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Increased carotid artery plaque score is an independent predictor of the presence and severity of coronary artery disease

Natsumi Morito[a,*], Yukiko Inoue[b], Makiko Urata[a], Eiji Yahiro[b], Sunao Kodama[b], Naoka Fukuda[a], Naoko Saito[b], Yoshihiro Tsuchiya[b], Hiroyuki Mihara[b], Yoshio Yamanouchi[b], Keijiro Saku[a], Hidenori Urata[b]

[a] *Department of Cardiology, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan*
[b] *Department of Cardiovascular Diseases, Fukuoka University Chikushi Hospital, Chikushino, Japan*

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Summary
Objectives: Carotid ultrasonography is noninvasive and effective for the assessment of atherosclerotic lesions. The relationship between carotid ultrasound findings and presence and severity of coronary artery disease (CAD) was examined in Japanese patients.
Methods and results: Subjects were 116 patients who underwent carotid ultrasonography and coronary angiography. In carotid ultrasonography, mean-intima-media thickness (IMT), common carotid artery max IMT, bifurcation max IMT, plaque number, and plaque score (PS). The coronary angiographic data was obtained in the same period as carotid ultrasonography was performed. Patients were divided into two groups based on the presence or absence of coronary artery stenosis (CAS and non-CAS) and CAS group was further categorized into three groups, 1 vessel disease (1VD), 2VD, and 3VD. Physical findings, biochemical data, and carotid ultrasonogram data between the groups were compared. Items showing a significant difference between CAS and non-CAS were age, gender (male), incidence of diabetes and dyslipidemia, fasting blood sugar (FBS), triglyceride, HDL-cholesterol (HDL-C), high-sensitivity C-reactive protein, and all carotid ultrasound findings. All of the above parameters also showed a significant difference between four different severity groups. Stepwise logistic regression analysis was performed to determine which factors predict the presence and/or severity of CAS. High PS showed the strongest predictive value for both and followed by low HDL-C and high FBS. The cut-off value of PS obtained by receiver operating characteristic curve for predicting the presence of CAS was 1.9.

* Corresponding author. Tel.: +81 92 801 1011; fax: +81 92 862 8200.
E-mail address: moriton@adm.fukuoka-u.ac.jp (N. Morito).

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Conclusions: Assessment of PS by carotid ultrasonography together with other risk factor assessment was clinically relevant to predict the presence and severity of CAS.

Introduction

Atherosclerosis is a fundamental cause of various cardiovascular diseases and furthermore causes fatal coronary artery disease (CAD). Namely, early detection of CAD and particularly detection while the patient is asymptomatic is clinically crucial. Carotid ultrasonography, a noninvasive examination, is effective in assessing atherosclerotic lesions. There are numerous reports on the relationship between carotid ultrasound findings and other risk factors like hypertension [1] or diabetes [2], aortic calcification [3,4], and CAD [5—7]. Most of them, however, are studies on predicting the onset of CAD or on its presence or absence based on carotid ultrasound findings. Moreover, very few reports were reported for the relation between carotid ultrasound findings and the severity of CAD [8]. Thus, if not only the presence of CAD but also its severity can be predicted with carotid ultrasound findings, this will prove of great clinical use in early detection and treatment of CAD.

Another focus of this work was parameters for carotid ultrasonography. Many papers have used intima-media thickness (IMT) as main parameter in carotid ultrasound findings, but relatively few reports have used assessments of plaque like the plaque score (PS) and plaque number (PN) [5,6,9,10].

In the present study, in addition to IMT, PS and PN were assessed to examine the relationship between these carotid ultrasound findings and the presence and severity of CAD in Japanese patients.

Methods

Subjects

Subjects were, of patients admitted to Fukuoka University Chikushi Hospital from April 2004 to December 2005 with CAD or its suspicion ($n = 119$), those who underwent carotid ultrasonography and coronary angiography simultaneously. Informed consent was obtained before enrollment in the trial, and the trial was reviewed and approved by the responsible institutional review boards. Of these patients, those following carotid angioplasty and those with aortitis syndrome were excluded ($n = 1$), and patients with poorly recorded carotid ultrasonograms precluding measurement were excluded ($n = 2$), yielding a total of 116 subjects (average age: 68.5 ± 10.8 years, male:female = 68:48).

The risk factor variables evaluated in the present study included age, sex, hypertension, dyslipidemia, diabetes mellitus (DM), and smoking status. Smoking was defined based on its active presence in the last 6 months; an ex-smoker was someone who quit the habit 6 months before, and a nonsmoker was someone who did not smoke in the last 15 years.

Hypertension was defined as receiving antihypertensive medication or if the averaged systolic or diastolic blood pressure measured was above 140 mmHg or 90 mmHg at least two different occasions, respectively. Dyslipidemia was defined as total plasma cholesterol of >220 mg/dl or HDL-cholesterol of <40 mg/dl or triglyceride levels of >150 mg/dl or documented hypercholesterolemia requiring lipid-lowering drug therapy. Diabetes mellitus was defined as present if the patient had a history of diabetes, diabetic therapeutic drug administration, or if fasting plasma glucose exceeded 126 mg/dl or 200 mg/dl at any time.

Upon admittance, height and weight were measured and BMI was calculated, and electrocardiography, chest radiography, and echocardiography were performed as routine examinations during admittance. Blood pressure levels were measured prior to carotid ultrasonography at least two times at a sitting position bilaterally. The averaged value was used for analysis. In addition, results of blood taken during early morning fasting were used for biochemical data.

Assessment of carotid ultrasonography

Atherosclerotic changes of the bilateral carotid arteries were assessed by ultrasonography. High resolution B mode, color Doppler, and pulse Doppler ultrasonography of both carotid arteries were performed with an ultrasound scanner (Toshiba Power Vision 8000) equipped with a 7.5 MHz linear array transducer. Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe was rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. A careful search was performed for all

interfaces of up to 12 different sites (right and left, near and far walls, distal common, bifurcation, and proximal internal carotid artery). When an optimal longitudinal image was obtained, it was stored on videotape. The mean-IMT was the averaged IMT of both distal common arteries. The C-maximum IMT (Cmax-IMT) was the most hypertrophic site measured at the distal common carotid artery. B-maximum IMT (Bmax-IMT) was the most hypertrophic site measured at the bifurcation and the internal carotid arteries.

Plaque was designated as focal intima-media thickening greater than or equal to 1.1 mm. The PS was calculated by summing all plaque thicknesses. The PN was the total number of plaques [11,12]. All measurements were performed by several sonographers who were unaware of detail the clinical information for each patient.

Assessment of coronary angiography

Coronary angiography was performed percutaneously using either a Judkins or multipurpose catheter. Coronary angiograms were recorded and divided into 15 segments according to the classification of the American Heart Association Grading Committee. The presence of stenosis was determined by several experienced skillful cardiologists based on viewing the angiographic cinefilm obtained after the direct intracoronary injection of isosorbide dinitrate. Arterial stenosis were categorized into seven different levels (0, 25, 50, 75, 90, 99% stenosis or total occlusion). More than 75% luminal narrowing, actually 51% or more stenosis, was considered significant coronary artery stenosis (CAS). Angiographic findings were analyzed by observers who were blinded to the carotid ultrasound data. In addition, the group with CAS was divided according to the number of diseased vessels into a group with single vessel disease (1VD), two vessel disease (2VD), or three vessel disease (3VD). In other words, all 116 subjects were subclassified into these four different severity groups.

Statistical analysis

To examine the relationship between carotid ultrasound findings and CAD, all of the 116 subjects were

Table 1 Comparison of clinical parameters between CAS and non-CAS patients

	CAS ($n=75$)	Non-CAS ($n=41$)	p value
General			
Gender (M/F)	49/26	19/22	0.0061
Age (years)	70.4 ± 9.4	65.1 ± 12.3	0.0179
BMI (%)	23.5 ± 3.7	23.2 ± 3.2	0.7133
HT (n (%))	58 (77.3%)	28 (68.3%)	0.2878
DM (n (%))	32 (42.7%)	7 (17.1%)	0.0053
DL (n (%))	52 (69.3%)	19 (46.3%)	0.0151
Smoker (n (%))	24 (32.4%)	10 (25.0%)	0.4078
Biochemical data			
FBS (mg/dl)	101 (89, 139)	93 (86, 104)	0.0148
HbA1c (%)	6.6 ± 1.8	5.8 ± 1.4	0.0642
T-chol (mg/dl)	191.4 ± 38.5	193.1 ± 34.2	0.8171
TG (mg/dl)	110 (84, 154)	91 (77, 123)	0.0181
HDL-C (mg/dl)	48.5 ± 11.0	56.6 ± 14.3	0.0012
WBC (μl)	6362 ± 1981	5760 ± 1964	0.1231
hs-CRP (mg/dl)	0.2 (0.1, 0.7)	0.1 (0.0, 0.2)	0.0015
Carotid data			
Mean-IMT (mm)	0.90 ± 0.36	0.77 ± 0.20	0.0106
Cmax-IMT (mm)	1.36 ± 0.79	1.02 ± 0.43	0.0124
Bmax-IMT (mm)	2.03 ± 1.47	0.90 ± 1.12	<0.0001
PS	5.7 (2.6, 11.9)	1.3 (0.0, 3.2)	<0.0001
PN	3.0 (1.0, 4.0)	1.0 (0.0, 1.3)	<0.0001

Data are means ± S.D., median (25th and 75th percentile), or n (%). We performed chi-square test for categorical data, Kruskal–Wallis test for FBS, TG, CRP, PS, and PN, while the others were followed by t-test. CAS, with >75% stenosis of coronary artery; non-CAS, no stenosis of coronary artery; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; FBS, fasting blood sugar; T-chol, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; Cmax-IMT, common maximum intima-media thickness; Bmax-IMT, bifurcation maximum intima-media thickness; PS, plaque score; PN, plaque number.

Table 2 Comparison of clinical parameters among groups with different severity of CAS

	Normal ($n=41$)	1VD ($n=31$)	2VD ($n=24$)	3VD ($n=20$)	p value
General					
Gender (M/F)	19/22	17/14	18/6	14/6	0.0211
Age (years)	65.1 ± 12.3	70.8 ± 9.4	67.7 ± 9.3	73.2 ± 9.0	0.0219
BMI (%)	23.1 ± 3.2	23.4 ± 3.9	23.4 ± 4.1	23.7 ± 2.9	0.9621
HT (n (%))	28 (68.3%)	24 (77.4%)	19 (79.2%)	15 (75%)	0.4487
DM (n (%))	7 (17.1%)	9 (29.0%)	12 (50.0%)	11 (55.0%)	0.0006
DL (n (%))	19 (46.3%)	20 (64.5%)	19 (79.2%)	13 (65.0%)	0.0398
Smoker (n (%))	10 (25.0%)	9 (30.0%)	9 (37.5%)	6 (30.0%)	0.4781
Biochemical data					
FBS (mg/dl)	93 (86, 104)	96 (84, 140)	115 (99, 137)	98 (91, 142)	0.0044
HbA1c (%)	5.8 ± 1.4	6.3 ± 1.7	6.6 ± 2.0	6.8 ± 1.9	0.2726
T-chol (mg/dl)	193.1 ± 34.2	189.1 ± 39.8	193.0 ± 37.7	192.8 ± 39.4	0.9717
TG (mg/dl)	91 (77, 123)	109 (83, 140)	116 (90, 167)	112 (86, 160)	0.0101
HDL-C (mg/dl)	56.6 ± 14.3	49.5 ± 12.0	49.4 ± 12.5	46.2 ± 7.2	0.0101
WBC (μl)	5760 ± 1964	5970 ± 1714	6883 ± 1898	6325 ± 2376	0.1567
hs-CRP (mg/dl)	0.1 (0.0, 0.2)	0.2 (0.1, 0.5)	0.4 (0.1, 0.9)	0.1 (0.1, 0.7)	0.0041
Carotid data					
Mean-IMT (mm)	0.77 ± 0.20	0.85 ± 0.25	0.86 ± 0.21	1.04 ± 0.56	0.0182
Cmax-IMT (mm)	1.02 ± 0.43	1.23 ± 0.59	1.28 ± 0.69	1.65 ± 1.09	0.0110
Bmax-IMT (mm)	0.90 ± 1.12	1.78 ± 1.55	1.62 ± 1.42	2.87 ± 1.05	<0.0001
PS	1.3 (0.0, 3.2)	3.8 (1.5, 8.4)	4.8 (2.0, 8.4)	7.9 (6.7, 12.0)	<0.0001
PN	1.0 (0.0, 1.3)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	4.0 (3.0, 5.0)	<0.0001

Data are means ± S.D., median (25th and 75th percentile), or n (%). We performed Kruskal–Wallis test with rank score for categorical data, FBS, TG, CRP, PS, and PN considering severity of CAS, while the others were analyzed by one-way ANOVA, and multiple comparison followed by Tukey–Kramer. BMI, body mass index; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; FBS, fasting blood sugar; T-chol, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; WBC, white blood cell; ha-CRP, high-sensitivity C-reactive protein; Cmax-IMT, common maximum intima-media thickness; Bmax-IMT, bifurcation maximum intima-media thickness; PS, plaque score; PN, plaque number.

divided into two groups, a group with significant CAS group and a group without such lesions (non-CAS group). Using a t-test and χ^2 test, the carotid ultrasound findings, incidence of risk factors, and biochemical data of the two groups were analyzed; based on these results, which factors predicted the presence of CAS were determined using stepwise logistic regression analysis.

The background features of four different CAS severity groups (non-CAS, 1VD, 2VD, and 3VD) were compared using Kruskal–Wallis test with rank score, and one-way ANOVA. Ordinal logistic regression analysis with stepwise was used to determine the most relevant factors predicting the severity of CAS. Receiver operating characteristic (ROC) curve analysis was performed to establish

Table 3 Proportion of medication among groups with different severity of CAS

	Normal ($n=41$)	1VD ($n=31$)	2VD ($n=24$)	3VD ($n=20$)	p value
ACEI	2 (4.9%)	3 (9.7%)	2 (8.3%)	1 (5.0%)	0.8496
ARB	15 (36.6%)	16 (51.6%)	10 (41.7%)	12 (60.0%)	0.3062
CCB	8 (19.5%)	15 (48.4%)	7 (29.2%)	6 (30.0%)	0.0734
Diuretics	6 (14.6%)	3 (9.7%)	1 (4.4%)	6 (30.0%)	0.1111
Co A vasodilator	4 (10.0%)	14 (45.2%)	10 (41.7%)	11 (55.0%)	0.0009
Beta-blocker	3 (7.3%)	2 (6.5%)	3 (12.5%)	1 (5.0%)	0.8116
Aspirin	5 (12.2%)	19 (61.3%)	12 (50.0%)	16 (80.0%)	<0.0001
Statin	9 (22.0%)	11 (35.5%)	10 (43.5%)	6 (30.0%)	0.3181
SU	2 (4.9%)	5 (16.1%)	4 (17.4%)	7 (35.0%)	0.0214
ISA	0 (0.0%)	2 (6.5%)	5 (20.8%)	2 (10.5%)	0.0105
α-GI	3 (7.3%)	1 (3.2%)	3 (12.5%)	3 (15.0%)	0.4057

Data are n (%) with regard to the proportion of subjects on the drug. Analyses were followed by chi-square test, or Fisher's exact test. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; Co A vasodilator, coronary artery vasodilator; SU, sulfonylurea; ISA, insulin-sensitizing agent; α-GL, α-glucosidase inhibitor.

the best threshold PS value of the presence of CAS.

Results

The initial comparative data between CAS and non-CAS groups are listed in Table 1. Several factors were significantly different between two groups. CAS group showed higher age, higher male ratio, higher incidence of DM and dyslipidemia (DL), higher fasting blood sugar (FBS) and triglyceride (TG), lower high-density lipoprotein cholesterol (HDL-C), and higher high sensitivity C-reactive protein (hs-CRP) compared to non-CAS group. Regarding the incidence of hypertension and total cholesterol level, there was no difference between the two groups. All of the IMT data (mean, Cmax, and Bmax), PS, and PN were significantly higher in CAS group compared to non-CAS group.

The second analysis was performed to examine the group difference depend on the severity of CAS (Table 2). Significant differences between four groups were observed for gender, age, the incidence of DM and DL, FBS, TG, HDL-C hs-CRP, and all of the carotid ultrasound findings.

To consider the effect of medication of the present study, medication treated for at least 2 months were considered to be on medication. The kinds of medications and the proportion of subjects on those medications were listed in Table 3. The proportion of drug treatment was significantly different in coronary vasodilators, aspirin, sulfonylurea, and insulin-sensitizing agent.

Stepwise logistic regression analysis was performed to determine the contributing factors to the presence of CAS and those results are shown in Table 4a. High PS and low HDL-C were significant contributors for the presence of CAS. The increase of PS by 1.0 or the decrease of HDL-C by 10 mg/dl correspond to 36% or 41% increased risk of the presence of CAS, respectively. Another stepwise logistic regression analysis was performed to determine the contributing factor to the severity of CAS and those data are summarized in Table 4b. The most contributing factor to the severity of CAS was high PS and followed by high FBS then low HDL-C. Therefore, high PS was quite significant contributing factor to both the presence and severity of CAS.

Fig. 1 shows data distribution in each severity grade. Based on these data distribution, the cut-off point for PS, which predicts the presence of CAS, was determined from the receiver operating characteristic curve. Results are shown in Fig. 2. The cut-off point for predicting the presence of CAS was 1.9.

Table 4a Stepwise multiple logistic regression analysis for CA

Variable	Unit	Odds ratio (95% CI)
PS	1	1.36 (1.18, 1.62)
HDL-C (mg/dl)	10	0.59 (0.38, 0.87)

CAS, stenosis of coronary artery; PS, plaque score; HDL-C, high density lipoprotein cholesterol; BMI, body mass index; FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-chol, total cholesterol; TG, triglyceride. Stepwise multiple regression analysis for CAS was performed using variables as quantitative traits together with age, gender, BMI, smoking status, FBS, SBP, DBP, T-chol, TG, HDL, and measurements in carotid ultrasonography. As a result, PS and HDL were significantly associated with CAS. The odds ratio of these independent contributors represented an increase per 1 PS, and 10 mg/dl HDL.

Table 4b Stepwise multivariable regression analysis for four grades of severity of CAS

Variable	Unit	Odds ratio (95% CI)
PS	1	1.33 (1.20, 1.48)
FBS (mg/dl)	10	1.15 (1.05, 1.26)
HDL-C (mg/dl)	10	0.60 (0.42, 0.83)

CAS, stenosis of coronary artery; PS, plaque score; FBS, fasting blood sugar; HDL-C, high density lipoprotein cholesterol. We used severity of CAS as the dependent variables, and the same independent variables in the analysis of Table 4a. Ordinal logistic regression analysis was calculated due to the rank order of the dependent variable. As a result, PS, FBS, and HDL were significantly associated with severity of CAS. The odds ratio of these independent contributors represented an increase per 1 PS, 10 mg/dl FBS and 10 mg/dl HDL.

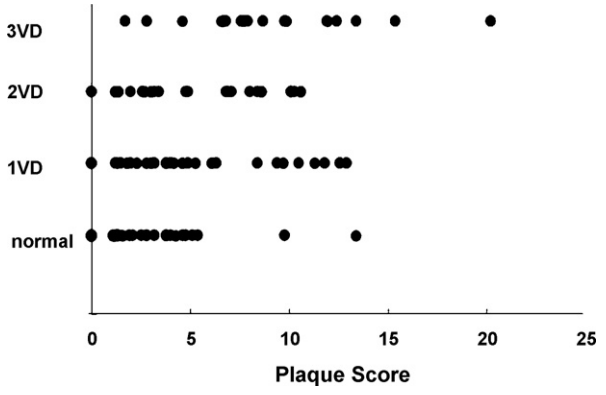

Figure 1 Distribution of plaque score value in the different severity group of coronary artery stenotic lesions (CAS). Of note are the higher levels of PS value in more severe CAS groups.

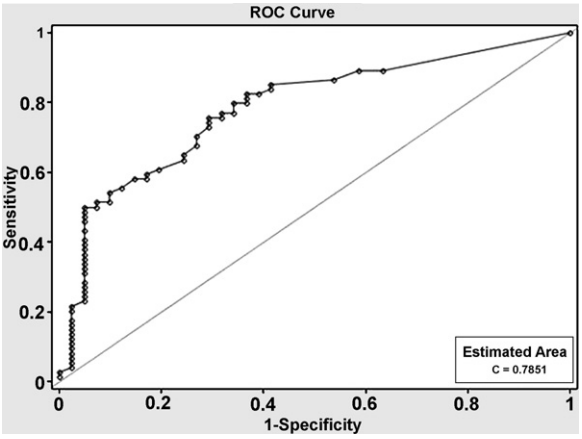

Figure 2 Receiver operating characteristics (ROC) curve for PS. Based on the ROC curve in all subjects, an arbitrary cut-off value of PS 1.9 was selected. Sensitivity: 79.7%; specificity: 63.4%; accuracy: 73.9%; false positive: 20.3%; false negative: 36.6%. Deviance goodness of fit statistic; $p = 0.8352$.

Discussion

The main aim of the present study was to clarify the relationship between carotid ultrasound findings and the presence or severity of CAS in Japanese patients. Our results provided new findings in that the presence of risk factors (high FBS and low HDL-C) and high PS value in the carotid ultrasonography have the most substantial impact on determining the presence and severity of CAS.

Many previous studies have indicated a strong relationship between ultrasound findings of the carotid arteries and CAD [3,7,8,13—18]. The Rotterdam study [3] recruited healthy adults aged 55 and more to examined their morbidity and cardiovascular mortality for the following 7—10 years and then found that the carotid ultrasound findings were the best indicator new onset of myocardial infarction compared to aortic calcification in chest X-ray films or ankle-arm index. Kallikazaros et al. [4] compared the predictive value for the presence of CAD between sclerotic lesions of the descending aorta observed by transesophageal echocardiography and carotid ultrasound findings and they concluded that the latter was a better indicator for the presence of CAD. Ogata et al. [5] studied the relationship between IMT and left main trunk calcification and Sonoda et al. [16] examined the relationship between coronary flow and IMT; both reported that high IMT value was a good indicator of the extent of CAD. Moreover, Kablak-Ziembicka et al. [8] reported that IMT is significantly thicker in a group in which CAD is present based on coronary angiography findings and that IMT increases with increased severity.

These previous reports have clearly shown that high IMT observed by carotid ultrasonography has a strong predictive value for the presence of CAD. Our results in the present study also indicated that IMT values such as mean-, Bmax- and Cmax-IMT values were significantly high in CAS group. However, most of previous reports have used mainly IMT value, i.e. mean-IMT and max-IMT, as the carotid ultrasound findings. A single measurement of carotid IMT is relatively simple and allows easier diagnosis. Among reports using plaque indicators such as the PS and PN [5,6,9,10], Sakaguchi et al. [6] studied the relationship between coronary angiographic findings and IMT, PS, or PN, and concluded that IMT and PS were equally good indicators of the presence of CAD. In the present study, stepwise logistic regression analysis was performed to identify significant contributor to the presence of CAS. It turn out that PS was better indicator than IMT. A wider range observation of the carotid arteries is required to obtain PS than IMT, therefore, PS value may represent more precisely the atherosclerotic condition of the carotid artery than IMT value does, that could bring the superiority of PS in predicting the presence of CAS.

Another important point in the present study was the positive relationship between PS value and the severity of CAS. The detail relation between both parameters has not been found as far as our survey reached. Our present results revealed that high PS value predict not only the presence but also the severity of CAS. The strong correlation between carotid artery plaque formation and CAS became apparent. Thus, greater IMT is certainly an important indicator for an initial stage of atherosclerotic lesions and a simple way of screening for the presence of CAS. However, in order to predict the severity of CAS our results indicated that high PS value is more useful than IMT.

Based on the cut-off value determined from the ROC curve, a PS of over 1.9 is considered to indicate the presence of CAS (Fig. 2). This value appeared to be lower than expected and several reasons might be in consideration. First, two cases in non-CAS group showed relatively high PS value (Fig. 1). Second, not only PS value but also other factor such as low HDL-C was significant predictor for the presence of CAS. Therefore, in addition to the carotid ultrasound findings, the effects of these metabolic factors appeared to be also important modifier of predicting the presence of CAS.

Carotid ultrasound findings like IMT have been studied in association to many risk factors of CAD. The association between DM and the scle-

rotic changes in carotid arteries is apparent, and there are a number of previous reports on this subject [19—21]. Mitsuhashi et al. [19] reported clear evidence that the IMT value of the diabetic CAD patients was significantly higher than those of the diabetic non-CAD patients. Yamasaki et al. [21] also reported that the predictors of the progression of carotid IMT in Japanese type 2 diabetic subjects were the baseline thickness of IMT and the average HbA1c during the follow-up. The data in the present study also showed association between high FBS and the presence of CAS (Table 1), even though some patients were under anti-diabetic medication. Thus, our present data regarding this association were in concordance with previous reports.

Additionally, factors showing a significant association with CAS severity in the present study were having a low HDL-C. It is a general consensus that low HDL-C level is an important risk factor for both new onset and recurrence of CAD. Alagona et al. [22] compared the degree of IMT between non-CAD subjects with genetically low HDL-C levels and those without and found that IMT was significantly greater in the subjects with low HDL-C. These previously reported results regarding HDL-C suggest that low HDL-C is an independent contributor to not only IMT but also CAD. Our finding of HDL-C contribution to the presence and severity of CAS also supports the reported role of HDL-C on the development of CAD.

In the present study, several factors in CAS group were significantly different those in non-CAS group, but most of them did not remain as a significant contributor of the presence or severity of CAS due to the calibration process of the stepwise logistic regression analysis. One of them was high hs-CRP level in CAS group, which could be important in considering the relation between atherosclerosis and increased inflammation. It has been reported that vascular inflammation can be induced by the presence of hypertension, dyslipidemia, or impaired glucose tolerance. Many reports have indicated such a relationship between inflammation and atherosclerosis: ICARAS [23] examined the relationship between inflammation and early carotid atherosclerosis and provided a close positive correlation between inflammation and morphological changes of rapidly progressive carotid atherosclerosis. Our data also showed a similar significant association between PS and hs-CRP ($r = 0.33$, $p < 0.01$, data are not shown), thereby this could cause that hs-CRP could not remain as a significant contributor to the presence of CAS in the stepwise logistic analysis.

With regard to hypertension, Sonoda et al. [16] studied the degree of IMT in three different groups: patients with CAD, patients with hypertension and without CAD, and without both, and reported substantially high IMT in the CAD group, followed by the hypertension group. In addition, Takiuchi et al. [10] studied the relationship between the carotid ultrasound findings and hypertensive organopathy in 350 hypertensive patients and found that the max IMT was the strongest indicator of the hypertensive organopathy. These previous results indicate that hypertension itself affects the carotid ultrasound finding. In the present study, however, the presence of hypertension and observed blood pressure levels did not differ between CAS and non-CAS groups. This might be because antihypertensive medications had been administered or the hypotensive effect of reduced salt intake under hospitalization even in short period. These conditions might influence our results because the observed blood pressure levels were not basal levels. This might have affected the present results. However, the averaged PS value in the hypertensive group (4.3 (1.3, 8.0)) was significantly higher than that in non-hypertensive group (1.6 (0.0, 4.0), $p < 0.02$, data not shown), indicating that hypertension itself might affect carotid plaque formation, but it was not clear for CAS due to modified blood pressure level in our study.

As regards limitations of the present study, the effect of drug compliance and the therapeutic period of medication were not sufficiently in consideration. This might affect the final results. Our investigation revealed that the uses of coronary vasodilator, aspirin, sulfonylurea, and insulin-sensitizing drug were significantly different between the different severity groups of CAS. However, regarding the effect of drug treatment on the carotid ultrasound findings, a prospective randomized trial is necessary. Since the present study was a cross-sectional observational study, the significance for the effects of drug treatment was not conclusive.

Another limitation was the subjects: the enrolled patients in the present study were symptomatic CAD or its suspicion due to some clinical discomfort such as chest pain. In fact, those subjects were relatively high risk because majority of the patients were complicated with several life style modification diseases such as hypertension, diabetes mellitus, hyperlipidemia and obesity. Therefore, it is not clear whether our results are applicable to the asymptomatic population. Obviously, a further study is necessary targeting general asymptomatic population and ideally should be prospective study to address the association between the carotid ultrasound findings and not only the presence but also the long-term prognosis of CAD.

Conclusions

Carotid ultrasound parameter especially high PS value was proved to predict the presence and severity of CAS. In addition, it has been reconfirmed that the detail assessment of risk factors for CAD was of great importance.

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