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Predictors of discordance between fractional flow reserve (FFR) and diastolic pressure ratio (dPR) in intermediate coronary lesions

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ABSTRACT

Background: Recently, non-hyperemic pressure ratios (NHPRs) have been validated as a reliable alternative to fractional flow reserve (FFR). However, a discordance between FFR and NHPRs is observed in 20–25% of cases. The aim of this study is to evaluate predictors of discordance between FFR and diastolic Pressure ratio (dPR).

Methods: PREDICT is a retrospective, single center, investigator-initiated study including 813 patients (1092vessels) who underwent FFR assessment of intermediate coronary lesions (angiographic 30%-80% stenosis). dPR was calculated using individual pressure waveforms and dedicated software. Clinical, angiographic and hemodynamic variables were compared between patients with concordant and discordant FFR and dPR values.

Results: Median age was 65 (IQR:59–73) years and 70% were male. Hemodynamically significant lesions, as defined by FFR $\leq$ 0.80, and dPR $\leq$ 0.89, were identified in 29.6% and 30.3% of cases, respectively. Overall, FFR and dPR values were discordant in 22.1% patients (17.4% of the vessels). Discordance was related to FFR+/dPR- and FFR-/dPR + in 11.8% and 10.3% of patients, respectively.

In case of FFR-dPR discordance, a higher prevalence of left anterior descending arteries lesions was observed (70.5% vs. 53.1%, $p < 0.001$) and mean values of both FFR and dPR were significantly lower (FFR 0.81 $\pm$ 0.05 vs 0.85 $\pm$ 0.08, $p < 0.001$, and dPR 0.89 $\pm$ 0.04 vs 0.92 $\pm$ 0.08,$p < 0.001$) as compared to vessels with FFR and dPR concordance. Following multivariable adjustment, dPR delta (defined as the absolute difference between measured dPR to the cut-off value of 0.89) turned out to be the only independent predictor of discordance (OR = 0.74, 95% CI 0.68–0.79, $p < 0.001$).

Conclusion: Our study suggests that FFR-to-dPR discordance occurs in approximately one-fifth of patients. Absolute dPR delta appears to be the only independent predictor of discordance.

1. Introduction

Physiological assessment using either fractional flow reserve (FFR) or instantaneous Wave-free ratio (iFR) is currently recommended for assessing the ischemic potential of an intermediate coronary artery stenosis when evidence of non-invasive ischemia testing is lacking [1–5]. FFR measurement requires administration of a vasodilatory drug to obtain a steady state of coronary hyperemia, which has been linked to transient side effects, prolongation of the procedure and extra costs [6–7]. To overcome these limitations, several non-hyperemic pressure ratios (NHPR) have been proposed as alternatives to FFR, as they have shown to be non-inferior in predicting major adverse cardiac events in large clinical outcome trials [8–12]. While most studies tested the patented iFR algorithm, recent evidences suggest that a variety of (generic) NHPRs had a nearly 100% correlation to iFR and thus, could also be used as a diagnostic alternative to FFR [7–8].

Abbreviations: ACS, Acute coronary syndrome; AUC, Area under the curve; CI, Confidence Interval; dPR, diastolic Pressure Ratio; FFR, Fractional flow reserve; HR, Hazard Ratio; iFR, Instantaneous Wave free ratio; IQR, Interquartile range; LAD, Left Anterior Descending; MACE, Major adverse cardiovascular events; NHPR, Non-hyperemic pressure ratio; PCI, Percutaneous coronary intervention; ROC, Receiver operating characteristic.

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Among those, diastolic pressure ratio (dPR), is a recently validated NHPR that can be obtained from any type of pressure wire or microcatheter using a dedicated software [7].

However, as NHPR is measured during resting conditions, a discordance between FFR and NHPRs has been observed in 20–25% of cases. As of to date, the mechanism of this discordance phenomenon has not been fully clarified [12–14].

Therefore, we sought to investigate clinical, angiographic and hemodynamic factors which contribute to FFR/dPR discordance.

2. Methods

PREDICT (Predictors of discordance between physiological indices in coronary arteries) is a retrospective, single center, investigator-initiated study which included patients with intermediate coronary artery disease who underwent coronary angiography and FFR measurements between November 1st, 2018, and December 31st, 2020.

Ethical approval was waived for this study by the Institutional Review Board of the Erasmus University Medical Center.

2.1. Patients and study settings

Patients $\geq$ 18 years old with stable angina or acute coronary syndrome (ACS) and at least one intermediate coronary artery disease (defined as angiographic 30% to 80% stenosis by visual estimation or online quantitative coronary angiography) were included. For patients presenting with ACS, only non-culprit lesions were assessed.

Exclusion criteria were 1) previous coronary artery bypass surgery, 2) chronic total occlusion in the target vessel, 3) adenosine intolerance, 4) pressure waveforms tracings not available, 5) pressure waveforms tracings with dampening or with drift larger than $>$ 0.03.

Comorbidities, as arterial hypertension, dyslipidemia, diabetes and chronic kidney disease, were defined using standard definition, according to European Society of Cardiology and Kidney disease Improving Global Outcomes guidelines [15–17].

2.2. Study procedure

All procedures were performed according to standard local clinical practice. Pressure measurements were performed after administration of an intracoronary bolus of nitrates (100–200 μg), in case there was doubt on the hemodynamic significance of intermediate coronary artery lesions. A 5F to 7F guiding catheter was used in all cases. The pressure–temperature sensor guide wire (PressureWire X, Abbott Vascular, St. Paul, Minnesota) was zeroed, equalized to aortic pressure, and then positioned at the distal segment of the target vessel. Coronary artery distal pressure (Pd) and aortic pressure (Pa) curves were acquired simultaneously at baseline (resting condition) and during administration of intravenous adenosine (hyperemic condition): Pd signal was obtained from a guidewire with a piezoresistive pressure transducer, and the Pa signal was obtained from the fluid-filled guiding catheter. Maximal hyperemia was achieved by a continuous intravenous infusion of adenosine at a rate of 140 μg/kg/min through an antecubital vein. After measurements were completed, the guidewire was pulled back to the guide catheter, and the presence of pressure drift was checked. FFR was calculated as the ratio of mean Pd to mean Pa during maximal hyperemia. The FFR was taken as the lowest stable value of the Pd/Pa ratio during maximal hyperemia. Pressure waveform data was prospectively collected for all cases and stored in a local database.

The dPR was defined by the ratio between the mean diastolic pressure distal to the stenosis and the mean diastolic aortic pressure in resting conditions. The diastolic period used to calculate the dPR was automatically delineated based on the pressure difference between sample (dP)/time difference between the same sample points (dt) curve of the aortic pressure at the point at which the resistance was low, constant, and stable. The dP/dt curve represents the increase and decrease of the pressure over time during the heart cycle. dP is the pressure difference between sample points, and dt is the time difference between the same sample points. The flat line of the dP/dt tracing was used as trigger for the software to detect the wave-free period within the range of 60% to 80% of the cardiac phase as a first default. [7].

Tracing data with a duration of 4 heartbeats or longer from each individual Dicom pressure waveform were retrospectively collected by a single analyst (AS), blinded to the FFR values and stored into a dedicated image archive. dPR was calculated off-line and post hoc in the context of this study and was therefore not available at the time of the revascularization.

The decision to perform revascularization was left at the operator's discretion and per local practice typically based on the FFR value.

2.3. Outcomes of interest

The goal of the study was to identify predictors of discordance between FFR and dPR. Established cut-off values of pressure-derived physiologic indices (FFR $\leq$ 0.80, and dPR $\leq$ 0.89) were used to dichotomize stenosis into concordantly classified (FFR+/dPR + and FFR–/dPR–) and discordantly classified (FFR+/dPR– and FFR-/dPR +) groups. As a secondary outcome of interest, we assessed the correlation and diagnostic accuracy between dPR and FFR. Absolute dPR delta was defined as the absolute difference (either positive or negative), from the measured dPR to the cut-off value (0.89).

2.4. Data collection and statistics

Demographic data, cardiovascular risk factors, clinical diagnoses, and procedural details were collected for each patient.

Categorical variables are expressed as number and percentages, continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Continuous variables related to coronary physiology are expressed as mean ± SD. Differences in patient-level characteristics between patients with discordant, defined as at least one vessel with discordant values and concordant (all vessels concordant) physiological indices were tested using unpaired t-tests or nonparametric Mann-Whitney U tests for comparisons of continuous variables and chi-square tests for categorical variables. For vessel-level variables, (generalized) linear mixed effect models with random intercepts were built to evaluate these differences while accounting for the clustering of vessels in patients.

A multivariate generalized linear mixed effect model with random intercepts was built to further identify predictors of discordance between FFR and dPR. Baseline variables with p-value $<$ 0.10 when tested univariately were entered in the full model, provided that they had $<$30% missing data.

Diagnostic performance of dPR against the gold standard of FFR was assessed by calculation of the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. Receiver operation characteristics (ROC) curve with area under the curve (AUC) was determined with FFR as a reference standard using a threshold of 0.80 [18]. All tests were two-tailed and a P value $<$ 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS (version 24.0, SPSS Inc., Chicago, Illinois, US) and R (R Core Team 2019; version 3.5.2).

3. Results

From November 2018 to December 2020, a total of 813 patients, corresponding to 1092 vessels, were included.

Patient baseline and procedural characteristics stratified according FFR/dPR discordance, are summarized in Table 1. The median age was 65 (IQR: 59 – 73) years, and 569 (70%) were men. Stable angina was the presenting symptom in 67.4% of the patients whereas 32.6% presented with acute coronary syndrome. No statistically significant differences in

Table 1
Patient baseline and procedural characteristics. Values are displayed as median (IQR) or % (n).

	Total (n) (N = 813)	FFR-dPR concordant (N = 633)	FFR-dPR discordant (N = 180)	p-value
Baseline characteristics on patient-level				
Age, yrs [IQR]	65 [59–73]	65 [59–73]	66 [60–73]	0.255
Male gender % (n)	70 (569)	69.8 (442)	70.6 (127)	0.883
Hypertension % (n)	62.5 (508)	61.3 (388)	66.7 (120)	0.272
Hypercholesterolemia % (n)	59.1 (59.1)	58.5 (370)	61.7 (110)	0.305
Diabetes % (n)	25.8 (210)	25.6 (162)	27.2 (49)	0.330
Current smoker % (n)	20.2 (164)	20.2 (128)	20.0 (36)	0.184
CKD (eGFR < 60 ml/min)% (n)	18.8 (153)	17.6 (113)	22.8 (41)	0.237
COPD % (n)	7.5 (61)	7.4 (47)	7.8 (14)	0.223
Atrial fibrillation % (n)	6.6 (54)	6.2 (39)	8.3 (15)	0.341
Prior stroke % (n)	8.9 (72)	7.3 (46)	13.3 (26)	0.265
Peripheral artery disease %(n)	8.0 (65)	7.3 (46)	10.6 (19)	0.145
Prior PCI % (n)	38.9 (316)	38.1 (241)	41.7 (75)	0.682
Prior PCI in target vessel	22.5 (183)	20.7 (131)	28.9 (52)	0.040
Prior MI	19.2 (156)	19.3 (122)	18.9 (34)	0.897
Prior MI in target vessel	7.7 (63)	7.7 (49)	7.8 (14)	0.140
Indication for PCI				
Stable angina % (n)	67.4 (548)	67.0 (424)	68.9 (124)	0.739
Unstable angina % (n)	6.6 (54)	6.8 (43)	6.1 (11)	
NSTEMI % (n)	18.9 (154)	19.3 (122)	17.8 (32)	
STEMI % (n)	7.0 (57)	7.0 (44)	7.2 (13)	
Echocardiographic data				
LVEF				
Good (>50%)	80.4 (477/593)	79.9 (366/458)	82.2 (111/135)	0.482
Moderate (30–49%)	12.3 (73/593)	12.4 (57/458)	11.9 (16/135)	
Poor (<30%)	7.3 (43/593)	7.6 (35/458)	5.9 (8/135)	
Procedural characteristics on patient-level				
Heart rate (bpm/min) [IQR]	70 [63–79]	69.8 [63–79]	70.4 [63–82]	0.405
Left Bundle Branch Block % (n)	9.9 (81)	11.3 (72)	5.0 (9)	0.360
Systolic Blood Pressure (mmHg) [IQR]	126 [112–142]	125 [111–142]	126.5 [113–141]	0.717
Diastolic Blood Pressure (mmHg) [IQR]	67.0 [60–74]	67 [60–75]	68 [59–74]	0.872
Heart rhythm				
Sinus rhythm % (n)	91.4 (759)	93.8 (594)	91.7 (165)	0.302
Atrial Fibrillation % (n)	6.6 (54)	6.2 (39)	8.3 (15)	

Abbreviations: bpm = beat per minute, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NSTEMI = non ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

baseline characteristics were observed between patients with at least one FFR/dPR discordant value and patients without FFR/dPR discordance.

Lesion and hemodynamic characteristics of all groups are summarized in Table 2. A total of 613 (56.1%) interrogated vessels were left anterior descending arteries (LAD), 230 (21.1%) were left circumflex arteries, 13 (1.2%) were isolated left main stems, and 236 (21.6%) were right coronary arteries. In the overall population, hemodynamically significant lesions, defined by FFR ≤ 0.80, and dPR ≤ 0.89, were identified in 29.6%, and 30.3% of cases, respectively. Mean FFR was 0.84 ± 0.08, and mean dPR was 0.92 ± 0.08, respectively. Overall, FFR and dPR values were discordant in 190 (17.4%) vessels, corresponding to 180 (22.1%) patients with at least one discordant value. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of dPR ≤ 0.89 for FFR ≤ 0.80 were 72%, 87%, 70%, 88%, and 83%, respectively. dPR showed a strong correlation (r = 0.74) and high discriminative ability as expressed by the AUC (0.88, 95% CI: 0.86–0.90) in predicting FFR ≤ 0.80 lesions (Supplementary Figs. 1 and 2).

Table 2
Lesion and hemodynamic characteristics. Values are displayed as mean ± standard deviation or % (n).

	Total (n) (N = 1092)	FFR-dPR concordant (N = 902)	FFR-dPR discordant (N = 190)	p-value
Procedural characteristics on vessel level				
Vessel identification				
Left Main % (n)	1.2 (13)	1.3 (12)	0.5 (1)	
Left Anterior Descending % (n)	56.1 (613)	53.1 (479)	70.5 (134)	**< 0.001**
Left Circumflex % (n)	21.1 (230)	22.0 (198)	16.8 (32)	
Right coronary artery % (n)	21.6 (236)	23.6 (213)	12.1 (23)	
FFR positive lesions % (n)	29.6 (323)	25.7 (232)	47.9 (91)	**< 0.001**
dPR positive lesions % (n)	30.3 (331)	25.7 (232)	52.1 (99)	**< 0.001**
Mean FFR	0.84 ± 0.08	0.85 ± 0.08	0.81 ± 0.05	**< 0.001**
Mean dPR	0.92 ± 0.08	0.92 ± 0.08	0.89 ± 0.04	**< 0.001**

Abbreviations: bpm = beat per minute, dPR = diastolic pressure ratio FFR = fractional flow reserve.

In case of FFR-dPR discordance, a higher prevalence of LAD lesions was observed (70.5% vs. 53.1%, p < 0.001). Moreover, mean values of both FFR and dPR were significantly lower (FFR 0.81 ± 0.05 vs 0.85 ± 0.08, p < 0.001, and dPR 0.89 ± 0.04 vs 0.92 ± 0.08, p < 0.001) in vessels with FFR-dPR discordance as compared to vessels that were FFR-dPR concordant (Table 2).

The distribution of concordant and discordant cases is shown in Fig. 1. Near the dPR cut-off value for hemodynamic significance (0.89), there is less certainty, with a classification agreement between dPR and FFR at its lowest in the dPR 0.87–0.92 range value.

3.1. Independent predictors of discordance between FFR and dPR

The results of the multivariate linear regression analysis are shown in Table 3. Univariate predictors of discordance were arterial hypertension (OR = 1.32), LAD artery location (OR = 2.11) and absolute dPR delta (OR = 0.75). Following multivariable adjustment, absolute dPR delta was the only independent predictor of discordance between dPR and FFR (OR = 0.74 for every 0.01 increase in absolute dPR delta, p < 0.001). More specifically, every 0.01 increase in absolute dPR delta was associated with a decreased risk of discordance, with an odds ratio of 0.75. No significant associations were present among the predictors, including LAD location and dPR delta.

3.2. Differences between FFR+/dPR- and FFR-/dPR + discordance

The patient characteristics of the FFR/dPR discordant groups, namely FFR+/dPR- and FFR/dPR + groups are summarized in Supplementary Table 1. Overall, FFR+/dPR- and FFR/dPR + were observed in 99 (9.1%) and 91 (8.3%) vessels, corresponding to 96 (11.8%) and 84 (10.3%) patients, respectively. In comparison to the FFR+/dPR- group, the FFR-/dPR + group demonstrated a significantly higher proportion of female patients (34% vs 19%, p = 0.002), a higher prevalence of chronic kidney disease (29% vs 12%, p < 0.001), peripheral artery disease (13% vs 6%, p = 0.036) and impaired left ventricular function (6% vs 2%, p = 0.046).

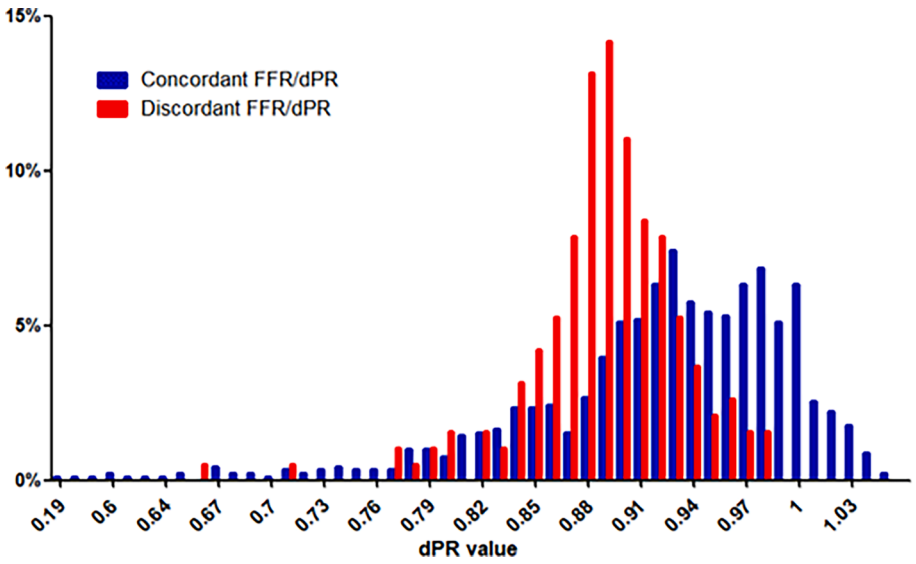

Fig. 1. Distribution of concordant (blue) and discordant (red) FFR/dPR cases according to dPR value expressed as percentage. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

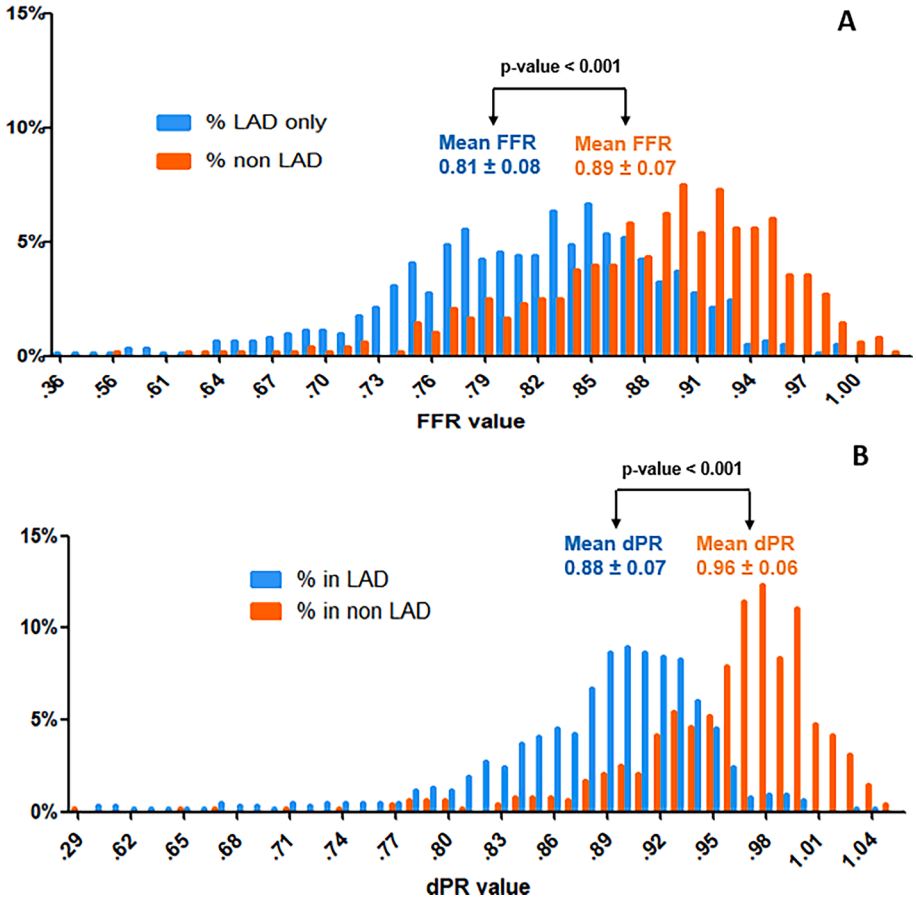

Fig. 2. Distribution of FFR and dPR value according to lesion location in the left anterior descending (LAD) (blue) versus non-LAD vessels (orange) expressed as percentage (Fig A, B). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Absolute dPR delta remained the only independent predictor of discordance of FFR-/dPR + lesions (OR = 0.78 for every 0.01 increase in absolute dPR delta, $p < 0.001$). Conversely, clinical characteristics as younger age, male sex, and heart rate next to absolute dPR delta appeared to be predictors of FFR+/dPR- lesions. The results of the multivariate linear regression analyses are shown in Supplementary Tables 2 and 3.

3.3. LAD versus non-LAD location

The distribution of FFR and dPR values according to lesion location is shown in Fig. 2. FFR and dPR positive lesions were significantly more

Table 3
Univariate and multivariate predictors of FFR- dPR discordance.

Variables	Univariate analysis		Multivariate analyses	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.01 (0.99–1.02)	0.42		
Prior MI	1.07 (0.71–1.59)	0.74		
Prior PCI	1.13 (0.82–1.56)	0.45		
Sex	1.01 (0.72–1.44)	0.95		
Arterial hypertension	**1.32 (0.95–1.86)**	**0.10**	1.43 (1.00–2.10)	0.053
Diabetes	1.13 (0.78–1.62)	0.51		
Hypercholesterolemia	1.21 (0.87–1.68)	0.26		
Smoke	0.93 (0.61–1.38)	0.72		
COPD	1.14 (0.61–2.00)	0.66		
Peripheral artery disease	1.41 (0.80–2.43)	0.21		
Atrial fibrillation during procedure	1.53 (0.83–2.72)	0.15		
Chronic kidney disease (eGFR < 60 ml/min)	1.08 (0.38–2.65)	0.88		
Heart rate	1.01 (1.00 – 1.02)	0.17		
Reason for PCI (stable vs ACS)	1.07 (0.76–1.52)	0.71		
Systolic Blood Pressure	1.00 (0.99–1.01)	0.95		
Vessel LAD	**2.11 (1.51–3.02)**	**< 0.001**	0.84 (0.55–1.26)	0.40
Bundle Branch Block	0.98 (0.62–1.49)	0.93		
Impaired LVEF	0.98 (0.60–1.55)	0.94		
Absolute dPR delta Per 0.01 increase	0.75 (0.69–0.80)	**< 0.001**	**0.74 (0.68–0.79)**	**< 0.001**

Abbreviations as in Tables 1 and 2.

frequent in the LAD as compared to other locations (FFR 42% vs 14% p < 0.001, and dPR 46% vs 10% p < 0.001, respectively). In the LAD group, mean FFR and dPR values were significantly lower as compared to other lesion locations (FFR 0.81 vs 0.90 p < 0.001, and dPR 0.88 vs 0.96 p < 0.001, respectively) (Fig. 2 and Supplementary Table 4).

Comparisons of diagnostic accuracy, sensitivity, and specificity between LAD versus other lesion locations are shown in Supplementary Fig. 1. The diagnostic accuracy of dPR was significantly lower in the LAD as compared to other vessel locations (78% vs 88%, p < 0.001) resulting in a higher number of discordances between FFR and dPR in the LAD (21.9%) vs. non-LAD lesion locations (11.7%) (Supplementary Table 4).

The correlation between FFR and dPR is shown in Supplementary Figure 3. dPR was significantly correlated with FFR, regardless of the lesion location (r = 0.69 in LAD group vs r = 0.65 in non-LAD group, p = 0.14).

4. Discussion

The main findings of the study were as follows. First, discordance between FFR and dPR values was present in up to 17.4% vessels and 22.1% of patients. Second, in comparison to patients with FFR+/dPR– discordant lesions, patients with FFR–/dPR + discordant lesions were more often female, had a higher prevalence of chronic kidney disease, peripheral artery disease and impaired left ventricular function. Third, mean FFR and dPR were significantly lower in LAD lesion location. Fourth, the only predictor of discordance between FFR and dPR is the absolute delta from the measured dPR to the cut-off value.

Although a discordance in lesion significance as assessed by either FFR or any of the NHPR (either iFR, dPR or resting full–cycle ratio (RFR)) is observed in 20–25% of cases, the exact physiological mechanism explaining this phenomenon is still unclear [13]. Possible causes of discordance have been linked to factors affecting coronary flow reserve, such as the presence of microvascular dysfunction and arterial stiffness, and differences in coronary resting flow velocity [19]. In the present study, patients with FFR+/dPR– lesions were most often male and had a lower prevalence of chronic kidney disease, peripheral artery disease and preserved left ventricular function – all of which are linked to lower risk of microvascular dysfunction [20–22]. Conversely, in patients with FFR–/dPR + lesions, the opposite was observed (patients were more frequently female and had a higher prevalence of chronic kidney disease, peripheral artery disease and impaired left ventricular function) [23–25].

Next to baseline characteristics intrinsically linked to a higher prevalence of arterial stiffness and microvascular dysfunction, another frequently encountered predictor of discordance between FFR and NHPR is lesion location in the LAD [23–24,26]. The larger amount of myocardium, and subsequently the greater increase in flow across these lesions during hyperemia, supplied by the LAD as compared to other vessel territories was hypothesized to be the most plausible explanation for this phenomenon [26–27]. In the present study, we found that in LAD lesions, the diagnostic accuracy of dPR, with FFR as a reference, was significantly lower as compared to other lesion locations (78% vs 88%, p < 0.001) and a higher rate of discordant cases was observed (21.9% vs 11.7%). However, the latter should be put into perspective to the significantly lower values of both FFR and dPR in the LAD, with absolute mean values closer to the diagnostic cut-off. In fact, in the present study, almost 58% of lesions in the LAD-group were FFR negative, as compared to 90% of lesions in the non-LAD group resulting in significantly lower FFR and dPR values in the LAD group as compared to the non-LAD-group (FFR 0.81 vs 0.90 p < 0.001, and dPR 0.88 vs 0.96p < 0.001, respectively). Hypothesizing that a measurement close to the diagnostic cut-off would result in a higher likelihood of discordance, we introduced a parameter called dPR delta to our predictive model, defined as the absolute distance from the measured dPR to the cut-off value. Following multivariable adjustment for discordance between dPR and FFR, dPR delta turned out to be the only independent predictor of discordance, whereas the significance of lesion location (LAD) disappeared. Moreover, lesion location in the LAD did not emerge as an independent predictor of discordance among both FFR+/dPR- and FFR-/dPR + discordant lesions.

Diagnostic accuracy depends on both the method's accuracy and the cases included in a study: the fewer cases close to the threshold, the better the diagnostic accuracy will appear and vice versa. Very high dPR values (>0.95), as well as very low dPR values (<0.84) provide a high degree of certainty on dPR and FFR concordance, while with values closer to the cut-off, there is less certainty. In this regard, the lesion classification agreement between dPR and FFR was lowest in the dPR 0.87–0.92 range value.

Petrarco et al. already demonstrated a diagnostic agreement between iFR and FFR of merely 50% in cases with dPR values close to the cut-off resulting in the initial adoption of a grey zone for iFR of 0.86–0.93 [28]. However, a drive for a discrete threshold led to the adoption of an iFR threshold of 0.89 [29]. With a single rule-in, rule out threshold, two recent large-scale trials demonstrated the non-inferiority of iFR- as compared to FFR guided revascularization with respect to major adverse cardiac events, despite a lower incidence of revascularization in the iFR-guided arm [11–12,30]. Of note, these studies precluded studying FFR/iFR discordance as only one index, either FFR or iFR was measured in each patient.

Nevertheless, the more relevant issue in daily practice is whether clinical outcomes of lesions with discordance values between FFR and NHPR are different from those with concordant results.

As of to date, there are limited data regarding patient prognosis in

those with lesions that have discordant values. A post hoc subgroup analysis on 374 lesions from the 3 V 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 did not show any significant differences in term of clinical outcomes of deferred lesions in any of the 4 groups based on discordant FFR and iFR values [30]. Acknowledging the limited sample size of the 3 V FFR FRIENDS study, the presence of discordance was not associated with an increased risk for major adverse cardiac events (MACE) in patients deferred from intervention. Subsequently, similar results were observed in an additional post hoc analysis of the study, evaluating the prognostic implications of discordance between FFR and several NHPR, including dPR, among deferred lesions. At two years, no differences in term of increased risk of vessel related events, were observed between the 4 groups [31].

With respect to lesion location, a recent post hoc analysis of DEFINE FLAIR evaluated the safety of deferral of PCI in LAD lesions, guided by either iFR or FFR. iFR guided deferral resulted in a significant lower rate of MACE at 1 year compared to FFR guided deferral (2.44% vs 5.46%, $p = 0.04$) [32]. Nevertheless, due to the nature of the analysis and the small sample size, the results should be considered hypothesis generating.

In conclusion, whereas larger studies on the prognostic implications of revascularization of patients with lesions with discordance between NHPR and FFR, more insights into the rationale for lesion discordance remain of interest. In this sense, the present studies, which is the largest on the topic to date, adds important nuances to the previously identified predictors of discrepancy (eg. LAD lesion location and gender) as in the present study, dPR delta appeared to be the only independent predictor of discrepancy.

5. Limitations

The findings of the study should be interpreted in the context of some limitations. First, it is a single-centre, retrospective cohort with all its inherent limitations. Second, the present study lacks clinical follow up, which might be of particular interest in patients with discordant FFR/dPR values.

6. Conclusion

Our study suggests that FFR-to-dPR discordance occurs in approximately one-fifth of patients. Whereas we did not observe any clinical determinants of discordance, the absolute dPR delta appeared to be the only independent predictor of discordance.

CRediT authorship contribution statement

Alessandra Scoccia: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. **Tara Neleman:** Methodology, Formal analysis, Visualization, Writing – review & editing. **Annemieke C. Ziedses des Plantes:** Methodology, Formal analysis, Visualization, Writing – review & editing. **Frederik T.W. Groenland:** Methodology, Formal analysis, Writing – review & editing. **Jurgen M R Ligthart:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Wijnand K. den Dekker:** Conceptualization, Methodology, Writing – review & editing. **Roberto Diletti:** Conceptualization, Methodology, Writing – review & editing. **Jeroen Wilschut:** Conceptualization, Methodology, Writing – review & editing. **Rutger Jan Nuis:** Conceptualization, Methodology, Writing – review & editing. **Felix Zijlstra:** Conceptualization, Methodology, Writing – review & editing. **Eric Boersma:** Methodology, Formal analysis, Visualization, Writing – review & editing. **Nicolas M Van Mieghem:** Conceptualization, Methodology, Writing – review & editing. **Joost Daemen:** Conceptualization, Methodology, Software, Supervision, Writing – review & editing.

Declaration of Competing Interest

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Appendix A. Supplementary data

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References

[1] F.J. Neumann, M. Sousa-Uva, A. Ahlsson, F. Alfonso, A.P. Banning, U. Benedetto, et al., 2018 ESC/EACTS Guidelines on myocardial revascularization, EuroIntervention 14 (14) (2019) 1435–1534.
[2] M. Writing Committee, J.S. Lawton, J.E. Tamis-Holland, S. Bangalore, E.R. Bates, T.M. Beckie, et al., 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines, J. Am. College of Cardiol. 79 (2) (2022) 197–215.
[3] B. De Bruyne, N.H. Pijls, B. Kalesan, E. Barbato, P.A. Tonino, Z. Piroth, et al., Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease, The New England J. Med. 367 (11) (2012) 991–1001.
[4] W.F. Fearon, T. Nishi, B. De Bruyne, D.B. Boothroyd, E. Barbato, P. Tonino, et al., Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (fractional flow reserve versus angiography for multivessel evaluation), Circulation 137 (5) (2018) 480–487.
[5] N.H. Pijls, P. van Schaardenburgh, G. Manoharan, E. Boersma, J.W. Bech, M. van't Veer, et al., Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study, J. Am. Coll. Cardiol. 49 (21) (2007) 2105–2111.
[6] B. De Bruyne, N.H. Pijls, E. Barbato, J. Bartunek, J.W. Bech, W. Wijns, et al., Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans, Circulation 107 (14) (2003) 1877–1883.
[7] J. Ligthart, K. Masdjedi, K. Witberg, F. Mastik, L. van Zandvoort, M.E. Lemmert, et al., Validation of resting diastolic pressure ratio calculated by a novel algorithm and its correlation with distal coronary artery pressure to aortic pressure, instantaneous wave-free ratio, and fractional flow reserve, Circ. Cardiovasc. Interv. 11 (12) (2018) e006911.
[8] M. Van't Veer, N.H.J. Pijls, B. Hennigan, S. Watkins, Z.A. Ali, B. De Bruyne, et al., Comparison of different diastolic resting indexes to iFR: are they all equal? J. Am. Coll. Cardiol. 70 (25) (2017) 3088–3096.
[9] J. Svanerud, J.M. Ahn, A. Jeremias, M. van 't Veer, A. Gore, A Maehara, et al., Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study, EuroIntervention 14 (7) (2018) 806–814.
[10] J. Escaned, N. Ryan, H. Mejía-Rentería, C.M. Cook, H.M. Dehbi, E. Alegria-Barrero, et al., Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes, J. Am. Coll. Cardiol. Intv. 11 (15) (2018) 1437–1449.
[11] J.E. Davies, S. Sen, H.M. Dehbi, R. Al-Lamee, R. Petraco, S.S. Nijjer, et al., Use of the instantaneous wave-free ratio or fractional flow reserve in PCI, N. Engl. J. Med. 376 (19) (2017) 1824–1834.
[12] M. Götberg, E.H. Christiansen, I.J. Gudmundsdottir, L. Sandhall, M. Danielewicz, L. Jakobsen, et al., Instantaneous wave-free ratio versus fractional flow reserve to guide PCI, N. Engl. J. Med. 376 (19) (2017) 1813–1823.
[13] A. Jeremias, A. Maehara, P. Généreux, K.N. Asrress, C. Berry, B. De Bruyne, et al., Multicenter core laboratory comparison of the instantaneous wave-free ratio and

resting Pd/Pa with fractional flow reserve: the RESOLVE study, J. Am. Coll. Cardiol. 63 (13) (2014) 1253–1261.

[14] N.P. Johnson, R.L. Kirkeeide, K.L. Gould, Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? J. Am. Coll. Cardiol. Img. 5 (2) (2012) 193–202.

[15] B. Williams, G. Mancia, W. Spiering, E. Agabiti Rosei, M. Azizi, M. Burnier, et al., 2018 ESC/ESH Guidelines for the management of arterial hypertension, Eur. Heart J. 39 (33) (2018) 3021–3104.

[16] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, et al., 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the european society of cardiology (ESC) and european atherosclerosis society (EAS), Eur. Heart J. 41 (1) (2019) 111–188.

[17] P.E. Stevens, A. Levin, Kidney disease: improving global outcomes chronic kidney disease guideline development work group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline, Ann. Intern. Med. 158 (11) (2013) 825–830.

[18] E.R. DeLong, D.M. DeLong, D.L. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach, Biometrics 44 (3) (1988) 837–845.

[19] S.G. Ahn, J. Suh, O.Y. Hung, H.S. Lee, Y.H. Bouchi, W. Zeng, et al., Discordance between fractional flow reserve and coronary flow reserve: insights from intracoronary imaging and physiological assessment, J. Am. Coll. Cardiol. Intv. 10 (10) (2017) 999–1007.

[20] S.S. Nijjer, G.A. de Waard, S. Sen, T.P. van de Hoef, R. Petraco, M. Echavarría-Pinto, et al., Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators, Eur. Heart J. 37 (26) (2016) 2069–2080.

[21] J.M. Lee, J. Layland, J.H. Jung, H.J. Lee, M. Echavarria-Pinto, S. Watkins, et al., Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve: insights from the International Index of Microcirculatory Resistance Registry, Circ. Cardiovasc. Interv. 8 (11) (2015) e002857.

[22] T. Yamazaki, Y. Saito, T. Kobayashi, H. Kitahara, Y. Kobayashi, Factors associated with discordance between fractional flow reserve and resting full-cycle ratio, J. Cardiol. 80 (1) (2022) 9–13.

[23] R. Goto, H. Takashima, H. Ohashi, H. Ando, A. Suzuki, S. Sakurai, et al., Independent predictors of discordance between the resting full-cycle ratio and fractional flow reserve, Heart Vessels 36 (6) (2021) 790–798.

[24] Y. Kato, T. Dohi, Y. Chikata, T. Fukase, M. Takeuchi, N. Takahashi, et al., Predictors of discordance between fractional flow reserve and resting full-cycle ratio in patients with coronary artery disease: evidence from clinical practice, J. Cardiol. 77 (3) (2021) 313–319.

[25] Natsuko Satomi II, Hiroyuki Arashi, Junichi Yamaguchi, Yutaka Konami, Hiromu Kadowaki, Kazuki Tanaka, Shintaro Haruki, Hisao Otsuki, Masashi Nakao, Kentaro Jujo, Yuichiro Minami, Hiroshi Ogawa and Nobuhisa Hagiwara. Predictors of Discordance Between Instantaneous Wave-Free Ration and Fractional Flow Reserve. Circulation. 2017.

[26] Y. Kobayashi, N.P. Johnson, C. Berry, B. De Bruyne, K.L. Gould, A. Jeremias, et al., The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements, J. Am. Coll. Cardiol. Intv. 9 (23) (2016) 2390–2399.

[27] Y. Chacko, W.F. Fearon, Should we just go with the flow? J. Am. Coll. Cardiol. Intv. 10 (24) (2017) 2525–2527.

[28] R. Petraco, J. Escaned, S. Sen, S. Nijjer, K.N. Asrress, M. Echavarria-Pinto, et al., Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry, EuroIntervention 9 (1) (2013) 91–101.

[29] J. Escaned, M. Echavarría-Pinto, H.M. Garcia-Garcia, T.P. van de Hoef, T. de Vries, P. Kaul, et al., Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (adenosine vasodilator independent stenosis evaluation II), J. Am. Coll. Cardiol. Intv. 8 (6) (2015) 824–833.

[30] J.M. Lee, E.S. Shin, C.W. Nam, J.H. Doh, D. Hwang, J. Park, et al., Clinical outcomes according to fractional flow reserve or instantaneous wave-free ratio in deferred lesions, J. Am. Coll. Cardiol. Intv. 10 (24) (2017) 2502–2510.

[31] J.M. Lee, T.M. Rhee, K.H. Choi, J. Park, D. Hwang, J. Kim, et al., Clinical outcome of lesions with discordant results among different invasive physiologic indices - resting distal coronary to aortic pressure ratio, resting full-cycle ratio, diastolic pressure ratio, instantaneous wave-free ratio, and fractional flow reserve, Circ. J. 83 (11) (2019) 2210–2221.

[32] S. Sen, Y. Ahmad, H.M. Dehbi, J.P. Howard, J.F. Iglesias, R. Al-Lamee, et al., Clinical events after deferral of LAD revascularization following physiological coronary assessment, J. Am. Coll. Cardiol. 73 (4) (2019) 444–453.