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Effects of Fluvastatin on the Carotid Arterial Media as Assessed by Integrated Backscatter Ultrasound Compared With Pulse-Wave Velocity

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OBJECTIVES Our goal is to show the effectiveness of fluvastatin in reducing arterial sclerosis using integrated backscatter (IB) values rather than depending on the pulse-wave velocity (PWV) and stiffness beta.

BACKGROUND Atherosclerotic changes consist of two components: atherosis as a structural change and sclerosis as a functional change; IB ultrasound of carotid media was useful for assessment of arterial sclerosis.

METHODS We measured IB values in the media of 40 segments of carotid arteries in 40 patients with hyperlipidemia before and after statin therapy or diet for 12 months (fluvastatin [F group] 40 mg/day, n = 20; control [C group]: diet, n = 20). Pulse-wave velocity, intima-media thickness, and stiffness beta were measured at the same time.

RESULTS At baseline, IB values correlated with PWV ($r = 0.71$, $p < 0.001$) and stiffness beta ($r = 0.47$, $p = 0.002$) in 40 patients with hyperlipidemia. Integrated backscatter values did not change in the C group but decreased in the F group (from 12.3 ± 2.1 dB to 11.3 ± 2.1 dB, $p = 0.002$). Also, PWV increased in the C group (from 1,728 ± 687 cm/s to 1,771 ± 716 cm/s, $p = 0.021$) but decreased in the F group (from 1,848 ± 582 cm/s to 1,768 ± 549 cm/s, $p = 0.012$). Stiffness beta decreased in the F group (from 14.0 ± 3.9 to 12.1 ± 3.5, $p = 0.002$).

CONCLUSIONS Statin therapy with fluvastatin improved arterial sclerosis as assessed by IB values. (J Am Coll Cardiol 2005;46:2031–7) © 2005 by the American College of Cardiology Foundation

Atherosclerotic changes consist of two components: atherosis as a structural change and sclerosis as a functional change. According to a pathological study, atherotic changes are recognized by an increase in the intima-media thickness (IMT), which is associated with structural atheromatous changes, and sclerotic changes are recognized by a decreased extensibility, which is associated with functional sclerotic changes in elastic and collagen fibers. Intima-media thickness measurement is widely used to evaluate atheromatous damages, which are associated with age and coronary risk factors (1). However, increased thickness of the wall as determined by IMT measurement is not always associated with the severity of "sclerosis" in patients with hypertension (HTN) (2). This lack of association may be due to the degenerative changes in the medial smooth muscle cells and variation in the increased amount of elastin and collagen in hypertensive vessels. Arterial stiffness is mainly correlated with the amounts of medial elastin and collagen, rather than the thickness of the arterial wall (3). On the other hand, there is another ultrasound parameter, stiffness beta, which is used to evaluate sclerosis and is associated with decreased extensibility of the arterial wall. Stiffness beta was found to be independent of blood pressure within the normal physiological range and was associated with the severity of coronary atherosclerosis (4,5).

With respect to atherosis of arterial plaques, we reported on the tissue characterization of arterial plaques in human carotid arteries (6). These studies showed that ultrasound integrated backscatter (IB) values accurately reflected the tissue characteristics of human carotid arterial plaques. Other investigators showed that measurements of IB values of the carotid arteries are clinically useful for risk assessment of coronary artery disease (CAD) patients (7). With respect to sclerosis, we reported that the measurement of the IB value of the carotid media is useful in evaluating arterial sclerosis in vivo as well as the stiffness beta and that IB values are associated with the structural change of the elastic fiber and collagen fiber of carotid media (8).

When considering therapies, we know that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor drugs (statins) reduce mortality of myocardial infarction and stroke, preventing the progression of atherosis as assessed by IMT (9,10). A previous study has shown an association between the IMT of carotid arteries and incidence of myocardial infarction and stroke (11). We previously reported that hydrophilic statin treatment did not improve arterial sclerosis as assessed by IB values (12). Hydrophilic statin cannot cross the cell membranes of the vascular wall. However, fluvastatin can and it has a strong anti-proliferative effect on smooth muscle cells because it is lipophilic (13). In the present study, we measured IB values in the carotid media in patients with hyperlipidemia (HL) before and after statin therapy to define whether fluvastatin reduces arterial scle-

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Abbreviations and Acronyms

ApoB/A-I	= ratio of apolipoprotein B to apolipoprotein A-I
CAD	= coronary artery disease
CVD	= cerebrovascular disease
DM	= diabetes mellitus
HL	= hyperlipidemia
hs-CRP	= high-sensitivity C-reactive protein
HTN	= hypertension
IB	= integrated backscatter
IMT	= intima-media thickness
LDL-C	= low-density lipoprotein cholesterol
PWV	= pulse-wave velocity
SBP	= systolic blood pressure

rosis. Our goal is to show the effectiveness of fluvastatin in reducing arterial sclerosis using IB values.

METHODS

Subjects. This study was a simple randomization, open-label, single-center study of patients with HL. Patients were either previously untreated or treated with drugs other than statins, but with total cholesterol concentrations remaining above 220 mg/dl. Patients with unstable angina or myocardial infarction within the previous three months, an ejection fraction <30%, and secondary causes of hypercholesterolemia were excluded from the present study. They were randomized to a statin treatment group of fluvastatin (F group: 40 mg/day, n = 20) or a control group (C group: n = 20). Study patients in the control group were referred to a nutritionist for individual counseling and were also provided with a lifestyle-changing program that included diet and smoking cessation. The protocol was approved by the institutional ethics committee, and informed consent was obtained from all patients before enrollment.

Study protocol. We measured IB values of one site in the far wall of the media of right common carotid arteries of each patient; IB values were evaluated at baseline and after 12 months in the patients with statin therapy and in patients with diet. At the same time, we also measured IMT and stiffness beta by conventional ultrasound in the same segment of the carotid arteries in which IB was measured. Furthermore, fasting plasma concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides, hemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hs-CRP), and body mass index were analyzed. Brachial-ankle pulse-wave velocity (PWV) was also measured on the same day as ultrasound analysis and blood examination. The same measurements were also performed in the C group. We also evaluated the incidence of other atherosclerotic risk factors in each patient including HTN, diabetes mellitus (DM), smoking status, history of cerebrovascular disease (CVD), and CAD.

IB system presets and data acquisition. Transverse and longitudinal scans were performed between the middle of the right common carotid arteries and bifurcation of the external carotid artery and the internal carotid artery using an ultrasound imaging system (SONOS 5500, Philips Medical Systems, Andover, Massachusetts). We performed IB measurements using cross-sectional images rather than longitudinal images because the same method had been used in our previous study. Cross-sectional IB images were acquired at a site of 10 mm away from the bifurcation. We used the distance between the site of measurement and the bifurcation to locate the corresponding sites after 12 months. Conventional echocardiography and IB images were easily acquired at the bedside using a 5- to 12-MHz transducer for all studies (Figs. 1A and 1B). The details of our measurements have been previously reported (8,12); IB values in the far wall of the arteries (an angle span of 30° between −15° and +15°) were measured (Fig. 1C). The IB values were determined by averaging the IB values from 10 sites continuously moving the region of interest above the far arterial site. The IB values of the far wall were corrected by subtracting the minimum IB values of the vessel lumen just above the far wall. The intraobserver variability of IB values was 6.5% to 7.2% ($r = 0.89$, $p < 0.01$), and the interobserver variability of IB values was 7.4% to 9.4% ($r = 0.87$, $p < 0.01$) (8).

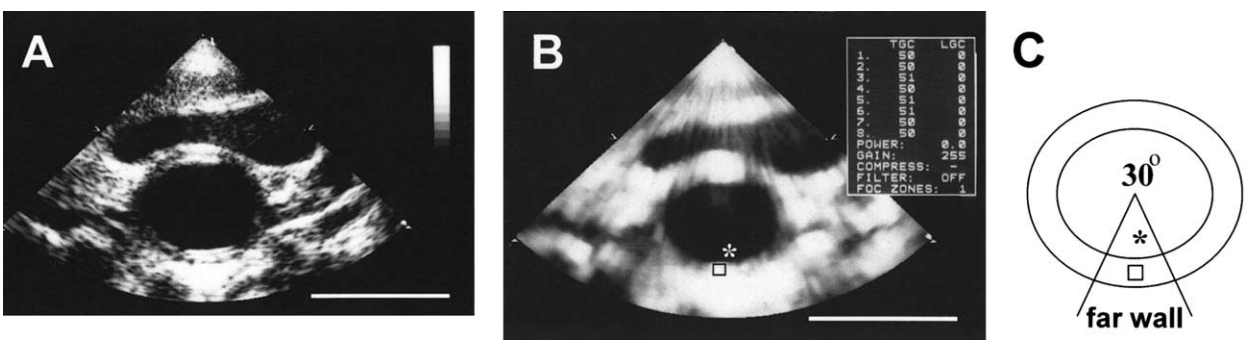

Figure 1. Integrated backscatter (IB) image from the carotid artery. **(A)** Conventional ultrasound image of common carotid artery. Intima-media thickness and diameter of artery were measured on conventional ultrasound image. Bar = 1 cm. **(B and C)** Integrated backscatter values in the entire far wall of the arteries (an angle span of 30° between −15° and +15°) were measured. The IB values were determined averaging the IB values from 10 sites continuously moving the region of interest above the far arterial site. Also, IB values of arterial lumen were measured just above far wall shown by an **asterisk**. Bar = 1 cm.

Table 1. Summary of Demographics and Baseline Characteristics of the Patients

Variables	Fluvastatin (n = 20)	Control (n = 20)	p Value
Men	7 (35)	8 (40)	0.74
Age, yrs	61 ± 10	61 ± 11	0.44
Body mass index, kg/m^2	24.1 ± 2.5	23.4 ± 2.7	0.52
Clinical history			
Ischemic heart disease	4 (20)	5 (25)	0.71
Hypertension	8 (40)	6 (30)	0.51
Diabetes mellitus type 2	3 (15)	3 (15)	1.00
Current smoker	4 (20)	5 (25)	0.71
Medication			
Aspirin	2 (10)	3 (15)	0.63
Ticlopidine	3 (15)	2 (10)	0.63
Nitrates	3 (15)	3 (15)	1.00
Nicorandil	3 (15)	4 (20)	0.68
Diuretic	2 (10)	2 (10)	1.00
Calcium-channel blockers	7 (35)	3 (15)	0.14
Beta-blockers	0 (0)	1 (5)	0.31
ACE inhibitors	1 (5)	1 (5)	1.00
Insulin	1 (5)	1 (5)	1.00

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme.

Non-invasive vascular parameters. Brachial-ankle PWV was measured using a pulse pressure analyzer (Form PWV/ABI, Colin Medical Technology, Komaki, Japan), which simultaneously record blood pressure, electrocardiogram, and heart sound after at least 5 min rest. Details of the measurements were described in a previous report (14). The validation of this method has been reported: the intraobserver coefficient of variation was 10.0% ($r = 0.87$, $p < 0.01$) and the interobserver coefficient of variation was 8.4% ($r = 0.98$, $p < 0.01$) (14). In addition, the stiffness beta was calculated from the measurement of blood pressure and arterial diameter. The arterial diameter of the carotid arteries was measured in the same segment in which IB values were measured.

Statistical analysis. Numerical data were expressed as mean values ± SD. The Kolmogrov-Smirnov test showed that all data were normally distributed. The significance of the differences between various parameters at baseline and after 12 months was tested using a paired *t* test. The significance of the differences in total cholesterol and LDL-C between the groups was tested using Welch's *t* test, because the variances of these parameters between the groups were significantly different as tested by the F-test. The significance of the differences between groups in other parameters was tested by an unpaired Student *t* test. Correlations among IB values, ultrasound parameters, and PWV of the patients with HL at baseline were tested by linear regression analysis. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics and parameters at baseline. No patient experienced significant (3 × upper limit of normal) elevations of liver-associated enzymes or had myositis. All of 40 patients (age 28 to 82 years, 61 ± 10 years, 15 men and 25 women) completed the study. There were no serious cardiovascular and cerebrovascular events including myocardial infarction, unstable angina, cerebral infarction, or death in both study groups. Table 1 presents the baseline characteristics of the study population. Baseline characteristics

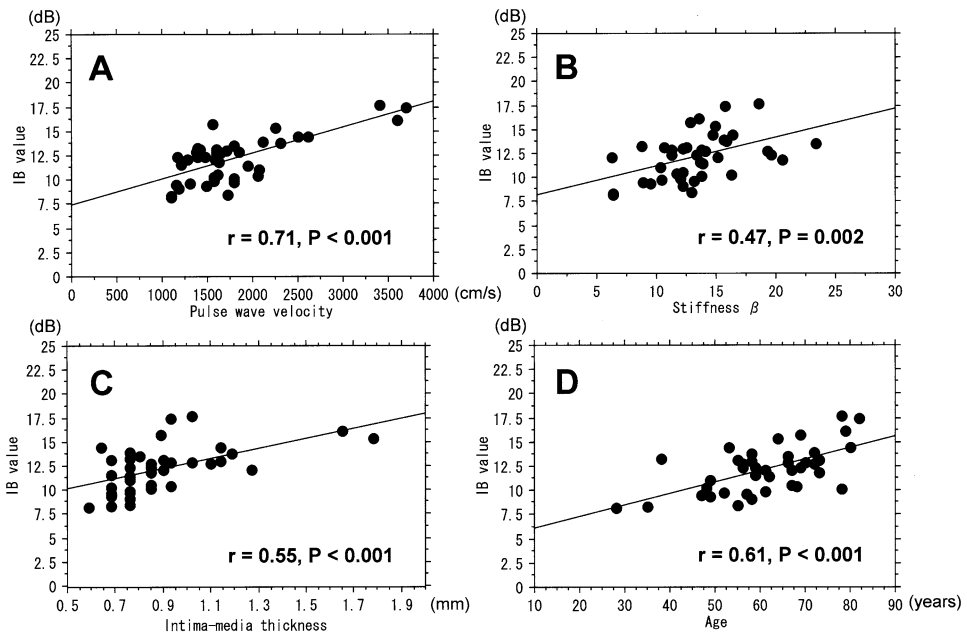

Figure 2. Correlation among integrated backscatter (IB) values, ultrasound parameters, and pulse-wave velocity (PWV) of the patients with hyperlipidemia at baseline. **(A)** Correlation between IB values and PWV. **(B)** Correlation between IB values and stiffness beta. **(C)** Correlation between IB values and intima-media thickness. **(D)** Correlation between IB values and age.

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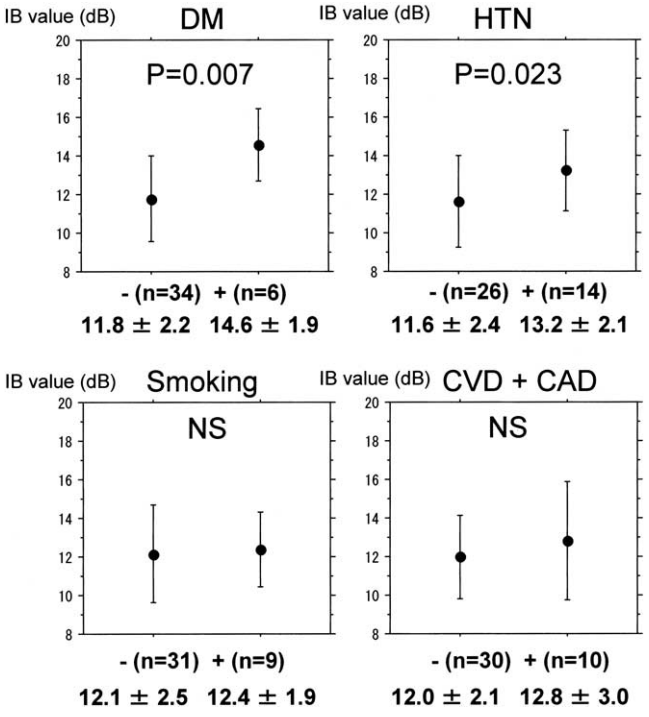

Figure 3. Comparison of integrated backscatter (IB) values between the patients with atherosclerotic risk factors and without risk factors. Values represent mean ± one SD. CAD = history of coronary artery disease; CVD = history of cerebrovascular disease; DM = diabetes mellitus; HTN = hypertension.

between the patients in the F group and the C group were not significantly different.

Pulse-wave velocity at baseline strongly correlated with IB values at baseline ($r = 0.71$, $p < 0.0001$). Stiffness beta, IMT, and age correlated with IB values ($r = 0.47$, 0.55, and 0.61, respectively) (Fig. 2). The ratio of apolipoprotein B to apolipoprotein A-I (ApoB/A-I), HbA1c, and systolic blood pressure (SBP) at baseline weakly correlated with IB values at baseline ($r = 0.37$, 0.46, and 0.46, respectively, $p < 0.01$). Integrated backscatter values in the patients with DM were significantly greater than those in the patients without DM; IB values in the patients with HTN were significantly greater than those in the patients without HTN. However, smoking and history of CVD and CAD did not correlate with IB values (Fig. 3).

Change of clinical parameters after statin therapy. Lipid values of patients in each group, at baseline and at 12 months, are shown in Table 2. At baseline, clinical parameters did not differ between groups. After initiating statin therapy, the lipid profile significantly improved, but remained unchanged in the control group.

Baseline IB values and other characteristics and parameters were similar between the study groups. Table 3 shows the non-invasively determined ultrasound parameters, blood pressure, and PWV. At baseline, no significant differences were found in these parameters between the F group and the C group. The IB values, PWV, and stiffness beta significantly decreased in the F group after 12 months. However, IB values and stiffness beta did not change significantly in the C group but decreased in the F group (from 0.90 ± 0.26 mm to 0.86 ± 0.27 mm, $p = 0.012$). However, IMT significantly increased in the C group (from 0.87 ± 0.25 mm to 0.92 ± 0.27 mm, $p = 0.018$). There was no significant change in SBP and diastolic blood pressure. However, SBP showed a slight decrease in the F group (from 141 ± 23 mm Hg to 136 ± 19 mm Hg, $p = 0.051$).

Table 2. Changes in Lipid Parameters

Parameters	Baseline	Month 12	Change (%)
Total-C (mg/dl)			
Fluvastatin	247 ± 58	202 ± 35*‡	−18.2
Control	250 ± 22	243 ± 20†	−2.8
HDL-C (mg/dl)			
Fluvastatin	52 ± 17	57 ± 14	9.6
Control	57 ± 18	55 ± 16	−3.5
LDL-C (mg/dl)			
Fluvastatin	154 ± 46	118 ± 29*‡	−23.4
Control	156 ± 18	156 ± 18	0
Triglycerides (mg/dl)			
Fluvastatin	189 ± 74	154 ± 88†	−18.5
Control	176 ± 65	167 ± 56	−0.5
HbA1c (mg/dl)			
Fluvastatin	6.1 ± 1.7	5.9 ± 1.2	−3.2
Control	5.7 ± 1.2	5.7 ± 1.0	0
hs-CRP (ng/ml)			
Fluvastatin	2,094 ± 2,712	1,775 ± 2,347	−15.2
Control	2,011 ± 1,937	2,142 ± 1,839	6.5
ApoB/A-I			
Fluvastatin	0.90 ± 0.24	0.72 ± 0.19*‡	−20.0
Control	0.91 ± 0.20	0.93 ± 0.23	2.2

*$p < 0.01$, †$p < 0.05$, difference between baseline and after 12 months; ‡$p < 0.01$, difference among fluvastatin and control.

ApoB/A-I = ratio of apolipoprotein B to apolipoprotein A-I; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

Table 3. Changes in Ultrasound and Hemodynamic Parameters

Parameters	Baseline	Month 12	Change (%)
IB value (dB)			
Fluvastatin	12.3 ± 2.1	11.3 ± 2.1*	−7.3
Control	12.1 ± 2.7	12.4 ± 2.2	2.4
Pulse-wave velocity (cm/s)			
Fluvastatin	1,848 ± 582	1,768 ± 549†	−4.3
Control	1,728 ± 687	1,771 ± 716†	2.4
IMT (mm)			
Fluvastatin	0.90 ± 0.26	0.86 ± 0.27†	−4.4
Control	0.87 ± 0.25	0.92 ± 0.27†	5.7
Stiffness parameter beta			
Fluvastatin	14.0 ± 3.9	12.1 ± 3.5*	−13.6
Control	12.7 ± 3.5	13.0 ± 4.2	2.4
Systolic blood pressure (mm Hg)			
Fluvastatin	141 ± 23	136 ± 19	−3.5
Control	129 ± 21	133 ± 18	3.1
Diastolic blood pressure (mm Hg)			
Fluvastatin	81 ± 15	78 ± 15	−3.7
Control	80 ± 12	81 ± 14	1.2

*$p < 0.01$, †$p < 0.05$, difference between baseline and after 12 months.
IB = integrated backscatter; IMT = intima-media thickness.

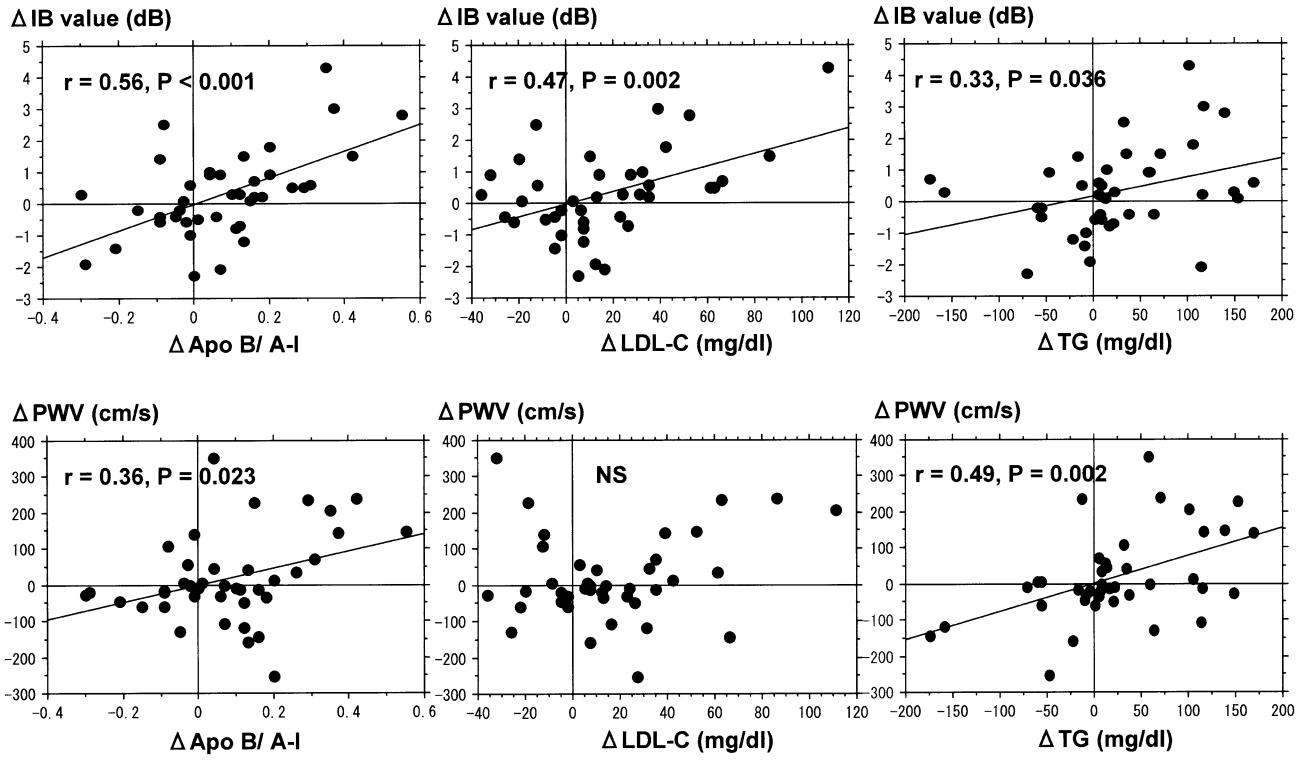

Figure 4. Correlation of the change (Δ) of integrated backscatter (IB) values between at baseline and after 12 months and Δpulse-wave velocity (PWV) with lipid change between baseline and after 12 months. ΔApoB/A-I = the change of the ratio of apolipoprotein B to apolipoprotein A-I between baseline and after 12 months; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

The change of IB values between baseline and after 12 months (ΔIB values) significantly correlated with the change between baseline and 12 months (Δ) of ApoB/A-I (ΔApoB/A-I), ΔLDL-C, Δtriglycerides, and ΔApoB (r = 0.56, 0.47, 0.33, and 0.38, respectively). The change of PWV between at baseline and after 12 months (ΔPWV) correlated with only ΔApoB/A-I and Δtriglycerides (r = 0.36 and 0.49, respectively) (Fig. 4); ΔIMT tended to correlate with ΔApoB/A-I (r = 0.28, p = 0.077) and ΔApoB (r = 0.27, p = 0.087).

DISCUSSION

IB values as a parameter for the assessment of arterial sclerosis. The elasticity of major arteries is affected by cardiovascular risk factors such as HTN, HL, DM, and aging. An increase in arterial stiffness has been reported as an early sign of atherosclerosis (4). On the other hand, one study found that there was increased carotid stiffness related to IMT only in patients whose IMT was in the highest quartile of IMT (15). Another study found no association between IMT and increased arterial stiffness except for patients with arterial walls rated in the top 10% for thickness (16). Our previous study found no relation between arterial sclerosis (as measured by stiffness beta and IB values of carotid media) and atherosis (as measured by IMT) in patients with systemic sclerosis (8). Therefore, sclerosis and atherosis should not be considered as the same physiological change.

Pulse-wave velocity represents a useful integrated index of vascular stiffness and hence cardiovascular risk (17). Integrated backscatter values at baseline significantly correlated with PWV and stiffness beta (Fig. 2). This fact suggests that high IB values of carotid media may indicate stiffness of the carotid arteries, although PWV is differentiated from IB values because PWV is affected by peripheral arteries, whereas the IB value of carotid media is affected only by carotid arteries.

Effects of statin therapy on arterial media. There are two types of statins: lipophilic, for example, fluvastatin, and hydrophilic, pravastatin. Fluvastatin, because it is lipophilic, can cross the cell membranes of nearly all tissues including the vascular wall. Several large-scale clinical trials using conventional ultrasound have demonstrated that hydrophilic and lipophilic statins prevent the progression of IMT, which indicates prevention of atherosis (9). However, effects of statins on sclerosis are still unclear. One study demonstrated that short-term therapy with pravastatin (hydrophilic) in patients with mild-to-moderate HL improved the lipid profile, but did not induce obvious changes in the functional properties of the large arteries (18). We also showed that pravastatin did not induce a decrease of the IB values of carotid media, which would indicate improvement of sclerosis (12). In addition, a randomized trial demon-

strated that pravastatin therapy for 12 months did not decrease PWV (19). These studies indicated that hydrophilic statin may have less effect on arterial sclerosis than atherosis.

It is recognized that the structure of the aortic media is closely related to the biomechanical tangential or circumferential strain resulting from intra-luminal hydrostatic pressure (20). In addition, the histological structure of the aortic media influences the degree of arterial sclerosis (21). We previously reported that the IB values of carotid media reflected both the fragmentation of elastic fiber and the density of collagen fiber (8). Elastic fiber in arterial media plays an important role in maintaining the elasticity of the arteries, whereas collagen fiber functions to maintain the strength of the arteries. In addition, changes in the ratio of collagen to elastin, rather than the deposition of lipids, have been known to affect the elastic behavior and function of the arterial wall (22). In the present study, fluvastatin (lipophilic) decreased IB values, indicating reduction of sclerosis. Changes of IB values after lipophilic statin therapy may be due to the direct effect of statin on these fibers. However, medial sclerosis is induced not only by the structural change of these fibers, but also by the degeneration of smooth muscle cells and deposits of calcium, lipids, and mucopolysaccharides in the arterial media (23). The precise mechanisms by which fluvastatin reduces arterial sclerosis have remained unclear. The present study cannot identify the direct mechanism by which statins affect arterial media, but does suggest the effect they have on arterial sclerosis.

There were interesting findings in the present study. The change in IB values after 12 months of statin therapy was significantly correlated with ΔApoB/A-I, ΔLDL-C, Δtriglycerides, and ΔApoB. Also, the change in PWV after 12 months of statin therapy significantly correlated with ΔApoB/A-I and Δtriglycerides. With respect to the atherosis, a previous study reported that the change in IMT after two years of statin therapy weakly correlated with percent LDL-C reduction ($r = 0.14$, $p = 0.01$) (24). In addition, a meta-analysis demonstrated that there was a correlation between the average IMT reduction and LDL-C reduction ($r = 0.65$, $p = 0.004$) (25). However, there has been no report of the relationship between the degree of lipid reduction and the degree of vascular stiffness parameters such as PWV and IB values. To our knowledge, this is the first report that demonstrates these relationships. Furthermore, the present study suggests the efficacy of ApoB/A-I as well as LDL-C as a target for statin treatment as demonstrated by other recent studies (26,27).

Study limitations. Because the number of patients in our analysis was small, the relationship between statin therapy and the reduction of hs-CRP, the correlation between ΔIMT and ΔApoB/A-I, and the relevant evidence between IB values and vascular events that could be indicated in a large study have not been shown. In addition, analysis of the incidence of vascular events was not possible because the present study is not a long-term follow-up study of several years. Large-scale follow-up studies, which include an analysis of the incidence of vascular events and strokes, will be required in the future. Future long-term studies addressing the relationship between arterial sclerosis and cardiovascular events must determine whether arterial sclerosis is a risk factor for cardiovascular events, independent of its association with arterial atherosis.

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