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● *Original Contribution*

INTEGRATED BACKSCATTER AND INTIMA-MEDIA THICKNESS OF THE THORACIC AORTA EVALUATED BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN HYPERCHOLESTEROLEMIC PATIENTS: EFFECT OF PITAVASTATIN THERAPY

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Abstract—The effect of a strong, lipophilic statin (pitavastatin) on the thoracic aorta has not yet been elucidated. The purpose of the present study was to evaluate the effects of pitavastatin (P) therapy on plaque components and morphology in the thoracic aorta by transesophageal echocardiography (TEE) and clarify the impact of the therapy on media and intima in patients with hypercholesterolemia. Sixty-four media and 64 intima of the thoracic aorta were investigated in 32 patients with hypercholesterolemia. The corrected integrated backscatter (c-IBS) values in the thoracic aortic wall and intima-media thickness (IMT) at the same site were measured before and after P therapy or diet (D) for 7 mo. Moreover, c-IBS values in media were measured in 168 patients without hypercholesterolemia to estimate age-dependent changes. C-IBS values in media were correlated with age ($r = 0.84$, $p < 0.001$). C-IBS and IMT of media in the P group significantly decreased from -17.8 ± 2.4 to -20.1 ± 3.7 dB and from 1.7 ± 0.3 to 1.5 ± 0.3 mm, respectively ($p < 0.001$), whereas those in the D group significantly increased from -18.3 ± 2.0 to -16.7 ± 2.1 dB and from 1.6 ± 0.3 to 1.7 ± 0.2 mm, respectively ($p < 0.001$). IMT in intima in the P group significantly decreased from 3.7 ± 0.4 to 3.3 ± 0.4 mm ($p < 0.001$). C-IBS in intima in the P group significantly increased from -10.2 ± 2.2 to -6.9 ± 1.7 dB, which indicated plaque stabilization. Pitavastatin improved the atherosis measured by IMT and sclerosis measured by c-IBS values in the media and induced stabilization and regression of plaques in the intima of the thoracic aorta. (E-mail: masanori@ya2.so-net.ne.jp)

Key Words: **Atherosclerosis, Statins, Transesophageal echocardiography, Integrated backscatter.**

INTRODUCTION

Plaque in the thoracic aorta is a risk factor of coronary artery disease and transesophageal echocardiography (TEE), magnetic resonance imaging (MRI) or computed tomography (CT) are useful tools for evaluation of atherosclerosis of the thoracic aorta (Tomochika et al. 1996; Fayad et al. 2000; Momiyama et al. 2006; Okane et al. 2006). With respect to ultrasound imaging, the integrated backscatter (IBS) signal obtained from ultrasound examination of the carotid arteries can discriminate the tissue characteristics of arterial plaques (Kawasaki et al. 2001, 2005). In the arterial intima, fibrosis and calcification give high IBS values while deposition of lipid gives low IBS values. Other investigators showed that measurements of IBS values of carotid arteries are clinically useful for risk assessment of patients with coronary artery disease (Honda et al. 2004). However, there are few studies of tissue characterization of the thoracic aorta by use of IBS-TEE.

Atherosclerotic changes consist of two components: atherosis as a structural change and sclerosis as a functional change. We previously reported that the IBS values of the arterial media were correlated with the stiffness parameter β and pulse wave velocity (PWV), indices of arterial stiffness (sclerosis) (Yokoyama et al. 2005). As the stiffness parameter β and PWV increased, the IBS values of the arterial media increased. An increase in arterial stiffness has been reported as an early sign of atherosclerosis and arterial stiffness has been

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shown to be a useful index for risk stratification of mortality from cardiovascular disease (Hirai et al. 1989; Willum-Hansen et al. 2006). Therefore, an improvement of arterial stiffness results in a reduction of the mortality from cardiovascular disease.

When considering therapies for atherosclerosis, several clinical trials have demonstrated that HMG-CoA reductase inhibitor (statins) can alter plaque volume and tissue characteristics of coronary and carotid arterial plaques (Nissen et al. 2004; Okazaki et al. 2004; Smilde et al. 2001; Kawasaki et al. 2005). A newly developed strong, lipophilic statin (pitavastatin), which was launched in Japan in 2003 exhibits a favorable and promising safety profile, as it is hardly metabolized by the cytochrome P-450 (CYP) system (Kajinami et al. 2003; Hayashi et al. 2007). It was reported that pitavastatin had an excellent lipid-lowering effect in Watanabe Heritable Hyperlipidemic rabbits, suppressing the progression of atherosclerosis and stabilizing atherosclerotic plaques (Suzuki et al. 2003). However, the effects of pitavastatin on the human thoracic aorta with respect to tissue characterization have not yet been assessed by IBS-TEE. The purpose of this study was to evaluate the effect of pitavastatin therapy on plaque components and morphology in the thoracic aorta by use of IBS-TEE and clarify the impact of the therapy on "arterial media" and "intimal plaque" separately in patients with hypercholesterolemia.

MATERIALS AND METHODS

Subjects and study protocol

This study was designed as a simple randomized, single-center, open-label prospective study that included 32 hypercholesterolemic patients with atrial fibrillation (AF), who underwent TEE to evaluate mural thrombus in the left atrium, cardiac function and valvular disease. These patients had not been previously treated with statin therapy. They were randomized to a statin-treatment group with oral administration of pitavastatin (P: 1-2 mg/d, n = 16) or a diet group (D: n = 16). Patients in the D group were referred to a nutritionist for individual counseling and were also provided with a lifestyle-changing program that included diet and smoking cessation. Patients in the D group were also given the option of statin therapy, if the component and morphology of their thoracic plaques worsened after the follow-up evaluation. This study was approved by the ethics committee of Gifu Prefectural General Medical Center and informed consent was obtained from all patients before enrollment. At baseline and 7 mo, all patients underwent TEE using a pediatric probe to enhance safety and minimize discomfort. The fasting plasma concentration of total cholesterol (TC), triglycerides (TG) and HDL-cholesterol (HDL-C) were measured by automated enzymatic assay (JCA−BM 2250, JEOL, Tokyo, Japan) at baseline and after 7 mo. LDL- cholesterol (LDL-C) was calculated using Friedewald's formula. Moreover, corrected integrated backscatter (c-IBS) values in arterial media were measured in 168 patients with AF who had not been treated with statins to evaluate age-dependent changes because c-IBS values in arterial media have been reported to increase in proportion to age (Kawasaki et al. 2005).

Transesophageal echocardiography

TEE was performed with an ultrasonic imaging system (SONOS 5500, Philips Medical Systems, Andover, MA, USA) and a 4-7 MHz multi-plane transducer with a 7.4 mm diameter "pediatric probe" (T6207, Philips Medical Systems, Andover, MA, USA) in the echocardiography laboratory by an operator who was blinded to the patients' treatment assignment. The oropharynx was anesthetized with lidocaine before esophageal intubation. After the cardiac examination, the transducer was rotated in a posterior direction to obtain aortic images. The c-IBS values in the intima and media of 128 segments of the thoracic aorta and the intima-media thickness (IMT) at the same site were measured. The P group consisted of 32 media and 32 intima and the D group consisted of 32 media and 32 intima. The positions of examination sites of media and intima in the thoracic aorta were determined by the distance from dental incisors and the origin of the left subclavian artery. In addition, we determined the cross-sections in which c-IBS values were measured at follow-up, which were the same lesions as those at baseline, using the reference distance between the incisors and the site of imaging measured by TEE, the shape of plaques and the location of calcification. These images were carefully recorded using an ultrasonic imaging system. Intimal plaques were defined as a clearly irregular surface with an IMT >2mm. All studies were recorded on S-VHS videotapes and built-in optical disk drives.

Measurement of c-IBS

IBS analysis was performed with a software package "Acoustic Densitometry" with the SONOS 5500. In this system, IBS values are calculated as the average power of the ultrasonic backscattered signal from the region-of-interest (ROI) and represent the tissue characteristics. The IBS values in the intima-media complex were corrected by subtracting the IBS values in the tunica externa as follows:

Corrected-IBS (c-IBS) = IBS values in the thoracic aortic wall - IBS values in the tunica externa (Katakami et al. 2005)

IBS values in the intima and media and those in the

tunica externa were measured at the site of lesions with the maximum IMT. When measuring IBS values of media, we set ROIs on just the inner side of tunica externa. The ROIs (21 × 21 pixels, 1.1 × 1.1 mm) placed at this site covered only arterial media because the thickness of the aortic wall, which increases with age, was more than 1.5 mm (mean 2.32 mm in men; 2.11 mm in women) (Li et al. 2004). We confirmed that the c-IBS values of media were similar to those at sites both 5 mm proximal and distal from the measurement site. IBS values were measured at three lesions and the average values were used to determine c-IBS values.

Statistical analyses

Numerical data are expressed as the mean ± one standard deviation. The Kolmogrov-Smirnov test was used to determine if data were normally distributed. If data were not normally distributed, testing for significant differences of each parameter between baseline and 7 mo was performed with a Wilcoxon single-ranks test. If the data were normally distributed but the variances between baseline versus 7 mo were significantly different (as determined by an F-test) then Welch's *t*-test was used. Otherwise, a paired Student's *t*- test was used. Comparisons of age, lipid data, c-IBS and IMT between the two groups were performed using an unpaired Student's *t*-test. Comparisons of percent changes in lipid data, changes in c-IBS and IMT between the two groups were assessed by a one-sample *t*- test. The relationship between c-IBS values and age were tested by linear regression analysis. A p value <0.05 was considered to be significant.

RESULTS

Reproducibility and reliability of data

We determined interobserver variability of c-IBS values and IMT in 30 recordings that were measured by two observers at randomly selected thoracic cross-sections. The interobserver variability of c-IBS values and IMT was 1.1 ± 3.0% and 0.5 ± 4.0%, respectively. The interobserver correlation coefficient was 0.98 for c-IBS values and 0.99 for IMT. Likewise, we determined intraobserver variability of c-IBS values and IMT in 30 recordings that were measured two times by one observer at randomly selected thoracic cross-sections. The intraobserver variability of c-IBS values and IMT was 0.5 ± 3.2% and 0.5 ± 3.0%, respectively. The intraobserver correlation coefficient was 0.98 for c-IBS values and 0.99 for IMT.

Relationship between c-IBS and age in arterial media

C-IBS values in media in 168 patients with AF who had not been treated with statin therapy were analyzed in order to examine the influence of age on the change of c-IBS values in media of the thoracic aorta. C-IBS values in media of the thoracic aorta were significantly correlated with age ($r = 0.84$, $p < 0.001$) (Fig. 1A).

Patient characteristics

Baseline clinical characteristics of the patients are shown in Table 1. There were no significant differences in age, lipid levels, coronary risk factors and concomitant medication use between the P and D groups at baseline. The other baseline parameters, such as c-IBS and IMT also showed no significant difference between the two groups. No patient experienced any adverse reactions such as elevation of liver-associated enzymes (3 times upper limit of normal) or myositis. There were no serious cardiovascular events including myocardial infarction, unstable angina, or death in either group. All patients completed the study. TC and LDL-cholesterol in the D group were decreased from 236 ± 12 to 218 ± 18 mg/dL and from 150 ± 14 to 141 ± 23 mg/dL, respectively, due to individual diet counseling. TC and LDL-cholesterol in the P group significantly decreased from 238 ± 19 to 179 ± 28 mg/dL and 150 ± 22 to 103 ± 21 mg/dL, respectively (Table 2).

Effects of pitavastatin on the thoracic aorta

After 7 mo, c-IBS and IMT of media in the D group significantly increased from −18.3 ± 2.0 to −16.7 ± 2.1 dB and from 1.6 ± 0.3 to 1.7 ± 0.2 mm, respectively. On the other hand, c-IBS and IMT of media in the P group significantly decreased from −17.8 ± 2.4 to −20.1 ± 3.7 dB and from 1.7 ± 0.3 to 1.5 ± 0.3 mm, respectively. C-IBS and IMT of intima in the D group significantly increased from −10.0 ± 1.6 to −8.1 ± 1.7 dB and from 3.6 ± 0.3 to 3.9 ± 0.3 mm, respectively. C-IBS of intima in the P group were significantly increased from −10.2 ± 2.2 to −6.9 ± 1.7 dB but IMT significantly decreased from 3.7 ± 0.4 to 3.3 ± 0.4 mm (Table 2, Fig. 1B). Representative examples of thoracic aortic plaque at baseline and after pitavastatin treatment are shown in Fig. 2. The changes in c-IBS values and LDL-cholesterol are shown in Fig. 3A. The change in c-IBS values in media and intima after 7 mo of P group and D group was significantly correlated with the change in LDL-cholesterol ($r = 0.69$, $p < 0.001$; $r = -0.52$, $p < 0.001$, respectively) (Fig. 3B). The change in IMT in media and intima was significantly correlated with the change in LDL-cholesterol ($r = 0.70$, $p < 0.001$; $r = 0.69$, $p < 0.001$, respectively).

DISCUSSION

Ultrasound parameters in aortic media

We previously demonstrated that c-IBS values of the arterial media increased in proportion to the degree of

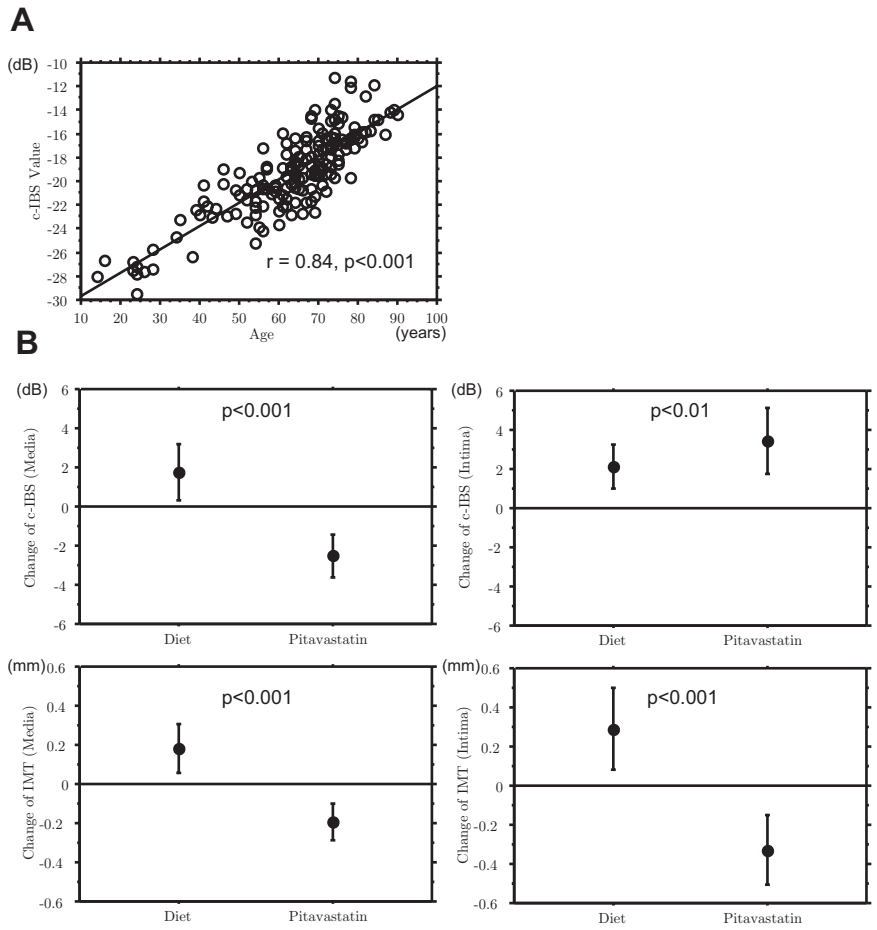

Fig. 1. (A) Relationship between c-IBS values and age in the arterial media. (B) Differences of c-IBS and intima-media thickness between before and after pitavastatin therapy and diet. Closed circle and bar = mean ± one standard deviation. C-IBS = corrected integrated backscatter; IMT = intima-media thickness.

fragmentation of the elastic fiber and reflected the stiffness of carotid arteries (Kawasaki et al. 2005). The thoracic aorta and carotid arteries are similar since they are elastic arteries. Therefore, we thought that we could evaluate the effect of the statin on arterial intima and arterial media separately using IBS-TEE. In the 168 patients with AF, who were not enrolled in the prospective study, the c-IBS values in media of the thoracic aorta were significantly correlated with age. This age-related increase in the c-IBS values in the thoracic aorta was concordant with previous findings that the c-IBS values of carotid media were correlated with age (Kawasaki et al. 2005; Ito et al. 2004). As the stiffness parameter β and PWV decreased, the c-IBS values of the arterial media decreased (Yokoyama et al. 2003). In the present study, the c-IBS values in the media that mostly consisted of arterial media significantly decreased after pitavastatin administration. That is, pitavastatin improved the stiffness of the thoracic aorta. Conversely, the fact that c-IBS values in media increased suggests that atherosclerosis progressed in the diet group. These data indicate that pitavastatin not only reduces the total cholesterol and LDL cholesterol, but also reduces the stiffness of the thoracic aorta.

A previous study found no association between IMT and increased arterial stiffness except in a subgroup of patients (10%) with the thickest arterial walls (Riley et al. 1997). Therefore, sclerosis measured by c-IBS values and atherosis measured by IMT should not be considered as the same pathological process. There have been many reports of a reduction in IMT of carotid arteries after statin therapy (Smilde et al. 2001; Amarenco et al. 2004). However, data on the effect of statins on arterial stiffness have been scarce. In the present study, the c-IBS values showed different behavior between media and intima, whereas IMT of the thoracic aorta decreased after pitavastatin therapy in both media and intima.

Ultrasound parameters in intimal plaques

We previously determined the definition of c-IBS values for each histological category comparing the histological images and c-IBS images in the carotid arteries

Table 1. Demographics and baseline characteristics of the patients

	Pitavastatin (n = 16)	Diet (n = 16)	P-value
Men, n (%)	10 (63)	10 (63)	0.61
Age, y	65 ± 8	67 ± 8	0.32
Lipid parameters, (mg/dL)			
Total cholesterol	238 ± 19	236 ± 12	0.76
HDL cholesterol	50 ± 14	55 ± 17	0.35
LDL cholesterol	150 ± 22	150 ± 14	0.98
Triglycerides	185 ± 116	151 ± 72	0.33
Clinical history, n (%)			
Hypertension	8 (50)	10 (63)	0.48
Diabetes mellitus type 2	1 (6)	4 (25)	0.14
Current smoker	4 (25)	3 (19)	0.63
Medication, n (%)			
Warfarin	11 (69)	9 (56)	0.47
Aspirin	5 (31)	4 (25)	0.69
Ticlopidine	2 (13)	1 (6)	0.54
Nicorandil	1 (6)	0 (0)	0.31
Diuretic	3 (19)	3 (19)	>0.99
Calcium channel blockers	6 (28)	7 (44)	0.72
β-blockers	0 (0)	4 (25)	0.11
ACE inhibitors or ARBs	3 (19)	4 (25)	0.67

Plus-minus values are mean ± one standard deviation.
ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

Table 2. Changes of lipid and ultrasound parameters from baseline to 7 mo

	Baseline	Month 7	Change (%)
Lipid parameter			
Total-C (mg/dL)			
Pitavastatin	238 ± 19	179 ± 28*	−27.8††
Diet	236 ± 12	218 ± 18*	−7.6
LDL-C (mg/dL)			
Pitavastatin	150 ± 22	103 ± 21*	−31.3††
Diet	150 ± 14	141 ± 23	−6.0
HDL-C (mg/dL)			
Pitavastatin	50 ± 14	51 ± 12	2.0
Diet	55 ± 17	53 ± 14	−3.6
Triglycerides (mg/dL)			
Pitavastatin	185 ± 116	152 ± 71	−17.8
Diet	151 ± 72	118 ± 43	−21.9
Ultrasound parameter			
Arterial media			
c-IBS (dB)			
Pitavastatin	−17.8 ± 2.4	−20.1 ± 3.7*	−12.9††
Diet	−18.3 ± 2.0	−16.7 ± 2.1*	8.7
IMT (mm)			
Pitavastatin	1.7 ± 0.3	1.5 ± 0.3*	−11.7††
Diet	1.6 ± 0.3	1.7 ± 0.2*	6.3
Intimal plaque			
c-IBS (dB)			
Pitavastatin	−10.2 ± 2.2	−6.9 ± 1.7*	32.4†
Diet	−10.0 ± 1.6	−8.1 ± 1.7*	19.0
IMT (mm)			
Pitavastatin	3.7 ± 0.4	3.3 ± 0.4*	−10.8††
Diet	3.6 ± 0.3	3.9 ± 0.3*	8.3

IMT = intima-media thickness; c-IBS = corrected integrated backscatter.
* $p < 0.001$, difference between baseline and after 7 mo.
† $p < 0.01$, difference between the pitavastatin group and diet group.
†† $p < 0.001$.

(Kawasaki et al. 2001). Although cut-off values to differentiate unstable and stable components of plaques have not been established in the thoracic aorta, unstable components of intimal plaques such as lipid pool and intra-plaque hemorrhage give low c-IBS values, while stable components of plaques give high c-IBS values. There have been several reports on the relationship between the carotid artery plaque components and morphology and c-IBS values (Kawasaki et al. 2001; Urbani et al. 1993; Waki et al. 2003), and c-IBS values increase in the following order: lipid lesion < fibrous lesion < calcified lesion. Our study showed that pitavastatin increased c-IBS values and decreased IMT in the intima. These findings indicate that pitavastatin reduced the lipid contents of plaques. Katakami et al. reported that atorvastatin treatment (5-20 mg/d) for 12.8 mo increased the c-IBS values of carotid plaques using the same ultrasound system as we used in the present study (Katakami et al. 2005). Watanabe et al. also reported that 6.2 mo of pravastatin treatment (10-20 mg/d) increased the c-IBS values of carotid plaques (Watanabe et al. 2005). Our results reinforce these previous results. However, IMT of carotid plaques did not change after statin treatment in both of these previous studies. In contrast, IMT of media and intima in the thoracic aorta were significantly decreased after pitavastatin treatment (1-2 mg/d) for 7 mo in the present study. The reason for the discrepancy between our study and previous studies is that carotid arteries have less plaque formation than the aorta (Corti et al. 2002, 2005) and, thus, aortic plaque thickness is more closely associated with coronary disease than carotid IMT (Couturier et al. 2006).

Ultrasound parameters and lipid changes

It was noteworthy that the change of IMT in both media and intima was significantly correlated with the change in LDL-cholesterol. Moreover, regression of IMT of the thoracic aorta was achieved by 30 mg/dL (20%) reduction in LDL-cholesterol. A previous study reported that the change in IMT after 2 y of statin therapy (atorvastatin and simvastatin) weakly correlated with the percent reduction in LDL-C ($r = 0.14$, $p = 0.01$) (Smilde et al. 2001). In the Asymptomatic Carotid Artery Progression Study (ACAPS), a 25% LDL reduction by lovastatin (20 - 40 mg/d) therapy resulted in a very small but significant decrease in IMT of the carotid artery (Furberg et al. 1994). Compared with these studies that examined carotid arteries, regression of IMT of the thoracic aorta was remarkable even in a relatively short period, and strongly correlated with the reduction in

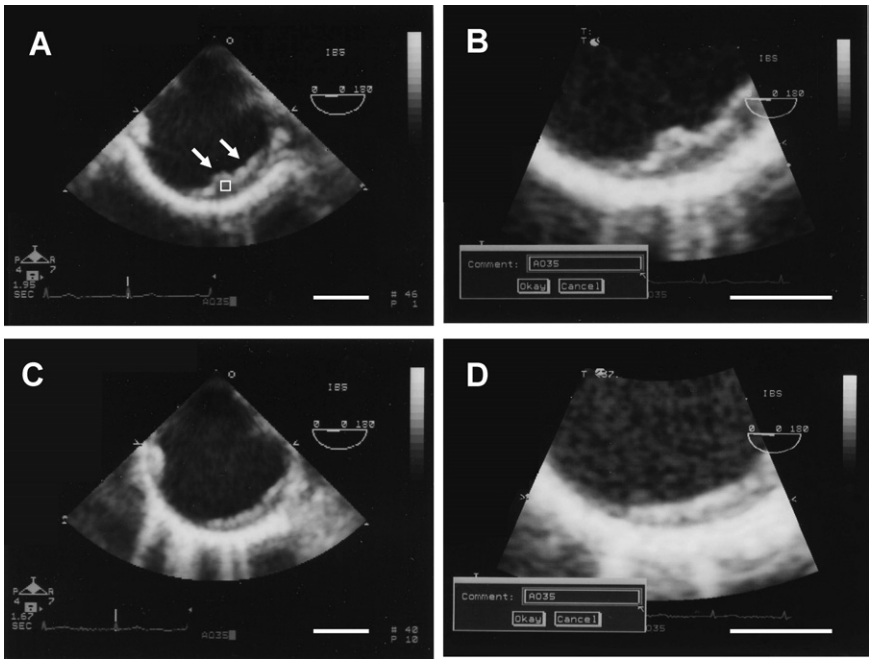

Fig. 2. Representative images of transesophageal echocardiography of the thoracic aorta. This patient started warfarin 3 y before enrollment in the present study and continued warfarin during the study. (A) Plaque in the thoracic aorta at baseline. Arrow indicates the plaque. Square indicates region-of-interest. (B) An enlarged image of the plaque site in A. (C) The same plaque as in A after pitavastatin therapy. (D) An enlarged image of the plaque site in C. Bar = 1cm.

LDL-cholesterol. These results are concordant with previous results that showed regression of thoracic plaques by the 35% in response to LDL-cholesterol reduction by atorvastatin therapy (20 mg/d) (Yonemura et al. 2005).

Likewise, the change in c-IBS values was significantly correlated with the change of LDL-cholesterol. To our knowledge, this is the first report to evaluate the effect of pitavastatin on tissue characteristics of the thoracic aorta and the relationship between the change in LDL-cholesterol and the change in tissue components using c-IBS values.

Usefulness of TEE to diagnose arteriosclerotic lesions

It is generally known that TEE allows good visualization of atherosclerotic lesions in the thoracic aorta, but there have been very few studies on the use of TEE to measure the IBS values and IMT to evaluate the morphology of the thoracic aorta. Although TEE is a semi-invasive method and there are patients that do not tolerate the TEE probe, radiation doses of CT and positron emission tomography (PET) are not negligible (Patel et al. 2008). In addition, TEE has better spatial resolution than MRI, PET or CT and can better depict the detailed structure of the arterial vessel such as the three layers of the aorta (Nusser et al. 2006). As shown in Fig. 2, TEE is able to identify atherosclerotic lesions clearly and can detect monitoring subtle changes in arterial sclerosis. We believe that the thoracic aorta, which has larger plaques compared with carotid arteries or coronary arteries, is a more appropriate vascular bed to assess changes of atherosclerosis. In addition, the pediatric probe has a short diameter of 7.4 mm and allowed minimization of discomfort during TEE examination. The present study was performed in the patients with AF during cardiac imaging. In these situations, we believe that TEE is clinically useful to evaluate the thoracic aorta and IBS measurements in the thoracic aorta added more clinical implication for the assessment of atherosclerotic disease.

Study limitations

There are several limitations of the present study. First, because the number of patients in our analysis was small, clinical endpoints could not be evaluated. Second, although there have been reports comparing c-IBS values with tissue characteristics of carotid arteries, the relation between c-IBS values and tissue characteristics of thoracic aorta has not been established. This study is based on the assumption that c-IBS values of thoracic aorta reflect the same type of histological changes indicated by the c-IBS values of carotid artery and, thus, histological evaluation of thoracic aorta is needed in the future. Third, this study was an incidental study of the mural thrombus due to AF and was limited to those patients with thoracic aortic plaques detected by TEE. Therefore,

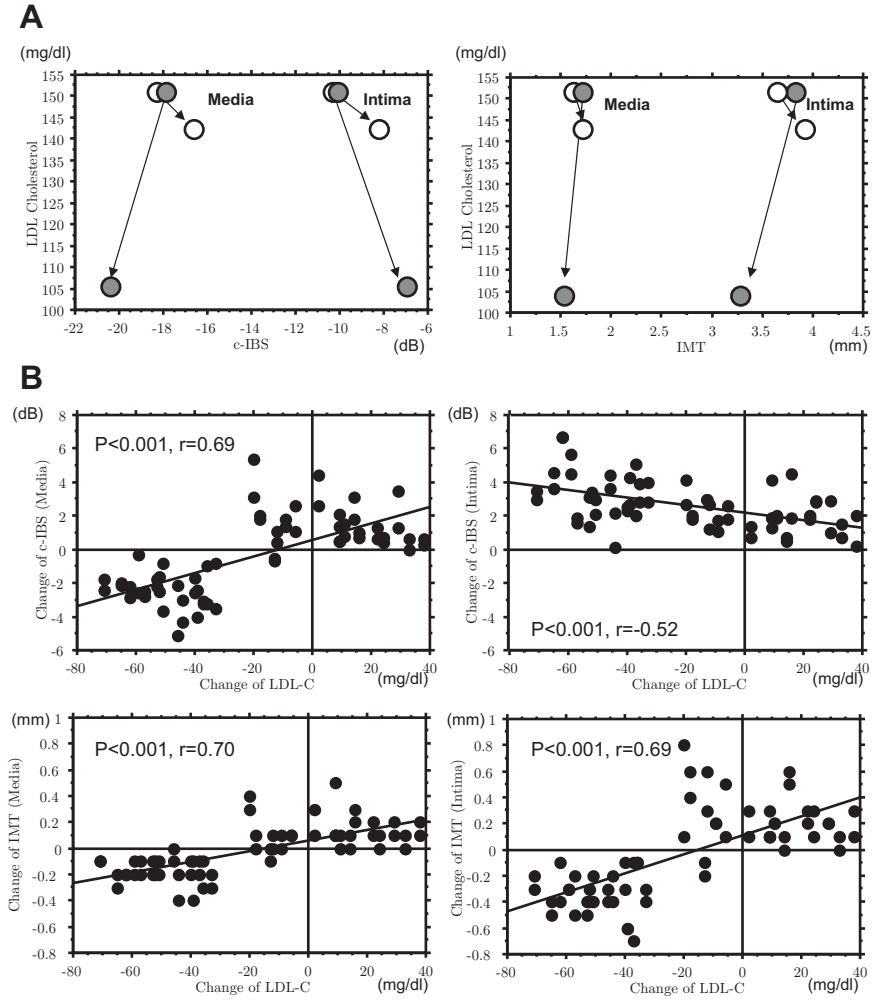

Fig. 3. (A) Change of LDL-cholesterol and change of c-IBS values and intima-media thickness. Open circle = Diet group. Closed circle = Pitavastatin group. (B) Relation between the change in c-IBS values and intima-media thickness and the change in LDL-cholesterol. IMT = intima-media thickness; C-IBS = corrected integrated backscatter.

the findings of the present study may not be applicable to the general population. It will be necessary to evaluate the thoracic aorta in the general population in future studies.

CONCLUSIONS

Oral administration of pitavastatin significantly decreased the c-IBS values and IMT in arterial media in the thoracic aorta. Alternatively, in intimal plaques, pitavastatin therapy significantly decreased IMT but increased c-IBS values. These data suggest that pitavastatin not only lowers the total cholesterol and LDL-cholesterol but also inhibits the progression of sclerosis of the thoracic aorta, as well as inducing regression and stabilization of plaques. We also conclude that measurement of c-IBS values and IMT by TEE is valuable in the assessment of atherosclerotic lesions in the thoracic aorta.

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