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ORIGINAL ARTICLE
Ischemic Heart Disease

Effect of Vessel Size on Lipid Content of Coronary Plaques Assessed by Integrated Backscatter Intravascular Ultrasound

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Background: Tissue characterization of coronary plaques is feasible using integrated backscatter intravascular ultrasound (IB-IVUS), and higher lipid content has been found in the target lesions of acute coronary syndrome (ACS). The present study was performed to identify clinical and IVUS parameters that correlate with plaque composition assessed by IB-IVUS.

Methods and Results: A total of 109 patients (age 60.0±9.7 years) were evaluated with IVUS and IB-IVUS prior to percutaneous coronary intervention. Patients with ACS had a larger vessel size and higher plaque burden in the target lesion than those with stable angina. Relative lipid content of the target lesion by IB-IVUS was also higher in ACS (43.6%±12.0% vs 29.9%±14.2%; P<0.001). The remodeling index (r=0.403, P<0.001), plaque burden (%) (r=0.495, P<0.001), and vessel size (r=0.572, P<0.001) significantly correlated with lipid content. In the multiple regression analysis, vessel size was the most important independent predictor of lipid content followed by presence of ACS and the remodeling index.

Conclusions: ACS, positive remodeling, and larger plaque burden were associated with higher lipid content of coronary plaque. However, the lipid content on IB-IVUS was also significantly affected by vessel size. Therefore, qualitative, morphologic assessment of coronary plaque rather than simple quantitative analysis of tissue components seems to be more appropriate for the identification of vulnerable plaque using IB-IVUS. (*Circ J* 2010; **74:** 754–759)

Key Words: Acute coronary syndrome; Intravascular ultrasound; Lipids; Plaque

Intravascular ultrasound (IVUS) is a useful imaging modality for assessing the morphology of atherosclerotic plaque and the vessel wall.[1] However, objective plaque characterization and quantification of each tissue component are not feasible with conventional IVUS. Recently, Kawasaki et al developed integrated backscatter (IB)-IVUS to assess plaque composition by spectral analysis of the radiofrequency ultrasound backscatter signals, which enables identification of tissue components, such as calcification, lipids, and fibrosis, based on the IB values, as well as visualization of each component in different colors.[2] The relative content of each tissue component of the coronary plaque on a vessel cross-section is automatically quantified. Higher lipid content of coronary plaque assessed by IB-IVUS has been reported to be associated with the presence of acute coronary syndrome (ACS) and metabolic syndrome.[3,4] Analysis of IB ultrasound signals has also shown that the use of statins or pioglitazone can reduce the lipid component in coronary as well as carotid plaques.[5,6] However, there are few data on the direct relationship between coronary artery remodeling, plaque eccentricity, and plaque burden at the percutaneous coronary intervention (PCI) target lesion with plaque composition assessed by IB-IVUS. Recent studies using virtual histology (VH, Volcano Therapeutics, Rancho Cordova, CA, USA) for tissue characterization by analyzing backscattered ultrasound signals showed conflicting results on this issue.[7] Therefore, in the present study, we analyzed the tissue composition of coronary plaques with IB-IVUS and investigated the correlations with various clinical and conventional IVUS parameters.

Methods

Study Patients

A total of 109 consecutive patients (72 with stable angina pectoris (AP), 37 with ACS) with a single target lesion undergoing PCI between December 2005 and June 2006 at Severance Cardiovascular Hospital, Yonsei University Health

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Table 1. Baseline Clinical and Laboratory Characteristics of the Patients

	Total patients (n=109)	ACS		P value
		Yes (n=37)	No (n=72)	
Age (years)	60.0±9.7	57.9±12.0	61.1±8.2	0.153
Male	83 (76.1%)	30 (81.1%)	53 (73.6%)	0.386
Diabetes mellitus	24 (24.2%)	10 (27.0%)	14 (19.4%)	0.366
Hypertension	50 (45.9%)	18 (51.4%)	32 (44.4%)	0.677
Hypercholesterolemia	62 (56.9%)	21 (56.8%)	41 (56.9%)	0.985
Current smoker	23 (21.1%)	8 (21.6%)	15 (20.8%)	0.924
Multivessel disease	24 (22.0%)	8 (21.6%)	16 (22.2%)	0.943
Total cholesterol (mg/dl)	166.7±45.5	169.5±35.2	165.2±50.2	0.646
LDL-cholesterol (mg/dl)	106.5±36.5	104.4±26.4	107.6±40.9	0.671
HDL-cholesterol (mg/dl)	44.2±11.4	43.9±11.3	44.3±11.5	0.880
Triglycerides (mg/dl)	138.2±86.2	134.3±96.3	140.2±81.2	0.740
hsCRP (mg/L)	5.6±13.8	7.8±16.6	2.16±3.3	0.053
Homocysteine (mg/L)	11.9±3.8	12.0±4.2	11.8±3.7	0.772
Lp(a) (mg/dl)	22.23±24.41	25.7±29.1	20.9±22.5	0.425
Previous medications				
Statin	46 (42.2%)	15 (40.5%)	31 (43.1%)	0.801
Fibrate	5 (4.6%)	2 (5.4%)	5 (4.2%)	0.999
ACEI/ARB	43 (39.4%)	13 (35.1%)	30 (41.7%)	0.509

ACS, acute coronary syndrome; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein A; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

System, were included in this study. The ACS patient group included 20 with unstable AP, 14 with non-ST-segment elevation myocardial infarction (MI), and 3 with ST-segment elevation MI. Acute MI was defined as continuous chest pain at rest with abnormal levels of cardiac biomarkers (creatinine kinase-MB or troponin T). Stable AP was defined as no change in frequency, duration, or intensity of symptoms within 6 weeks before the intervention. The culprit lesion in ACS or the target lesion of stable AP was identified by the combination of left ventricular wall motion abnormalities, ECG findings, angiographic lesion morphology, and scintigraphic perfusion defects. Lesions not crossable with IVUS (chronic total occlusion or severe angulations), located at a bifurcation, or containing severe calcification (arc >90°) were excluded, as were patients with unstable hemodynamics, previous PCI, or bypass surgery of the target lesion. All patients gave written informed consent, and the study protocol was approved by the institutional ethics committee.

IB-IVUS Data Acquisition

All IVUS and IB-IVUS assessments were performed after intracoronary administration of 200 μg of nitroglycerin and prior to PCI at the target lesion. Conventional IVUS images and ultrasound signals were obtained using a commercially available IVUS system (Galaxy; Boston Scientific, Natick, MA, USA) with a 40-MHz mechanically rotating IVUS catheter and automatic motorized 0.5 mm/s pullback device. During acquisition of IVUS images, radiofrequency signal output, signal trigger output, and video image output were automatically exported to a personal computer equipped with software (IB-IVUS, YD Co, Ltd, Nara, Japan) connected to the IVUS system. IB values were calculated as the average power, measured in decibels, of the ultrasound signal backscattered from a small volume of tissue using a fast Fourier transform. The whole length of the PCI target lesion, including proximal and distal reference segments, was assessed by IB-IVUS and images of a 10-mm segment centered on the minimal lumen area were analyzed for plaque tissue composition. The plaque tissue components were classified as calcification, dense fibrosis, soft fibrosis or lipid pool according to the signal level and color-coded red, yellow, green, and blue, respectively. The definitions of the IB values for each histological category were the same as reported previously:[8] −11 to −29 dB for calcification, −29 to −35 dB for dense fibrosis, −35 to −49 dB for soft fibrosis, and −49 to −130 dB for lipid pool.

Conventional IVUS and IB-IVUS Parameters

In conventional IVUS analysis, cross-sectional images are quantified for lumen, external elastic membrane (EEM), and plaque plus media (EEM–lumen) areas using commercially available software (TapeMeasure/EchoPlaque, Indec System, Mountain View, CA, USA). The eccentricity index of plaque plus media is calculated as: (maximum plaque+media thickness–minimum plaque+media thickness)/maximum plaque+media thickness. The remodeling index is defined as the ratio of the EEM area at the measured lesion (minimum luminal site) to the reference EEM area (average of the proximal and distal reference segments). The eccentricity and remodeling indices are calculated in the segment with minimal lumen area. The percentages of calcified area (calcified area/plaque area), dense fibrous area (dense fibrous area/plaque area), soft fibrous area (soft fibrous area/plaque area), and lipid area (lipid area/plaque area) are automatically calculated by the IB-IVUS system. In the present study, the segment of coronary artery wall shadowed by the guidewire and hypoechoic areas behind a calcified mass were excluded from calculation of the percentage of tissue component area. Coronary plaques with a hypoechoic area larger than 20% of the plaque area because of the guidewire and calcified mass were also excluded from the analysis.

Statistical Analysis

Statistical analysis was performed with SPSS (SPSS, Inc,

Table 2. Baseline IVUS and IB-IVUS Characteristics

	Total patients (n=109)	ACS		P value
		Yes (n=37)	No (n=72)	
Target coronary artery				0.834
LAD	74 (67.9%)	24 (64.9%)	50 (69.4%)	
LCX	7 (6.4%)	3 (8.1%)	4 (5.6%)	
RCA	28 (25.7%)	10 (27.3%)	18 (25.0%)	
EEM area (mm^2)	12.9±4.6	15.1±3.9	11.8±4.5	<0.001
Lumen area (mm^2)	3.0±0.9	3.1±0.9	3.0±0.9	0.758
Plaque area (mm^2)	9.9±4.2	12.0±3.8	8.8±3.9	<0.001
Plaque burden (%)	74.8±7.5	78.7±6.8	72.9±7.1	<0.001
Eccentricity rate	0.70±0.21	0.75±0.20	0.67±0.21	0.095
Remodeling index	0.93±0.26	0.98±0.26	0.89±0.26	0.094
Lesion length (mm)	21.8±7.5	20.1±7.2	22.7±7.5	0.091
Minimal lumen area				
Lipid pool (%)	34.6±14.9	43.6±12.0	29.9±14.2	<0.001
Soft fibrotic tissue (%)	56.2±10.7	51.5±10.1	58.6±10.3	0.001
Dense fibrotic tissue (%)	6.9±5.1	3.9±3.1	8.5±5.3	<0.001
Calcification (%)	2.3±2.8	1.1±1.8	3.0±3.0	<0.001
Mean				
Lipid pool (%)	34.6±13.0	42.4±11.2	30.6±12.0	<0.001
Soft fibrotic tissue (%)	56.8±9.1	52.5±9.3	59.0±8.2	<0.001
Dense fibrotic tissue (%)	6.4±4.0	4.0±2.8	7.6±4.0	<0.001
Calcification (%)	2.2±2.2	1.1±1.5	2.8±2.2	<0.001

IVUS, intravascular ultrasound; IB, integrated backscatter; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; EEM, external elastic membrane.

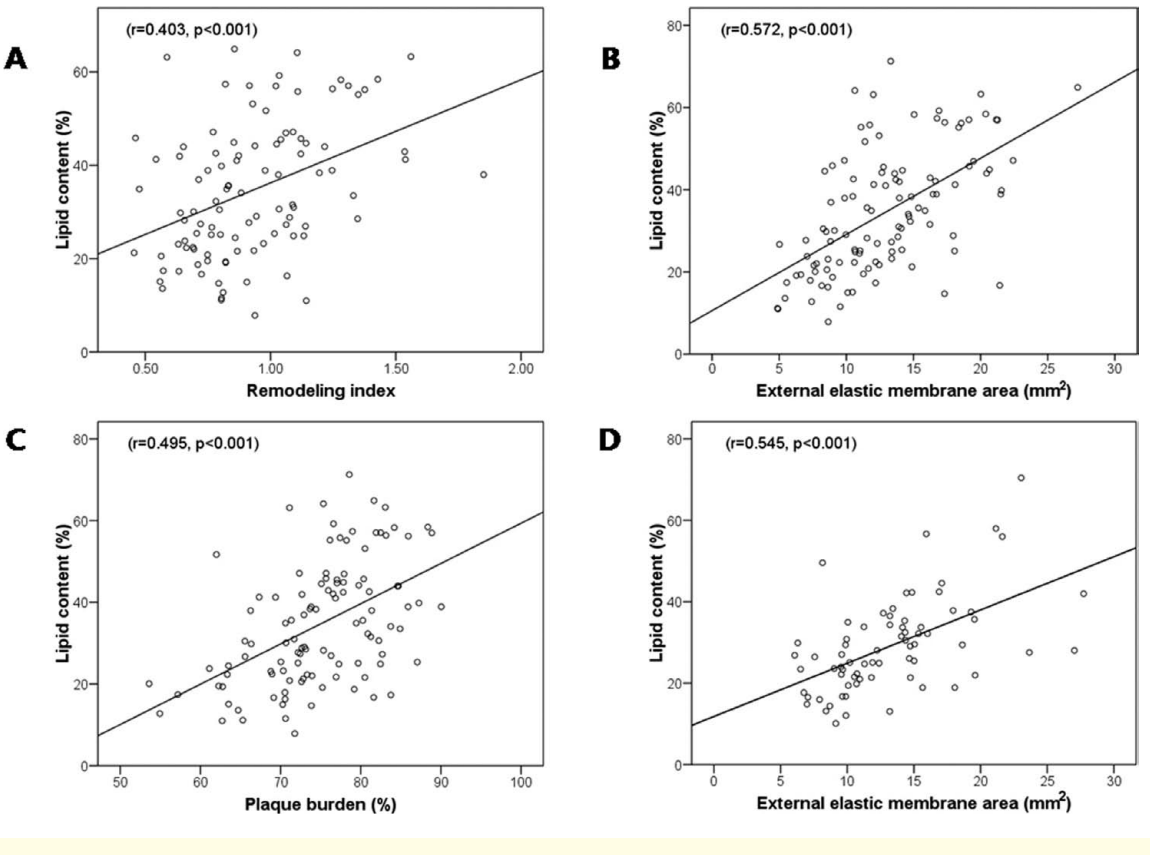

Figure 1. Correlations of relative lipid content with external elastic membrane area (**A**), plaque burden (**B**), and remodeling index (**C**) at the target lesion and with external elastic membrane area in reference vessel segment with plaque burden <30% (**D**).

Table 3. Univariate and Multivariate Linear Regression Analysis for Relative Lipid Content of the Target Lesion on IB-IVUS

	Univariate analysis		Multivariate analysis	
	β	P value	β	P value
ACS	0.435	<0.001	0.238	0.004
Diabetes mellitus	0.082	0.397		
Body mass index	0.172	0.154		
Log hsCRP	−0.005	0.674		
LDL-cholesterol	0.042	0.604		
EEM area	0.572	<0.001	0.423	<0.001
Plaque burden	0.495	<0.001	0.077	0.452
Remodeling index	0.403	<0.001	0.157	0.061
Eccentricity index	0.124	0.213		

Abbreviations see in Tables 1,2.

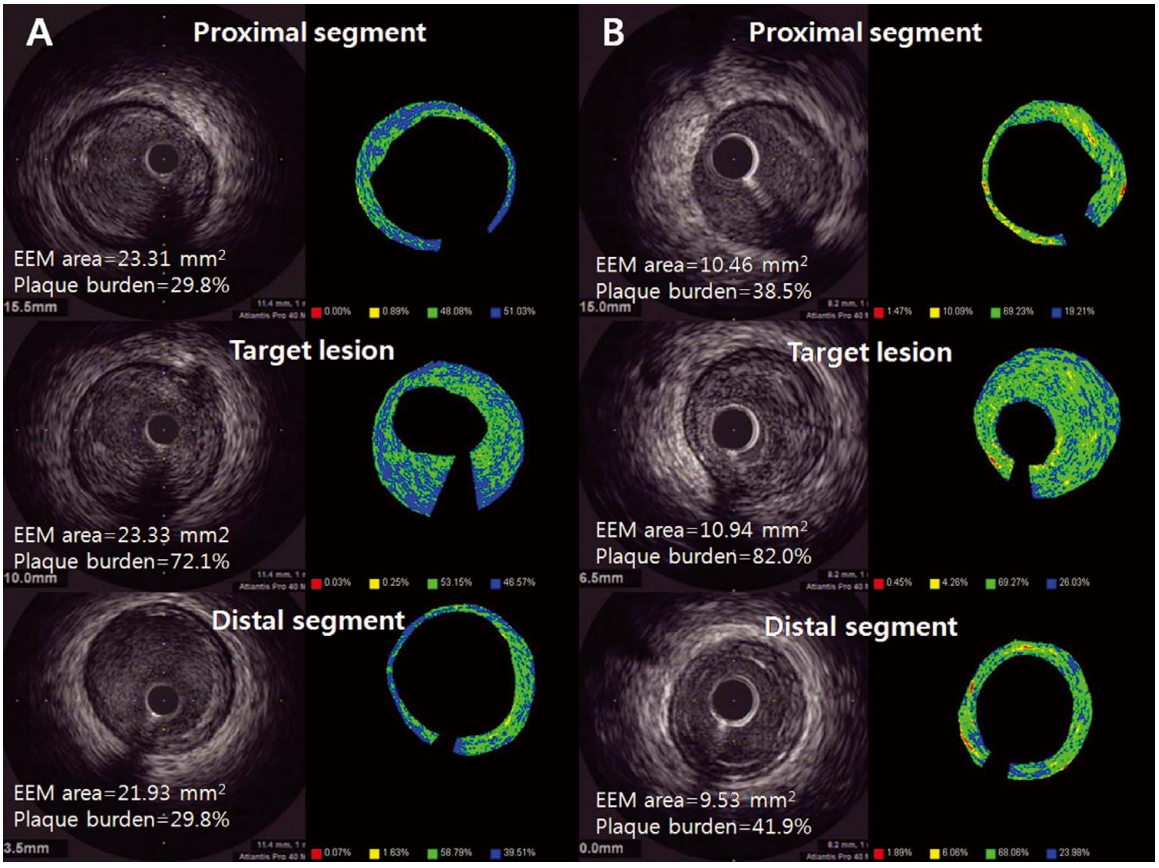

Figure 2. Representative cases of acute coronary syndrome. IVUS and IB-IVUS images of plaque in a large vessel (**A**) and a small vessel (**B**). IB-IVUS image: red, calcification; yellow, dense fibrosis; green, soft fibrosis; blue, lipid pool. IB, integrated backscatter; IVUS, intravascular ultrasound; EEM, external elastic membrane.

Chicago, IL, USA). Data are reported as frequencies or mean±SD. Comparisons were performed with chi-square statistics, unpaired Student's t-test, or analysis of variance. Correlations of each clinical, laboratory, or conventional IVUS parameter with the IB-IVUS data were tested for significance by Pearson's correlation coefficient. Multiple linear regression analysis by the enter method was performed to assess independent predictors for relative lipid content. P<0.05 was considered statistically significant.

Results

Baseline clinical and laboratory characteristics of the enrolled patients are shown in Table 1. Among the total of 109 enrolled patients, there were 37 patients with ACS, including 17 AMI patients. Between the patient groups with and without

ACS, there was no significant difference in these characteristics.

Gray-scale IVUS and IB-IVUS parameters of the PCI target lesions are summarized in Table 2. The majority (67.9%) of the PCI target lesions were located in the left anterior descending artery. Target lesions in patients with ACS were in larger sized vessels (EEM area, 15.1±3.9 vs 11.8±4.5 mm^2, P<0.001), had greater plaque burden (78.7±6.8% vs 72.9±7.1%, P<0.001) and showed a trend toward a higher rate of eccentricity (0.75±0.20 vs 0.67±0.21, P=0.095) and remodeling index (0.98±0.26 vs 0.89±0.26, P=0.091) compared with non-ACS patients. The patients with ACS showed a higher relative lipid content (43.6±12.0% vs 29.9±14.2%, P<0.001), and less soft (51.5±10.1% vs 58.6±10.3%, P=0.001) and dense fibrotic tissues (3.9±3.1% vs 8.5±5.3%, P<0.001) and less calcification (1.1±1.8% vs 3.0±3.0, P<0.001) in the cross-section of the PCI target lesion with minimal lumen area compared with non-ACS patients. Between diabetic and non-diabetic patients, there was no significant difference in the plaque composition of the target lesion (lipid pool 37.5±15.5% vs 33.8±14.8%, P=0.303; soft fibrotic tissue 52.6±11.1% vs 57.1±10.6%, P=0.076; dense fibrotic tissue 7.0±5.2% vs 6.9±5.1%, P=0.928, calcification 2.9±2.9% vs 2.2±2.7%, P=0.257).

The relative lipid content of the target lesion showed correlations with the remodeling index (r=0.403, P<0.001), plaque burden (r=0.495, P<0.001), and EEM area (r=0.572, P<0.001) (Figure 1, Table 3). However, there was no significant correlation with body mass index, baseline high-sensitivity C-reactive protein (log value), low-density lipoprotein cholesterol, or the eccentricity index (Table 3). Multivariate linear regression analysis revealed that EEM area was the most important independent determinant of lipid content (%) in the target lesion factor followed by the presence of ACS and the remodeling index (Table 3).

To validate the relationship between relative lipid content assessed by IB-IVUS and vessel size, we analyzed the IVUS and IB-IVUS data of reference vessel segments with a plaque burden <30% (n=71, EEM area 13.33±5.04 mm^2, plaque burden 26.2±2.6%) and found a significant correlation (Figure 1D, r=0.545, P<0.001). Reprensentative cases of acute coronary syndrome with different vessel sizes are shown in Figure 2.

Discussion

In the present study we found correlations of lipid content assessed by IB-IVUS with the presence of ACS, remodeling index, plaque burden, and vessel size (EEM area). A higher lipid content was found in the target lesion of ACS patients and in coronary plaques with positive remodeling, larger plaque burden, and bigger vessel size. However, multivariate linear regression analysis showed that vessel size was the most independent determinant of relative lipid content in the target lesion followed by presence of ACS and the remodeling index.

Gray-scale IVUS has been widely used to evaluate the morphology and dimensions of coronary plaques.[1] It has been reported that target lesions in patients with ACS tend to have more positive remodeling and a large plaque area whereas patients with stable AP more frequently show negative remodeling and smaller plaque area.[9,10] Coronary artery lesions with positive remodeling tend to be more echolucent, softer, and have less calcified plaque than those with negative remodeling.[11,12] Soft plaques considered to have higher lipid content are found more commonly in patients with ACS than in those with stable AP.[9,13]

However, objective analysis of plaque composition and quantification of each tissue component, such as lipids, calcification and fibrosis, are not feasible with conventional IVUS. Recently, Kawasaki et al developed IB-IVUS, which enables both characterization of plaque composition and quantitative analysis of the different tissue components.[2] In a study using postmortem histology specimens, IB-IVUS demonstrated high diagnostic accuracy for tissue characterization of coronary plaques and better diagnostic potential for identification of fibrous lesions and lipid pools compared with conventional IVUS.[12] Previous analysis of coronary plaques using IB-IVUS showed that vulnerable plaques causing ACS contain more lipids and are associated with higher plaque burden, rate of eccentricity, and remodeling index,[3] similar to the findings from our study. It has been also reported that patients with metabolic syndrome have a significant increase in the percentage lipid area and percentage lipid volume in mild to moderate coronary lesions compared with those without metabolic syndrome.[4] However, few data on the direct relationship between lipid content and various IVUS parameters, such as the remodeling index, eccentricity, plaque burden, and vessel size using IB-IVUS, are available.

Recent studies using VH for tissue characterization by analyzing backscattered ultrasound signals have had contradictory results. Whereas Rodriguez-Granillo et al reported that coronary lesions with positive remodeling have larger necrotic cores than intermediate or negative remodeling lesions,[15] Surmely et al demonstrated the opposite.[16] Necrotic core as defined by VH is considered to be a highly lipidic, necrotic region with remnants of foam cells and dead lymphocytes. Even though the necrotic core on VH is not identical to the lipid area on IB-IVUS, our findings concur with those of Rodriguez-Granillo et al. Recently, Okubo et al compared IB-IVUS with VH for accuracy in assessing plaque composition and found that IB-IVUS had higher diagnostic accuracy than VH based on histology as the gold standard.[17] Thus, we believe IB-IVUS can better clarify the relationship between arterial remodeling and plaque composition than VH.

In the present study, we found good correlations between lipid content and the presence of ACS, positive remodeling index, and plaque burden using IB-IVUS for tissue characterization. However, the relative lipid content of the coronary plaque was also significantly affected by vessel size. In order to validate this finding indirectly, we analyzed the correlation of vessel size with lipid content in reference coronary artery segments with less than 30% plaque burden, which revealed that vessel size correlates closely with lipid content, even in coronary arteries with little plaque burden. Within the limits of the present study, we cannot completely rule out that even the reference vessels with little plaque burden may have had early changes of positive remodeling. In fact, Glagov et al demonstrated a positive correlation between arterial size and plaque area, even in sections with 20% or less stenosis.[19] Therefore, large vessels without significant luminal stenosis may have positive remodeling and more lipid accumulation than smaller vessels. On the other hand, Chinali et al[18] investigated in an experimental setting the effect of the depth of the reflecting structure on the intensity of the IB signal and found that it linearly decreased with increasing depth. Their findings suggest that backscattered ultrasound signals in large vessels might be attenuated and falsely interpreted as lipid signals. Thus, there may be overestimation of the lipid content in large vessels by IB-IVUS. Furthermore, Okubo et al also reported that IB-IVUS tends

to falsely interpret small areas of lipid accumulation mixed with fibrosis or fibrosis abundant in inflammatory cells and fibroblasts as lipid pool and thereby overestimates the lipid content of the lesion.[17] Therefore, qualitative, morphologic assessment of coronary plaque rather than simple quantitative analysis of tissue components seems to be more appropriate for the identification of vulnerable plaque using IB-IVUS.

Study Limitations

We did not perform a pathologic validation study, so it is unclear whether the correlation of lipid content by IB-IVUS with vessel size is related to a technical limitation of IB-IVUS or to atherosclerotic changes in large vessels. Therefore, further validation studies will be required to clarify this issue. This was a single-center retrospective study with a relatively small sample size. Because IB-IVUS cannot identify thrombus, plaque characterization in ruptured plaques filled by thrombus may have been affected, even though occluding thrombus was aspirated before PCI in infarct-related lesions with total occlusion. There could be bias in the selection of coronary segments for the analysis, although consecutive patients with single target lesion undergoing PCI were included in the study. Furthermore, complex lesions such as chronic total occlusion, bifurcation, tortuous lesions, or severely calcified lesions were excluded from analysis. Therefore, data in the present study might not represent the whole spectrum of coronary plaques.

Conclusions

IB-IVUS is a useful diagnostic tool for assessing the tissue composition of coronary plaques. In the present study, lipid content measured by IB-IVUS correlated with the presence of ACS, positive remodeling index, and plaque burden. However, lipid content on IB-IVUS was significantly affected by vessel size, so qualitative, morphologic assessment of coronary plaque rather than simple quantitative analysis on tissue component seems to be more appropriate for the identification of vulnerable plaque using IB-IVUS.

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