ORIGINAL RESEARCH

Impact of Sex Difference on the Discordance of Revascularization Decision Making Between Fractional Flow Reserve and Diastolic Pressure Ratio During the Wave-Free Period

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***Background*—**Sex difference in fractional flow reserve (FFR) and resting index has not been fully clarified. We sought to investigate the impact of sex on the discordance of revascularization decision making between FFR and diastolic pressure ratio during the diastolic wave-free period (dPR_{WFP}).

***Methods and Results*—**A total of 759 angiographically intermediate lesions with 30% to 80% diameter stenosis by quantitative coronary angiography in 577 patients in whom FFR and dPR_{WFP} were measured were investigated. dPR_{WFP} was measured during the wave-free window of 5 heart cycles at an independent core laboratory. FFR ≤0.80 and dPR_{WFP} ≤0.89 were considered positive studies. A total of 164 vessels in 126 women (21.6%) and 595 vessels in 451 men (78.4%) were included. In lesions with negative dPR_{WFP}, positive FFR was less frequently observed in women (13 of 73; 17.8%) than in men (97 of 286; 33.9%) (P=0.009). In lesions with positive dPR_{WFP}, the frequency of negative FFR was observed in 22 of 91 vessels (24.2%) in women and 51 of 309 vessels (16.5%) in men, which did not reach statistical significance (P=0.098). In multivariable analyses, female sex was independently associated with FFR-dPR_{WFP} discordance both in negative dPR_{WFP} cohort (odds ratio, 0.44; 95% CI, 0.21–0.98; P=0.036) and in positive dPR_{WFP} cohort (odds ratio, 2.41; 95% CI, 1.17–4.96; P=0.017) after adjustment for age, weight, quantitative coronary angiography data, and baseline physiological indexes.

***Conclusions*—**The frequency of FFR-dPR_{WFP} discordance was significantly associated with sex, which may indicate potential shift of optimal threshold of either FFR or dPR_{WFP}, or both of them, according to sex. **(*J Am Heart Assoc*. 2020;9:e014790. DOI: 10.1161/JAHA.119.014790.)**

Key Words: angina pectoris • diastolic pressure ratio • fractional flow reserve

Fractional flow reserve (FFR) is globally accepted as the standard measure of myocardial ischemia in the catheterization laboratory to guide percutaneous coronary intervention (PCI),[1–3] in which an FFR threshold ≤0.80 has been applied for the indication of revascularization. Recently, the instantaneous wave-free ratio (iFR) has been rapidly spreading in the catheterization laboratories since iFR-guided PCI with use of a cutoff of iFR ≤0.89 has been shown to be noninferior to FFR-guided PCI.[4,5] Nevertheless, there has not been a clear answer whether the FFR or resting index including iFR was superior to the other for the guidance of PCI. In clinical practice, ≈20% of the lesions show discordance between FFR and iFR when each threshold is given to dichotomize the value,[6] and the discrepancy between FFR and resting indexes is gathering research interests. In previous studies, women showed higher FFR values than men if the angiographic stenosis severity was similar.[7] However, the same threshold of FFR, ≤0.80, is widely used for FFR-guided PCI in both sexes because the clinical outcomes were not different in the substudy of previous clinical trials between sexes when the same threshold was applied.[8] As of present, data on the sex differences in the measurements of resting indexes and discordance between FFR and resting indexes are limited. In this study, we sought to investigate the frequency

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Clinical Perspective

What Is New?

- Female sex was independently associated with fractional flow reserve–diastolic pressure ratio during the diastolic wave-free period (dPR_{WFP}) discordance in both dPR_{WFP} negative and dPR_{WFP} positive lesions.
- Women showed a trend toward higher fractional flow reserve value and lower dPR_{WFP} in the distribution of those values in comparison with men.

What Are the Clinical Implications?

- The sex difference in the distribution of fractional flow reserve and dPR_{WFP} may indicate the potential room for sex-specific optimization of the cutoff values of those indexes, which requires future research.

of discordance of revascularization decision making between FFR and diastolic pressure ratio during the diastolic wave-free period (dPR_{WFP}), which has been shown to be identical to iFR, as well as determinants of such discordance to explore the possible sex difference in the optimal threshold of the resting index in comparison with FFR.

Methods

Study Population

From the institutional database of FFR measurements in Tsuchiura Kyodo General Hospital between January 2015 and September 2017, which consisted of a total of 1100 measurements of FFR, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) with pressure-temperature sensor-tipped wire (PressureWire) in 625 patients, 840 vessels with angiographically intermediate lesions with 30% to 80% diameter stenosis, assessed by quantitative coronary angiography in stable coronary disease, were selected for the analysis. Patients with acute coronary syndrome, left-main disease, contraindication for adenosine, shock status, congestive heart failure, atrial fibrillation, in-stent lesions, and a history of coronary artery bypass grafting and lack hemodynamic data during the examination were excluded from the analysis. In addition, waveform tracings with insufficient quality or pressure drift ≥3 mm Hg were excluded from the analysis, as described later. The final data set included a total of 759 vessels in 577 patients, consisting of 126 women (21.8%) and 451 men (78.2%). This study was approved by institutional review boards of Tokyo Medical and Dental University and Tsuchiura Kyodo General Hospital. Informed consent was obtained from all patients. The data that support the findings of this study are available from the corresponding author on reasonable request.

Cardiac Catheterization and Coronary Angiography

Standard selective coronary angiography was initially performed via the radial or femoral artery using 6F system. Minimal lumen diameter, reference lumen diameter, percentage diameter stenosis, and lesion length were measured with off-line quantitative coronary angiography analysis software (QAngio XA; Medis Medical Imaging Systems, Leiden, the Netherlands). All patients received a bolus injection of heparin (5000 IU) before the procedure; thereafter, 2000 IU was additionally injected intravenously every hour. Intracoronary nitroglycerin of 200 μg was administered at the beginning of the procedure and before each physiological measurement.

FFR Measurements

A pressure-temperature sensor-tipped wire (PressureWire Certus; Abbott Vascular, Santa Clara, CA) with RadiAnalyzer Xpress console was used for the acquisition of the distal coronary pressure (Pd) and the thermodilution curve. After coronary angiography, the pressure wire was introduced into the coronary artery via a guiding catheter and was zeroed and equalized to the catheter tip pressure. Afterward, the pressure sensor was positioned 8 to 10 cm distal to the ostium of the studied artery across the lesion. At 2 minutes after the intracoronary injection of nitroglycerin and elimination of contrast media and blood from the guiding catheter by flushing saline, baseline pressures were recorded for at least 20 seconds. Thereafter, ATP was administered intravenously at 150 μg/kg per minute to induce hyperemia, and FFR measurements were performed by calculating the ratio of Pd/aortic pressure (Pa) at stable hyperemia. Pressure drift was determined when the pressure sensor was pulled back to the tip of the guiding catheter after FFR measurements. As per our institutional protocol recommendation, when the pressure drift was ≥3 mm Hg, measurement was repeated on the basis of the operators' discretion. Measurements with the final pressure drift ≥3 mm Hg were excluded from the analysis. All pressure and ECG tracings of the consoles were submitted to the in-hospital physiological analysis laboratory, which is operated independently by expert engineers and cardiologists. Waveforms were excluded from the analysis in cases with loss of pressure signal at any point during the measurement phase (n=2), bradycardia with a heart rate <50 beats per minute, or tachycardia >120 beats per minute (n=12), suggestive of catheter-damped Pa recording (n=23) or inappropriate Pd waveform quality (n=19).

CFR and IMR Measurements

Three injections of room temperature saline (3 mL) were administered from the guiding catheter, and thermodilution curves (3 times each) were obtained at the temperature sensor of the wire. The mean transit time (Tmn) from the proximal to the distal sensor, which is considered a surrogate marker of coronary flow velocity, was measured. CFR was determined simultaneously with FFR using the Tmn at rest and during hyperemia, as described elsewhere.[9] IMR was calculated as the product of the mean Pd during stable hyperemia and hyperemic Tmn and corrected by using the following formula proposed by Yong et al[10]:

$$\mathrm{IMR} = \mathrm{Pa} \times \mathrm{Tmn} \times ((1.35 \times \mathrm{Pd/Pa}) - 0.32).$$

dPR_{WFP} Measurements

Baseline pressure and ECG tracing at 2 minutes after intracoronary injection of nitroglycerin were anonymized and sent to an independent, blinded core laboratory (Coroventis Research, Uppsala, Sweden) for the measurements of dPR_{WFP}. dPR_{WFP} was a resting index measured in the WFP, defined as the time window from 25% in diastole to 5 ms before the end of diastole, which was validated to be exactly close to iFR.[11] We performed linear regression and receiver operating characteristic analyses between dPR_{WFP} and Pd/Pa in the current data set to test the feasibility of the dPR_{WFP} measurement as an alternative to iFR (Figure S1). The regression line and receiver operating characteristic curve were almost identical to those reported in a previous study comparing iFR and Pd/Pa,[12] which can indicate the validity of dPR_{WFP} measurement in the present study. dPR_{WFP} was calculated from each individual waveform in a blinded manner using fully automated off-line software algorithm (CoroLab; Coroventis Research AB, Uppsala, Sweden). dPR_{WFP} was calculated for 5 heart cycles and averaged.

Definitions of Discordance Between FFR and dPR_{WFP}

The cutoff thresholds of FFR and dPR_{WFP} were defined as ≤0.80 and ≤0.89, respectively. Vessels were divided into 4 groups according to positive or negative results of FFR and dPR_{WFP}, as shown in Figure 1: group 1, FFR−/dPR_{WFP}−; group 2, FFR+/dPR_{WFP}−; group 3, FFR−/dPR_{WFP}+; or group 4, FFR+/dPR_{WFP}+. Distributions of the studied vessels to the 4 groups were compared between sexes. Frequency and determinants of the discordance between FFR and dPR_{WFP} (FFR-dPR_{WFP} discordance) were assessed in the negative dPR_{WFP} cohort, which consisted of group 1 and group 2, and in the positive dPR_{WFP} cohort, which consisted of group 3 and group 4, separately, and the impact of sex difference on the FFR-dPR_{WFP} discordance was determined.

Left Ventricular Mass

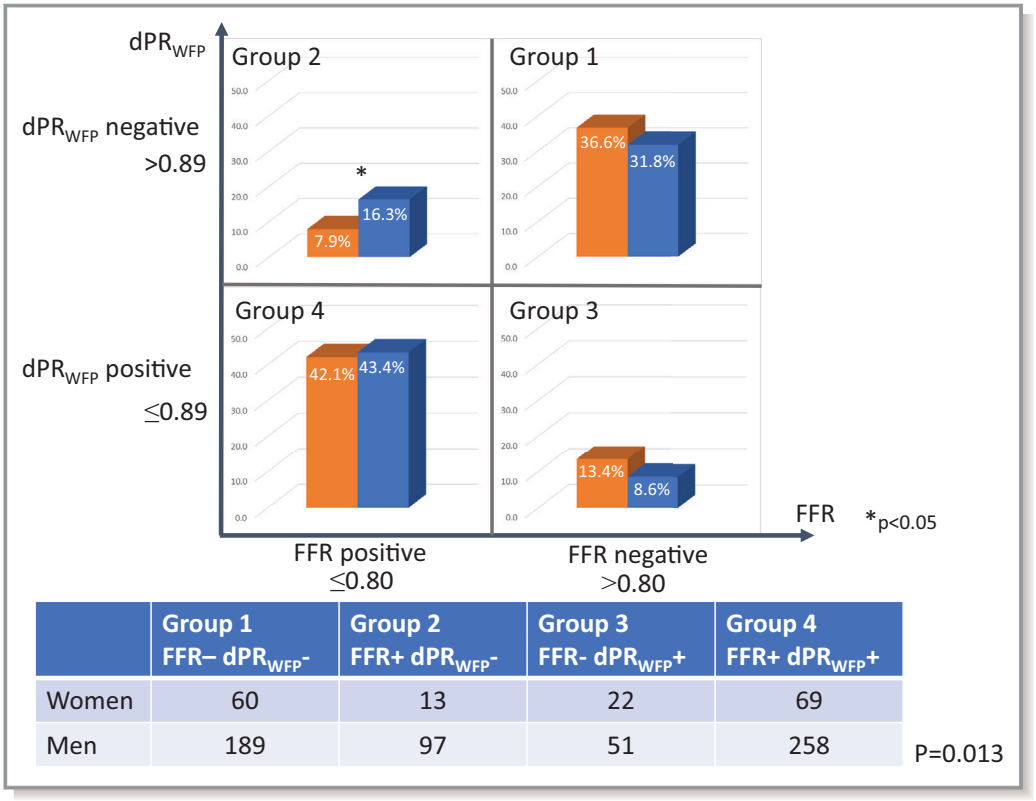
Left ventricular mass was retrospectively examined in the subset of patients who underwent computed tomography coronary angiography within 3 months before the physiological assessment. Quantitative assessment of whole left ventricular mass was performed using the Aquarius iNtuition Workstation Edition, version 4.4.13 (TeraRecon Inc, Foster City, CA), at the mid-diastole phase.

Statistical Analysis

Statistical analysis was performed using SPSS, version 23.0 (IBM, Chicago, IL), and R, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as absolute number and frequency and were compared using χ^2 or Fisher's exact tests, as appropriate. Distribution normality of each continuous variable was examined with Kolmogorov-Smirnov test. Continuous variables were expressed as mean±SD for normally distributed variables or as median (25th–75th percentile) for nonnormally distributed variables and were compared using Student *t* tests or Mann-Whitney *U* tests, respectively. Kruskal-Wallis analysis was performed to compare CFR among the 4 groups, and Bonferroni correction was exercised for post hoc pairwise comparisons. Univariate and multivariable logistic generalized estimating equation models with robust SEs, which account for the clustering of multiple lesions within a patient, were analyzed to identify the determinants of the FFR-dPR_{WFP} discordance. The associated variables on patients' clinical characteristics, angiographic findings, hemodynamic variables during catheterization, or thermodilution data in the univariate analysis (P<0.150) were entered into the multivariable model. In addition, CFR, IMR, and body weight, which were considered to be potential mechanisms of sex difference in FFR and dPR_{WFP}, were also forcedly entered into the model. The number of determinants was limited to less than one tenth of the number of FFR-dPR_{WFP} discordance. On the basis of 110 FFR-dPR_{WFP} discordances in dPR_{WFP} negative cohort and 73 discordances in dPR_{WFP} positive cohort, the number of determinants was limited to 10 and 7, respectively, to avoid overfitting. Variables with variance inflation factor of >5 were excluded from the multivariable model to take multicollinearity into account.

Results

Of a total of 759 lesions, FFR ≤0.80 and dPR_{WFP} ≤0.89 showed discordance in 183 (24.4%). Patient characteristics



	Group 1 FFR− dPR$_{WFP}$-	Group 2 FFR+ dPR$_{WFP}$-	Group 3 FFR- dPR$_{WFP}$+	Group 4 FFR+ dPR$_{WFP}$+
Women	60	13	22	69
Men	189	97	51	258

P=0.013

Figure 1. Sex difference in fractional flow reserve (FFR)–diastolic pressure ratio during the diastolic wave-free period (dPR$_{WFP}$) categorization. Lesions were categorized into 4 groups according to FFR and dPR$_{WFP}$. Group 1 included lesions with FFR >0.80 and dPR$_{WFP}$ >0.89 (FFR− dPR−); group 2, FFR ≤0.80 and dPR$_{WFP}$ >0.89 (FFR+ dPR−); group 3, FFR >0.80 and dPR$_{WFP}$ ≤0.89 (FFR− dPR+); and group 4, FFR ≤0.80 and dPR$_{WFP}$ ≤0.89 (FFR− dPR+). Discordance was observed in 183 lesions (24.1%). Proportions shown in each group of the top panel indicate the proportion of the number of the lesion in the group to the total number in women (orange bar) and men (blue bar). Prevalence of group 2 was greater in women than in men. *: A significant difference between women and men (p<0.05).

were compared between sexes in Table 1. In this study, 621 lesions (621/759; 81.8%) exhibited FFR values between 0.60 and 0.90, indicating a real-world population of intermediate lesions indicative of FFR measurements. Women showed older age, less prevalent current smoking, lower creatinine level, and higher cholesterol level compared with men. Lesion characteristics in terms of angiographical findings, hemodynamic status during catheterization, and coronary physiological parameters in both sexes are summarized in Table 2. In terms of lesion location, left anterior-descending artery lesion showed nonsignificant trends toward more prevalence in women than in men, which did not reach statistical significance. Although the lesions in women tended to show smaller reference diameter, there were no significant differences in minimal lumen diameter and diameter stenosis in the quantitative coronary angiography analysis. At the baseline of the coronary physiological test, women exhibited higher heart rate, higher pressure-rate product, and lower Tmn, which indicates higher coronary flow, than men. With regard to the angiographic and physiological indexes, women showed higher FFR value than men did, whereas no significant differences were observed in dPR$_{WFP}$, Pd/Pa, CFR, IMR, and angiographic stenosis severity. Eligible computed tomography coronary angiography data were available in 243 patients (63 women and 180 men), and left ventricular mass was determined. Left ventricular mass was significantly smaller in women than in men (129.7±33.8 versus 168.4±43.1 mL; P<0.001) in those patients (Table 1). When the lesions were divided into 4 groups according to FFR and dPR$_{WFP}$ criteria, the distribution of the lesions across the groups was different between the sexes (P=0.013) (Figure 1). Patient and lesion characteristics are summarized in Table 3. In lesions with dPR$_{WFP}$ >0.89 (dPR$_{WFP}$ negative cohort), FFR was concordantly negative in 249 lesions (group 1) and FFR was discordantly positive in 110 lesions (group 2). Group 1 showed older age, more prevalence of women, smaller-diameter stenosis, and greater reference diameter than group 2 (Table 3). No significant differences in CFR and IMR were found between the 2 groups. In the multivariate logistic regression analysis with generalized estimating equation, female sex was an

independent, negative predictor of discordantly positive FFR in the negative dPR_{WFP} cohort. Younger age and greater diameter stenosis were independent predictors of discordance in the negative dPR_{WFP} cohort (Table 4).

In lesions with $dPR_{WFP} \leq 0.89$ (dPR_{WFP} positive cohort), FFR was discordantly negative in 73 lesions (group 3) and concordantly positive in 327 lesions (group 4) (Table 3). The prevalence of women was higher, albeit nonsignificant, in group 3 than in group 4. Group 3 showed larger minimal lumen diameter and smaller-diameter stenosis than those of group 4 (Table 3). No significant differences in heart rate or rate-pressure product at the baseline were found between group 3 and group 4. In the multiple logistic regression analysis, female sex remained as an independent predictor of negative FFR as well as smaller-diameter stenosis, greater reference diameter, higher IMR, and higher CFR. Both in the dPR_{WFP} negative and dPR_{WFP} positive cohorts, female sex was significantly associated with negative FFR. Considering coronary thermodilution results, hyperemic Tmn was significantly lower and CFR was significantly higher in group 3 than in group 4. When compared among the 4 groups, CFR was significantly lower in group 4 compared with the other 3 groups and group 3 showed significantly lower CFR compared with group 1 (Figure S2). When the lesions were stratified by the quartile of dPR_{WFP}, the second and third quartiles, 0.83 to 0.89 and 0.89 to 0.93, respectively, exhibited lower positive rate of FFR in women than in men, whereas the frequency of positive FFR was almost identical between men and women in the first quartile (dPR_{WFP} <0.83) (Figure 2). Moreover, the FFR value was significantly higher in women than in men in each dPR_{WFP} quartile (Figure 2). When the lesions were stratified by the quartile of FFR, women showed numerically higher rate of positive dPR_{WFP} in second and third FFR quartiles (0.72–0.86), which did not reach statistical significance (Figure 3). dPR_{WFP} value was significantly lower in the second and fourth FFR quartiles (Figure 3). In the receiver operating characteristic analysis, the optimal dPR_{WFP} threshold to predict FFR ≤0.80 was 0.86 in women (sensitivity, 0.768; specificity, 0.915; and area under the curve, 0.883) and 0.89 in men (sensitivity, 0.727; specificity, 0.788; and area under the curve, 0.831) (Figure S3). Scattergrams and linear regression lines between FFR and dPR_{WFP} for men and women are depicted in Figure 4. Pearson's correlation coefficient between dPR_{WFP} and FFR was 0.740 (95% CI, 0.662–0.802) in women and 0.732 (95% CI, 0.692–0.767) in men. The regression lines with 95% CI margins were separated at the middle of the chart, and the regression line for women was located toward the lower right, which indicates higher FFR and lower dPR_{WFP}, in comparison with that for men.

Discussion

The main findings of the present study are as follows: (1) the distribution of the lesions across the 4 groups stratified by

Table 1. Patient Characteristics in Women and Men

Characteristic	Women	Men	*P* Value
No. of patients	126	451	. . .
Age, y	72.2±8.4	66.4±10.1	<0.001
Body weight, kg	54.4 (48.3–61.8)	67.0 (60.1–73.6)	<0.001
Hypertension, n (%)	86 (68.3)	306 (67.8)	1.000
Diabetes mellitus, n (%)	42 (33.3)	187 (41.5)	0.101
Dyslipidemia, n (%)	77 (61.1)	285 (63.2)	0.678
Current smoking, n (%)	20 (15.9)	129 (28.6)	0.004
Statin use, n (%)	109 (86.5)	387 (85.8)	1.000
Creatinine, mg/dL	0.66 (0.55–0.80)	0.86 (0.75–1.00)	<0.001
eGFR, mL/min per 1.73 m^2	67.4 (54.9–81.7)	68.8 (56.1–81.4)	0.809
HbA1c, %	6.0 (5.6–6.6)	6.0 (5.5–6.7)	0.605
Total cholesterol, mg/dL	181 (158–207)	169 (148–197)	0.001
LDL-C, mg/dL	108 (86–126)	97 (79–119)	0.015
HDL-C, mg/dL	50 (41–59)	44 (37–52)	<0.001
Triglyceride, mg/dL	125 (88–166)	122 (88–176)	0.810
LVM, mL*	129.7±33.8	168.4±43.1	<0.001

Normally distributed variables are expressed as mean±SD, and nonnormally distributed variables are expressed as median (25th percentile–75th percentile). eGFR indicates estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVM, left ventricular mass.
*LVM was determined in the subset of patients (n=243) in whom computed tomography coronary angiography was available.

Table 2. Angiographical and Physiological Parameters of Lesions in Women and Men

Variable	Women	Men	*P* Value
No. of lesions	164	595	. . .
LAD, n (%)	111 (67.7)	357 (60.0)	0.085
Quantitative coronary angiography			
Diameter stenosis, %	53.7 (47.0–61.0)	54.1 (45.1–61.9)	0.829
Minimal lumen diameter, mm	1.2 (0.9–1.5)	1.2 (1.0–1.6)	0.153
Reference diameter, mm	2.6 (2.3–3.0)	2.7 (2.3–3.1)	0.021
Lesion length, mm	11.9 (8.5–14.7)	11.6 (8.3–16.1)	0.769
Hemodynamic and coronary physiological parameters at rest			
HR, bpm	70 (63–77)	66 (60–74)	0.002
Pa, mm Hg	96 (88–105)	93 (85–102)	0.012
Pd, mm Hg	86 (78–98)	84.00 (76–94)	0.049
Tmn, sec.	0.71 (0.50–0.96)	0.87 (0.61–1.24)	<0.001
Double product	6590 (5690–7874)	6160 (5340–7160)	0.001
Hemodynamic and coronary physiological parameters during hyperemia			
HR, bpm	78 (71–85)	74 (66–82)	<0.001
Pa, mm Hg	85 (74–93)	83 (75–93)	0.686
Pd, mm Hg	66 (57–77)	64 (56–73)	0.059
Tmn, sec.	0.27 (0.20–0.43)	0.33 (0.21–0.49)	0.013
Double product	6460 (5460–7426)	6006 (5161–7056)	0.007
Coronary physiological indexes			
Pd/Pa	0.92 (0.86–0.95)	0.91 (0.87–0.96)	0.599
CFR	2.38 (1.67–3.46)	2.58 (1.71–3.87)	0.264
FFR	0.80 (0.73–0.88)	0.78 (0.71–0.85)	0.007
FFR ≤0.80	82 (50.0)	355 (59.7)	0.027
dPR_{WFP}	0.88 (0.81–0.93)	0.89 (0.83–0.95)	0.150
dPR_{WFP} ≤0.89	91 (55.5)	309 (51.9)	0.420
IMR	18.4 (13.5–26.7)	20.5 (13.8–31.8)	0.075

Nonnormally distributed variables are expressed as median (25th percentile–75the percentile). Bpm indicates beats per minute; CFR, coronary flow reserve; dPR_{WFP}, diastolic pressure ratio during the diastolic wave-free period; FFR, fractional flow reserve; HR, heart rate; IMR, index of microcirculatory resistance; LAD, left anterior-descending artery; Pa, aortic pressure; Pd, distal coronary pressure; Tmn, mean transit time.

FFR and dPR_{WFP} was statistically different between men and women, which was mainly driven by more prevalent discordantly positive FFR in negative dPR_{WFP} group in men; (2) the female sex was significantly associated with FFR-dPR_{WFP} decision discordance in both lesions with negative dPR_{WFP} and those with positive dPR_{WFP}; (3) FFR was significantly higher and tended to be less positive in women than in men in the 2 middles of dPR_{WFP} quartiles; and (4) in women, FFR favors more deferral than dPR_{WFP}, and dPR_{WFP} tends to defer more lesions than FFR in men. To the best of our knowledge, this is the first study indicating the impact of sex difference on the discordant revascularization decisions between FFR and dPR_{WFP}, which are one of the resting indexes reported to be virtually equal to each other.[11,13]

Sex Difference in FFR Value

Sex difference in the assessment of FFR has been previously reported,[8,14–16] which showed that FFR value tended to be higher and FFR examination with the binary cutoff of ≤0.80 tended to show negative results more frequently in women than in men if the angiographical stenosis is matched between sexes. In the present study, FFR values in women tended to be higher and more frequently negative for the given dPR_{WFP} values divided into quartiles. Potential explanations for higher FFR values in women have been proposed as follows: older age, higher prevalence of hypertension, left ventricular hypertrophy, less subtended myocardial mass, small vessel size, or microvascular dysfunction, which may result in limited peak coronary flow. Park et al investigated

Table 3. Patient and Lesion Characteristics Stratified by dPR_{WFP} and FFR

Group	dPR_{WFP} Negative Cohort (n=359)			dPR_{WFP} Positive Cohort (n=400)		
	1: FFR− dPR_{WFP}−	2: FFR+ dPR_{WFP}−	*P* Value for 1 vs 2	3: FFR− dPR_{WFP}+	4: FFR+ dPR_{WFP}+	*P* Value for 3 vs 4
N (%)	249 (69.4)	110 (30.6)	. . .	73 (18.3)	327 (81.8)	. . .
Proportion to total cohort, %	32.8	14.5	. . .	9.6	43.1	. . .
Clinical characteristics						
Age, y	68.1±8.9	64.8±11.0	0.002	68.8±10.5	68.2±9.9	0.673
Body weight, kg	64.0 (56.6–73.0)	67.3 (60.2–73.2)	0.031	62.2 (52.8–70.0)	64.1 (56.2–71.6)	0.223
Women, n (%)	60 (24.1)	13 (11.8)	0.007	22 (30.1)	69 (21.1)	0.122
Hypertension, n (%)	172 (69.1)	70 (63.6)	0.330	47 (64.4)	231 (70.6)	0.326
Dyslipidemia, n (%)	152 (61.0)	69 (62.7)	0.814	46 (63.0)	199 (60.9)	0.791
Diabetes mellitus, n (%)	92 (36.9)	40 (36.4)	1.000	28 (38.4)	148 (45.3)	0.300
Current smoking, n (%)	70 (28.1)	31 (28.2)	1.000	17 (23.3)	66 (20.2)	0.528
Statin use, n (%)	214 (85.9)	97 (88.2)	0.618	66 (90.4)	276 (84.4)	0.269
EF, %	63.0±9.7	62.9±11.1	0.924	61.0±11.9	61.2±10.2	0.894
Creatinine, mg/dL	0.80 (0.68–0.96)	0.82 (0.72–0.94)	0.825	0.84 (0.68–0.97)	0.84 (0.70–0.97)	0.331
eGFR, mL/min per 1.73 m^2	68.2 (56.8–81.8)	72.8 (60.0–85.2)	0.079	67.2 (57.1–82.4)	66.7 (55.4–80.4)	0.632
HbA1c, %	6.0 (5.5–6.7)	6.0 (5.5–6.6)	0.796	6.0 (5.6–6.8)	6.0 (5.6–6.8)	0.542
Total cholesterol, mg/dL	170 (149–196)	163 (147–192)	0.351	174 (155–197)	176 (151–204)	0.891
LDL-C, mg/dL	99 (78–120)	93 (77–116)	0.328	98 (83–118)	101 (83–126)	0.487
HDL-C, mg/dL	44 (38–54)	46 (39–54)	0.460	44 (36–50)	45 (39–53)	0.377
Triglyceride, mg/dL	127 (89–178)	117 (82–178)	0.418	128 (96–210)	125 (89–172)	0.313
Angiographic findings						
LAD, n (%)	98 (39.4)	48 (43.6)	0.485	60 (82.2)	262 (80.1)	0.747
MLD, mm	1.5 (1.2–1.7)	1.2 (1.0–1.4)	<0.001	1.3 (1.1–1.6)	1.1 (0.9–1.3)	<0.001
RD, mm	2.9 (2.5–3.2)	2.7 (2.3–3.1)	0.013	2.7 (2.3–3.1)	2.5 (2.2–3.0)	0.089
DS, %	50.5 (42.6–58.0)	56.5 (48.6–62.4)	<0.001	48.7 (40.3–55.6)	57.3 (49.3–64.4)	<0.001
Lesion length, mm	10.9 (8.2–15.0)	11.7 (8.0–16.2)	0.321	10.6 (8.1–13.4)	12.5 (8.7–17.2)	0.012
DS ≥50%, n (%)	129 (51.8)	80 (72.7)	<0.001	33 (45.2)	238 (72.8)	<0.001
Hemodynamic and coronary physiologic findings						
Baseline						
HR, bpm	66 (60–74)	63 (58–72)	0.068	71 (61–78)	68 (62–77)	0.437
Pa, mm Hg	94 (85–105)	94 (87–101)	0.952	90 (83–102)	93 (85–102)	0.602
Pd, mm Hg	91 (82–101)	88 (81–96)	0.054	83 (75–96)	80 (71–88)	0.005
Tmn, sec.	0.96 (0.64–1.35)	0.96 (0.65–1.30)	0.614	0.82 (0.58–1.04)	0.76 (0.50–1.06)	0.431
DP, mm Hg/min	6110 (5396–7209)	6095 (5167–6992)	0.369	6438 (5244–7904)	6365 (5537–7346)	0.689
Hyperemia						
HR, bpm	74 (65–82)	71 (66–79)	0.152	79 (72–87)	77 (68–83)	0.058
Pa, mm Hg	84 (74–94)	86 (79–92)	0.152	82 (72–96)	83 (74–91)	0.865
Pd, mm Hg	73 (65–83)	64 (59–70)	<0.001	70 (61–80)	57 (50–65)	<0.001
Tmn, sec.	0.27 (0.19–0.42)	0.28 (0.18–0.46)	0.692	0.28 (0.21–0.40)	0.35 (0.24–0.54)	0.007
DP, mm Hg/min	5980 (5159–7056)	6111 (5164–6952)	0.816	6141 (5175–8099)	6216 (5319–7314)	0.372

Continued

Table 3. Continued

Group	dPR_{WFP} Negative Cohort (n=359)			dPR_{WFP} Positive Cohort (n=400)		
	1: FFR− dPR_{WFP}−	2: FFR+ dPR_{WFP}−	*P* Value for 1 vs 2	3: FFR− dPR_{WFP}+	4: FFR+ dPR_{WFP}+	*P* Value for 3 vs 4
Physiological indexes						
Pd/Pa	0.97 (0.94–0.99)	0.95 (0.93–0.97)	<0.001	0.90 (0.89–0.91)	0.86 (0.82–0.89)	<0.001
CFR	3.22 (2.29–4.30)	3.13 (2.12–4.06)	0.256	2.53 (1.79–3.86)	1.95 (1.32–2.89)	<0.001
IMR	20.8 (13.9–29.5)	18.3 (12.2–30.8)	0.140	19.4 (14.3–27.3)	20.3 (14.1–30.6)	0.948
FFR	0.88 (0.85–0.91)	0.77 (0.74–0.79)	<0.001	0.84 (0.82–0.88)	0.72 (0.65–0.75)	<0.001
dPR_{WFP}	0.96 (0.92–0.99)	0.93 (0.91–0.96)	<0.001	0.87 (0.85–0.88)	0.81 (0.74–0.86)	<0.001

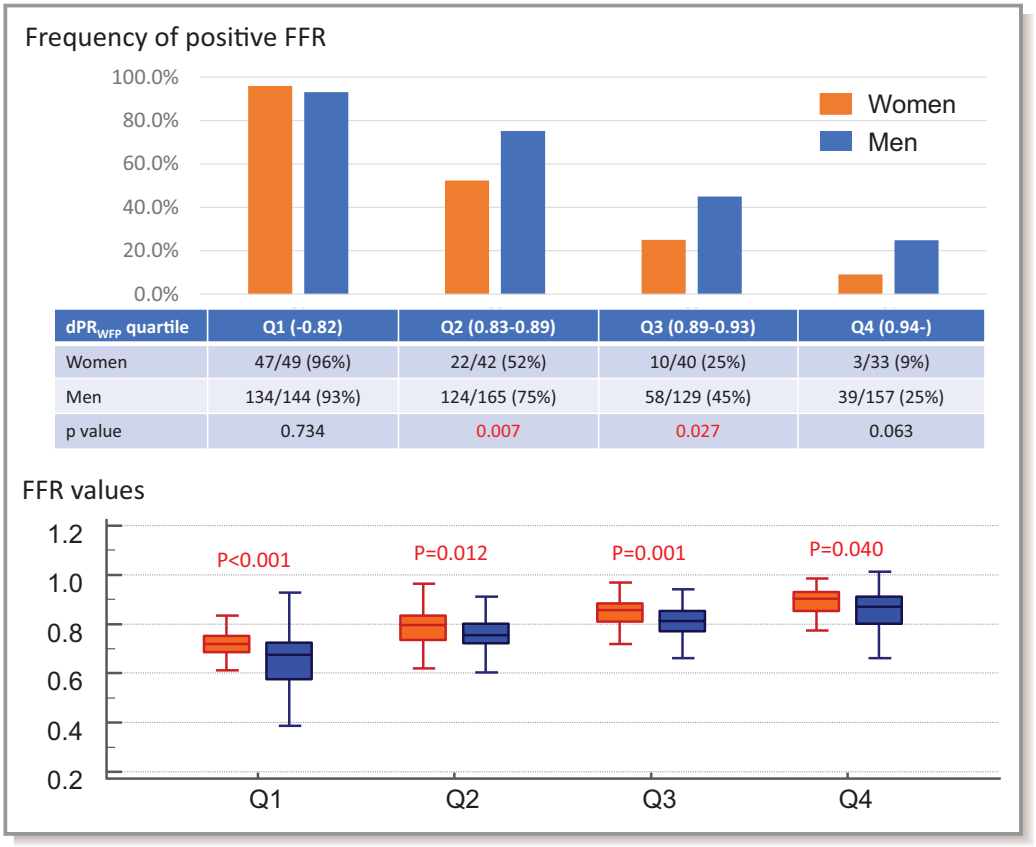
Bpm indicates beats per minute; CFR, coronary flow reserve; dPR_{WFP}, diastolic pressure ratio during the diastolic wave-free period; DP, double product; DS, diameter stenosis; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; IMR, index of microcirculatory resistance; LAD, left anterior-descending artery; LDL-C, low-density lipoprotein cholesterol; MLD, minimal lumen diameter; Pa, aortic pressure; Pd, distal coronary pressure; RD, reference diameter; Tmn, mean transit time.

the predictors of mismatch between anatomical stenosis, as assessed by quantitative coronary angiography, and physiological significance, assessed by FFR, and demonstrated that older age was a significant predictor of mismatch, indicating negative FFR results in anatomically significant stenosis; and younger age was an independent predictor of reverse mismatch, indicating positive FFR results in anatomically nonsignificant stenosis,[17] which means that FFR tended to be higher for a given stenosis in elderly patients. In line with the previous study, women were significantly older than men in the current study, which may have affected the higher FFR values in women than in men. Nevertheless, multivariable logistic regression analysis showed that female sex was significantly associated with negative FFR in the negative

Table 4. Predictors of FFR-dPR_{WFP} Discordance

Variable	Univariate				Multivariate			
	OR	95% CI Lower	95% CI Upper	*P* Value	OR	95% CI Lower	95% CI Upper	*P* Value
Predictors of positive FFR in negative dPR_{WFP} cohort								
Women	0.42	0.22	0.81	0.009	0.44	0.21	0.98	0.036
Age/10 y	0.70	0.56	0.89	0.004	0.65	0.50	0.86	0.002
Weight	1.01	1.00	1.03	0.096	1.00	0.98	1.02	0.941
DS/10%	1.47	1.19	1.82	<0.001	1.51	1.20	1.89	<0.001
RD	0.69	0.47	1.00	0.052	0.66	0.43	1.02	0.063
HR	0.83	0.67	1.02	0.079	0.98	0.96	1.00	0.097
IMR	0.99	0.98	1.01	0.299	0.98	0.96	1.00	0.050
CFR	0.94	0.81	1.08	0.370	0.84	0.68	1.02	0.079
Predictors of negative FFR in positive dPR_{WFP} cohort								
Women	1.08	0.98	1.19	0.120	2.41	1.17	4.96	0.017
Weight	1.00	0.97	1.02	0.844	1.01	0.98	1.03	0.609
DS/10%	0.92	0.89	0.95	<0.001	0.51	0.39	0.67	<0.001
RD	1.07	1.00	1.14	0.058	1.64	1.01	2.66	0.044
LL	0.99	0.99	1.00	0.023	0.96	0.92	1.01	0.110
IMR	1.00	1.00	1.00	0.720	1.02	1.00	1.04	0.012
CFR	1.05	1.01	1.09	0.007	1.33	1.05	1.67	0.016

CFR indicates coronary flow reserve; dPR_{WFP}, diastolic pressure ratio during the diastolic wave-free period; DS, diameter stenosis; FFR, fractional flow reserve; HR, heart rate; IMR, index of microcirculatory resistance; LL, lesion length; OR, odds ratio; RD, reference diameter.



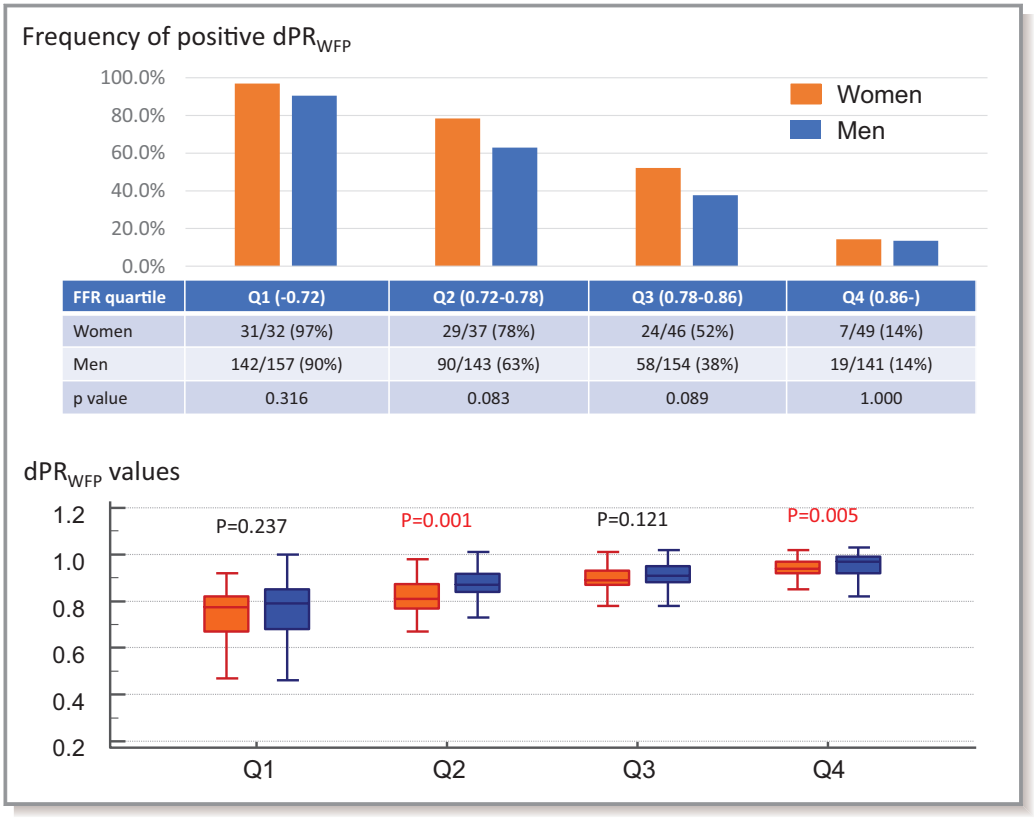
dPR_{WFP} quartile	Q1 (-0.82)	Q2 (0.83-0.89)	Q3 (0.89-0.93)	Q4 (0.94-)
Women	47/49 (96%)	22/42 (52%)	10/40 (25%)	3/33 (9%)
Men	134/144 (93%)	124/165 (75%)	58/129 (45%)	39/157 (25%)
p value	0.734	0.007	0.027	0.063

Figure 2. Frequency of positive fractional flow reserve (FFR) and FFR value in each diastolic pressure ratio during the diastolic wave-free period (dPR_{WFP}) quartile (Q). **Top**: The frequency of positive FFR in women and men in each dPR_{WFP} Q. FFR was significantly less frequently positive (≤0.80) in women in the second and third Qs (0.83–0.93) of dPR_{WFP}. **Bottom**: Comparison of FFR values between sexes in each dPR_{WFP} Q. FFR was higher in women than in men in all dPR_{WFP} Qs.

dPR_{WFP} cohort, independent of age (Table 4), which suggested that the difference in age by itself does not explain the sex difference of our results. Impaired microvascular function in women was reported in previous studies,[18,19] which can be one of the mechanisms of higher FFR values. As an animal study has shown that FFR value increased as the downstream microvascular resistance increased,[20] FFR may be higher if the microvascular resistance is higher in women. However, microvascular dysfunction in women has been advocated on the basis of the lower CFR in the previous studies. Kobayashi et al assessed the sex difference in microvascular indexes in nonobstructive lesions and revealed that lower CFR in women was attributable to higher resting coronary flow rather than lower hyperemic flow and the IMR was not different between men and women.[15] Supporting their hypothesis, the previous studies using positron emission tomography showed even higher hyperemic myocardial blood flow in women than in men[21,22]; therefore, it is controversial whether men or women show higher coronary flow at hyperemia. Sex difference in myocardial resistance has not been intensively investigated in vivo. In the present study, IMR showed nonsignificant trend toward lower value in women than in men, which might have been affected by smaller subtended myocardial mass in women. Hyperemic coronary flow velocity, absolute flow volume, and myocardial resistance vary according to the modality for measurements, patient characteristics, or the coronary anatomical characteristics. Further investigation is needed to clarify the extent and mechanisms of sex difference in hyperemic coronary physiological characteristics. In addition to the patient characteristics that showed significant sex differences in the present study, including age, prevalence of current smoking, or lipid profiles, undetermined factors, such as ventricular myocardium volume and endothelial function, might have affected the FFR value as clustering factors of women-specific characteristics. Further studies are needed to clarify the mechanisms of the sex difference in FFR value.

Sex Difference in dPR_{WFP}

In addition to FFR that requires administration of adenosine to acquire maximal hyperemia, resting indexes, including iFR,



FFR quartile	Q1 (-0.72)	Q2 (0.72-0.78)	Q3 (0.78-0.86)	Q4 (0.86-)
Women	31/32 (97%)	29/37 (78%)	24/46 (52%)	7/49 (14%)
Men	142/157 (90%)	90/143 (63%)	58/154 (38%)	19/141 (14%)
p value	0.316	0.083	0.089	1.000

Figure 3. Frequency of positive diastolic pressure ratio during the diastolic wave-free period (dPR$_{WFP}$) and dPR$_{WFP}$ value in each fractional flow reserve (FFR) quartile (Q). **Top**: The frequency of positive dPR$_{WFP}$ in women and men in each FFR Q. Positive dPR$_{WFP}$ showed nonsignificant trend toward a higher frequency in women than in men. **Bottom**: The comparison of dPR$_{WFP}$ value between sexes in each FFR Q. dPR$_{WFP}$ was lower in the second and fourth Qs.

dPR$_{WFP}$, and resting full-cycle ratio, have been increasingly used recently in the catheterization laboratory, given the user-friendly features and supportive evidences.[4,5,11] Different algorithms have been proposed by different vendors and laboratories, of which iFR measured with a proprietary software provided by a single vendor is the only index clinically validated by large clinical trials. Although the differences among the definitions of resting indexes are attributed to the time window within the cardiac cycle for the analysis, those indexes have been shown to exhibit almost identical values with iFR.[11,23] dPR is one of the resting indexes that is originally defined as the average Pd/Pa ratio over the entire diastole.[24] In a previous study comparing the diagnostic agreement with iFR of dPR$_{WFP}$ measurements with different time windows, including dPR in entire diastole, dPR from 25% to 75% in diastole, dPR in mid diastole, and dPR in WFP, those resting indexes demonstrated almost similar diagnostic performance, with an area under the curve of ≥0.995 and small absolute difference from iFR <0.01.[11] The present study used dPR$_{WFP}$ analyzed in the core laboratory, which is a simulated iFR by its definition. There have been limited reports on the sex difference in resting indexes. Shah et al evaluated the sex difference in the diagnostic accuracy of iFR in comparison with FFR as the standard in a subanalysis of CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) study.[14] In their study, the iFR value and the frequency of positive iFR results were not different between men and women in each category stratified by visual diameter stenosis. In the present study, although the frequency of positive dPR$_{WFP}$ was not statistically different between the sexes when stratified by FFR quartiles (Figure 3, top), there existed signs toward lower dPR$_{WFP}$ values in women (Figure 3, bottom), which was the opposite trend to higher FFR values for the given dPR$_{WFP}$ in women. Thus, the present study revealed a statistically marginal trend of lower dPR$_{WFP}$ in women than in men for given FFR values, especially in intermediate stenosis ranging from FFR 0.72 to 0.86.

Clinical Outcomes in Women After Physiological Characteristic–Guided PCI

Although the FFR value was shown to be higher in women than in men, the identical threshold FFR ≤0.80 has been used

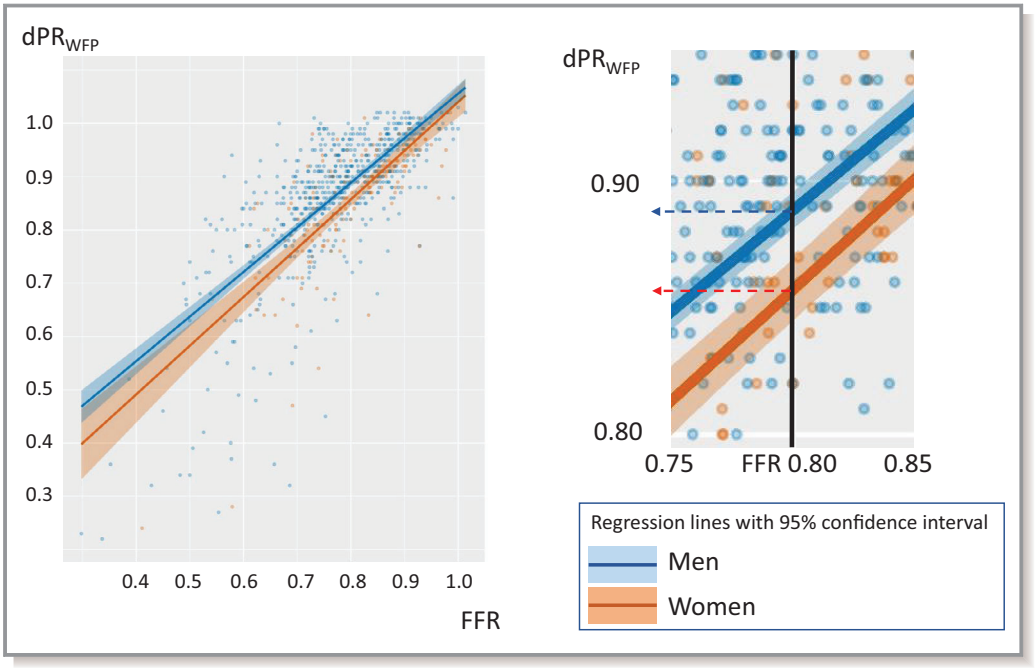


Figure 4. Scattergrams and linear regression lines between fractional flow reserve (FFR) and diastolic pressure ratio during the diastolic wave-free period (dPR_{WFP}) in men and women. Linear regression lines with 95% CIs for men and women are depicted. The regression line for women is located below that for men, which indicates the distribution shift to higher FFR and lower dPR_{WFP}. Two lines were separated in the middle of the chart, whereas there were overlaps between the 2 lines in both ends of the chart. The middle part of the chart around FFR 0.80 is magnified in the right panel. The reference line of FFR 0.80 (black line) and the corresponding points for men (blue dashed line) and for women (red dashed line) are overlaid.

in both sexes. In the substudy of FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, major adverse cardiac event rate was not different between men and women 2 years after FFR-guided PCI (17.3% versus 19.2%; *P*=0.657), even after adjustment with baseline risk factors,[8] by which the application of the same FFR threshold, 0.80, to both sexes has been justified. For iFR-guided PCI, a post hoc analysis of DEFINE-FLAIR (Functional Lesion Assessment of Intermediate stenosis to guide Revascularisation) study showed that major adverse cardiovascular event rates were not different between iFR- and FFR-guided strategies in both women and men, which mean it may be reasonable to use the same threshold of iFR in women as men.[16] However, the nonsignificant difference in major adverse cardiovascular event rate between men and women by applying the same cutoff FFR value does not necessarily indicate that the optimal FFR thresholds for men and women are the same. In other words, if another optimal cutoff threshold is given to women, this may potentially result in better clinical outcomes in women than in men. In fact, the relative risk reductions of FFR-guided PCI to angiographically-guided PCI for death, myocardial infarction, and revascularization were 37%, 42%, and 17% in men and 18%, 27%, and 17% in women, respectively, in FAME trial, which were numerically greater in men than in women, although they did not reach statistical significance. Also in the subanalysis of DEFINE-FLAIR, Kaplan-Meier curves showed nonsignificant trend for higher cumulative major adverse cardiovascular event rate in iFR-guided group than in FFR-guided group within the first 10 months in women, and vice versa in men, which may indicate a difference in risk reduction with physiological characteristic–guided PCI between the sexes. Better cutoff value of those indexes for women may result in more risk reduction with physiological guidance for PCI. Nevertheless, in clinical practice, there is wide agreement not to apply sex-specific FFR or resting index threshold for revascularization decision making, which may need further discussion.

Thresholds of FFR and dPR_{WFP} in Women

Our results, in line with previous studies, showed nonsignificant sex difference in dPR_{WFP} value (women: 0.88 [0.81–0.93]; and men: 0.89 [0.83–0.95]; *P*=0.150) in the total cohort in the absence of difference in angiographical stenosis severity, whereas FFR showed significantly higher values in women than in men (women: 0.80 [0.73–0.88]; and men: 0.78 [0.71–0.85]; *P*=0.007). In terms of dPR_{WFP} and FFR categorizations, the lesions in women tended to be distributed into the section with negative (higher) FFR and positive (lower) dPR_{WFP} in comparison with those in men (Figure 1). A recent

study by Lee et al, composed of 840 vessels, showed that patient-oriented adverse event rates at 5 years in deferred lesions with iFR-FFR discordance were not significantly different from rates in those with concordantly negative iFR and FFR.[25] Therefore, the discordance between dPR_{WFP} and FFR may not have a direct impact on the clinical outcomes in total cohort including both sexes. However, the study did not perform sex-specific analysis, and it is still unclear whether the same iFR and FFR thresholds can be applied to both sexes. Besides, both iFR and FFR are continuous values and it has been shown that lower values are linearly correlated with worse clinical outcomes,[26] which may highlight the importance of the distribution of the indexes as continuous variables. Consistent with categorical distribution, the linear regression line between dPR_{WFP} and FFR for women was shifted to the direction toward higher FFR and lower dPR_{WFP} (Figure 4). Hence, one concern may arise: FFR tends to be higher and the resting indexes show oppositely lower values in women; however, both FFR and resting index have the same threshold for women as men. If the best clinically accepted threshold of the FFR value to provide the best clinical outcomes for women as well as men is ≤0.80, the best threshold dPR_{WFP} for women might be lower considering the distribution shift, as shown in Figure 4, specifically calculated in the present study as ≤0.86 for women and ≤0.89 for men (Figure S3). Furthermore, it has been shown that there still exists residual risk for subsequent events after physiological characteristic–guided PCI or deferral in previous trials, which may indicate the room for optimization of the threshold for decision making. Currently, there has been no definitive evidence that tested the optimization of FFR or iFR cutoff value for clinical outcomes. Sex-specific threshold may be a part of the research avenue. Although this is a hypothesis and the determination of the optimal values lies outside the scope of the present study, further studies are warranted to identify the standard modality and the best cutoff threshold for decision making based on the best clinical outcome as the gold standard.

Limitations

This study has some limitations. First, this is a single-center, retrospective study and the analysis included the intermediate lesions arbitrarily defined with diameter stenosis between 30% and 80%, which may have led to a selection bias. Second, given the lack of longitudinal outcome data, the impact of sex difference and FFR-dPR_{WFP} discordance on clinical outcomes could not be determined. Third, this registered database lacked the detailed information on medication, such as β blocker, which has been reported to be associated with FFR and resting index measurements. Moreover, the morphological pattern, focal or diffuse, has been reported to be associated with the discordance between FFR and iFR,[27] which was not available in the present study. Fourth, this is a relatively large cohort composed of 759 lesions from 577 patients; however, it is still underpowered for the extensive subgroup analysis to determine the impact of each sex-specific characteristic because of the limited number of FFR-dPR_{WFP}. Finally, the current data lack measurements of ventricular mass, which may be largely associated with sex and physiological indexes.

Conclusions

Sex was significantly associated with the frequency of disagreement between FFR- and dPR_{WFP}-guided revascularization decision making, independent of age, anatomical stenosis, and other confounders, which may raise a hypothesis about the need for sex-specific threshold optimizations of physiological indexes.

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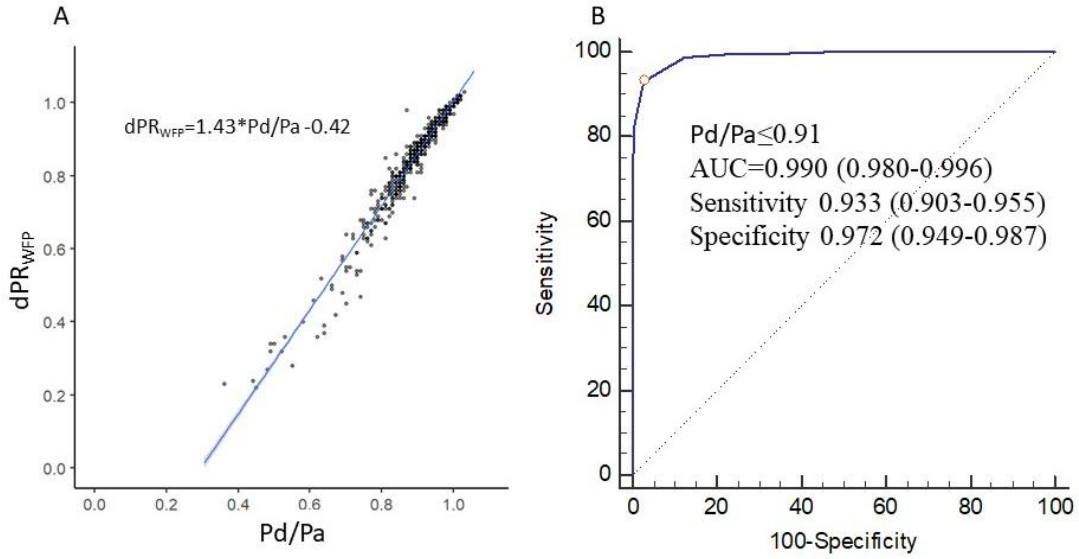
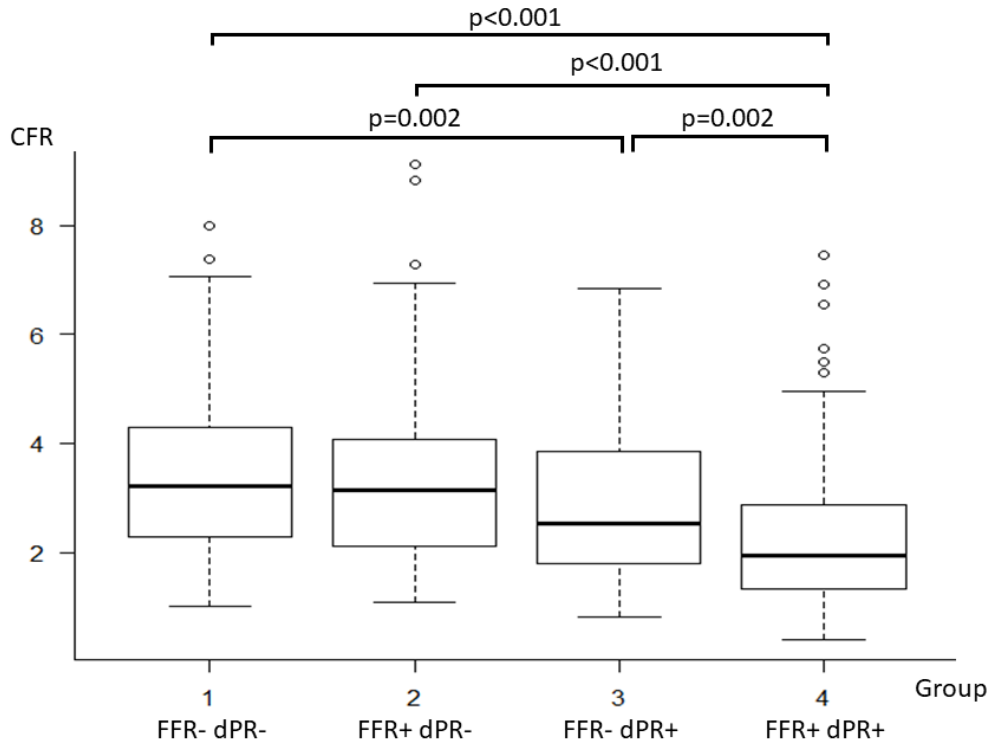
SUPPLEMENTAL MATERIAL

Figure S1. Linear regression analysis between Pd/Pa and dPR_{WFP} and ROC analysis to determine the best cut-off Pd/Pa to predict $dPR_{WFP} \leq 0.89$.



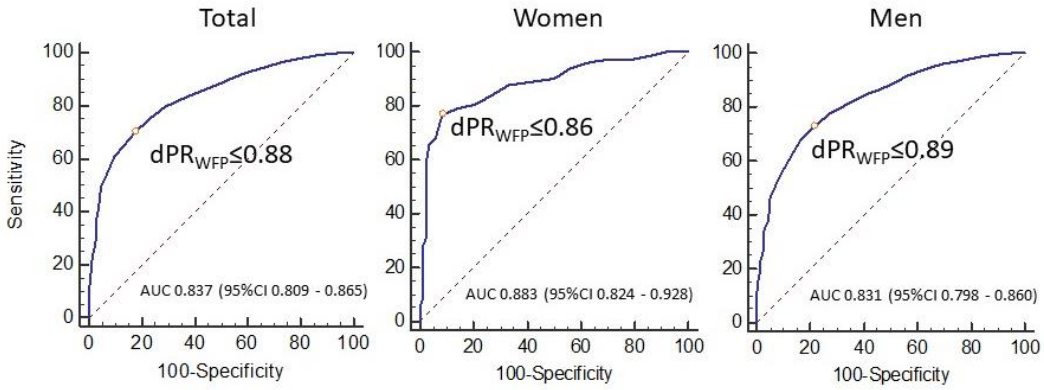
Linear regression analysis (A) and ROC analysis (B) showed highly correlated dPR_{WFP} and Pd/Pa.

Figure S2. Comparison of coronary flow reserve among the groups according to FFR and dPR_{WFP} categorization.



Median CFR was 3.22 (2.29-4.30), 3.13 (2.12-4.06), 2.53 (1.79-3.86), and 1.95 (1.32-2.89) respectively from Group 1 through 4. CFR was significantly lower in Group 4 as compared with Group 1, 2, and 3. Group 3 showed lower CFR value than Group 1.

Figure S3. Receiver operator characteristics (ROC) curves to identify the best cut-off dPR_{WFP} with reference to FFR.



	Value	95% CI
Sensitivity	0.748	0.705-0.788
Specificity	0.773	0.724-0.818
PPV	0.818	0.776-0.854
NPV	0.694	0.643-0.741
Accuracy	0.759	0.727-0.789

	Value	95% CI
Sensitivity	0.768	0.662-0.854
Specificity	0.915	0.832-0.965
PPV	0.900	0.814-0.948
NPV	0.798	0.726-0.855
Accuracy	0.841	0.776-0.894

	Value	95% CI
Sensitivity	0.727	0.677-0.772
Specificity	0.788	0.730-0.838
PPV	0.835	0.797-0.867
NPV	0.661	0.619-0.700
Accuracy	0.751	0.714-0.786

In total cohort (right panel), area under curve (AUC) was 0.837 and the optical cut-off dPR_{WFP} value was 0.88. The best cut-off dPR_{WFP} value was 0.86 in women (middle panel) and 0.89 in men (right panel).