

Review

Pathophysiological factors contributing to fractional flow reserve and instantaneous wave-free ratio discordanceBenjamin Fogelson^{1,†}, Hassan Tahir^{1,*†}, James Livesay^{1,†}, Raj Baljepally^{1,†}¹Department of Medicine, University of Tennessee Graduate School of Medicine, Knoxville, TN 37920, USA*Correspondence: doctorhassantahir@gmail.com (Hassan Tahir)

†These authors contributed equally.

Academic Editors: Abdul Hakeem, Bobby Ghosh, Gianluca Rigatelli and Peter Kokkinos

Submitted: 28 September 2021 Revised: 27 November 2021 Accepted: 16 December 2021 Published: 18 February 2022

Abstract

The diagnostic accuracy and clinical benefits of instantaneous wave-free ratio (iFR) compared to fractional flow reserve (FFR) have been well-established in the literature. Despite the advantages of non-hyperemic pressure indices, approximately 20% of iFR and FFR measurements are discordant. Efforts have been made to establish the mechanisms as well as identify causative factors that lead to such a discordance. Recent studies have identified many factors of discordance including sex differences, age differences, bradycardia, coronary artery stenosis location, elevated left ventricular end-diastolic pressure, and diastolic dysfunction. Additionally, discordance secondary to coronary artery microcirculation dysfunction, as seen in diabetics and patients on hemodialysis, has sparked interest amongst experts. As more interventional cardiologists are utilizing iFR independent of FFR to guide percutaneous coronary intervention an emphasis has been placed on identifying factors leading to discordance. The aim of this review is to outline recent studies that have identified factors of FFR and iFR discordance.

Keywords: fractional flow reserve; instantaneous wave-free ratio; discordance; microcirculation dysfunction**1. Background**

Fractional flow reserve (FFR) is a diagnostic pressure index that is used to assess the physiological significance of a coronary artery stenotic lesion in stable ischemic heart disease (SIHD). It is defined as a ratio of maximal blood flow in a coronary artery with stenosis compared to the maximal blood flow through a normal coronary artery [1,2]. Using a pressure wire during coronary angiography, FFR is obtained by simultaneously measuring the coronary pressure distal to a stenotic lesion and the aortic pressure [1]. FFR is the ratio of the distal coronary pressure (P_d) to the aortic pressure (P_a), thus FFR is equal to P_d/P_a [2]. To fully minimize microvascular resistance, FFR is measured during a period of maximal blood flow, also known as a maximal hyperemic state [3]. This period of hyperemia is achieved through intra-coronary or intravenous injection of a vasodilating agent such as adenosine [3]. Theoretically, FFR in a normal coronary artery during hyperemia should be 1.0 [3]. A FFR of less than or equal to 0.80 indicates that the stenotic lesion is physiologically significant and therefore, likely “ischemia-causing” [1,4].

FFR has been used by many clinicians to guide percutaneous coronary intervention (PCI) of intermediate (40% to 70%) coronary artery stenosis in SIHD [5]. The use of FFR-guided PCI in patients with stable coronary artery disease (CAD) has been associated with better long-term outcomes when compared to angiographically guided PCI [6,7]. Two large clinical studies, the FAME and FAME2 trials, found that FFR in patients with multivessel CAD

undergoing PCI reduces combined endpoints of mortality, myocardial infarction, and need for urgent revascularization. In addition to improving long-term outcomes in SIHD, FFR guided PCI is also economically attractive compared to medical management [8,9]. Multiple studies have also demonstrated that deferring PCI in patients with hemodynamically non-significant coronary lesions (FFR >0.80) is associated with better outcomes [10,11].

Despite guideline recommendations, the use of FFR has been limited in clinical practice due to increased procedural costs, difficulties with reimbursement, and the side effects of inducing hyperemia with adenosine [12–14]. Studies have found that the commonly used hyperemic agent, adenosine, has been associated with clinically significant adverse effects including tachyarrhythmias, bradyarrhythmias, interactions with other medications, and prolonged procedure times [12,13]. For these reasons, non-adenosine requiring indices such as instantaneous wave-free ratio (iFR) to guide PCI of intermediate stenotic coronary lesions were developed. Like FFR, iFR can determine the hemodynamic significance of intermediate coronary artery stenosis in SIHD. However, iFR differs from FFR in that it does not require the use of hyperemic agents [15,16]. Instead, iFR is obtained by simultaneously measuring the pressure distal to a stenotic lesion and the aortic pressure during a specific time interval in cardiac diastole known as the “wave-free period” [15,17]. During this naturally occurring period, capillary resistance is stable and minimal, while coronary blood flow is maximal [18,19]. Therefore, while at a



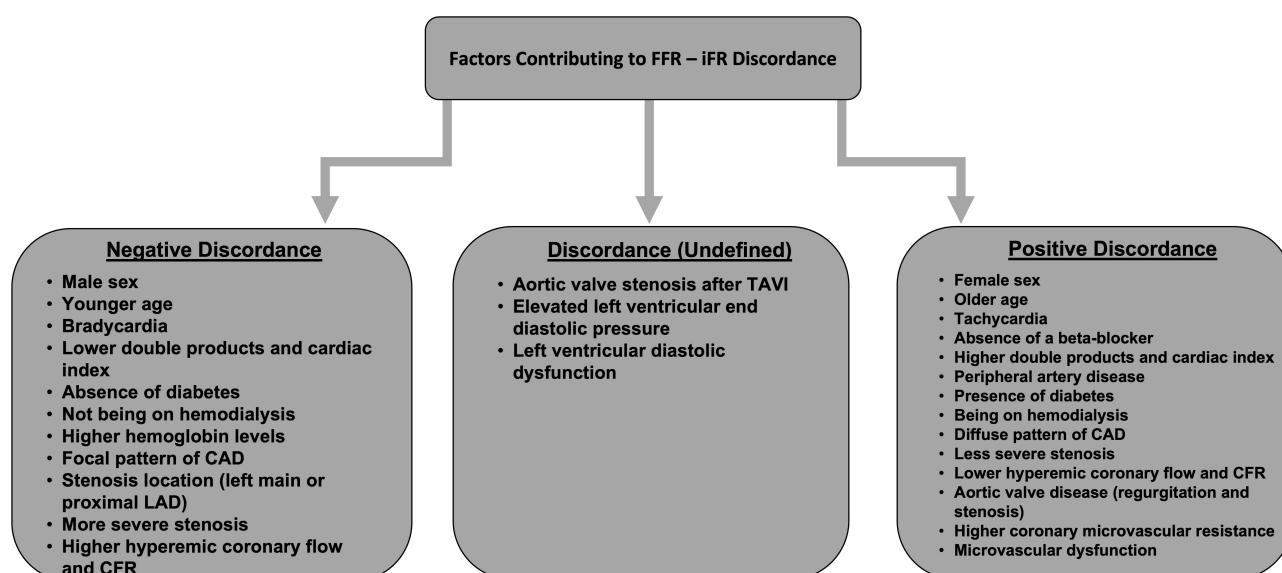


Fig. 1. Factors reported by various studies contributing to positive discordance (FFR+/iFR+), negative discordance (FFR+/iFR–), or undefined discordance. Abbreviations: CAD, coronary artery disease; LAD, left anterior descending; TAVI, transcatheter aortic valve implantation; CFR, coronary flow reserve.

stable coronary resistance, the change in pressure across a stenotic lesion is approximately equal to the change in blood flow across the coronary lesion [17,18]. Compared to the FFR cutoff value of 0.80, an intermediate coronary lesion is deemed hemodynamically significant when the iFR is less than or equal to 0.89 [20].

2. FFR and iFR comparison

Multiple studies have compared the diagnostic accuracy and the clinical outcomes of iFR to FFR [20–23]. The ADVISE study was one of first to conclude that iFR was comparable to FFR in producing a severity index of coronary artery stenosis [21]. The diagnostic accuracy of iFR compared to FFR was further evaluated in both the ADVISE II and RESOLVE trials. They concluded that iFR strongly correlated with FFR with a diagnostic accuracy of approximately 80% [20,22]. In addition to its diagnostic accuracy, one of the primary benefits of iFR is that it is calculated by measuring a natural wave-free period during diastole. Through this measurement, the use of hyperemic agents as well as their potential side effects are avoided. Given the many side effects of hyperemic agents, the use of iFR may be preferred over FFR in the elderly population and patients with baseline sinus node dysfunction [13].

Two large studies have compared the impact of iFR on clinical outcomes to FFR [12,24]. The DEFINE-FLAIR trial was a large multicenter randomized controlled study that compared the outcomes of patients undergoing iFR-guided PCI to patients undergoing FFR-guided PCI [12]. They concluded that iFR-guided coronary revascularization was noninferior to FFR-guided coronary revascularization regarding 1-year major adverse cardiac events (MACE)

[12]. Another multicenter randomized control trial, iFR SWEDHEART, also concluded that the use of an iFR-guided revascularization strategy in SIHD was noninferior to FFR, with respect to 1-year MACE [24]. Although both the DEFINE-FLAIR and iFR SWEDHEART trials demonstrated that iFR is noninferior to FFR, questions remain about the use of iFR without also measuring FFR. We believe that the primary concern is likely driven by an iFR to FFR discordance rate of approximately 20% as well as limited data on the causative factors leading to discordance.

3. FFR and iFR discordance

Discordance is considered when iFR or FFR is positive, and the other is negative. Negative discordance is defined by a FFR <0.80 and an iFR >0.89, whereas positive discordance is the opposite (FFR >0.80 and an iFR <0.89). Theoretically, any index below the cutoff point would indicate that a lesion is hemodynamically significant, however, the management of lesions with discordant indices can be difficult when iFR and FFR are numerically close to their cutoff values. Currently, there is limited data on whether the numerical difference between discordant iFR and FFR values is clinically significant.

Multiple studies have found that the agreement between iFR and FFR is around 80%, which indicates that approximately 20% of iFR and FFR measurements are discordant [20–25]. Experts have recently shifted focus to further understand the etiology of iFR and FFR discordance as well as factors leading to negative (FFR+/iFR–) or positive (FFR–/iFR+) discordance.

Measurement variability has been found to be a major source of discordance between iFR and FFR, primarily

around the cutoff values of ≤ 0.89 and ≤ 0.80 , respectively [17]. Additionally, various procedural factors including suboptimal positioning of the guide catheter and aortic pressure damping as well as insufficient hyperemia secondary to preprocedural caffeine consumption or inadequate adenosine dosing have contributed to discordance [17]. Although measurement and procedural variability are major contributors of iFR and FFR discordance, certain pathophysiological factors affecting iFR and FFR agreement have also been identified. The etiology of iFR and FFR discordance is now thought to be multifactorial in nature with aspects of measurement variability, procedural variability, and multiple pathophysiological factors [17].

4. Factors causing FFR and iFR discordance

There are many pathophysiological factors reported in the literature that can lead to iFR and FFR discordance (Table 1 and Fig. 1, Ref. [25–38]). Sex differences have been associated with both positive and negative discordance [25–28]. Specifically, females are more commonly found to have positive discordance while males are more likely to have negative iFR and FFR discordance [25–28]. In a large post hoc analysis, Dérimay *et al.* [29] demonstrated that younger age was associated with negative discordance while older age was associated with positive discordance. Similarly, Goto *et al.* [30] also concluded that younger age correlated with negative discordance.

The impact of coronary artery disease on iFR and FFR agreement has also been investigated including the location of coronary stenosis, severity of stenosis, and overall extent of coronary disease [29–33]. Dérimay *et al.* [29] demonstrated that left main coronary artery or proximal left anterior descending (LAD) artery stenosis was associated with negative discordance. A large multicenter prospective observational study also found that left main coronary artery and proximal LAD artery stenosis were significant factors leading to negative discordance [31]. In contrast, Goto *et al.* [30] found that left main coronary artery and proximal LAD artery stenosis contributed to positive discordance. The discrepancies between these studies are unclear, however they demonstrate the underlying complexity of CAD pathophysiology.

There is conflicting data regarding the impact of coronary artery stenosis severity on iFR and FFR discordance. Lee *et al.* [32] found lower percent diameter coronary artery stenosis was associated with negative discordance whereas smaller coronary artery diameter/ higher percent diameter stenosis led to positive discordance. Dérimay *et al.* [29] found the opposite, in that more severe stenosis correlated with negative discordance while less severe stenosis was associated with positive discordance. In addition to the location and severity of stenosis, the extent of coronary artery disease can contribute to iFR and FFR discordance. Wari-sawa *et al.* [33] concluded that patients with a focal pattern of CAD were associated with negative discordance whereas

a diffuse pattern of CAD correlated with positive discordance.

Valvular heart disease has also been linked to iFR and FFR discordance. Scarsini *et al.* [34] found that transaortic gradient pressure changes induced by transaortic valve intervention caused significant variations in iFR measurements. Similarly, a computational model that evaluated the effects of aortic valve disease on iFR and FFR discordance found that aortic stenosis and regurgitation led to positive discordance [35]. Overall, data on the effects of valvular heart disease on iFR and FFR discordance is limited and necessitates further investigation.

Central venous pressure (Pv) is ignored in calculating FFR as it is assumed to be close to zero. This can be a problem in conditions where Pv is significantly elevated. For example, right and left heart conditions associated with high central venous pressure can theoretically result in erroneous calculation of FFR. In practice, the impact has been demonstrated to be trivial [36]. Such studies, however, did not focus on iFR and FFR discordance. In our own experience, elevated LVEDP resulted in a graded, higher discordance between iFR and FFR [37].

We recently published two studies that evaluated the effects of elevated left ventricular end diastolic pressure (LVEDP) and left ventricular diastolic dysfunction on FFR and iFR discordance [37,38]. We found that approximately 43% of patients with elevated LVEDP had FFR and iFR discordance [37]. Therefore, we concluded that patients with elevated LVEDP were more likely to have discordant iFR and FFR measurements compared to patients with normal LVEDP. Similarly, the impact of left ventricular diastolic dysfunction on FFR and iFR discordance was significant. We found that approximately 45% of patients with discordance had left ventricular diastolic dysfunction based on transthoracic echocardiography [38]. Therefore, we believe that both LVEDP and left ventricular diastolic function should be considered when using FFR and iFR to guide PCI.

5. The effect of coronary microcirculation dysfunction on FFR and iFR discordance

The effects of diabetes and hemodialysis on FFR and iFR discordance has been presented in the literature [27,28,30,35]. Goto *et al.* [30] concluded that diabetics and patients on hemodialysis were commonly found to have positive discordance. Similarly, Lee *et al.* [32] found that diabetes is associated with positive discordance while the absence of diabetes is associated with negative discordance. The effects of diabetes on discordance have been linked to dysfunctions in coronary artery microcirculation [17,32,35,39]. Recent studies have attempted to further understand the impact of the coronary microcirculation dysfunction on FFR and iFR discordance (Table 2, Ref. [32,35,39,40]). According to van de Hoef *et al.*, both healthy and dysfunctional coronary microcirculation can

Table 1. Factors reported by various studies causing FFR and iFR positive (FFR-/iFR+) or negative discordance (FFR+/iFR-).

Study	Study type	No. of patients	Factors of discordance	Negative or positive discordance
Aoi <i>et al.</i> [25]	Single-center, retrospective study	423	Male sex. Female sex.	Negative Positive
Dérinmay <i>et al.</i> [29]	Post hoc analysis	587	Stenosis location (left main or proximal LAD), more severe stenosis, younger age, and slower heart rate.	Negative
			Absence of a beta-blocker, older age, and less severe stenosis.	Positive
Satomi <i>et al.</i> [26]	Retrospective study	225	Lower heart rate, lower double products, and lower cardiac index.	Negative
			Female sex, higher heart rate, and higher double products.	Positive
Goto <i>et al.</i> [30]	Post hoc analysis	156	Younger age, absence of diabetes and higher hemoglobin levels.	Negative
Kobayashi <i>et al.</i> [31]	Multicenter, prospective, investigator-initiated observational study	763	Hemodialysis, peripheral artery disease, left main and LAD artery stenosis.	Positive
Warisawa <i>et al.</i> [33]	Analysis of international multicenter registry	345	Left main/ proximal LAD artery stenosis.	Negative
			Focal pattern of CAD.	Negative
			Diffuse pattern of CAD.	Positive
Arashi <i>et al.</i> [27]	Retrospective study	225	Not being on hemodialysis.	Negative
			Female sex and high rate-pressure product.	Positive
Scarsini <i>et al.</i> [34]	Prospective, observational study	66	Aortic valve stenosis after TAVI	-
Ge <i>et al.</i> [35]	Computational model	-	Aortic valve disease, regurgitation and stenosis.	Positive
Lee <i>et al.</i> [28]	Post hoc analysis	393	Male sex, absence of diabetes and lower percent diameter stenosis.	Negative
			Female sex, diabetes, smaller reference vessel diameter and higher percent diameter stenosis.	Positive
Tahir <i>et al.</i> [37]	Single-center, nonrandomized both retrospective and prospective study	65	Elevated left ventricular end diastolic pressure	-
Tahir <i>et al.</i> [38]	Single-center nonrandomized retrospective observational study	100	Left ventricular diastolic dysfunction	-

Abbreviations: CAD, coronary artery disease; LAD, left anterior descending; TAVI, transcatheter aortic valve implantation.

Table 2. Factors and findings associated with microcirculation dysfunction reported by various studies leading to FFR and iFR positive (FFR–/iFR+) or negative discordance (FFR+/iFR–).

Study	Study type	No. of patients	Factors and associated findings of discordance	Negative or positive discordance
Ge <i>et al.</i> [35]	Computational model	-	Diabetes, higher coronary microvascular resistance, lower coronary flow	Positive
Cook <i>et al.</i> [39]	Post hoc, retrospective analysis	454	Higher hyperemic coronary flow and CFR, and lower prevalence of diabetes.	Negative
			Lower hyperemic coronary flow and CFR, and higher prevalence of diabetes.	Positive
Lee <i>et al.</i> [40]	Retrospective analysis	113	Higher coronary flow, higher CFR and significantly higher reduction of microvascular resistance during hyperemia	Negative
Lee <i>et al.</i> [32]	Post hoc, retrospective analysis	393	Male sex and lower probability of predictors of microvascular dysfunction.	Negative
			Older age, female sex, diabetes, and microvascular dysfunction.	Positive

Abbreviations: CFR, coronary flow reserve.

contribute to discordance. They further explain that healthy coronary microcirculation allows for adenosine-mediated vasodilation during periods of hyperemia causing a significant pressure gradient that was not present during non-hyperemic states [17]. Therefore, patients with non-flow-limiting CAD and normal coronary microcirculation can have a positive FFR but a negative iFR [17,39]. In contrast, adenosine-mediated coronary vasodilation is inhibited in patients with microcirculation dysfunction, such as diabetics, and therefore are more likely to have a normal FFR but an abnormal iFR [39]. Lee *et al.* [40] concluded that patients with negative discordance were found to have higher hyperemic myocardial blood flow, higher coronary flow reserve, and a significantly higher reduction of microvascular resistance at hyperemia. These findings are likely secondary to the presence of healthy microcirculation allowing for coronary vasodilation and thus large pressure gradients across coronary lesions during hyperemia. In a computational model, Ge *et al.* [35] concluded that diabetic patients with secondary coronary microcirculation dysfunction had higher coronary microvascular resistance and lower coronary flow during hyperemia. Similarly, Lee *et al.* [32] concluded that male sex and a lower probability of predictors of microvascular dysfunction are associated with negative discordance while older age, female sex, diabetes, and possible microvascular dysfunction are associated with positive discordance. We believe that coronary microcirculation dysfunction contributes significantly to FFR and iFR discordance, however, additional studies are needed.

6. Clinical implications of FFR and iFR discordance

Despite the many benefits of iFR, its use in the catheterization lab, independent of FFR, is variable. To determine the hemodynamic significance of an intermedi-

ate coronary lesion, iFR is commonly measured and then confirmed with FFR. The use of FFR to confirm iFR is primarily due to the known 20% diagnostic inaccuracy of iFR compared to FFR as well as its novelty. To support the independent use of iFR, studies have compared long-term clinical outcomes of patients with concordant iFR and FFR indices to those with discordant measurements. While initial studies demonstrated no increased risk in vessel-oriented composite outcomes (VOCO) or Patient-oriented composite outcomes (POCO) for patients with discordant values, more recent studies have challenged these conclusions [32,41,42]. Lee *et al.* [43], found that patients with discordant iFR and FFR values, in which revascularization was deferred, demonstrated a similar risk of VOCO when compared to all revascularized lesions up to 5 years of follow-up. Given these findings, the authors concluded that lesions with discordant physiologic indices require close follow-up and medical management [43].

While the decision to revascularize is straightforward with concordant FFR and iFR values, interpreting discordant values is more complex in the clinical setting [44]. Overall, discordance has complicated the management of intermediate coronary lesions. Currently, there is no clear evidence to support whether iFR or FFR should be used to guide PCI in the setting of discordance. Therefore, when iFR and FFR discordance is encountered in the clinically setting, the decision to revascularize is left to the proceduralist. Depending on prior training and comfortability with iFR, some operators will revascularize a positive discordant (FFR–/iFR+) intermediate coronary lesion if their clinical suspicion is high that it is the culprit. However, many proceduralist question the clinical equivalency of iFR to FFR given the frequency of discordant measurements and are thus, faced with the dilemma on whether to revascularize. Most commonly, operators follow FFR to guide their de-

cision to revascularize an intermediate coronary lesion in the setting of negative discordance (FFR+/iFR−). As previously discussed, this is secondary to the operators' prior experience with iFR as well as uncertainties due to the lack of standardized guidelines and inconsistent clinical outcome data on the revascularization of iFR and FFR discordant lesions.

While some have concluded that iFR is a suitable and cost-effective alternative to FFR, others have adopted iFR-FFR hybrid models [14]. These hybrid models have expanded the standard cutoff value for iFR, which has increased confidence in its use and decreased the frequency of having to interpret discordant values. With most hybrid strategies, revascularization is performed on lesions with an iFR of <0.86 and deferred when >0.93. However, when iFR is 0.86–0.93, referred to as the “grey zone”, FFR is performed to confirm and guide PCI. By adjusting the standard iFR cutoff value and utilizing FFR confirmation for iFR values that fall in the “grey zone”, the diagnostic accuracy of iFR has been shown to be as high as 95% [45–47]. Furthermore, by decreasing the cutoff value of iFR to 0.86 with these hybrid strategies, the need to perform confirmatory FFR has decreased. Paul *et al.* [44] presented a slightly different hybrid model that included “grey zones” for both iFR and FFR, in which a second index would be needed to confirm any measurement within these zones. Unfortunately, even with the use of these various hybrid models, operators still encounter the dilemma of discordance [44]. Considering the multiple clinical factors that have been identified as predisposing factors for iFR and FFR discordance, the current standardized iFR and FFR cutoff values need to again be revisited [48]. Many factors have been identified as independent predictors of iFR including diabetes mellitus, aortic stenosis, high-sensitivity CRP, and renal function [49]. Similarly, there are many factors, as previously discussed in this review, that can be used to predict iFR and FFR discordance. Using these known factors of discordance, iFR and FFR cutoff values can be adjusted. As experts continue to identify factors and conditions that lead to discordance, it is necessary that these factors be accounted for when interpreting iFR in the clinical setting. Therefore, we believe that additional research is needed to not only identify factors of discordance but more importantly, determine how we can adjust the current iFR and FFR cutoff values to account for these individual factors.

7. Conclusions

The diagnostic accuracy and clinical benefits of iFR compared to FFR in stable ischemic heart disease have been clearly outlined in the literature and supported by multiple large randomized clinical trials. However, given that the percentage of FFR and iFR discordance was not negligible in these studies, it must be considered when using these measurements to guide PCI. Recently, efforts have been made to identify the factors leading to FFR and iFR

discordance. Common factors identified include gender, coronary artery stenosis severity and location, heart rate, and valvular heart disease. More recent studies found that elevated LVEDP and the presence of diastolic dysfunction are important factors of discordance that should be considered when interpreting iFR and FFR. Additionally, the presence of diabetes as well as hemodialysis have been identified as discordance causing factors primarily through their effects on the coronary microvasculature. Although multiple causative factors have been identified and presented in the literature, we believe that further studies are necessary to identify additional factors of discordance and to further investigate the impacts of coronary microvascular dysfunction.

Author contributions

All authors reviewed the literature and helped write the manuscript. BF, HT, JL, and RB—performed critical revisions of the article and approved the final version of manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. We would also like to thank all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, *et al.* Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *New England Journal of Medicine*. 2009; 360: 213–224.
- [2] Pijls NH, Sels JW. Functional measurement of coronary stenosis. *Journal of the American College of Cardiology*. 2012; 59: 1045–1057.
- [3] Corcoran D, Hennigan B, Berry C. Fractional flow reserve: a clinical perspective. *International Journal of Cardiovascular Imaging*. 2017; 33: 961–974.
- [4] De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, *et al.* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *New England Journal of Medicine*. 2012; 367: 991–1001.
- [5] Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. *Journal of the American College of Cardiology*. 2012; 60: 2337–2339.

- [6] Li J, Elrashidi MY, Flammer AJ, Lennon RJ, Bell MR, Holmes DR, *et al.* Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. *European Heart Journal*. 2013; 34: 1375–1383.
- [7] Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, *et al.* Fractional Flow Reserve and Cardiac Events in Coronary Artery Disease: Data From a Prospective IRIS-FFR Registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation*. 2017; 135: 2241–2251.
- [8] Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, *et al.* Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *Journal of the American College of Cardiology*. 2010; 56: 177–184.
- [9] Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, *et al.* Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation*. 2018; 137: 480–487.
- [10] Muller O, Mangiacapra F, Ntalianis A, Verhamme KM, Trana C, Hamilos M, *et al.* Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. *JACC Cardiovascular Interventions*. 2011; 4: 1175–1182.
- [11] Van Belle E, Rioufol G, Pouillot C, Cuisset T, Bougrini K, Teiger E, *et al.* Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. *Circulation*. 2014; 129: 173–185.
- [12] Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, *et al.* Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *New England Journal of Medicine*. 2017; 376: 1824–1834.
- [13] Mallet ML. Proarrhythmic effects of adenosine: a review of the literature. *Emergency Medicine Journal*. 2004; 21: 408–410.
- [14] Maini R, Moscona J, Katigbak P, Fernandez C, Sidhu G, Saleh Q, *et al.* Instantaneous wave-free ratio as an alternative to fractional flow reserve in assessment of moderate coronary stenoses: A meta-analysis of diagnostic accuracy studies. *Cardiovascular Revascularization Medicine*. 2018; 19: 613–620.
- [15] Soos MP, Gonzalez-Morales D, McComb D. *Instantaneous Wave-Free Ratio*. Treasure Island (FL): StatPearls Publishing. 2021.
- [16] Petraco R, Park JJ, Sen S, Nijjer SS, Malik IS, Echavarría-Pinto M, *et al.* Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. *EuroIntervention*. 2013; 8: 1157–1165.
- [17] van de Hoef TP, Lee JM, Echavarría-Pinto M, Koo BK, Matsuo H, Patel MR, *et al.* Non-hyperaemic coronary pressure measurements to guide coronary interventions. *Nature Reviews Cardiology*. 2020; 17: 629–640.
- [18] Baumann S, Chandra L, Skarga E, Renker M, Borggrefe M, Akin I, *et al.* Instantaneous wave-free ratio (iFR®) to determine hemodynamically significant coronary stenosis: A comprehensive review. *World Journal of Cardiology*. 2018; 10: 267–277.
- [19] Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, *et al.* Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study. *Journal of the American College of Cardiology*. 2013; 61: 1409–1420.
- [20] Jeremias A, Maehara A, Gèneux P, Asrress KN, Berry C, De Bruyne B, *et al.* Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *Journal of the American College of Cardiology*. 2014; 63: 1253–1261.
- [21] Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, *et al.* Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *Journal of the American College of Cardiology*. 2012; 59: 1392–1402.
- [22] Escaned J, Echavarría-Pinto M, García-García HM, van de Hoef TP, de Vries T, Kaul P, *et al.* Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance: Results of ADVISE II International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II). *JACC Cardiovascular Interventions*. 2015; 8: 824–833.
- [23] Shiode N, Okimoto T, Tamekiyo H, Kawase T, Yamane K, Kagawa Y, *et al.* A Comparison between the Instantaneous Wave-free Ratio and Resting Distal Coronary Artery Pressure/Aortic Pressure and the Fractional Flow Reserve: The Diagnostic Accuracy Can Be Improved by the Use of both Indices. *Internal Medicine*. 2017; 56: 749–753.
- [24] Götzberg M, Christiansen EH, Gudmundsdóttir IJ, Sandhall L, Danielewicz M, Jakobsen L, *et al.* Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *New England Journal of Medicine*. 2017; 376: 1813–1823.
- [25] Aoi S, Toklu B, Misumida N, Patel N, Lee W, Fox J, *et al.* Effect of Sex Difference on Discordance Between Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *Cardiovascular Revascularization Medicine*. 2021; 24: 57–64.
- [26] Satomi N, Ishida I, Arashi H, Yamaguchi J, Konami Y, Kadowaki H, *et al.* Abstract 16416: Predictors of Discordance Between Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *Circulation*. 2017; 136: A16416-A.
- [27] Arashi H, Satomi N, Ishida I, Soontornthada K, Ebihara S, Tanaka K, *et al.* Hemodynamic and Lesion Characteristics Associated with Discordance between the Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *Journal of Interventional Cardiology*. 2019; 2019: 3765282.
- [28] Lee SH, Choi KH, Lee JM, Hwang D, Rhee TM, Park J, *et al.* Physiologic Characteristics and Clinical Outcomes of Patients With Discordance Between FFR and iFR. *JACC Cardiovascular Interventions*. 2019; 12: 2018–2031.
- [29] Dérimay F, Johnson NP, Zimmermann FM, Adjedj J, Witt N, Hennigan B, *et al.* Predictive factors of discordance between the instantaneous wave-free ratio and fractional flow reserve. *Catheterization and Cardiovascular Interventions*. 2019; 94: 356–363.
- [30] Goto R, Takashima H, Ohashi H, Ando H, Suzuki A, Sakurai S, *et al.* Independent predictors of discordance between the resting full-cycle ratio and fractional flow reserve. *Heart Vessels*. 2021; 36: 790–798.
- [31] Kobayashi Y, Johnson NP, Berry C, De Bruyne B, Gould KL, Jeremias A, *et al.* The Influence of Lesion Location on the Diagnostic Accuracy of Adenosine-Free Coronary Pressure Wire Measurements. *JACC Cardiovascular Interventions*. 2016; 9: 2390–2399.
- [32] Lee JM, Shin ES, Nam CW, Doh JH, Hwang D, Park J, *et al.* Discrepancy between fractional flow reserve and instantaneous wave-free ratio: Clinical and angiographic characteristics. *International Journal of Cardiology*. 2017; 245: 63–68.
- [33] Warisawa T, Cook CM, Howard JP, Ahmad Y, Doi S, Nakayama

- M, *et al.* Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance. *Circulation Cardiovascular Interventions*. 2019; 12: e007494.
- [34] Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, *et al.* Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2018; 13: 1512–1519.
- [35] Ge X, Liu Y, Yin Z, Tu S, Fan Y, Vassilevski Y, *et al.* Comparison of Instantaneous Wave-Free Ratio (iFR) and Fractional Flow Reserve (FFR) with respect to Their Sensitivities to Cardiovascular Factors: A Computational Model-Based Study. *Journal of Interventional Cardiology*. 2020; 2020: 4094121.
- [36] Benenati S, De Maria GL, Scarsini R, Porto I, Banning AP. Invasive “in the cath-lab” assessment of myocardial ischemia in patients with coronary artery disease: When does the gold standard not apply? *Cardiovascular Revascularization Medicine*. 2018; 19: 362–372.
- [37] Tahir H, Livesay J, Fogelson B, Baljepally R. Effect of Elevated Left Ventricular End Diastolic Pressure on Instantaneous Wave-Free Ratio and Fractional Flow Reserve Discordance. *Cardiology Research*. 2021; 12: 117–125.
- [38] Tahir H, Livesay J, Fogelson B, Baljepally R. Association of Echocardiographic Diastolic Dysfunction with Discordance of Invasive Intracoronary Pressure Indices. *Journal of Clinical Medicine*. 2021; 10: 3670.
- [39] Cook CM, Jeremias A, Petraco R, Sen S, Nijjer S, Shun-Shin MJ, *et al.* Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses: An Analysis Using Doppler-Derived Coronary Flow Measurements. *JACC Cardiovascular Interventions*. 2017; 10: 2514–2524.
- [40] Lee JM, Hwang D, Park J, Tong Y, Koo BK. Physiologic mechanism of discordance between instantaneous wave-free ratio and fractional flow reserve: Insight from (13)N-ammonium positron emission tomography. *International Journal of Cardiology*. 2017; 243: 91–94.
- [41] Lee JM, Rhee TM, Choi KH, Park J, Hwang D, Kim J, *et al.* Clinical Outcome of Lesions With Discordant Results Among Different Invasive Physiologic Indices - Resting Distal Coronary to Aortic Pressure Ratio, Resting Full-Cycle Ratio, Diastolic Pressure Ratio, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve. *Circulation Journal*. 2019; 83: 2210–2221.
- [42] Lee JM, Shin ES, Nam CW, Doh JH, Hwang D, Park J, *et al.* Clinical Outcomes According to Fractional Flow Reserve or Instantaneous Wave-Free Ratio in Deferred Lesions. *JACC Cardiovascular Interventions*. 2017; 10: 2502–2510.
- [43] Lee JM, Lee SH, Hwang D, Rhee TM, Choi KH, Kim J, *et al.* Long-Term Clinical Outcomes of Nonhyperemic Pressure Ratios: Resting Full-Cycle Ratio, Diastolic Pressure Ratio, and Instantaneous Wave-Free Ratio. *Journal of the American Heart Association*. 2020; 9: e016818.
- [44] Paul TK, Seto AH, White CJ. Nonhyperemic Pressure Ratios Versus Fractional Flow Reserve: What to Do With Discordant Results? *Journal of the American Heart Association*. 2020; 9: e018344.
- [45] Picard F, Pighi M, Ly HQ. Fractional flow reserve and resting indices for coronary physiologic assessment: Practical guide, tips, and tricks. *Catheterization and Cardiovascular Interventions*. 2017; 90: 598–611.
- [46] Härle T, Bojara W, Meyer S, Elsässer A. Comparison of instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR)—first real world experience. *International Journal of Cardiology*. 2015; 199: 1–7.
- [47] Rivero F, Cuesta J, Bastante T, Benedicto A, García-Guimaraes M, Fuentes-Ferrer M, *et al.* Diagnostic accuracy of a hybrid approach of instantaneous wave-free ratio and fractional flow reserve using high-dose intracoronary adenosine to characterize intermediate coronary lesions: Results of the PALS (Practical Assessment of Lesion Severity) prospective study. *Catheterization and Cardiovascular Interventions*. 2017; 90: 1070–1076.
- [48] Modi BN, Rahman H, Kaier T, Ryan M, Williams R, Briceno N, *et al.* Revisiting the Optimal Fractional Flow Reserve and Instantaneous Wave-Free Ratio Thresholds for Predicting the Physiological Significance of Coronary Artery Disease. *Circulation Cardiovascular Interventions*. 2018; 11: e007041.
- [49] Onishi K, Watanabe H, Kakehi K, Ikeda T, Takase T, Yamaji K, *et al.* Determinants and prognostic implications of instantaneous wave-free ratio in patients with mild to intermediate coronary stenosis: Comparison with those of fractional flow reserve. *PLoS ONE*. 2020; 15: e0237275.