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Comparison of Tissue Characteristics Between Acute Coronary Syndrome and Stable Angina Pectoris

– An Integrated Backscatter Intravascular Ultrasound Analysis of Culprit and Non-Culprit Lesions –

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Background: Patients with acute coronary syndrome (ACS) have multiple complex coronary plaques associated with plaque vulnerability. The present study assessed the tissue characteristics of coronary plaques between ACS and stable angina pectoris (SAP) of culprit and non-culprit lesions using integrated backscatter intravascular ultrasound (IB-IVUS).

Methods and Results: IVUS was performed in 165 patients (40 patients with ACS) with 225 culprit (65 lesions in ACS) and 171 non-culprit lesions (42 lesions in ACS). The percentage of fibrous area (fibrous area/plaque area, %FIB) and the percentage of lipid area (lipid area/plaque area, %LIP) at the segment with minimal luminal area were calculated using IB-IVUS system. Culprit and non-culprit lesions with ACS showed a significant increase in %LIP (38±18 vs. 30±15%, P=0.002, and 38±21 vs. 32±17%, P=0.03, respectively) and a significant decrease in %FIB (59±15 vs. 63±12 %, P=0.04, and 57±18 vs. 62±14%, P=0.04, respectively) compared to those with SAP. On logistic regression analysis, not only culprit lesions but also non-culprit lesions with ACS patients were significantly associated with the lipid-rich plaque.

Conclusions: Non-culprit coronary lesions with ACS patients are associated with the lipid-rich plaque, suggesting the extensive development of plaques instability in these patients. (*Circ J* 2011; **75:** 383–390)

Key Words: Acute coronary syndrome; Plaque; Ultrasound

Previous studies have revealed that the disruption of plaques might play a critical role in the development of acute coronary syndrome (ACS), where the lipid-rich plaques impact on plaque vulnerability.[1–3] However, an angiographic study reported that plaque instability is not merely a local vascular accident but presumably reflects more generalized pathophysiologic processes with the potential to destabilize atherosclerotic plaques throughout the coronary tree.[4] Angioscopic studies have suggested that, in patients with ACS, all 3 major coronary arteries are widely diseased and have multiple yellow plaques, suggesting the incidence of lipid-rich plaque.[2,5] Lipid-rich plaques, which closely associated with lesion vulnerability, are also observed in 90–95% of patients with ACS and in 50–70% of patients with stable angina pectoris (SAP).[5,6] To assess the relevant detail of clinical syndrome (stable and unstable) and coronary plaque morphology is more important for the prevention of ACS. However, the difference of tissue components of atheromatous plaque in the culprit and non-culprit lesions between ACS and SAP has not been fully clarified by use of intravascular ultrasound (IVUS). Recently developed integrated backscatter IVUS (IB-IVUS) has allowed analyzing tissue components of coronary plaques in vivo.[3,7–13] In the present study, we thus assessed the tissue characteristics of coronary plaques between ACS and SAP of culprit and non-culprit lesions using IB-IVUS, taking into account

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of possible confounding factors.

Methods

Patients and Study Design

This study was a prospectively planned observational study for culprit and non-culprit coronary lesions in patients with ACS and SAP who underwent percutaneous coronary intervention (PCI). ACS included acute myocardial infarction (AMI) and unstable angina pectoris (UAP). The diagnosis of AMI was based on elevation of at least 1 positive biomarker [creatine kinase (CK), CK-MB or troponin T], characteristic electrocardiogram changes and a history of prolonged acute chest pain. UAP was defined as angina with a progressive crescendo pattern or angina that occurred at rest. IVUS was performed before PCI to 165 consecutive patients (40 with ACS) with 225 culprit (65 lesions in ACS) and 171 non-culprit coronary arteries (42 lesions in ACS) between September 2005 and December 2006.

Definitions of Analysis Segments and Measurements of IVUS Parameters

In patients with SAP, the lesions of >75% diameter lumen reduction by quantitative coronary angiography (QCA) analysis were identified as culprit lesions. Culprit lesions responsible for ACS were identified on the basis of the combination of the angiographic lesion appearance, electrocardiographic changes, and the wall motion abnormality on the echocardiography. SAP was defined as no change in frequency, duration or intensity of chest pain. In patients with both ACS and SAP, non-culprit lesions were defined as the lesions of <50% diameter lumen reduction by QCA analysis and the segments more than 10 mm from culprit lesions. The lesions with 50–75% diameter stenosis (moderate stenotic lesions) were not included in either culprit or non-culprit lesions. Before performing coronary angiography and PCI, patients were administered an intracoronary 0.5 mg of isosorbide dinitrate in order to prevent coronary spasm. QCA analysis was conducted, and reference diameter and percentage diameter stenosis were measured by a validated automated edge-detection program (CMS-MEDIS Medical Imaging System, Leiden, The Netherlands). Coronary arteries within 4 weeks after the onset of ACS were classified as lesions with ACS. In IVUS analysis, conventional cross-sectional images were quantified for lumen cross-sectional area (CSA), external elastic membrane (EEM) CSA, and plaque (P)+media (M) CSA using software built in IVUS system. Eccentricity index was calculated by the formula of (maximum P+M thickness–minimum P+M thickness)/maximum P+M thickness. Remodeling index was defined as a ratio of EEM CSA at the measured lesion (minimum luminal site) to reference EEM CSA (average of the proximal and distal reference segments). IB-IVUS analysis was performed as previously reported.[8–13] In brief, a personal computer equipped with custom software (IB-IVUS, YD Co, Ltd, Nara, Japan) was connected to the IVUS imaging system (Clear View, Boston Scientific, Natick, MA, USA) in order to obtain radio frequency signal output and signal trigger output. Ultrasound backscattered signals were acquired using a 40 MHz (motorized pullback 0.5 mm/s) mechanically rotating IVUS catheter in order to be digitized and subjected for spectral analysis. IB values for each tissue component were calculated using a fast Fourier transform of the frequency component of the backscattered signal from a small volume of tissue. On the basis of previous study, the definition of IB values for each plaque component (lipid, fibrous, and calcified) was determined. We then manually excluded the vessel lumen and area outside of the intima in the 2-dimensional IB IVUS images. Color-coded maps were constructed for each 1 mm slice to illustrate the tissue characteristics in the target lesions. The percentage of fibrous area (fibrous area/plaque area, %FIB) and the percentage of lipid area (lipid area/plaque area, %LIP) were automatically calculated by IB-IVUS system. A total of 10 IB-IVUS images were captured at an interval of 1 mm for 10 mm length at each plaque of non-culprit lesion. With regard to the culprit lesion, IB-IVUS images (mean 19 images) were captured at an interval of 1 mm for lesion length (mean 18.9 mm). Then the segments with minimum luminal area were evaluated in the culprit and non-culprit lesions. The QCA and IVUS measurements were conducted independently by 2 physicians who were blinded to the patient's characteristics. The variability on %LIP and %FIB determined by 2 physicians was also considered from 50 randomly selected records.

Statistical Analyses

Statistical analysis was performed by use of the SAS statistical software package (version 8.02, SAS Institute Inc, Cary, NC, USA). Continuous and categorized variables were expressed as median and interquartile, mean±SD and proportions. The mean values of continuous variables with normal distribution, including ejection fraction, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, body mass index (BMI) were compared between ACS and SAP by use of unpaired Student's t-test. The Mann–Whitney U tests were used to evaluate differences in age, high-density lipoprotein (HDL) cholesterol and C-reactive protein (CRP). The frequency for gender, hypertension, diabetes mellitus, smoking history, multiple vessel disease, old myocardial infarction, analyzed plaque location and medication therapy were compared between ACS and SAP by use of chi-squared tests and Fisher's exact tests. Comparisons of various IVUS parameters among the lesion groups (ACS-culprit, ACS-non-culprit, SAP-culprit and SAP-non-culprit) were evaluated using ANOVA, and Bonferroni test was performed for multiple comparisons. We defined the cut-off point for the lipid-rich plaque as %LIP >60% or %FIB <30% as previously reported.[3,9,14] Following this definition, multivariate logistic regression analysis was applied to study for the predictors of the lipid-rich plaque. In order to account for repeated assessments to 1 patient, a generalized estimation equations (GEE) logistic regression was performed to estimate corrected probability values.[15] A P-value<0.05 was considered as statistically significant.

Results

Study Populations and Baseline Characteristics

There were no significant differences in confounding factors (age, gender and BMI), clinical history, target plaque location and medication therapy between the 2 groups. LDL cholesterol in patients with ACS was significantly increased compared to those with SAP. Compared to patients with SAP, patients with ACS were more likely to show a low HDL cholesterol level and a high total cholesterol and CRP concentrations (Table 1).

Quantitative Parameters of Conventional and IB IVUS

In the conventional IVUS analysis, vessel area, plaque area and percentage of area stenosis for culprit and non-culprit lesions were comparable between ACS and SAP (Table 2).

Table 1. Baseline Clinical Characteristics

	ACS (n=40)	SAP (n=125)	P values
Male, no. (%)	32 (80)	83 (66)	0.15
Age, years			0.67
Median	70	69	
Interquartile range	64–75	60–77	
Ejection fraction, %	65±13	67±11	0.32
BMI, kg/m²	24±3	24±3	0.40
Clinical history, no. (%)			
Hypertension	26 (65)	85 (68)	0.87
Diabetes mellitus	19 (48)	71 (57)	0.40
Current smoker	14 (35)	30 (24)	0.24
Coronary artery disease, no. (%)			
Old myocardial infarction	7 (18)	31 (25)	0.46
Multiple vessel	28 (70)	66 (53)	0.08
Target plaque location (culprit), no. (%)			
Left anterior descending	27 (42)	80 (50)	0.25
Left circumflex	15 (23)	26 (16)	0.21
Right	23 (35)	54 (34)	0.82
Target plaque location (non-culprit) , no. (%)			
Left anterior descending	18 (43)	69 (51)	0.23
Left circumflex	8 (19)	16 (12)	0.31
Right	16 (38)	44 (34)	0.64
Blood lipid levels, mg/dl			
Total cholesterol	205±39	193±36	0.07
Triglycerides	141±82	150±90	0.56
HDL cholesterol			0.11
Median	45	42	
Interquartile range	38–54	39–47	
LDL cholesterol	133±35	115±28	0.001
C-reactive protein, mg/dl			0.08
Median	0.1	0.1	
Interquartile range	0.1–0.3	0.1–0.2	
Medication, no. (%)			
Aspirin	35 (88)	116 (93)	0.47
Ticlopidine	24 (60)	86 (69)	0.40
Statins	27 (68)	66 (53)	0.15
Angiotensin converting enzyme inhibitors, no. (%)	8 (20)	24 (19)	>0.99
Angiotensin II type 1 receptor antagonists, no. (%)	13 (33)	43 (34)	0.98
Nitrates, no. (%)	18 (46)	60 (48)	0.86
Calcium-channel blockers, no. (%)	16 (40)	48 (38)	>0.99
β-blockers, no. (%)	22 (55)	59 (47)	0.50

Plus-minus values are means ± SD.
ACS, acute coronary syndrome; SAP, stable angina pectoris; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Lesion Characteristics

	Culprit			Non-culprit		
	ACS (n=65)	SAP (n=160)	P value	ACS (n=42)	SAP (n=129)	P value
Vessel area, mm²	11.7±3.7	11.1±3.9	0.27	11.5±4.1	11.3±4.0	0.72
Plaque area, mm²	9.19±3.46	8.59±3.59	0.24	6.25±2.60	6.64±2.97	0.46
Area stenosis, %	77.8±13.9	76.1±13.8	0.23	54.7±13.7	57.7±13.7	0.24

Values are means ± SD.
Abbreviations see in Table 1.

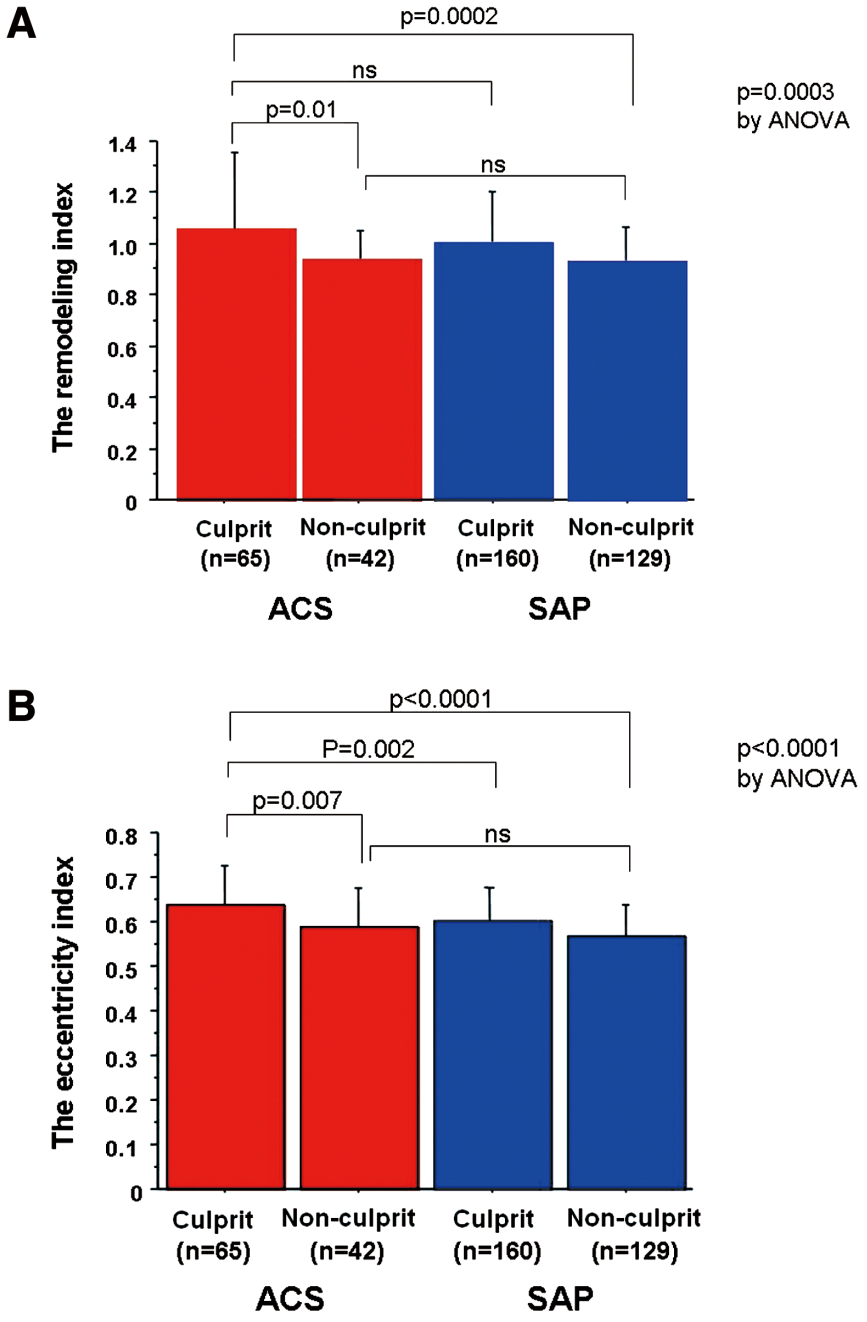

Figure 1. Comparisons of the conventional intravascular ultrasound parameters among the lesion groups. (**A**) The remodeling index, (**B**) the eccentricity index. As compared with acute coronary syndrome (ACS) patients with the non-culprit lesions, those with the culprit lesions were significantly increased in the remodeling index (1.06 vs. 0.94, P=0.01) and the eccentric index (0.64±0.09 vs. 0.59±0.09, P=0.007). SAP, stable angina pectoris.

Within the ACS patients, culprit lesions were significantly increased in the remodeling index (1.06 vs. 0.94, P=0.01) and the eccentricity index (0.64±0.09 vs. 0.59±0.09, P=0.007) compared to non-culprit lesions, whereas the other parameters were comparable between culprit and non-culprit lesions (**Figures 1A**, **1B**). IB-IVUS analysis revealed that culprit and non-culprit lesions in patients with ACS significantly increased in %LIP (38±18 vs. 30±15%, P=0.002, and 38±21 vs. 32±17%, P=0.03, respectively) and significantly decreased in %FIB (59±15 vs. 63±12%, P=0.04, and 57±18 vs. 62±14%, P=0.04, respectively) compared to those with SAP (**Figures 2A**, **2B**). **Figures 3**, **4** show the representative images of conventional and 2-dimensional IB-IVUS color-coded maps of culprit and non-culprit lesions in patients with SAP and ACS. The %LIP of culprit and non-culprit lesions in patients with ACS were 69% (**Figure 3**) and 43% (**Figure 4**), respectively. The correlations of %LIP and %FIB measured by 2 independent physicians were r=0.94 (P<0.01) and r=0.95 (P<0.01), respectively.

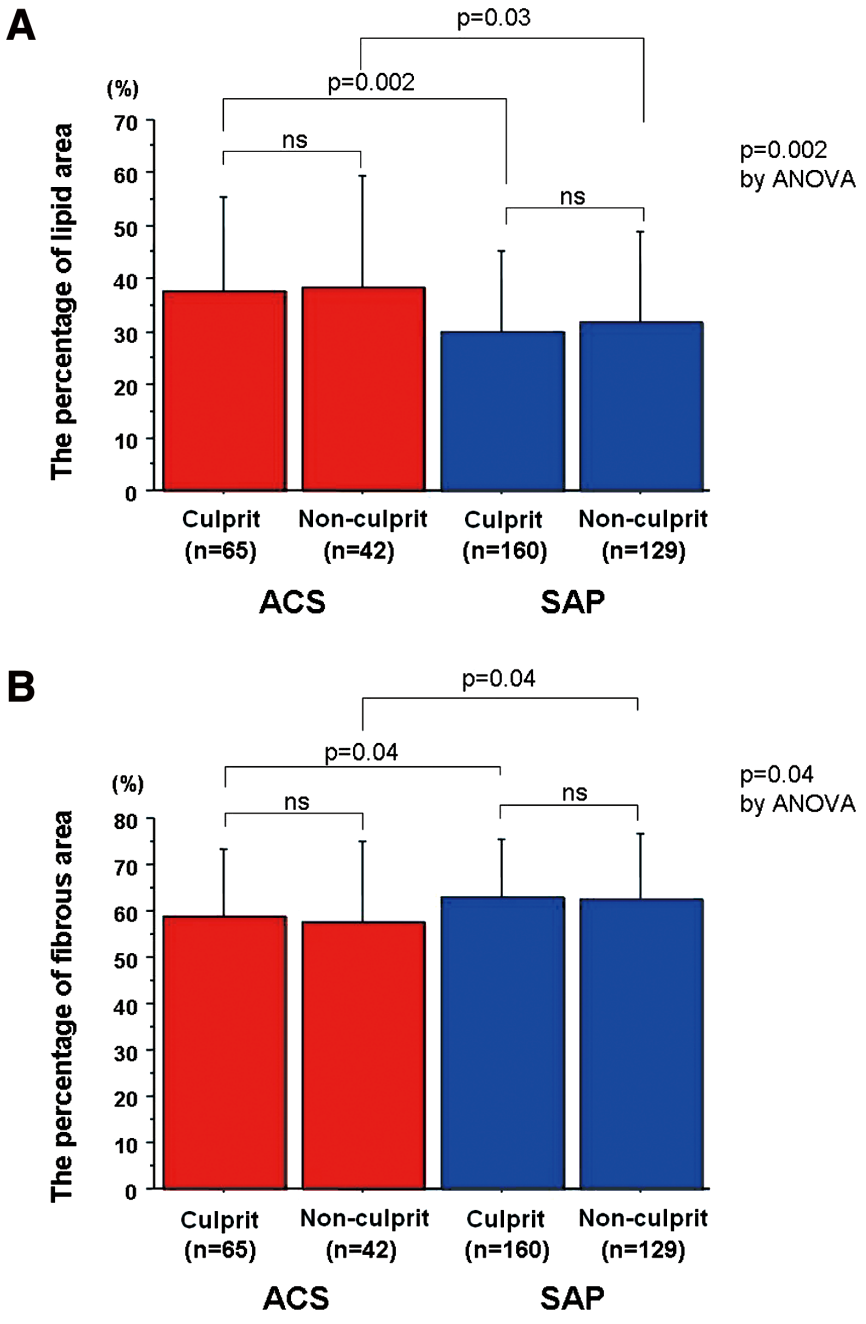

Figure 2. Comparisons of the integrated backscatter intravascular ultrasound (IB-IVUS) parameters among the lesion groups. (**A**) Percentage of lipid area (%LIP), (**B**) percentage of fibrous area (%FIB). Culprit and non-culprit lesions in patients with acute coronary syndrome (ACS) significantly increased in %LIP (38±18 vs. 30±15%, P=0.002, and 38±21 vs. 32±17%, P=0.03, respectively) and significantly decreased in %FIB (59±15 vs. 63±12%, P=0.04, and 57±18 vs. 62±14%, P=0.04, respectively) compared to those with stable angina pectoris (SAP).

Logistic Model for the Prediction of Lipid-Rich Plaque

On logistic regression analysis, after adjusting for confounding (age, gender and BMI) and various risk factors (hypertension, diabetes mellitus, LDL cholesterol, HDL cholesterol and multiple vessel disease), besides culprit lesions with ACS patients, non-culprit lesions with those were proved to be an independent predictor for the lipid-rich plaque (OR 7.10, 95%CI 1.86–27.2, P=0.004) (**Table 3**).

Discussion

The results of this study, using IB-IVUS, demonstrated that not only culprit lesions but also non-culprit lesions with ACS are significantly associated with the increase in %LIP and the decrease in %FIB. Furthermore, non-culprit lesions with ACS patients were proved to be an independent predictor for the lipid-rich plaque, supporting the concept that plaque

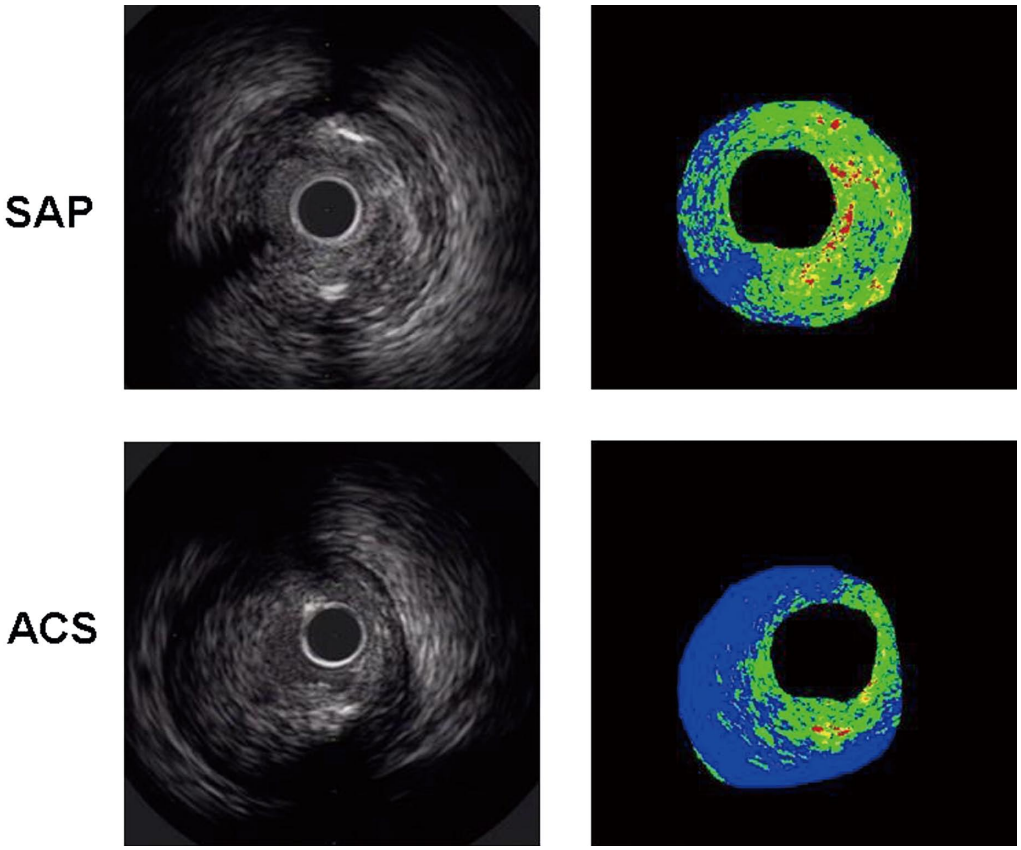

Figure 3. Representative images of conventional intravascular ultrasound and 2-dimensional integrated backscatter intravascular ultrasound color-coded maps of culprit lesions in patients with or without acute coronary syndrome (ACS). Color-coded maps demonstrate lipid (blue), fibrous (green and yellow) and calcified (red) areas. The percentage of lipid area was 27% in stable angina pectoris (SAP) patients and 69% in ACS patients. The percentage of fibrous area was 60 % in SAP patients and 28% in ACS patients.

instability might not represent merely a local vascular accident but reflect a 'pan-coronary' process.[4,5]

In the present study, there were no significant differences in vessel area, plaque area and percentage of area stenosis of culprit and non-culprit lesions between ACS and SAP patients. However, the remodeling index is significantly increased in the culprit lesions of ACS patients, while this factor showed no differences when compared to the culprit lesions of SAP patients. These results suggest that vessels at culprit site might be compensatory enlarged in order to prevent building atheroma from encroaching in the lumen, thereby presenting the positive remodeling.[1] With regard to the eccentricity index, the culprit lesions of ACS patients were significantly increased compared to the other lesions of ACS and SAP patients, consistent with the previous reports showing this factor as an important prerequisite for the plaque morphology leading to ACS.[3,16] Taken together, the remodeling index and the eccentricity index appear more important in the occurrence of plaque rupture, although these 2 indexes were not significantly associated with the lipid-rich plaque.

We used IB-IVUS for detection of tissue characteristics of coronary plaques. This system uses a conventional IVUS instrument, a digital analog converter, and computer software to identify and quantitate various plaque characteristics. Several histological studies validated that IB measurements accurately reflect the tissue characteristics of human coronary plaques.[17,18] IB-IVUS analysis revealed that culprit and non-culprit lesions with ACS showed a significant increase in %LIP and a significant decrease in %FIB compared to those with SAP, suggesting the incidence of lipid-rich plaques in patients with ACS, irrespective of the degree of lesion stenosis. Furthermore, not only the culprit but also the non-culprit lesions of ACS patients were proved to be an independent predictor for the lipid-rich plaque. Previous IVUS study reported that 70% of patients with ACS had at least one atherosclerotic lesion that had rupture criteria in an artery distinct from the culprit lesions.[19] Angioscopic studies also demonstrated that in patients with ACS, all 3 major coronary arteries are widely diseased and have multiple yellow plaques, suggesting the incidence of lipid-rich plaque.[2,5] These reports were supported and further confirmed by our finding that non-culprit lesions with ACS patients are relevant to the lipid-rich plaque. In the present study, the predictive value for the lipid-rich plaque seems to be relatively strong in the non-culprit lesions with ACS patients as compared to the culprit lesions. This is mainly because of the definition of the lipid-rich plaque focusing on plaques before

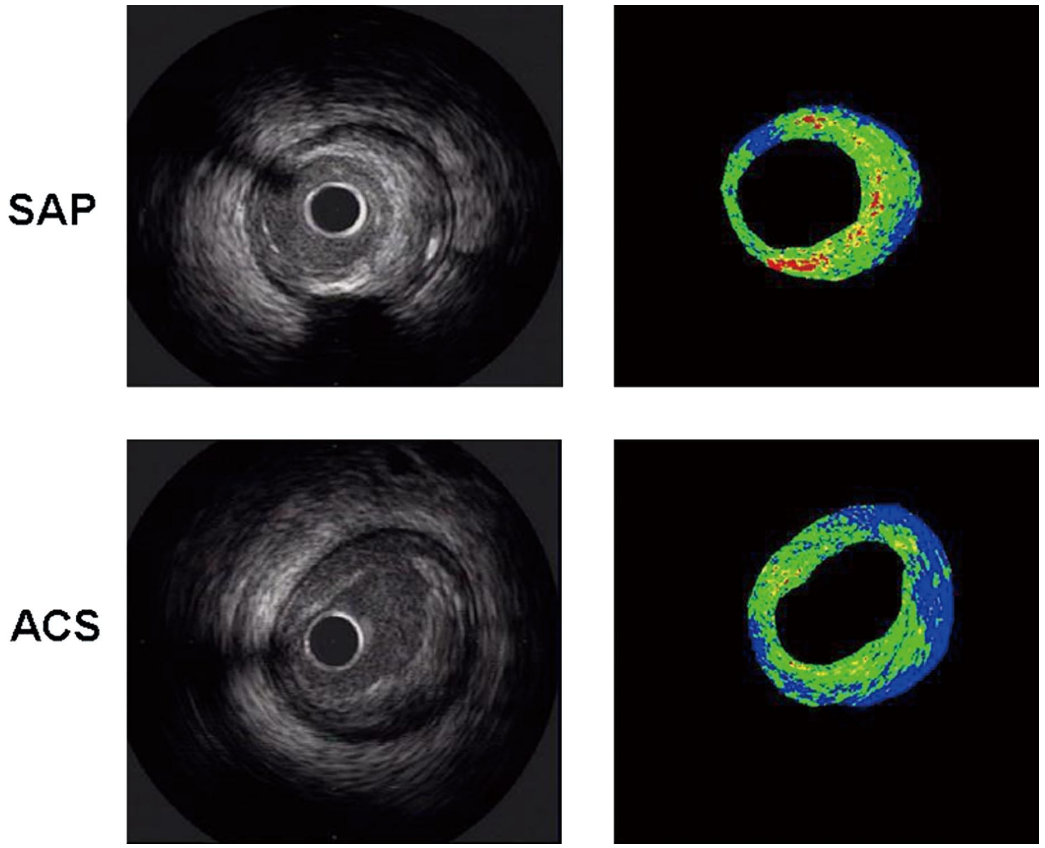

Figure 4. Representative images of conventional intravascular ultrasound and 2-dimensional integrated backscatter intravascular ultrasound color-coded maps of non-culprit lesions in patients with or without acute coronary syndrome (ACS). The percentage of lipid area was 22% in stable angina pectoris (SAP) patients and 43% in ACS patients. The percentage of fibrous area was 71% in SAP patients and 56% in ACS patients.

the occurrence of rupture.[3]

In the present study, patients with ACS significantly increased in LDL cholesterol and had a tendency to be increased in CRP concentrations. These findings might also have implications regarding the pathophysiology of plaque instability. Inflammation of the plaque might arise from systemic processes and thereby affect the atherosclerotic coronary vasculature in a more diffuse pattern.[4,20,21] With respect to lipid metabolism, intrinsic plaque instability might develop owing to the expansion of intraplaque contents such as lipid-pool swelling, which might also reflect systemic derangements. Nevertheless, CRP concentration and statin treatments were not significantly associated with the lipid-rich plaque. Consequently, the lack of these 2 factors for the prediction of the lipid-rich plaque suggests either that patients with ACS were relatively small, or that lipid-lowering interventions in patients with ACS would have been insufficient. Further studies will be needed to answer these questions definitively.

Table 3. Logistic Regression Model for Prediction of the Lipid-Rich Plaque

	OR	95%CI	P value
ACS			
All	5.88	1.89–18.3	0.002
Culprit	5.09	1.41–18.3	0.01
Non-culprit	7.10	1.86–27.2	0.004
Eccentricity index	1.03	0.99–1.07	0.14
C-reactive protein	1.50	0.85–2.64	0.16
Statins	0.91	0.34–2.46	0.85
Remodeling index	2.26	0.26–19.6	0.46
Smoking	1.48	0.53–4.11	0.46

After adjusting for confounding (age, gender and BMI) and coronary risk factors (hypertension, diabetes mellitus, LDL cholesterol, HDL cholesterol and multiple disease).
OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 1.

Study Limitation

First, thrombus formation which is even with gray scale ultrasound often not detected, is not color-coded and analyzed by the method described, thereby harboring a rigorous calculation of the area of each component, especially in the culprit lesions with ACS patients. Because it is well established that the culprit lesion with ACS patients is a typical presentation of the plaque vulnerability, the emphasis of this study was thus placed on the predictive value of non-culprit lesions for the plaque vulnerability. Second, some selection

bias can not be neglected because we selected 1 to 4 plaques in each patient. However, with adjusted for GEE analysis in order to account for repeated assessments to one patient, culprit and non-culprit lesions with ACS patients significantly associated with the lipid-rich plaque. Third, with regard to the lesion classification, sometimes it was difficult to distinguish clearly culprit lesion from stenotic non-culprit lesion. This is due to the lack of gold standard for identification of culprit lesion. Fourth, the time lag between the onset of ACS and IVUS study might have influenced IVUS findings of plaque.

Conclusions

Non-culprit coronary lesions with ACS patients as well as culprit lesions are associated with the lipid-rich plaque, suggesting the extensive development of plaques instability in these patients.

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