causing myocardial ischemia, with an accuracy of 90%.[14,15] To date, FFR is the gold standard for the detection of myocardial ischemia because it is much more accurate in distinguishing functionally significant stenoses than noninvasive provocative tests, such as exercise electrocardiogram, myocardial perfusion scintigraphy, and stress echocardiography.[14] Despite the class IA recommendation by current guidelines,[5] however, real-life data showed that the use of physiology-based guidance to assist coronary revascularization decisions is performed in lower than 10% of the procedures.[16]

EVIDENCE FOR FRACTIONAL FLOW RESERVE–GUIDED PERCUTANEOUS CORONARY INTERVENTION STRATEGY IN STABLE CORONARY ARTERY DISEASE PATIENTS

Currently, FFR is a diagnostic tool routinely available and used in most catheterization laboratories for clinical decision making. Several studies have validated that FFR-guided PCI is safe and reduces the rate of major adverse cardiovascular events, including the need for urgent revascularization. The DEFER[8] study randomized nonsignificant stenoses (FFR >0.75) to be treated either medically or by stenting. The 15-year follow-up showed that the rate of MI was significantly lower in the deferred group (2.2%) compared with patients who underwent revascularization (10%).[3] The FAME[9,17] study showed that in patients with multivessel disease (MVD) a strategy of FFR-guided PCI resulted in a significant decrease of major adverse cardiac events for up to 2 years after the index procedure. The FAME 2[18] study was the first large randomized trial in which patients in whom at least 1 stenosis was functionally significant (FFR $\leq$0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical therapy group), whereas patients with nonfunctionally significant stenosis (FFR >0.80) were entered into a registry and treated with medical treatment only. A total of 888 patients were randomized between PCI and medical therapy. The trial was stopped prematurely due to an increased rate of major adverse cardiovascular events in the medical-therapy group compared with the PCI group. Also, the 5-year results confirmed that FFR-guided PCI plus the best available medical therapy improved outcomes, with a significantly lower rate of the primary composite endpoint of death, MI, or urgent revascularization compared with the best available medical therapy alone.[19] The ongoing FAME 3[20] trial will investigate whether in patients with MVD an FFR-guided PCI approach using contemporary drug-eluting stents is noninferior compared with surgical revascularization. Finally, a large individual patient data meta-analysis[2] provided strong evidence that an FFR-guided strategy improves both clinical outcomes (with a significant reduction in death and MI) and quality of life. Conversely to this, large amount of data favoring and FFR based PCI strategy, the Functional Testing Underlying Coronary Revascularisation study was prematurely halted due to a doubling in the risk of death within the first year, with no beneficial impact seen on other outcomes, in patients with MVD undergoing FFR-guided PCI.

FRACTIONAL FLOW RESERVE IN ACUTE CORONARY SYNDROME PATIENTS

Physiologic evaluation by FFR of infarct-related artery (IRA) is neither practical nor valid due to heightened microvascular resistance after MI that falsely increases the FFR measurement of the culprit vessel. In acute coronary syndrome (ACS) patients with MVD, however, FFR evaluation of nonculprit lesions has theoretic appeal and several data showed the feasibility of FFR use in this setting (**Table 1**).

In the Fractional Flow Reserve vs Angiography in Guiding Management To Optimize Outcomes in Non-ST-Segment Elevation Myocardial Infarction study,[21] 350 patients with non–ST-elevation MI (STEMI) and MVD, were randomly assigned to an FFR-guided PCI or angiography-guided standard care. Revascularization rate was significantly lower in the FFR-guided group compared with angiography guidance alone, with otherwise no detectable difference in health outcomes and quality of life between the 2 populations, underlying the feasibility and safety of this strategy in these patients.

Also, in patients presenting with STEMI and MVD, incomplete revascularization showed to be

Table 1
Main studies of validation and outcomes of physiologic diagnostic tools

Study	Tool	Patients, n	Study Design	Population	Primary Endpoint	Follow-up	Outcomes
DEFER[8,3]	FFR	325	Prospective, randomized comparing medical therapy vs PCI for non-ischemic lesions (FFR>0.75)	Stable CAD	Adverse cardiac events	15 y	No differences in rate of death MI significantly lower in defer group
FAME[9,16]	FFR	1005	Prospective, randomized comparing FFR-guided (FFR<0.80) vs angio-guided PCI	Multivessel disease	Composite of death, MI and repeat revascularization	5 y	Lower rate of the composite endpoint in the FFR-guided vs angiography-guided group
FAME 2[17,18]	FFR	888	Prospective, randomized comparing OMT vs PCI + OMT in significant lesions (FFR<0.80)	Stable CAD	Composite of death from any cause, nonfatal MI and urgent revascularization	5 y	Significantly lower rate of priary endpoint in PCI group vs OMT group
FAMOUS NSTEMI[20]	FFR	350	Prospective, randomized comparing FFR-guided (FFR<0.80) vs angiography guided PCI	NSTEMI and Multivessel disease	The between-group difference in the proportion of patients allocated to medical management	12 mo	Higher rate of medically managed patients in the FFR- vs angiography group.
DANAMI 3 PRIMULTI[23]	FFR	627	Prospective, randomized comparing complete FFR-guided (FFR<0.80) PCI vs IRA-only PCI	STEMI and Multivessel disease	Composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation of lesions in non-IRA	27 mo	Significantly fewer repeat revascularisations in the FFR-guided PCI group No differences in all-cause mortality and non-fatal reinfarction

COMPARE-ACUTE[24,25]	FFR	885	Prospective, randomized comparing complete FFR-guided (FFR<0.80) PCI vs IRA-only PCI	STEMI and Multivessel disease	Composite of all-cause death, MI, any revascularization and cerebrovascular event	3 y	FFR-guided complete revascularization is more beneficial in terms of outcome and health-care costs compared to IRA-only revascularization
RESOLVE[27]	Pd/Pa, iFR and FFR	1768	Non-randomized, retrospective	Coronary artery disease undergoing physiologic assessment	Level of diagnostic accuracy of iFR and Pd/Pa compared with FFR	-	iFR and Pd/Pa compared with FFR demonstrated an overall accuracy of ~80%
RINASCI[28]	cFFR vs FFR	104	Observational, prospective evaluating diagnostic accuracy of cFFR (<0.83) vs FFR	Intermediate coronary stenoses	Accuracy of cFFR in comparison to FFR	-	Strong correlation between cFFR and FFR values
DEFINE-FLAIR[29]	iFR vs FFR	2492	Prospective, randomized study comparing iFR (iFR<0.89) vs FFR-guided PCI	CAD with at least one intermediate stenosis in a native artery	Composite of death, nonfatal MI or unplanned revascularization	12 mo	iFR guided PCI was noninferior to FFR-guided PCI with respect to primary endpoint rate
iFR-SWEDEHEART[30]	iFR vs FFR	2037	Prospective, randomized evaluating non inferiority of iFR (iFR<0.89) vs FFR in detecting functionally significant lesions	Stable angina or acute coronary syndromes	Composite of death from any cause, nonfatal MI or unplanned revascularization	12 mo	iFR-guided revascularization strategy was non-inferior to FFR-guided PCI with respect to primary endpoint rate
VALIDATE RFR[31]	RFR vs iFR	651	Retrospective, designed to derive and validate the RFR	Intermediate coronary stenoses	Agreement between RFR and iFR	-	RFR was highly correlated to iFR

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Table 1
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Study	Tool	Patients, n	Study Design	Population	Primary Endpoint	Follow-up	Outocomes
Lee et al,[32] 2019	RFR or dPR	435 (1024 vessels)	Study population derived from the 3 V FFR-FRIENDS study (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease; NCT01621438) and the 13N-ammonia PET registry.	Intermediate coronary stenoses	Agreement of RFR or dPR with IFR and FFR and the risk of composite endopinf of cardiac death, vessel-related MI, and vessel-related ischemia-driven revascularization	2 y	Both RFR and dPR showed a significant correlation with iFR which was higher than that FFR. All tools showed significant association with the risk of 2-y vessel-oriented composite outcomes
FAVOR[38]	QFR and FFR	73 (84 vessels)	Prospective, observational	Intermediate coronary stenoses	Correlation and agreement between QFR and FFR	-	fQFR, cQFR and aQFR showed a good correlation with FFR
WIFI II[39]	QFR and FFR	362	Prospective, observational	Unselected consecutive patients	Feasibility and diagnostic performance of QFR	-	QFR assessment showed good agreement and diagnostic accuracy compared with FFR
FAVOR II China[40]	QFR and FFR	308	Prospective, multicenter	Intermediate coronary stenoses	Improvement of the diagnostic accuracy of coronary angiography by QFR	-	Sensitivity and specificity in identifying hemodynamically significant stenosis were significantly higher for QFR than for QCA

FAVOR II Europe and Japan[41]	QFR, 2D-QCA and FFR	329	Prospective, observational	Stable angina	Sensitivity and specificity of QFR compared with 2D-QCA using FFR as a reference standard	-	Sensitivity and specificity by QFR significantly higher than by 2D-QCA
HAWKEYE[42]	QFR	602	Prospective, multicenter evaluating the prognostic value of QFR (<0.80) measured immediately after PCI	Patients undergoing complete revascularization with successful PCI	Vessel-oriented composite endpoint, defined as vessel-related cardiovascular death, vessel-related myocardial infarction, and ischemia-driven target vessel revascularization	12 mo	Lower values of QFR after complete and successful revascularization predict subsequent adverse events

Data from Refs.[3,8,9,16–18,20,23,25,27-32,38–42]

an independent risk factor for non–target vessel–related adverse events[22] and FFR showed to be useful a tool for the identification of nonculprit lesions needing revascularization.[23] The Complete Revascularisation vs Treatment of the Culprit Lesion Only in Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Disease trial[24] (n = 627) showed a reduction in composite endpoint with FFR-guided complete revascularization performed as a staged procedure during the hospitalization versus IRA-PCI only, and similarly the Fractional Flow Reserve–Guided Multivessel Angioplasty in Myocardial Infarction trial[25,26] (n = 885; 12-month follow-up) showed that FFR-guided complete revascularization during the index procedure significantly reduced the primary endpoint rate compared with IRA-only PCI. The ongoing Functional vs Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease randomized trial (NCT03772743) will investigate if, in elderly patients (>75 years) with MI and MVD, a functional-guided PCI (FFR, iFR, cFFR, and QFR all are allowed and left to operator discretion) is superior to a culprit-only strategy in the reduction of 1-year adverse cardiovascular events.

NONHYPEREMIC INDICES FOR CORONARY STENOSIS ASSESSMENT

Although a critical mass of evidence supports the use of FFR for guiding revascularization strategy in patients with CAD, this tool remains flawed by substantial underutilization in clinical practice.[27] Among the barriers preventing more extensive use of FFR, the requirement of adenosine administration to achieve maximal hyperemia often is flagged, because it adds time and complexity to the procedure and exposes patients to adverse side effects.[27] Moreover, the usefulness of FFR is limited in the presence of true bifurcations and/or tandem lesions, which are challenging to interrogate properly.[27] To overtake these limits, in recent years numerous studies investigated the use of nonhyperemic indices alternative to FFR, such as the simple resting Pd/Pa measurement, cFFR,[28] iFR (the most widely validated after FFR[27,29,30]), RFR,[31,32] diastolic hyperemia-free ratio (DFR), and the diastolic pressure ratio (dPR) (**Table 2**).[32]

The iFR grounds on the concept that at a specific time in diastole—the so-called wave-free period—intracoronary pressure and flow decline together in a linear fashion, whereas microvascular resistance remains more stable and significantly lower than the rest of cardiac cycle.[27] Therefore, over this period, the pressure gradient across coronary stenosis can be measured obviating generating hyperemia through adenosine infusion. Another advantage of iFR is the ability to individually assess lesions severity in the context of diffuse vessel disease, thus minimizing FFR limitations in the setting of serial coronary stenoses. Specifically, by using the coregistration of the iFR pullback trace and the coronary angiogram (ie, plotting measured values directly over angiographic views), iFR is able to detect lesion-specific pressure drop along the whole length of the vessel and differentiate focal from diffuse coronary disease.[27] This allows the cardiologist to (1) properly identify which lesion/s should be treated (if any), (2) accurately predict to what extent coronary physiology will improve after PCI per each lesion, and (3) confidently decide the number, length, and position of stents to be used to pursue a successful procedure.[27] When its performance has been tested by meta-analyzed data,[33] iFR showed a significant correlation (0.79 [0.78–0.82]) with the gold-standard of FFR and good diagnostic accuracy for the identification of FFR-positive stenoses (area under the curve = 0.88 [0.86–0.90]), confirming its role of reliable adenosine-free alternative in practice.[33] Recently, 2 large randomized, controlled trials, the blinded Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation[29] and the open-label Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome,[30] established that iFR-guided revascularization (cutoff point of 0.89) is as safe and effective as FFR-guided revascularization (cutoff point of 0.80) with respect to adverse cardiac events at 12 months.[29,30] Besides patients with stable CAD, both studies tested iFR for nonculprit lesions evaluation in patients with ACS, proving the noninferiority of iFR to FFR in this setting.[29,30] Although evidence overall speaks in favor of substantial equivalence of the 2 techniques,[29,30,33] the enduring controversy on how to manage patients with iFR values that are borderline or discordant with FFR[34] (especially for left main and proximal left anterior descending artery lesions)[35] warrants further investigations for a full understanding of their synergistic use (**Figs. 1** and **2**).

The rise of iFR encouraged the development of additional hyperemia-free indices, intending to overcome potential iFR limitations, such as the sensitive automated landmarking of pressure waveform components and the assumption that maximal flow and minimal resistance occur during a specific (fixed) period of diastole.[27] In this background, the RFR has been proposed as a novel hyperemia-free tool able to measure coronary pressure at the point of absolute lowest resting Pd/Pa in the cardiac cycle.[31] In other words, the

Table 2
Main features, strengths, and limitations of actually available tools for coronary lesions severity assessment

Tool	Definition	Ischemia Cut-off	Need of Pressure Wire	Need of Hyperemia	Strengths	Limits
FFR	Average Pd/Pa during adenosine induced hyperemia	≤ 0.80	Yes	Yes	Gold standard for lesion severity assessment Supported by outcome studies	Invasive Need of guidewire use and adenosine administration
Pd/Pa	Average Pd/Pa during the entire cardiac cycle	≤ 0.91	Yes	No	Adenosine not required	Invasive Need of guidewire No outcomes studies available
cFFR	Average Pd/Pa during contrast-induced hyperemia	≤ 0.83	Yes	Contrast-induced hyperemia	Adenosine not required	Invasive Need of guidewire No outcomes studies available
iFR	Average Pd/Pa during the WFP	≤ 0.89	Yes	No	Adenosine not required Supported by outcomes studies	Invasive Need of guidewire
RFR	Lowest mean Pd/Pa during the entire cardiac cycle	≤ 0.89	Yes	No	Adenosine not required	Invasive Need of guidewire No outcomes studies available
DFR	Average Pd/Pa during diastolic period when Pa < mean Pa	≤ 0.89	Yes	No	Adenosine not required	Invasive Need of guidewire No outcomes studies available
DPR	Average Pd/Pa during the entire diastolic period	≤ 0.89	Yes	No	Adenosine not required	Invasive Need of guidewire No outcomes studies available
dPR	Pd/Pa during the flat period (identified using dP/dt) of WFP	≤ 0.89	Yes	No	Adenosine not required	Invasive Need of guidewire No outcomes studies available
QFR	Fluid dynamic equations, emulating hyperaemic flow velocity	≤ 0.80	No	Adenosine needed only for aQFR	Less invasive Not requiring pressure wire No need for adenosine (aQFR only). Faster than FFR and iFR.	Outcome studies not available yet

Abbreviations: aQFR, adenosine quantitative flow ratio; cFFR, contrast FFR; DFR, diastolic hyperemia-free ratio; dP/dt, change in pressure/change in tim; DPR, diastolic pressure ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; Pd/Pa, pressure $_{distal}$/pressure $_{aorta}$; QFR, quantitative flow ratio; RFR, resting full-cycle ratio.

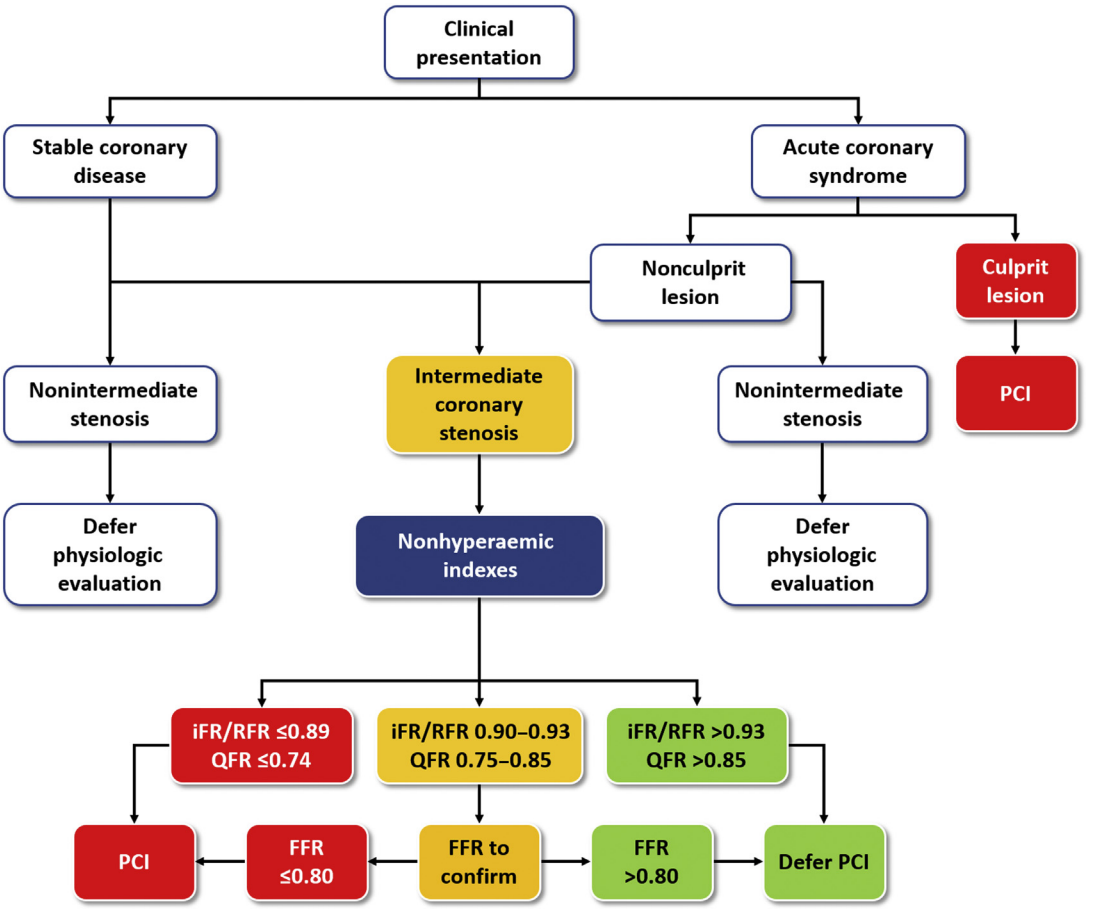

Fig. 1. Integrated revascularization strategy with hyperemic and nonhyperemic indices for coronary physiology evaluation.

RFR measures the maximal relative pressure difference during the entire cardiac cycle (and not limited to diastole), aiming at simplifying iFR assumptions and limiting potential biases.[31] The diagnostic performance of RFR (at a cutoff point of 0.89) has been tested and validated in large population studies,[31,32] suggesting its potential use as an alternative to iFR or FFR to guide revascularization in patients with CAD.[31,32] Considering the current lack of randomized clinical trials, however, as well as its potential inaccuracies in specific (and more complex) settings,[36] while awaiting solid evidence, RFR-guided strategy cannot be yet considered as interchangeable to FFR on iFR in clinical practice.

THREE-DIMENSIONAL QUANTITATIVE CORONARY ANGIOGRAPHY AND BLOOD FLOW SIMULATION DERIVED INDEX: QUANTITATIVE FLOW RATIO

Although hyperemic and nonhyperemic indices for coronary stenosis assessment have proved their undisputable benefit, their penetration in clinical practice remains low. In recent years, modern software for 3-dimensional (3-D) vessel reconstruction and flow model calculation has been developed for functional assessment of coronary stenosis. QFR is an innovative angiographic-based technique allowing computation of FFR from 3-D–QCA and thrombolysis in MI frame counting based on computational fluid dynamics technology.[37]

For 3-D reconstruction, 2 diagnostic angiographic projections (at least 25° apart) must be obtained; frame rate count is analyzed in both angiographic views to obtain patient-specific hyperemic flow velocity evaluation during contrast injection and/or adenosine administration. QFR uses 3 different flow simulation models: (1) fixed-flow QFR (fQFR), with a fixed empiric hyperemic flow velocity of 0.35 m/s; (2) contrast-flow QFR (cQFR), with a modeled virtual hyperemic flow velocity derived from contrast flow without adenosine use; and (3) adenosine-flow QFR (aQFR),

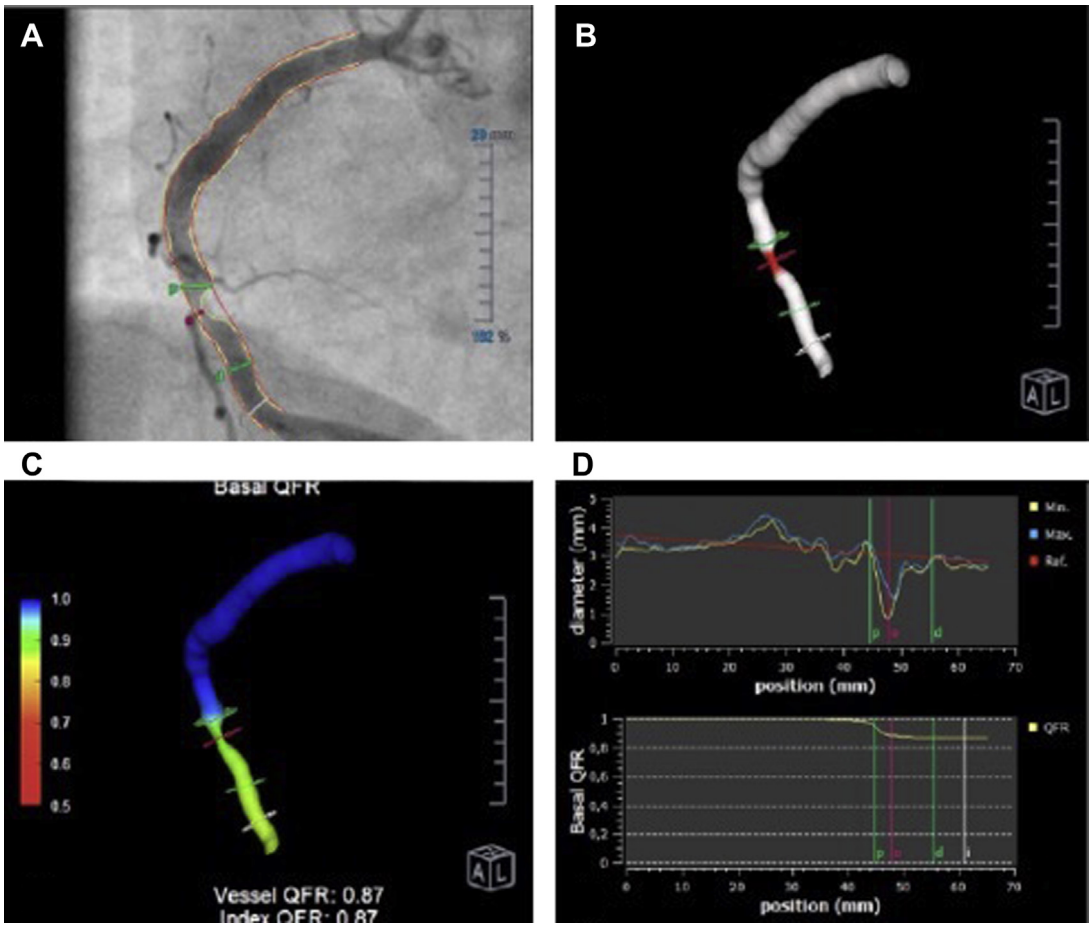

Fig. 2. Discordance between angiographic and functional severity of a lesion in the right coronary artery. (*A*) Oblique left projection of the right coronary artery. (*B*) 3-D QCA derived with diameter stenosis of 73.6%. (*C*) QFR = 0.87. (*D*) Luminal diameter and QFR pull-back.

with adenosine administration to induce maximum hyperemia. The cutoff point has been set at 0.80 and these 3 models were compared with the measured FFR. In the Functional Assessment by Various Flow Reconstructions (FAVOR) pilot trial, fQFR, cQFR, and aQFR showed good correlation with FFR (r = 0.69, *P*<.001; r = 0.77, *P*<.001; and r = 0.72, *P*<.001; respectively).[38] Similar results were obtained in the Wire-Free Functional Imaging II, where QFR showed a good correlation with FFR (r = 0.70, *P*<.0001).[39]

Diagnostic accuracy of QFR was evaluated in both the FAVOR II China and FAVOR II Europe and Japan studies.[40,41] In the first, QFR analysis showed diagnostic accuracy of 92.7% and 93.3% when it was performed online and offline, respectively, using FFR as reference. In the European-Japanese study, online QFR proved e more effective than 2-dimensional QCA in detecting severe coronary stenosis, with sensitivity and specificity of 87% and positive and negative predictive values of 78% and 94%, respectively, with FFR as reference. Several recent meta-analyses[42–44] confirmed good performance of QFR with an excellent agreement and correlation with FFR.

QFR computation can be applied in several clinical scenarios. In patients with prior MI, QFR accuracy in assessing functional lesion severity might be reduced[45] (not considering the vital myocardium). In STEMI, however, it can be a useful tool to assess nonculprit lesions in patients with MVD[46] as well as residual microvascular dysfunction.[47] Furthermore, QFR appears to be a reliable tool in assessing the functional relevance of coronary stenosis in patients with concomitant severe aortic stenosis scheduled for transcatheter aortic-valve implantation.[48]

Focusing on outcomes, the Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation[49] study showed that lower QFR values after complete revascularization could predict subsequent adverse events. In daily practice, QFR also can be useful in risk stratification of patients without coronary stenosis, because low QFR values correspond to an increased risk of developing future cardiovascular events.[50] The ongoing FAVOR III study (NCT03656848) is adequately powered to investigate if a strategy QFR-guided PCI provides superior clinical outcome and cost-effectiveness compared with standard coronary angiography–guided PCI in CAD patients.

The reliability of QFR and its benefits in terms of cost-effectiveness and less invasiveness make this technique attractive for interventional cardiologists in assessing intermediate coronary stenosis, and its routine use in the catheterization laboratory is expected to increase in the near future.

SUMMARY

Thanks to the advantages in pharmacologic treatment and procedural techniques that significantly reduced complications rates,[51,52] PCI is one of the most wildly performed interventional procedures worldwide. Stenting nonischemic lesions is not cost effective, however, and worsens the outcomes. Detecting functionally significant stenosis is a key aspect to decide which lesion (if any) need to be treated. FFR is considered the gold standard but is still underutilized in practice. Nowadays, technological advances have led to the development of new invasive physiology techniques, such as the nonhyperemic indices as well as the less invasive QFR, which showed good reproducibility and correlation with FFR. In modern catheterization, laboratory physiologic assessment with any of these tools (according to operator expertise) should be routinely available and used to improve the appropriateness of revascularization and define the optimal intervention strategy to increase safety, efficiency, and successful outcomes after PCI.

CONFLICTS OF INTEREST

None.

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