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Volumetric Quantitative Analysis of Tissue Characteristics of Coronary Plaques After Statin Therapy Using Three-Dimensional Integrated Backscatter Intravascular Ultrasound

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OBJECTIVES The purpose of the present study was twofold: 1) to evaluate the usefulness of three-dimensional (3D) integrated backscatter (IB) intravascular ultrasound (IVUS) for quantitative tissue characterization of coronary plaques; and 2) to use this imaging technique to determine if six months of statin therapy alters the tissue characteristics of coronary plaques.

BACKGROUND Three-dimensional IVUS techniques for quantitative tissue characterization of plaque composition have not been developed.

METHODS Radiofrequency (RF) signals were obtained using an IVUS system with a 40-MHz catheter. The IB values of the RF signal were calculated and color-coded. The 3D reconstruction of the color-coded map was performed by computer software. A total of 18 IB IVUS images were captured at an interval of 1 mm in each plaque. A total of 52 patients with hyperlipidemia were randomized to treatment with pravastatin (20 mg/day, n = 17), atorvastatin (20 mg/day, n = 18), or diet (n = 17) for six months. The tissue characteristics of arterial plaque in each patient (one arterial segment per patient) were analyzed with 3D IB IVUS before and after treatment.

RESULTS Significant increases of fibrous volume (pravastatin: 25.4 ± 6.5% to 28.1 ± 6.1%; atorvastatin: 26.2 ± 5.7% to 30.1 ± 5.5%) and mixed lesion volume (atorvastatin: 25.5 ± 6.6% to 28.7 ± 5.1%) and a reduction of lipid volume (pravastatin: 25.5 ± 5.7% to 21.9 ± 5.3%; atorvastatin: 26.5 ± 5.2% to 19.9 ± 5.5%) were observed after statin therapy.

CONCLUSIONS Statin therapy reduced the lipid component in patients with stable angina without reducing the degree of stenosis. Three-dimensional IB IVUS offers the potential for quantitative volumetric tissue characterization of coronary atherosclerosis. (J Am Coll Cardiol 2005;45: 1946–53) © 2005 by the American College of Cardiology Foundation

Intravascular ultrasound (IVUS) allows tomographic imaging of coronary arteries and provides a more comprehensive assessment of the atherosclerotic plaques in vivo than the "luminal silhouette" furnished by coronary angiography.

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Furthermore, three-dimensional (3D) image reconstruction techniques have been developed to perform volumetric analyses (1–3). Electrocardiographic (ECG)-gated acquisition of 3D IVUS image sets is feasible and permits the application of automated contour detection to provide reproducible measurements of the lumen and atherosclerotic plaque cross-sectional area and volume in a relatively short analysis time (4,5).

Previously, many techniques for the tissue characterization of plaque composition have been developed using two-dimensional (2D) IVUS (6–8). Recently, it has been reported that autoregressive classification techniques allow the analysis of IVUS data, enabling in vivo plaque characterization (9). Also, we developed an integrated backscatter (IB) IVUS system in which 2D color-coded maps for tissue characterization of coronary plaques were constructed by computer (10). This method is based on the analysis by IB signals. We reported on the tissue characterization of arterial plaques in human carotid and coronary arteries in vivo using IB ultrasound (10,11). These studies showed IB measurements accurately reflected the tissue characteristics of human carotid arterial plaques, and IB values recorded in vivo were precisely correlated with either the IB values obtained just after excision at autopsy or the IB values after fixation (11). Moreover, it was reported that IB values of carotid arteries reflected the risk of atherosclerosis in pa-

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Abbreviations and Acronyms

2D = two-dimensional
3D = three-dimensional
DM = diabetes mellitus
ECG = electrocardiogram/electrocardiographic
HL = hyperlipidemia
HTN = hypertension
IB = integrated backscatter
IVUS = intravascular ultrasound
RF = radiofrequency
ROI = region of interest

tients with ischemic heart disease (12). However, 3D IVUS techniques for tissue characterization of plaque composition have not been developed.

Substantial reduction of acute cardiac events has been shown in most of the lipid-lowering trials, despite only a minimal geometric regression of plaque (13–16). The prevention of acute coronary syndrome with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is associated with stabilization of coronary plaques but no improvement of the degree of stenosis (17,18). Statin-induced plaque stabilization is thought to be due to a change in plaque composition from a large lipid core with a thin fibrous cap into a small lipid core with a thick fibrous cap (17). Although animal studies support this hypothesis, there are little data on the tissue characteristics of coronary plaques in patients before and after statin therapy (19).

The purpose of the present study was two-fold: 1) to evaluate the usefulness of 3D IB IVUS for quantitative tissue characterization or coronary plaques; and 2) to use this imaging technique to determine if six months of statin therapy alters the tissue characteristics of coronary plaques.

METHODS

Patients and study design. This study was a simple randomization, open-label, single-center study of patients with hyperlipidemia. The study included 52 patients stable angina pectoris not currently on statin therapy, but with total cholesterol concentrations above 220 mg/dl at the time of enrollment. Patients with unstable angina or myocardial infarction within the previous four weeks, ejection fraction <30%, secondary causes of hypercholesterolemia, and severe hypertriglyceridemia (>400 mg/dl) were excluded. Patients were randomized to one of three groups: pravastatin (20 mg/day, n = 19), atorvastatin (20 mg/day, n = 20), and control (n = 18). The control group was treated with dietary stabilization only. Study patients were referred to a nutritionist for individual counseling and were also provided with a lifestyle-changing program that included cessation of smoking. Informed consent was obtained from patients and their relatives before randomization in all cases. The patients in the control group were given the option of statin therapy if the lipid volume of their coronary plaques increased after six months. Two patients in the pravastatin group and two patients in the atorvastatin group did not complete the study because of interruption of treatment. One patient in the control group did not complete the study because of relocation. There were no serious cardiovascular events, such as myocardial infarction, unstable angina, or death, in any group. At baseline and after six months, all patients had intracoronary interventions and IB IVUS analyses performed in coronary arteries with mild or moderate stenosis. The plaques analyzed in this study had to be more than 20 mm from the intervention site. Another coronary artery was analyzed if there was no plaque with mild or moderate stenosis in the vessel that was the target of the intervention. Coronary arteries were excluded if an IVUS catheter could not be inserted because of severe stenosis. Risk factors for coronary artery disease were evaluated in each patient, including diabetes mellitus (medication-dependent, including oral hypoglycemic drugs and insulin), hypertension (medication-dependent only), and smoking status (current smoker or quit <6 months before the study).

IB system presets and data acquisition. An analog-digital converter (Wavepro 960, LeCroy, Chestnut Ridge, New York) and ECG monitor were connected, and a trigger was set in coordinate with the ECG. The radiofrequency (RF) signals were acquired at the top of the R-wave of the ECG after detection of a regular R-R interval at one site. Then, the catheter was pulled back at 1-mm interval by activating the pull-back motor. Conventional IVUS images and IB signals were acquired at end diastole using an IVUS imaging system (Clear View, Boston Scientific, Natick, Massachusetts) and a 40-MHz intravascular catheter. For the prevention of coronary spasm, we administered an intracoronary optimal dose of isosorbide dinitrate before the measurements. A target coronary segment was selected by the presence of an easily definable branch to ensure a reliable comparison between baseline and six-month follow-up. A total of 18 IB IVUS images were captured at an interval of 1 mm using a motorized pull-back system in each plaque. We used an analog-digital converter, which enabled acquisition, storage, and retrieval of signals that were digitized at 2 GHz with 8-bit resolution. Off-line calculation of IB values of the acquired RF signals was performed by retrieving the previously stored data from the built-in memory (Compact Flash, San Disk, Sunnyvale, California), using software we developed for this study. Our definition of IB

Table 1. Definition of IB Values in Each of Histological Categories in Plaque

Histology	IB Values (dB) Mean ± SD	Definition (dB)
Calcification	−26.7 ± 3.6	$-30 < IB \leq -23$
Mixed lesion	−40.7 ± 4.6	$-55 < IB \leq -30$
Fibrosis	−58.9 ± 3.6	$-63 < IB \leq -55$
Lipid pool	−67.5 ± 3.6	$-73 < IB \leq -63$

Our definition of IB values in each histological category was based on the mean IB values ± 1 SD reported in our previous study (10).
IB = integrated backscatter.

values for each histologic category was determined by comparing the histologic images reported in our previous study (Table 1) (10). In the present study, we used 256 vector lines per image (1.4 grade/line) and set 20 regions of interest (ROIs) for each 100 μm depth on each vector line (total 5,120 ROIs/image).

Construction of 3D color-coded maps using IB values. In the polar coordinates we used in the 2D color-coded maps, the size of each ROI was different. To make the volumetric analysis more accurate in the present study, polar coordinates were transformed into cartesian coordinates (64 × 64 pixels) using computer software. We then manually excluded the vessel lumen and area outside of the intima in the 2D IB IVUS images. Three-dimensional construction and calculation of the number of voxels of each tissue characteristic were automatically performed by commercially available computer software (T3D, Fortner Research LLC, Sterling, Virginia). The software connected 18 consecutive images.

Conventional IVUS and IB IVUS parameters. Each conventional IVUS and IB IVUS parameter was measured at baseline and after six months in each group. After coronary angiography, IVUS studies were performed by an experienced investigator blinded to the treatment. Cross-sectional lumen area, cross-sectional vessel area within the external elastic membrane, and plaque area (external elastic membrane area minus lumen area) were determined by use of the software attached to the IVUS system. Conventional 3D IVUS image analysis was performed using an automated 3D IVUS image analysis system (NetraIVUS, ScImage, Los Altos, California) consisting of a semiautomatic user-guided boundary delineation tool for segmentation of structures of interest. The system, which has been applied successfully to the volumetric analysis in computed tomography and magnetic resonance imaging, utilizes a shape-based interpolation algorithm.

The IVUS determinations were based on the observance of two specialists who were blinded to the patients' characteristics. High-signal lesion (the part of the calcification on the inner surface that could be measured), volume (number of voxels of high-signal lesion/total number of plaque voxels), fibrous volume (number of voxels of fibrosis/total number of plaque voxels), lipid volume (number of voxels of lipid pool/total number of plaque voxels), and mixed lesion volume (number of voxels of mixed lesion/total number of plaque voxels) were automatically measured in each plaque using T3D software (Fig. 1).

Statistical analyses. Laboratory and ultrasound parameters were reported as the mean value ± SD. Whether or not data were normally distributed was examined by the Kolmogrov-Smirnov test. If data were not normally distributed, testing for significant differences of each parameter between baseline and six months was performed with the Mann-Whitney *U* test. If the data were normally distributed, but the variances were significantly different when comparing baseline versus six months, Welch's *t* test was used. Otherwise, the paired Student *t* test was used. Whether variances were significantly different was examined by the *F* test. The significance of the differences among those parameters in the three study groups was tested using one-way analysis of variance followed by Scheffe's method of multiple comparisons, which was used for the post-hoc comparisons between groups. A p value <0.05 was considered to be statistically significant.

RESULTS

Reproducibility of data. We determined intraobserver and interobserver variabilities of fibrous volume, lipid volume, mixed lesion volume, and high-signal lesion volume in 20 randomly selected recordings that were measured twice by the same observer and once each by two independent

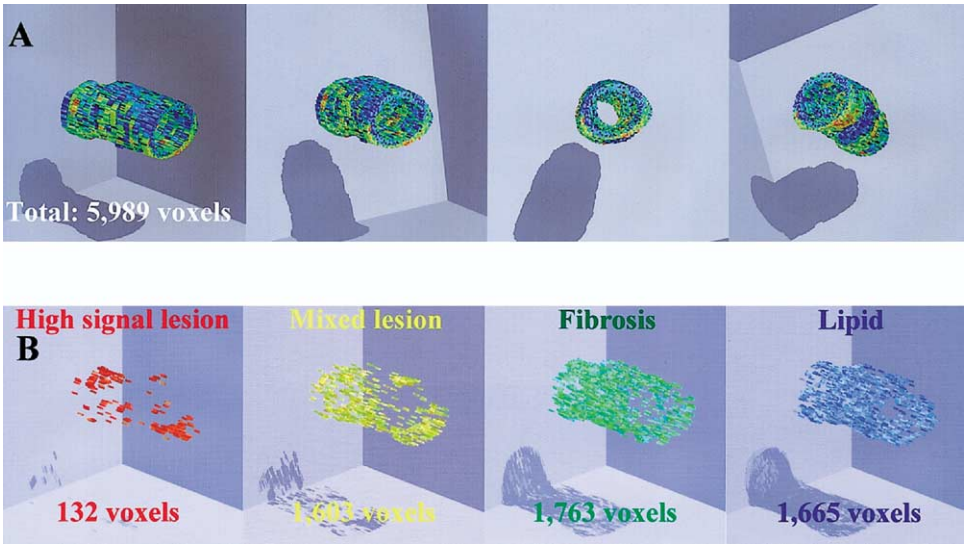

Figure 1. (A) The three-dimensional (3D) color-coded maps of the coronary arterial plaques constructed by 3D integrated backscatter intravascular ultrasound. **(B)** The 3D color-coded maps of each characteristic. The number of voxels of each tissue characteristic was automatically calculated.

Table 2. Baseline Characteristics of the Patients

Variable	Atorvastatin	Pravastatin	Control	p Value
Gender, n (%)				
Men	12	13	14	NS
Women	5	5	3	NS
Age, yrs	66 ± 8.7	67 ± 7.8	66 ± 6.4	NS
Body mass index (kg/m^2)	23.5 ± 3.3	24.1 ± 3.0	23.1 ± 3.5	NS
Clinical history, n (%)				
Myocardial infarction	1 (6)	0 (0)	1 (6)	NS
Hypertension	8 (47)	9 (50)	7 (41)	NS
Diabetes mellitus type 2	4 (24)	5 (28)	3 (18)	NS
Current smoker	4 (24)	5 (28)	3 (18)	NS
Prior statin use	2 (12)	2 (11)	1 (6)	NS
Number of coronary artery disease, n (%)				
Single vessel	5 (29)	4 (22)	6 (35)	NS
Multiple vessel	12 (71)	14 (78)	11 (65)	NS
Target plaque location, n (%)				
LAD	7 (41)	7 (39)	6 (35)	NS
LCX	5 (29)	7 (39)	5 (29)	NS
RCA	5 (29)	4 (22)	6 (35)	NS
Medication, n (%)				
Aspirin	17 (100)	18 (100)	17 (100)	NS
Ticlopidine	17 (100)	18 (100)	17 (100)	NS
Nitrates	12 (71)	15 (83)	12 (71)	NS
Calcium channel blockers	11 (65)	13 (72)	10 (56)	NS
Beta-blockers	3 (18)	4 (22)	3 (18)	NS
Insulin	2 (12)	2 (11)	3 (18)	NS
ACE inhibitors	9 (53)	10 (56)	7 (41)	NS
AT_1 antagonists	5 (29)	4 (22)	6 (35)	NS

ACE = angiotensin-converting enzyme; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery.

observers. Intraobserver variabilities of each relative volume were 2.6 ± 2.1%, 3.6 ± 2.4%, 3.4 ± 2.5%, and 1.9 ± 1.1%, respectively. Interobserver variabilities of each relative volume were 2.1 ± 2.3%, 3.6 ± 2.4%, 2.6 ± 2.1%, and 1.3 ± 0.9%, respectively. Intraobserver correlations of each relative volume were $r = 0.95$ ($p < 0.01$), $r = 0.92$ ($p < 0.01$), $r = 0.91$ ($p < 0.01$), and $r = 0.97$ ($p < 0.01$), respectively. Interobserver correlations of each relative volume were $r = 0.96$ ($p < 0.01$), $r = 0.94$ ($p < 0.01$), $r = 0.95$ ($p < 0.01$), and $r = 0.97$ ($p < 0.01$), respectively.

Construction of 3D color-coded map. The 3D IB IVUS images consisted of a total of 8,989 ± 1,432 voxels in each plaque. The 3D IB IVUS images presented here can visualize lipid pools, fibrous lesions, mixed lesions, and high-signal lesions (the part of the calcification on the inner surface that could be measured) in the plaque of human coronary arteries in vivo (Fig. 1). By looking at these images, we were able to know the location of lipid pools, fibrous lesions, mixed lesions, and high-signal lesions in the plaque. Tissue characterization of each 3D IB IVUS image was performed by analyzing all voxels in each plaque.

Different tissue characteristics of plaques at baseline. There were no significant differences in the distribution of patients with coronary risk factors among the three groups (Table 2). However, there were significant differences in high-signal lesion volume among the patients with hyperlipidemia (HL), HL plus hypertension (HTN), HL plus diabetes mellitus (DM), and HL plus HTN plus DM at baseline, although there were no significant differences in the fibrous, lipid, and mixed lesion volumes among these patients (Table 3).

Laboratory profiles. There were no significant differences with regard to baseline characteristics and blood lipid parameters at baseline among the three groups (Tables 2 and 4). Total cholesterol significantly decreased in the pravastatin and atorvastatin groups. After six months of statin therapy, the mean reduction in total cholesterol was 22% in the pravastatin group and 29% in the atorvastatin

Table 3. Three-Dimensional Integrated Backscatter Intravascular Ultrasound Parameters of Patients Stratified by Baseline Risk Factors

Parameter	HL (n = 21)	HL + HTN (n = 19)	HL + DM (n = 7)	HL + HTN + DM (n = 5)
Fibrous volume (%)	23.9 ± 7.1	27.0 ± 5.9	23.9 ± 4.2	29.3 ± 4.0
Lipid volume (%)	25.5 ± 5.1	25.5 ± 5.5	26.2 ± 7.0	27.5 ± 3.1
Mixed lesion volume (%)	27.0 ± 6.3	26.7 ± 6.0	26.7 ± 7.4	27.0 ± 4.7
High signal lesion volume (%)	2.0 ± 0.5	2.5 ± 0.5*	2.7 ± 0.4*	2.9 ± 0.4*

Values are mean ± SD. *$p < 0.05$ vs. % high signal lesion volume in HL using analysis of variance.
DM = diabetes mellitus; HL = hyperlipidemia; HTN = hypertension.

Table 4. Changes in Laboratory Profiles

Parameter	Baseline	Month 6	Reduction (%)
Total cholesterol (mg/dl)			
Atorvastatin	244 ± 21	174 ± 22*	29
Pravastatin	250 ± 22	196 ± 23*	22
Control	241 ± 27	240 ± 46	0
HDL cholesterol (mg/dl)			
Atorvastatin	50 ± 9	56 ± 10*	−12
Pravastatin	54 ± 12	56 ± 10	−4
Control	50 ± 10	51 ± 11	−2
LDL cholesterol (mg/dl)			
Atorvastatin	155 ± 22	95 ± 15*	39
Pravastatin	149 ± 19	102 ± 13*	32
Control	152 ± 20	149 ± 24	2
Triglycerides (mg/dl)			
Atorvastatin	146 ± 27	129 ± 26*	12
Pravastatin	155 ± 26	139 ± 28*	11
Control	155 ± 29	160 ± 32	−3
C-reactive protein (mg/dl)			
Atorvastatin	0.38 ± 0.47	0.13 ± 0.17†	65
Pravastatin	0.33 ± 0.16	0.27 ± 0.19†	18
Control	0.30 ± 0.31	0.35 ± 0.43	−17

Values are mean ± SD. *$p < 0.01$, †$p < 0.05$ between at baseline and after 6 months. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

group. The mean reductions in low-density lipoprotein cholesterol, triglycerides, and C-reactive protein were 32%, 11%, and 18% in the pravastatin group and 39%, 12%, and 65% in the atorvastatin group, respectively. High-density lipoprotein cholesterol significantly increased in the atorvastatin group. However, there was no significant difference of those parameters between baseline and six-month follow-up in the control group.

Conventional IVUS and IB IVUS measurement. There were no significant differences among the three treatment groups in vessel area, lumen area, plaque area, and stenosis diameter or area at baseline. There were also no significant differences between baseline and six months in the stenosis diameter, stenosis area, and plaque volume in the three treatment groups (Table 5). However, a significant increase in fibrous volume and a reduction in lipid volume were observed, despite no significant differences in fibrous volume or lipid volume in the control group. Mixed lesion volume significantly increased only in the atorvastatin group (Table 6). Figure 2 illustrates changes in IB IVUS images of a plaque before and after statin therapy.

DISCUSSION

Previous studies suggest that plaque rupture and acute occlusion occur at the site of unstable plaques, where there is a high lipid content covered by a thin fibrous cap (20,21). The presence of lipid-rich plaque may be an important prerequisite for plaque vulnerability (22). Conventional echocardiographic techniques, especially IVUS imaging, are widely used to determine calcification of the three layers of the arterial vessel wall and the degree of plaque calcification. However, it is difficult to detect vulnerable plaques using conventional IVUS. Detecting vulnerable plaques is one of the most important endeavors in the field of cardiology. Recently, mathematical analysis of RF signals from IVUS and color mapping of angle-dependent echo-intensity variation have been developed for detecting vulnerable plaques (6,7). In addition, IVUS elastography has been shown to distinguish different plaque morphologies in vivo (9).

In this study, we describe a method of tissue characterization of coronary plaques using an IB IVUS imaging system. The present system with the commercially available IVUS imaging system (Boston Scientific), digital-analog converter (Wavepro 960, LeCroy), and computer software (T3D, Fortner Research LLC) made tissue characterization of coronary plaques possible without any reconstruction from video recorder images (10).

Reconstruction of 3D IB IVUS color-coded maps. Previously, several 3D reconstruction techniques of conventional IVUS images have been established. Computer-aided 3D reconstruction connecting cross-sectional IVUS images, digitized every 0.2 mm using a motorized pull-back device, allows the reproducible and reliable measurement of plaque volume that reflects the morphologic features of the plaque (23). Volumetric measurements derived from IVUS images are highly reproducible and useful for monitoring the progres-

Table 5. Changes in Lesion Characteristics

Parameter	Baseline	Month 6	Reduction (%)	p Value
Angiographic stenosis diameter (%)				
Atorvastatin	40.9 ± 5.2	40.3 ± 5.0	1	NS
Pravastatin	41.3 ± 6.7	41.6 ± 7.1	0	NS
Control	38.3 ± 5.3	39.5 ± 5.5	−3	NS
Vessel area (mm^2)				
Atorvastatin	12.8 ± 2.2	13.2 ± 2.4	−3	NS
Pravastatin	13.4 ± 1.9	13.2 ± 2.1	1	NS
Control	12.5 ± 2.2	12.8 ± 2.1	−2	NS
Lumen area (mm^2)				
Atorvastatin	4.4 ± 0.8	4.8 ± 1.2	−9	NS
Pravastatin	4.8 ± 0.9	4.7 ± 1.2	2	NS
Control	5.0 ± 0.9	4.9 ± 1.1	2	NS
Plaque area (mm^2)				
Atorvastatin	8.4 ± 2.2	8.3 ± 2.3	0	NS
Pravastatin	8.9 ± 2.1	8.7 ± 2.4	2	NS
Control	7.5 ± 2.1	8.0 ± 2.4	−7	NS
Plaque burden (%)				
Atorvastatin	65.5 ± 12.6	62.3 ± 11.3	0	NS
Pravastatin	66.1 ± 10.1	66.3 ± 10.4	0	NS
Control	60.7 ± 9.1	62.3 ± 10.4	−3	NS
Vessel volume (mm^3)				
Atorvastatin	232.6 ± 39.6	230.6 ± 43.2	1	NS
Pravastatin	239.2 ± 34.2	237.6 ± 37.8	1	NS
Control	230.1 ± 39.6	231.4 ± 37.8	−1	NS
Lumen volume (mm^3)				
Atorvastatin	72.3 ± 15.1	75.1 ± 14.2	−4	NS
Pravastatin	74.1 ± 12.9	73.6 ± 15.2	1	NS
Control	72.1 ± 13.2	72.4 ± 15.8	0	NS
Plaque volume (mm^3)				
Atorvastatin	159.2 ± 31.6	155.4 ± 32.8	2	NS
Pravastatin	166.2 ± 29.5	164.6 ± 34.5	1	NS
Control	159.0 ± 30.2	159.0 ± 29.5	0	NS

IVUS = intravascular ultrasound.

Table 6. Changes in Three-Dimensional Integrated Backscatter Intravascular Ultrasound Parameters

Parameter	Baseline	Month 6	Reduction (%)
Fibrous volume (%)			
Atorvastatin	26.2 ± 5.7	30.1 ± 5.5*	−15
Pravastatin	25.4 ± 6.5	28.1 ± 6.1†	−11
Control	24.6 ± 6.8	25.6 ± 6.3	−4
Lipid volume (%)			
Atorvastatin	26.5 ± 5.2	19.9 ± 5.5*‡	25
Pravastatin	25.5 ± 5.7	21.9 ± 5.3†	14
Control	25.5 ± 5.7	26.9 ± 4.2	−5
Mixed lesion volume (%)			
Atorvastatin	25.5 ± 6.6	28.7 ± 5.1*	−13
Pravastatin	27.5 ± 5.8	29.8 ± 5.8	−8
Control	27.6 ± 4.1	28.1 ± 5.2	−2
High signal lesion volume (%)			
Atorvastatin	2.3 ± 0.6	2.4 ± 0.6	−4
Pravastatin	2.2 ± 0.6	2.4 ± 0.7	−9
Control	2.4 ± 0.6	2.5 ± 0.6	−4

Values are mean ± SD. *$p < 0.01$, †$p < 0.05$ between baseline and 6 months. ‡$p < 0.01$ vs. control using a one-way analysis of variance.

sion and regression of atherosclerotic plaque volume in a longitudinal study (24). The acoustic characterization of the composition of a coronary plaque by use of conventional IVUS has been validated by in vitro and in vivo studies (25,26). However, 3D reconstruction of conventional IVUS images showed a good reflection of morphologic features but not histologic features of the plaques. The 3D IB IVUS color-coded maps consecutively connecting 18 images digitized every 1 mm offer the potential to characterize coronary plaques and count the ratio of each tissue characteristic (Fig. 1).

Plaque stabilization after statin therapy. There are some data obtained by a few maneuvers that indicate plaque stability after statin therapies. Recently, angioscopy has shown that atorvastatin treatment (10 to 30 mg/day) for one year changed plaque color and morphology and led to coronary plaque stabilization (27). In that study, the mean yellow score significantly decreased after statin therapy. The results of the present study are compatible with that study because our previous work showed that the surface color of the plaque evaluated with angioscopy reflects the thickness of the fibrous cap determined with 2D IB IVUS imaging (10).

Previous analysis of plaque stability using conventional IVUS showed that atorvastatin treatment for one year in the German Atorvastatin Intravascular Ultrasound (GAIN) study was associated with an increased hyperechogenic plaque area, which in turn was associated with a larger fraction of dense fibrous and elastic tissue without plaque volume regression (28). In that study, there was no significant difference in hypoechogenic plaque area between

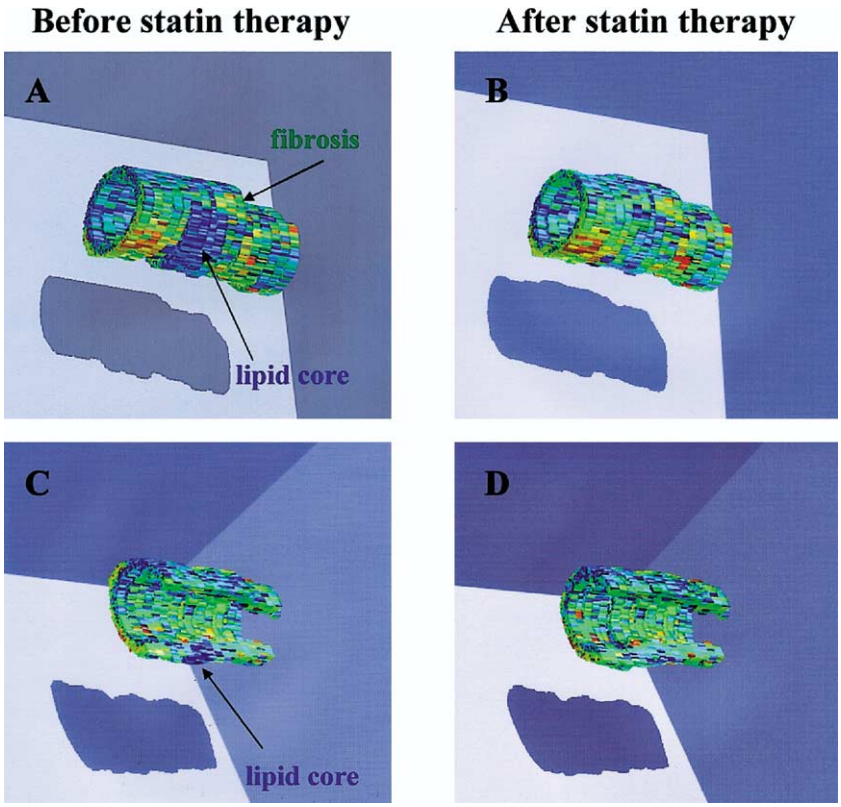

Figure 2. Color-coded maps of the coronary arterial plaques constructed by three-dimensional (3D) integrated backscatter intravascular ultrasound imaging at baseline and after statin therapy. **(A)** At baseline, the plaque consisted of a large lipid core **(blue)**, which is covered with a fibrous cap **(green)**. **(B)** After statin therapies, the lipid core **(blue)** decreased and the fibrous area **(green)** increased. **(C)** Cut-out image of 3D color-coded map at baseline. There was a small lipid core **(blue)** in the center of the plaque. **(D)** Cut-out image of 3D color-coded map after statin therapy. Note the reduction in the lipid core. **Red** = high signal lesion; **yellow** = mixed lesion.

baseline and one year, because the detection of the lipid core by use of conventional IVUS was not quantitative. In the present quantitative study, the relative fibrous volume significantly increased and the relative lipid volume significantly decreased after therapy with both atorvastatin and pravastatin, without improvement in the degree of stenosis.

With respect to the relationship between the regression of the plaque area and the follow-up period, it was reported that progression and regression did not occur after 1.5 years of statin therapy (atorvastatin 80 mg/day) in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study (18). In addition, in the GAIN study, regression of the plaque area did not occur after one year of statin therapy (atorvastatin 20 to 40 mg/day) (28). On the other hand, the regression of the plaque occurred after one year of statin therapy (simvastatin 40 mg/day) and three years of statin therapy (pravastatin 10 mg/day) (29,30). A recent single-center, small study indicated that the decrease of lumen volume without shrinkage of coronary arteries resulted in a significant reduction of plaque volume after six months of statin therapy (atorvastatin 20 mg/day) in patients with acute coronary syndrome (31). Taking an overall view of these studies, a significant regression of the plaque can be seen from six months to three years after statin therapy. However, previous large-scale, long-term studies, which indicated the prognosis of the patients with hyperlipidemia, showed improvements in the event-free ratio of the statin therapy group after only six months (32,33). This means that plaque stability is achieved by the change of plaque contents, such as the removal of lipids from the lipid-rich plaques and an increase in fibrous tissue, despite only a minimal morphologic regression of plaque after only six months of the statin therapy.

Study limitations. First, we manually excluded the vessel lumen and the area outside of the coronary artery intima from the entire 2D IB IVUS image. To improve the accuracy (intraobserver and interobserver variabilities of the analysis), computerized assessment of the coronary lumen and atherosclerotic plaque dimensions will be required in the future. Second, the 3D IB IVUS images presented in this study do not represent a true spatial reconstruction of plaque geometry, but simply a connection of consecutive 18 IB IVUS images captured at an interval of 1 mm using motorized pull-back system. The number of captured images depends on the storage capacity and processing speed of the personal computer. Future studies will address these problems. Third, calcification is a perfect reflector for ultrasound, causing the acoustic shadowing so typical in the IVUS images. The RF signals not able to penetrate or pass through the calcified layer are reflected back toward the transducer (34). Therefore, an accurate calculation of calcified volume was not possible, although the calculation for the high RF signal lesion was performed in the present study. Fourth, previous histologic studies showed that IB measurements accurately reflected the tissue characteristics of human coronary arterial plaques. However, these comparisons between IB values and histologic categories were performed in two-dimensional color-coded maps. A 3D comparison will be required in the future. Furthermore, because the number of patients in this study was small and the follow-up period was short, analysis of the incidence of vascular events was not possible. In addition, six months was not enough to detect changes in plaque composition. Large-scale, long-term studies, which include an analysis of the incidence of acute coronary syndrome, will be required in the future.

Conclusions. Three-dimensional IB IVUS, which depicts tissue characteristics of plaques, offers an improvement over conventional IVUS techniques for the tissue characterization of plaques and the assessment of the history of coronary atherosclerosis. Statin therapy reduced the lipid component in patients with stable angina without reducing the degree of stenosis. Quantitative evaluation using 3D IB IVUS images may lead to elucidation of the progression process of unstable plaques in the clinical settings and prevention of acute coronary syndrome.

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