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ORIGINAL RESEARCH

CORONARY

Physiological Disease Pattern as Assessed by Pull Back Pressure Gradient Index in Vessels With FFR/iFR Discordance

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ABSTRACT

BACKGROUND Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are discordant in approximately 20% of cases, and it is unclear whether this is influenced by the physiological pattern of coronary artery disease (CAD). The pull back pressure gradient index (PPGi) can objectively characterize the physiological pattern of CADs.

OBJECTIVES The aim of this study was to evaluate whether PPGi differed in discordant groups (FFR+/iFR− vs FFR−/iFR+).

METHODS The study enrolled 355 patients (390 vessels) with chronic coronary syndrome who had ≥1 epicardial coronary artery lesion with 40% to 90% diameter stenosis by visual assessment on invasive coronary angiography and had analyzable FFR, iFR, and PPGi derived from quantitative flow ratio. Cutoffs for hemodynamic significance were FFR ≤0.80 and iFR ≤0.89. Vessels were classified as FFR+/iFR+ (n = 103 [26.4%]), FFR−/iFR+ (n = 27 [6.9%]), FFR+/iFR− (n = 38 [9.7%]), and FFR−/iFR− (n = 222 [57%]) groups.

RESULTS Median FFR, iFR, and quantitative flow ratio were 0.84 (Q1-Q3: 0.77-0.90), 0.92 (Q1-Q3: 0.88-0.97), and 0.83 (Q1-Q3: 0.73-0.90), respectively. FFR disagreed with iFR in 16.7% of cases (65 of 390). The median PPGi was 0.75 (Q1-Q3: 0.67-0.85). The physiological pattern of CAD was classified according to the PPGi as predominantly physiologically focal (PPGi ≥0.75) in 209 of 390 vessels (53.6%) or diffuse (PPGi < 0.75) in 181 of 390 vessels (46.4%). The median PPGi was significantly lower in FFR−/iFR+ vs FFR+/iFR− vessels (0.65 [Q1-Q3: 0.60-0.69] vs 0.82 [Q1-Q3: 0.75-0.85]; $P < 0.001$). Predominantly physiologically focal disease was significantly associated with FFR+/iFR− (76.3% [29 of 38]), while predominantly physiologically diffuse disease was significantly associated with FFR−/iFR+ (96.3% [26 of 27] [$P < 0.001$] for pattern of CAD between FFR+/iFR− and FFR−/iFR+ groups).

CONCLUSIONS The physiological pattern of CAD is an important influencing factor in FFR/iFR discordance. (Radiographic Imaging Validation and Evaluation for Angio iFR [REVEAL iFR]; NCT03857503)
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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CFV = contrast flow velocity

DS = diameter stenosis

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

LAD = left anterior descending coronary artery

PCI = percutaneous coronary intervention

PPGi = pull back pressure gradient index

PW = pressure wire

QFR = quantitative flow ratio

RCA = right coronary artery

ROC = receiver-operating characteristic

Since the introduction of fractional flow reserve (FFR) nearly 30 years ago,[1] and the subsequent validation of instantaneous wave-free ratio (iFR), physiology-guided revascularization has become integral in the contemporary management of stable coronary artery disease (CAD). Invasive physiological assessment enables the precise quantification of ischemia related to epicardial coronary artery stenoses and assists in strategic planning and the optimization of percutaneous coronary intervention (PCI).[2-4] Crucially for their widespread clinical adoption, both indexes are supported by robust randomized controlled clinical trial data and are endorsed in international treatment guidelines.[5-10] Discordance between hyperemic and nonhyperemic ratios occurs in about 20% of cases,[11-15] with prior work hypothesizing that this could be due to different physiological patterns of coronary atherosclerosis (focal or diffuse CAD), but these observations were subjective and based on visual interpretation of nonhyperemic wire-based iFR pull back curves.[11] The pull back pressure gradient index (PPGi) is based on a hyperemic wire-based FFR pull back curve and has been proposed as a more objective and quantitative method of defining the pattern of coronary atherosclerosis.[16] In addition, PPGi based on quantitative flow ratio (QFR) can now be calculated noninvasively using the virtual QFR pull back curve.[17] Angiography-based virtual FFR pull back curve-derived PPGi has been validated against wire-based FFR-derived PPGi.[18] Considering these hypotheses, the aim of this study was to evaluate whether the physiological pattern of CAD differed among patients with discordant hyperemic and nonhyperemic values (FFR+/iFR− vs FFR−/iFR+).

METHODS

PATIENT SELECTION. The REVEAL iFR (Radiographic Imaging Validation and Evaluation for Angio iFR; NCT03857503) study is a centralized off-line analysis by an independent academic core laboratory (CORRIB Core Lab, University of Galway) of a prospective cohort of 444 vessels with both pressure wire (PW) iFR and PW FFR (PW-FFR) measurements).[19] The study was conducted across 32 centers in Europe, Japan, and the United States. The study protocol was approved by the Institutional Review Boards or ethics committees at all relevant sites. The details of the study design have been previously published.[19]

The study population consisted of patients with chronic coronary syndrome with ≥1 epicardial coronary artery lesion with a 40% to 90% diameter stenosis (DS) by visual assessment on invasive coronary angiography. Angiographic exclusion criteria consisted of left main disease (isolated or non-isolated), aorto-ostial right CAD, any (treated or untreated) chronic total occlusion in the ipsilateral territory of the target vessel or untreated chronic total occlusion in the contralateral territory of the target vessel, target vessel with heavy calcification, TIMI flow grade 1 or 0, target lesion associated with myocardial bridge, and any vascular abnormality precluding optimal contrast opacification. After confirmation of the eligibility criteria, the following angiographic acquisition and physiological assessments were performed. The study procedure was conducted using a guiding catheter ≥5-F in size. After the mandatory administration of intracoronary nitrates, 2 angiographic projections ≥30° apart and in the absence of any guidewires were recorded.

PW iFR AND PW FFR MEASUREMENTS. In this prospective cohort of 355 patients with 444 target vessels, all patients had PW FFR and PW iFR measured at a point at least 3 times the reference vessel diameter distal to the lesion. Thereafter, angiography was acquired to localize the exact position of the PW sensor in the target vessel. Following dissipation of the hyperemia induced by either angiographic contrast medium or saline solution, 2 iFR measurements were recorded, together with the resting heart rate, distal pressure, and aortic pressure. Intracoronary adenosine (200 μg for left and 100 μg for right) was then administered, and once hyperemia was achieved, heart rate, FFR, distal pressure, and aortic pressure measurements were recorded. After hyperemia had abated, a manual iFR pull back was performed under continuous fluoroscopy. Data sets that had aortic pressure wave damping, distortion in either the aortic or coronary pressure waveforms, or coronary pressure

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Patient and Vessel Characteristics

Patients (N = 355)	
Age, y	68 ± 10
Male	249 (70)
BMI, kg/m^2	28 ± 5
Hypertension	253 (71)
Dyslipidemia	237 (67)
Diabetes mellitus	99 (28)
Chronic kidney disease	12 (3)
Prior PCI	97 (27)
History of myocardial infarction	67 (19)
Vessels (N = 390)	
Coronary artery	
Left anterior descending coronary artery	219 (56.2)
Left circumflex coronary artery	83 (21.3)
Right coronary artery	88 (22.6)
Stenosis characteristics by 2D QCA	
MLD, mm	1.48 (1.19-1.76)
Lesion length, mm	10.3 ± 4.8
Percentage diameter stenosis, %	46.0 ± 10.1
Physiological indexes	
FFR	0.84 (0.77-0.90)
iFR	0.92 (0.875-0.97)
QFR	0.83 (0.73-0.90)
PPGi derived from angiography-based virtual pressure pullback curve	0.75 (0.67-0.85)
dQFR/dS	0.022 (0.013-0.036)

Values are mean ± SD, n (%), or median (Q1-Q3).

2D = 2-dimensional; BMI = body mass index; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; MLD = minimal luminal diameter; PCI = percutaneous coronary intervention; PPGi = pull back pressure gradient index; QCA = quantitative coronary angiography; QFR = quantitative flow ratio.

drift exceeding 2 U were excluded from the present study according to the design protocol.[19] The relationship between PW iFR and PW FFR was tested using Pearson correlation and receiver-operating characteristic (ROC) curve analysis. FFR ≤0.80 and iFR ≤0.89 were regarded as being positive.

ANGIOGRAPHY-DERIVED FFR ANALYSIS. QFR. QFR was calculated using the QAngio XA 3D 2.1 (Medis Medical Imaging) by estimating the pressure drop using simplified equations[20-22] based on models from Young and Tsai[22] and Gould et al.[23] QFR analysis requires 2 diagnostic angiographic projections ≥25° apart. The foreshortening of the target vessel in each projection is reported as a percentage. The target vessel is reconstructed on the basis of automatic contour detection without assessment of fractal division. Minimal contour adjustment is allowed and documented. The estimated contrast flow velocity (CFV) is based on frame counting analysis. Hyperemic flow velocity (HFV) is modeled from contrast flow as $a_0 + a_1 \times \mathrm{CFV} + a_2 \times \mathrm{CFV}^2$, where $a_0 = 0.10$, $a_1 = 1.55$, and $a_2 = -0.93$.[21]

PPGi from QFR. Disease patterns were characterized by both physiological distribution and local severity of coronary atherosclerosis using QFR-derived indexes acquired from pre-PCI angiograms. First, the physiological distribution of coronary atherosclerosis was assessed using the PPGi derived from angiography-based virtual pressure pull back curve, which was recently introduced to discriminate focal from diffuse disease and is a continuous metric based on the magnitude of maximum pressure drop >20 mm and on the extent of functional disease over the entire interrogated vessel.[16] A high PPGi (close to 1) represents predominantly focal disease, whereas low values (close to 0) represent predominantly diffuse disease. Although the original PPGi concept was derived from invasive pressure pull back curves, it can be applied to any pull back curve, including angiography-derived FFR.[17,18]

The median value of the PPGi in the present population was 0.75 (Q1-Q3: 0.67-0.85) which was used to define predominantly focal (≥0.75) vs diffuse (<0.75) disease, although PPGi should be considered a continuous metric.

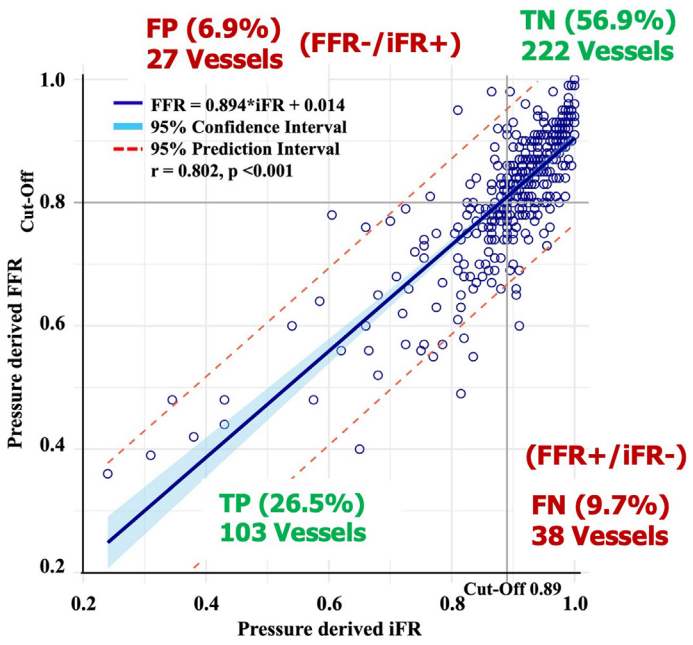
Second, the physiological local severity of coronary atherosclerosis was assessed using instantaneous QFR gradient per unit length (dQFR/dS), with a cutoff value of ≥0.025/mm used to define a major gradient according to a previous study.[17]

The location of the PW FFR measurement was indicated on a screenshot of the selected angiographic cine by the "matcher investigator" and provided to the 2 independent analysts, who then separately computed a PPGi using the colocalized angiogram.[24] All analysts were blinded to the results of PW FFR and PW iFR, QFR, and the angiography-derived PPGi.

ANGIOGRAPHIC EVALUATION. Coronary angiograms were centrally collected and analyzed by an independent core laboratory blinded to the clinical and physiological data. The anatomical pattern of CAD was adjudicated by visual inspection of the target vessel as focal or diffuse by 2 independent observers (P.C.R. and G.F.-C.). Focal CAD was defined visually on the basis of angiographic lesion length ≤20 mm. Quantitative coronary angiographic analyses were performed using CAAS Workstation 8.2 (Pie Medical Imaging).

STATISTICAL ANALYSIS. Categorical data are expressed as number (percentage), whereas continuous variables are expressed as mean ± SD or as median (Q1-Q3) as appropriate. Normality of distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using Student's

FIGURE 1 Scatterplot Showing the Relationship Between Pressure-Derived iFR and FFR



The dark blue line represents the line of best fit. The gray lines represent the respective cutoff values for instantaneous wave-free ratio (iFR) (≤0.89) and fractional flow reserve (FFR) (≤0.80). FN = false negative; FP = false positive; TN = true negative; TP = true positive.

t-test or the Mann-Whitney *U* test and categorical variables using the chi-square or Fisher exact test, as appropriate. Univariable binary logistic regression was used to identify correlates of discordance between FFR and iFR. Significant correlates ($P < 0.20$) identified on univariable regression were input into the multivariable binary logistic regression model to identify the independent correlates of discordance between FFR and iFR. All probability values were 2 sided, and *P* values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS Statistics for Windows version 24.0 (IBM) and package proc for R version 3.5.2 (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION. The study enrolled 355 patients with 444 target vessels, 390 (87.8%) of which met the criteria for optimal quality (no table movement, optimal contrast filling, and separated angulation by 30° in the 2 angiographic views with minimal overlap and foreshortening). Patient and vessel characteristics are shown in Table 1. The mean age of patients was 68 ± 10 years, and 70% were men. The vessels included 219 left anterior descending coronary arteries (LADs) (56.2%), 83 left circumflex coronary arteries (21.3%), and 88 right coronary arteries (RCAs) (22.6%). The mean %DS was 46.0% ± 10.1%. A full description of baseline, vessel, and lesion characteristics is provided in Table 1. Median FFR and iFR values for the 390 vessels analyzed were 0.84 (Q1-Q3: 0.77-0.90) and 0.92 (Q1-Q3: 0.875-0.97), respectively. The median QFR and PPGi values for the same vessels were 0.83 (Q1-Q3: 0.73-0.90) and 0.75 (Q1-Q3: 0.67-0.85), respectively. The relationship between FFR and iFR values is displayed in Figure 1 ($R = 0.80$; $P < 0.001$). Among 390 vessels, 357 vessels had FFR < 0.95. The mean and median PPGi were 0.75 ± 0.11 and 0.75 (Q1-Q3: 0.66-0.84), respectively. The PPGi cutoff of 0.75 was used to classify disease as either focal or diffuse. In vessels with hemodynamically significant lesion (FFR ≤0.80 and/or iFR ≤0.89), the mean and median PPGi were 0.70 ± 0.11 and 0.69 (Q1-Q3: 0.61-0.79), respectively.

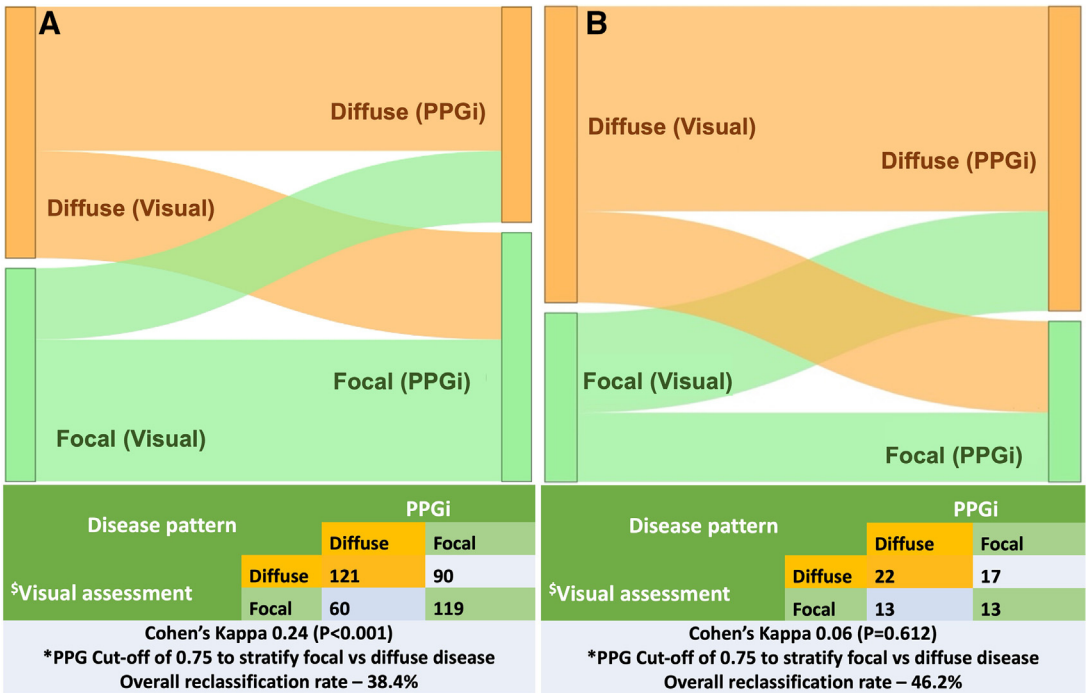
ADJUDICATION OF CAD PATTERNS ON THE BASIS OF VISUAL ASSESSMENT OF CORONARY ANGIOGRAPHY AND PPGi DERIVED FROM VIRTUAL QFR PULL BACK CURVE (PPGi CUTOFF OF 0.75 USED TO CLASSIFY CAD PATTERN AS EITHER FOCAL OR DIFFUSE). Across all vessels (n = 390), the correlation between visual assessment and PPGi-based classification was modest (Cohen's kappa = 0.24; 95% CI: 0.14-0.33; $P < 0.001$), with a reclassification rate of 38.4% (Figure 2).

In vessels with discordance between FFR and iFR (n = 65), there was no correlation between visual assessment and PPGi-based classification (Cohen's kappa = 0.06; 95% CI: −0.18 to 0.30; $P = 0.612$), and the reclassification rate was 46.2% (Figure 2).

Supplemental Figures 1 to 3 and Supplemental Tables 1 to 4 detail the adjudication of CAD patterns using visual assessment and PPGi-based classification in hemodynamically significant vessels (FFR ≤0.80 and/or iFR ≤0.89) and when the PPGi cutoff of 0.70 is applied.

CLASSIFICATION BY FFR AND iFR VALUES AND QFR-DERIVED PPGi. FFR agreed with iFR in 83.33% of vessels (325 of 390), with FFR+/iFR+ occurring in 26.4% (n = 103) and FFR−/iFR− occurring in 57% (n = 222). Discordance between FFR and iFR was seen in 16.67% of vessels (65 of 390), with FFR−/iFR+ in 6.9% (n = 27) and FFR+/iFR− in 9.7% (n = 38). The physiological pattern of disease as per the PPGi was predominantly physiologically focal in 53.6% (209 of 390) and diffuse in 46.4% (181 of 390) (Table 2). Univariable and multivariable binomial logistic regression did not identify any significant predictors of

FIGURE 2 Adjudication of CAD Patterns on the Basis of Visual Assessment of Coronary Angiography and PPGi Derived From Virtual QFR Pull Back Curve



$Visual assessment	PPGi: Diffuse	PPGi: Focal
Diffuse	121	90
Focal	60	119

Cohen's Kappa 0.24 (P<0.001)
*PPG Cut-off of 0.75 to stratify focal vs diffuse disease
Overall reclassification rate – 38.4%

$Visual assessment	PPGi: Diffuse	PPGi: Focal
Diffuse	22	17
Focal	13	13

Cohen's Kappa 0.06 (P=0.612)
*PPG Cut-off of 0.75 to stratify focal vs diffuse disease
Overall reclassification rate – 46.2%

(A) All vessels (390). (B) Discordant vessels. $The anatomical pattern of coronary artery disease (CAD) was adjudicated by visual inspection of the target vessel as focal or diffuse by 2 independent observers. Focal CAD was defined visually on the basis of angiographic lesion length ≤20 mm and diffuse >20 mm. PPG = pull back pressure gradient; QFR = quantitative flow ratio.

discordance (Supplemental Table 5). On multivariable logistic regression analysis, diabetes mellitus was associated with lower odds of discordance (OR: 0.498; 95% CI: 0.254-0.975; $P = 0.04$) (Supplemental Table 5).

COMPARISON AMONG GROUPS CLASSIFIED BY FFR AND iFR. Clinical and lesion characteristics between concordant and discordant groups are displayed in Supplemental Table 6. There were no statistically significant between-group differences in patient, vessel, and lesion characteristics. However, in the LAD, there were numerically more discordant than concordant values (63.1% vs 52.3%; $P = 0.112$), with the opposite noted for the RCA (15.4% vs 24%; $P = 0.129$). The prevalence of proximal lesions, defined as SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) segments 1, 6, and 11, was also similar (31.7% [103 of 325] vs 33.8% [22 of 65]).

In the FFR/iFR discordant groups (FFR−/iFR+ and FFR+/iFR−), the median FFR and iFR values were 0.80 (Q1-Q3: 0.76-0.83) and 0.90 (Q1-Q3: 0.88-0.93), respectively. The median QFR and PPGi values were 0.76 (Q1-Q3: 0.65-0.83) and 0.73 (Q1-Q3: 0.65-0.83), respectively. Baseline characteristics and quantitative coronary angiographic characteristics were comparable between the 2 discordant groups ($P > 0.05$), except that men were more frequently FFR+/iFR− (76.3%; $P = 0.019$) (Table 3), while diabetes mellitus was numerically more prevalent in the FFR−/iFR+ group (25.9% vs 13.2%; $P = 0.191$). Among vessel characteristics, the LAD was more frequently FFR−/iFR+ (85.2% vs 74.4%; $P = 0.002$), while the RCA was more frequently FFR+/iFR− (0% vs 26.3%; $P = 0.004$) (Table 3). Apart from this, only the physiological pattern of disease as determined by the PPGi (Figure 2) was significantly different between the discordant groups. PPGi was significantly lower in the FFR−/iFR+ group compared with the FFR+/iFR− group (0.65 [Q1-Q3: 0.60-0.69) vs 0.82 [Q1-Q3: 0.75-0.85); $P < 0.001$) (Figure 3), as was dQFR/dS (0.023 [Q1-Q3: 0.016-0.041) vs 0.0415 [Q1-Q3: 0.003-0.05]; $P < 0.001$) (Figure 3). In comparison with the FFR+/iFR− group, the FFR−/iFR+ group had a significantly

TABLE 2 Classification by FFR/iFR and Pull Back Pressure Gradient (N = 390)

Physiological indexes	
FFR+/iFR+	103 (26.4)
FFR−/iFR+	27 (6.9)
FFR+/iFR−	38 (9.7)
FFR−/iFR−	222 (57)
Physiological pattern of disease	
Predominantly physiologically focal (PPGi ≥0.75)	209 (53.6)
Predominantly physiologically diffuse (PPGi <0.75)	181 (46.4)
Vessels with major gradient (dQFR/dS ≥0.025/mm)	178 (45.6)
Vessels without major gradient (dQFR/dS <0.025/mm)	212 (54.4)

Values are n (%).
Abbreviations as in Table 1.

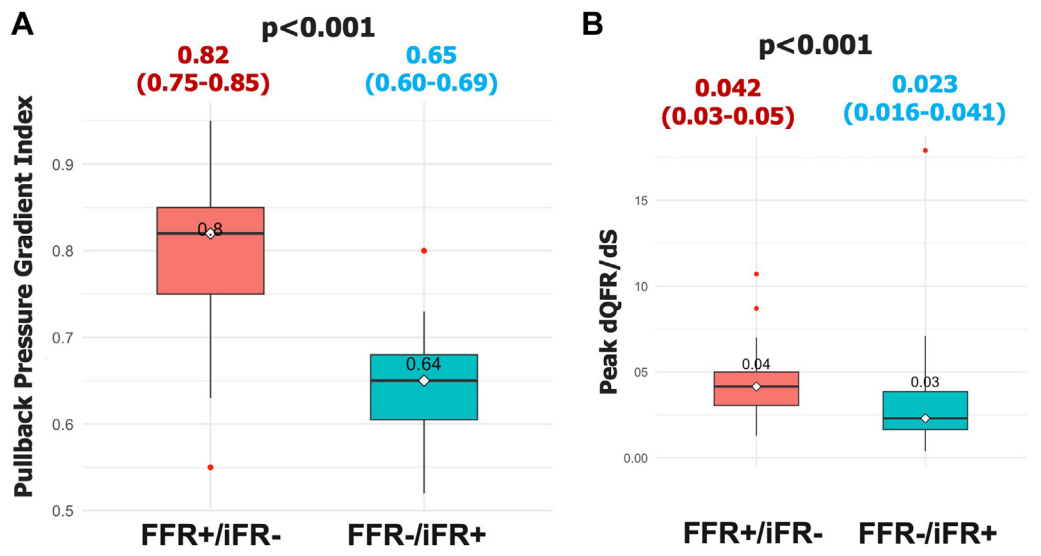
higher prevalence of predominantly physiologically diffuse disease (96.3% [26 of 27] vs 23.7% [9 of 38]; Figure 4 and Central Illustration). The proportion of patients with focal and diffuse disease did not differ when different PPGi cutoff (0.70) was used in the discordant groups (Supplemental Figure 4). FFR+/iFR− vessels had a higher prevalence of major gradients (dQFR/dS ≥0.025/mm) compared with vessels that were FFR−/iFR+ (81.6% vs 44.4%; $P = 0.002$); in contrast, FFR−/iFR+ vessels had a higher prevalence (55.6% vs 18.4%; $P = 0.002$) of absent major gradients (dQFR/dS <0.025/mm). The mean PPGi did not differ significantly between patients with (113 vessels) and without (277 vessels) diabetes mellitus (0.74 ± 0.12 vs

TABLE 3 Comparison of Discordant Groups (FFR−/iFR+ vs FFR+/iFR−)

	FFR−/iFR+ Group (n = 27)	FFR+/iFR− Group (n = 38)	*P* Value
Patient characteristics			
Age, y	69.56 ± 9.10	66.39 ± 10.48	0.211
Men	13 (48.15)	29 (76.32)	0.019
BMI, kg/m^2	29.59 ± 5.83	27.67 ± 5.19	0.170
Hypertension	22 (81.5)	24 (63.2)	0.109
Dyslipidemia	20 (74.1)	20 (52.6)	0.080
Diabetes mellitus	7 (25.9)	5 (13.2)	0.191
Renal insufficiency	0 (0)	1 (2.6)	0.396
Previous MI	4 (14.8)	8 (21.1)	0.523
History of heart failure	0 (0)	3 (7.9)	0.135
Past history of CAD	13 (48.1)	24 (63.2)	0.228
Previous PCI	6 (22.2)	11 (28.9)	0.543
Target vessel and lesion location			
LAD	23/27 (85.2)	18/38 (47.4)	0.002
LCX	3/27 (11.1)	10/38 (26.3)	0.131
RCA	0/27 (0)	10/38 (26.3)	0.004
Diagonal branch	1/27 (3.7)	0/38 (0)	0.232
Proximal lesions (LAD, LCX, RCA)	8/27 (29.6)	14/38 (36.8)	0.545
Quantitative coronary angiography			
Diameter stenosis, %	44.94 ± 12.13	49.09 ± 11.30	0.162
Minimum luminal diameter, mm	1.37 (0.99-1.55)	1.30 (1.03-1.67)	0.396
Lesion length, mm	9.5 ± 4.3	11.5 ± 4.7	0.083
Physiological indexes			
FFR	0.83 (0.82-0.86)	0.78 (0.74-0.79)	
iFR	0.88 (0.865-0.885)	0.92 (0.905-0.95)	
QFR	0.79 (0.64-0.82)	0.74 (0.65-0.83)	
PPGi	0.64 ± 0.064	0.795 ± 0.089	<0.001
dQFR/dS	0.023 (0.016-0.041)	0.0415 (0.03-0.05)	<0.001
Physiological pattern of disease			
Predominantly physiologically focal (PPGi ≥0.75)	1/27 (3.7)	29/38 (76.3)	<0.001
Predominantly physiologically diffuse (PPGi <0.75)	26/27 (96.3)	9/38 (23.7)	<0.001
Major gradient (dQFR/dS ≥0.025/mm)	12/27 (44.4)	31/38 (81.6)	0.002
No major gradient (dQFR/dS <0.025/mm)	15/27 (55.6)	7/38 (18.4)	0.002

Values are mean ± SD, n (%), n/N (%), or median (Q1-Q3).
CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery; other abbreviations as in Table 1.

FIGURE 3 Box Plot Illustrating the Distribution of PPGi Derived From Angiography-Based Virtual Pressure Pull Back Curve Between Discordant Groups (FFR−/iFR+ vs FFR+/iFR−)



(A) The median pull back pressure gradient index (PPGi) was significantly lower in the FFR−/iFR+ group compared with the FFR+/iFR− group. (B) The median peak dQFR/dS PPGi was significantly lower in the FFR−/iFR+ group compared with the FFR+/iFR− group. Abbreviations as in Figures 1 and 2.

0.75 ± 0.11; P = 0.17) (Supplemental Figure 5). The distribution of disease patterns in patients with diabetes mellitus is shown in Supplemental Figure 6. A ROC curve analysis to determine the PPGi cutoff that could differentiate between concordant and discordant vessels revealed that the model's quality (0.49) was no better than random prediction at a PPGi cutoff of 0.70, with an area under the curve of 0.57 (95% CI: 0.49-0.64; P = 0.081) (Supplemental Figure 7). ROC analysis to identify the PPGi cutoff that could differentiate between vessels with normal and abnormal physiology indicated good model quality (0.67), with a PPGi cutoff of 0.73 achieving an area under the curve of 0.72 (95% CI: 0.67-0.77; $P < 0.001$), effectively ruling out hemodynamically significant disease (Supplemental Figure 8).

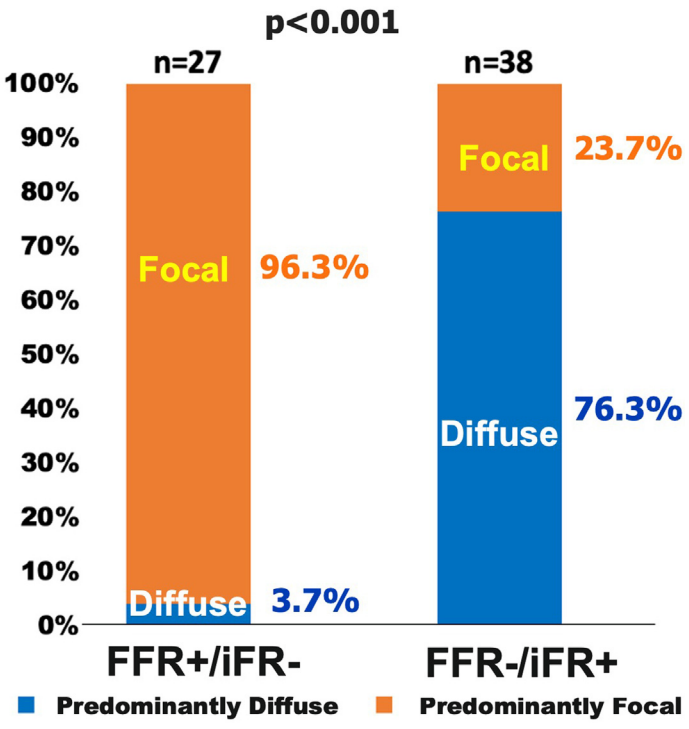
DISCUSSION

The aim of this study was to determine whether the physiological pattern of CAD as assessed by the PPGi was an influencing factor in the discordance between FFR and iFR. The main findings of this study are as follows: 1) unlike most patient and lesion characteristics, the physiological pattern of CAD significantly influenced the discordance between FFR and iFR; 2) FFR+/iFR− discordance was significantly associated with a physiologically focal pattern of disease, while FFR−/iFR+ discordance was significantly associated with a physiologically diffuse pattern of disease (**Central Illustration**); 3) a major gradient (dQFR/dS ≥0.025/mm) was significantly more prevalent in FFR+/iFR− vessels; and 4) the absence of a major gradient (dQFR/dS <0.025/mm) was significantly more prevalent in FFR−/iFR+ vessels.

Classification of the physiological pattern of CAD (focal vs diffuse) on the basis of visual assessment is subject to intra- and interobserver variability.[16] To overcome this, the PPGi, which is derived from mechanical pull back curves of invasive FFR, has been proposed as a method to quantitatively characterize the pathophysiological pattern of CAD.[16] Physiologically diffuse CAD, as defined by PPGi, has been associated with poor clinical outcomes and persistent angina following PCI.[25,26]

Recently, PPG Global, a large-scale, multicenter study using invasive pull back pressure gradient derived from FFR pull backs, showed that pathophysiological CAD patterns defined by pull back pressure gradient distinctly affect the safety and effectiveness of PCI. Patients with high pull back pressure gradients had improved hemodynamic outcomes and reduced periprocedural myocardial infarction compared with vessels with low pull back

FIGURE 4 The Association Between the Physiological Pattern of Disease as Defined by PPGi Derived From Angiography-Based Virtual Pressure Pull Back Curve and FFR/iFR Discordance

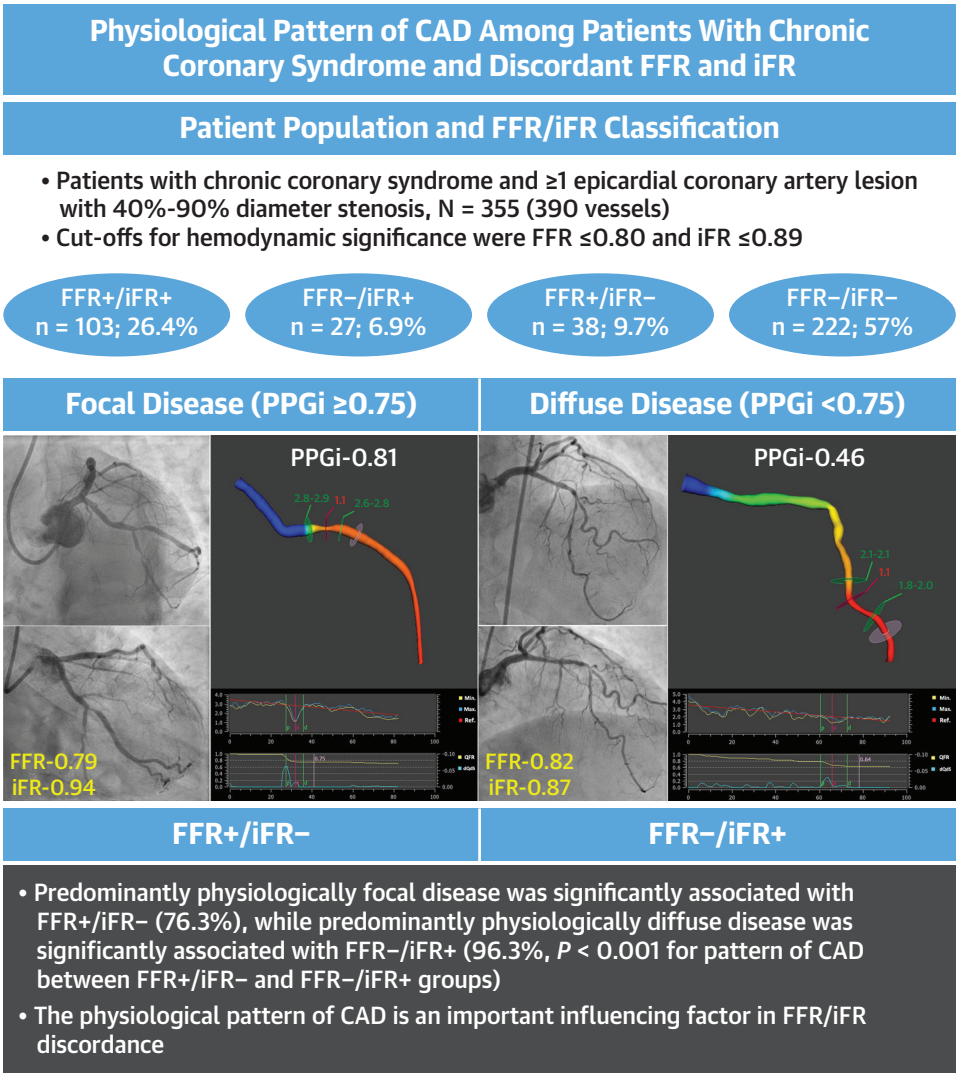


FFR−/iFR+ was significantly more associated with a physiologically diffuse pattern of disease, whereas FFR+/iFR− was significantly more associated with a physiologically focal pattern of disease. Abbreviations as in Figures 1 and 3.

pressure gradient values.[27] PPGi can be derived from any virtual FFR-based pull back curve.[18] Angiography-based virtual FFR pull back curve-derived PPGi has been validated against wire-based FFR-derived PPGi with moderate agreement.[18] Reports suggest only modest agreement between virtual PPGi and visual assessment of virtual pull back curves in classifying vessels as having focal or diffuse disease, with a Cohen's kappa of 0.28 (95% CI: 0.14-0.41). This suggests that visually adjudicating pull back curves as focal or diffuse disease patterns could be suboptimal and prone to considerable inter- and intraobserver variability. However, quantitative analysis (using PPGi cutoff to stratify disease pattern on the basis of median or mean) has shown moderate agreement in PPGi values ($r = 0.64$) between wire-based and virtual pull back curves. Nonhyperemic pressure indexes are increasingly used preferentially to FFR in the functional evaluation of coronary artery stenoses, as they eliminate the time, cost, and adverse effects of pharmacologic hyperemia. The best validated index is the resting iFR, which measures the pressure ratio during a specified period of diastole when the coronary microvascular resistance is relatively low and stable. The diagnostic accuracy of iFR has been investigated in several trials.[28-31] The ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) trial demonstrated overall good agreement (80%) between FFR ≤0.80 and iFR ≤0.83, with the iFR threshold later raised to 0.89.[32] The VERIFY 2 (A Comparative Study of Resting Coronary Pressure Gradient, Instantaneous Wave-Free Ratio and Fractional Flow Reserve in an Unselected Population Referred for Invasive Angiography) study demonstrated that using binary cutoffs for iFR and FFR resulted in iFR's misclassifying 20% of lesions when using FFR as the reference standard.[33] Likewise, many studies have shown that iFR and FFR disagree with each other on up to a one-fifth of occasions,[11-15] and consistent with this was the rate of discordance in the present study of 16.7%. In the IDEAL (Iberian-Dutch-English) collaborators registry, FFR/iFR disagreement was attributed to differences in the hyperemic coronary flow velocity on the basis of Doppler signal-based flow measurements. FFR+/iFR− vessels exhibited flow characteristics akin to angiographically unobstructed vessels, while FFR−/iFR+ vessels had flow characteristics similar to concordantly positive vessels (FFR+/iFR+).[12] Unfortunately, our study did not include data on coronary flow velocity to enable a similar analysis. In the same registry, lesion length was not significantly different between the FFR−/iFR+ and FFR+/iFR− groups (17.6 ± 13.1 mm vs 18.9 ± 6.32 mm; $P = 0.54$), which is consistent with our findings, wherein lesion length was also numerically lower in the FFR−/iFR+ group (9.5 ± 4.3 mm vs 11.5 ± 4.7 mm; $P = 0.083$).[12] The IDEAL study also revealed that the FFR−/iFR+ group was associated with low coronary flow reserve and a high prevalence of diabetes mellitus, whereas the FFR+/iFR− group was associated with high coronary flow reserve and a low prevalence of diabetes mellitus.[12] Similarly, we observed a numerically higher prevalence of diabetes in the FFR−/iFR+ group, reflecting the impact of profound adenosine-mediated vasodilatation in healthy microcirculations compared with those in patients with diabetes. Multivariable logistic regression analysis also revealed that diabetes was associated with lower odds of discordance (OR: 0.498; 95% CI: 0.254-0.975; $P = 0.04$). Consistent with prior studies, we also found that the RCA was more frequently FFR+/iFR−, with the LAD more frequently FFR−/iFR+.[13,14,34,35]

So how can FFR/iFR discordance improve our understanding rather than add confusion?

CENTRAL ILLUSTRATION Study Overview and Findings



Revaiah PC, et al. JACC Cardiovasc Interv. 2025;18(7):823-834.

Physiological pattern of disease assessed by pull back pressure gradient index (PPGi) derived from angiography-based virtual pressure pull back curve has an influence on fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) discordance. FFR+/iFR− was significantly more associated with a physiologically focal pattern of disease, whereas FFR−/iFR+ was significantly more associated with a physiologically diffuse pattern of disease. Diffuse disease generates a steady decrease in pressure along the vessel without evidence of focal drop, as pressure losses arise primarily from the frictional component of fluid dynamics. In contrast, in focal lesions, separation forces at the lesion exit (where flow is squared) dominate, and amplified during hyperemia. CAD = coronary artery disease.

Discordance can help distinguish between diffuse and focal CAD. Warisawa et al[11] compared FFR/iFR discordance with the pattern of CAD on the basis of visual assessment of the iFR pull back and found that diffuse disease was more likely to be associated with vessels that were FFR−/iFR+ (81.6% [31 of 38 lesions]). These findings align with those of our study, in which we objectively characterized disease patterns using the PPGi. This finding may be explained by the pressure loss across the stenosis being related to both separation and frictional components. The pressure gradient across a stenosis can

be described by the equation $\Delta P = fQ + sQ^2$, where ΔP is the change in pressure, f is the frictional coefficient (influenced by lesion length and DS), s is the separation coefficient (influenced by DS and the laminar flow separation), and Q is the blood flow through the stenosis. At rest, the pressure loss (ΔP) and arterial flow velocity (V) are related by $\Delta P = fV + sV^2$. Here, f represents the pressure loss due to viscous friction, and s represents the pressure loss due to flow separation.[36]

At resting coronary flow, viscous friction accounts for 65% and flow separation 35% of total pressure loss.[36] At peak coronary flow, after vasodilation, viscous friction accounts for 33% and flow separation for 67% of total pressure loss. The pressure gradient-velocity relationship at high flow follows the same equation but with larger values for coefficient s, resulting in greater pressure loss due to flow separation than at resting flow.[36] In diffuse disease, pressure losses arise mainly from the frictional component and are directly proportional to coronary flow. In focal lesions, separation forces (where flow is squared) dominate.[11,37] Consequently, a hyperemic index such as FFR is more likely to be positive for focal lesions, which are easier to relieve with stenting, whereas iFR is more likely to be positive in diffuse disease. The focal vs diffuse pattern of CAD can now be assessed objectively with PPGi, but FFR/iFR discordance has a reassuring clinical outcome.

In a recent study that stratified CAD as focal and diffuse on the basis of wire-based PPGi, plaque analysis using coronary computed tomographic angiography and optical coherence tomography revealed that focal CAD had a higher plaque burden and was predominantly lipid rich, with a high prevalence of thin-cap fibroatheroma. In contrast, calcifications were more prevalent in diffuse CAD. In other words, a nonhyperemic index such as iFR defers hemodynamically significant focal vulnerable lesions, whereas a hyperemic index such as FFR defers hemodynamically significant, relatively stable calcified diffuse lesions.[38]

The present study provides physiological observations that can be useful in interpreting the results of large clinical trials comparing iFR and FFR. Discordance between hyperemic and resting indexes is a common and important clinical finding.

According to the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) study, patients with concomitant abnormal FFR and iFR had a significantly increased risk for major adverse cardiac events compared with those with normal FFR and iFR values (HR: 7.7; $P < 0.001$).[15] Notably, the risk for major adverse cardiac events was no higher between patients with discordance between FFR and iFR and those with concordant normal values.[15]

Future prospective studies should evaluate not only how discordance between FFR and iFR predicts clinical outcomes but also whether the incremental addition of a positive iFR to a positive FFR, or a negative iFR to a negative FFR, would lead to better revascularization decisions.

STUDY LIMITATIONS. First, discordance was identified on the basis of differences in functional classification using a binary cutpoint value. Although myocardial ischemia likely exists along a continuum, the use of binary cutpoints to distinguish hemodynamic significance is ubiquitous in the literature, clinical outcome trials, and revascularization and appropriate use criteria guidelines. However, in clinical practice, the strict use of cutoff points may not be appropriate.

Second, although the total number of discordant stenoses was relatively small, the REVEAL iFR study represents one of the largest investigations involving patients with CAD undergoing physiological lesion assessment using both FFR and iFR.

Third, consistent with previous studies on discordance between hyperemic and resting pressure indexes, our analysis used vessels rather than patients as the statistical unit. This approach acknowledges potential statistical and biological interactions among different vessels analyzed within the same patient. However, across both the FFR−/iFR+ and FFR+/iFR− discordant groups, no patient contributed more than 1 vessel to both discordant groups.

Fourth, our findings should be interpreted within the context of patients with isolated stable CAD. It has been demonstrated that conditions such as acute coronary syndrome, cardiac hypertrophy, and severe aortic stenosis may dampen the hyperemic response of the microcirculation to adenosine. Consequently, the prevalence and possibly the underlying mechanisms of FFR/iFR discordance may differ in these specific populations.

Fifth, our study did not include combined measurements of coronary flow velocity. Such measurements would be necessary to fully establish the proposed association between hyperemic coronary flow characteristics and physiological patterns of CAD on the basis of the PPGi, which remains speculative at this stage.

Last, the study protocol did not mandate intravascular imaging. This could have further clarified the relationship between focal and diffuse disease and its relation to PPGi and discordance between FFR and iFR measurements.

CONCLUSIONS

Discordance between hyperemic and resting indexes is a common and important clinical finding. Predominantly focal disease pattern quantified objectively by PPGi derived from angiography-based virtual pressure pull back curve was significantly associated with FFR+/iFR−, while predominantly diffuse disease pattern was significantly associated with FFR−/iFR+. Future prospective studies should evaluate how discordance between FFR and iFR predicts clinical outcomes.

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Prof Serruys is a consultant for Sahajanand Medical Technologies, Meril Life Sciences, Philips, and Xeltis, outside the submitted work. Prof Onuma is a consultant for Sahajanand Medical Technologies, Meril Life Sciences, Philips, and Xeltis, outside the submitted work. All other authors have reported that they have no relationship relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Lesion location, vessel involved, and differences in coronary flow have been suggested as factors contributing to FFR/iFR discordance.

WHAT IS NEW? Pattern of CAD (focal vs diffuse quantified objectively by PPGi derived from angiography-based virtual pressure pull back curve) appears to be a critical determinant of FFR/iFR discordance.

WHAT IS NEXT? Future prospective studies should evaluate how discordance between FFR and iFR predicts clinical outcomes and whether the incremental addition of a positive iFR to a positive FFR, or a negative iFR to a negative FFR, would lead to better revascularization decisions

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KEY WORDS fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), pull back pressure gradient index (PPGi)

APPENDIX For supplemental tables and figures, please see the online version of this paper.



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