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REVIEW ARTICLE

FFR and iFR: Similarities, Differences, and Clinical Implication

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Abstract

Fractional flow reserve (FFR) is now accepted as the reference standard to indicate whether a stenosis is likely to be responsible for ischemia. It is generally accepted that a stenosis with an ischemic value of FFR is responsible for symptom and a worse outcome and should be revascularized, whereas lesions with a non-ischemic FFR have a more favorable prognosis and can be treated medically. Furthermore, FFR-guided revascularization strategy has been definitely proven to be better than angiography-guided strategy in pivotal landmark studies. Instantaneous wave free ratio (iFR) is another physiological index which can be obtained at rest without hyperemic stimulation. iFR is conceptually different from FFR, leading to lively scientific debate about this index. In this review article, the concept, differences and similarities of FFR and iFR are reviewed.

Keywords: Coronary circulation, Coronary revascularization, Fractional flow reserve, Instantaneous wave free ratio, Pressure wire

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The potential benefit of revascularization depends on the presence and extent of myocardial ischemia. Performing PCI on non-ischemic stenoses is not beneficial and is potentially harmful (1, 2). Thus, careful selection of ischemia-inducing stenoses is essential for deriving the greatest benefit from revascularization in patients with stable coronary artery disease. Fractional flow reserve (FFR) is a pressure wire-based index that is used during coronary angiography to assess the potential of a coronary stenosis to induce myocardial ischemia (1). The usefulness of FFR-guided PCI as compared with PCI guided by angiography alone is supported by robust clinical outcome data (3). On the other hand, iFR is a resting index of stenosis severity that provides a physiological quantification of the effect of a stenosis on the coronary circulation (4). In this review article, similarities and differences between iFR and FFR are described.

Fractional flow reserve (FFR)

Basic concept of FFR

The concept of coronary pressure-derived FFR has been extensively studied and clinically validated (5-7). Fig. 1 shows a schematic illustration of the FFR concept (2). Under maximum achievable arteriolar vasodilatation, the resistance imposed by the myocardial bed is minimized, and blood flow becomes proportional to driving pressure. Therefore, hyperemic perfusion in a myocardial territory is proportional to perfusion pressure in this condition. FFR is defined as maximum myocardial blood flow in a stenotic territory, divided by normal maximum blood flow in that same territory in the hypothetical case that the supplying coronary artery would be completely normal. Because of the linearity between hyperemic pressure and blood flow, this ratio of maximum flows can be represented by the ratio of pressures, whereby, the distal coronary pressure is divided by aortic pressure at hyperemia under the assumption that venous pressure is zero. With this methodology, aortic pressure is measured by the guiding catheter and distal coronary pressure by a pressure monitoring guidewire. Thus, FFR can easily be simply derived from the ratio of mean distal coronary artery pressure to aortic pressure during maximal hyperemia. FFR is a vessel specific index, (although it is still influenced by collaterals) and represents the fraction of normal maximum flow that remains despite the stenosis. The theoretical value for FFR of a normal coronary artery is 1.0, regardless of vessel or patient. There is

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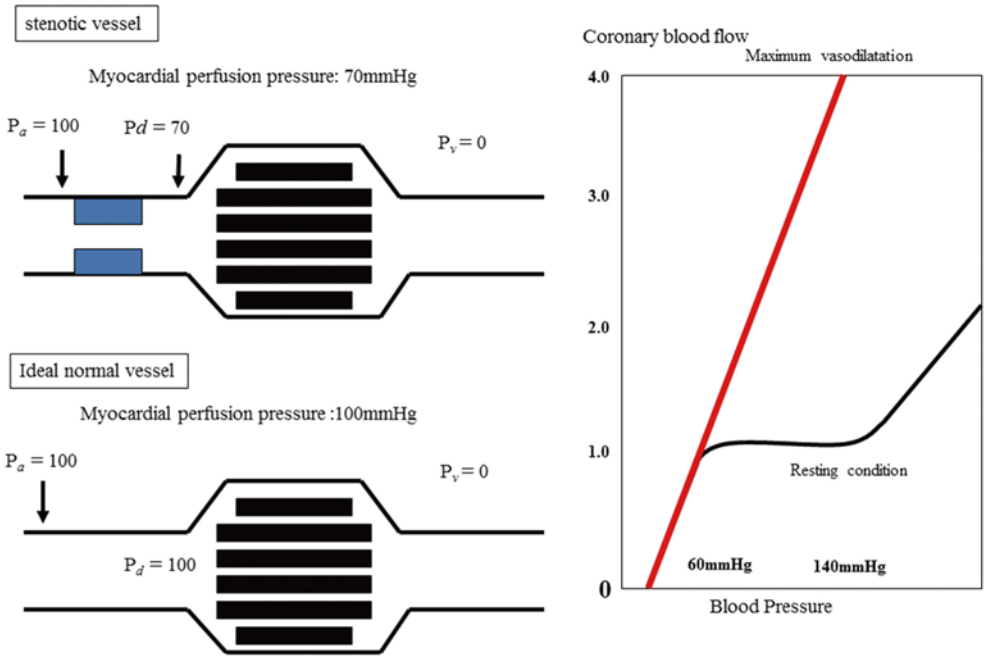

Fig. 1 Concept of fractional flow reserve (FFR): if epicardial stenosis is not present, the driving pressure Pa determines a normal (100%) maximal myocardial blood flow. In the case of stenosis responsible for a hyperemic pressure gradient of 30 mmHg, the driving pressure will no longer be 100 mmHg, will be 70 mmHg (Pd). Because the relationship between driving pressure and myocardial blood flow is linear during maximal hyperemia (as shown in red line in pressure flow relationship), myocardial blood flow will only reach 70% of its normal value. Pv=central venous pressure.

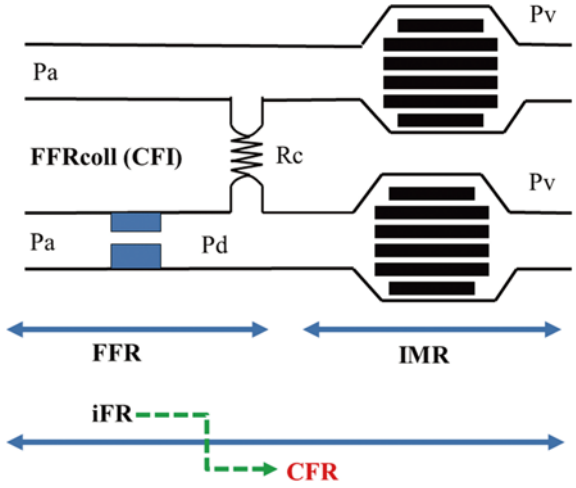

Fig. 2 Model of the coronary circulation and invasive physiology-derived indexes. Indexes in red can be obtained by pressure wire only. Indexes in black need Doppler flow parameters.
FFRmyo: myocardial fractional flow reserve, iFR: instantaneous wave-free ratio, IMR: index of microcirculatory resistance, FFRcoll: fractional collateral flow reserve

sharp discrimination by FFR between ischemic and non-ischemic lesions. FFR ≥0.80 excludes inducible ischemia by a particular stenosis with an accuracy of 95% and FFR <0.75 indicates inducible ischemia in almost 100% of lesions, thereby justifying PCI if technically feasible. FFR has been validated well by comparing with other reference standards in an prospective quasi multi-testing Bayesian approach (7). However, there are several conceptual pitfalls about FFR. Fig. 2 showed theoretical model of the coronary circulation and invasive physiology-derived indexes (8). Although FFR provides valuable information on obstructive disease, its theoretical framework largely neglects the importance of non-obstructive concomitant involvement such as microvascular dysfunction (9). Thereby justifying PCI if technically feasible. Van de Hoff et al. reported that discordance between Coronary flow velocity reserve (CFVR) and FFR originates from the involvement of the coronary microvasculature. Importantly, the risk for major adverse cardiac events associated with FFR/CFVR discordance is mainly attributable to stenoses where FFR are normal and CFVR are abnormal subset (10).

Instantaneous wave-free ratio (iFR)

Recently, physiologic indices that do not require hyperemia have been introduced and have attracted attention, since these indices can reduce the procedural time, improve cost efficiencies as well as improve patient comfort. The instantaneous wave-free ratio (iFR) is one such index that was developed from investigation of coronary flow, velocity, and resistance.

Theoretical basis of iFR

iFR is founded on the basis that there is a certain period in each cardiac cycle during which resistance at rest is stable (the wave-free period). During this phase the ratio of the proximal and distal pressures are proportional to coronary flow (Fig. 3).

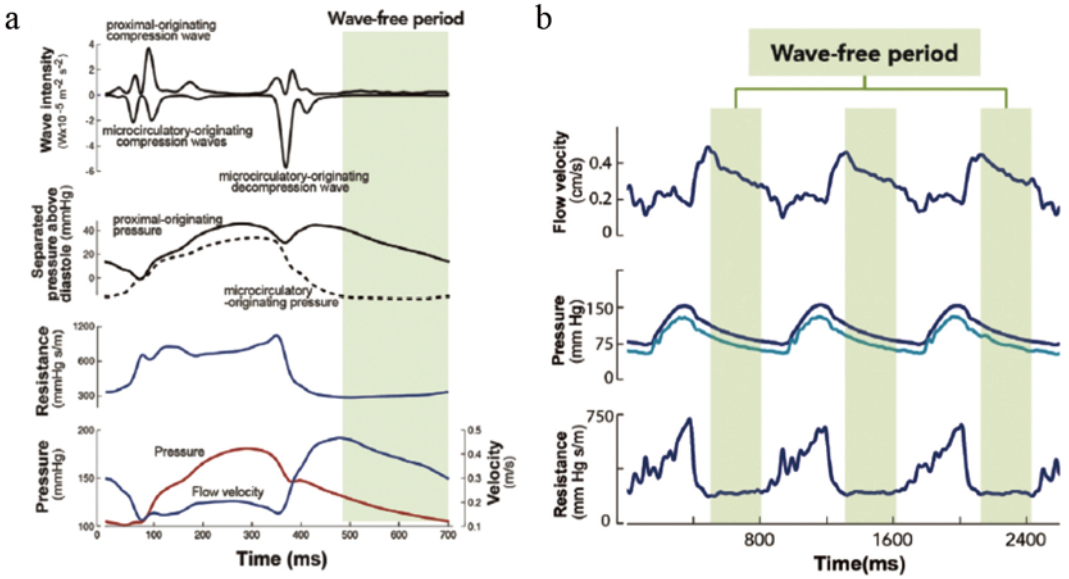

Fig. 3 **a**: Separated wave intensity plot shows how multiple different waves propagating from the proximal and distal ends of the vessel influence coronary flow. The waves are quiescent during the wave-free period in diastole. Instantaneous resistance plotted throughout the cardiac cycle demonstrates that resistance is low and most stable during the wave-free period. Coronary pressure and flow are linearly related during the wave-free period. **b**: Flow velocity, proximal and distal pressure traces and instantaneous resistance demonstrate the stability of the wave-free period beat to beat. Flow velocity over the wave-free period is higher than that over the whole cycle, giving greater discrimination between stenosis severities than the whole cycle at rest. Adapted with permission from Sen S, Davis J, et al. 4

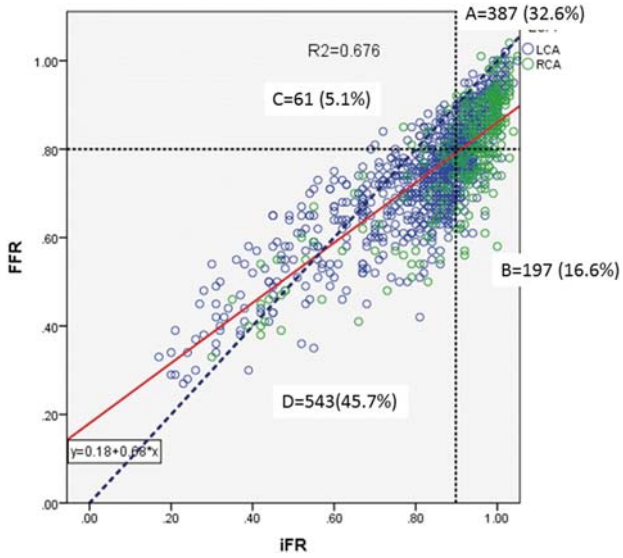

Fig. 4 Scatter plot showing the relationship between FFR and iFR from 1188 patients is shown. Best cutoff point which discriminate lesions with FFR≦0.80 revealed iFR<0.9. By using this cutoff, about 21.7% lesions are discordant between these indices. Subset B :iFR≧0.90 FFR≦0.80 is 16.6%, Subset C : iFR<0.90 FFR>0.80 5.1%. iFR based decision making with cutoff value 0.90 may miss about 16.6% of the FFR positive lesions.

The relationship between a pressure gradient and blood flow velocity can be expressed as Bernoulli's equation: $PG = fv + Sv^2$. In the presence of stenosis, the coronary pressure gradient shows a quadratic relation to flow. Each stenosis has a specific pressure-flow curve, which is determined by its morphological characteristics (11). The pressure gradient across a stenosis is determined by the coronary flow velocity. To assess the severity of a stenosis from the pressure gradient across it, two flow conditions are required. First, the flow velocity must be constant, and second, it must be high enough. The pressure gradient only depends on the severity of a stenosis if the flow velocity is constant. If the flow velocity varies, different pressure gradients may be generated by stenoses of differing severities, but also by the same stenosis. From this perspective, resting state is ideal because blood flow at resting condition was preserved across wide range of stenosis severities by autoregulation, and this likely occurs by compensatory microcirculatory vasodilatation in response to the stenosis for the decrease of distal perfusion pressure, which falls even at rest as shown in Fig. 4 (12). Because pressure falls at rest with stenosis severity, then a resting index should be sufficient to quantify severity, provided there is sufficient flow velocity to distinguish between stenoses. This is the reason why iFR must be measured under resting conditions when flow velocity is constant irrespective of the severity of stenosis.

Another important issue is that flow velocity needs to be high enough for the severity of stenosis to be assessed from the pressure gradient. iFR could be expected to show more discriminatory power than the resting whole cycle Pd/Pa, because mean flow velocity is 26% higher during the wave-free period than the overall velocity for the cardiac cycle, as

demonstrated by the CLARIFY study (13). Pressure-based index of coronary stenosis severity should ideally be calculated at a constant and high coronary flow velocity. The resting wave-free period satisfies these requirements under physiological conditions. Therefore, iFR which is defined as instantaneously measured pressure ratio during wave free period at resting state, without hyperemic stimulation, is theoretically an ideal index.

Clinical implication of FFR and iFR based coronary intervention

Landmark studies supporting FFR guided PCI compared with angiography guided PCI

Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis (DEFER) trial, the FFR versus Angiography for Guiding Percutaneous Coronary intervention (FAME) and Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease (FAME-2) clinical trials have established FFR-guided PCI as the standard of care in patients undergoing invasive management. In DEFER trial, 325 patients who were planned to undergo PCI underwent FFR measurement. Patients with an FFR≥0.75 were randomised to deferral of PCI (defer group) or to undergo PCI (perform group), whereas those with an FFR<0.75 underwent PCI as planned (reference group). There was no significant difference in the primary endpoint of absence of adverse cardiac events at 24 months follow-up in the defer versus perform groups, demonstrating that patients with negative-FFR values (defined as >0.75) did not benefit from PCI when compared to medical therapy. At 15-years follow-up, there remained no significant difference in the rate of death in patients with functionally insignificant lesions (FFR＞0.75) that were managed with medical therapy, and there was a lower rate of myocardial infarction (MI) in the defer group compared to the perform group (2.2% vs. 10.0%, p=0.03). FAME tested the hypothesis that PCI guided by FFR measurement in patients with stable angina and multivessel CAD (defined as ＞50% stenosis in ≥2 main epicardial vessels) would alter lesion classification and improve health and economic outcomes. After the decision to undertake PCI based on ICA, 1,005 patients were randomised to FFR-guided PCI (PCI performed if FFR≤0.8) or to continue with PCI guided by visual interpretation of the angiogram alone. The composite primary outcome of death, MI or repeat revascularisation at 1 year was lower in the FFR-guided group than in the angiography-guided group, [13.2% (67 patients) vs. 18.3% (91 patients), p=0.02]. This difference was sustained at 2 years follow-up. At 5 years follow-up, there was no difference in the primary endpoint between the FFR- and angiography-guided groups (28% vs. 31%, p=0.3), but the absolute difference in events persisted, and this was driven by the difference in cardiac mortality. FAME-2 enrolled 1,220 patients with stable CAD who were undergoing invasive management and being considered for PCI of one or more angiographically severe stenosis. In the subset of patients with lesions with an FFR≤0.80 that were amenable to PCI (n＝888), patients were randomised (1:1) to PCI of all lesions with OMT versus OMT alone without PCI. Patients with lesions with an FFR＞0.80 were not randomised but included in a follow-up registry involving OMT alone. On the recommendation of the Data and Safety Monitoring Committee, the trial was stopped prematurely due to a statistically significant reduction in hospital re-admission for urgent coronary revascularisation in the OMT group. It has been proposed that urgent revascularisation is a ‘soft’ endpoint, and as patients were aware they had a coronary lesion which had not undergone PCI, this may have influenced the likelihood of re-presentation to hospital. Urgent coronary revascularisation for the primary outcome was defined as urgent unplanned hospital admission with persistent or increasing symptoms with or without ECG evidence of ischaemia (26.8%) or elevated cardiac biomarker levels (21.4%), and that the revascularisation be performed within 24 h of admission. Cardiologists blinded to the treatment group assignment adjudicated this outcome. After follow-up to 2 years, the observed between-group difference in the primary outcome was maintained. Based on these publication, the European Society of Cardiology gives FFR a class 1A indication for the assessment of intermediate severity stenosis (defined as 50-90% diameter stenosis). In the USA, the increasing frequency of FFR guidance has also been stimulated by recent appropriate use criteria and some private insurance companies require evidence of ischaemia by FFR assessment if percutaneous coronary intervention (PCI) is to be undertaken.

Impact of FFR measurement in diagnostic angiography

FFR is considered to be a reliable index for the assessment of clinically relevant coronary artery stenosis. However, mismatch in assessing the severity of coronary stenosis between coronary angiography and the FFR has been pointed out. The cardiovascular intervention therapeutics (CVIT)-DEFER registry is a prospective multicenter registry study that has enrolled 3,228 consecutive patients among 3,804 patients with angiographically moderate coronary artery lesions in whom FFR analysis was clinically indicated. In this registry, Angiographic-FFR “mismatch,” which was defined as visual stenosis≧75% with FFR ＞0.80, was found in 43.4% of lesions, while reverse angiographic mismatch (visual stenosis ＜75% with FFR≦0.8) was found in 23.2% (14). The independent predictors for “angiographic-FFR mismatch” were the presence of percutaneous coronary intervention (PCI) history, one-vessel disease, non-left anterior descending artery

(LAD) location, non-diffuse lesion, non- ostial lesion, and non-tandem lesion. Conversely, “reverse angiographic mismatch” was independently associated with the multi-vessel disease, LAD location, and diffuse lesion. In CVIT registry analyzing 3,093 subjects, the treatment strategy based on angiographic findings was medical management in 34.5%, percutaneous coronary intervention (PCI) in 63.5%, and coronary artery bypass grafting in 2.1%. The FFR was ≤0.8 in 1,566 lesions (42.2%). After FFR measurement, medical treatment was changed to revascularization in 19.7%, while PCI was switched to medical treatment in 57.4% at the lesion level. As a result, reclassification of the treatment strategy at the patient level was done in 39.0% of the patients (15). Revascularization was frequently switched to medical treatment after FFR measurement. Other reports from England and French also emphasized similar results with CVIT-DEFER registry. In the RIPCORD study, 200 patients undergoing coronary angiography had a management plan made based only on the angiographic findings. FFR was then measured in all vessels with ≥2.25 mm diameter and used to guide a second management plan. One-quarter of the patients had a change in management after measurement of FFR; 9 of 72 patients (12.5%) in whom medical therapy was chosen on the basis of angiography were recommended for revascularization when the FFR was known. Similarly, one-quarter of patients first recommended for revascularization required medical therapy once the FFR was known. In total, one-third of vessels were considered significantly changed after FFR assessment (16). The R3F study was a larger study with a similar design, enrolling over 1,075 consecutive patients undergoing coronary angiography in 20 French centers. Unlike RIPCORD, patients were only included if at least 1 ambiguous lesion was present, and FFR was performed only in the vessel of interest. Although the overall proportion of medical therapy, PCI and coronary artery bypass grafting appeared similar, with only a modest but statistically significant change, individual patients had a marked change in plan, with 464 (43%) patients having a different management plan made after FFR disclosure. Importantly, from a safety perspective, the event rate after 1 year of follow-up was identical in the cohort of patients who were reclassified by FFR and those in whom angiographic-guided plans were concordant with the FFR findings (11.2% vs. 11.9% major adverse cardiac event (MACE) rate, P=0.78) (17). Taken together, CVIT defer, RIPCORD, and R3F strongly suggest that routine coronary physiology should be considered in all patients referred for coronary angiography. The ESC guidelines define an intermediate stenosis as 50-90%. In a diagnostic study of 200 patients, 47% of lesions defined as >70% diameter stenosis were FFR-negative and 13% of lesions graded as <30% were FFR-positive. This suggests that rather than only using FFR for ‘intermediate’ stenoses, more discrete areas of coronary plaque should be interrogated, especially in younger patients, in epicardial vessels with proximal lesions subtending a large myocardial mass (namely left main stem and left anterior descending artery lesions), or lesions of long length.

FFR as a marker of ischemia and as a marker for the event

If revascularization is performed for ischemia, a continuous benefit should be expected related to the severity of ischemia, and FAME-2 demonstrates that the FFR value related to the event rate (18, 19). First, decisions were made using the 0.80 threshold; although not specifically validated during the original FFR studies, there is data to suggest there are increased events when stenoses between 0.75-0.80 are deferred (20-22), suggesting that the higher 0.80 cut-point is reasonable. An FFR of 0.65 had significant interaction with the primary endpoint at 7 months. At 2 years, however, the interaction only showed a trend towards significance (P = 0.07). This suggests that the majority of benefit for revascularization is when stenoses are truly ischemic (FFR ≤0.65), and this value is similar to the mean FFR in FAME-1 in stenoses undergoing PCI (0.60 ± 0.14) (23, 24). Further supporting data come from a comprehensive meta-analysis of lesion data (9,173 lesions) and patient-level (6,961 lesions) data from FFR studies which reported the ischemia and events. Clinical events increase as the FFR decreases and revascularization demonstrates the greatest benefit the lower the FFR value. Using patient-level data, the optimal FFR threshold to predict benefit from revascularization over medical therapy for a composite of death, MI and revascularization was found to be 0.67 (25). Interestingly 0.66-0.67 is the value at which rest flow starts to decrease as reported by Nijjer et al. (12). Taken these together, the real value of the FFR is in the assessment of the severity of all stenoses rather than just the intermediate stenoses. Because anatomical stenosis severity poorly predicts the FFR value, limiting FFR to only “intermediate” stenosis will poorly identify and may lead to miss the presence of potential ischemia; all stenosis should be assessed to gain maximum benefit by FFR.

Concordance and discordance between iFR and FFR

In the first clinical study (ADVISE), iFR showed a good correlation with FFR ($r = 0.9$, $p < 0.001$) and also showed excellent diagnostic performance. In this study, the best cut-off value of the iFR for predicting an FFR ≤0.8 was 0.83 and the overall diagnostic accuracy for FFR ≤0.8 was 88% (4) Since the ADVISE study was published, there has been considerable debate about the background and clinical relevance of this index much of which is based around the scatter plots between iFR and FFR. However, as these two indices have different foundations, it is reasonable that there

values are similar but, there is no good reason that they should be identical. The equivalent diagnostic performance of the iFR and FFR in the ADVISE study is consistent with the findings of other studies, including the ADVISE Registry (26), a prospective blinded South Korean study (27), the CLARIFY study (13). Importantly, in all of the studies that demonstrated good diagnostic performance, the same automated algorithm was used for calculation of the iFR by off-line analysis. With regard to real-time online analysis, the ADVISE in-practice study (an international, multicenter evaluation of iFR in clinical practice) also showed similar good diagnostic performance of the iFR (28). In a large retrospective multicenter core laboratory comparison of the iFR and FFR (n=1593), the overall sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of an iFR ≤0.90 (for predicting an FFR ≤0.80) were 78.9%, 82.4%, 85.2%, 73.3%, and 80.4%, respectively (8, 29). We have performed an on-line comparison between iFR and FFR, in which FFR was measured with intravenous ATP. Fig. 4 represented the relationship between FFR and iFR in 1,188 lesions from 889 patients in Gifu Heart Center. We found a good correlation between iFR and FFR (r2＝0.67, 95% CI 0.71-0.82), and the best cut-off value of iFR for predicting FFR ≤0.8 was 0.90. This value is in complete concordance with the results of other smaller studies. The best cutoff value which discriminate lesions with FFR ≦0.80 revealed iFR <0.9. By using this cutoff, about 21.7% lesions are discordant between these indices. Among these discordant segments, 16.6% of the lesions were in Subset B: iFR ≧0.90 FFR ≦0.80, and 5.1% of the lesions were in Subset C: iFR <0.90 FFR >0.80. These data suggests iFR based decision making with cut-off value 0.90 defers about 16.6% of the FFR positive lesions. However, iFR based decision making may miss only 1.3% of the lesion with FFR below 0.67 which is the threshold to predict benefit from revascularization over medical therapy for a composite of death, and MI. Furthermore, the lesions plotted to subset B can be interpreted as the lesions with large pressure gradients generated by hyperemic stimulation despite small pressure gradients at resting condition. This means the flow across the stenosis is significantly increased by hyperemia which may denote well preserved coronary flow reserve in these lesions or a large effect from collateral branches. This phenomenon was confirmed by the JUSTIFY-CFR study (30). This study clearly demonstrated that when iFR was negative and FFR was positive, CFR >2 was noted in 97% of cases. These findings suggest that when iFR and FFR appear to disagree, iFR provides a greater degree of information about the state of coronary flow than does FFR. Clinical study to investigate the natural course of these discordant lesions between iFR and FFR are now underway.

Clinical outcome study comparing FFR and iFR based decision making

Recently published DEFINE-FLAIR and iFR-SwedeHeart studies provided the first clinical outcomes data comparing the use of iFR and FFR guided reascularization therapy in around 2, 500 and 2, 000 patients respectively (31, 32). DEFINE FLAIR trial allocated 2,492 patients into FFR guided PCI and iFR guided PCI, this study clearly demonstrated that coronary revascularization guided by iFR was non-inferior to the revascularization guided by FFR with respect to the risk of major adverse cardiac events at 1 year. They found the rate of adverse procedural signs and symptoms was lower and the procedural time was shorter with iFR than with FFR. iFR Swedeheart study demonstrate that an iFR-guided revascularization strategy was non-inferior to an FFR-guided revascularization strategy with respect to the rate of major adverse cardiac events at 12 months among patients with stable angina or an acute coronary syndromes. Both studies results were concordant in that iFR based coronary intervention is not inferior to FFR guided coronary intervention.

Conclusion

The coronary pressure-based physiological assessment using FFR provides clinical benefit over coronary angiography for the guidance of coronary intervention supported by many evidences. However, clinicians should aware of potential pitfalls of this index. iFR a emerging clinical index is also expected to be clinically applicable. This concept may simplify physiological assessment in the catheter laboratory and may provide significant added benefit on FFR based coronary intervention, and now in the stage for routine clinical use.

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Conflicts of interest

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