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Effect of Coronary Risk Factors on Arterial Compensatory Enlargement in Japanese Middle-Aged Patients with de novo Single-Vessel Disease—An Intravascular Ultrasound Study

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Summary

Background: Compensatory enlargement (CE) of atherosclerotic human arteries has been reported; however, the pattern of arterial remodeling in response to plaque formation is not unique.

Hypothesis: The study was undertaken to determine the extent of coronary artery compensatory enlargement at stenotic lesions and to correlate the arterial compensatory enlargement with risk factors.

Methods: We studied 62 patients with stable angina and de novo single-vessel disease using intravascular ultrasound and obtained good images in 42 patients (68%). The vessel cross-sectional area (VA), lumen cross-sectional area (LA), and plaque cross-sectional area (PA) were measured at the lesion site and at proximal and distal reference sites. Positive CE was defined as increase in VA of lesion site > 10% compared with that of proximal reference site (CE group, n = 15); shrinkage was defined as reduction in VA of lesion site > 10% compared with that of proximal reference site (S group, n = 14); inadequate CE was defined as intermediate between CE and S (IE group, n = 13). All subjects had coronary risk factors measured before this study.

Results: There was no difference in VA, LA, or PA among the three groups at the proximal and distal reference sites, nor in LA at the lesion site; however, VA and PA were significantly smaller in the S group than in the other groups ($p < 0.01$). Of coronary risk factors, increased systolic blood pressure (SBP), increased diastolic blood pressure (DBP), and decreased high-density lipoprotein cholesterol (HDL-c) levels had the strongest association with shrinkage ($p < 0.05$).

Conclusion: Hypertension and decreased HDL level may contribute to the shrinkage response in middle-aged patients with stable angina.

Key words: atherosclerosis, compensatory enlargement, coronary risk factors

Introduction

Compensatory enlargement of atherosclerotic human arteries has been demonstrated by pathological examination of postmortem specimens.[1] Generally, a positive correlation in cross sections between the plaque area and the vessel cross-sectional area was inferred. Employment of an intravascular ultrasound (IVUS) technique permitted us to examine the extent to which native coronary artery stenosis is accompanied by compensatory enlargement. However, compensatory enlargement was not always seen in a clinical setting. The IVUS studies showed compensatory enlargement occurring at stenotic coronary lesions in only 30–50% of patients examined.[2,3]

Mechanisms underlying compensatory enlargement are still under investigation. However elucidation of the factors affecting vessel remodeling may aid in the development of new therapeutic strategies to prevent luminal narrowing by atherosclerotic lesions. In the present study, IVUS was used (1) to determine the extent of coronary artery compensatory enlargement at stenotic lesions, and (2) to correlate the arterial compensatory enlargement with lipoprotein variables and other risk factors.

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Methods

Study Patients

In all, 62 consecutive patients (54 men, 8 women; mean age 57 ± 9 years) with stable angina undergoing diagnostic cardiac catheterization or percutaneous transluminal coronary angioplasty were selected for IVUS study. The patients were chosen at the time of diagnostic catheterization and IVUS study because the cardiologist performing and reviewing the study considered that the patients had at least one vessel with a significant (> 50% diameter) narrowing de novo lesion and that the cross-sectional diameter of the proximal reference site was > 3 mm. In this study, we examined the patients whose proximal reference sites were > 3 mm; this was done for the purpose of excluding the effect of vessel size to compensatory enlargement because a previous study[3] reported that artery size might have an effect on compensatory enlargement of the artery in response to plaque accumulation. All study groups included patients with stable angina (Canadian Cardiovascular Society class I or II angina unchanged over ≥ 2 months). None of the patients had undergone prior intracoronary intervention in the target vessel, nor did they undergo prior thrombolytic therapy for myocardial infarction. To prevent catheter-induced spasms, 200 μg nitroglycerin was administered before insertion of the IVUS catheter. Despite that, patients showing vessel spasm by IVUS imaging were not included in this study. The study was approved by the Institutional Review Board of National Defense Medical College. All subjects gave written, informed consent to participate in this study.

Intravascular Ultrasound

After completion of the diagnostic catheterization or before coronary angioplasty, an 8F sheath was inserted into the right or left femoral artery. An 8F guiding catheter was then introduced into either the left main or right coronary artery. A 3.5F monorail catheter with a 30 MHz mechanical transducer proximal to its tip (Boston Scientific Corporation, Watertown, Mass., USA) was then advanced into the distal coronary artery over a 0.014" guide wire under fluoroscopy. According to the manufacturer, the optimal axial resolution (within the focal point of 1 mm) is 150 μm and the lateral resolution is 150 μm. Beyond the focal point of the transducer, lateral resolution decreases to a greater degree than axial resolution.

The mechanical transducer was connected to an imaging console (Hewlett-Packard Sonos Intravascular Imaging System, Andover, Mass., USA). The image could then be optimized using compression, time-gain compensation, and postprocessing controls to give the blood in the coronary lumen a slight degree of reflectivity. Images were then recorded on videotape (sVHS, 0.5") during pullback from the distal to the more proximal segments of the vessel.

Imaging Protocol

The vessel that appeared significantly diseased by qualitative angiography (> 50% diameter narrowing) was chosen for IVUS imaging. Pulsed fluoroscopy or cineangiography of the ultrasound catheter was performed at each segment to ensure that this same region was analyzed by quantitative angiography. The IVUS images were analyzed by two observers blinded to the patient's coronary risk factors, using a Cardio 500 system (Kontron Elektronik, Everett, Mass., USA). The vessel cross-sectional diameter and area, lumen cross-sectional area, and plaque cross-sectional area were measured at the lesion site, the proximal reference site, and the distal reference site. The proximal reference site was selected as the most visually normal cross section within 10 mm proximal to the target lesion but distal to a major side branch. The distal reference site was selected as the most visually normal cross section within 10 mm distal to the target lesion but proximal to a major side branch. Plaque area was calculated by subtracting lumen cross-sectional area from vessel cross-sectional area. Percent area stenosis was equal to plaque cross-sectional area times 100 divided by vessel cross-sectional area. Thereafter, changes in vessel dimensions from proximal reference to lesion site were calculated (Δvessel cross-sectional area, Δlumen cross-sectional area, Δplaque cross-sectional area). Positive arterial remodeling was defined as an increase of > 10% in Δvessel cross-sectional area (CE group, Fig. 1A). Inadequate compensatory enlargement was defined as $-10\% \leq$ Δvessel cross-sectional area $\leq 10\%$ (IE group, Fig. 1B). Shrinkage was defined as Δvessel cross-sectional area $< -10\%$ (S group, Fig. 1C). Six patients who could not be crossed, four patients with lesions which were so narrow that the vessel was enlarged by the IVUS catheter, and seven patients with severe calcification, plus three patients with vasospasm were all excluded because of their conditions. The four patients were the only ones in whom the catheter actually occluded the artery, and all other patients had antegrade flow while the IVUS catheter was in place. However, Mintz *et al.*[4] suggested that crossing a tight stenotic lesion with the IVUS catheter may cause underperfusion of the distal vessel and cause the cross-sectional measurements to be unreliably small. Therefore we used only a proximal reference site for the comparison with the culprit lesion.

Intra- and interobserver variabilities in lumen area and plaque area measurements were assessed in 20 arteries; no significant observer bias was present (paired differences were not significantly different from zero). The following criteria were used to define the plaque morphology:[5] Soft plaque is composed of a homogeneous echodensity less than that seen for the adventitia; hard plaque is composed of dense echoes involving the intimal leading edge with a homogeneous echodensity greater than that seen for the adventitia without acoustic shadowing; calcium deposits are bright echoes with acoustic shadowing.

Body Size, Blood Pressure, Lipid, and Lipoprotein Measurement

Height was recorded to the nearest 0.5 cm and weight to the nearest 0.1 kg; body mass index was calculated by dividing weight by height^2. Three random-zero blood pressure mea-

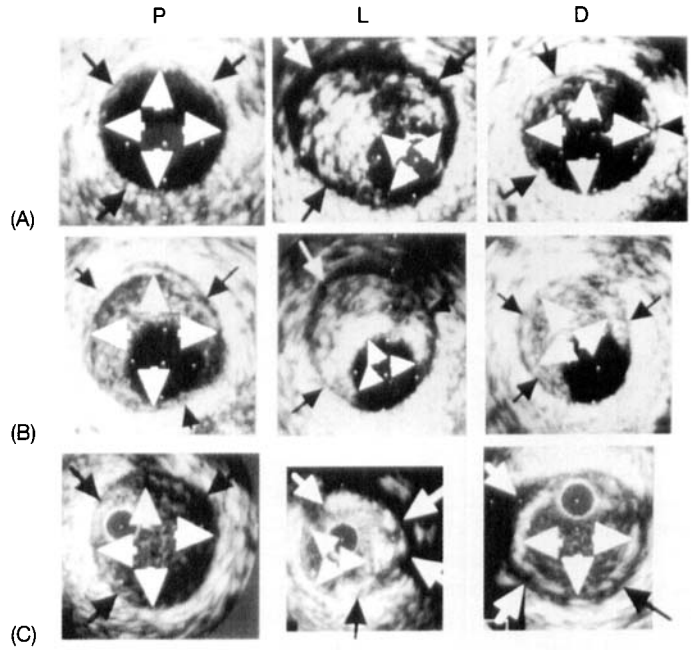

FIG. 1 (A) Intravascular ultrasound study (IVUS) images of the left anterior descending coronary artery from a patient with compensatory enlargement (CE). Left, proximal reference site (P); middle, lesion site (L); right, distal reference site (D). Images show that the vessel cross-sectional area at the lesion site is significantly larger than that at the proximal reference site. The area within the external elastic lamina is 11.6 mm^2 at the proximal reference site, 14.2 mm^2 at the lesion site, and 11.0 mm^2 at the distal reference site. An increase of 22.4% in vessel cross-sectional area is shown in this patient (CE group); (B) IVUS images of the left anterior descending coronary artery from a patient with inadequate compensatory enlargement (IC). Images show that the vessel cross-sectional area at the lesion site is not significantly larger than that at the proximal reference site. The area within the external elastic lamina is 15.3 mm^2 at the proximal reference site, 14.3 mm^2 at the lesion site, and 11.3 mm^2 at the distal reference site. A decrease of 6.5% in vessel cross-sectional area is shown in this patient (IE group); (C) IVUS images of the left anterior descending coronary artery from a patient with coronary artery shrinkage(s). Images show that the vessel cross-sectional area at the lesion site is significantly smaller than that at the proximal reference site. The area within the external elastic lamina is 16.3 mm^2 at the proximal reference site, 13.6 mm^2 at the lesion site, and 16.0 mm^2 at the distal reference site. A decrease of 16.6% in vessel cross-sectional area is shown in this patient (S group). The arrowheads indicate the intima-lumen border. The arrows indicate the media. P = proximal reference site, L = lesion site, D = distal reference site.

surements were recorded for each subject after a 5 min seated rest period and measurement of pulse obliteration pressure. Cuff size was appropriate for arm size. First and fifth Korotkoff sounds were recorded as systolic and diastolic blood pressures, and the mean of three measurements was the variable used for analysis.

Blood samples from fasting patients on admission were allowed to clot for 1 h at room temperature; serum was then separated by low-speed centrifugation. Serum levels of total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-c) concentrations were measured by automated enzymatic procedures on fresh serum. Serum apolipoprotein (Apo) AI, AII, B, CII, CIII, and E concentrations were analyzed by an automated immunoturbidimetric method. Serum lipoprotein(a) (Lp[a]) concentration was determined by a commercially available enzyme-linked immunosorbent assay (Biopool, Umea, Sweden). Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation (LDL-c = total cholesterol - HDL-c - triglycerides / 5). Hyperlipidemia was defined as a total cholesterol concentration of > 220 mg/dl, a triglyceride concentration of > 150 mg/dl, or requirement for medication (e.g., HMG coenzyme A reductase inhibitor, probucol, colestyramine, clofibrate, or other similar agents).

Statistical Analysis

Data are presented as means ± standard deviation (SD). Measured and calculated areas at three different sites were compared using repeated measures analysis of variance (ANOVA), and comparison of data among the three different groups was performed using Kruskal-Wallis test and ordinary 1-way ANOVA with Dunnett test. Simple regression and stepwise linear regression analysis were used to determine correlates of Δvessel cross-sectional area. Comparison of data was performed by using a two-tailed Fisher's exact test for comparison of dichotomous and categorical variables. Probability values of < 0.05 were considered statistically significant.

Results

Patient Demographics

As mentioned before, adequate IVUS visualization across the lesion and its reference segments was obtained in 42 of

TABLE I Patient demographics

	CE no.	IE no.	S no.	p Value
Male	13/15	12/13	12/14	NS
Age (years)	56 ± 9	56 ± 10	56 ± 10	NS
% Stenosis by QCA (%)	71 ± 9	67 ± 12	68 ± 9	NS
Investigational vessels				
LAD (%)	12 (80)	10 (85)	11 (71)	
RC (%)	2 (13)	2 (15)	3 (29)	
LCx (%)	1 (7)	0 (0)	0 (0)	
Medications				
Beta blocker (%)	7 (47)	4 (31)	5 (36)	NS
Calcium blocker (%)	8 (53)	5 (39)	6 (43)	NS
ACE inhibitor (%)	3 (20)	2 (15)	4 (28)	NS
Nitrates (%)	10 (67)	9 (69)	10 (71)	NS
Aspirin (%)	14 (93)	12 (92)	13 (93)	NS

Abbreviations: ACE = angiotensin-converting enzyme, CE = compensatory enlargement, IE = inadequate compensatory enlargement, S = shrinkage, LAD = left anterior descending, LCx = left circumflex, RC = right coronary, NS = not significant, QCA = qualitative coronary angiography, no. = number.

the 62 patients (68%). Therefore, final analysis was performed in 42 patients (37 men, 5 women; mean age 56 ± 9 years). All 42 patients had a single vessel de novo lesion, and the cross-sectional diameter of the proximal reference site was more than 3 mm as determined by qualitative angiography and IVUS study. Compensatory enlargement was observed in 15 of the 42 patients, IE in 13 patients, and S in 14 patients. Table I lists patient demographics for the three groups. No significant differences were found in any demographic variable among the three groups.

Prevalence and Effect of Coronary Artery Remodeling

The measured and calculated data for coronary arteries are summarized in Figure 2. There was no difference in vessel cross-sectional area, lumen cross-sectional area, or plaque cross-sectional area among the three groups at the proximal or distal reference sites, nor in lumen cross-sectional area at the lesion site. However, changes in vessel cross-sectional area and plaque cross-sectional area were significantly ($p < 0.01$) smaller in the S group than in the other groups. Despite comparable stenosis areas (%), the largest change in plaque cross-sectional area was observed by IVUS in the CE group.

Association between Coronary Risk Factors and Coronary Artery Compensatory Enlargement

The factors evaluated in this study are shown in the Table II. The significant factors are shown in bold characters in Table II (Kruskal-Wallis and ANOVA). Both systolic and diastolic blood pressures were significantly lower in the CE group than in the IE and S groups (Fig. 3A, B); however, there were no significant differences between the IE and S groups (Fig. 3A, B). On the other hand, apolipoprotein AI and HDL-c levels were significantly lower in the S group than in the other two groups (Fig. 4A, B). Furthermore, these levels were significantly lower in the IE group than in the CE group (Fig. 4A, B).

On simple regression analysis, positive correlations were observed between Δvessel cross-sectional area and HDL-c ($r = 0.614$; $p < 0.0001$) (Fig. 5) and apolipoprotein AI ($r = 0.474$; $p = 0.0025$), while negative correlations were observed between Δvessel cross-sectional area and systolic blood pressure ($r = -0.491$; $p = 0.001$) and diastolic blood pressure ($r = -0.454$; $p = 0.0022$). On stepwise regression analysis, HDL-c and systolic blood pressure were associated with Δvessel cross-sectional area ($p < 0.0001$). These variables explained 43.7% of the variance in Δvessel cross-sectional area.

Association between Character of Lesion Detected by Intravascular Ultrasound and Coronary Artery Compensatory Enlargement

The relationship between lesion brightness and mode of remodeling detected by IVUS of the lesion is shown in Table III. A trend in the distribution of the three remodeling modes among the soft and hard plaques was noted ($p = 0.15$). There were no significant differences.

The relationship between calcium deposits and mode of remodeling of the lesion is shown in Table IV. A trend in the distribution of the three remodeling modes among the presence and absence of calcium deposit was noted ($p = 0.015$). The S group had significantly more lesions with calcium deposits than the CE group (9/14 vs. 2/15, $p < 0.001$).

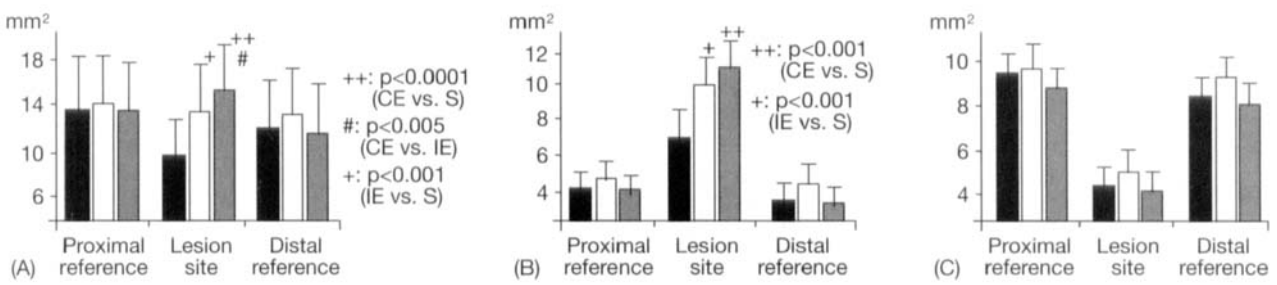

FIG. 2 The measured and calculated data in the three groups. (A) Changes of vessel area (VA), (B) changes of plaque area (PA), (C) changes of lumen area (LA). Values represent mean ± standard deviation. Abbreviations as in Figure 1. ■ = S, □ = IE, ■ = CE.

TABLE II Coronary risk factor levels in the compensatory enlargement and inadequate compensatory enlargement groups

	CE	IE	S	p Value
Height (cm)	161 ± 7	162 ± 5	163 ± 5	
Weight (kg)	62 ± 12	66 ± 11	66 ± 9	
BMI (kg/m^2)	24 ± 4	25 ± 4	24 ± 3	
Cigarette smoking, n (%)	11 (73)	8 (62)	10 (71)	
Family history, n (%)	8 (53)	6 (46)	7 (50)	
Systolic BP (mmHg)	**123 ± 14**	**137 ± 13**	**142 ± 19**	**<0.01**
Diastolic BP (mmHg)	**71 ± 7**	**84 ± 10**	**84 ± 12**	**<0.001**
Total cholesterol (mg/dl)	201 ± 39	197 ± 34	211 ± 51	
Triglycerides (mg/dl)	121 ± 39	141 ± 51	142 ± 19	
HDL-c (mg/dl)	**56 ± 10**	**41 ± 12**	**36 ± 6**	**<0.0001**
LDL-c (mg/dl)	122 ± 34	128 ± 31	144 ± 52	
Apo AI (mg/dl)	**131 ± 20**	**114 ± 23**	**98 ± 17**	**<0.001**
Apo AII (mg/dl)	33 ± 6	32 ± 5	29 ± 6	
Apo B (mg/dl)	106 ± 26	93 ± 22	120 ± 27	
Apo CII (mg/dl)	4 ± 1	4 ± 2	5 ± 3	
Apo CIII (mg/dl)	12 ± 4	8 ± 2	11 ± 6	
Apo E (mg/dl)	5 ± 2	4 ± 1	5 ± 1	
Lipoprotein(a) (mg/dl)	25 ± 19	19 ± 10	33 ± 26	
HbA1c (%)	5.4 ± 0.4	6.0 ± 0.8	5.6 ± 1.0	

Significant factors are shown in bold (Kruskal-Wallis and ANOVA).

Abbreviations: Apo = apolipoprotein, BMI = body mass index, BP = blood pressure, CE = compensatory enlargement, IE = inadequate compensatory enlargement, S = shrinkage, HDL-c = high-density lipoprotein-cholesterol, LDL = low-density lipoprotein- cholesterol.

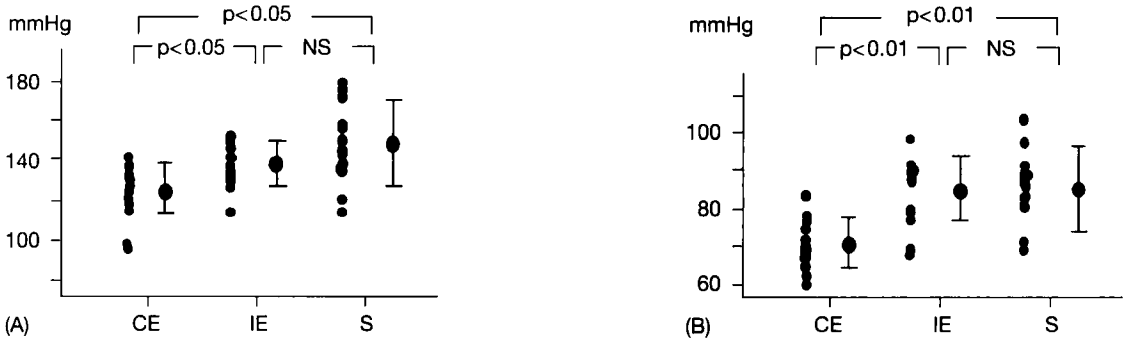

FIG. 3 The levels of systolic (A) and diastolic (B) blood pressure in the three groups. SBP = systolic blood pressure, DBP = diastolic blood pressure, NS = not significant. Other abbreviations as in Figure 1. Values represent mean ± standard deviation.

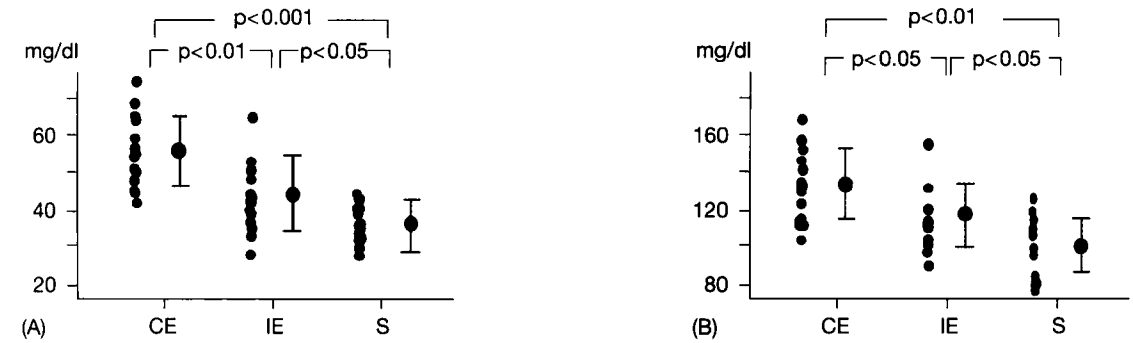

FIG. 4 The levels of high-density lipoprotein cholesterol (HDL-c) (A) and apolipoprotein AI (B) in the three groups. Abbreviations as in Figure 1. Values represent mean ± standard deviation.

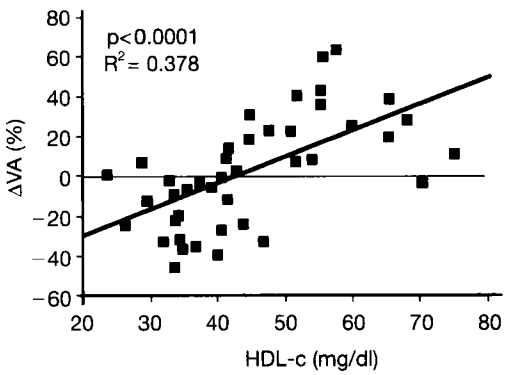

FIG. 5 The correlation Δvessel cross-sectional area and high-density lipoprotein cholesterol (HDL-c) levels. ΔVA = Δvessel cross-sectional area.

TABLE III The brightness of the lesion versus remodeling mode

	Soft plaque	Hard plaque
CE	4	11
IE	5	8
S	1	13

Abbreviations as in Table II.

TABLE IV Calcium deposit versus remodeling mode

	Calcium deposit +	Calcium deposit −
CE	2	13
IE	4	9
S	9	5

Abbreviations as in Table II.

Discussion

Prevalence and Effect of Coronary Artery Compensatory Enlargement

Using histopathologic techniques, Glagov *et al.*[1] studied the left main trunk and were the first to demonstrate that human coronary arteries undergo compensatory enlargement as a result of atherosclerotic obstructions. Their findings were supported by previous animal studies that demonstrated hindlimb and compensatory enlargement in monkeys fed atherogenic diets.[6,7] Recently, Hermiller *et al.*,[8] using IVUS in vivo, reported results that were quite similar to the original necropsy work of Glagov *et al.*[1] However, Pasterkamp *et al.*[3] found that in the femoral artery, compensatory enlargement was observed in only 40% (IVUS examination) and 36% (histological examination) of the cases. The results of the present study are in agreement with their findings. In our patients with significant coronary stenosis (>50% diameter), CE was observed in 15 of the 42 patients, IE was observed in 13 patients, and S was observed in 14 patients. In addition, changes in vessel cross-sectional area and plaque area were significantly ($p<0.05$) larger in the CE group than in the other two groups. These results suggest that arterial enlargement is one of the compensatory mechanisms that maintain lumen area of epicardial coronary arteries and myocardial blood flow.

Recently Schoenhagen *et al.*[9] reported that positive remodeling was associated with unstable clinical presentation. However, the positive remodeling they investigated in that study may be morbid vessel enlargement, which might be induced by accumulation of oxidized LDL[10] rather than compensatory enlargement. Ehara *et al.*[11] demonstrated that plasma oxidized LDL levels in patients with severe acute coronary syndromes were significantly higher than in patients with stable angina, although serum levels of total or LDL cholesterol did not differ between these groups. On the other hand, Hamasaki *et al.*[12] reported that cholesterol-lowering treatment was associated with improvement in coronary lumen area that resulted not from a decrease in plaque area but from an increase in vessel area and endothelial function in patients with mildly diseased coronary arteries. Thus, we believe that the vessel enlargement in patients with acute coronary syndromes differs from that in patients with stable angina in character, and arterial enlargement is one of the important compensatory mechanisms that maintain lumen area of coronary arteries in the patients with stable angina.

Coronary Risk Factors and Coronary Artery Compensatory Enlargement

The mechanisms underlying compensatory arterial expansion are still unknown. As plaque accumulates and lumen area declines, coronary flow velocity and shear stress increase. In response to the increase in shear stress, endothelial cells from the nondiseased portion of the vessel wall may release vasodilating compounds, such as endothelial-dependent relaxing factor, that elicit vasodilation.[13] In the present study, blood pressure, HDL-c, and apolipoprotein AI were significantly related to coronary artery compensatory enlargement. To our knowledge, these are the first findings linking HDL-c level to evidence of arterial compensatory enlargement in patients with a de novo lesion in one vessel in vivo. These results may be supported by the recent study,[14] which described that there was a modest linear relationship between higher HDL-c and the propensity for positive remodeling in 97 autopsy cases. However, in the autopsy study, the medication or blood pressure to arterial remodeling was not evaluated. In our study, we demonstrated that HDL-c and systolic blood pressure were associated with Δvessel cross-sectional area in the patients whose medications were almost same.

As shown in Figures 4 and 5, Δvessel cross-sectional area decreased in a stepwise fashion across decremental levels of both HDL-c and apolipoprotein AI levels. The following may be reasons for these results. First, Mahoney *et al.*[15] reported that decreased HDL-c level was the coronary risk factor ex-

hibiting the strongest association with coronary artery calcification in young adults. In our study, significantly more lesions that had calcium deposits were in the S group than the CE group, and this result may be supported by those of a previous study,[4] which found that calcification was a predictor of inadequate compensatory enlargement and suggested the fibrocalcific elements may have limited the adaptive response to plaque accumulation. Furthermore, previous studies have shown that maturing of the atherosclerotic lesion with an increase in fibrosis, calcification, and apoptosis may result in a decrease in vessel cross-sectional area of lesion site.[16] Thus, decreased HDL-c level may promote coronary artery calcification, and coronary artery calcification may then contribute to coronary artery shrinkage. The low mean age (56 years) of our patients might also strengthen the effect of HDL-c level on coronary artery calcification, as in the study by Mahoney *et al.*,[15] since, had the mean age of study patients been higher, the effect of HDL-c level on coronary artery calcification would have been masked by the effect of aging. Second, several studies have shown that HDL-c has an anti-inflammatory effect.[17] Some studies have shown that several components of the inflammatory response to oxidized LDL were associated with the initiation and progression of atherosclerosis,[18] and a previous report suggested that the formation of lipoprotein oxidation products, mediated by an increased influx into the balloon injury site of plasma lipoproteins and free radical-production inflammatory cells, might influence the chronic constriction and restenosis after angioplasty.[19] Furthermore, in vitro studies have shown that osteocalcin and osteopontin function in inflammation and tissue healing.[20, 21] Thus, decreased HDL-c level may promote inflammatory response in atheromatous plaque, and lasting inflammation may affect vessel constriction and calcification in de novo lesions such as those in the S group. Third, Kuhn *et al.*[22] demonstrated that endothelium-dependent vasodilator response to acetylcholine was impaired in patients with low HDL-c levels. In addition, Matsuda *et al.*[23] recently reported that HDL-c reversed oxidized LDL-c-induced impairment of endothelium-dependent relaxation by removing lysophosphatidylcholine from oxidized LDL-c and preventing lysophosphatidylcholine from acting on the endothelium. Thus, an increase in HDL-c level may promote normal endothelial cell function even in atherosclerotic coronary segments. Further, Tauber *et al.*[24] demonstrated that HDL-c is a major promoter of endothelial cell proliferation and repair. Therefore, the beneficial effects of HDL-c on coronary artery compensatory enlargement observed in the present study may be related to the increased number of functioning endothelial cells from which endothelial-derived relaxing factor can be released. Fourth, HDL-c-induced increases in prostacyclin production and half-life[25] may also contribute to its beneficial effects on coronary artery compensatory enlargement.

There has been widespread acceptance of the concept that hypertension is a causative factor in the pathogenesis of coronary atherosclerosis and of coronary events. Studies of experimental animals indicated that decrease in blood pressure reduced the development of atherosclerosis[26] and improved endothelium-dependent relaxation.[27] Our results suggest that increased blood pressure induced inadequate compensatory enlargement or shrinkage and culminated in rapid progression of coronary stenosis.

Study Limitations

Using IVUS, we found that the presence of hypertension and the decrease in HDL-c levels contributed to impairment compensatory arterial response; however, the methodology of this study has technical limitations that need to be overcome. Catheter angulation in epicardial vessels that did not take a straight course may have caused overestimation of vessel cross-sectional area; however, the size of the coronary artery relative to the catheter was small. Thus, we considered the impact of catheter angulation on vessel lumen measurements to be negligible.

Arterial tapering might influence the differences in vessel cross-sectional areas between cross sections in one segment. However, the vessel cross-sectional area in the most proximal and most distal cross sections did not differ significantly in this study. Therefore, we considered the effect of arterial tapering to be minimal, if at all.

Lesions with extensive calcified plaques were excluded from our analysis, since we believed the outer border of calcified lesions could not be measured accurately by IVUS due to the shadowing effect. In this study, seven patients were excluded because of extensive calcified plaques.

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