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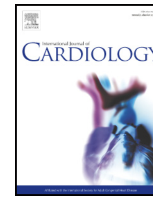

Discrepancy between fractional flow reserve and instantaneous wave-free ratio: Clinical and angiographic characteristics

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ABSTRACT

Background: The invasive physiologic index such as fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) is used in clinical practice to identify ischemia-causing stenosis and to guide treatment strategy. We investigated clinical and angiographic characteristics of lesions with discrepancy between FFR and iFR.

Methods: From the 3V FFR-FRIENDS study, 975 vessels (393 patients) with available pre-intervention FFR and iFR were included in this study. The vessels were classified according to FFR and iFR into: concordant normal (Group 1 [$n = 724$]: FFR > 0.80 and iFR ≥ 0.90); high FFR and low iFR (Group 2 [$n = 33$]: FFR > 0.80 and iFR < 0.90); low FFR and high iFR (Group 3 [$n = 82$]: FFR ≤ 0.80 and iFR ≥ 0.90); and concordant abnormal (Group 4 [$n = 136$]: FFR ≤ 0.80 and iFR < 0.90).

Results: Angiographic stenosis severity assessed by percent diameter stenosis, minimum lumen diameter and lesion length was increased from Group 1 to Group 4 (all $p < 0.001$). SYNTAX score increased and FFR decreased proportionally from Group 1 to Group 4 (all $p < 0.001$). In multivariable GEE model, female, diabetes mellitus, smaller reference vessel diameter, and higher %DS were significantly associated with low iFR among high FFR groups (Group 2 discordance). Conversely, males, absence of diabetes mellitus and lower %DS were significantly associated with high iFR among low FFR groups (Group 3 discordance).

Conclusions: Four groups classified according to FFR and iFR were different in clinical and angiographic characteristics, SYNTAX score, and predictors of discordance. The lesions with discordant FFR and iFR may need to be interpreted as a different clinical entity.

1. Introduction

The physiologic assessment of coronary artery disease and ischemia-guided percutaneous coronary intervention (PCI) has become a standard practice for patients with coronary artery disease. Fractional flow reserve (FFR) represents hyperemic flow limitation caused by an epicardial coronary stenosis and its clinical usefulness has been proven by many clinical studies [1]. Recently, a physiologic index which does not require hyperemia, instantaneous wave free ratio (iFR), was introduced and is also used in clinical practice [2]. As there have been debates on the diagnostic agreement between FFR and iFR, previous studies have focused on the diagnostic performance of iFR in the definition of ischemia-causing coronary artery stenosis [2–8]. Although recent trials showed non-inferiority of iFR-guided strategy for 1-year clinical outcome, compared with FFR-guided strategy [9,10], there has been a lack of understanding about why there are discrepancies between FFR and iFR and clinical and angiographic characteristics of discordant lesions. As iFR is measured during resting status whereas FFR is during hyperemic status, each index may represent a different aspect of pathophysiology in patients with coronary artery disease. Furthermore, no previous research has focused on discordant lesions between FFR and iFR, and this issue cannot be addressed by recent trials due to those trials' design with exclusive allocation between FFR and

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iFR-guided strategy groups. In this regard, the current study sought to investigate clinical, angiographic and physiological characteristics of discordant lesions between FFR and iFR.

2. Methods

2.1. Study design and patient population

The study population was derived from the 3V FFR-FRIENDS study (3-vessel fractional flow reserve for the assessment of total stenosis burden and its clinical impact in patients with coronary artery disease, NCT01621438) which was designed to investigate the clinical relevance of total stenosis burden assessed by 3-vessel FFR measurement. Patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-elevation myocardial infarction within 72 h, previous coronary artery bypass graft surgery (CABG), chronic renal disease, abnormal epicardial coronary flow (TIMI flow <3) or planned CABG after diagnostic angiography were excluded.

This substudy was performed to investigate the clinical relevance of the discrepancy between FFR and iFR. Among the main study cohort, 975 vessels (393 patients) with available native vessel FFR and iFR values were included. The current study was conducted in 4 pre-defined centers which utilized a uniform protocol for both resting and hyperemic pressure recording. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating center and all patients provided written informed consent.

2.2. Angiographic analysis and quantitative coronary angiography

Coronary angiography was performed using standard techniques. Angiographic views were obtained after administration of intracoronary nitrate (100 or 200 μg). All angiograms were analyzed at a core laboratory (Seoul National University Hospital) in a blinded fashion. Quantitative coronary angiography (QCA) was performed in optimal projections with validated software (CAAS II, Pie Medical System, Maastricht, The Netherlands). Minimum lumen diameter (MLD), reference vessel size, percent diameter stenosis (%DS), and lesion length were measured. Angiographic disease severity was also assessed by SYNTAX score [11].

2.3. Coronary physiologic measurements

All coronary physiologic measurements were performed after diagnostic angiography. Briefly, a 5 − 7 Fr guide catheter without side holes was used to engage the coronary artery, and a pressure-temperature sensor guide wire (St. Jude Medical, St. Paul, MN, USA) was used for FFR measurement. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200 μg) was administered before each physiological measurement. iFR was calculated as the mean pressure distal to the stenosis, divided by the mean aortic pressure during the diastolic wave-free period. Baseline tracing data with a duration of 5 heart beats or longer were extracted from the FFR console platforms. The iFR was calculated using automated algorithms acting over the wave-free period over a minimum of 5 beats as previously described [2]. Continuous intravenous infusion of adenosine was used to induce hyperemia for FFR measurement. Hyperemic proximal aortic pressure (Pa) and distal arterial pressure (Pd) were obtained during sustained hyperemia, and FFR was calculated as the lowest average of 3 consecutive beats during stable hyperemia. After measurements, the pressure wire was pulled back to the guide catheter and the presence of pressure drift was checked. All pressure readings were collected and validated at the core laboratory in a blinded fashion.

2.4. Cut-off values of physiologic indices and lesion classifications

The cut-off values of 0.80 and 0.90 [7] were used for FFR and iFR, respectively. All vessels were classified according to FFR and iFR into concordant normal (Group 1: FFR > 0.80 and iFR ≥ 0.90); high FFR and low iFR (Group 2: FFR > 0.80 and iFR < 0.90); low FFR and high iFR (Group 3: FFR ≤ 0.80 and iFR ≥ 0.90); and concordant abnormal (Group 4: FFR ≤ 0.80 and iFR < 0.90).

2.5. Statistical analysis

Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables were presented as means and standard deviations or median with interquartile range (IQR) according to their distribution, which was checked by the Kolmogorov-Smirnov test. Data were analyzed on a per-patient basis for clinical characteristics and on a per-vessel basis for all other analyses. For per-patient analysis, patients with different 4 group classifications among interrogated vessels were allocated as with the classification of left anterior descending artery (LAD). Linear regression analysis was used to estimate the correlation coefficient (Pearson or Spearman according to the normality of the variables) between quantitative variables.

For per-vessel analyses, the generalized estimating equation (GEE) was used to account for the clustering of multiple vessel measurements in the same patient. Estimated mean and 95% confidence interval (CI) were presented as summary statistics. To compare per-vessel variables among the 4 groups, we used GEE with pairwise comparison but without post-hoc adjustment. Multivariable GEE models were also constructed to explore independent predictors for discordance between FFR and iFR (Group 2 and Group 3). The covariates that were considered clinically relevant or that showed a univariate relationship with discordance phenomenon ($p < 0.1$) were entered into multivariable GEE models. Variables selected for inclusion were carefully chosen, given the number of discordance available, to ensure parsimony of the final models. All probability values were two-sided, and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of patients and lesions

Table 1 shows baseline characteristics of patients and lesions. Mean angiographic %DS, iFR and FFR were 44.2 ± 17.5% (median: 42.8%, Q1–Q3: 30.6–56.2%), 0.94 ± 0.09 (median: 0.97, Q1–Q3: 0.92–1.00) and 0.87 ± 0.10 (median: 0.90, Q1–Q3: 0.81–0.95), respectively. The FFR and iFR showed a significant correlation ($r = 0.801$, $p < 0.001$) and 11.8% (Group 2: 3.4% and Group 3: 8.4%) showed discordant results between FFR and iFR (Fig. 1). The proportion of vessels with %DS ≥ 50% increased from Group 1 to 4 (23.9%, 51.5%, 67.1%, and 83.8% from Group 1 to 4, respectively, $p < 0.001$) (Fig. 1). Supplementary Table 1 shows the comparison of lesion characteristics between high- and low-FFR or between high- and low-iFR groups. Fig. 2 shows the distribution of FFR and iFR values and proportions of 4 groups according to the target vessels. The LAD showed the highest prevalence of discordance between FFR and iFR values (20.7%, 7.8% and 6.0% for LAD, left circumflex and right coronary artery, respectively, $p < 0.001$).

3.2. Clinical and angiographic characteristics

Table 2 shows the comparison of clinical, angiographic and physiologic characteristics of the 4 groups. Regarding patient demographics and cardiovascular risk factors, the 4 groups showed distinct differences. Among the high FFR group (>0.80), Group 2 with low iFR showed older age, higher proportion of females and higher prevalence of diabetes mellitus compared with Group 1. Conversely, among the low

Table 1
General characteristics of patients and lesions.

Patients ($N = 393$)	
General characteristics	
Age (years)	63.8 ± 9.7
Male	303 (77.1%)
Ejection fraction (%)	61.7 ± 6.6
Cardiovascular risk factors	
Hypertension	248 (63.3%)
Diabetes mellitus	142 (36.2%)
Hypercholesterolemia	270 (68.9%)
Current smoker	72 (18.4%)
Clinical presentation	
Stable angina	337 (85.8%)
Unstable angina	37 (9.4%)
Myocardial infarction	19 (4.8%)
Multivessel disease	238 (60.6%)
SYNTAX score	11.0 (7.0–18.0)
Lesions ($N = 975$)	
Measured vessel location	
Left anterior descending artery	343 (35.2%)
Left circumflex artery	335 (34.4%)
Right coronary artery	297 (30.5%)
Quantitative coronary angiography	
Reference diameter, mm	2.97 ± 0.60
Minimum lumen diameter (mm)	1.68 ± 0.69
Diameter stenosis, %	44.2 ± 17.5
Lesion length, mm	10.5 ± 8.0
Coronary physiologic parameters	
FFR[a]	0.87 ± 0.11[a]
iFR[b]	0.95 ± 0.10[b]

Values are n (%) or mean ± SD.
[a] FFR: median 0.90 (interquartile ranges, 25th–75th: 0.81–0.95).
[b] iFR: median 0.97 (interquartile ranges, 25th–75th: 0.92–1.00).

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