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ORIGINAL ARTICLE

Comparison between minimum lumen cross-sectional area and intraluminal ultrasonic intensity analysis using integrated backscatter intravascular ultrasound for prediction of functionally significant coronary artery stenosis

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Abstract

Intravascular ultrasound (IVUS)-derived minimum lumen cross-sectional area (MLA) is useful to predict myocardial ischemia using fractional flow reserve (FFR). Recent studies reported an increase in the intraluminal ultrasonic integrated backscatter (IB) value using IVUS across the coronary artery stenosis (CAS) was significantly correlated with FFR. However, these details have not been fully understood. We evaluated the utility of intraluminal IB analysis for predicting myocardial ischemia based on FFR measurements by comparing that with conventional IVUS-derived MLA. A total of 65 patients with 75 intermediate lesions underwent both FFR and IB-IVUS simultaneously were analyzed. We measured IVUS-derived MLA and intraluminal IB value at the coronary ostial site, 5 mm distal site to the CAS, and far distal site, which is the same as the position of the pressure wire sensor. The increase in IB values was calculated as the distal IB value − the ostial IB value (focal ΔIB) and the far distal IB value − the ostial IB value (total ΔIB). MLA did not show a significant correlation with FFR ($p = 0.13$); however, focal ΔIB and total ΔIB showed significant correlations with FFR ($p = 0.008$ and $p < 0.001$, respectively). The receiver operating characteristic curve analysis shows that the best cut-off value of focal ΔIB and total ΔIB was 8 and 14, respectively. Although the diagnostic abilities to predict FFR ≤ 0.75 among IVUS-derived MLA ≤ 3.0 mm^2, focal ΔIB ≥ 8, and total ΔIB ≥ 14 were similar, a multivariate analysis showed that total ΔIB was the most useful index ($p < 0.001$). In conclusion, total ΔIB, which is measured at the same as the position of FFR measurement, might be useful for functional assessment of intermediate CAS.

Keywords Coronary artery stenosis · Integrated backscatter intravascular ultrasound · Fractional flow reserve · Minimum lumen area

Introduction

Physiological assessment for coronary artery disease is essential for determining the treatment strategy, such as percutaneous coronary intervention (PCI) or optimal medical therapy [1]. Fractional flow reserve (FFR) is generally used for determining functional severity of coronary artery stenosis (CAS) in the catheterization room. Routine measurements of FFR are important not only for assessing CAS, but also for the management of patients [2, 3]. The previous studies reported that lesions with an FFR ≤ 0.75 are a criterion for myocardial ischemia and that deferring PCI for lesions with an FFR > 0.75 is safe and beneficial [4, 5]. On

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the other hand, intravascular ultrasound (IVUS) can assess more detailed morphological information compared with coronary angiography (CAG), and is useful for optimizing PCI procedures [6–8]. Morphological parameters obtained by IVUS, such as the minimum lumen cross-sectional area (MLA), were significantly correlated with FFR values, and an MLA < 3.0 mm^2 was the most common cut-off value for identifying an FFR < 0.75 in non-left main trunk disease (LMTD) [9]. However, a recent study reported that the MLA was not a sufficient index for evaluating functional severity of CAS [10]. Integrated backscatter (IB)-IVUS is generally used to identify the tissue characterization of coronary atherosclerosis and neointima [11–13]. Ultrasonic IB has also been applied to assess echogenic properties of red blood cell aggregation [14]. A recent study reported that the increase in intraluminal ultrasonic integrated backscatter (IB) value across the lesion in the single discrete moderate CAS was significantly correlated with FFR in the left anterior descending artery (LAD) [15]. A subsequent paper reported that the method for evaluating the difference in IB value to estimate the FFR value has been applied in complex lesions [16]. However, those details such as exact measurement site have not been fully understood. In the present study, we evaluated the IB value at the ostium of the target vessel; the distal site, as the post 5 mm distal of the CAS; and the far distal site, which is the same as the position of the pressure wire sensor after advancing IVUS catheter to the far distal position. We compared the diagnostic ability of functionally significant CAS based on FFR between IVUS-derived MLA and IB value differences.

Methods

A flow chart of the patient selection process in this study is shown in Fig. 1. From March 2013 to August 2017, 208 consecutive patients who had intermediate stenosis and who underwent FFR measurements in our hospital were selected. Among those, 91 patients who underwent FFR and IVUS evaluation simultaneously were enrolled in this study. Exclusion criteria were as follows: patients with LMTD, ostial lesion of right coronary artery (RCA), valvular disease, old myocardial infarction of the target vessel, and coronary artery ectasia. Furthermore, patients who underwent IVUS without the data of IB analysis were also excluded. Finally, 75 lesions in 65 patients were included in this study. This study was performed in accordance with the Declaration of Helsinki, and was approved by the research ethics committee of the University of Occupational and Environmental Health. We obtained written informed consent from all patients.

Angiographic analysis

Qualitative and angiographic analyses were performed by a standard technique with automated edge-detection algorithms (CAAS, GOODMAN, Nagoya, Japan) in our institution. The external diameter of a contrast-filled catheter was used as the calibration standard. Minimum lumen diameter, reference diameter, percentage of the diameter stenosis, and lesion length were measured in the least foreshortened view. The lesion location was based on the site of the minimal lumen diameter.

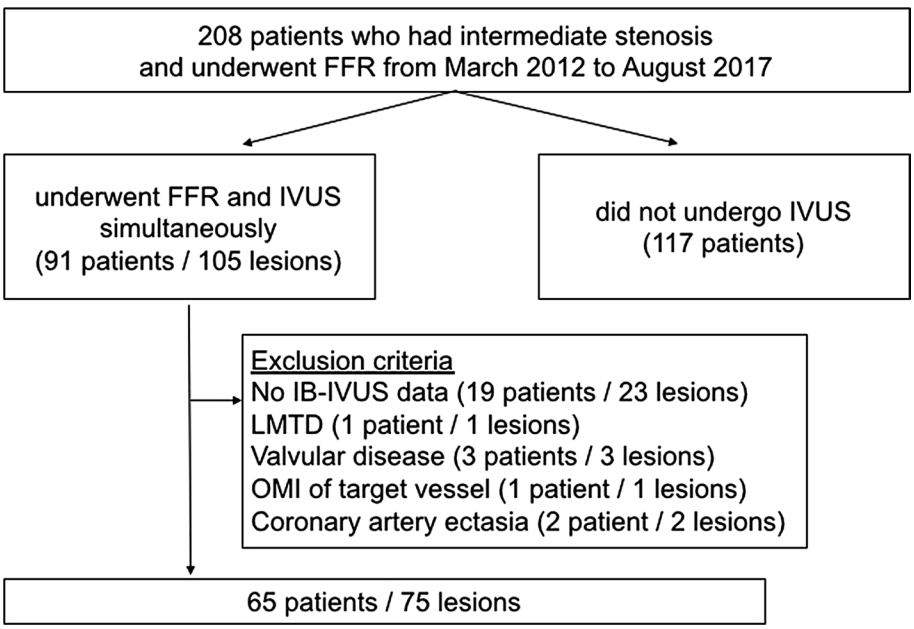

Fig. 1 Flow chart of patient selection. *FFR* fractional flow reserve, *IVUS* intravascular ultrasound, *IB* integrated backscatter, *LMTD* left main trunk disease, *OMI* old myocardial infarction

FFR measurement

Equalization was performed with a pressure guidewire sensor that was positioned at the guiding catheter tip. A 0.014-in pressure guidewire was then advanced into the coronary artery and positioned far distal to the stenotic lesion. FFR values were measured at maximal hyperemia induced by intravenous adenosine 5′-triphosphate infusion, administered at 180 μg/kg/min through a peripheral or central vein [17]. An FFR ≤ 0.75 was considered to indicate physiologically significant CAS [4].

IVUS imaging analysis

Intravascular ultrasound imaging and FFR were performed simultaneously after the diagnostic catheterization procedure. IVUS imaging was performed by IntrafocusViewIT (Terumo, Tokyo, Japan) consisting of a rotating 40-MHz transducer within a 3.2 F imaging sheath and VISIWAVE system (Terumo, Tokyo, Japan). Pullback IVUS imaging was performed after intracoronary administration of 0.5–1.0-mg isosorbide dinitrate with motorized transducer pullback (0.5 mm/s). Off-line quantitative IVUS analysis was performed with computerized analysis (VISI ATLAS, Terumo, Tokyo, Japan). Attenuation by flowing blood was previously reported as 4.0 dB/mm [18–20]. This value was used to correct ultrasonic signal attenuation of IB analysis by vessel diameter. The lumen area and external elastic membrane (EEM) area were measured, and the plaque area was calculated as follows: (EEM area − lumen area)/EEM area × 100 (%). These variables were measured in cross-sectional area per 1 mm. Lesion length was defined as cross-sectional area with a plaque burden > 40%. Plaque volume was calculated as follows: mean plaque area × lesion length. IB analyses were performed at the coronary ostial site, the distal site to the lesion, and the far distal site to the lesion. We defined the coronary ostial site as the point just distal to the guide catheter and the distal site as the point 5-mm distal of the CAS; the reason for these definitions was to allow for focal evaluation and to avoid turbulence immediately after the CAS. Moreover, we measured the far distal IB value which was the same as the position of the pressure wire sensor after advancing IVUS catheter. The IB values were measured using 3 slices in the late diastolic phase, and the average was taken as the IB value; this measurement technique was used to reduce cardiac motion artifacts. Cross sections with major side branches were avoided and adjacent slices were adequately selected for this analysis. IB values were obtained at the intraluminal area (lumen area removing IVUS catheter area and guidewire artifact), and then, the average IB value was calculated automatically. Focal ΔIB was calculated as follows: 5 mm distal IB value − the ostial IB value. Furthermore, we defined the increase in IB values (total ΔIB) as the far distal IB value − the ostial IB value. Representative cases of IB values and total ΔIB analysis are shown in Fig. 2. To evaluate the reliability of intraluminal IB value measurements, IB values were independently measured in 10 randomly selected patients by 2 experienced cardiologists and the intra-observer and inter-observer variabilities of IB values were compared.

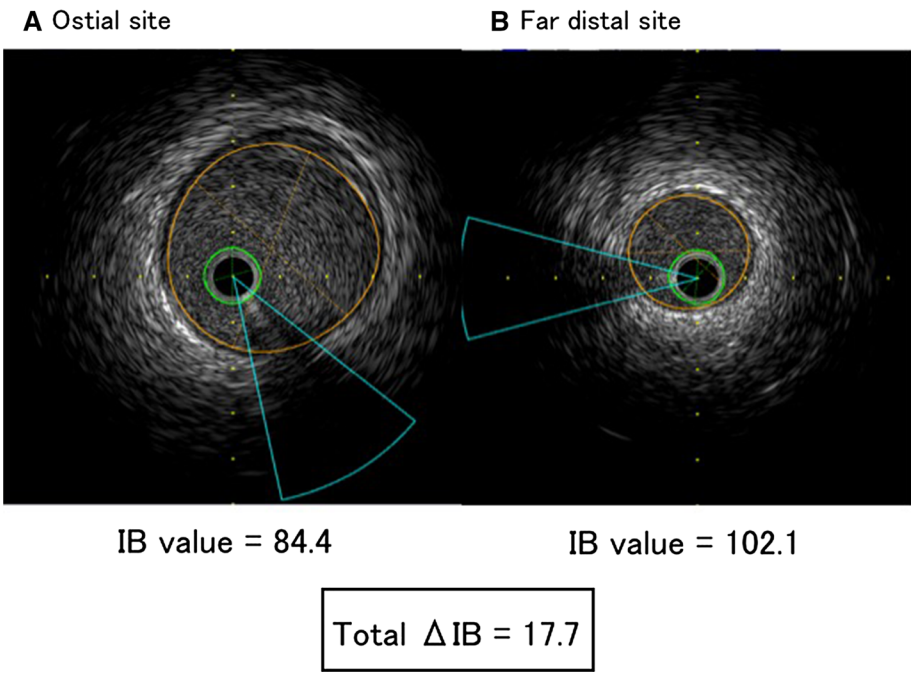

Fig. 2 Schema of IB-IVUS analysis. Orange and green circles indicate lumen and IVUS catheter areas, respectively. Light blue triangles indicate the artifact area by an IVUS catheter. The target area to calculate IB values consisted of the lumen area after removing the IVUS catheter and artifact areas. *IB* integrated backscatter, *IVUS* intravascular ultrasound

Statistical analysis

All statistical analyses were performed with JMP11.0 (SAS institute, Cary, NC, USA). All values are expressed as mean ± SD (continuous variables) or as count and percentage (categorical variables). Continuous variables were compared with the Student's *t* test or Wilcoxon's rank-sum test. Categorical variables were compared between groups by Chi-square analysis or Fisher's exact test. A stepwise multiple linear regression analysis was performed among the variables with $p < 0.10$ by a univariate correlation analysis to confirm the utility of ΔIB.

To determine the FFR ≤ 0.75, receiver operating characteristic (ROC) curves were analyzed to assess the best cut-off IB values derived from IVUS assessment that minimized the distance between the curve and the upper corner. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence interval (CI) were obtained. McNemar's test was performed to compare the diagnostic performance for predicting FFR ≤ 0.75 between IVUS-derived MLA or focal ΔIB and total ΔIB. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

The patient characteristics are shown in Table 1. The mean age of the study population was 68.9 ± 10.6 years, 80% were male, and 52% of the patients had diabetes. Left ventricular ejection fraction and renal function was preserved in most of patients, but 6 patients were undergoing hemodialysis. Nearly, half of the patients were symptomatic and asymptomatic. Most patients had received an antiplatelet or anticoagulant therapy; however, 8 patients who did not performed PCI had not received any of these drugs.

Angiographic analysis

Angiographic analyses are shown in Table 2. Forty-eight lesions were located at the left anterior descending artery (LAD), 15 in the left circumflex artery (LCX), and 12 in the RCA. Mean reference diameter was 2.55 ± 0.58 mm (95% CI 2.45–2.71), minimum lumen diameter was 1.30 ± 0.48 mm (95% CI 1.21–1.39), percentage of the diameter stenosis was 49.4 ± 12.2% (95% CI 46.6–52.2), and lesion length was 12.5 ± 8.7 mm (95% CI 10.5–14.5).

Table 1 Baseline clinical characteristics and the results of simple linear regression between these parameters and FFR

Variable	$n = 65$	Coefficient	p value
Age (years)	68.9 ± 10.6	0.296	0.424
Sex (male)	52 (80)	0.166	0.158
Body mass index (kg/m^2)	24.1 ± 3.5	− 0.037	0.098
Hypertension	48 (74)	0.124	0.254
Dyslipidemia	49 (75)	0.095	0.373
Diabetes mellitus	34 (52)	0.018	0.552
Current smoker	21 (32)	0.140	0.522
Symptomatic angina	34 (52)	0.014	0.878
Silent myocardial ischemia	31 (48)	0.014	0.878
Heart rate (bpm)	68.8 ± 11.7	0.013	0.915
Systolic blood pressure (mmHg)	132.2 ± 20.9	0.114	0.332
Diastolic blood pressure (mmHg)	70.3 ± 15.1	0.217	0.061
Total protein (g/dl)	6.88 ± 0.60	0.178	0.139
Albumin (g/dl)	3.86 ± 0.56	0.261	0.024
Hemoglobin (g/dl)	12.8 ± 2.2	0.192	0.098
Hematocrit (%)	37.9 ± 6.1	0.176	0.132
eGFR (ml/min/1.73 m^2)	55.3 ± 26.6	0.031	0.791
Hemodialysis	7 (11%)	0.107	0.429
Left ventricular hypertrophy	13 (25%)	0.151	0.151
Left ventricular ejection fraction (%)	57.7 ± 12.2	0.027	0.820
Left ventricular mass index (g/m^2)	106.0 ± 36.0	0.155	0.183
Antiplatelet and anticoagulation		0.149	0.652
None	8 (12)		
Single antiplatelet (SAP)	15 (23)		
Dual antiplatelet (DAP)	36 (55)		
Anticoagulant	1 (2)		
Anticoagulant with SAP	3 (5)		
Anticoagulant with DAP	2 (3)		
β Blocker	31 (48)	0.106	0.316
ARB or ACE inhibitor	36 (55)	0.123	0.243
Statin	49 (75)	0.024	0.832

Values are mean ± SD or number (percentage of total)

eGFR estimated glomerular filtration rate, *SAP* single antiplatelet, *DAP* dual antiplatelet, *ARB* angiotensin receptor blocker, *ACE* angiotensin-converting enzyme

Measurement of FFR

In all patients, coronary pressure measurements were successfully performed without complications. Measurements of FFR are shown in Table 2. The mean FFR value was 0.79 ± 0.10 (95% CI 0.76–0.81). Figure 3 shows the distribution of FFR values by 0.05. There were 31 (41%) lesions associated with an FFR value of ≤ 0.75, which was considered to be physiologically significant CAS. There was no significant difference in FFR between patients with

Table 2 Findings for angiographic parameters and FFR

Variable	$n=75$
Target vessel	
Left anterior descending	48 (64)
Left circumflex	15 (20)
Right coronary artery	12 (16)
QCA analysis	
Reference diameter (mm)	2.55 ± 0.58
Minimum lumen diameter (mm)	1.30 ± 0.48
Diameter stenosis (%)	49.4 ± 12.2
Lesion length (mm)	12.5 ± 8.7
FFR measurement	
FFR value	0.79 ± 0.10
Left anterior descending	0.78 ± 0.09
Left circumflex	0.84 ± 0.08
Right coronary artery	0.75 ± 0.12
FFR ≤ 0.75	31 (41)
FFR ≤ 0.80	44 (59)

Values are mean ± SD or number (percentage of total)

QCA quantitative coronary angiography, *FFR* fractional flow reserve

symptomatic angina and those with silent myocardial ischemia (0.79 ± 0.09 vs. 0.78 ± 0.10, $p=0.88$, SD = 0.02).

IVUS findings

Intravascular ultrasound findings are shown in Table 3. The mean MLA was 2.6 ± 1.0 mm^2 (95% CI 2.3–2.8), and 57 (76%) lesions showed MLA < 3.0 mm^2. Mean EEM, lumen, and plaque areas were 13.2 ± 4.6 mm^2 (95% CI 12.1–14.3), 4.9 ± 1.9 mm^2 (95% CI 4.5–5.4), and 8.1 ± 3.0 mm^2 (95% CI 7.4–8.8), respectively. Mean lesion length, as well as EEM, lumen, and plaque volumes were 22.6 ± 13.1 mm (95% CI 19.6–25.7), 322.6 ± 238.0 mm (95% CI 266.2–378.9), 113.6 ± 83.3 mm (95% CI 93.9–133.3), and 191.3 ± 128.3 mm^3 (95% CI 161.0–221.7), respectively.

The mean IB value at the ostial, distal, and far distal sites was 100.5 ± 12.9 (95% CI 97.5–103.5), 114.3 ± 15.2 (95% CI 110.8–117.8), and 121.7 ± 16.5 (95% CI 117.9–125.5), respectively. The mean IB value at the far distal site was significantly higher than that at the ostial and distal sites ($p<0.0001$ and $p<0.0001$, respectively). The focal ΔIB and total ΔIB values were calculated as 13.6 ± 7.6 (95% CI 11.9–15.4) and 21.4 ± 11.9 (95% CI 18.6–24.1), respectively. For total ΔIB values, the intra- and inter-observer coefficients were 0.99 and 0.99, respectively.

Correlations of FFR and IVUS findings

There was no significant correlation between FFR and MLA in all lesions ($r=0.176$, $p=0.130$) (Fig. 4a); however, LAD lesions had a moderate correlation ($r=0.287$, $p=0.048$) (Fig. 4b). There was a significant correlation between FFR and focal or total ΔIB in all lesions ($r=-0.305$, $p=0.008$ and $r=-0.410$, $p<0.001$, respectively) (Fig. 4c). There was significant correlation between FFR and total ΔIB in LAD lesions ($r=-0.496$, $p<0.001$) (Fig. 4d), but not in LCX and RCA lesions. A multiple linear regression analysis showed that lumen volume and total ΔIB were the most useful index ($p<0.001$) (Table 4).

The diagnostic ability using the criteria of IVUS-derived MLA < 3.0 mm^2 in all lesions showed a sensitivity,

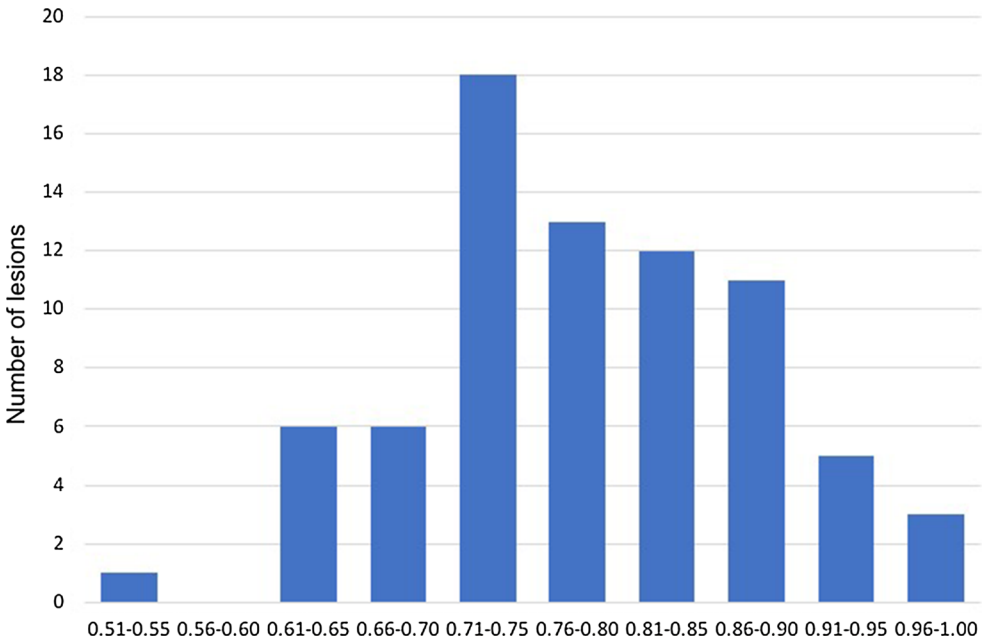

Fig. 3 Distribution of FFR values by 0.05. *FFR,* fractional flow reserve

Table 3 Findings for IVUS parameters and the results of simple linear regression between these parameters and FFR

Variable	$n=75$	Coefficient	p value
Minimum lumen area (mm^2)	2.6 ± 1.0	0.176	0.130
Left anterior descending	2.7 ± 1.0	0.287	0.048
Left circumflex	2.2 ± 0.8	−0.033	0.906
Right coronary artery	2.6 ± 1.2	0.327	0.300
EEM area (mm^2)	13.2 ± 4.6	0.036	0.722
Lumen area (mm^2)	4.9 ± 1.9	0.043	0.980
Plaque area (mm^2)	8.1 ± 3.0	0.032	0.789
Area stenosis (%)	63.2 ± 7.7	−0.013	0.916
Lesion length (mm)	22.6 ± 13.1	−0.369	0.002
EEM volume (mm^3)	322.6 ± 238.0	−0.297	0.012
Lumen volume (mm^3)	113.6 ± 83.3	−0.363	0.002
Plaque volume (mm^3)	191.3 ± 128.2	−0.294	0.013
IVUS-analyzed length (mm)	89.5 ± 24.6	−0.209	0.072
IB value (ostium)	100.5 ± 12.9	0.078	0.507
IB value (5 mm distal)	114.3 ± 15.2	−0.091	0.437
IB value (far distal)	121.7 ± 16.5	−0.242	0.037
Focal ΔIB value	13.6 ± 7.6	−0.305	0.008
Total ΔIB value	21.4 ± 11.9	−0.410	< 0.001
Left anterior descending	21.5 ± 10.5	−0.496	< 0.001
Left circumflex	22.8 ± 15.8	−0.521	0.056
Right coronary artery	19.0 ± 12.5	−0.393	0.206

Values are mean ± SD or number (percentage of total)

EEM external elastic membrane, *IB* integrated backscatter, *IVUS* intravascular ultrasound

specificity, PPV, NPV, and accuracy of 81, 27, 44, 67, and 49%, respectively. ROC curve analysis showed that the best cut-off value of focal ΔIB and total ΔIB for detecting myocardial ischemia were 8 and 14, respectively. The diagnostic ability using the index of focal ΔIB in all lesions showed a sensitivity, specificity, PPV, NPV, and accuracy of 90, 36, 50, 84, and 59%, respectively. On the other hand, the diagnostic ability using the index of total ΔIB in all lesions showed a sensitivity, specificity, PPV, NPV, and accuracy of 91, 39, 52, 89, and 61%, respectively (Fig. 5). There was no significant difference between IVUS-derived MLA or focal ΔIB and total ΔIB in their diagnostic performance ($p=0.180$ and $p=0.317$, respectively).

Discussion

The major findings of this study are as follows: (1) IVUS-derived IB values showed an increase from the coronary ostial site to the distal and far distal sites to the CAS; (2) IVUS-derived MLA did not have a significant correlation with FFR, whereas focal ΔIB and total ΔIB had a significant correlation with FFR; and (3) there was no significant difference in terms of the diagnostic ability for predicting myocardial ischemia between IVUS-derived MLA or focal ΔIB and total ΔIB; however, total ΔIB was the most useful index to predict FFR.

In the present study, we measured the far distal IB value same as the position of the pressure wire sensor after advancing IVUS catheter in all patients who underwent both FFR and IVUS imaging, whereas the previous two studies did not performed IVUS imaging same as the position of the pressure wire sensor [9, 21]. As shown in the results, IB value at the far distal site is higher than the coronary ostial and distal sites to the CAS. The previous studies showed that there was a significant inverse correlation between FFR and an increase in IB value across the CAS [15, 16]. These reports showed that a focal evaluation of an increase in IB value can be an alternative to FFR. On the other hand, the present study evaluated the whole vessel including all stenotic sites as well as FFR measurement in the complex lesions. If CAG shows a focal atherosclerosis, IVUS often reveals the presence of the entire atherosclerosis. As compared with the previous methods, the present method might also be useful as an alternative analysis [15, 16]. In fact, total ΔIB showed a strong correlation with FFR. Although there was no significant difference between IVUS-derived MLA or focal ΔIB and total ΔIB in their diagnostic performance to predict FFR ≤ 0.75, a multivariate analysis shows that total ΔIB and lumen volume are the independent predictors of FFR.

The previous studies have shown that IVUS-derived MLA and FFR have a significant correlation [9, 21]. However, recent studies have shown a variety of cut-off values (2.1–4.4 mm^2) for the diagnosis of an FFR ranging from ≤ 0.75 to 0.80 [10]. The reason why there is a discordance between FFR and MLA is due to that the following criteria of IVUS-derived MLA for physiological assessment: vessel size, lesion location, and plaque characteristics such as plaque rupture [22, 23]. Measurement of IB value is also concerned with the problem of vessel size; however, the previous studies showed that the effect of attenuation was corrected for IB value measurements [18–20]. This may allow us to evaluate intraluminal IB value regardless of vessel size.

The cut-off value of total ΔIB for identifying an FFR ≤ 0.75 was 14 in our study, although the criteria showed a relatively low specificity and PPV, but relatively high sensitivity and NPV. An examination with high sensitivity shows low undetected error probability, and thus identifying a serious, but treatable disease, is important. Moreover, a high NPV in our study indicated that this method is superior for the determination of an exclusive diagnosis. This method might not provide a long-term prognosis. Total ΔIB may not have a superior diagnostic ability for assessing myocardial ischemia statistically; however, it showed the most useful index for predictor of

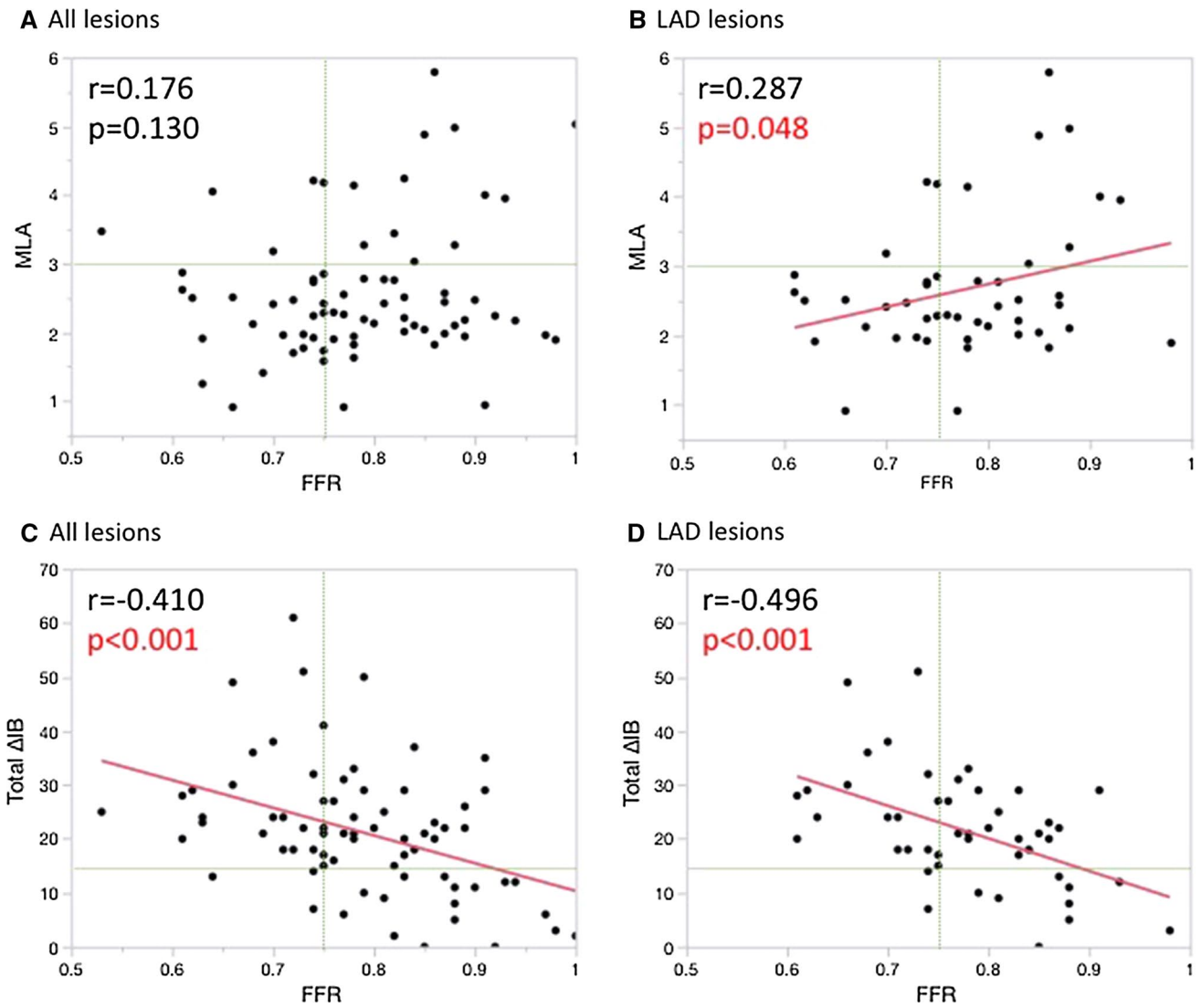

Fig. 4 Correlation between FFR values and MLA in all lesions (**a**) and LAD lesions (**b**). Correlation between the FFR value and total ΔIB in all lesions (**c**) and LAD lesions (**d**). *FFR* fractional flow reserve, *MLA* minimum lumen area, *IB* integrated backscatter, *LAD* left anterior descending artery

FFR by a multivariate analysis. Lumen volume was indicated to be an additional useful index to predict FFR.

Another point should be considered in this methodology. The proof of concept study of the correlation between an increased intraluminal IB value across the CAS included only LAD lesions [15]. The subsequent study revealed a strong correlation in LAD lesions and a moderate correlation in RCA lesions, but not in LCX lesions [16]. The present study showed a strong correlation in LAD lesions, but not in LCX and RCA lesions. These three studies clearly indicate that a strong correlation was present between an increased intraluminal IB value across the CAS in LAD lesions, but further study is needed for LCX and RCA lesions because of our small sample size.

Intraluminal IB values reflect the intensity of blood speckle (mainly red blood cells) and are affected by coronary blood flow [24, 25]. Other factors also affect ultrasound backscatter, such as hematocrit, erythrocyte, plasma fibrinogen, shear rate, blood flow velocity, vessel size, pulse rate, and ultrasound frequency [26]. Furthermore, coronary artery pressure across stenosis is determined by the sum of viscous and separation losses [27]. Poiseuille's law describes the relation between a drop in pressure and blood flow in a stiff tube under steady flow. In this setting, pressure is lost because of viscous friction at the entrance and inner area of the stenotic lesion [28, 29]. In addition, Bernoulli's law describes that as the speed of blood flow increases, the pressure within blood decreases. In this setting, narrowing

Table 4 Results of multiple linear regression analysis between IVUS parameters and FFR

Variable	Coefficient	*p* value
Diastolic blood pressure (mmHg)	0.583	0.518
Albumin (g/dl)	0.566	0.257
Hemoglobin (g/dl)	0.597	0.630
Lesion length (mm)	−0.589	0.518
EEM volume (mm^3)	−0.601	0.721
Lumen volume (mm^3)	−0.555	< 0.001
Plaque volume (mm^3)	−0.595	0.320
IVUS-analyzed length (mm)	0.580	0.209
IB value (far distal)	−0.599	0.605
Focal ΔIB value	−0.601	0.794
Total ΔIB value	−0.410	< 0.001

IB integrated backscatter

of the cross-sectional area accelerates convection along the stenotic lesion [29]. Furthermore, flow separation and disturbed flow prevent complete pressure recovery at the presence of stenotic lesions [28]. In this study, FFR during hyperemia correlated with not only focal but also total delta IB during basal condition. Recently, instantaneous wave-free ratio (iFR) is known to correlate closely with FFR. iFR is calculated from the ratio of resting distal coronary pressure and aortic pressure over a specific period in late diastole, the wave-free ratio, during which intracoronary resistance is purportedly naturally constant and minimal [30]. We measured intraluminal IB values in the late diastolic phase with reference to reduce cardiac motion in this study. Therefore, the non-hyperemic intraluminal IB measurements might be used for physiological assessment of coronary artery stenosis severity at rest. Furthermore, the ultrasound IB values are originally measured in decibels. The delta IB may correspond to measuring the ratio of calculated values across the stenosis like FFR and coronary flow reserve. However, further study is needed to evaluate whether focal and total ΔIB during hyperemia improve the correlation with FFR or not.

Clinical implications

Current guidelines on myocardial revascularization recommend appropriate intervention (not only PCI, but also optical medical therapy) for ischemic heart disease [31, 32]. FFR is generally used for determining the presence of myocardial ischemia, but IVUS-guided PCI is widely used for obtaining a better outcome than angiography-guided PCI. However, both modalities have a high medical cost. This method may lead to curtail FFR measurements during PCI.

Limitations

The results from the present study should be interpreted with consideration of some limitations. First, the relatively small sample size limited the statistical power and the strength of the conclusions. Especially, the influence of antiplatelet

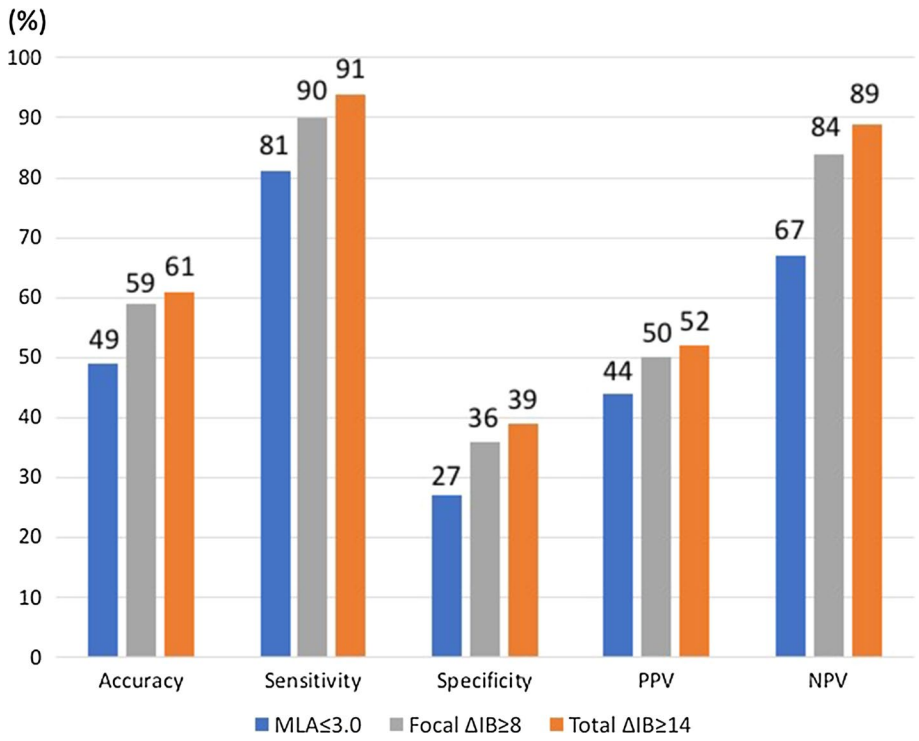

Fig. 5 Diagnostic accuracy of IVUS-derived MLA, focal ΔIB, and total ΔIB for FFR ≤ 0.75 in all lesions. *MLA* minimum lumen area, *IB* integrated backscatter, *FFR* fractional flow reserve, *PPV* positive predictive value, *NPV* negative predictive value

or anticoagulant therapy was not fully excluded from this result because of small sample size. In addition, we used the statistical analysis conventionally performed in the previous similar researches [22, 33, 34]. However, there was a statistical problem owing to the normality of distribution in the variables. Second, patients were only recruited from our hospital. One hundred seventeen of the 208 patients who underwent FFR did not undergo IVUS evaluation. Although we compared the clinical characteristics between 91 patients who underwent both FFR and IVUS evaluation and the other remaining 117 patients, there was no significant difference in all variables between them. Third, measurement of vessel size was not unified. Therefore, the effect of the IVUS analysis software system might not have been completely equal in each patient. However, the previous studies showed that the effect of attenuation was corrected for IB value measurements [18–20]. Finally, IB values were measured without hyperemia; however, FFR values were measured with hyperemia. The difference in these conditions may have affected the correlation between FFR and total ΔIB, whereas the present method is clinically reasonable, because we usually undergo IVUS-guided PCI without hyperemia. Further studies comparing total ΔIB with hyperemia and FFR are required.

Conclusion

Total ΔIB, which is measured at the same as the position of FFR measurement, might be useful for functional assessment of intermediate CAS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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