Per-Vessel Level Analysis of Fractional Flow Reserve and Instantaneous Wave-Free Ratio Discordance
— Insights From the AJIP Registry —

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Background: The per-vessel level impact of physiological pattern of disease on the discordance between fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) has not been clarified.

Methods and Results: Using the AJIP registry, vessels with FFR/iFR discordance (133/671 [19.8%]) were analyzed. In the left anterior descending artery (LAD), physiologically diffuse disease, as assessed by pressure-wire pullback, was associated with FFR−/iFR+ (83.3% [40/48]), while physiologically focal disease was associated with FFR+/iFR− (57.4% [31/54]), significantly (P<0.0001). These differences were not significant in non-LAD (P=0.17).

Conclusions: The impact of physiological pattern of disease on FFR/iFR discordance is more pronounced in the LAD.

Key Words: Diffuse disease; Fractional flow reserve; Instantaneous wave-free ratio

Recent studies have provided insights into the physiological pattern of disease, which is known to influence the discordance between fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). Specifically, low-iFR/high-FFR discordance was significantly more associated with a physiologically diffuse pattern of disease, while high-iFR/low-FFR discordance was significantly more associated with a physiologically focal pattern of disease (P<0.001). However, the per-vessel level impact of this finding is yet to be clarified.

The aim of this study was to assess the impact of physiological pattern of disease on FFR/iFR discordance in the left anterior descending artery (LAD) and non-LAD.

Methods

Study Design
This investigation is an additional analysis of the previously reported study using the same design and same registry; the details of the AJIP (Anglo-Japanese instantaneous wave-free ratio pullback) registry has been described previously. The per-vessel level analysis of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) discordance has been described previously (Warisawa T, et al. JACC 2019;74:486-95).
In summary, in this study, patients with isolated coronary artery disease of intermediate severity and combined measurements of iFR, FFR, and iFR-pullback were included. The cases were collected between March 2015 to March 2019, which was a longer period than that of a previous study and the number of participating centers has increased. Accordingly, more cases were included for this analysis; the number of vessels assessed increased from 360 to 671. Routine cut-off values of hemodynamic significance (FFR ≤0.80 and iFR ≤0.89) were used to classify stenoses into 4 groups: (1) FFR+/iFR+ (FFR ≤0.80/iFR ≤0.89); (2) FFR−/iFR+ (FFR >0.80/iFR ≤0.89); (3) FFR+/iFR− (FFR ≤0.80/iFR >0.89); and (4) FFR−/iFR− (FFR >0.80/iFR >0.89). iFR-pullback recordings were performed manually at a pullback speed of approximately 0.5–1.0 mm/s. Based on iFR-pullback traces, the physiological pattern of disease was classified as predominantly focal or predominantly diffuse by the consensus opinion of experts. More detailed methodological information is available elsewhere. All patients provided written informed consent. This study was approved by the local ethics committees at each participating center and was conducted according to the principles of the Declaration of Helsinki.

**Statistical Analysis**

Categorical data were expressed as numbers and percentages, while continuous variables were expressed as mean and (±) standard deviation (SD) or as median accompanied by interquartile range (IQR) as appropriate. Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were compared by using the Student’s t or Mann-Whitney U-tests, and categorical variables with chi-squared or Fisher’s exact tests, as appropriate. A logistic regression model was used for multivariate analysis to detect influencing factors on FFR/iFR discordance. Results were reported using the odds ratio (OR) and 95% confidence interval (CI). All probability values were 2-sided, and P values <0.05 were considered statistically significant. All statistical analysis was performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Study Population**

Full descriptions of patient and vessel characteristics are provided in Table 1. A total of 671 coronary vessels (626 patients) were analyzed. The most frequently assessed vessel was the LAD (77.0% [517/671]). Among 53 left main cases, 3 cases showed isolated left main lesions, in which physiological measurements were performed in the LAD. Accordingly, these were classified as the LAD group (n=520). The remaining 151 vessels were assessed as the non-LAD group. Median FFR and iFR were 0.80 (IQR: 0.74–0.85) and 0.89 (IQR: 0.84–0.92), respectively; both of which were on the respective cut-off values.

**FFR/iFR Discordance in the LAD**

In the LAD group, FFR agreed with iFR in 80.4% (418/520) of cases, consisting of FFR+/iFR+ (n=261, 50.2%) and FFR−/iFR− (n=157, 30.2%). FFR disagreed with iFR in 19.6% (102/520) of cases, consisting of FFR−/iFR+ (n=48, 9.2%) and FFR+/iFR− (n=54, 10.4%). The physiological pattern of disease was classified as 53.8% (280/520) physiologically diffuse and 46.2% (240/520) physiologically focal.

Table 2 demonstrates the differences in patient and lesion characteristics between FFR−/iFR+ and FFR+/iFR− discordant groups. Only diabetes mellitus and physiological pattern of disease were significantly associated with FFR/iFR discordance (P=0.018 and P<0.0001, respectively). Specifically, comorbidity of diabetes mellitus was associated with FFR−/iFR+: the physiologically diffuse disease was significantly associated with FFR−/iFR+ (83.3% [40/48]), while physiologically focal disease was significantly associated with FFR+/iFR− (57.4% [31/54]) (Figure 1A). Both were confirmed as significantly different in the multivariate analysis as well (diabetes mellitus: OR: 3.96, 95% CI: 1.43–10.9; P=0.0079; and physiological pattern of disease: OR: 8.00, 95% CI: 2.93–21.9, P<0.0001).

**FFR/iFR Discordance in the Non-LAD**

In the non-LAD group, FFR/iFR discordance was observed in 20.5% (31/151) of cases: FFR+/iFR+ (n=43, 28.5%), FFR−/iFR+ (n=15, 9.9%), FFR+/iFR− (n=16, 10.6%), and FFR−/iFR− (n=77, 51.0%). The physiological pattern of disease was classified as 18.5% (28/151) physiologically focal.

| Table 1. Patient and Vessel Characteristics |
|---------------------------------------------|
| **Patients**                                 |
| Age, years                                  | 66.9±10.6 |
| Male                                        | 479 (76.5) |
| Height, cm                                  | 166±9.1   |
| Weight, kg                                  | 72.9±15.5 |
| Hypertension                                | 448 (71.6) |
| Dyslipidemia                                | 409 (65.3) |
| Diabetes mellitus                           | 209 (33.4) |
| Chronic kidney disease                      | 119 (19.0) |
| Current or Ex-smoker                        | 202 (32.3) |
| Family history of CAD                       | 105 (16.8) |
| Previous myocardial infarction              | 139 (22.2) |
| Impaired LV function EF <30%                | 23 (3.7)   |
| **Vessels**                                 |
| Coronary artery                             | 671        |
| Left anterior descending                    | 517 (77.0) |
| Left circumflex                             | 73 (10.9)  |
| Right coronary artery                       | 69 (10.3)  |
| Left main trunk                             | 53 (7.9)   |
| Others                                      | 9 (1.3)    |
| **Quantitative coronary angiography**       |
| Diameter stenosis, %                        | 51.5±13.7 |
| Minimum lumen diameter, mm                  | 1.40±0.49 |
| Reference diameter, mm                      | 2.89±0.62 |
| Lesion length, mm                           | 21.2±13.9 |
| **Physiologic indices**                     |
| FFR                                         | 0.80 (0.74–0.85) |
| iFR                                         | 0.89 (0.84–0.92) |
| **Physiological pattern of disease**        |
| Predominantly physiologically diffuse       | 308 (45.9) |
| Predominantly physiologically focal         | 363 (54.1) |

Values are presented as n, n (%), mean±standard deviation, or median (interquartile range). CAD, coronary artery disease; EF, ejection fraction; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LV, left ventricular.
FFR/iFR Discordance in the Diffuse LAD

ologically diffuse disease, frictional losses would be the predominant mode of a pressure energy loss, which would be already evident at rest (iFR+) and increase only slightly during hyperemia (FFR−). The relatively small change of pressure loss would be partly attributed to the concomitant microvascular dysfunction.

Conversely, in physiologically focal disease, separation losses would be the predominant mode of a pressure energy loss, which would be minimally present at rest (iFR−) and become evident only during hyperemia (FFR+). Accordingly, the potential needs for treatment optimization based on the physiological pattern of disease beyond the FFR/iFR cut-off values was proposed. Namely, they suggested that consideration should be given on clinical benefit of focal stenting in patients with FFR+/iFR− despite presumably having coronary flow response within the normal range.

Conversely, they emphasized the balance between risks and benefits of long-stenting in the diffuse lesions with FFR−/iFR+ discordance, which may not achieve optimal post-stent physiologic results or favorable long-term outcomes.

The present study further strengthens this recommendation, as the LAD stenosis subtends a larger myocardial territory and the prognosis of coronary artery disease is largely determined by the amount of ischemic myocardium at risk.

Discussion

The present analysis demonstrated that the impact of physiological pattern of disease on FFR/iFR discordance was more pronounced in the LAD: FFR−/iFR+ discordance was characterized by diffuse disease, while FFR+/iFR− was characterized by focal disease.

Recently, Warisawa et al explained the FFR/iFR discordance in terms of the relationship between physiological pattern of disease and stenosis geometry-dependent coronary flow pattern. In their simplified hypothesis, in physiologically diffuse disease, frictional losses would be the predominant mode of a pressure energy loss, which would be already evident at rest (iFR+) and increase only slightly during hyperemia (FFR−). The relatively small change of pressure loss would be partly attributed to the concomitant microvascular dysfunction. Conversely, in physiologically focal disease, separation losses would be the predominant mode of a pressure energy loss, which would be minimally present at rest (iFR−) and become evident only during hyperemia (FFR+). Accordingly, the potential needs for treatment optimization based on the physiological pattern of disease beyond the FFR/iFR cut-off values was proposed. Namely, they suggested that consideration should be given on clinical benefit of focal stenting in patients with FFR+/iFR− despite presumably having coronary flow response within the normal range. Conversely, they emphasized the balance between risks and benefits of long-stenting in the diffuse lesions with FFR−/iFR+ discordance, which may not achieve optimal post-stent physiologic results or favorable long-term outcomes.

The insights from this study suggest one explanation of the results of the DEFINE-FLAIR LAD sub-analysis, which demonstrated superior clinical outcomes among patients deferred with iFR in the LAD compared to FFR. The rate the composite of cardiovascular death, myocard-

In comparison, between FFR−/iFR+ and FFR+/iFR− discordance in non-LAD, none of the features were statistically different, including previously reported influencing factors such as gender, diabetes mellitus, proximal location of lesion defined as Syntax segments 1, 5, 6, and 11, and physiological pattern of disease (all P>0.05). Regarding the physiological pattern of disease, diffuse disease was observed in 26.7% (4/15) FFR−/iFR+ and 6.3% (1/16) FFR+/iFR− (P=0.17) (Figure 1B). Taking account of the significantly different baseline frequency of diffuse disease between the LAD (53.8% [280/520]) and non-LAD (18.5% [28/151], P<0.0001), it should be noted that a numerically higher frequency of diffuse disease in FFR−/iFR+ than in FFR+/iFR− of the non-LAD group was similar to that of the LAD group; however, this difference was not statistically significant in the non-LAD.

Table 2. Difference Between FFR−/iFR+ and FFR+/iFR− Discordance in the LAD

| Patient characteristics | FFR−/iFR+ (n=48) | FFR+/iFR− (n=54) | P value |
|-------------------------|----------------|----------------|--------|
| Age, years              | 68.1±12.1      | 64.2±10.0      | 0.08   |
| Male                    | 35 (72.9)      | 43 (79.6)      | 0.49   |
| Height, cm              | 163±9.1        | 167±9.5        | 0.09   |
| Weight, kg              | 72.7±15.4      | 75.6±17.2      | 0.38   |
| Hypertension            | 38 (79.2)      | 37 (68.5)      | 0.27   |
| Dyslipidemia            | 29 (60.4)      | 33 (61.1)      | 1.00   |
| Diabetes mellitus       | 21 (43.8)      | 11 (20.4)      | 0.018  |
| Chronic kidney disease  | 6 (12.5)       | 12 (22.2)      | 0.30   |
| Current or Ex-smoker    | 14 (29.2)      | 16 (29.6)      | 1.00   |
| Family history of CAD   | 8 (16.7)       | 8 (14.8)       | 1.00   |
| Previous myocardial infarction | 7 (14.6) | 10 (18.5) | 0.79   |
| Impaired LV function EF <30% | 1 (2.1) | 3 (5.6) | 0.62   |

| Lesion characteristics  | FFR−/iFR+ (n=48) | FFR+/iFR− (n=54) | P value |
|-------------------------|----------------|----------------|--------|
| Proximal lesion         | 23 (47.9)      | 23 (42.6)      | 0.59   |
| Diameter stenosis, %    | 42.9±11.3      | 44.9±10.6      | 0.40   |
| Minimum lumen diameter, mm | 1.67±0.48   | 1.65±0.40      | 0.82   |
| Reference diameter, mm  | 2.93±0.61      | 3.00±0.52      | 0.54   |
| Lesion length, mm       | 18.4±11.2      | 18.4±12.0      | 0.99   |

| Physiologic indices     | FFR−/iFR+ (n=48) | FFR+/iFR− (n=54) | P value |
|-------------------------|----------------|----------------|--------|
| FFR                     | 0.83 (0.82–0.85) | 0.79 (0.77–0.80) |        |
| iFR                     | 0.88 (0.87–0.89) | 0.91 (0.90–0.92) |        |

| Physiological pattern of disease | FFR−/iFR+ (n=48) | FFR+/iFR− (n=54) | P value |
|--------------------------------|----------------|----------------|--------|
| Predominantly physiologically diffuse | 40 (83.3) | 23 (42.6) | <0.0001 |
| Predominantly physiologically focal   | 8 (16.7)   | 31 (57.4) | <0.0001 |

Values are presented as n (%), mean±standard deviation, or median (interquartile range). LAD, left anterior ascending artery. Other abbreviations as in Table 1.
Considering that the majority of discordance naturally occurs close to the respective FFR/iFR cut-off values, the following phenomenon might occur, which cannot be verified in that trial due to the parallel allocation (each dial infarction, and unplanned revascularization at 1 year was significantly lower in the iFR-guided than the FFR-guided deferral group (2.44% vs. 5.26%; hazard ratio: 0.46; 95% CI: 0.22–0.95; P=0.04). Of note, in this trial, the mean FFR and iFR were 0.83±0.09 and 0.91±0.09, respectively, both of which were around the respective cut-off values. Considering that the majority of discordance naturally occurs close to the respective FFR/iFR cut-off values, the following phenomenon might occur, which cannot be verified in that trial due to the parallel allocation (each
patient had FFR or iFR, but not both). If we imagine a case that would have FFR–/iFR+, albeit with FFR alone being measured because of the trial design (Figure 2A), the target lesion was likely to be characterized by a physiologically diffuse pattern in this type of discordance. This case would be followed up in the FFR-deferred arm. If, in contrast, this patient was randomized to the iFR arm, this patient would be followed up as part of the revascularized group according to the iFR cut-off value, which would not affect the results of the deferred LAD sub-study. Conversely, if we imagine a patient with the opposite pattern of discordance (FFR+/iFR–), the lesion would be likely characterized by a physiologically focal pattern of disease (Figure 2B). This case would be followed up in the iFR-deferred arm or the FFR-revascularized arm depending on allocation. In other words, in the DEFINE-FLAIR LAD sub-analysis, clinical outcomes might be compared between FFR-deferred diffuse disease and iFR-deferred focal disease in some cases. It should be noted that diffuse atherosclerotic involvement of coronary arteries is one of the major factors affecting morbidity and mortality in patients with coronary artery disease.10 Our findings in this brief report are not conclusive but only hypothesis-generating. Furthermore, findings are only applicable for stable intermediate stenosis; FFR/iFR discordance is actually a multifactorial matter.1 5 However, it is plausible that diagnosis in patients with diffuse disease is worse than that of those with focal disease, even if the FFR or iFR value is above their respective cut-off. Further studies could examine the impact of physiological pattern of disease on clinical outcomes in revascularization-deferred patients.

Exact explanations of the difference between LAD and non-LAD remained unclear within this study. One possible reason is simply due to the relatively small number of cases in the non-LAD discordant group (31/151), which limited to conclude for the non-LAD group. A different baseline frequency of diffuse disease between the LAD and non-LAD groups assessed in this study should be also acknowledged. Another explanation might be the fact the LAD has more side-branches. Previous investigation on computational fluid dynamics demonstrated the distal resting coronary flow would be lower with more side-branches compared to that in the virtual vessel with less side-branches, which would result in a higher resting pressure-derived index in such cases.11 Specifically, the impact of the number of side-branches would be strengthened in the resting conditions. Conversely, the impact of non-stenotic side-branches would be relatively diminished during maximum hyperemia, theoretically. Due to the association between side-branches and resting/hyperemic conditions, our results might be magnified in the LAD. The exact mechanism of our results should be elucidated in further studies. Nevertheless, it is of clinical interest that our results were pronounced in the LAD: which subtends a larger myocardial territory,7 in which a reverse mismatch between visual and functional assessment is more frequent;12 and accordingly, in which the importance of coronary physiology is much greater.

Conclusions

The physiological pattern of disease was an important influencing factor for FFR/iFR discordance in the LAD. More specifically, FFR–/iFR+ discordance was more frequently associated with diffuse disease, whereas FFR+/iFR– was more frequently associated with focal disease.

Conflicts of Interest

T.W. has received consulting fees from Abbott Vascular and Philips. C.M.C. has received speaker’s honoraria from Philips. H.S. has received a research grant from Amgen. J.P.H. is supported by the Wellcome Trust (213183/Z/18/Z). Y.A. is supported by the Academy of Medical Sciences and Imperial Biomedical Research Centre. Y. Kikuta reports speaker fees from Abbott Vascular and Philips. H.M. has received speaker’s honoraria from Abbott Vascular, Boston Scientific, Philips, and Zenon Medical. J.E.D. holds patents pertaining to the iFR technology and is a consultant for Phillips and has received research grants from Philips. All other authors declare no conflicts of interest.

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References

1. 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. Circ Cardiovasc Interv 2019; 12: e007494.
2. 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. Int J Cardiol 2017; 245: 63–68.
3. Hennigan B, Oldroyd KG, Berry C, Johnson N, McClure J, McCartney P, et al. Discordance between resting and hyperemic indices of coronary stenosis severity: The VERIFY 2 Study. Circ Cardiovasc Interv 2016; 9: e004016.
4. 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 Cardiovasc Interv 2019; 12: 2018–2031.
5. Cook CM, Jeremias A, Petracco 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 Cardiovasc Interv 2017; 10: 2514–2524.
6. Baranauskas A, Peace A, Kibarskis A, Shannon J, Abravits V, Bajoras V, et al. FFR result post PCI is suboptimal in long diffuse coronary artery disease. EuroIntervention 2016; 12: 1473–1480.
7. Kim HY, Lim HS, Doh JH, Nam CW, Shin ES, Koo BK, et al. Physiological severity of coronary artery stenosis depends on the amount of myocardial mass subtended by the coronary artery. JACC Cardiovasc Interv 2016; 9: 1548–1560.
8. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: Results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008; 117: 1283–1291.
9. Sen S, Ahmad Y, Dehti HM, Howard JP, Ipsiladis JF, Al-Lamee R, et al. Clinical events after deferral of LAD revascularization following physiological coronary assessment. J Am Coll Cardiol 2019; 73: 444–453.
10. Uren NG, Melin JA, De Bruyne B, Wijns W, Bandhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994; 330: 1782–1788.
11. Li Y, Gutiérrez-Chico JL, Holm NR, Yang W, Hebsgaard L, Christiansen EH, et al. Impact of side branch modeling on computation of endothelial shear stress in coronary artery disease: Coronary tree reconstruction by fusion of 3D angiography and OCT. J Am Coll Cardiol 2015; 66: 125–135.
12. Arashi H, Yamaguchi J, Nakazawa M, Otsuki H, Haruki S, Nakao M, et al. Lesion characteristics of coronary arteries associated with a mismatch between angiographic severity of stenosis and fractional flow reserve. Cardiovasc Interv Ther 2017; 32: 120–126.