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Instantaneous Wave-Free Ratio: Novel Adenosine-Free Method to Assess Intracoronary Physiology

Anlık Dalgasız Oran: İntrakoroner Fizyolojiyi Değerlendirmek için Yeni Adenozin Bağımsız Metot

REVIEW
DERLEME

ABSTRACT

Fractional flow reserve assessment was accepted as a crucial strategy in stable patients undergoing coronary angiography without prior noninvasive evaluation in the presence of borderline lesions and in patients with multivessel coronary artery disease. Instantaneous wave-free ratio, measured during a specific diastolic interval, emerged as a nonhyperemic pressure ratio. Due to its advantages such as not requiring a vasodilating agent, rapidity of procedure, pullback phenomena for the assessment of individual stenosis in tandem lesions or diffusely infiltrated vessels, and virtual percutaneous coronary intervention which allows the assessment and justification 'of' optimal coronary revascularization, instantaneous wave-free ratio became a valuable option in the field of coronary physiology. This review aims to address coronary physiological concept with fractional flow reserve and emergence of instantaneous wave-free ratio through cornerstone studies as well as the use of instantaneous wave-free ratio in different clinical scenarios.

Keywords: Interventional cardiology, myocardial ischemia, myocardial revascularization, percutaneous coronary intervention

ÖZET

Fraksiyonel akım rezervi, çoklu koroner arter hastalığı olan hastalarda ve borderline lezyon varlığında daha önce non-invaziv değerlendirilmemiş koroner anjiyografi işlemine giren hastalarda önemli bir strateji olarak kabul edilmiştir. Spesifik bir diyastolik aralıkta ölçülen *instantaneous wave free ratio* hiperemik olmayan bir basınç oranıdır. Vazodilatatör ajan gerektirmeme, işlem hızı, geri çekme fenomeni ile ardışık ve yaygın infiltre damarlarda birbirinden ayrı darlıkların değerlendirilmesi ve optimal koroner revaskülarizasyonun değerlendirilmesi ile gerekçelendirilmesine izin veren sanal perkütan koroner girişim gibi avantajlarına bağlı olarak *instantaneous wave-free ratio*, koroner fizyoloji alanında değerli bir seçenek olmuştur. Bu derlemede fraksiyonel akım rezervi ile koroner fizyolojik kavramını ve köşe taşı çalışmalarla *instantaneous wave-free ratio*'nun ortaya çıkışını farklı klinik senaryolarda kullanımıyla birlikte işaret etmek amaçlanmıştır.

Anahtar Kelimeler: Girişimsel kardiyoloji, miyokardial iskemi, miyokardiyal revaskülarizasyon, perkütan koroner girişim

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The revascularization of ischemia-causing coronary stenosis is globally employed in the treatment of coronary artery disease (CAD). Patients with ischemic symptoms can be referred for coronary angiography without being investigated by noninvasive tests. Once coronary angiography is performed, the decision for revascularization can generally be challenging when it comes to assessing lesions between 30% and 70%.[1] Fractional flow reserve (FFR) assessment was accepted as a valuable option in stable patients undergoing coronary angiography without prior noninvasive evaluation in the presence of the borderline lesions and in patients with multivessel CAD.[2] Due to the difficulties of the use of adenosine (i.e. cost and contraindications), the utilization of FFR has remained limited worldwide.[3] Instantaneous wave-free ratio (iFR) has emerged as a new adenosine-independent, pressure-derived index of coronary stenosis severity in the recent years.[4] It has been compared with FFR in 2 prospective and randomized trials,[5,6] and it was recommended in the latest European Society of Cardiology myocardial revascularization guidelines in order to evaluate the hemodynamic significance of

intermediate-grade stenosis.[2] In this review, we aim to describe the application of coronary physiology with FFR and emergence of iFR through cornerstone studies as well as its employment in different clinical scenarios.

Fractional Flow Rate

Basic Principles

Fractional flow reserve hemodynamic basis relies on Ohm's law which states that the flow is comparable with the pressure if the resistance is minimal and invariable. The pressure in a normal coronary artery is equal to the aortic pressure (Pa) under normal conditions.[7] As the pressure can be used as a representative of flow under maximal hyperemia (minimal resistance) according to Ohm's law, FFR is calculated as the ratio of the pressure distal to a stenosis (Pd) and the pressure proximal to the stenosis (Pa) during maximal hyperemia induced by a vasodilating agent.[3,7] Fractional flow reserve is linearly related to maximum blood flow, and its normal value is 1.0, irrespective of the patient, artery, and blood pressure. Therefore, FFR could be used to assess the flow-limiting potential of a coronary artery stenosis under optimal experimental conditions.[8] The practical aspect of performing an FFR is identical to that of routine percutaneous coronary intervention (PCI). The use of guiding catheters is generally recommended. Before passing the stenosis, the pressures recorded by a 0.014-inch sensor wire and by the guiding catheter should be equal. Adequate anticoagulation should be administered. It is necessary to induce maximal vasodilatation in both the epicardial and microvascular arteries.[8] Along with intracoronary nitrate, recommended to counteract epicardial vasoconstriction, intravenous or intracoronary adenosine is used to induce coronary hyperemia.[3,8] Pd/Pa is theoretically equal to 1 in a healthy coronary artery, as there is no decrease in pressure along its course, not even during maximal hyperemia. Stenoses with Pd/Pa < 0.75 almost invariably induce myocardial ischemia, whereas stenoses with Pd/Pa > 0.80 are almost never associated with exercise-induced ischemia. Thus, in clinical practice, stenting is always justified in a stenosis with a Pd/Pa < 0.75, whereas in a stenosis with Pd/Pa > 0.80, stenting can be delayed and optimal medical treatment is sufficient.[8]

Specific clinical and technical features may affect the feasibility and accuracy of FFR measurement. Pd/Pa values between 0.75 and 0.80 are called gray zones, and treatment strategies for this range are still controversial.[9] A recently published meta-analysis including 2683 patients with a median follow-up of 32 months assessed patients with coronary stenosis and gray zone FFR.[10] The analysis demonstrated that while revascularization significantly reduced the risk of major adverse cardiac events and target vessel revascularization in these patients, it was not significantly superior to deferral in terms of all-cause death, cardiac death, and myocardial infarction.[10] Additionally, microvascular impairment related with the factors such as diabetic microangiopathy, former myocardial infarction, and left ventricular hypertrophy could reduce maximal hyperemia, and thus FFR values may be misjudged.[9] Besides interpretation difficulties, technical aspects and specific clinical features may limit the accuracy of FFR. Prolongation of procedural time, extra costs due to pressure wire and vasodilator drugs and discomfort with side effects related with adenosine are potential procedural challenges.[11]

Clinical Trials

There are 3 cornerstone randomized trials related with FFR (Table 1). In the DEFER study, 325 patients with stable coronary disease were enrolled to assess whether FFR is a valuable tool for appropriate percutaneous coronary transluminal angioplasty (PTCA). Patients with the FFR > 0.75 were randomized to deferral group (n=91) or performance group (n=90) of PTCA. If the FFR were < 0.75, PTCA was performed as planned (reference group: n=144).[12] Depending on the results, event-free survival was similar between the deferral and performance groups (P=.27; 95% CI of absolute difference –15.7% to 4.6%). Event-free survival in the reference group was significantly lower than in the deferral group (P = .03). While the incidence of myocardial infarction or revascularization was similar in the deferral and performance groups (P=.14), it was significantly higher in the reference group (P < .001 compared with deferral group and P < .05 compared with performance group).[12] In the FAME study, a total of 1005 patients with lesions requiring PCI were randomized to angiography-guided PCI and FFR-guided PCI (stent deployment only for stenosis with FFR ≤0.80). At 1-year follow-up, the primary end point had occurred in 91 patients (18.3%)

ABBREVIATIONS

ACS	Acute coronary syndrome
CAD	Coronary artery disease
FFR	Fractional flow reserve
iFR	Instantaneous wave-free period
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PTCA	Percutaneous coronary transluminal angioplasty
STEMI	St-segment elevation myocardial infarction
TAVI	Transcatheter aortic valve implantation
WFP	Wave-free period

Table 1. Summary of Clinical FFR Trials[12-14]

Trials	Number of Patients	Clinical Presentation	FFR Threshold for Treatment	Primary End Point	Follow-up
DEFER	325	Stable coronary disease	≤0.75	Adverse cardiac event[a]	24 months
FAME	1005	Multivessel coronary artery disease	≤0.80	Major adverse cardiac events[b]	12 months
FAME 2	1220	Stable coronary artery disease	≤0.80	Major adverse cardiac events[c]	24 months

FFR, fractional flow reserve.
[a]All-cause mortality, myocardial infarction, CABG, coronary angioplasty, and any procedure-related complication necessitating major intervention or prolonged hospital stay.
[b]Composite of death, myocardial infarction, and any repeat revascularization.
[c]Death from any cause, nonfatal myocardial infarction, or unplanned hospitalization, leading to urgent revascularization.

in the angiography-guided group and in 67 patients (13.2%) in the FFR-guided group ($P=.02$).[13] As having assessed the benefit of FFR-guided PCI in previous clinical trials, the FAME 2 trial hypothesized whether FFR-guided PCI plus the best available medical therapy would be superior to the best available medical therapy alone.[14] A total of 1220 patients were enrolled and randomly allocated in the PCI group and medical therapy group. The inclusion criteria required the presence of at least 1 stenosis in a coronary artery with an FFR ≤ 0.80. The study was prematurely discontinued (mean follow-up 206 $\pm$ 119 days) due to significant difference in terms of primary end point between 2 groups. The primary end point was lower in the PCI group than in the medical therapy group (4.3% vs.12.7%; hazard ratio with PCI, 0.32; 95% CI, 0.19 to 0.53; $P < .001$).[14]

Instantaneous Wave-Free Ratio

Basic Principles and Early Validation Studies

Instantaneous wave-free ratio emerged as a nonhyperemic pressure ratio, which does not require the administration of hyperemic agents such as adenosine. It is measured during a specific diastolic interval, named as the wave-free period (WFP).[3] A pioneering study used wave intensity analysis with intracoronary wires in 20 individuals with normal coronary angiograms to identify and quantify the waves driving human coronary artery blood flow.[15] The study demonstrated that ventricular relaxation decreased the resistance of the microcirculation and lowers the pressure at the distal end of the coronary artery. This led to a suction wave propagating backward which was essential in the initiation of forward coronary blood flow.[15] During the WFP, it was observed that no new waves occurred and competing waves affecting coronary blood flow were quiescent (Figure 1).[16] Additionally, this period of the cardiac cycle was shown to have the lowest and most stable resistance attainable under resting conditions without the need for maximal pharmacological vasodilation.[17] Consequently, trans-stenotic pressure measurement during this period led to the discovery of a new pressure-derived index of stenosis severity that did not require pharmacologic vasodilation. Additionally, iFR can be measured on a beat-by-beat basis without the need of several beats to be averaged.[4,17]

After the emergence of the iFR concept, several studies assessed its validation with other functional tests. The ADVISE study included 131 patients undergoing coronary angiography and PCI. A total of 157 stenoses were detected to assess WFP and compare the diagnostic accuracy of iFR with FFR.[4] Wave-intensity analysis showed that the magnitude and variability of the intracoronary resistance observed during the WFP were identical with those realized over the entire cardiac cycle during pharmacologic vasodilation ($P=.70$ for the magnitude of resistance and $P=.96$ for the variation of resistance). In addition, the iFR was shown to be closely correlated with the FFR ($r=0.90$, $y = 1.0x + 0.03$).[4] The CLARIFY study that included 51 stenoses used the hyperemic stenosis resistance index (an invasive pressure and flow-based index) as the reference standard to compare the accuracy of iFR and FFR in terms of assessing the severity of the lesions.[18] Pressure and flow velocity were recorded distal to the target vessel coronary stenosis at rest and during adenosine-induced hyperemia. The iFR during adenosine administration (iFRa) was also calculated. The iFR cutoff point of 0.86 was compared with the ischemic cutoff points of hyperemic stenosis resistance (0.8) and FFR (0.75). iFR, iFRa, and FFR had equally diagnostic agreement with hyperemic stenosis resistance (receiver operating characteristic area under the curve 0.93 iFR vs. 0.94 iFRa and 0.96 FFR, $P=.48$). Additionally, even though iFR measurements after adenosine administration reduced intracoronary microvascular resistance more than conventional iFR, the concordance in diagnostic categorization to hyperemic stenosis resistance was equivalent for both iFR and iFRa.[18] Another study that included 49 intermediate coronary stenoses (≥40% diameter) in 34 patients undergoing coronary angiography compared iFR and FFR to quantification by H2150 positron emission tomography (PET) imaging.[19] Cutoff values were defined as 0.80 for FFR and 0.90 for iFR. The results

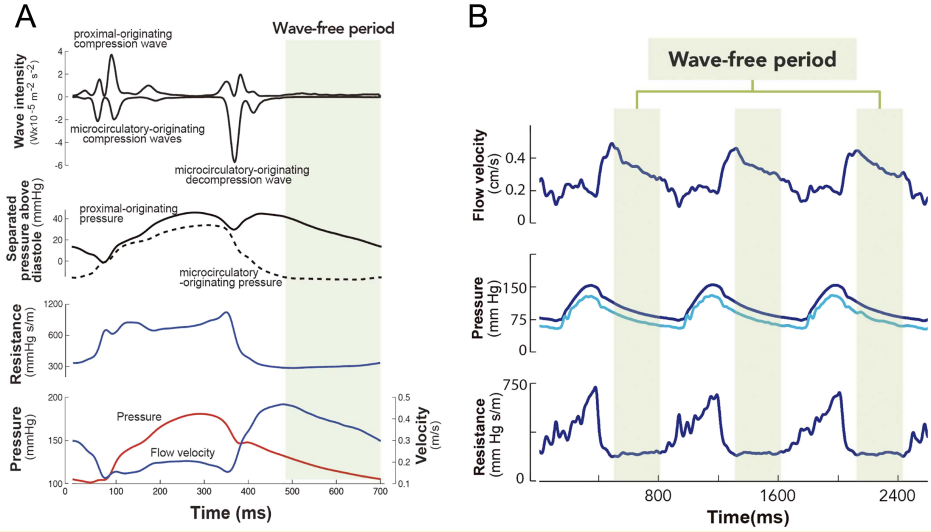

Figure 1. (A) The wave-intensity concept demonstrates that different waves originated from the proximal and distal sections of the coronary vessel. During the wave-free period in diastole, while no waves emerged, the resistance is minimal and constant. (B) Coronary flow velocity, proximal and distal pressure traces, and instantaneous resistance demonstrate the stability of the wave-free period beat to beat.[16]

Table 2. Summary of Clinical iFR Trials[5,6]

Trials	Number of Patients	FFR Arm	iFR Arm	Mean ± SD FFR Value	Mean ± SD iFR Value	Primary End Point in the FFR Group	Primary End Point in the iFR Group	Hazard Ratio (95% CI)	*P*
DEFİNE-FLAİR	2492	1250	1242	0.83 ± 0.09	0.91 ± 0.09	7.0	6.8	0.95 (0.68-1.33)	.78
İFR-SWEDEHEART	2037	1019	1018	0.82 ± 0.10	0.91 ± 0.10	6.1	6.7	1.12 (0.79-1.58)	.53

FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; primary end point: death from any cause, nonfatal myocardial infarction, or unplanned revascularization, at 12 months.

showed that both iFR and FFR had a 76% classification agreement with PET, and the area under the receiver operator curve was similar for both physiological indices [0.85 for FFR and 0.86 for iFR ($P=.71$)].[19] In the JUSTIFY-CFR study, both FFR and iFR were compared with coronary flow velocity reserve as using a correlation coefficient as well as area under the receiver operator curve.[20] Diagnostic and prognostic value of coronary flow reserve was previously validated in patients with CAD. Throughout the study, FFR, iFR, and coronary flow velocity reserve were measured in 216 stenosis from 186 patients. Exclusion criteria included significant valvular pathology and prior coronary artery bypass graft (CABG). The study showed that iFR had a stronger diagnostic correlation with underlying coronary flow velocity reserve than FFR (iFR–CFVR, $P=.68$ vs. FFR–CFVR, $P=.50$; $P<.001$).[20]

Clinical Trials

Two randomized clinical trials addressed the feasibility of iFR-guided strategy in comparison with FFR (Table 2). The DEFINE-FLAIR was a multicenter, randomized, blinded trial whose aim was to compare iFR-guided strategy versus an FFR-guided strategy for coronary revascularization.[5] The exclusion criteria included left main disease, restenotic lesions, and chronic total occlusions. The physiological measurements were made in the routine way with the use of a coronary-pressure guidewire (Philips Volcano, Amsterdam, the Netherlands and San Diego, CA, US). In patients with acute coronary syndrome (ACS), the physiological measurements were obtained only in the vessels with nonculprit lesions after the revascularization of the culprit vessels. While the value of FFR or iFR for a stenosis was equal to or lower than the threshold, the stenoses were revascularized with either PCI or CABG. The primary end point was defined as the 1-year risk of major adverse cardiac events (composite of death, nonfatal myocardial infarction, or unplanned revascularization). The primary end point occurred in 78 patients (6.8%) in the iFR group and in 83 patients (7.0%) in the FFR group at 1 year (difference in risk, −0.2 percentage points; 95% CI, −2.3 to 1.8; $P<.001$ for noninferiority; hazard ratio, 0.95; 95% CI, 0.68 to 1.33; $P=.78$). These results demonstrated that coronary revascularization guided by iFR was noninferior to revascularization guided by FFR in terms of the risk of major adverse cardiac events at 1 year. Moreover, patients who had adverse procedural symptoms and clinical signs such as chest pain and dyspnea were significantly lower in the iFR group than in the FFR group [39 patients (3.1%) vs. 385 patients (30.8%), $P<.001$], and the median procedural time was significantly shorter (40.5 minutes vs. 45.0 minutes, $P=.001$) in the iFR group.[5]

The iFR-SWEDEHEART was a multicenter, randomized, controlled, open-label clinical trial which enrolled patients from Swedish Coronary Angiography and Angioplasty Registry. The aim of the study was to assess if iFR-guided revascularization was noninferior to FFR-guided revascularization with respect to clinical outcomes among patients who have an indication for physiologically guided intervention of a coronary lesion (with 40% to 80% stenosis on visual examination).[6] The primary end point was defined as the rate of composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months. The primary end point event occurred in 68 of 1012 patients (6.7%) in the iFR group and in 61 of 1007 (6.1%) in the FFR group (difference in event rates, 0.7 percentage points; 95% CI, −1.5 to 2.8; $P=.007$ for noninferiority; hazard ratio, 1.12; 95% CI, 0.79 to 1.58; $P=.53$). Similar to DEFINE-FLAIR trial, chest discomfort during the procedure reported in the FFR group was significantly higher than in the iFR group (68.3 vs. 3.0%, respectively; $P<.001$).[6] Both DEFINE-FLAIR and iFR-SWEDEHEART studies highlighted that iFR could be an evidence-based novel technique to evaluate intermediate coronary lesions in the field of invasive cardiology.

Instantaneous Wave-Free Ratio Pullback and Co-registration

The clinical assessment of an individual stenosis in tandem lesions or diffusely infiltrated vessels represents a challenge in practice. Determining FFR between 2 tandem stenoses can be misleading due to the hemodynamic interdependence (cross-talk) between serial stenoses.[17] In other words, under maximal hyperemia, pressure assessment in the distal vessel with 2 tandem stenosis is not selective to either stenosis. Hyperemic flow through one stenosis is limited by the presence of another stenosis and vice versa.[21] Resting flow remains constant until almost subtotal occlusion of the vessel; therefore, the basal state is favorable to the assessment of vessels with diffuse or tandem lesions. Basal flow across the lesion of interest is expected to be negligibly affected by other lesions in the vessel as long as they are not critical or subtotal occlusions.[21] In a study in 2014, automated iFR pullback recordings in 29 patients with tandem and diffusely diseased vessels were realized to produce physiological maps showing lesion severity.[22] After coronary angiography and pressure wire assessment of coronary stenoses, mechanized pressure wire pullback as well as regular fluoroscopic recordings of the wire position were carried out. This allowed co-registration of the pressure wire data with the angiographic location, namely visualization of the change or decrease in iFR for each stenosis in the vessel (iFR physiological map). Afterward, using a dedicated software (virtual PCI), stenoses were manually selected for removal on the physiological map which permitted the calculation of the post-PCI iFR value – the value that would be expected if that stenosis was treated by intervention. Despite the

encouraging results of the study, there were major limitations with motorized pressure wire pullback and offline interpretation with the software.[22] Rapidly advancing technology has allowed the iFR co-registration technique to create a real-time physiological map of the coronary vessel under manual pullback. Thus, treatment strategies including medical, surgical, or percutaneous approach with extensive or limited angioplasty may be planned according to predicted post-PCI iFR values in patients with diffusely diseased vessels.[3]

Instantaneous Wave-Free Ratio and Fractional Flow Reserve Discordance

Despite the fact that it was shown that there was a significant correlation between FFR and iFR, they can disagree on the hemodynamic significance of a lesion in 20% of cases.[23,24] Multiple factors were suggested in order to explain this phenomenon. In a study, 587 patients who underwent coronary physiologic assessment were divided into 4 categories depending on FFR and iFR values: both negative or positive, iFR was negative discordant (FFR+/iFR–) or positive discordant (FFR–/iFR+). While more severe stenosis location and severity (left main or proximal left anterior descending), younger age, and slower heart rate were shown to be predictors of a negative discordant iFR, absence of a betablocker, older age, and less severe stenosis were predictors of a positive discordant iFR.[25] Another study evaluated 345 patients in the same manner by using FFR, iFR, and iFR pullback. The results revealed that the physiological pattern of disease was the main feature relating to FFR/iFR discordance: While predominantly physiologically focal was significantly associated with FFR+/iFR–, predominantly physiologically diffuse was significantly associated with FFR–/iFR+.[26] Recently, a study classified 596 patients according to FFR and iFR. In addition to the previous studies, coronary flow reserve, microcirculatory resistance, and resistance reserve ratio (resting distal arterial pressure × mean transit time/hyperemic distal arterial pressure × hyperemic mean transit time) were evaluated.[27] Patients were followed at 5 years in terms of patient-oriented composite outcomes (all-cause death, any myocardial infarction, and any revascularization). Depending on the results, among the 4 groups, coronary flow reserve and resistance reserve ratio were all significantly different, except for microcirculatory resistance. Yet, discordance between the iFR and FFR was not significantly associated with patient-oriented composite outcomes in patients with deferral lesions at 5 years.[27] These studies highlight the clinical factors and lesion-related features that contribute to the discordance between FFR and iFR. Further dedicated studies are needed to improve our understanding on this aspect.

Physiologic Approach in Patients with Acute Coronary Syndrome

Despite emerging evidence supporting the role of coronary physiology in stable CAD, it remains controversial to employ functional evaluation of nonculprit lesions in the setting of ACS. When and how to perform a functional test in order to assess intermediate lesions in patients with ACS is still a subject of debate.[28] The COMPARE-ACUTE and DANAMI3-PRIMULTI trials have demonstrated that complete revascularization by PCI guided by FFR of nonculprit lesions in patients with St-segment elevation myocardial infarction (STEMI) reduces the rate of ischemic recurrence with a median follow-up of 12 and 27 months, respectively, compared to PCI of culprit lesion alone.[28] On the other hand, a French study demonstrated in 1171 STEMI patients with multivessel disease undergoing complete revascularization that an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with regard to the risk of death, myocardial infarction, or urgent revascularization at 1 year.[29] Multiple issues remain open. Patients with ACS may not respond adequately to adenosine administration in the acute setting due to the increase in microvascular resistance and the reduction in the coronary flow reserve. A study with 49 acute myocardial infarction patients compared with 46 stable angina patients analyzed noninfarct-related arteries during the subacute phase by assessing FFR, coronary flow reserve, and the index of microcirculatory resistance.[30] Time interval between acute myocardial infarction and physiological assessment was 5.9 ± 2.4 days. The results showed that noninfarct-related arteries displayed lower coronary flow reserve compared with stable angina patients. Nevertheless, microcirculatory resistance and adenosine-induced hyperemic response were similar to those found in stable angina patients. Of note, the authors highlighted less statistical power than intended due to lower-than-expected incidence of events.[30] In this context, iFR has emerged as an option to evaluate nonculprit lesions in patients with ACS without the need for a hyperemic agent.[28] In a recent randomized study involving 73 patients with STEMI, the use of iFR, FFR, coronary flow reserve, hyperemic index of microcirculatory resistance, and resting microcirculatory resistance in nonculprit lesions were evaluated in the acute setting and at 1-month follow-up. While the FFR decreased [mean, 0.88 (0.07) vs. 0.86 (0.09); $P=.001$], iFR did not change significantly [0.93 (0.07) vs. 0.94 (0.06); $P=.12$]. Coronary flow reserve significantly increased at follow-up [2.9 (1.4)] to 1-month follow-up [4.1 (2.2)] ($P < .001$). Hyperemic index of microcirculatory resistance decreased and resting microcirculatory resistance increased from the acute moment to follow-up.[31] Another study including 120 STEMI patients evaluated iFR in nonculprit lesions during acute admission and at a median of 16 days. The authors demonstrated that an acute iFR measurement was lower than a follow-up iFR, particularly in patients with a longer duration between the 2 readings.[32] Pooled analysis from the DEFINE-FLAIR and iFR SWEDEHEART studies compared FFR and iFR for the physiological assessment of nonculprit vessels in 440 patients with ACS. Patients with ACS who were deferred using FFR were associated with a significantly worse outcome compared with those deferred with stable angina (hazard ratio: 0.52; 95% CI: 0.27 to 1.00; $P < .05$). Nevertheless, patients deferred using iFR showed similar outcomes among deferred patients, regardless of clinical presentation (hazard ratio: 0.74; 95% CI: 0.38 to 1.43; $P=.37$).[3] An ongoing study, the iMODERN trial (iFR Guided Multi-Vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction; NCT03298659) that aims to compare iFR-guided intervention of noninfarct lesions during acute intervention in STEMI patients with multivessel lesions will provide crucial data on this topic.

Physiologic Approach in Patients with Aortic Stenosis

The evaluation of intermediate stenoses is challenging in patients with severe aortic stenosis, and an optimal method has still not

been established. Recently, several studies demonstrated crucial insights concerning the role of coronary physiology. In a study with 95 patients suffering from severe aortic stenosis, iFR values were compared with FFR values and adenosine stress myocardial perfusion imaging.[33] The iFR values correlated well with the FFR values ($R=0.854$; $P < .0001$). Yet, the optimal iFR cutoff value indicating myocardial ischemia on perfusion scintigraphy was suggested to be 0.82 (area under the curve: 0.84; 95% CI: 0.752 to 0.919; $P < .0001$).[33] In another study including 145 coronary lesions in patients with aortic stenosis, iFR and FFR measurements were assessed before and after transcatheter aortic valve implantation (TAVI). While mean iFR values remained identical before and after TAVI (0.89 ± 0.12 vs. 0.89 ± 0.12, $P=.66$), individual iFR values varied after TAVI and the 0.89 iFR threshold was crossed by 15% of the investigated coronary lesions.[34] A study evaluating 23 coronary lesions in 14 patients with aortic stenosis assessed iFR and FFR at baseline, immediately after TAVI and at 14 (7-29) months of follow-up.[35] The angiographic severity of the lesions did not progress at follow-up [54 (45-64) vs. 54 (49-63), $P = .53$]. While FFR decreased in 3 lesions (13%) with abnormal baseline value, it remained stable in lesions with FFR > 0.80. Conversely, iFR did not show a systematic trend at long-term after TAVI and iFR demonstrated a higher reclassification rate at follow-up compared with FFR ($P=.02$).[35] A recent study of 13 patients who underwent TAVI assessed long-term coronary hemodynamics before and after TAVI. While FFR decreased from 0.85 (0.76-0.88) pre-TAVI to 0.79 (0.74-0.83) post-TAVI, and then to 0.71 (0.65-0.77) at 6-month follow-up ($P < .001$ for all comparisons), iFR was not significantly different: 0.82 (0.80-0.90) pre-TAVI, 0.83 (0.77-0.88) post-TAVI, and 0.83 (0.73-0.89) at 6 months ($P=.735$).[36] More evidence is needed from large randomized clinical trials to assess the clinical value of coronary physiology, particularly the role of iFR, in the context of aortic stenosis.

Conclusion

The treatment of borderline lesions is challenging in routine clinical practice, particularly in patients with multivessel diseases. Recent guidelines recommend both FFR and iFR with high class of evidence to assess the severity of intermediate-grade lesions in the case of multivessel disease or absence of noninvasive tests. FFR is currently a widely accepted coronary physiology index for the functional assessment of lesion severity. Instantaneous wave-free ratio is a contemporary tool to start a new era in the coronary physiology domain with its advantages such as not requiring a vasodilating agent, rapidity of the procedure, pullback phenomena for the assessment of individual stenosis in tandem lesions or diffusely infiltrated vessels, and virtual PCI which allows for the assessment and justification for optimal coronary revascularization. More evidence is expected from ongoing randomized trials to improve our understanding in the coronary physiology field.

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