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Original article

Predictors of discordance between fractional flow reserve and resting full-cycle ratio in patients with coronary artery disease: Evidence from clinical practice

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ABSTRACT

Background: Fractional flow reserve (FFR) is an established method for assessing functional myocardial ischemia. Recently, the resting full-cycle ratio (RFR) has been introduced as a non-hyperemic index of functional coronary stenosis. However, the effects of clinical characteristics on discordance between RFR and FFR have not been fully evaluated. We aimed to identify clinical characteristics that influence FFR–RFR concordance.

Methods: We included 410 patients with 573 intermediate coronary lesions who underwent clinically indicated invasive coronary angiography, as well as assessments of FFR and RFR. Receiver-operating characteristic (ROC) curves were created to assess the optimal cut-off values of RFR for predicting FFR $\leq$0.80.

Results: RFR exhibited a strong correlation with FFR (r = 0.66, $p < 0.0001$). ROC analysis identified an optimal RFR cut-off value of 0.92 for categorization based on an FFR cut-off value of 0.8. The discordance of FFR >0.8 and RFR $\leq$0.92 (high FFR/low RFR) was observed in 112 lesions (20.9%), whereas the discordance of FFR $\leq$0.8 and RFR >0.92 (low FFR/high RFR) was observed in 35 lesions (6.5%). Higher rate of hemodialysis and lower hemoglobin levels were observed in the high FFR/low RFR group. Multivariate analyses identified female sex, left anterior descending artery (LAD) lesions, and hemodialysis as significant predictors of high FFR/low RFR. Conversely, body surface area and non-LAD lesions were significantly associated with low FFR/high RFR. Hemodialysis [odds ratio (OR): 2.41, 95% confidence interval (CI) 1.31–4.41; $p = 0.005$] and LAD lesions (OR: 1.86, 95% CI: 1.25–2.79; $p = 0.002$) were identified as independent predictors of overall FFR–RFR discordance.

Conclusions: RFR exhibited good diagnostic performance in the identification of functionally significant stenosis. However, RFR may overestimate functional severity in patients undergoing hemodialysis or in those with LAD lesions. Further prospective trials are required to demonstrate the non-inferiority of RFR to FFR.

Introduction

Evidence of inducible myocardial ischemia is a fundamental prerequisite for revascularization in patients with stable coronary artery disease [1]. To date, fractional flow reserve (FFR) has been

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widely regarded as a physiological index of myocardial ischemia, based on the results of large-scale clinical studies [2–4]. However, our clinical practice has recently utilized the instantaneous wave-free ratio (iFR), another pressure-derived index that does not require hyperemia. Evidence from recent randomized controlled trials suggests that iFR-guided strategies are not inferior to FFR-guided strategies, based on a comparison of clinical outcomes at 1 year [5,6]. However, there are several inherent limitations to iFR, including the sensitivity of automated landmarking algorithms for components of the pressure waveform. Furthermore, iFR relies on the assumption that maximal flow and minimal resistance during resting conditions occur during a precise period within diastole—a finding contested based on previous evidence [7]. The resting full-cycle ratio (RFR) has recently been introduced for the unbiased identification of the lowest distal arterial pressure (Pd)/arterial pressure (Pa) within the entire cardiac cycle [8]. Lee et al. investigated the use of the RFR for guiding treatment strategies in patients with coronary artery disease [9]. Muroya et al. recently reported high concordance between between RFR and FFR [10]. However, the effects of clinical characteristics on discordance between RFR and FFR have not been fully evaluated. Therefore, in the present study, we aimed to identify clinical characteristics that influence discordance between FFR and RFR in clinical settings.

Methods

Study population

This prospective, single-center, observational study enrolled 410 consecutive patients with coronary artery disease (CAD) who underwent clinically indicated invasive coronary angiography as well as both FFR and RFR examinations at Juntendo University Hospital from September 2018 to August 2019. Only patients exhibiting at least one intermediate lesion with angiographic stenosis and a stenosis diameter >50% were included. Standard exclusion criteria for pressure-wire studies were applied and included the following: severe calcific coronary disease, severe tortuosity rendering pressure-wire studies difficult or impossible, myocardial infarction within the previous 24 h, ongoing unstable chest pain, known intolerance to papaverine or adenosine, and severe asthma. This study was approved by the Juntendo University ethics committee and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Coronary assessments

All coronary assessments were performed following diagnostic angiography. Briefly, a 5–7 Fr guide catheter without side holes was used to engage the coronary artery, and a pressure sensor guidewire (Abbott Vascular, Santa Clara, CA, USA) was used for the measurement of resting Pd/Pa, RFR, and FFR. First, resting Pd/Pa was calculated as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state. RFR was measured under hyperemia-free resting conditions and automatically calculated online using a fully automated off-line software algorithm (CoroLab; Coroventis Research AB, Uppsala, Sweden) [8]. RFR was defined as the point at which the ratio of Pd and Pa was lowest during the entire cardiac cycle and averaged over five consecutive heart cycles. FFR was measured during maximal hyperemia. Hyperemia in the target coronary artery was achieved with either an intracoronary bolus injection of 8−12 mg of papaverine or continuous intravenous administration of adenosine at 140−180 g/kg/min [4,11]. At the end of each measurement, the pressure sensor was retracted to the tip of the guide catheter to avoid pressure drift. If pressure drift exceeded 0.03, the assessment was repeated.

All angiograms were analyzed at our laboratory in a blinded fashion. Quantitative coronary angiography (QCA) was performed in optimal projections using a validated software (Medis QAngio, Medis, Leiden, The Netherlands). Reference vessel size, minimum lumen diameter (MLD), percent stenosis diameter (%DS), and lesion length were measured.

Data collection and blood sampling

Data related to patient characteristics, CAD risk factors, and medication use were retrieved from our institutional database. Blood samples were collected in the early morning after overnight fasting, and blood pressure (BP) was measured on admission. Patients with BP >140/90 mmHg or those taking antihypertensive drugs were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol ≤40 mg/dL, triglycerides ≥150 mg/dL, or current treatment with statins and/or lipid-lowering agents [12]. Diabetes mellitus (DM) was defined as either HbA1c ≥6.5% or use of relevant medications, such as insulin or oral hypoglycemic drugs. A current smoker was defined as a person who identified as a smoker at the time of percutaneous coronary intervention (PCI) or who had quit smoking within 1 year prior to PCI.

Statistical analysis

Quantitative data are presented as the mean ± standard deviation (SD) or median [interquartile range (IQR)]. Categorical variables are presented as frequencies. Results were compared using analyses of variance (ANOVA), Kruskal–Wallis tests, or chi-square tests, as appropriate. Dunnett's post-hoc analysis was used for multiple comparisons between groups in the baseline clinical characteristics. Correlations between parameters were tested using Pearson's or Spearman's correlation coefficients. Receiver-operating characteristic (ROC) curves were created to assess the optimal cut-off values of RFR for predicting FFR ≤0.80. Factors identified as potentially significant ($p < 0.10$) in the univariate analysis were included in the multiple logistic regression model. A p-value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using JMP Pro 14.0 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline clinical characteristics

The present study included 410 patients (mean age: 69.6 ± 10.8 years) with 537 intermediate coronary stenoses on coronary angiography. The clinical characteristics of these patients are shown in Table 1. Hypertension, DM, and hemodialysis treatment were noted in 72.0%, 43.9%, and 9.2% of patients, respectively. Mean Pd/Pa, RFR, and FFR were 0.93 ± 0.06 (median: 0.93, IQR: 0.90–0.98), 0.89 ± 0.09 (median: 0.91, IQR: 0.85–0.96), and 0.82 ± 0.09 (median: 0.82, IQR: 0.76–0.89), respectively. Correlation coefficients for Pd/Pa versus RFR was 0.94 ($p < 0.001$). Furthermore, correlation coefficients for Pd/Pa versus FFR and RFR versus FFR were similar at 0.73 and 0.66, respectively (both $p < 0.001$) (Fig. 1). In our ROC analyses for the detection of an FFR value <0.80, the area under the curve values were 0.83 for RFR and 0.85 for Pd/Pa (both $p < 0.001$). The best RFR cut-off for prediction of an FFR of 0.8 in our population was 0.92 (Fig. 2).

Table 1
Baseline clinical characteristics of study population.

	n = 410
Age, years	69.6 ± 10.8
Male, n (%)	286 (75.7)
Body surface area, m^2	1.7 ± 0.2
Body mass index, kg/m^2	24.3 ± 3.7
Hypertension, n (%)	273 (72.0)
Diabetes mellitus, n (%)	166 (43.9)
Dyslipidemia, n (%)	277 (72.9)
Current smoker, n (%)	52 (13.9)
Previous MI, n (%)	42 (11.1)
Post-PCI, n (%)	132 (34.2)
Post-CABG, n (%)	11 (2.9)
Chronic kidney disease, n (%)	84 (22.2)
Hemodialysis, n (%)	35 (9.2)
LVEF, %	63.3 ± 11.5
E/e'	12.6 ± 5.6
TC, mg/dL	161.3 ± 34.1
LDL-C, mg/dL (Friedewald)	87.8 ± 28.8
HDL-C, mg/dL	49.6 ± 14.2
TG, mg/dL	105 [77, 145]
FBG, mg/dL	107.9 ± 32.3
HbA1c, %	6.4 ± 1.1
hs-CRP, mg/L	0.07 [0.03, 0.2]
Measured vessel location	n = 537
RCA	134 (25.0)
LAD	290 (54.0)
LCX	113 (21.0)
Hyperemic agents	n = 537
ATP, n (%)	319 (59.4)
Papaverine, n (%)	212 (39.5)
Others, n (%)	6 (1.1)

ATP, adenosine triphosphate; CABG, coronary artery bypass grafting; E/e', ratio of early left ventricular inflow wave to early diastolic annulus wave; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; TC, total cholesterol; TG, triglyceride.

Clinical, physiological, and angiographical characteristics of the FFR and RFR groups

Overall, FFR and RFR values were concordant in 390 lesions (72.6%) and discordant in 147 lesions (27.4%). As shown in Fig. 3, discordance of FFR >0.8 and RFR ≤0.92 (high FFR/low RFR) was observed in 112 lesions (20.9%), whereas discordance of FFR ≤0.8 and RFR >0.92 (low FFR/ high RFR) was observed in 35 lesions (6.5%).

The characteristics of the concordant (low FFR/low RFR and high FFR/high RFR) and discordant (low FFR/high RFR and high FFR/low RFR) groups are summarized in Table 2. Age, proportion of female patients, and rates of previous hemodialysis treatment were higher in the low FFR/low RFR group than in the low FFR/high RFR group, while the proportion of current smokers was lower (all $p < 0.05$). Age, proportion of female patients, rates of hemodialysis, prevalence of left ventricular hypertrophy (LVH), and proportion of left anterior descending artery (LAD) lesions were higher in the high FFR/low RFR group than in the low FFR/high RFR group. However, body surface area (BSA) was lower in the high FFR/low RFR group than in the low FFR/high RFR group (all $p < 0.05$).

Angiographic lesion severity assessed by %DS increased progressively from the high FFR/low RFR group, to the high FFR/high RFR group, the low FFR/low RFR group, and finally the low FFR/high RFR group. Relative to the high FFR/high RFR group, the low FFR/high RFR and low FFR/low RFR groups exhibited more severe stenosis and longer lesion length.

Clinical predictors of discordance between FFR and RFR

The univariate analysis revealed that female sex ($p = 0.004$), LVH ($p = 0.01$), LAD lesions ($p < 0.001$), anemia ($p = 0.004$), and hemodialysis ($p < 0.001$) were potentially associated with discordance of FFR >0.8 and RFR ≤0.92. In the multivariate analysis, female sex [odds ratio (OR): 1.80, 95% confidence interval (CI): 1.09–2.95; $p = 0.02$], LAD lesions (OR: 4.18, 95% CI: 2.52–7.18; $p < 0.001$), and hemodialysis (OR: 3.61, 95% CI: 1.81–7.20; $p = 0.0003$) were identified as independent predictors of discordance between FFR >0.8 and RFR ≤0.92.

Our univariate analysis further revealed that male sex ($p = 0.07$), BSA ($p = 0.0007$), and non-LAD lesions ($p = 0.0004$) were potentially associated with discordance between FFR ≤0.8 and RFR >0.92. In the multivariate analysis, BSA (OR: 1.38, 95% CI 1.11–1.72; $p = 0.004$) and non-LAD lesions (OR: 3.62, 95% CI: 1.70–8.40; $p = 0.0006$) were identified as independent predictors of discordance between FFR ≤0.8 and RFR >0.92.

The overall multivariate analysis identified hemodialysis (OR: 2.41, 95% CI 1.31–4.41; $p = 0.005$) and LAD lesions (OR: 1.86, 95% CI: 1.25–2.79; $p = 0.002$) as independent predictors of FFR–RFR mismatches (Table 3).

Discussion

In the present study, we utilized data from our clinical practice to identify clinical characteristics that influence the relationship between FFR and RFR. Our ROC analysis revealed that the optimal

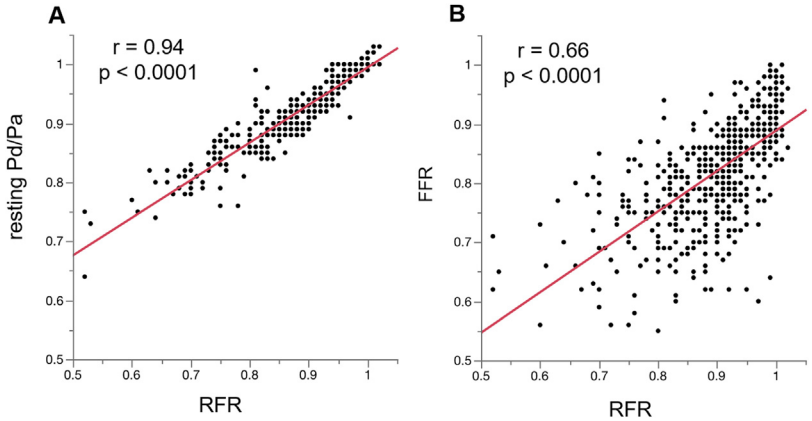

Fig. 1. Comparison of basal resting Pd/Pa and fractional flow reserve (FFR) to resting full-cycle ratio (RFR). RFR was correlated with basal resting Pd/Pa (r = 0.94, A) and FFR (r = 0.66, B).
Pd, distal arterial pressure; Pa, arterial pressure within the entire cardiac cycle.

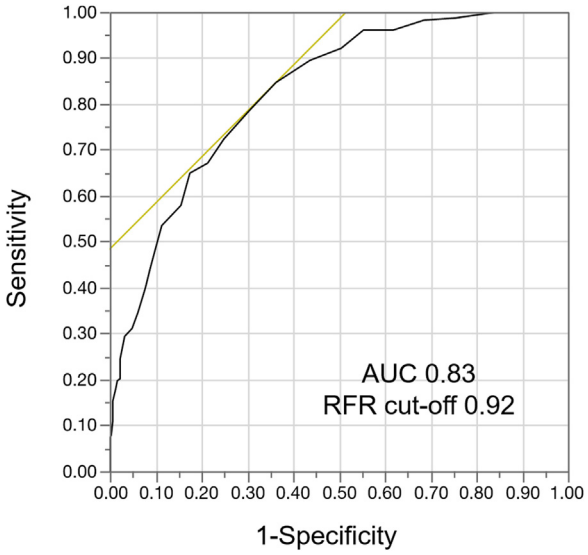

Fig. 2. Diagnostic characteristics of the resting full-cycle ratio (RFR). Receiver operating characteristic curve analyses were performed to determine the classification accuracy of RFR for discrimination at the reference standard of fractional flow reserve ≤0.8. The area under the curve was 0.83, and the optimal RFR threshold was 0.92.

cut-off value for RFR for identifying stenoses with an FFR of 0.80 was 0.92. In addition, our data indicated that 27.4% of the discordance between RFR and FFR occurred in cases of intermediate coronary artery stenosis. Female sex, LAD lesions, and hemodialysis were identified as independent predictors of discordance between FFR >0.8 and RFR ≤0.92, while BSA and non-LAD lesions were identified as independent predictors of discordance between FFR ≤0.8 and RFR >0.92. Lastly, our analysis identified hemodialysis and LAD lesions as independent predictors of overall FFR–RFR mismatches.

Our results validate the diagnostic utility of RFR for the physiological assessment of CAD in real clinical practice. Several recent reports have also shown that RFR is diagnostically equivalent to iFR (and to Pd/Pa) [8,10]. In the present study, the optimal established cut-off value for RFR to identify stenoses with an FFR of 0.80 was 0.92. This value is higher than the optimal RFR cut-off (0.89) observed in the VALIDATE RFR study and a recent study from Lee et al. [8,9]. Among our 537 lesions, 140 (26.0%) showed discordant results in the FFR and RFR measurements when the RFR cut-off was set at 0.89. As shown in Online Table 1, there was no significant difference in clinical and angiographic characteristics between the two cut-off values. The accuracy of cut-off values determined using ROC curves is highly dependent on adequate power around the cut-off. Given that most lesions exhibited intermediate stenosis, our sample was both reflective of the population in which such physiological assessments are routinely performed and allows for sufficient power when determining the best RFR cut-off reflecting an FFR of 0.8. It is also possible that age, coronary lesion characteristics, and hyperemic agents influenced cut-off values. Indeed, mean patient age was higher in our study than in the previous studies, while lesion length was longer. We therefore believe that intermediate coronary lesions may have been more severe in our study than in these previous studies. In addition, we utilized two different hyperemic agents (papaverine and adenosine) to achieve maximal hyperemia. Thus, our FFR measurements may have been influenced by differences in the conditions used to achieve maximal hyperemia. Together, these clinical factors may explain differences in the optimal cut-off value among studies.

In the present study, we compared clinical characteristics among four groups classified based on FFR and RFR. Notably, the four groups exhibited significant differences in the distribution of sex and cardiovascular risk factors. Muroya et al. reported that the proportion of female patients was significantly higher in the high FFR/low RFR group [10]. Recent iFR studies have also indicated that the proportion of female patients is higher in the high FFR/low iFR group than in the concordant group [13,14]. Such discordance may be explained by higher coronary baseline flow in female patients than in male patients or high rate-pressure products [15].

Our results indicated that the diagnostic accuracy of RFR depends on the location of the lesion (LAD or non-LAD). Previous studies have demonstrated that the visual-functional mismatch between angiography and FFR is associated with older age, female sex, lower BSA, the presence of non-LAD lesions, smaller vessel size, and shorter lesion length [16,17]. Moreover, Derimay et al. reported a relationship between left main/proximal LAD stenoses and greater discordance between FFR and iFR [18]. As the actual sizes of subtended territories vary based on the type of vessel involved, the location of the lesion, and the size of the myocardium, these factors should be considered when interpreting FFR, iFR, and RFR.

Conversely, our analysis identified higher BSA as a significant predictor of low FFR and high RFR. Given that BSA and vessel size are greater in male than in female patients, a larger myocardial territory in male patients may explain the higher frequency of this type of mismatch (i.e. low FFR and high RFR). Moreover,

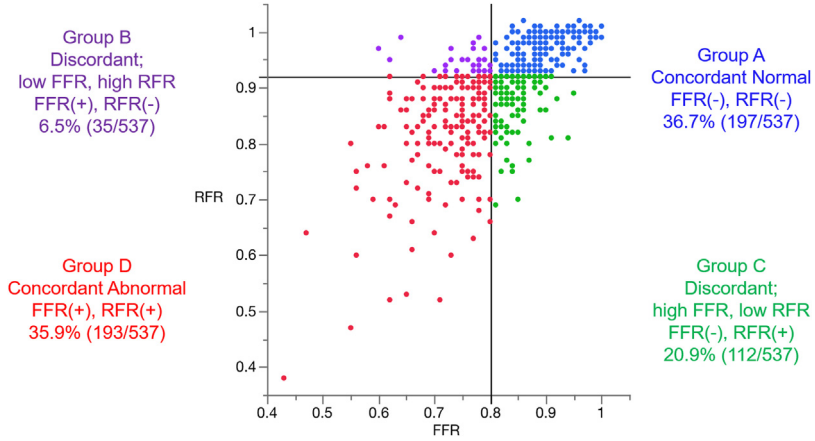

Fig. 3. Distribution of lesions according to fractional flow reserve (FFR) and resting full-cycle ratio (RFR). Among 537 lesions, classification was discordant for 27.3%, based on FFR and RFR cutoff values of ≤0.80 and ≤0.92, respectively. A: Concordant normal, 36.7% (197/537), B: low FFR/High RFR, 6.5% (35/537), C: high FFR/low RFR, 20.9% (112/537), D: concordant abnormal, 35.9% (193/537).

Table 2
Clinical and lesion characteristics of the four groups classified based on FFR and RFR.

	High FFR/High RFR FFR > 0.80 and RFR > 0.92	Low FFR/high RFR FFR ≤ 0.8 and RFR > 0.92	High FFR/low RFR FFR > 0.8 and RFR ≤ 0.92	Low FFR/low RFR FFR ≤ 0.8 and RFR ≤ 0.92	*p*-Value
Vessel, n (%)	197 (36.7)	35 (6.5)	112 (20.9)	193 (35.9)	
Baseline characteristics					
Age, years	70.0 ± 9.2	64.5 ± 9.8	71.3 ± 10.3	69.0 ± 11.2	0.005
Female, n (%)	42 (21.3)	4 (11.4)	38 (33.9)	41 (21.2)	0.01
Body surface area, m^2	1.74 ± 0.20	1.83 ± 0.14	1.66 ± 0.22*	1.73 ± 0.20	<0.0001
Body mass index, kg/m^2	24.3 ± 3.4	25.1 ± 2.3	24.1 ± 4.4	24.2 ± 3.5	0.53
HR, bpm	69.7 ± 11.1	70.1 ± 11.3	71.3 ± 12.3	69.6 ± 11.8	0.65
Systolic BP, mmHg	125.9 ± 14.4	123.5 ± 13.7	126.4 ± 15.3	125.4 ± 15.2	0.77
Diastolic BP, mmHg	68.0 ± 10.0	68.5 ± 10.2	68.5 ± 11.7	67.3 ± 9.8	0.78
Hypertension, n (%)	138 (70.1)	22 (62.9)	85 (75.9)	142 (73.6)	0.41
Diabetes mellitus, n (%)	82 (41.6)	13 (37.1)	56 (50.0)	88 (45.6)	0.41
Dyslipidemia, n (%)	145 (73.6)	33 (94.3)	81 (72.3)	139 (72.0)	0.04
Current smoker, n (%)	34 (17.3)	9 (25.7)	15 (13.4)	18 (9.5)	0.006
Chronic kidney disease, n (%)	42 (21.3)	8 (22.9)	21 (18.9)	38 (19.7)	0.93
Hemodialysis, n (%)	8 (4.1)	0 (0.0)	22 (19.8)	20 (10.4)	<0.0001
Atrial fibrillation, n (%)	17 (8.7)	1 (2.9)	9 (8.0)	14 (7.3)	0.68
Echocardiography findings					
LVEF, %	63.9 ± 10.8	66.5 ± 7.8	63.4 ± 12.1	63.4 ± 11.6	0.50
E/e'	11.8 ± 4.7	10.6 ± 3.4	13.6 ± 6.0	12.8 ± 5.7	0.005
LVH (IVS or PW ≥12), n (%)	23 (11.9)	2 (5.7)	26 (24.1)	32 (17.2)	0.01
Aortic stenosis ≥ moderate, n	9 (4.6)	0 (0.0)	15 (13.9)	18 (9.7)	0.008
LV mass index, g/m^2	104.6 ± 36.1	90.5 ± 20.9	116.0 ± 43.6	102.5 ± 34.6	0.16
Laboratory findings					
TC, mg/dL	163.3 ± 31.7	159.6 ± 24.6	159.6 ± 39.5	161.3 ± 33.1	0.78
LDL-C, mg/dL (Friedewald)	88.7 ± 27.5	81.1 ± 23.6	86.9 ± 31.2	89.1 ± 28.7	0.46
HDL-C, mg/dL	50.6 ± 13.4	45.7 ± 12.2	50.7 ± 15.1	48.5 ± 13.1	0.13
TG, mg/dL	111 [85, 142]	157 [113, 198]*	99 [67, 143]	102 [77, 144]	<0.0001
FBG, mg/dL	107.1 ± 26.6	102.4 ± 17.1	108.7 ± 44.9	106.6 ± 24.5	0.75
HbA1c, %	6.4 ± 0.9	6.4 ± 0.9	6.5 ± 1.4	6.4 ± 0.9	0.72
hs-CRP, mg/L	0.06 [0.03, 0.1]	0.06 [0.03, 0.2]	0.08 [0.04, 0.2]	0.07 [0.03, 0.2]	0.14
NT-proBNP, pg/mL	147 [55, 301]	81 [47, 179]	207 [62, 910]*	136 [58, 409]	0.02
White blood cell count, /μL	5500 [4600, 6500]	5300 [4400, 6100]	5850 [4900, 7450]	5500 [4700, 6700]	0.15
Hemoglobin, g/dL	13.6 ± 1.7	13.9 ± 1.0	12.8 ± 1.8*	13.3 ± 1.8	<0.0001
eGFR, mL/min/1.73 m^2 (excluding hemodialysis group)	67.4 ± 17.4	72.8 ± 17.9	70.1 ± 19.3	68.5 ± 18.1	0.31
Measured vessel location					
RCA, n (%)	90 (45.7)	15 (42.9)	8 (7.1)	21 (10.9)	<0.0001
LAD, n (%)	39 (19.8)	9 (25.7)	87 (77.7)	155 (80.3)	<0.0001
LCX, n (%)	68 (34.5)	11 (31.4)	17 (15.2)	17 (8.8)	<0.0001
Lesion location					0.02
Proximal	58 (29.1)	14 (40)	46 (41)	91 (47.1)	
Mid	99 (49.7)	18 (51.4)	52 (46.4)	82 (42.5)	
Distal	40 (20.1)	3 (8.6)	14 (12.5)	20 (10.4)	
Angiographic characteristics					
Reference diameter, mm	2.72 ± 0.66	2.38 ± 0.60*	2.47 ± 0.65*	2.40 ± 0.56*	<0.0001
MLD, mm	1.58 ± 0.48	1.15 ± 0.36*	1.50 ± 0.46	1.20 ± 0.44*	<0.0001
Stenosis diameter, %	41.8 [49.5,33.8]	54.1 [60,46.7]*	40.2 [47.5,31.6]	50.3 [60.4,40]*	<0.0001
Lesion length, mm	11.0[7.6,18.4]	16.1[11.6,30.3]*	13.4[8.5,22.1]	20.8[13.8,36.2]*	<0.0001
Diffuse lesion in LAD, %	7 (15.9)	3 (25.0)	22 (26.8)	51 (33.8)	0.11
Medication					
ACE-I/ARB, n (%)	90 (45.9)	14 (40.0)	50 (44.6)	99 (51.3)	0.48
β-Blocker, n (%)	92 (46.9)	20 (57.1)	47 (42.0)	88 (45.6)	0.46
OHA, n (%)	56 (28.6)	8 (22.9)	42 (37.5)	73 (37.8)	0.10
Insulin, n (%)	22 (11.2)	2 (5.7)	14 (12.5)	19 (9.8)	0.68
Statin, n (%)	154 (78.6)	31 (88.6)	84 (75.0)	135 (70.0)	0.06

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; E/e', ratio of early left ventricular inflow wave to early diastolic annulus wave; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; FFR, fractional flow reserve; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; IVS, interventricular septum; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein-cholesterol; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MLD, minimum lumen diameter; NT-proBNP, N-terminal pro B-type natriuretic peptide; OHA, oral hypoglycemic agents; PW, posterior wall; RCA, right coronary artery; RFR, resting full-cycle ratio; TC, total cholesterol; TG, triglycerides.
* $p < 0.01$ post-hoc analysis in relation to the high FFR/high RFR group.

hemodialysis was identified as a significant predictor of not only high FFR and low RFR but also overall FFR–RFR mismatches. Similarly, Arashi et al. reported that hemodialysis was an independent predictor of mismatches between FFR and iFR [14], while Morioka et al. noted that iFR values tended to be lower in patients undergoing hemodialysis than in those not undergoing such treatment [19]. In our study, we observed significant differences in RFR values between patients treated with and without hemodialysis (0.84 ± 0.10 vs. 0.90 ± 0.09; $p < 0.001$). However, there was no significant difference in lesion stenosis or length between patients in the hemodialysis and non-hemodialysis subgroups. High baseline coronary blood flow in patients undergoing hemodialysis may explain these differences. RFR values, which are obtained under resting sub-maximal

Table 3
Univariate and multivariate logistic regression analysis for predictors of discordance between FFR and RFR.

	Univariate analysis OR (95% confidence interval)	*p*-Value	Multivariate analysis OR (95% confidence interval)	*p*-Value
Predictors of high FFR/low RFR				
Female	2.00 (1.26–3.14)	0.004	1.80 (1.09–2.95)	0.02
LVH (IVS or PW thickness ≥12 mm)	1.99 (1.16–3.32)	0.01	1.51 (0.82–2.72)	0.18
LAD	3.81 (2.38–6.28)	<0.0001	4.18 (2.52–7.18)	<0.0001
Hemodialysis	3.50 (1.90–6.40)	<0.0001	3.61 (1.81–7.20)	0.0003
Anemia (Hemoglobin <11 g/dl)	2.42 (1.33–4.30)	0.004	1.89 (0.97–3.61)	0.06
Predictors of low FFR/high RFR				
Male	2.46 (0.95–8.40)	0.07	0.91 (0.29–3.51)	0.88
BSA, per 0.1 m^2 higher	1.38 (1.14–1.68)	0.0007	1.38 (1.11–1.72)	0.004
Non-LAD	3.67 (1.75–8.44)	0.0004	3.62 (1.70–8.40)	0.0006
Predictors of overall FFR-RFR discordance				
Female	1.48 (0.96–2.27)	0.08	1.43 (0.92–2.22)	0.11
Hemodialysis	2.29 (1.26–4.15)	0.007	2.41 (1.31–4.41)	0.005
LAD	1.90 (1.29–2.83)	0.001	1.86 (1.25–2.79)	0.002

BSA, body surface area; FFR, fractional flow reserve; IVS, interventricular septum; LAD, left anterior descending artery; LVH, left ventricular hypertrophy; PW, posterior wall; RFR, resting full-cycle ratio.

hyperemic conditions, were indeed similar to FFR values obtained under maximal hyperemic conditions in patients undergoing hemodialysis. Our results suggest that if the RFR is functionally significant for intermediate stenosis in patients with hemodialysis, further FFR evaluations should be conducted in these patients, given the discordance between FFR and RFR.

The present study possesses several limitations of note. First, this was a retrospective observational cohort study conducted at a single center, and the number of study patients was relatively small. Second, this study included patients in whom FFR assessments were performed via the intravenous (60%) or intracoronary (40%) route. Such differences in methodology may have introduced differences between the groups. Third, rates of DM and hemodialysis were higher in our study than in previous studies. These comorbidities may affect myocardial perfusion and coronary capacity, which may in turn influence the relationship between FFR and RFR.

Conclusions

Our findings suggest that the diagnostic relationship between RFR and FFR is highly concordant in patients with intermediate coronary artery lesions. Clinical characteristics and predictors of discordance differed significantly among four groups classified based on FFR and RFR. Given our findings, clinicians should exercise caution when selecting physiological assessments for intermediate stenotic lesions in patients undergoing hemodialysis. Such decisions should also be made in consideration of lesion location.

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Disclosures

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2020.10.014.

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