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ORIGINAL ARTICLE

Comparison between instantaneous wave-free ratio versus morphometric assessments by intracoronary imaging

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Abstract

Anatomical measurements obtained by intracoronary imaging devices are reported to correlate significantly with fractional flow reserve (FFR). Instantaneous wave-free ratio (iFR) is a nonhyperemic index of stenosis severity with discordant reports regarding its accuracy in relation to FFR. There is no information on the correlation of iFR with measurements derived from intracoronary imaging devices. The purpose of this study was to assess the relationship among iFR, intravascular ultrasound (IVUS), and optical frequency domain imaging (OFDI) parameters. Eighty lesions in 72 patients who underwent elective angiography and had intermediate lesions were enrolled. All lesions were assessed by iFR, FFR, IVUS, and OFDI. iFR was ≤ 0.89 in 21 (26%) lesions and FFR was ≤ 0.80 in 41 (51%) lesions. iFR correlated significantly with both IVUS-derived minimum lumen area (MLA) ($r=0.375$, $p=0.003$) and OFDI-derived MLA ($r=0.357$, $p=0.005$). FFR also correlated significantly with both IVUS-derived MLA ($r=0.472$, $p<0.001$) and OFDI-derived MLA ($r=0.445$, $p<0.001$). Among the lesions with FFR ≤ 0.80, iFR > 0.89 (mismatch) was observed in 20 lesions. There was no lesion with iFR ≤ 0.89 (reverse mismatch) among the lesions with FFR > 0.80. The lesion location among three major coronary vessels was related with the discrepancy between iFR and FFR (p = 0.007). In conclusion, iFR and FFR showed a significant correlation with IVUS and OFDI measurements. The discrepancy of iFR and FFR was associated with the lesion locations.

Keywords Instantaneous wave-free ratio · Fractional flow reserve · Intravascular ultrasound · Optical frequency domain imaging

Introduction

Although coronary angiography has been widely used to evaluate coronary artery disease, angiographic assessment does not always accurately predict functional significance of coronary stenosis [1], especially in intermediate coronary lesions. Therefore, additional diagnostic methods are recommended for full assessment of the clinical impact of intermediate coronary lesions. Fractional flow reserve (FFR) is an established invasive index that evaluates the functional significance of coronary stenosis [2]. Moreover, FFR-guided percutaneous coronary intervention (PCI) does not only improve clinical outcome [3] but also saves costs [4] by reducing unnecessary PCI compared with angiography-guided PCI.

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are intracoronary imaging techniques for anatomic/morphological assessment of coronary lesion

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and used to optimize stent deployment. Several studies have reported the presence of a significant correlation between minimum lumen area (MLA), measured by IVUS, and FFR [5–7]. The presence of small IVUS-derived MLA was associated with the incidence of major cardiac events (MACE) [8] which were mainly caused by revascularization. Recently, OCT is reported to have better diagnostic efficiency in identifying hemodynamically significant coronary stenoses [6], compared with IVUS. Although the association of OCT-derived MLA with clinical outcome is unclear at the moment, OCT has superior ability to visualize the true lumen–intima interface, compared with IVUS [9], indicating that OCT-derived MLA may also have the potential to predict the risk of MACE.

The instantaneous wave-free ratio (iFR) is a new vasodilator-free index of severity of coronary stenosis, representing the trans-lesion pressure ratio during a specific period of baseline diastole, when distal resistance is lowest and stable. iFR would simplify intracoronary functional assessments with lower cost, less patient discomfort, and shorter procedure time by avoiding the use of vasodilator [10]. Previous studies indicated that iFR correlates significantly with FFR, although such relationships varied among the studies [11–13]. However, the correlations between iFR and indexes computed using intracoronary imaging devices have not been reported.

The objective of this study was to assess the relationship between pressure indices iFR and FFR against anatomical measurements by IVUS and optical frequency domain imaging (OFDI) in patients undergoing functional assessments of coronary artery disease. We sought to evaluate whether iFR would agree with anatomical measurements as is the case for FFR.

Materials and methods

Study population

Yokohama-defer study was a prospective single-center registry of 77 patients who underwent elective angiography and had intermediate coronary lesions at one or more epicardial coronary arteries at Yokohama City University Medical Center between December 2013 and January 2016. Stenoses located in small vessels (< 2.0 mm), serial stenosis or diffuse coronary narrowings, and vessels providing circulation to previously infarct regions were excluded. Other exclusion criteria included left main coronary artery or graft, contraindications to adenosine administration, patients with hemodynamic instability and hemodialysis, and anatomical characteristics such as vessel tortuosity and severe calcification that precluded the advancement of IVUS and OFDI catheters.

The study was approved by the Ethics Committee of our institution and all patients provided informed consent. IVUS and OFDI images were analyzed by an independent core laboratory (Stanford University Cardiovascular Core Analysis Laboratory), and the analysts were blinded to the patients and procedural characteristics.

Angiographic analysis

Angiographic views were obtained after an intracoronary bolus injection of 2–3 mg of isosorbide dinitrate (ISDN). Coronary angiograms were reviewed separately by an independent observer unaware of all clinical data, physiological assessments, and intracoronary imaging findings. Lesion length, minimum lumen diameter (MLD), percent diameter stenosis, and reference vessel diameter were analyzed by experienced personnel using Cardiovascular Angiographic Analysis System software (CAAS 5.9; Pie Medical Imaging, Maastricht, The Netherlands). Standard quantitative measurements [14] were used to calibrate and measure coronary dimensions.

Hemodynamic data collection and analysis

iFR and FFR were measured with a coronary pressure guidewire (Volcano Corporation, San Diego, CA). iFR was computed using software embedded onto the hemodynamic consoles, which uses proprietary iFR algorithms acting on electrocardiogram (ECG)-gated, time-aligned pressure traces, as described in detail previously [11]. iFR was calculated as the ratio of distal (Pd)-to-proximal (Pa) coronary pressures at the baseline iFR window. FFR was also automatically computed as the ratio of whole-cycle Pd/Pa during hyperemia. Maximal hyperemia was induced by intravenous adenosine triphosphate, administered at 150 µg/kg/min.

IVUS acquisition and analysis

IVUS images of the target stenosis were obtained with commercially available VISIWAVE system (Terumo Corp., Tokyo, Japan) using the ViewIT catheter (40 MHz, Terumo Corp.) during automated motorized pullback at 0.5 mm/s. All patients received intracoronary bolus injection of 2–3 mg of ISDN before intracoronary imaging. Images were digitally stored for offline analysis.

IVUS analysis was performed using validated planimetry system (VISIATLAS Ver0.2.0, Terumo Corp.) [15]. At the MLA site, we measured 1) MLA; 2) External elastic membrane (EEM) cross-sectional area (CSA); 3) plaque + media (P+M) CSA. Plaque burden at the MLA site was calculated as: P+M CSA/ EEM CSA×100. MLD was selected independently from the MLA site. The reference cross-sections were defined as the frame with the largest lumen within 10 mm proximal or distal to the MLA and before any side branch. At the reference site, we measured lumen CSA, EEM CSA, and P+M CSA. We assessed reproducibility of the IVUS findings in a random sample of 12 patients. IVUS images were reviewed separately by two independent observers blinded to the physiological assessments.

OFDI acquisition and analysis

OFDI imaging of the target stenosis was obtained using the commercially available LUNAWAVE system (Terumo Corp., Tokyo, Japan) and the FastView catheter (Terumo Corp., Tokyo, Japan). All patients received an intracoronary bolus injection of 2–3 mg of ISDN before intracoronary imaging. The automated pullback was performed at 20 mm/s while blood was removed by brief injection of contrast medium through the guiding catheter. The images were digitally stored for offline analysis.

OFDI measurements were performed using the proprietary software for offline analysis (Echoplaque 4, INDEC Systems, Mount View, CA). In the same way as described above for IVUS, we selected the MLA, MLD, and reference sites. To ensure that the same stenosis was measured with both techniques, synchronization of the IVUS and OFDI pullbacks was performed precisely using landmarks such as side branches, vein, and calcium. After selecting the MLA, MLD, and reference sites, OFDI analysis was performed by an experienced analyst blinded to the IVUS results. At the reference cross-section, we measured the reference lumen CSA, EEM CSA, and P+M CSA. The reproducibility of OFDI findings was also assessed in a random sample of 12 patients by 2 independent observers blinded to the physiological assessments.

Statistical analysis

Continuous variables are expressed as mean ± SD or median and inter-quartile values, while categorical variables are expressed as frequencies with percentage values for summary of patients' clinical characteristics. Linear regression analysis was used to determine the correlation coefficients between iFR and FFR. Polynomial regression analysis was used to identify the relationship and variability between physiological and anatomical measurements. Differences between iFR and FFR, and IVUS and OFDI in the same stenosis were calculated and expressed in Bland–Altman plots. The sensitivity and specificity curves were constructed to identify the optimal cutoff values of IVUS and OFDI measurements to predict iFR ≤ 0.89 and FFR ≤ 0.80. One-way analysis of variance (ANOVA) test was used to analyze continuous variables that showed normal distribution to identify the difference of clinical, angiographic, and intracoronary characteristics among discordant (FFR ≤ 0.80 and iFR > 0.89, FFR > 0.80 and iFR ≤ 0.89) and concordant (FFR ≤ 0.80 and iFR ≤ 0.89, FFR > 0.80 and iFR > 0.89) groups as well as the difference of iFR and FFR values among three coronary vessels, with pairwise post hoc comparisons adjusted by the Tukey–Kramer method. For continuous variables with skewed distribution, the Kruskal–Wallis test was used to examine differences in median values, with pairwise post hoc comparisons by the Steel–Dwass test. $p < 0.05$ was considered statistically significant. Analyses were performed using JMP 9 software® (SAS Institute, Cary, NC).

Results

Patients' characteristics

A total of 85 intermediate coronary stenoses in 77 patients were included in the study. No complications were recorded during the use of coronary pressure guidewire and intracoronary imaging devices. Five patients were excluded for the following reasons: the IVUS catheter could not be passed through the target lesion in two patients, and the OFDI was not evaluable due to incomplete blood clearance in two patients, while one patient had diffuse coronary narrowing. Thus, 80 stenoses in 72 patients were analyzed for iFR, FFR, IVUS, and OFDI. The clinical data and stenosis characteristics are summarized in Tables 1 and 2.

Table 1 Clinical characteristics of participating patients ($n = 72$)

Age (years)	67.3 ± 11.1
Male	62 (86.1)
Body height (cm)	163.1 ± 86.2
Body weight (kg)	64.2 ± 13.3
Body mass index	24.0 ± 3.8
Hypertension	43 (59.7)
Dyslipidemia	41 (56.9)
Diabetes mellitus	27 (37.5)
Renal dysfunction (eGFR < 60)	17 (23.6)
Hemodialysis	0 (0)
Current smoker	18 (25.0)
Familial history of coronary artery disease	18 (25.0)
Previous percutaneous coronary intervention	30 (41.7)
Previous myocardial infarction	25 (34.7)
Initial clinical presentation	
Stable angina	59 (81.9)
Unstable angina	5 (6.9)
Non-ST-segment elevation myocardial infarction	5 (6.9)
Recent myocardial infarction	3 (4.2)

Values are mean ±SD or *n* (%)

eGFR estimated glomerular filtration rate

Table 2 Lesion characteristics ($n=80$)

Angiography-related parameters	
Lesion location	
LAD	47 (58.8)
LCX	10 (12.5)
RCA	23 (28.8)
Physiological parameters	
iFR	0.92 ± 0.09
FFR	0.81 ± 0.10
iFR ≤ 0.89	21 (26.3)
FFR ≤ 0.80	41 (51.3)
QCA parameters	
Reference diameter (mm)	2.94 ± 0.56
Diameter stenosis (%)	49.0 ± 10.0
MLD (mm)	1.49 ± 0.33
Lesion length (mm)	12.9 ± 6.1
IVUS-related parameters	
MLA (mm^2)	2.19 ± 1.01
MLD (mm)	1.41 ± 0.31
Proximal reference lumen cross-sectional area (mm^2)	8.07 ± 2.79
Distal reference lumen cross-sectional area (mm^2)	7.13 ± 3.06
Plaque burden at MLA (%)	89.4 ± 5.1
OFDI-related parameters	
MLA (mm^2)	2.11 ± 1.05
MLD (mm)	1.36 ± 0.35
Proximal reference lumen cross-sectional area (mm^2)	8.04 ± 2.89
Distal reference lumen cross-sectional area (mm^2)	7.01 ± 3.04
Plaque burden at MLA (%)	NA

Values are mean ± SD or *n* (%)

FFR fractional flow reserve, *iFR* instantaneous wave-free period, *IVUS* intrvascular ultrasound, *LAD* left anterior descending artery, *LCX* left circumflex artery, *MLA* minimum lumen area, *MLD* minimum lumen diameter, *NA* not applicable, *OFDI* optical frequency domain imaging, *QCA* quantitative coronary arteriography, *RCA* right coronary artery

Relationship between iFR and FFR

Figure 1a shows a scatter plot between iFR and FFR, demonstrating moderate overall linear correlation between the two variables, with *r* value of 0.63 (95% confidence interval [CI] 0.47–0.75) ($p<0.001$). Figure 1b shows the Bland–Altman plot for iFR and FFR. On average, iFR exceeded FFR by 0.11 (95% CI − 0.05 to 0.27).

Comparison of MLA and MLD measurements with IVUS and OFDI

Measurements of MLD and MLA by IVUS and OFDI are shown in Fig. 2a, b. MLD and MLA by OFDI were significantly smaller than those by IVUS (1.36 ± 0.35 mm vs. 1.41 ± 0.31 mm, $p=0.002$ and 2.11 ± 1.01 mm^2 vs. 2.19 ± 1.05 mm^2, $p<0.001$, respectively). Figure 2c, d show the Bland–Altman analyzes for the MLD and MLA. The intra- and interobserver intra-class correlation coefficients for MLA by IVUS and OFDI were 0.999 and 0.998 and 0.999 and 0.999, respectively ($p<0.001$ for all).

Relation among IVUS measurements and iFR and FFR values

Regression analysis showed significant correlations between IVUS-derived MLA and iFR ($r=0.375$, $p=0.003$) (Fig. 3a), and between IVUS-derived MLA and FFR ($r=0.472$, $p<0.001$) (Fig. 3b). Significant correlations were also observed between IVUS-derived MLD and iFR ($r=0.378$, $p=0.003$), and between IVUS-derived MLD and FFR ($r=0.434$, $p<0.001$).

The sensitivity and specificity curves for IVUS-derived MLA to predict iFR ≤ 0.89 was MLA < 1.8mm^2 (sensitivity 67%, specificity 69%) (Fig. 4a) and that to predict FFR ≤ 0.80 was MLA<2.0mm^2 (sensitivity 66%, specificity 69%) (Fig. 4b).

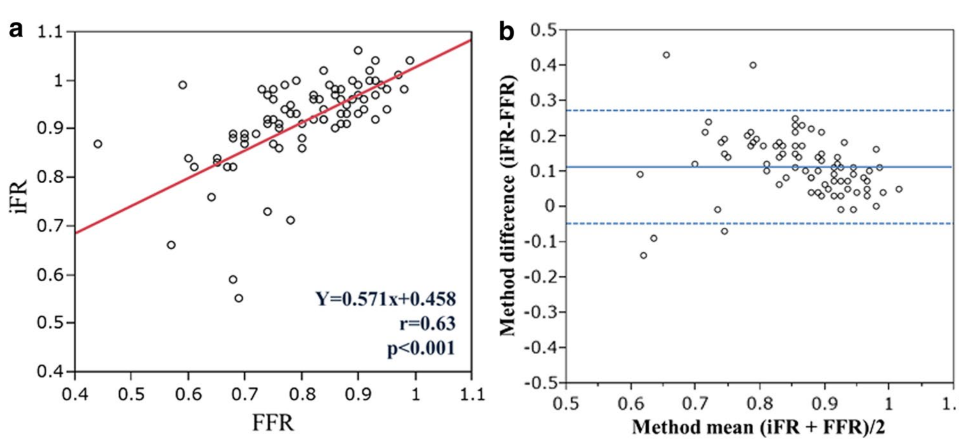

Fig. 1 Scatterplots and Bland–Altman Plots of iFR and FFR values. **a** Linear regression between iFR and FFR. The red line represents the line of best fit. **b** Bland–Altman plots of iFR and FFR. Mean bias is represented by the solid blue line (with 95% CI represented by the dashed blue line). *CI* confidence interval, *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio

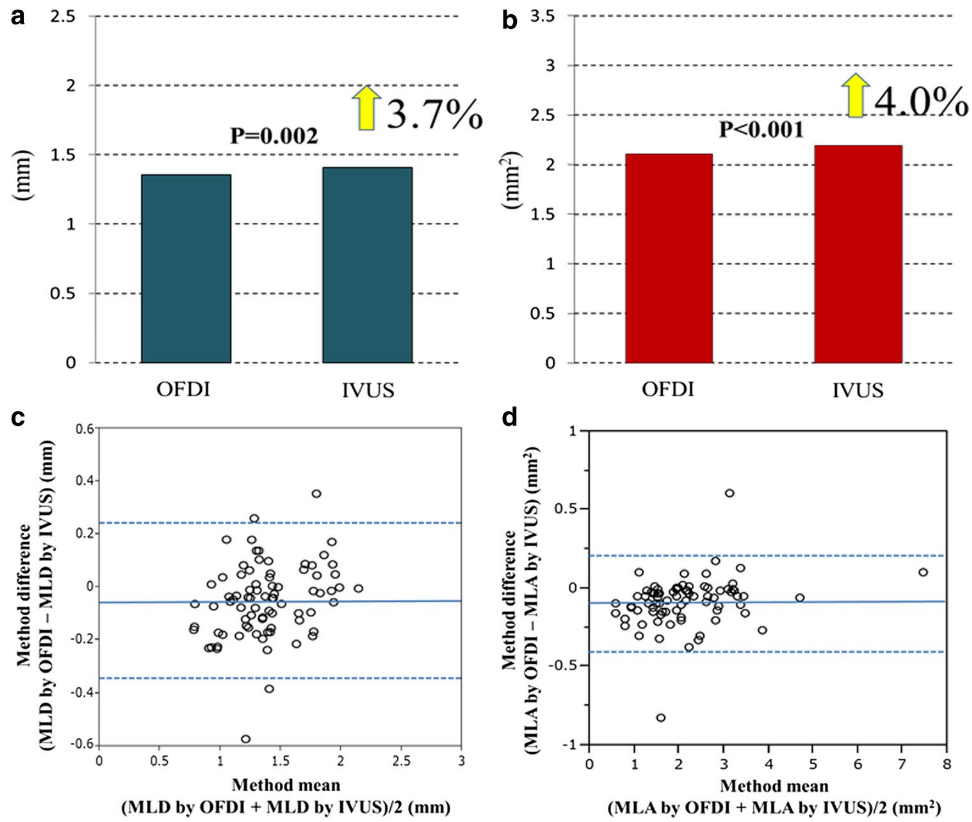

Fig. 2 Measurements of MLD and MLA by IVUS and OFDI. **a** MLD by IVUS was greater than that by OFDI (relative reference 3.7%). **b** MLA by IVUS was greater than that by OFDI (relative reference 4.0%). **c** Bland–Altman plots for measurements of MLD. **d** Bland–Altman plots for measurements of MLA. Mean bias is represented by the solid blue line (with 95% CI represented by the dashed blue line). *CI* confidence interval, *IVUS* intravascular ultrasound, *MLA* minimum lumen area, *MLD* minimum lumen diameter, *OFDI* optical frequency domain imaging

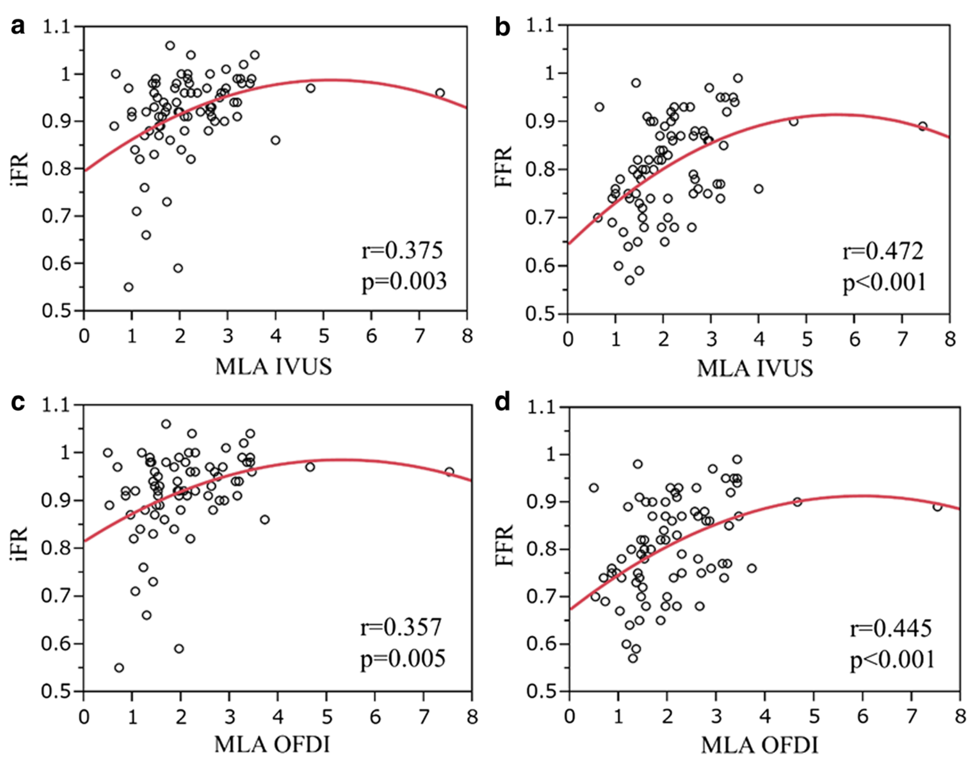

Fig. 3 Relation between IVUS- and OFDI-derived MLA and iFR and FFR values. **a** Correlation between iFR and IVUS-derived MLA. **b** Correlation between FFR and IVUS-derived MLA. **c** Correlation between iFR and OFDI-derived MLA. **d** Correlation between FFR and OFDI-derived MLA. *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio, *IVUS* intravascular ultrasound, *MLA* minimum lumen area, *OFDI* optical frequency domain imaging

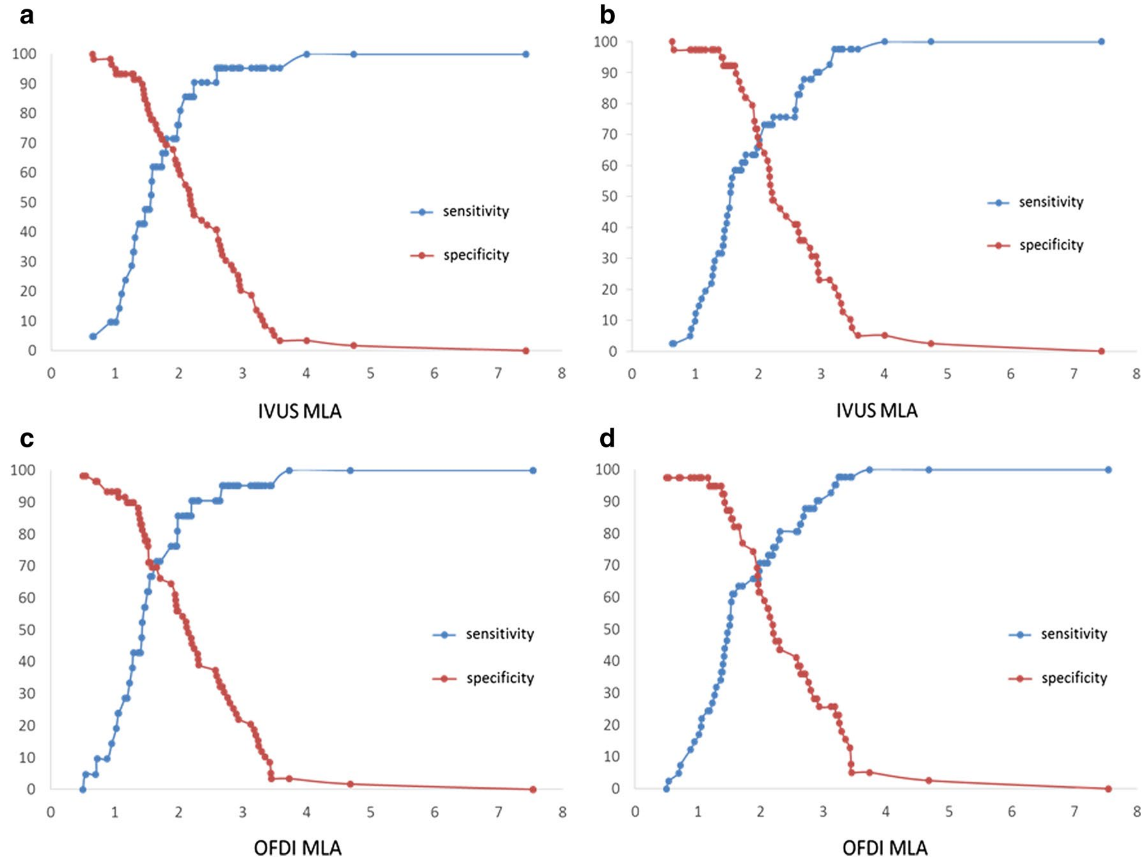

Fig. 4 Sensitivity and specificity curves for IVUS- and OFDI-derived MLA to predict iFR ≤ 0.89, and FFR ≤ 0.80. **a** Sensitivity and specificity curve for IVUS-derived MLA to predict iFR ≤ 0.89. **b** Sensitivity and specificity curve for IVUS-derived MLA to predict FFR ≤ 0.80. **c** Sensitivity and specificity curve for OFDI-derived MLA to predict iFR ≤ 0.89. **d** Sensitivity and specificity curve for OFDI-derived MLA to predict FFR ≤ 0.80. *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio, *IVUS* intravascular ultrasound, *MLA* minimum lumen area, *OFDI* optical frequency domain imaging

Relation among OFDI measurements and iFR and FFR values

Regression analysis showed significant correlations between OFDI-derived MLA and iFR ($r=0.357$, $p=0.005$) (Fig. 3c), and between OFDI-derived MLA and FFR ($r=0.445$, $p<0.001$) (Fig. 3d). Significant correlations were also observed between OFDI-derived MLD and iFR ($r=0.417$, $p<0.001$), and between OFDI-derived MLD and FFR ($r=0.460$, $p<0.001$).

The sensitivity and specificity curves for OFDI-derived MLA to predict iFR ≤ 0.89 was MLA < 1.65 mm^2 (sensitivity 67%, specificity 69%) (Fig. 4c) and that to predict FFR ≤ 0.80 was MLA < 1.96 mm^2 (sensitivity 66%, specificity 67%) (Fig. 4d).

Factors associated with the discrepancy between iFR and FFR

Among the 41 lesions with FFR ≤ 0.80, iFR > 0.89 (mismatch) was observed in 20 lesions. On the other hand, among the 39 lesions with FFR > 0.80, there was no lesion with iFR ≤ 0.89 (reverse mismatch). Comparison of the clinical characteristics, angiographic measurements, IVUS, and OFDI parameters according to iFR and FFR is shown in Tables 3 and 4. None of the lesions with both FFR ≤ 0.80 and iFR ≤ 0.89 were located in the right coronary artery (RCA) ($p=0.007$). The IVUS and OFDI measurements indicated that morphologic severity of the lesions in the mismatch group was between the two matched groups.

Table 3 Clinical and angiographic characteristics in concordant and discordant groups

	FFR ≤ 0.80		FFR > 0.80		p value
	iFR > 0.89 (n = 20)	iFR ≤ 0.89 (n = 21)	iFR > 0.89 (n = 39)	iFR ≤ 0.89 (n = 0)	
	Discordant	Concordant	Concordant	Discordant	
Age (years)	63.4 ± 11.5	68.3 ± 9.7	69.5 ± 11.1	–	0.12
Men	18 (90)	19 (90)	33 (85)	–	0.75
Body height (cm)	165.6 ± 81.5	163.2 ± 68.9	162.0 ± 95.9	–	0.33
Body weight (kg)	70.6 ± 16.9	61.9 ± 12.2	61.6 ± 10.2*	–	0.03
Body mass index	25.6 ± 4.9	23.1 ± 3.5	23.4 ± 3.0	–	0.06
Hypertension	12 (60)	15 (71)	21 (54)	–	0.42
Dyslipidemia	13 (65)	11 (52)	21 (54)	–	0.66
Diabetes mellitus	6 (30)	11 (52)	13 (33)	–	0.25
Renal dysfunction	5 (25)	4 (19)	9 (23)	–	0.89
Hemodialysis	–	–	–	–	–
Current smoker	7 (35)	5 (24)	7 (18)	–	0.35
Familial history	4 (20)	4 (19)	11 (28)	–	0.66
Lesions					0.007
LAD	11 (55)	19 (90)	17 (44)	–	
LCX	2 (10)	2 (10)	6 (15)	–	
RCA	7 (35)	0 (0)	16 (41)	–	

Data are expressed as n (%) unless otherwise specified. Continuous variables are presented by mean ±SD or median (IQR)

LAD left anterior descending, *LCX* left circumflex branch, *RCA* right coronary artery

*$p < 0.05$, group FFR > 0.80 iFR > 0.89 vs. FFR ≤ 0.80 iFR > 0.89

Table 4 IVUS and OFDI measurements in concordant and discordant groups

	FFR ≤ 0.80		FFR > 0.80		p value
	iFR > 0.89 (n = 20)	iFR ≤ 0.89 (n = 21)	iFR > 0.89 (n = 39)	iFR ≤ 0.89 (n = 0)	
	Discordant	Concordant	Concordant	Discordant	
Imaging parameters (IVUS)					
MLA (mm^2)	2.0 ± 0.8	1.7 ± 0.7*	2.6 ± 1.1	–	0.002
MLD (mm)	1.3 ± 0.3	1.1 ± 0.3*	1.5 ± 0.3	–	< 0.001
Calcium arc (°)	40.4 (0–77.9)	83.6 (12.1–149.7)	18.8 (0–89.5)	–	0.054
Lumen eccentricity index	0.18 ± 0.15	0.20 ± 1.3	0.19 ± 0.11	–	0.94
Atheroma eccentricity index	0.73 ± 0.21	0.75 ± 0.14	0.69 ± 0.18	–	0.51
Remodeling index	0.87 ± 0.13	0.88 ± 0.19	0.86 ± 0.16	–	0.82
Plaque burden	88.8 ± 4.9	88.3 ± 5.1	90.3 ± 5.2	–	0.36
Imaging parameters (OFDI)					
MLA (mm^2)	1.9 ± 0.8	1.6 ± 0.7*	2.5 ± 1.2	–	0.002
MLD (mm)	1.3 ± 0.3	1.1 ± 0.3*	1.5 ± 0.3	–	< 0.001
Calcium arc (°)	35.6 (0–78.1)	86.3 (37.5–149.1)*, †	22.6 (0–88.4)	–	0.02
Lipid arc (°)	100.8 (0–174.0)	76 (0–152.7)	108 (0–158.7)	–	0.58
Lumen eccentricity index	0.23 ± 0.13	0.27 ± 0.12	0.24 ± 0.13	–	0.58
Fibrous cap thickness (μm)	125 (85–285)	140 (120–200)	130 (90–150)		0.40
TCFA	0 (0)	0 (0)	0 (0)	–	–

Data are expressed as n (%) unless otherwise specified. Continuous variables are presented by mean ±SD or median (IQR)

IVUS intrvascular ultrasound, *MLA* minimum lumen area, *MLD* minimum lumen diameter, *OFDI* optical frequency domain imaging, *TCFA* thin-cap fibroatheroma

*$p < 0.05$, group FFR ≤ 0.80 iFR ≤ 0.89 vs. FFR > 0.80 iFR > 0.89; †$P < 0.05$, group FFR ≤ 0.80 iFR ≤ 0.89 vs. FFR ≤ 0.80 iFR > 0.89

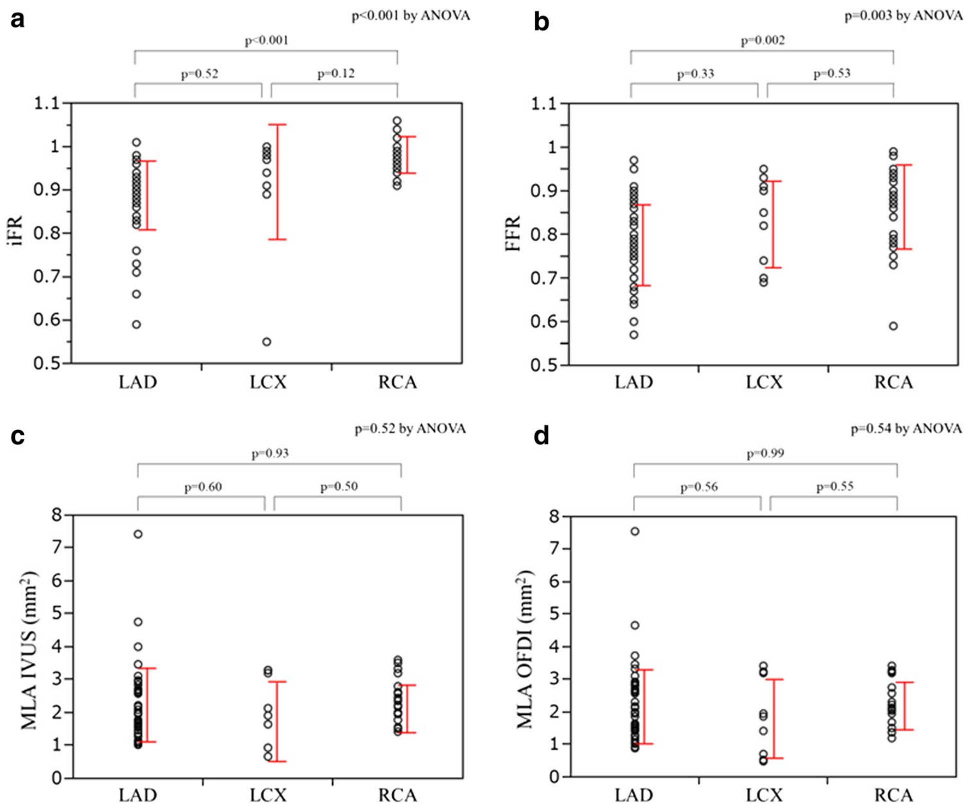

Fig. 5 Evaluation of iFR, FFR, IVUS-derived MLA, and OFDI-derived MLA for three different coronary arteries. **a** iFR value, **b** FFR value, **c** IVUS-derived MLA, and **d** OFDI-derived MLA for three different coronary arteries. *FFR* fractional flow reserve, *iFR* instantaneous wave-free ratio, *IVUS* intravascular ultrasound, *MLA* minimum lumen area, *OFDI* optical frequency domain imaging

Effect of lesion location on iFR and FFR values

As described previously, the percentage of functionally significant stenosis was different in each coronary artery segment (Table 3). Although the MLA values derived by IVUS and OFDI were similar among each major coronary artery ($p = 0.52$ and $p = 0.54$ by ANOVA), the mean values of iFR and FFR were highest in RCA lesions and lowest in left anterior descending lesions ($p < 0.001$ and $p = 0.003$ by ANOVA) (Fig. 5).

Discussion

The main findings of the present study are the followings: (1) iFR correlated significantly with IVUS- and OFDI-derived MLA; (2) similar diagnostic efficiencies of iFR and FFR in identifying anatomically significant coronary stenosis; (3) the discrepancy between iFR and FFR was related to the lesion location, and (4) good concordance between IVUS and OFDI measurements of lumen size. To the best of our knowledge, this is the first clinical study that assesses the relation between iFR and measurements using intracoronary imaging devices.

Several studies have shown significant correlation between iFR and FFR [11–13]. The diagnostic accuracy of iFR for myocardial ischemia is equivalent to FFR when hyperemic stenosis resistance (HSR) is used as the reference standard [12], and is also superior to FFR when coronary flow velocity reserve is used as the reference standard [13]. However, all physiological indices are influenced by the pressure and flow properties of the coronary artery. Therefore, an independent reference standard is needed to compare these two devices. Recently, van de Hoef et al. [16] reported that using a combined reference standard of myocardial perfusion scintigraphy and HSR index, the area under the curve by receiver-operating characteristic curve analysis for myocardial ischemia was similar between iFR and FFR (0.84 vs. 0.88, $p = 0.20$). They concluded that iFR and FFR have an equivalent diagnostic accuracy for the detection of ischemia-generation coronary lesions. In the present study, we used IVUS- and OFDI-derived MLA as the independent reference standards, which have been reported to correlate significantly with FFR [5, 6, 17, 18].

IVUS-derived MLA has the potential to predict positive myocardial perfusion scintigraphy test [19] and is also reported to correlate with clinical outcomes. Abizaid et al. [8] reported that deferring PCI in intermediate lesions on the basis of an IVUS-derived MLA of > 4.0 mm^2 criterion was safe, with a low event rate (2% death or myocardial infarction) during 13-month follow-up. This cutoff value has been used as an anatomic predictor for significant physiological lesion such as abnormal FFR [20]. However, there is concern on whether a MLA threshold of < 4.0 mm^2 is appropriate for treatment of lesions in small size vessels. Recent studies have demonstrated that the best cutoff values of IVUS-derived MLA to predict FFR of < 0.80 are 2.36 mm^2 [6], 3.07 mm^2 [7], and 2.4 mm^2 [17], which are smaller than the previous criteria. Moreover, the reported thresholds of OCT-derived MLA to predict FFR < 0.80 are 1.95 mm^2 [6], which is even smaller than the cutoff value of IVUS-derived MLA.

Since FFR values are influenced by clinical features, lesion location, amount of supply of the myocardium, and lesion length, recent studies reported that the cutoff value of single slice IVUS-derived MLA for FFR < 0.80 can range from 1.9 to 3.5 mm^2 [6, 7, 17, 18]. The present study enrolled patients with relatively short and focal lesions, which could have accounted for the small MLA cutoff values. According to the sensitivity and specificity curves for IVUS- and OFDI-derived MLA to predict iFR ≤ 0.89 and FFR ≤ 0.80 (Fig. 4), the intersection points indicate the cutoff values were around MLA of 2.0 mm^2 where the sensitivity and specificity were both approximately 70%. Previous publications have indicated that the sensitivity and the specificity for IVUS- and OCT-derived MLA to predict FFR ≤ 0.80 were similar to our results [6, 7], suggesting that iFR of ≤ 0.89 may also predict anatomically significant stenosis like FFR in patients with intermediate coronary lesions.

What is the effect of lesion location on physiological assessment? In the present study, the percentage of functionally significant stenosis varied among the coronary arteries. Previous studies reported that RCA lesions have the lowest incidence of functionary significant stenosis [7], which may be explained by its small perfusion territory and low coronary flow velocity [22]. A higher coronary flow velocity produces a larger pressure gradient, which may likely render stenosis to be functionally significant [21]. Since RCA has the lowest peak diastolic velocity, especially at the resting phase, iFR may tend to be negative even when FFR is positive for ischemia. A study that compared iFR, Pd/Pa, and contrast-based FFR when FFR of ≤ 0.80 was used as a reference standard suggested that the diagnostic accuracy of those indices was no more than 80% in the RCA [23]. Further evaluation of clinical studies is needed to compare the diagnostic accuracy of iFR with FFR in RCA using an independent reference standard.

In the present study, the cutoff values to predict iFR ≤0.89 and FFR ≤ 0.80 were slightly smaller in OFDI-derived MLA as compared with IVUS-derived MLA which are consistent with the results that the MLA measurements are 4% smaller in OFDI than in IVUS. Kubo et al. [9] demonstrated previously that MLD and MLA measured by frequency domain OCT were approximately 10% smaller than those by IVUS (1.91 ± 0.69 mm vs. 2.09 ± 0.60 mm, p < 0.001 and 3.27 ± 2.22 mm^2 vs. 3.68 ± 2.06 mm^2, $p < 0.001$). They also indicated that IVUS overestimated lumen area and OCT had the advantage of accurately estimating lumen in the phantom model. Therefore, caution should be taken to apply literature-validated IVUS-derived MLA when assessing lesion significance by OFDI.

The present study has certain limitations. First, although spatial matching of IVUS and OFDI pullbacks was optimized using landmarks such as side branches and other anatomical features, some errors introduced by inadequate co-registration between the two techniques cannot be excluded. Second, the cutoff values of MLA were not evaluated for each major coronary vessel because of the limited sample size.

Conclusion

iFR correlated significantly with IVUS and OFDI measurements. Lesion location was related with the discordant results between iFR and FFR.

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Compliance with ethical standards

Conflict of interest KM has received remuneration for lectures from Philips japan and St. Jude Medical Japan. KH has received remuneration for lectures from Daiichi-Sankyo and Boston Scientific Japan; has received research grants from AstraZeneca, MSD, Solve, Biosensors Japan, Teijin Parma, Terumo, Mochida Pharmaceutical, Goodman, Medtronic Japan, and St. Jude Medical Japan. KT has received research grants from AstraZeneca, Ono, Tsumura, Daiichi-Sankyo, Novartis, Astellas, MSD, Pfizer, Research Institute for Production Development, Takeda, Kyowa Hakko Kirin., Chugai Pharmaceutical, Mochida, and Mitsubishi Tanabe. Honoraria from Mochida, Pfizer, Research Institute for Production Development, Sumitomo Dainippon Pharma and Kyowa Hakko Kirin. KK has received remuneration for lectures from AstraZeneca, Toa Eiyo, MSD, Bayer and Daiichi-Sankyo; has received research grants from Toa Eiyo, Bayer, MSD, Astellas, AstraZeneca, Sanofi, Eli Lilly Japan, Research Institute for Production Development, Pfizer, Shionogi, Kowa, Daiichi-Sankyo, Mitsubishi-Tanabe, Nihon Boehringer-Ingelheim, Takeda, Otsuka, and Ono. All other authors report no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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