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Original article

Severity of morphological lesion complexity affects fractional flow reserve in intermediate coronary stenosis

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ABSTRACT

Background: Although functional ischemia identification is important when determining revascularization, angiographic assessment alone is challenging in intermediate coronary stenosis. Previous studies have reported that lesion-specific characteristics affected the fractional flow reserve (FFR). However, the relationship between morphological lesion complexity and FFR has not yet been fully evaluated. This study aimed to evaluate the impact of morphological lesion complexity on FFR in intermediate coronary stenosis.
Methods: A total of 109 consecutive patients with 136 intermediate coronary stenoses (visually estimated diameter stenosis: 40–70%) were assessed via quantitative coronary angiography, lesion-specific characteristics, and FFR. Indexed lesions were assessed according to 6 morphological lesion characteristics: eccentricity, bend, irregularity, calcification, bifurcation, and diffuse. The lesions were then classified into 3 groups according to the morphological severity count represented by the number of present characteristics (mild-complex: 0–1, moderate-complex: 2–3, and severe-complex: 4–6), and their functional severities were evaluated. Lesions with an FFR <0.80 were considered functionally significant coronary stenoses.
Results: Of the 136 lesions, 51% were located in the left anterior descending artery (LAD) and 47% had an FFR <0.80. The FFR differed significantly among the 3 lesion complexity groups (0.84 ± 0.10 vs. 0.79 ± 0.10 vs. 0.73 ± 0.07, for mild-, moderate-, and severe-complex, respectively; $p < 0.01$). In a multivariate logistic analysis, LAD lesions, moderate- and severe-complex, and diameter stenosis were independently associated with an FFR <0.80 [odds ratio (OR): 5.65, 95% confidence interval (CI): 2.50–12.80, $p < 0.01$; OR: 2.96, 95% CI: 1.30–6.72, $p < 0.01$; OR: 7.11, 95% CI: 1.25–40.37, $p = 0.03$, and OR: 2.65, 95% CI: 1.04–6.72, $p = 0.04$, respectively].
Conclusions: Both indexed vessels and the degree of diameter stenosis affected the FFR. In addition, the severity of morphological lesion complexity correlated with the degree of functional severity in intermediate coronary stenosis.

Introduction

Revascularization improves the symptoms and clinical outcomes of inducible ischemia, whereas optimal medical treatment provides a better prognosis for patients without any evidence of this condition [1,2]. The most important prognostic factor associated with revascularization is the presence and extent of inducible ischemia [3,4]. Excellent results have been reported for patients with myocardial infarction, with cardiovascular death rates of <1.0% per year in those with normal myocardial perfusion images [5]. Therefore, we should evaluate whether such lesions represent functionally significant stenosis when making decisions regarding revascularization.

Despite the development of noninvasive coronary imaging, coronary angiography still plays a pivotal role for interventional cardiologists when deciding to perform revascularization. However, it is challenging to develop a therapeutic strategy for

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intermediate coronary stenosis based on an angiographic assessment alone because of potential discrepancies between the visual and functional assessments. Fractional flow reserve (FFR) has been recognized as the gold-standard modality for evaluating epicardial coronary stenosis associated with ischemia in interventional cardiac catheterization laboratories [6–8]. Previous studies have demonstrated that the use of FFR evaluation as a guide for decisions regarding the need for revascularization resulted in better clinical outcomes for intermediate lesions when compared with angiographic guidance alone [9–12]. Other studies have shown that each lesion characteristic, including the lesion length, affected the FFR values [13,14]. However, the relationship between the presence of multiple morphological lesion characteristics and FFR values has not yet been fully evaluated. Therefore, this study aimed to evaluate the cumulative impact of morphological lesion complexity on the FFR in intermediate coronary stenosis.

Methods

Study design and population

Between August 2009 and September 2011, consecutive stable angina patients with intermediate coronary stenosis who underwent elective coronary angiography and invasive physiological assessment were prospectively enrolled in this study. Intermediate stenosis was defined as a 40–70% diameter stenosis (DS) by visual assessment. The exclusion criteria were as follows: (1) left main coronary artery lesions; (2) in-stent restenosis; (3) bypass graft lesions; (4) previous percutaneous coronary intervention (PCI) in the index vessel; (5) culprit vessels in the setting of an old myocardial infarction; (6) multiple stenoses (DS >40%) within the same index vessel; (7) a donor artery for the chronic total occlusive lesion; (8) side-branch stenosis in the bifurcation lesion; and (9) contraindication to hyperemic stimuli agents. The study protocol was approved by the institutional review board, and all eligible patients provided written informed consent prior to the procedure.

FFR measurement

Index vessel engagement was performed via the radial or femoral approach with 5–7 French guide catheters. Coronary angiographic images were acquired following intracoronary nitroglycerin (100–200 μg) administration. Equalization was performed with the guide wire sensor positioned at the guide catheter tip. The 0.014-inch pressure guide wire (St. Jude Medical, Minneapolis, MN, USA) was then advanced distally to the stenosis. The FFR was measured at maximal hyperemia, which was induced via the administration of intravenous adenosine triphosphate (ATP; 150 μg/kg/min) through the forearm vein. The FFR was calculated as the mean distal coronary pressure divided by the mean aortic pressure during maximal hyperemia. Hyperemic pressure pullback tracings were performed as described previously [7,15]. A lesion with an FFR threshold of <0.80 was defined as a functionally significant coronary stenosis [11].

Angiographic parameters

Quantitative coronary angiography (QCA) was independently performed by 2 experienced observers at Aichi Medical University who were blinded to the FFR results and patient characteristics. Conventional angiograms were assessed using an off-line QCA system (CMS, Medis, Leiden, the Netherlands). The external diameter of the contrast-filled guide catheter was used for calibration. The reference diameter, minimum lumen diameter, and lesion length were measured using an edge detection system, and the DS was subsequently calculated.

All indexed lesions were evaluated according to the following morphological lesion characteristics based on the American Heart Association or American College of Cardiology guidelines for lesion classification: (1) lesion eccentricity, (2) lesion bend (>45°), (3) lesion irregularity, (4) calcification (moderate to heavy calcification equivalent to spinal density), (5) bifurcation (major side branch involvement), and (6) diffuse (>20 mm length) [16]. The lesions were then classified into the following 3 groups according to the morphological severity count as determined by the number of present characteristics: mild-complex (0–1), moderate-complex (2–3), and severe-complex (4–6). Regarding lesion location, the proximal location was defined as one-third proximal to the target coronary vessel; all other locations were defined as distal.

Statistical analysis

The descriptive statistics are presented as means ± standard deviations (SDs) or *n* (%). Differences between the 2 groups were assessed with the Student's *t*-test for continuous variables. Comparisons of more than 2 groups were conducted using an analysis of variance (ANOVA) and Dunnett's test to adjust for multiple statistical tests. Correlations between 2 variables were estimated with the Pearson correlation coefficient. The incidence of an FFR <0.80 was analyzed using both univariate and multivariate logistic regression models to identify potential and independent predictors of functionally significant coronary stenosis. The independent predictors in the multivariate model were set based on the results of the univariate analysis. In cases wherein the candidate predictors in the multivariate analysis exhibited a few strong correlations, more clinically meaningful predictors were selected from among the candidates to avoid the multicollinearity of variables. All statistical analyses were performed using SAS 9.3 software (SAS institute, Cary, NC, USA). Statistical significance was defined as a p-value <0.05.

Results

Patient population

Between August 2009 and September 2011, a total of 113 stable angina patients were enrolled, in whom 143 isolated intermediate coronary stenoses were detected. Seven lesions were excluded from the analysis for the following reasons: 2 lesions were located in the left main coronary artery; 2 lesions were located in coronary artery bypass grafts; 1 lesion was related to an old myocardial infarction; and in 2 lesions, hyperemia could not be achieved via intravenous ATP infusion because of an atrioventricular block. Finally, 136 isolated intermediate coronary stenoses in 109 patients were analyzed.

The baseline patient and lesion-specific characteristics are summarized in Table 1 and Table 2. Regarding lesion location, 70 (51%) lesions were located in the left anterior descending artery (LAD) and 42 (31%) were located in the proximal segment. The overall mean DS was 56.0 ± 8.0%, and the mean FFR value was 0.81 ± 0.11. Functionally significant coronary stenosis, defined as an FFR <0.80, was observed in 64 (47%) lesions. Overall, there was no correlation between DS and the FFR and a significant correlation between the morphological severity count and FFR ($r = -0.15$, $p = 0.09$ and $r = -0.38$, $p = 0.01$, respectively; Fig. 1A and B). In the study subjects, revascularization was deferred for 65 (48%) lesions, whereas 70 (51%) and 1 (1%) lesions were subjected to PCI and bypass surgery, respectively.

Impact of the morphological lesion characteristics on DS as determined by QCA and FFR

Although angiographic DS via QCA did not differ between the presence and absence of any of the morphological lesion

Table 1
Patient characteristics.

Patients	$n = 109$
Age (years)	69 ± 9
Male gender, *n* (%)	91 (83)
BMI (kg/m^2)	23.5 ± 3.9
Hypertension, *n* (%)	64 (59)
Diabetes mellitus, *n* (%)	62 (57)
Dyslipidemia, *n* (%)	73 (67)
Smoking, *n* (%)	47 (43)
Hemodialysis, *n* (%)	9 (8)
OMI, *n* (%)	28 (26)
PCI history, *n* (%)	37 (34)
Ejection fraction (%)	69 ± 8
CCS classification of angina, *n* (%)	
I/II/III/IV	41 (38)/52 (48)/14 (13)/2 (2)

Values are shown as means ± standard deviations or *n* (%). BMI, body mass index; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; CCS, Canadian Cardiovascular Society.

Table 2
Lesion characteristics.

Lesions	$n = 136$
Vessel distribution, *n* (%)	
LAD/LCX/RCA	70 (51)/32 (24)/34 (25)
Lesion location, *n* (%)	
Proximal/distal	42 (31)/94 (69)
QCA morphology	
Eccentricity, *n* (%)	78 (57)
Bend, *n* (%)	17 (13)
Irregularity, *n* (%)	30 (22)
Calcification, *n* (%)	20 (15)
Bifurcation, *n* (%)	42 (31)
Diffuse, *n* (%)	34 (25)
QCA analysis	
Reference diameter (mm)	2.7 ± 0.5
Minimal lumen diameter (mm)	1.2 ± 0.3
DS (%)	56.0 ± 8.0
Lesion length (mm)	16.1 ± 8.5
FFR	0.81 ± 0.11
FFR <0.80, *n* (%)	64 (47)
Lesion with DS >50% and FFR ≥0.80, *n* (%)	49 (36)
Lesion with DS ≤50% and FFR <0.80, *n* (%)	13 (10)

Values are shown as means ± standard deviations or *n* (%). FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; QCA, quantitative coronary angiography; DS, diameter stenosis.

characteristics, the FFR was significantly lower in the presence of lesion eccentricity, lesion irregularity, bifurcation, and diffuse relative to the absence of these characteristics (Table 3).

With respect to lesion complexity as assessed by morphological severity count, 69 (51%) lesions were mild-complex, 56 (41%) were moderate-complex, and 11 (8%) were severe-complex (Fig. 2). There was no significant difference in DS via QCA among the 3 groups (55.5 ± 7.8% vs. 56.8 ± 8.3% vs. 54.9 ± 7.9%, respectively; $p = 0.61$; Fig. 3A). However, the FFR differed significantly among the 3 groups (0.84 ± 0.10 vs. 0.79 ± 0.10 vs. 0.73 ± 0.07, respectively; $p < 0.01$; Fig. 3B). The moderate- and severe-complex groups exhibited significantly lower FFR values when compared with the mild-complex group ($p < 0.01$ for both comparisons, Fig. 3B).

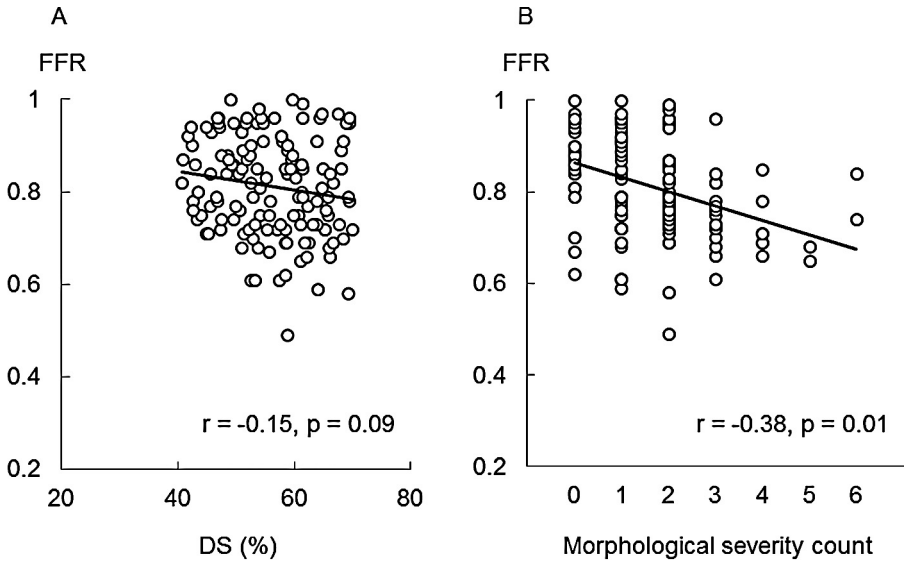

Fig. 1. Correlations of the FFR with the DS (A) and morphological severity count (B). (A) The scatterplots indicate no correlation between the FFR and DS ($r = 0.15$, $p = 0.09$); however, (B) a significant correlation exists between the FFR and morphological severity count ($r = -0.38$, $p = 0.01$). DS, diameter stenosis; FFR, fractional flow reserve.

Table 3
Differences in DS and FFR among morphological lesion characteristics.

Class	*N*	DS (%)			FFR		
		Presence	Absence	$p^\dagger$	Presence	Absence	$p^\dagger$
Eccentricity	78	56.6 ± 8.1	55.3 ± 7.8	0.35	0.79 ± 0.10	0.84 ± 0.10	<0.01
Bend	17	55.1 ± 8.3	56.1 ± 8.0	0.61	0.80 ± 0.08	0.82 ± 0.11	0.50
Irregularity	30	58.0 ± 8.3	55.4 ± 7.8	0.12	0.77 ± 0.10	0.82 ± 0.10	0.02
Calcification	20	55.6 ± 7.4	56.1 ± 8.1	0.82	0.78 ± 0.09	0.82 ± 0.11	0.18
Bifurcation	42	56.5 ± 7.9	55.8 ± 8.0	0.62	0.77 ± 0.10	0.83 ± 0.10	<0.01
Diffuse	34	55.4 ± 8.1	56.2 ± 8.0	0.62	0.77 ± 0.10	0.83 ± 0.10	<0.01

Values are shown as means ± standard deviations or *n*. FFR, fractional flow reserve; DS, diameter stenosis.
† Student's *t*-test.

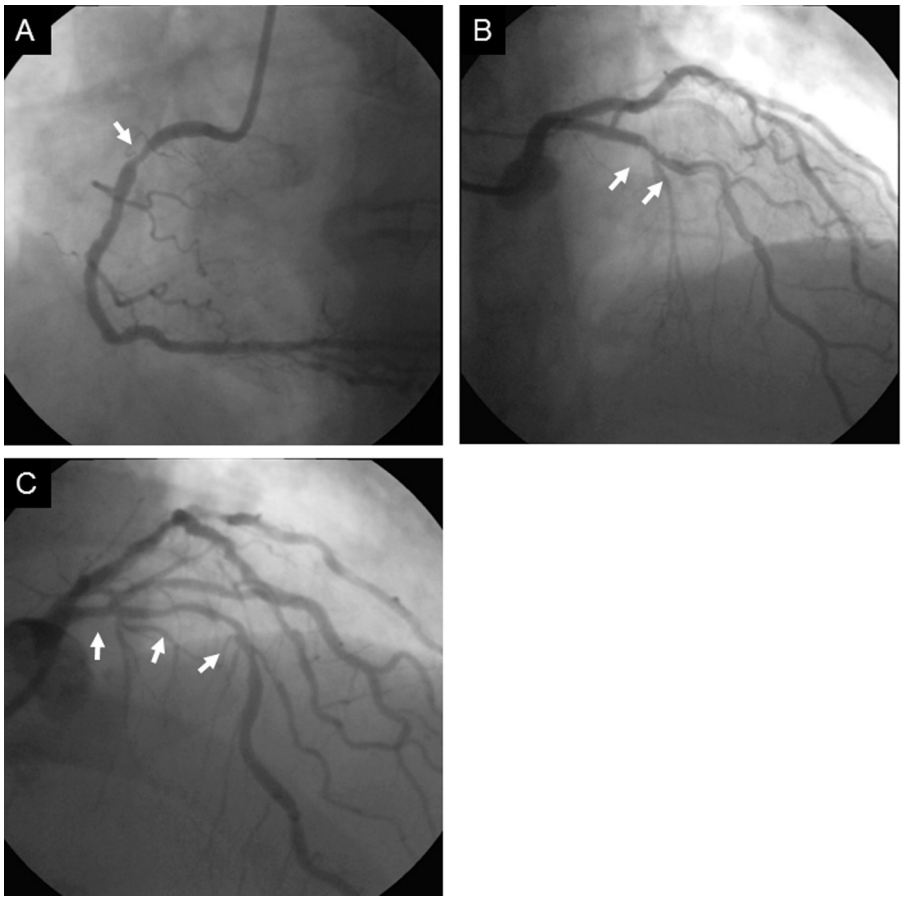

Fig. 2. Examples of the different morphological lesion complexity groups. (A) Mild-complex case. A focal lesion was observed in the proximal right coronary artery (white arrow). The DS was 45.7%, morphological severity count was 0, and FFR was 0.93. (B) Moderate-complex case. A lesion with eccentricity, irregularity, and calcification was observed in the proximal LAD (white arrow). The DS was 49.9%, morphological severity count was 3, and FFR was 0.77. (C) Severe-complex case. A lesion featuring all of the morphological lesion characteristics was observed in the proximal LAD (white arrow). The DS was 47.4%, morphological severity count was 6, and FFR was 0.74. DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending artery.

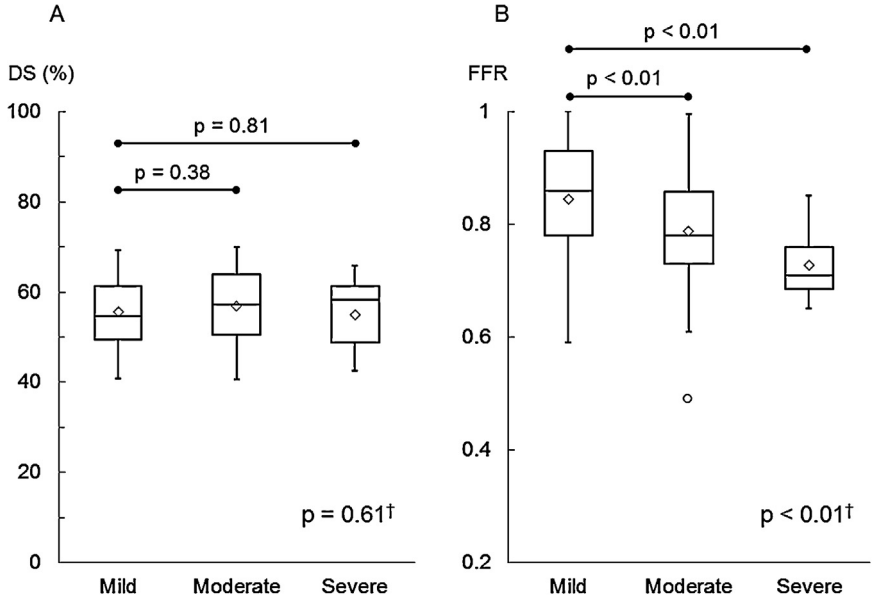

Fig. 3. Comparison of the DS (A) and FFR values (B) among the 3 morphological lesion complexity groups. (A) There was no significant difference in the DS on QCA among the 3 morphological lesion complexity groups (55.5 ± 7.8% vs. 56.8 ± 8.3% vs. 54.9 ± 7.9% for mild-, moderate-, and severe-complex, respectively; $p = 0.61^{\dagger}$). (B) However, the FFR differed significantly among the 3 morphological lesion complexity groups (0.84 ± 0.10 vs. 0.79 ± 0.10 vs. 0.73 ± 0.07, respectively; $p < 0.01^{\dagger}$). The moderate- and severe-complex groups had significantly lower FFR values relative to the mild-complex group ($p < 0.01^{\P}$ for both comparisons). The circle indicates an outlier. †Analysis of variance; ¶Dunnett's test; DS, diameter stenosis; FFR, fractional flow reserve; QCA, quantitative coronary angiography.

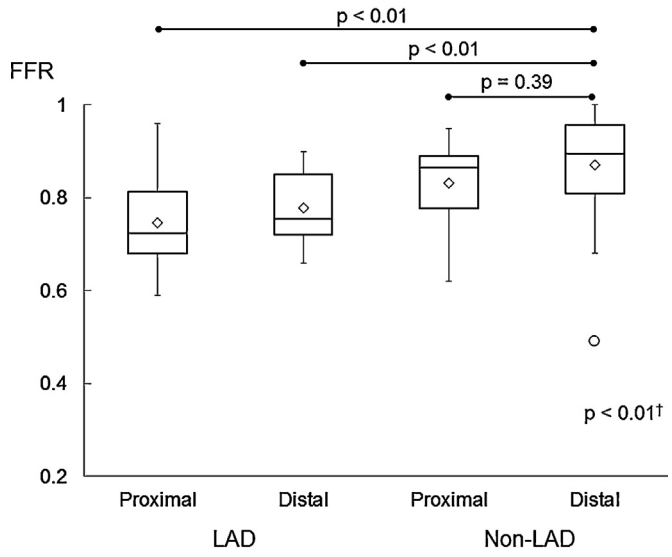

Fig. 4. Effects of indexed vessels and lesion location on the FFR. The FFR differed significantly among the 4 locations as determined by LAD or non-LAD with proximal or distal lesions (0.75 ± 0.11 vs. 0.78 ± 0.07 vs. 0.83 ± 0.09 vs. 0.87 ± 0.10, respectively; $p < 0.01^{\dagger}$). Lesions located in the proximal and distal LAD had significantly lower FFR values than did those in the distal non-LAD ($p < 0.01^{\P}$ for both comparisons). The FFR did not differ between the proximal and non-proximal lesions located in the non-LAD ($p = 0.39^{\P}$). The circle indicates an outlier. †Analysis of variance; ¶Dunnett's test; FFR, fractional flow reserve; LAD, left anterior descending artery.

Regarding the lesion location, the FFR was significantly lower in LAD than in non-LAD lesions (0.77 ± 0.09 vs. 0.86 ± 0.10, $p < 0.01$) and tended to be lower in proximal lesions than in distal lesions (0.78 ± 0.11 vs. 0.83 ± 0.10, $p = 0.054$). Fig. 4 summarizes the effects of index vessels (LAD vs. non-LAD) and the lesion location (proximal vs. distal) on the FFR values. Lesions located in the proximal and distal LAD had significantly lower FFR values when compared with those in the distal non-LAD. The FFR did not differ between proximal and non-proximal lesions located in the non-LAD ($p = 0.39$).

Association between lesion-specific factors and an FFR <0.80

In a univariate logistic regression analysis, the vessel distribution (LAD or non-LAD), lesion location (proximal or distal), morphological lesion characteristics (eccentricity, irregularity, bifurcation, or diffuse), lesion complexity (mild-complex or moderate-/severe-complex), and lesion length were significantly associated with an FFR <0.80 (Table 4). Among the factors with p-values ≤0.15 as shown in Table 4, eccentricity, irregularity, bifurcation, diffuse, and lesion length were excluded from the multivariate analyses to avoid the multicollinearity of variables, as these variables were strongly correlated with lesion complexity or DS. The final multivariate logistic model and analysis results are shown in Fig. 5. The vessel distribution (LAD), moderate- and severe-complex lesions, and DS >50% were independently associated with an FFR <0.80 [odds ratio (OR): 5.65, 95% confidence interval (CI): 2.50–12.80, $p < 0.01$; OR: 2.96, 95% CI: 1.30–6.72, $p < 0.01$; OR: 7.11, 95% CI: 1.25–40.37, $p = 0.03$; and OR: 2.65, 95% CI: 1.04–6.72, $p = 0.04$, respectively].

Table 4
Univariate logistic regression analysis for an FFR <0.80.

Variable	Level	OR (95% CI)	p
Sex	Male vs. female	1.63 (0.60–4.43)	0.34
Age	1 year	0.99 (0.95–1.03)	0.51
BMI	1 kg/m^2	0.97 (0.87–1.07)	0.53
LAD	Yes vs. no	5.89 (2.80–12.39)	<0.01
Lesion location	Proximal vs. distal	2.07 (0.99–4.35)	0.053
Eccentricity	Yes vs. no	4.20 (2.01–8.76)	<0.01
Bend	Yes vs. no	1.31 (0.47–3.62)	0.60
Irregularity	Yes vs. no	2.82 (1.20–6.60)	0.02
Calcification	Yes vs. no	1.45 (0.56–3.77)	0.44
Bifurcation	Yes vs. no	2.77 (1.30–5.90)	<0.01
Diffuse	Yes vs. no	2.62 (1.17–5.87)	0.02
Lesion complexity	Moderate vs. mild	3.07 (1.47–6.39)	<0.01
	Severe vs. mild	9.61 (1.91–48.27)	<0.01
Reference diameter	1 mm	0.62 (0.32–1.20)	0.16
DS	10%	1.47 (0.95–2.27)	0.08
	>50% vs. ≤50%	1.84 (0.84–4.04)	0.13
Lesion length	1 mm	1.06 (1.01–1.11)	<0.01

OR, odds ratio; CI, confidential interval; BMI, body mass index; LAD, left anterior descending artery; DS, diameter stenosis.

Discussion

The main findings of this study were as follows: (1) although there was no significant difference in DS via QCA, the FFR differed significantly among the 3 morphological lesion complexity groups; (2) the FFR in LAD lesions was significantly lower than that in non-LAD lesions; and (3) the LAD lesions, moderate- and severe-complex lesions, and DS >50% associated independently with an FFR <0.80.

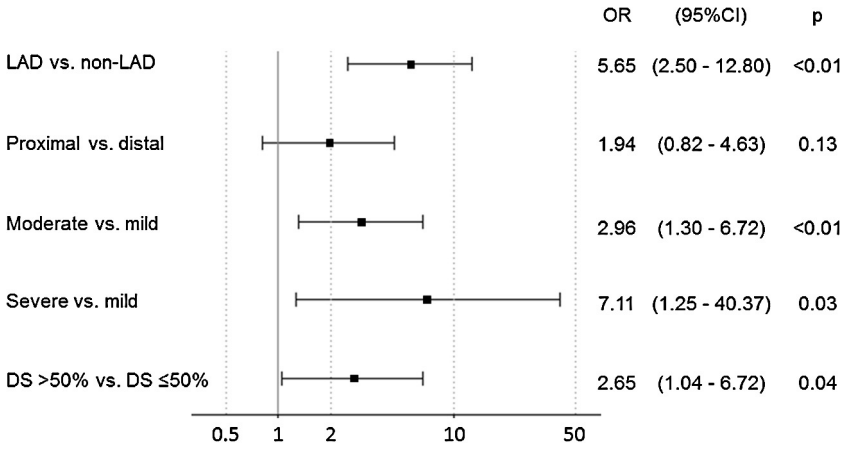

Fig. 5. Forest plot of the multivariate analysis for factors predictive of an FFR <0.80. The vessel distribution (LAD), moderate- and severe-complex lesions, and DS >50% were independently associated with functionally significant ischemia in intermediate coronary stenosis. OR, odds ratio; CI, confidence interval; LAD, left anterior descending artery; DS, diameter stenosis; FFR, fractional flow reserve.

Anatomical and physiological lesion assessment

The revascularization of coronary artery lesions with inducible ischemia can improve patients' outcomes [2,17]. Guidelines have recommended using noninvasive stress imaging tests to evaluate functional ischemia, although noninvasive assessments are limited in their ability to accurately localize the ischemic segment [18]. Although coronary angiography often underestimates or overestimates a lesion's functional severity, it remains the standard modality for PCI lesion selection in daily clinical practice [19,20].

FFR, which was recently adopted for clinical practice, can evaluate coronary physiology with more specific and better spatial resolution. As shown in previous studies, there are discrepancies in the anatomical and physiological assessments of lesions, suggesting that physicians might be able to avoid suboptimal treatment strategies, including unnecessary revascularization [1,9–12]. Therefore, FFR has been recognized as the gold-standard modality for identifying functional ischemia in intermediate coronary stenosis [10,21,22].

However, as the number of cases with FFR measurements has increased, relatively higher frequencies of visual–functional discrepancies in intermediate coronary stenosis have been observed [14]. In that study, lesions with DS >50% and FFR ≥0.80 (called "mismatch") were observed in 57% of lesions, whereas lesions with DS ≤50% and FFR <0.80 (called "reverse mismatch") were observed in 16%. In our cohort, 49 (36%) lesions were detected as mismatch cases and 13 (10%) were detected as reverse-mismatch cases (Table 2). Clinical and lesion specific-factors, which are unrecognizable via angiography, were among the factors affecting FFR values. Therefore, angiography cannot accurately predict the functional severity. However, if we can appropriately detect a particular type of patient characteristic and/or lesion characteristic/morphology, we might be able to more accurately predict functional severity from angiography.

Morphological lesion complexity and FFR

Previous studies have reported an association between FFR values and the lesion length, minimal lumen diameter, and minimal lumen area [23–26]. In addition to QCA parameters, our results showed that particular morphological lesion characteristics, including eccentricity, irregularity, or bifurcation, were associated with significantly lower FFR values relative to those of lesions without these characteristics. As the coronary pressure gradient is determined by the flow velocity and the separation and friction coefficients in a stenotic lesion are based on Bernoulli principals [27,28], these morphological factors could reduce the FFR value by producing a greater flow resistance and fluid energy loss consequent to friction, separation, and turbulence.

Although several studies have evaluated the relationship between lesion characteristics and the FFR [13,14], to our best knowledge this is the first report to evaluate the cumulative impact of morphological lesion complexity on functional lesion severity. Our results suggest that moderate- to severe-complex lesions with multiple morphological lesion characteristics induce greater pressure drops when compared with mild-complex lesions, even in cases with similar degrees of angiographic stenosis. In addition, moderate- and severe-complex lesions were identified as independent predictors of functionally significant ischemia in intermediate coronary stenosis (Table 4).

Lesion location and FFR

The current study showed that different lesion locations (LAD vs. non-LAD) influenced the FFR. The FFR is well known to depend on the myocardial supply territorial area [29]. Therefore, it was not surprising that lesions located in the LAD had significantly lower FFR values and were independently associated with an FFR <0.80. Leone et al. reported that lesions localized in the proximal LAD correlated with significantly lower FFR values and a higher FFR positivity rate than did those in the distal LAD, left circumflex artery, and right coronary artery [30].

Finally, as described previously, cases involving discrepancies between the anatomical and functional assessments were frequently observed in daily clinical practice. Our results would facilitate a better understanding of the possible mechanisms that cause this discrepancy.

Study limitations

First, the number of study patients was relatively small, which might have led to a selection bias. Therefore, additional large-scale studies will be needed to confirm our results. Second, we evaluated a single segment of an angiographically moderate stenosis; therefore, we did not consider other mild stenoses within the same coronary artery that might have affected the FFR value. However, we carefully performed a pressure pullback tracing curve to exclude tandem lesions with FFR value stepwise increases of >0.10. Third, since this study aimed to clarify the relationship between angiographic and functional lesion assessments, we did not evaluate the relationship between FFR measurement and other functional studies such as exercise electrocardiogram or stress nuclear study. Therefore, we did not refer to the impacts of differences in treatment strategies on the clinical outcomes.

Conclusions

Both indexed vessels and the degree of DS affect the FFR. In addition, the morphological lesion complexity as assessed by cumulative morphological lesion characteristics correlated with the degree of functional severity in intermediate coronary stenosis. Our results will facilitate further elucidation of the possible mechanisms and/or causes in cases involving visual-functional discrepancies.

Conflict of interest

The authors declare that there are no conflicts of interest.

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