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Visual-Functional Mismatch Between Coronary Angiography and Fractional Flow Reserve

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Objectives The goal of this study was to identify clinical and lesion-specific local factors affecting visual-functional mismatch.

Background Although lesion severity determined by coronary angiography has not been well correlated with physiological significance, the mechanism of the discordance remains poorly understood.

Methods The authors assessed quantitative coronary angiography, intravascular ultrasound (IVUS), and fractional flow reserve (FFR) in a prospective cohort of 1,000 patients with 1,129 coronary lesions. Three-dimensional computational simulation studies were performed.

Results Lesions with angiographic diameter stenosis (DS) ≥50% and FFR >0.80 ("mismatches") were seen in 57% of non–left main lesions and in 35% of the left main lesions, respectively ($p = 0.032$). Conversely, among the lesions with DS <50% and FFR <0.80 ("reverse mismatches") 16% were found in the non–left main lesions and 40% in the left main lesions ($p < 0.001$). The independent predictors for mismatch were advanced age, non–left anterior descending artery location, absence of plaque rupture, short lesion length, large minimal lumen area, smaller plaque burden, and greater minimal lumen diameter. Conversely, reverse mismatch was independently associated with younger age, left anterior descending artery location, the presence of plaque rupture, a smaller minimal lumen area, and larger plaque burden. In a computational simulation study, FFR was influenced by DS, lesion length, different lesion shape, plaque eccentricity, surface roughness, and various shapes of plaque rupture.

Conclusions There were high frequencies of visual-functional mismatch between angiography and FFR. The discrepancy was related to the clinical and lesion-specific factors frequently unrecognizable by angiography, thus suggesting that coronary angiography cannot accurately predict FFR. (Natural History of FFR-Guided Deferred Coronary Lesions [IRIS FFR-DEFER]; NCT01366404) (J Am Coll Cardiol Intv 2012;5:1029–36) © 2012 by the American College of Cardiology Foundation

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Because revascularization treatment based on objective ischemia may improve patients' functional status and clinical outcomes, guidelines have recommended noninvasive functional evaluation before revascularization treatment. However, noninvasive functional evaluations are underutilized in daily practice. Instead, coronary angiography is still used as a cornerstone for decision making regarding revascularization treatment for patients without any evidence of objective ischemia (1,2).

Coronary angiography often underestimates or overestimates a lesion's functional severity (3–11). A subanalysis of the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial demonstrated that two-thirds of coronary lesions with a diameter stenosis (DS) >50% were not ischemia producing. Conversely, for left main coronary artery (LMCA) lesions, approximately one-fifth of the lesions with a DS <50%, were ischemia producing. Although such a "visual-functional mismatch" is frequently encountered, the mechanism of this phenomenon is poorly understood. This issue has important implications for many physicians attempting to overcome angiography-dependent decision making to avoid unnecessary revascularization procedures.

We, therefore, attempted to identify lesion-specific, local factors associated with the visual-functional mismatch in a prospective cohort of 1,000 consecutive patients with 1,129 coronary lesions with complete quantitative coronary angiography (QCA), intravascular ultrasound (IVUS), and fractional flow reserve (FFR). For theoretical validation, computational simulation studies were performed.

Abbreviations and Acronyms

DS = diameter stenosis
EEM = external elastic membrane
FFR = fractional flow reserve
IVUS = intravascular ultrasound
LAD = left anterior descending artery
LCX = left circumflex artery
LMCA = left main coronary artery
MLA = minimal lumen area
MLD = minimal lumen diameter
QCA = quantitative coronary angiography
RCA = right coronary artery
RLD = reference lumen diameter

Methods

Study design. This trial was a prospective, single-center, observational study that was designed by the principle investigator, and the protocol was approved by the institutional review board. All patients provided written informed consent.

Study population. Between November 2009 and June 2011, in a prospective cohort, 1,000 consecutive patients with 1,129 coronary lesions, underwent angiographic, IVUS, and invasive physiological assessment before intervention and were included in the current analysis. All patients were 35 to 85 years of age and had at least 1 target vessel with >30% of angiographic DS seen on visual estimation. Exclusion criteria included multiple stenoses (DS >30% on visual estimation) within a single target vessel, bypass graft lesions, sidebranch lesions, in-stent restenosis, previous percutaneous coronary intervention in the target vessel, culprit vessels in the setting of a myocardial infarction, Thrombolysis In Myocardial Infarction flow grade <3, angiographic thrombi-containing lesions, and cases in which the IVUS imaging catheter or FFR wire failed to cross the lesion due to tight stenosis or tortuosity. In addition, patients with acute myocardial infarction seen within 72 h after onset and those with scarred myocardium or regional wall motion abnormality in the territory of the studied vessel were excluded from the study. Isolated LMCA lesions were also included in the current analysis after excluding significant distal disease (DS >30%) within either the left anterior descending artery (LAD) or the left circumflex artery (LCX). Considering the unique morphological characteristics of LMCA with a large supplied myocardium, the data from 63 patients with 63 LMCA lesions were separately assessed from 937 patients with 1,066, non-LMCA lesions.

Angiographic FFR "mismatch" was defined as angiographic DS >50% and FFR ≥0.80, whereas "reverse

Table 1. Clinical Characteristics in 1,000 Patients With 1,129 Lesions

Clinical characteristics, N = 1,000	
Age, yrs	61 ± 9
Male	731 (73%)
Ejection fraction, %	61 ± 6
Diabetes	322 (32%)
Hypertension	589 (59%)
Smoking	493 (49%)
Hyperlipidemia	670 (67%)
Previous PCI	122 (12%)
Left main coronary artery disease	63 (6%)
Clinical manifestation	
Stable angina	742 (74%)
Unstable angina	219 (22%)
Non-ST elevation MI	39 (4%)
Lesion location, N = 1,129	
Syntax no. 5 (left main coronary artery)	63 (6%)
Syntax no. 6 (proximal LAD)	236 (21%)
Syntax no. 7 (mid LAD)	432 (38%)
Syntax no. 8 (distal LAD)	36 (3%)
Syntax no. 11 (proximal LCX)	39 (3%)
Syntax no. 13 (distal LCX)	60 (5%)
Syntax no. 1 (proximal RCA)	111 (10%)
Syntax no. 2 (mid RCA)	114 (10%)
Syntax no. 3 (distal RCA)	38 (3%)
FFR at maximal hyperemia	
FFR in non–left main lesions	0.82 ± 0.09
FFR in left main lesions	0.80 ± 0.09
FFR <0.80	368 (32.6%)

Values are n (%) or mean ± SD.
FFR = fractional flow reserve; LAD = left anterior descending artery; LCX = left circumflex artery; LMCA = left main coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

Table 2. Clinical, Angiographic, and IVUS Parameters in 1,066, Non-LMCA Lesions

	QCA-DS > 50%		QCA-DS ≤ 50%	
	FFR < 0.80 n = 262	FFR ≥ 0.80 ("Mismatch") n = 343	FFR ≥ 0.80 n = 386	FFR < 0.80 ("Reverse mismatch") n = 75
Age, yrs	59.7 ± 10.0	62.1 ± 10.0*	62.9 ± 9.2	59.7 ± 10.0*
Female	55 (21%)	107 (31%)*	103 (27%)	13 (17%)
Diabetes	82 (31%)	111 (32%)	121 (31%)	17 (23%)
Hypertension	157 (60%)	201 (59%)	227 (59%)	43 (57%)
Smoking	142 (54%)	160 (47%)	195 (51%)	45 (60%)
Acute coronary syndrome	72 (28%)	101 (29%)	115 (30%)	20 (27%)
Left anterior descending artery	201 (77%)	191 (56%)*	246 (64%)	66 (88%)*
Left circumflex artery	14 (5%)	49 (14%)*	30 (8%)	6 (8%)
Right coronary artery	47 (18%)	103 (30%)*	110 (29%)	3 (4%)*
Proximal segment	91 (35%)	129 (38%)	139 (36%)	27 (36%)
Mid segment	142 (54%)	156 (46%)*	205 (53%)	43 (57%)
Distal segment	29 (11%)	58 (17%)*	42 (11%)	5 (7%)
Lesions length, mm	24.1 ± 13.4	18.8 ± 10.6*	16.7 ± 11.2	19.3 ± 12.3
QCA-DS, %	62.3 ± 9.2	57.6 ± 7.4*	40.1 ± 6.6	43.2 ± 5.2*
QCA-MLD, mm	1.2 ± 0.3	1.4 ± 0.3*	1.9 ± 0.3	1.7 ± 0.3*
Averaged RLD, mm	3.1 ± 0.5	3.2 ± 0.5*	3.1 ± 0.5	3.0 ± 0.5*
MLA, mm^2	1.9 ± 0.7	2.6 ± 0.9*	3.4 ± 1.3	2.4 ± 0.8*
Plaque burden, %	80.8 ± 8.7	74.7 ± 9.9*	67.8 ± 13.0	73.1 ± 12.1*
Plaque rupture	44 (17%)	35 (10%)*	32 (8%)	12 (16%)*

Values are n (%) or mean ± SD. *p value <0.05 versus 262 lesions with QCA-DS >50 and FFR <0.80.

DS = diameter stenosis; MLA = minimal lumen area; MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RLD = reference lumen diameter; other abbreviations as in Table 1.

mismatch" was defined as angiographic DS ≤50% and FFR <0.80. Treatment strategies were determined at the operator's discretion.

Fractional flow reserve. "Equalizing" was performed with the guidewire sensor positioned at the guiding catheter tip. The 0.014-inch, pressure guidewire (Radi, St. Jude Medical, Uppsala, Sweden) was then advanced distal to the stenosis. For isolated LMCA lesions, a pressure guidewire was advanced into the coronary artery and positioned ≥3 cm distal to the LMCA lesion into the LAD or LCX depending on which was least diseased distally. In patients with ostial LMCA stenosis, care was taken to pull the guiding catheter out of the LMCA during FFR assessment. FFR was measured at maximal hyperemia induced by an intravenous adenosine infusion administered at 140 μg/kg/min through a central vein and increased up to 200 μg/kg/min in

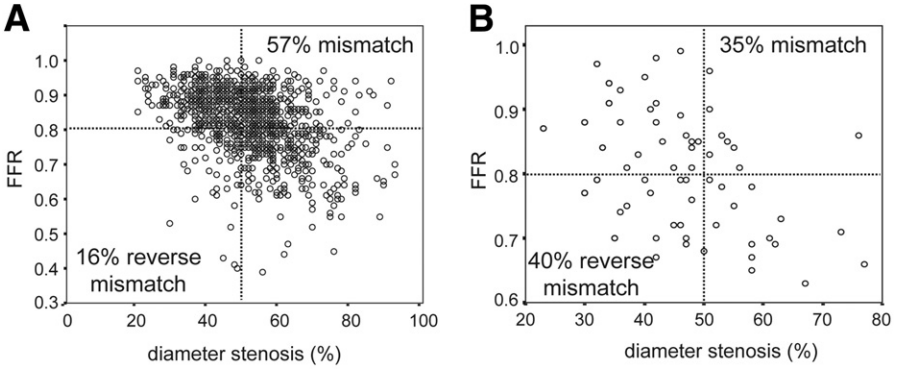

Figure 1. Correlation Between Angiographic DS and FFR

(A) Non-LMCA lesions; **(B)** LMCA lesions. DS = diameter stenosis; FFR = fractional flow reserve; LMCA = left main coronary artery.

non-LMCA lesions and up to 280 μg/kg/min in LMCA lesions to enhance detection of hemodynamically relevant stenoses. Hyperemic pressure pullback recordings were performed as described previously (4–6). The stenosis was considered functionally significant when the FFR was <0.80.

Quantitative coronary angiography. QCA was performed using standard techniques with automated edge-detection algorithms (CAAS-5, Pie-Medical, Best, the Netherlands) in the angiographic analysis center of the CardioVascular Research Foundation, Seoul, Korea. According to the SYNTAX classification, coronary segments consisted of the LMCA (segment 5), right coronary artery (RCA) (segments 1, 2, and 3), the LAD (segments 6, 7, and 8), and the LCX (segments 11 and 13) (12,13). Using QCA, angiographic DS, minimal lumen diameter (MLD), lesion length, and the reference lumen diameter (RLD) of the proximal and distal reference segments were measured. QCA-derived DS was compared to visually estimated DS that was determined by operators during the procedure.

Intravascular ultrasound. After FFR assessment and intracoronary administration of 0.2 mg of nitroglycerin, IVUS imaging was performed using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific/SCIMED, Minneapolis, Minnesota) consisting of a rotating, 40-MHz transducer within a 3.2-F imaging sheath. Using computerized planimetry (EchoPlaque 3.0, Indec Systems, Mountain View, California), off-line quantitative IVUS analysis was performed as described in a core laboratory at the Asan Medical Center (14). The proximal and distal reference segments were within 5 mm of the lesion. The averaged proximal and distal reference external elastic membrane (EEM) and lumen areas and mean reference lumen diameter were measured. We also measured the minimal lumen area (MLA) and the EEM area at the site of the smallest lumen and then calculated the plaque burden at the MLA site as: (EEM area − lumen area)/EEM area × 100 (%) (14).

Computational simulation. To better understand the relationship between the local factors and the physiological effect of the stenosis, we simulated the geometric effects of stenosis on the FFR. A detailed description of the methods for computational simulation is provided in the Methods section of the Online Appendix.

Statistical analysis. All statistical analyses were performed using SAS release 9.1 (SAS Institute, Cary, North Carolina) or SPSS (version 10.0, SPSS, Chicago, Illinois). Data were analyzed on a per-patient and per-lesion basis for the corresponding calculations. All values are expressed as mean ± 1 SD (continuous variables) or as counts and percentages (categorical variables). For per-patient data, continuous variables were compared using unpaired *t* tests or nonparametric Mann-Whitney tests; categorical variables were compared using chi-square statistics or Fisher exact test. For per-lesion data, a logistic generalized estimated equation model with robust standard errors that accounted for the clustering between lesions in the same subject was created.

Receiver-operating curves were analyzed to assess the best cutoff values of the angiographic and IVUS parameters to predict FFR <0.80 with maximal accuracy and using MedCalc Software (Mariakerke, Belgium). The optimal cutoff was calculated using the Youden index.

The sensitivity, specificity, positive predictive value, and negative predictive value with their 95% confidence intervals (CI), were determined. Multivariable logistic regression analysis was performed to identify the independent determinants for angiographic-FFR "mismatch" and "reverse mismatch." A p value <0.05 was considered statistically significant.

Figure 2. Examples of Mismatch and Reverse Mismatch

(A) A 60-year-old man with stable angina. Angiographic DS was 80% **(black arrow)** and IVUS-MLA was 2.3 mm^2, whereas FFR was 0.84 (mismatch). The lack of inducible ischemia of the stenosis was supported by normal perfusion on thallium scan and negative treadmill test. **(B)** A 55-year-old man with unstable angina. Angiographic DS was 40% **(black arrow)** and IVUS-MLA was 4.1 mm^2. Plaque rupture was shown **(red arrow)**. FFR was reduced to 0.74 (reverse mismatch). **(C)** A 50-year-old man with unstable angina. Angiographic DS at the proximal LMCA was only 35%. IVUS showed MLA 5.2 mm^2 and ruptured plaque **(red arrow)**. FFR of LMCA was 0.71 (reverse mismatch). IVUS = intravascular ultrasound; MLA = minimal lumen area; other abbreviations as in Figure 1.

Results

Patient population. One thousand consecutive patients (1,129 de novo coronary lesions) who underwent coronary angiography, IVUS, and FFR assessment were enrolled. Their baseline characteristics are provided in Table 1. The average patient age was 61 years, 73% were men, 32% had a history of diabetes, and 6% had isolated LMCA lesions. FFR <0.80 was seen in 368 (32.6%) lesions. The FFR at maximal hyperemia was 0.82 ± 0.09.

Baseline functional and anatomical study. QCA, IVUS, and FFR data were evaluated in all enrolled patients and lesions; these data are provided in Tables 1 and 2 in the Online Appendix. FFR was significantly higher in females than in males (0.84 ± 0.09 vs. 0.82 ± 0.10, p = 0.005) and showed a weak correlation with patient age (r = 0.161, p < 0.001). FFR significantly correlated with angiographic DS assessed by QCA, MLD, and lesion length and IVUS-MLA, plaque burden (Online Table 3).

In LMCA lesions, FFR was related to angiographic DS and MLD and IVUS-MLA and plaque burden. Plaque rupture was observed in 22 (35%) lesions. FFR was significantly lower in lesions with plaque rupture than in those without (0.76 ± 0.09 vs. 0.83 ± 0.09, p = 0.007). Similarly, in non-LMCA lesions, lesions with plaque rupture showed a lower FFR value compared with those without plaque rupture (0.79 ± 0.11 vs. 0.83 ± 0.09, p < 0.001). However, there were no significant differences in IVUS-MLA between lesions with versus without plaque rupture in both the non-LM group (2.8 ± 1.2 mm^2 vs. 2.7 ± 1.2 mm^2, p = 0.224) and the LM group (4.4 ± 1.8 mm^2 vs. 5.3 ±2.2 mm^2, p = 0.087).

Diagnostic accuracy of quantitative coronary angiography. Figures 1 and 2 in the Online Appendix show the diagnostic accuracy of the parameters of QCA and IVUS assessment for the identification of functionally significant stenosis (FFR <0.80). The optimal cutoff value of angiographic DS in the non-LMCA group for predicting FFR <0.80 was 52%, which had a sensitivity of 66% and a specificity of 67% (area under the curve: 0.73, 95% CI: 0.70 to 0.76, p < 0.001). The overall diagnostic accuracy was only 66%, and its positive and negative predictive values were 48% and 81%, respectively. In the LMCA group, an angiographic DS >46% was the optimal cutoff, although it was a poor predictor of FFR <0.80 (sensitivity: 61%, specificity: 59%, diagnostic accuracy: 60%, area under the curve: 0.657, 95% CI: 0.53 to 0.772, p = 0.070).

Factors associated with the discrepancy between QCA and FFR. There was a significant, but modest, correlation between angiographic DS and FFR in the non-LMCA (r = −0.395, p < 0.001) and LMCA (r = −0.428, p < 0.001) groups. Among the 605 non-LMCA lesions with angiographic DS >50%, FFR ≥0.80 (mismatch) was seen in 343 (57%) lesions. Conversely, among the 461 non-LMCA lesions with DS ≤50%, FFR <0.80 (reverse mismatch) was found in 75 (16%) lesions. In the LMCA group, mismatch was observed in 8 (35%) lesions, whereas reverse mismatch was seen in 16 (40%) lesions. The LMCA group showed significantly lower frequency of mismatch (35% vs. 57%, p = 0.032) and much higher frequency of reverse mismatch (40% vs. 16%, p < 0.001) compared with the non-LMCA group (Figs. 1 and 2).

Table 3. Clinical, Angiographic, and IVUS Parameters in 63 LM Lesions

	QCA-DS >50%		QCA-DS ≤50%	
	FFR <0.80 (n = 15)	FFR ≥0.80 ("Mismatch") (n = 8)	FFR ≥0.80 (n = 24)	FFR <0.80 ("Reverse Mismatch") (n = 16)
Age, yrs	64 (58–68)	61 (54–75)	62 (50–70)	55 (49–63)
Female	4 (27%)	2 (25%)	9 (38%)	2 (13%)
Diabetes	5 (33%)	2 (25%)	98 (33%)	6 (38%)
Hypertension	11 (73%)	3 (38%)	12 (50%)	8 (50%)
Smoking	8 (53%)	5 (62%)	9 (38%)	12 (75%)*
Hyperlipidemia	12 (80%)	7 (88%)	15 (62%)	12 (75%)
Acute coronary syndrome	8 (53%)	2 (25%)	13 (54%)	7 (44%)
Lesions length, mm	11.3 (8.9–15.6)	6.2 (5.2–8.5)	7.4 (5.9–13.4)	10.3 (7.8–19.8)
QCA-DS, %	58.0 (53.0–63.0)	53.5 (51.0–55.7)	41.5 (34.5–46.0)	42.0 (36.3–46.7)
QCA-MLD, mm	1.4 (1.2–1.6)	1.8 (1.3–1.9)	2.3 (2.0–2.6)	2.0 (1.8–2.4)
Averaged RLD, mm	3.5 (3.2–3.9)	3.8 (3.6–4.1)	3.6 (3.3–4.1)	3.4 (3.1–3.9)
MLA, mm^2	3.1 (2.5–3.8)	5.2 (3.2–6.1)†	6.2 (5.1–7.8)	4.1 (2.7–5.5)*
Plaque burden, %	83.6 (73.7–85.8)	67.0 (61.2–86.8)	64.7 (53.1–71.5)	74.2 (66.2–79.2)*
EEM area, mm^2	17.6 (14.9–21.3)	16.1 (13.2–24.8)	19.8 (13.9–21.3)	16.3 (13.7–18.5)
Plaque rupture	10 (67%)	3 (38%)	4 (17%)	8 (50%)*

Values are n (%) and median (interquartile range). *p value <0.05 versus 24 lesions with QCA-DS ≤50% and FFR ≥0.80 †p value <0.05 versus 15 lesions with QCA-DS >50 and FFR <0.80
EEM = external elastic membrane; other abbreviations as in Tables 1 and 2.

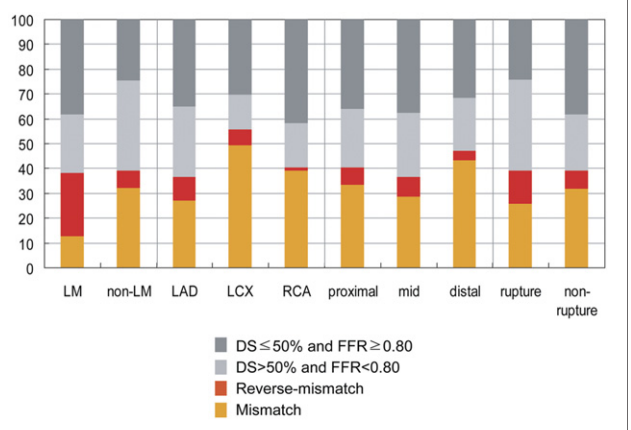

Figure 3. Frequencies of Mismatch and Reverse Mismatch According to Vessel Type, Location, and the Presence of Plaque Rupture

n = 63 for LMCA, n = 1,066 for non-LMCA, n = 704 for LAD, n = 99 for LCX, n = 263 for RCA, n = 386 for proximal segments, n = 546 for mid segments, n = 134 for distal segments, n = 148 for those with plaque rupture, and n = 981 for those without plaque rupture. LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; other abbreviations as in Figure 1.

Comparison of the baseline characteristics, QCA, and IVUS parameters according to FFR and QCA is summarized in Table 2 (for non-LMCA lesions) and in Table 3 (for LMCA lesions). Figure 3 showed the frequencies of mismatch and reverse-mismatch relative to the involved vessel, lesion location, and the presence of plaque rupture.

For non-LMCA lesions, univariable analysis of factors predicting "mismatch" and reverse-mismatch, are shown in Online Table 4. Multivariate analysis identified the independent predictors for mismatch as older age, non-LAD lesions, the absence of plaque rupture, shorter lesion length, larger IVUS-MLA, smaller plaque burden, and greater angiographic MLD; independent predictors for reverse mismatch were younger age, LAD lesions, presence of plaque rupture, smaller IVUS-MLA, and larger plaque burden (Table 4). For LMCA lesions, mismatches were associated with a larger IVUS-MLA, and reverse mismatches were associated with smoking, smaller IVUS-MLA, larger plaque burden, and the presence of plaque rupture (Table 3).

Diagnostic accuracy of visually estimated DS. The DS by visual estimation was significantly greater compared with DS calculated by QCA analysis (58 ± 16% vs. 51 ± 12%, $p < 0.001$). Visually estimated DS significantly correlated with QCA-DS in both non-LMCA ($r = 0.57$, $p < 0.001$) and LMCA ($r = 0.64$, $p < 0.001$) lesions, but with a wide scatter. Similarly, visually estimated DS significantly correlated with FFR in both non-LMCA ($r = -0.46$, $p < 0.001$) and LMCA lesions ($r = -0.36$, $p = 0.004$), but again with a wide scatter. Among non-LMCA lesions with visually estimated DS >50%, FFR ≥0.80 (mismatch) was seen in 351 (56%) lesions. Conversely, among non-LMCA lesions with DS ≤50%, FFR <0.80 (reverse mismatch) was found in 55 (13%) lesions. In the LMCA group, mismatch was observed in 13 (36%) lesions, whereas reverse mismatch was seen in 8 (30%) lesions.

Table 4. Multivariable Analysis of Independent Factors Predicting "Mismatch" and "Reverse Mismatch" Between Angiographic DS and FFR in 1,066 Non-LMCA Lesions

	Beta	SE	p Value	Adjusted Odds Ratio	95% Confidence Intervals
Predictors for "mismatch"*					
Age	0.040	0.012	<0.001	1.040	1.017–1.064
Female	0.430	0.250	0.085	1.537	0.942–2.508
LAD location	−1.094	0.227	<0.001	0.335	0.214–0.522
Plaque rupture	−0.956	0.334	0.004	0.385	0.200–0.740
Lesion length	−0.0335	0.008	<0.001	0.966	0.950–0.982
IVUS-MLA	0.687	0.189	0.001	1.989	1.371–2.886
Plaque burden	−0.050	0.014	<0.001	0.951	0.926–0.977
QCA-MLD	0.086	0.040	0.034	1.089	1.007–1.179
Predictors for "reverse mismatch"*					
Age	−0.044	0.015	0.003	0.957	0.929–0.985
LAD location	1.691	0.457	<0.001	5.427	2.216–13.29
Plaque rupture	1.150	0.452	0.011	3.159	1.301–7.667
IVUS-MLA	−1.064	0.203	<0.001	0.345	0.232–0.514
Plaque burden	0.032	0.014	0.027	1.032	1.003–1.061

*Assessed by generalized estimating equations in 937 patients with 1,066. non-LMCA lesions included age, female sex, lesion length, LAD location, proximal segment, plaque rupture, RLD, MLA, plaque burden, and averaged reference lumen diameter.

IVUS = intravascular ultrasound; other abbreviations as in Tables 1 and 2.

FFR ≥0.80 was seen in 316 (60%) of 528 non-LMCA lesions with DS 50% to 70% and 27 (35%) of 77 lesions with DS ≥70%.

Explanatory computational simulation of coronary artery stenosis. To understand the current observations, we simulated various circumstances of coronary artery stenosis and demonstrated that FFR changes according to the change of geometry, including DS, lesion length, eccentricity, plaque morphology, surface roughness, or plaque rupture; these are illustrated in Figure 4, and Online Figures 3 to 5.

Discussion

In this prospective cohort study, our data demonstrated that visual-functional mismatches between coronary angiography and FFR are frequently encountered and are as high as 40%. In addition, the physiological effect of the stenosis is determined by many clinical and local factors. FFR reflects the summary effect of all of these individual factors and also accounts for the variable myocardial blood flow requirements. Therefore, FFR should be more reliable in the assessment of coronary artery stenosis than anatomy alone; and the understanding of our findings may help to overcome physicians' habitual preoccupation with coronary angiography as the decision criterion for revascularization.

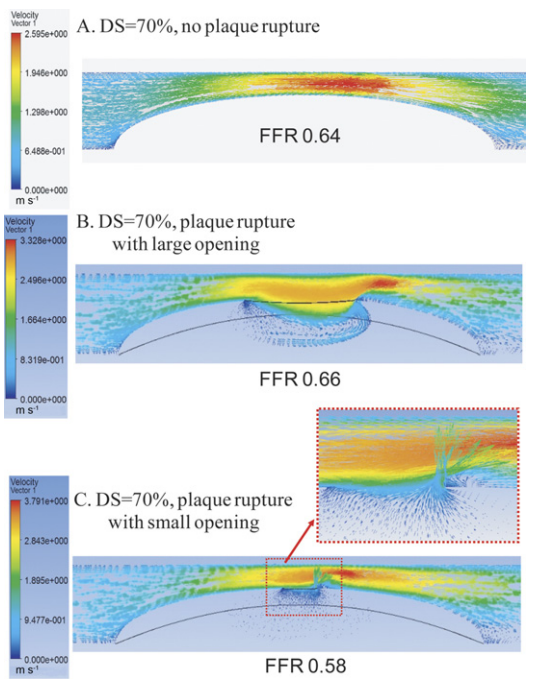

Figure 4. Hemodynamic Effect of Plaque Rupture Was Assessed by the 3D Stenotic Models

(A) The stenotic lesion (70% of DS) without plaque rupture showed FFR = 0.68. **(B)** In the same degree of stenosis (70% of DS), the lesion with large opening plaque rupture showed FFR = 0.66. **(C)** In the same degree of stenosis (70% of DS), the lesion with small opening plaque rupture showed FFR = 0.58. The small opening of plaque rupture makes a higher velocity turbulence of fluid **(blue arrows)**, which may induce more energy loss of fluid compared to the larger opening plaque rupture, and result in a lower FFR. 3D = 3-dimensional; other abbreviations as in Figure 1.

Among our major findings, patient age affected the physiological effect of a stenosis. For a given degree of stenosis, older patients may have a higher FFR than younger patients. This could be explained by aging-related loss of functional myocytes or attenuation of the vasodilator response to the adenosine (15–17). Further study will also be required to determine the effect of aging on the physiological effect of stenosis.

This study suggested that lesion location influenced the functional severity of the stenosis. Compared with non-LMCA disease, isolated LMCA lesions more frequently showed reverse mismatches, i.e., insignificant angiographic stenosis, but positive FFR (<0.80). As LMCA supplied a large myocardial territory, a moderate stenosis was more functionally significant. As a practical matter, FFR measurement should be considered for insignificant, isolated LMCA disease with clinically suspected angina.

The presence of plaque rupture may influence the functional significance of a stenosis. Currently, the impact of innocent plaque rupture on functional significance is poorly understood. We previously reported that the presence of plaque rupture is associated with reduced FFR in isolated LMCA disease (18). To better understand the contribution of local factors on the physiological effect of a stenosis, we simulated lesion-based geometric effects of a stenosis on FFR. Theoretically, a complex or irregular lumen produces greater flow resistance and energy loss of fluid, thus resulting in more pressure drop and reduction of FFR. Not surprisingly, in addition to lumen size, many factors, such as plaque shape, length, and surface roughness or plaque rupture may be associated with the change of FFR, supporting the results of our clinical data. Among lesions with same degree of angiographic stenosis, the various shapes of a ruptured plaque influence the FFR such that there is no common value among them. We simulated this scenario in Figure 4, although a further study will be required. In addition, thrombotic material superimposed on a ruptured site may increase the roughness of the vessel surface and subsequently increase the flow resistance, thus adding to the physiological effect of plaque rupture.

Study limitations. First, from a methodological standpoint, the fact that our studies were not blinded could have led to a bias. However, data collection, data processing, and statistical analyses were conducted by independent research personnel, independent clinicians, and independent statisticians. Second, the number of LMCA lesions was underpowered for predictor analysis. Third, the purpose of this study was confined to an explanation of the discrepancy between coronary angiography

and FFR. Therefore, the treatment strategy for lesions showing this discrepancy was beyond the scope of this study.

Conclusions

The discrepancy between coronary angiography and FFR in assessing coronary artery stenoses was attributable to various clinical and lesion-specific factors frequently unrecognizable in diagnostic coronary angiography, thus suggesting that coronary angiography cannot sufficiently predict the result of FFR. Therefore, FFR, a clinical ischemia index integrating various local factors, is more reliable than angiographic stenosis severity.

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Key Words: fractional flow reserve ■ quantitative coronary angiography ■ visual-functional mismatch.

APPENDIX

For supplementary tables, figures, and Methods, please see the online version of this paper.