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● *Original Contribution*

EQUIVALENCE OF PLAQUE SCORE AND INTIMA-MEDIA THICKNESS OF CAROTID ULTRASONOGRAPHY FOR PREDICTING SEVERE CORONARY ARTERY LESION

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Abstract—Carotid atherosclerosis appears to be predictive of myocardial infarction. Because several sonographical indices are available for carotid ultrasound (US), we compared "blindly" the potential utilities of those indices for predicting coronary lesions in 270 patients. Carotid atherosclerosis was evaluated by the following four indices: plaque score (PlaS), intima-media thickness (IMT) of common carotid artery (CCA-IMT), IMT of bulb to internal carotid artery (Bulb-ICA-IMT), and combined IMT measurement from all segments. The existence of coronary lesions was diagnosed by > 50% stenosis in diameter in coronary arteries. All indices were associated with coronary lesions independent of risk factors. By receiver-operating characteristic (ROC) curve analyses, ROC areas defined by Bulb-ICA-IMT (0.76 to 0.86), combined IMT (0.76 to 0.86) and PS (0.76 to 0.87) were greater than that defined by CCA-IMT (0.64 to 0.76). In conclusion, PlaS, Bulb-ICA-IMT and combined IMT are equally effective and could be better than CCA-IMT for predicting coronary lesions in a population with cardiovascular risk. (E-mail: kitagawa@medone.med.osaka-u.ac.jp) © 2003 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Plaque score, Intima media thickness, Ultrasonography, Carotid atherosclerosis, Coronary artery lesion.**

INTRODUCTION

Carotid atherosclerosis as assessed by ultrasound (US) is often used as a surrogate for systemic atherosclerosis. Most epidemiologic and clinical studies are based on measurement of the intima-media thickness (IMT), a method first described by Pignoli et al. (1985). Previous cross-sectional studies have shown associations between IMT and the prevalence of cardiovascular disease (O'Leary et al. 1992; Burke et al. 1995; Allan et al. 1997). Recently, prospective studies showed that an increased IMT was associated with an increased risk of myocardial infarction and stroke (Salonen and Salonen 1991; Chambless et al. 1997; Bots et al. 1997; O'Leary et al. 1999).

Although IMT has been widely used as an index of carotid atherosclerosis, measurements of IMT varied considerably. Combined IMT measurements of common carotid artery (CCA), carotid bulb (Bulb) and internal carotid artery (ICA) have been used in the Cardiovascular Health Study (CHS) (O'Leary et al. 1991, 1999), Atherosclerosis Risk in Communities (ARIC) Study (Burke et al. 1995; Chambless et al. 1997), and the Asymptomatic Carotid Artery Plaque Study (Riley et al. 1992). In contrast, measurements of CCA-IMT have also been used in the Rotterdam Study (Bots et al. 1997), the Étude du Profil Génétique de l' Infarctus Cérébral (GÉNIC) Study (Touboul et al. 2000) and by several other investigators (Salonen and Salonen 1991; Nagai et al. 1998; Simons et al. 1999). Because it has been suggested that IMT of up to 1.0 mm may, in part, reflect an adaptive response to changes in tensile and shear stress (Bots et al.

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1997), several investigators and study groups have used a plaque-scoring system (Crouse et al. 1986), where only atheromatous plaques were included and diffuse thickening of IMT of less than 1.0 mm was ignored. We also developed plaque score (PlaS) (Handa et al. 1990) and showed that PlaS categorization was useful for predicting future ischemic stroke events (Handa et al. 1995). There have only been a few studies comparing the strength of several indices of carotid atherosclerosis for the prediction of cardiovascular events. O'Leary et al. (1999) showed that combination of the CCA and ICA IMT was more strongly associated with the prevalence of cardiovascular disease, with traditional risk factors and with new cardiovascular events, than either variable used alone. However, it is unclear whether or not a plaque-scoring system such as PlaS is as good a predictor of the prevalence of cardiovascular disease and future cardiovascular events as several measurements of IMT.

We, therefore, measured several indices of carotid atherosclerosis and angiographic severity of coronary artery disease in 270 consecutive patients to compare the potential utilities of PlaS and several IMT measurements for predicting coronary lesions in a population with higher cardiovascular risk.

PATIENTS AND METHODS

Subjects

We studied 270 patients, 40 years old or older, who had consecutively undergone elective coronary angiography at our institute. Subjects were excluded when they had histories of carotid surgery or Takayasu's arteritis. Coronary angiography was performed for the evaluation of ischemic heart disease in 177 (65.6%), valvular heart disease in 61 (22.6%), cardiomyopathy in 8 (3.0%), congenital heart disease in 14 (5.2%) and others in 10 patients (3.7%). Informed consent was obtained from all the patients, and the institutional ethics committee approved the study. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Before cardiac catheterization, the patients were asked to assess symptoms, risk factor profile, and current medical therapy.

For definition of risk factors, hypercholesterolemia was defined as total serum cholesterol $\geq$ 5.7 mmol/L or current use of lipid-lowering agents. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg or current use of antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose $\geq$ 7.0 mmol/L, glycosylated hemoglobin (HbA1c) $\geq$ 5.8% or current use of hypoglycemic agents. Smoking status was categorically defined on the basis of self-reports, with a smoker defined by current or past smoking $\geq$ 10 cigarettes per day for $>$ 1 year.

Evaluation of vascular status

To evaluate the carotid atherosclerosis, high-resolution B-mode ultrasonography was performed with a 7.5-MHz linear-type probe (Toshiba SSA-260A CE, Tokyo, Japan). Three different longitudinal views (anterior oblique, lateral, and posterior oblique) and transverse views of both carotid systems were obtained. The IMT was evaluated as the distance between the luminal-intimal interface and the medial-adventitial interface, and it was measured with the use of an electronic caliper on the frozen frame of a suitable longitudinal image. The severity of carotid atherosclerosis was evaluated based on the following four indices: plaque score (PlaS), CCA-IMT, Bulb-ICA-IMT and combined IMT. These indicies of IMT are similar to those reported in the CHS (O'Leary et al. 1991; O'Leary et al. 1999), ARIC study (Burke et al. 1995; Chambless et al. 1997) and Rotterdam study (Bots et al. 1997). To obtain each index, the extracranial carotid artery was divided into four segments of 15 mm each with a flow divider and termed ICA (S1), carotid bulb (S2), beginning at the tip of the flow divider and extending 15 mm proximal, distal CCA (S3) and proximal CCA (S4), extending 15 to 30 mm and 30 to 45 mm proximal to the tip of the flow divider into the CCA (Fig. 1). To obtain the plaque score (PlaS), protruding lesions with an IMT $\geq$ 1.1 mm were defined as atheromatous plaque. PlaS was calculated by summing all the plaque thickness measurements in both carotid arteries (S1 to S4) (Handa et al. 1990; Nagai et al. 2001; Hashimoto et al. 2001). The IMT at each segment, except for the proximal CCA, was defined as the mean of the maximal wall thickness of the near and far wall on both the left and right sides. CCA-IMT was defined as the mean of the maximal wall thickness at the distal CCA (S3). Bulb-ICA-IMT was defined as the mean of the maximal wall thickness at eight points in the carotid bulb and ICA (S1 and S2). Combined IMT was defined as mean of the maximal wall thickness at 12 points in the distal CCA, carotid bulb, and ICA (S1, S2 and S3). All measurements (PlaS, CCA-IMT, Bulb-ICA-IMT, combined IMT) were performed by M. Sakaguchi. When intraobserver reproducibility was assessed for 30 patients, the interrater correlation of PlaS was 0.89, and 0.93 for CCA-IMT, 0.87 for Bulb-ICA-IMT, and 0.88 for combined IMT.

Coronary angiography was performed by the percutaneous technique using either the Judkins or multipurpose catheters. The patients were divided into those with coronary lesions when they showed $>$ 50% stenosis in diameter or occlusion in either of the coronary arteries (Scanlon and Faxon 1999). The patients with histories of coronary angioplasty or coronary artery bypass surgery

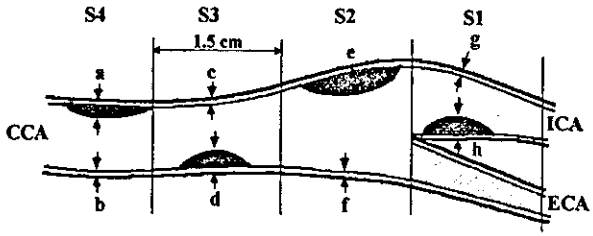

Fig. 1. Diagrams of carotid bifurcation and measurements obtained from B-mode ultrasonography. S1 = proximal internal carotid artery (ICA); S2 = carotid bulb; S3 = distal common carotid artery (CCA); S4 = proximal CCA. Shadowing is added within the vascular wall of external carotid artery (ECA). All measurements of plaque score and IMT were performed in the CCA, carotid bulb and ICA. Arrows outside the vascular wall indicate the measuring sites of either side for averaging IMT. The plaque score was calculated by summing all the plaque thickness measurements in both carotid arteries of S1, S2, S3 and S4 (a+d+e+h+ contralateral plaque). CCA-IMT was defined as the mean of the maximal wall thickness of the near and far wall on both the left and right sides at distal CCA of S3(*i.e.*, c+d+ contralateral sides/4). Bulb-ICA-IMT was defined as the mean of the maximal wall thickness at eight points in the carotid bulb and ICA (near and far walls on both sides of S1 and S2), (*i.e.*, e+f+g+h+ contralateral sides/8). Combined IMT was defined as the mean of the maximal wall thickness at 12 points (near and far walls on both sides of S1, S2 and S3), (*i.e.*, c+d+e+f+g+h+ contralateral sides/12).

were classified into those with coronary lesions. Angiographic findings were recorded by observers (T. Ohtsuki and T. Masuyama) who were "blinded" to the carotid PlaS and IMT values and whose only involvement in the study was recording the angiograms.

Statistical analysis

All statistical analyses were performed with SPSS/Windows System, version 9.0J (SPSS Japan Inc, Tokyo, Japan). All descriptive data are expressed as mean ± SD. Values of age, PlaS and IMT indices were compared with the unpaired *t*-test and the percentage of males, hypertension, hypercholesterolemia, diabetes mellitus and smokers was compared with the χ^2 test between the patients with and without coronary lesions. The ability of PlaS and each IMT index to predict coronary atherosclerosis was examined by logistic regression analysis after adjustment for cardiovascular risk factors, followed by ROC curve analyses.

RESULTS

The baseline characteristics of patients are shown in Table 1. Cardiovascular risk factors were more prevalent and all indices of carotid atherosclerosis were higher in the patients with coronary lesions than in those without (Table 1). Additionally, the prevalence of coronary lesions was examined by quartile of PlaS and each IMT index (Fig. 2). The prevalence increased with increasing quartiles for each index.

To examine the contribution of PlaS and each IMT index to predict coronary lesions, we performed logistic regression analyses and computed the odds ratios associated with 1 SD difference in PlaS and each IMT. In univariate analyses, each 1 SD greater than PlaS, CCA-IMT, Bulb-ICA-IMT and combined IMT was associated with a 5.4-fold, 2.7-fold, 5.2-fold and 5.3-fold higher risk of coronary lesions, respectively (Table 2). After adjustments for cardiovascular risk factors, all indices remained independently associated with coronary lesions.

Given these results, the ability of PlaS and each IMT index to predict coronary lesions was further examined by ROC curve analyses (Fig. 3). The ROC areas for PlaS (0.82; 95%CI, 0.76 to 0.87), Bulb-ICA-IMT (0.81; 95%CI, 0.76 to 0.86) and combined IMT (0.81; 95%CI,

Table 1. Baseline characteristics of subjects

Subjects	Total	Coronary lesions (+)	Coronary lesions (−)	*p* value
Number	270	186	84	–
Age (years mean ± SD)	63.4 ± 9.4	64.2 ± 9.5	61.6 ± 8.9	0.03
Male (%)	70	77	52	<0.0001
Hypertension (%)	58	67	39	<0.0001
Diabetes mellitus (%)	30	39	10	<0.0001
Hypercholesterolemia (%)	51	59	36	0.0003
Smoking (%)	60	70	38	<0.0001
Plaque score (mean ± SD)	11.2 ± 9.6	14.1 ± 9.5	4.6 ± 5.9	<0.0001
CCA-IMT (mm) (mean ± SD)	1.01 ± 0.40	1.08 ± 0.44	0.84 ± 0.25	<0.0001
Bulb-ICA-IMT (mm) (mean ± SD)	1.30 ± 0.51	1.46 ± 0.51	0.95 ± 0.30	<0.0001
Combined IMT (mm) (mean ± SD)	1.20 ± 0.42	1.33 ± 0.42	0.92 ± 0.25	<0.0001

Age, plaque score and respective indices of IMT are compared with the unpaired *t*-test and percentage of males, hypertension, hypercholesterolemia, diabetes mellitus and smoking is compared with the χ^2 test between the subjects with and without coronary lesions (> 50% stenosis in diameter or occlusion in either of coronary arteries). CCA = common carotid artery; ICA = internal carotid artery; IMT = intima-media thickness.

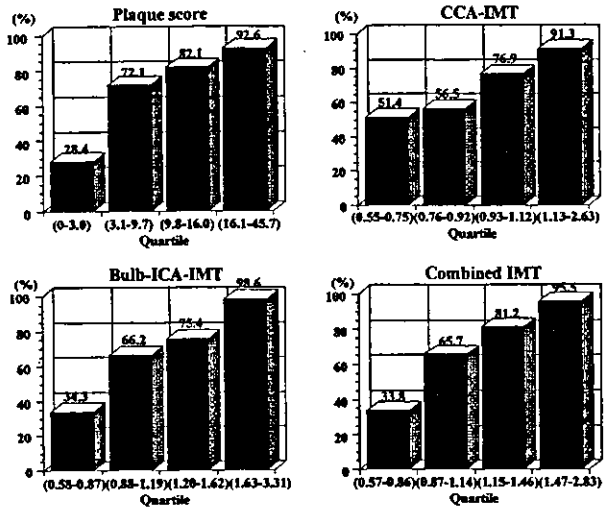

Fig. 2. Increasing frequency of coronary artery lesions according to quartile of plaque score and each IMT index.

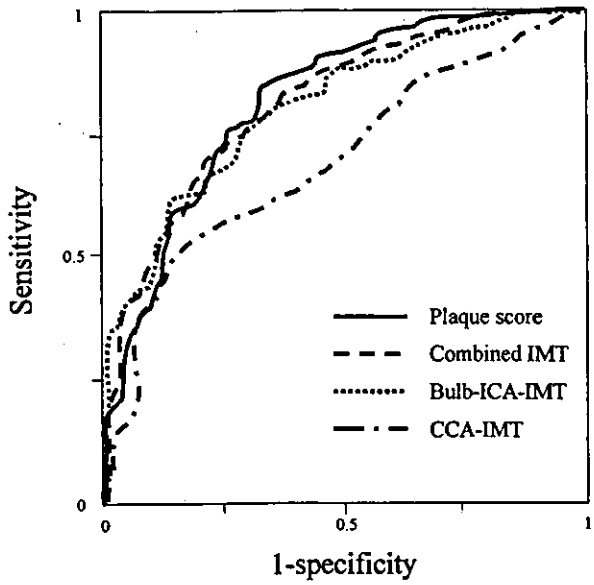

Fig. 3. ROC plots for use of plaque score and each IMT to predict the presence of coronary artery lesions. The areas under ROC curves for plaque score, Bulb-ICA-IMT and combined IMT were greater than those for CCA-IMT.

0.76 to 0.86) were greater than those for CCA-IMT (0.70; 95%CI 0.64 to 0.76).

DISCUSSION

Although we were aware that all indices of carotid atherosclerosis, PlaS and IMT indices, are associated with cardiovascular risk factors, we have shown that every index is a predictor of coronary lesions even after statistical adjustment for other risk factors. Previous studies examined the relation between B-mode US measurements of carotid atherosclerosis and coronary lesions. Craven et al. (1990) used the B-mode score, the sum of measurements of the maximum near and far wall thickness in the low common, high common, and low ICA on the left and right sides, and compared it between coronary patients and those who were not. They found the B-mode score to be strongly and independently associated with coronary artery disease in patients older than 50 years. Kallikazaros et al. (1999) also showed that carotid disease (lumen diameter stenosis of > 50%) was significantly correlated with severe coronary artery disease in patients with chest pain. In contrast, Adams et al. (1995) showed that CCA-IMT was only weakly associated with the severity of coronary atherosclerosis. However, there are no published data to indicate which index of carotid atherosclerosis with the B-mode is the most sensitive or specific for predicting coronary atherosclerosis.

Table 2. Odds ratio for coronary lesions as a function of a 1-SD difference in one of the indices of carotid atherosclerosis

	Relative Risk (95% CI)	
Variable	Unadjusted	Adjusted for age, gender and other risk factors*
Plaque score	5.42 (3.32–8.84)	4.54 (2.55–8.08)
CCA-IMT	2.71 (1.74–4.22)	2.03 (1.27–3.25)
Bulb-ICA-IMT	5.24 (3.27–8.38)	4.65 (2.63–8.23)
Combined IMT	5.25 (3.26–8.45)	4.94 (2.71–9.02)

*Other risk factors are hypertension, diabetes mellitus, hypercholesterolemia and smoking. CCA = common carotid artery; ICA = internal carotid artery; IMT = intima-media thickness; CI = confidence interval.

The present study suggested that both PlaS and IMT, indices including carotid bulb and ICA, are more strongly associated with coronary lesions than CCA-IMT. Furthermore, PlaS is at least as good a predictor of coronary atherosclerosis as carotid bulb to ICA IMT indices commonly used in large clinical trials such as CHS (O'Leary et al. 1991) and the ARIC study (Burke et al. 1995). Because focal plaques are more frequent in the carotid bulb and ICA, compared to CCA, it is likely that PlaS and carotid bulb to ICA IMT indices more directly reflect them than CCA-IMT.

The main limitation of this study was that the subjects were not population-based. It remains unclear whether or not PlaS is as good a predictor of coronary atherosclerosis in healthy individuals and in the patients without histories of cardiovascular events as IMT, which CHS and ARIC study groups used. Furthermore, it should be taken into account that more than 80% of patients in the present study showed atheromatous

plaques in the carotid arteries. PlaS may be an effective index to predict coronary lesions, especially in elderly patients with higher cardiovascular risk. However, in a healthy, middle-aged population, carotid atherosclerosis is generally minimal, but myocardial infarction could occur in those people. In that population, PlaS may have a low sensitivity and IMT measurement of diffuse intima-media thickening at CCA may be a better predictor of coronary lesions or events. Furthermore, CCA-IMT measurements are quicker, more accurate and more reproducible than PlaS and bulb-to-ICA IMT indices. It may be worthwhile to compare indices in terms of easiness to measure intra- and interobserver variabilities. It may be of interest, too, to investigate the possible superiority of indices extracted from 3-D scans. We should properly use the various indices of carotid atherosclerosis according to different groups of subjects.

SUMMARY

PlaS and mean value of maximal IMT in the CCA, carotid bulb and ICA are equally effective and could be better indices than CCA-IMT to predict coronary atherosclerosis. The plaque-scoring system such as PlaS may be one of the best indices to screen individuals with coronary atherosclerosis when patients with several risk factors are managed in the hospital.

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● *Original Contribution*

EFFECTS OF ALDEHYDE DEHYDROGENASE GENOTYPES ON CAROTID ATHEROSCLEROSIS

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Abstract—Atherosclerotic diseases are thought to be less frequent in Asians compared with Caucasians. Unlike Caucasians, nearly half of Asians have a functional deficiency in the low K_m aldehyde dehydrogenase (ALDH2), a key enzyme in alcohol metabolism, which potentially modifies the prevalence of atherosclerosis. This study examined the associations between *ALDH2* genotypes ("typical homo," "hetero" or "atypical homo") and carotid atherosclerosis in 304 Japanese patients. As a measure of carotid atherosclerosis, plaque score (PS) was evaluated by B-mode ultrasonography. Age- and sex-adjusted PS was lower in "atypical homo" genotype patients (2.7 ± 1.2 [mean ± standard error], $n = 21$) ($p < 0.05$) and tended to be lower in "hetero" patients (4.5 ± 0.5, $n = 116$) ($p = 0.07$) compared with "typical homo" patients (5.7 ± 0.4, $n = 167$). When we controlled for traditional cardiovascular risk factors and alcohol intake, the "atypical homo" genotype was found to be associated with lower PS ($\beta = -0.13$, $p < 0.05$). Based on these findings, the *ALDH2* genotypes seem to be associated with the severity of carotid atherosclerosis, potentially modifying the prevalence of atherosclerosis in Asians. (E-mail: kitagawa@medone.med.osaka-u.ac.jp) © **2003 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Alcohol, Atherosclerosis, Carotid arteries, Ultrasound.**

INTRODUCTION

Atherosclerotic diseases are thought to be less frequent in Asians than in Caucasians, which is often attributed to differences in their dietary habits. Additionally, congenital factors have been identified that may promote or inhibit the process of atherosclerosis (Scheuner 2001, Stein et al. 2002), including gene polymorphisms of apolipoprotein E (de Andrade et al. 1995, Horejsi and Ceska 2000), thrombomodulin (Li et al. 2001) and alcohol dehydrogenase type 3 (Hines et al. 2001). Thus, underlying genetic factors could also contribute to the racial differences in prevalence of atherosclerotic diseases.

The low K_m aldehyde dehydrogenase (ALDH2) is one of the key enzymes in alcohol metabolism whose genotype composition is markedly different between Asians and Caucasians. Unlike Caucasians, nearly half of Asians (Japanese, Han Chinese and Korean) have a single point mutation in exon 12 of the *ALDH2* gene (Harada et al. 1981, Hsu et al. 1985), resulting in a functional deficiency in alcohol metabolism (Harada et al. 1981, Takeshita et al. 1993). Because alcohol intake can be both harmful and beneficial for the cardiovascular system (Bo et al. 2001, Demirovic et al. 1993, Kiechl et al. 1994), heterogeneity of *ALDH2* genotypes could potentially modify the prevalence of atherosclerotic diseases in Asians. To date, little effort has been devoted to elucidating the effects of *ALDH2* genotypes in the evolution of atherosclerosis.

Here, we investigated whether *ALDH2* genotypes are associated with an ultrasonographic parameter of carotid atherosclerosis.

MATERIALS AND METHODS

Subjects

The subjects for this investigation were enrolled from among patients of the Department of Internal Medicine and Therapeutics at Osaka University Hospital who

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had undergone carotid ultrasonography and given consent for *ALDH2* genotype analyses between September 1997 and May 1999. The majority of those had been referred from other hospitals or departments, for the assessment of cerebral circulation or for perioperative risk assessment before surgery. Because of the high prevalence of cardiovascular risk factors in such patients, carotid ultrasonography was performed for the screening of carotid atherosclerosis and stenosis or, in some cases, for the assessment of vertebral artery circulation.

During the study period, carotid ultrasonography was performed on approximately 400 patients and 345 of those consented to *ALDH2* genotype analyses. However, because we focused on unmodified atherosclerosis, we excluded patients who had carotid endarterectomy or collagen diseases, including Takayasu's and other arteritis. After exclusion of 41 patients with such criteria, the subjects for this study were 304 Japanese patients (age, 63.6 ± 9.5 years [mean ± standard deviation]), comprising 161 men and 143 women.

This study was approved by the Osaka University Institutional Review Board and written informed consent was obtained from all subjects after the purposes and procedures had been explained. Also, the investigation conforms with the principles outlined in the Declaration of Helsinki.

Carotid ultrasonography

Duplex carotid ultrasonography was performed with a linear array 7.5-MHz transducer (EUB-525, Hitachi, Inc., Tokyo, Japan). In accordance with our prior studies (Hashimoto et al. 2001, Nagai et al. 2001), the plaque score (PS) was used as a measure for carotid atherosclerosis.

Briefly, the subject lay in the supine position in a dark room and the examinations were done with the head held in the midline position or slightly tilted to either side. Initially, the common and internal carotid arteries were scanned cross-sectionally and longitudinally, whereby distributions of atherosclerotic plaques, as defined by local increases in intima-media thickness of 1.1 mm, were roughly evaluated. During the initial scanning, optimal insonation angles were determined for the estimation of respective plaque heights and the measurements were performed on the frozen frame, perpendicular to the vascular walls. Bilateral carotid arteries were examined following the same procedures. Thereafter, PS was computed by summing the maximum thickness of all plaques located in bilateral carotid arteries (Fig. 1). Length of individual plaques was not considered for the calculation of this score.

All measurements were performed by the stroke neurologists/cardiologists of our department, who were unaware of the patients' clinical details. In our prior study (Nagai et al. 2001), the interrater correlation of PS was 0.86 (n = 65), with similar averages between observers.

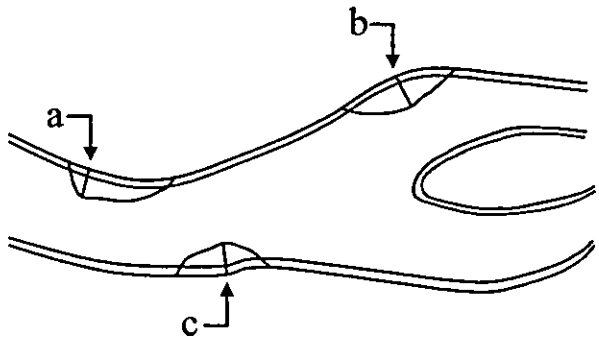

Fig. 1. Calculation of the plaque score (PS) is computed by summing the maximum thickness (in mm) of each plaque located in bilateral carotid arteries, where it is defined to be a dimensionless number (*i.e.*, PS = a + b + c + contralateral plaques).

Determination of ALDH2 *genotypes*

Blood samples were drawn from the antecubital vein of seated patients. DNA was extracted from 100 mL of white blood cell–rich plasma with a QIAamp DNA Blood kit (Qiagen Inc., Valencia, CA, USA). *ALDH2* genotypes were determined as "typical homo" (*ALDH2*1/*1*), "hetero" (*ALDH2*1/*2*) or "atypical homo" (*ALDH2*2/*2*), as previously described (Takeshita et al. 1994). Briefly, exon 12 of the *ALDH2* gene was amplified by a 10-min preincubation at 95°C and subsequently by 30 to 35 cycles of polymerase chain reaction (1 min at 94°C, 10 s at 52°C and 30 s at 72°C). One amplification primer contained a base substitution to create a Ksp632I (Roche Diagnostics, Mannheim, Germany) recognition site in the typical allele. Polymerase chain reaction products were incubated with 2 to 3 units of Ksp632I at 37°C for 3 to 6 h. Digested samples were resolved by electrophoresis.

Data analyses

Carotid PS, cardiovascular risk factors and alcohol intake were compared by respective *ALDH2* genotypes with the use of one-way analysis of variance, followed by Bonferroni multiple comparison tests. Subsequently, intergroup differences in PS were further examined by adjusting for age and sex. Finally, associations of PS with cardiovascular risk factors, *ALDH2* genotypes and alcohol intake were examined by multiple linear regression analyses, with "typical homo" genotype taken as the reference to "hetero" or "atypical homo." Cardiovascular risk factors considered in this study were age, male sex, hypertension (casual blood pressure 140/90 mmHg, or on

Table 1. Baseline characteristics by *ALDH2* genotypes

	"Typical homo"	"Hetero"	"Atypical homo"
n	167	116	21
Age (y)	63 ± 10	65 ± 8	64 ± 10
Sex (% men)	57	50	33
Hypertension (%)	75	66	57
Hyperlipidemia (%)	41	49	67
Diabetes mellitus (%)	19	20	10
Smoking (%)	38	30	24
Alcohol intake (drink/d)	0.60 ± 0.74	0.21 ± 0.43*	0.01 ± 0.06*
Plaque score	5.6 ± 6.6	4.6 ± 5.2	2.2 ± 2.1*

ALDH2 = low Km aldehyde dehydrogenase; "Typical homo" = *ALDH2*1/*1*; "Hetero" = *ALDH2*1/*2*; "Atypical homo" = *ALDH2*2/*2*.
*$p < 0.05$ *vs.* "Typical homo" group.

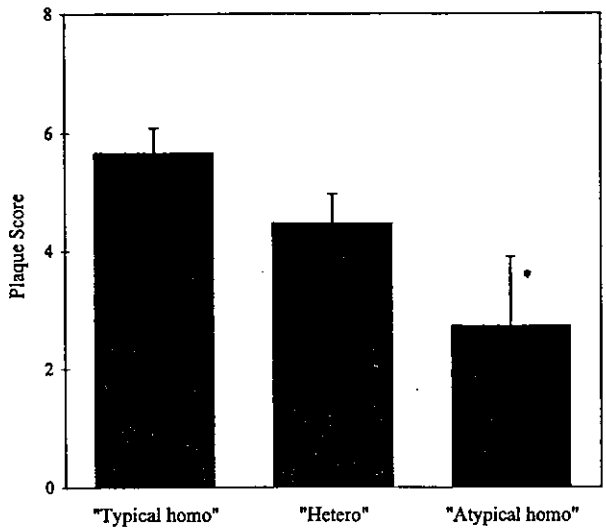

Fig. 2. Age- and sex-adjusted plaque score in respective *ALDH2* genotype patients. *ALDH2*: low K_m aldehyde dehydrogenase. See footnote of Table 1 for group definitions. Error bars indicate standard errors after adjustments for age and sex. *$p < 0.05$ *vs.* "Typical homo" group.

medication), hyperlipidemia (total cholesterol 220 mg/dL, or on medication), diabetes mellitus (HbA1c > 5.8%, or on medication) and smoking. Smoking was defined by current smoking 10 cigarettes per day or past smoking 400 cigarette-years, based on self-reports. Similarly, mean alcohol intake was calculated as the number of alcoholic beverages consumed per day during the preceding several months, multiplied by the amount of alcohol in each beverage. Specifically, 355 mL of regular beer, 118 mL of wine, 44 mL of 80-proof distilled spirits and 113 mL of Japanese rice wine sake contain the same amount of alcohol and were regarded as one "drink" equivalent. Because the study sample comprised patients of our department, they included no heavy drinkers as defined by Sacco et al. (1999). Also, almost no patients were drinking hard liquor.

Data are presented as mean ± standard deviation unless otherwise specified and a two-tailed p value < 0.05 was considered to be statistically significant. All analyses were performed with the use of SPSS 9.0 (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Baseline characteristics

ALDH2 genotypes were found to be "typical homo" in 167 patients (55%), "hetero" in 116 patients (38%) and "atypical homo" in 21 patients (7%). Table 1 summarizes their baseline characteristics stratified by respective genotypes. Prevalence of traditional cardiovascular risk factors was generally high in each group, with no significant differences between the groups. Although alcohol intake was low in all groups, it was less in "hetero" and "atypical homo" patients than in those with "typical homo."

As a measure for carotid atherosclerosis, PS was lower in "atypical homo" patients and tended to be lower in "hetero" patients than in "typical homo" patients. Of note, adjustments for age and sex modified the magnitudes of PS minimally and the difference found between "atypical homo" and "typical homo" patients persisted (Fig. 2).

Associations of carotid atherosclerosis with cardiovascular risk factors, ALDH2 *genotypes and alcohol intake*

Because of the high prevalence of cardiovascular risk factors, the magnitudes of PS might be modified by such risk factors. By univariate regression analyses, PS was linearly associated with age ($r = 0.35$, $p < 0.001$) and was higher in men than in women (6.4 ± 6.9 *vs.* 3.4 ± 4.2, $p < 0.001$). Also, PS was higher in patients with hypertension, diabetes or smoking than in those not (hypertension: 5.7 ± 6.3 *vs.* 3.5 ± 4.7, diabetes: 7.8 ± 6.2 *vs.* 4.4 ± 5.7, smoking: 7.4 ± 6.9 *vs.* 3.8 ± 5.0, all $p < 0.01$). Additionally, PS did not have significant associations with alcohol intake ($r = 0.10$, P = NS), even when quadratic, cubic and exponential terms were examined.

Further to examine the link of PS with cardiovascular risk factors and *ALDH2* genotypes, multiple linear regression analyses were performed (Table 2). When PS was regressed on traditional cardiovascular risk factors (model 1), age, male sex, hypertension, diabetes and smoking were independently associated with higher PS. When *ALDH2* genotypes were included in the model (model 2), the "atypical homo" genotype was found to be associated with lower PS ($\beta = -0.11$, $p < 0.05$), little

Table 2. Associations of plaque score with cardiovascular risk factors and *ALDH2* genotypes

	Model 1	Model 2	Model 3
Age	0.31*	0.32*	0.32*
Sex (men = 1)	0.14*	0.13*	0.16*
Hypertension	0.16*	0.14*	0.15*
Hyperlipidemia	0.09	0.11*	0.11*
Diabetes mellitus	0.12*	0.11*	0.10
Smoking	0.21*	0.20*	0.23*
"Hetero"		−0.08	−0.10
"Atypical homo"		−0.11*	−0.13*
Alcohol intake			−0.09
(model r2)	(0.26)	(0.27)	(0.28)

ALDH2 = low Km aldehyde dehydrogenase; "Hetero" = *ALDH2*1/*2*; "Atypical homo" = *ALDH2*2/*2*. %Values represent standardized regression coefficients. "Hetero" and "Atypical homo" genotypes did not have interactions with alcohol intake and other regressors.
*$p < 0.05$.

modifying the associations between PS and cardiovascular risk factors. When alcohol intake was additionally included in the model (model 3), the association between "atypical homo" and PS remained significant ($\beta = -0.13$, $p < 0.05$). No interactions were observed between *ALDH2* genotypes and alcohol intake.

DISCUSSION AND CONCLUSIONS

Proportions of respective *ALDH2* genotypes were in agreement with other studies derived from the Asian populations (Goedde et al. 1992, Takeshita et al. 1994). Because the study sample comprised patients of our department, prevalence of cardiovascular risk factors was high and alcohol intake was low in all genotype patients (Table 1). Of note, compared with "typical homo" patients, alcohol intake was less in "hetero" and "atypical homo" patients, probably owing to intolerance to alcohol. As a measure of carotid atherosclerosis, PS was lower in "atypical homo" patients and tended to be lower in "hetero" patients than in "typical homo" patients, with the relationships little modified when age and sex were adjusted (Fig. 2). These findings are consistent with lesser severity of atherosclerosis in patients with *ALDH2* mutations compared with those with the wild type.

For the better understanding of relationships between carotid atherosclerosis and *ALDH2* genotypes, influence of other factors might need to be considered. Particularly, given the high prevalence of cardiovascular risk factors in patients with each genotype, intergroup differences in PS might be modified by such risk factors. Indeed, PS increased with age and was higher in men and in patients with hypertension, diabetes or smoking, suggesting associations between carotid atherosclerosis and cardiovascular risk factors. Additionally, despite cardiovascular protective effects of alcohol reported for Caucasians (Berger et al. 1999, Sacco et al. 1999), PS did not have significant associations with alcohol intake in the current study. This result was not unexpected, because cardiovascular protective effects of alcohol, even if they exist, are only modest compared with the risk induced by other risk factors (Bogousslavsky et al. 1990, Thun et al. 1997).

Further to examine associations of PS with cardiovascular risk factors and *ALDH2* genotypes, multiple regression analysis was performed (Table 2). In the model including only traditional cardiovascular risk factors, age, male sex, hypertension, diabetes and smoking were independently associated with higher PS (model 1), supporting associations between carotid atherosclerosis and such risk factors. When *ALDH2* genotypes were included in the model (model 2), "atypical homo" genotype was found to be associated with lower PS, suggesting its atheroprotective effects. Moreover, inclusion of *ALDH2* genotypes little modified the associations between PS and cardiovascular risk factors, which implies that the effects are essentially independent of such risk factors. When alcohol intake was added to the model (model 3), "atypical homo" genotype remained significantly associated with lower PS, further supporting its atheroprotective effects. On the basis of these findings, heterogeneity of *ALDH2* genotypes might be associated with the severity of carotid atherosclerosis. Particularly, the "atypical homo" *ALDH2* genotype seems to confer a resistance to atherosclerosis, potentially contributing to the less prevalent atherosclerotic diseases in Asians. To our knowledge, this is the first study that has suggested the associations between *ALDH2* genotypes and severity of carotid atherosclerosis. However, the mechanism to explain such associations is not clear from the data presented. Although cardiovascular protective effects of light-to-moderate drinking have been reported for Caucasians (Bo et al. 2001, Kiechl et al. 1994), alcohol intake was very low and less in "atypical homo" patients than in those with "typical homo" (Table 1). Accordingly, the associations might not be explicable on the basis of alcohol intake, and further studies are required to determine whether "atypical homo" genotype *per se* has atheroprotective effects or whether the effects are induced by other incidental factors.

Certain limitations exist for the current study. First, because of the high prevalence of cardiovascular risk factors in our study subjects (sample bias), the results of this study cannot be directly transferred to the general population. Second, because alcohol intake was generally low in all genotype patients, our statistical power was limited to examine its effects and interactions with *ALDH2* genotypes. Finally, although we realize the importance of duration and severity of cardiovascular risk

factors, we defined them as dichotomous variables, potentially diluting their influence on carotid atherosclerosis. Taken together, further studies are still necessary to separate the effects of *ALDH2* genotypes, alcohol and cardiovascular risk factors in the evolution of carotid atherosclerosis.

In summary, we have demonstrated associations between *ALDH2* genotypes and severity of carotid atherosclerosis in Japanese patients. Particularly, "atypical homo" *ALDH2* genotype seems to confer a resistance to atherosclerosis, potentially contributing to the less prevalent atherosclerotic diseases in Asians, compared with Caucasians.

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Top Journal Up To Date

低輝度頸動脈プラークは将来の脳卒中発症を予測する

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Gronholdt ML *et al*：Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* **104**：68-73, 2001

背景/目的 高度の頸動脈狭窄を有し症候性脳血管障害の既往のある患者に対しては，1例の脳卒中発症を予防するために7件以上の予防的頸動脈内膜剥離術（CEA）が必要とされ，無症候性の患者に対しては20件以上の手術が必要となる[1]．75％未満の頸動脈狭窄に関連する脳血管イベントはatheroembolicなものが多いため，非侵襲的にruptureを起こしやすいプラークを検出し，選択的に手術をおこなえば手術成績が向上することが予測される．超音波検査上の低輝度のプラークはlipid rich coreをもつといわれ，B-mode上の低輝度プラークは神経学的イベントと関連すると報告[2]されている．今回は症候性患者と無症候性患者に分けて50％以上の頸動脈狭窄を呈する低輝度プラークが脳卒中の発症に関連するかどうかのprospectiveな検討をおこなった．

方法 1994年から1996年までのあいだにCopenhagen University Hospitalにて頸動脈超音波検査を施行した1,556例から，頸動脈に50％以上の狭窄をもつ連続246例を対象とした．以前に狭窄と同側半球の脳卒中，TIA，または一過性黒内障（AF）を生じた既往のある症例を症候性群（135例）とし，狭窄はあるがこれらの既往のないものを無症候性群（111例）とした．両側内頸動脈閉塞，神経症状が重篤なもの，致死的な悪性腫瘍，重度痴呆，CEAのフォローアップ目的のものは除外した．

S-VHSにて記録した頸動脈超音波画像を取り込み，Windows用Image-Pro Plus ver.1.2.01を用いて，プラーク，血液，血管外膜の輪郭を描画し，内部のピクセルよりmedian gray-scale valueを計算し，血液が0，血管外膜が190になるよう線形補正をおこなった．プラークの輝度は74未満を低輝度，74以上を高輝度とした．Doppler上，収縮期流速が120cm/sec以上を50％以上狭窄とし，拡張期流速が135cm/sec以上を80％以上狭窄とした[3]．

6ヵ月ごとの診察もしくは電話による聞き取り調査をおこない，1次エンドポイントを同側脳梗塞発症，2次エンドポイントを同側TIA/AFの発症，3次エンドポイントを心血管イベントと死亡として解析した．

結果 平均4.4年間（3.0～5.8）で，同側脳梗塞44人，同側TIA/AF 35人，心血管イベント36人，死亡64人を生じた．17人にCEAが施行された．全体としては低輝度群のほうが高輝度群より有意に狭窄と同側の脳梗塞を生じた（log-rank $P=0.02$）が，内訳では症候性群では有意（log-rank $P=0.005$，4.4年間で29％ vs. 12％）で，無症候性群では有意差はなかった（$P=0.85$）．年齢補正回帰分析では，症候性群の患者で，高輝度群に対しての低輝度群のリスクは3.1倍（95％CI, 1.3-7.3）であった．

80～99％狭窄は50～79％狭窄より同側脳梗塞発症頻度が高い傾向にあった（有意差なし）．プラーク輝度と狭窄率はいずれも，同側のTIA/AF，心血管イベント，死亡率との関連は認めなかった．

症候性群において，高輝度50～79％狭窄に対する，高輝度80～99％狭窄，低輝度50～79％狭窄，低輝度80～99％狭窄の患者の相対危険度はそれぞれ3.1，4.2，

表❶ 頸動脈プラーク輝度と狭窄度の同側脳梗塞に与える相対危険率

患者	輝度	狭窄度，%	患者数，n	相対危険率（95% CI）	4.4年間の絶対危険率，%	絶対危険率の増加度，%
全体（n＝246）	高輝度	50～79	77	1	12	
	高輝度	80～99	31	1.1（0.3～3.6）	13	1
	低輝度	50～79	96	1.7（0.8～3.8）	20	8
	低輝度	80～99	42	3.1（1.3～7.4）	29	17
無症候性	高輝度	50～79	38	1	16	
（n＝111）	高輝度	80～99	10	0	0	-16
	低輝度	50～79	43	0.6（0.2～1.8）	12	-4
	低輝度	80～99	20	1.4（0.4～4.9）	20	4
症候性	高輝度	50～79	39	1	8	
（n＝135）	高輝度	80～99	21	3.1（0.7～14）	19	11
	低輝度	50～79	53	4.2（1.2～15）	26	18
	低輝度	80～99	22	7.9（2.1～30）	36	28

相対危険率は年齢補正Cox回帰分析による．低輝度は gray scale median < 74，高輝度は gray scale median ≧ 74

7.9で絶対危険増加率は11％，18％，28％であった．無症候性群においてはリスクの増加はみられなかった．

考察

症候性群において，客観的に評価された低輝度プラークが高輝度プラークに対して同側の脳梗塞発症危険率が3.1倍であった．とくに低輝度の80～99％狭窄については高輝度50～79％狭窄と比較して約8倍のリスクがある．以前より50％以上の狭窄をもつ症例へのCEAの有用性は確立されているが，今回の客観的プラーク輝度評価は脳卒中発症リスクの評価において，部分的ではあるが有用であるものと思われる．狭窄をもつ症候性の患者に対して，今回のコンピュータを用いた輝度評価を追加することで，より適切なCEA施行症例の選択に役立つものと思われる．

コメント

頸動脈超音波検査における低輝度プラークの脳卒中発症リスクについては近年多くの報告がなされている．無症候の4,886人を対象とした研究[2]で低輝度プラークの相対危険度は2.5（95％CI, 1.4-4.5），他のリスクファクターで補正すると1.7（P＝0.015）と有意に高いリスクをもつとされる．同研究での50％以上の狭窄の相対危険度は2.3（P＝0.004）である．また，別の報告[4]では約19％の症例で狭窄度の増悪が生じ，低輝度プラークによる狭窄は有意に進行しやすく（P＝0.02），神経学的イベントを生じやすい（P＝0.01）としている．本研究においては無症候性群でのリスクが有意でなかったが，全体の症例数が少ないためである可能性がある．低輝度プラークの評価については現在のところ主観的な半定量的評価が一般に用いられている．冒頭でも述べられているように，脳卒中予防のためのCEAは有益ではあるものの全体では効率が悪く，術中の合併症の危険もある．本研究の手法がさらに進歩すれば，プラーク局所の更なる詳細な情報が得られ，CEA適応症例のより適切な選別が可能になると期待される．なお，本研究では狭窄度の評価にDoppler上の血流速を用いているが，一般的ではなく，CEAの適応決定に際してよく用いられているNASCET[5]やECST[6]での狭窄度評価法を用いておれば，より対応づけが明確になったものと思われる．

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特集／降圧薬の正しい使い方

特殊な病態における降圧薬の使い方

脳血管障害・痴呆

松本昌泰

はじめに

高血圧は洋の東西を問わず脳血管障害の最大の危険因子であり，我国では高血圧の標的臓器障害の中でも脳血管障害の頻度が最も高い。また，近年の脳卒中急性期治療法の進歩や致死的な脳出血の減少に伴い脳卒中の死亡率は著減しているが，なお死因の第3位を占め，その発症率や罹病率は人口構造の高齢化の進行によりむしろ増加しつつある。このような脳血管障害罹病者の増加は本邦のみならず欧米先進諸国でも保健衛生上の問題となっており，米国では世界に先駆けて脳卒中予防ガイドラインを作成，発表しているが[1)2)]，ここでも高血圧のコントロールがその筆頭に掲げられている。

また，高齢高血圧患者では無症候性脳血管障害を合併する頻度も多く，脳卒中や脳血管性痴呆の予備軍としても注目されている。さらに，最近欧米で実施された高齢高血圧患者を対象とした大規模臨床試験では降圧療法により脳卒中のみならず脳血管性痴呆やアルツハイマー型痴呆の発症をも抑制しうる可能性が示唆されており注目を集めている。

本稿では，まず脳血管障害の主な病型と高血圧との関係を整理し，脳卒中の一次・二次予防における降圧療法の意義について解説するとともに，降圧療法による痴呆発症抑制の可能性についても論じる。

Ⅰ．脳血管障害の分類と高血圧

脳血管障害は多様な病態の総称であり，高血圧との関係を論じる際には，本来病型ごとに区別して考えなければならない。以下には，米国NINDSによる脳血管障害の分類[3)]にそって，その高血圧との関連を論ずる。

1．無症候性脳血管障害

CT，MRIなどの画像診断技術の進歩により，高頻度に診断されるようになった病態である[4)]。日米ともに1990年に発表された脳血管障害の分類(NINDSⅢおよび厚生省委託平井班による分類)で初めて診断名として登場している。ただし，本邦における診断名はこの時点では無症候性脳梗塞のみに限られており，今日では，1997年に発表された無症候性脳血管障害の診断基準(厚生省委託澤田班)が用いられている。無症候性脳血管障害には画像診断により脳実質病変または脳血管病変を認めるものが，区別されているが，高血圧との関連で最も注目を集めているのが，前者の大部分を占める無症候性脳梗塞である。無症候性脳梗塞の殆どはラクナ梗塞と同様の小梗塞であり，高血圧や加齢が最大の危険因子となる小血管病(small vessel disease)と考えられている。なかでも，血圧日内変動パターンとの関係が注目を集めており，夜間も高血圧状態が持続するnon-dipper型や夜間に高度の血圧低下を示すextreme dipper型で高頻度に見出されることが明らかとされている。ただし，無症候性脳梗塞にも，心原性脳梗塞やアテローム血栓性脳梗塞と同様な病態と考えられる症例も少なからず報告されており，そのコントロールに際しては，症候性脳梗塞と同様にその発症要因をできるだけ究明して対処することが望まれる。

2．一過性脳虚血発作(TIA)

明らかな脳の局所神経症状が発現し，24時間以内に完全に消失するものと定義されている。ただし通常は，数分から数10分以内に症状が完全消失し，長くても1時間以内に良くなる場合が大部分である。通常，頚動脈分岐部のアテローム動脈硬化病変に形成された壁在性血栓が剥離して微小塞栓として脳動脈を一過性に閉塞し，発症する(微小塞栓機序)。ただし，高度の狭窄や閉塞による潜在的な脳血流不全状態がある時に，脱水や血圧低下などにより，一過性に血流不全状態が強くなり症状を発現することもある(血行力学機序)。いずれにしても，原則的

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に大血管病 (large vessel disease) に属する病態と考えられ，高血圧の本病態への直接的関与は少ない。ただし，患者の訴える一過性の症状のみが診断の根拠となっているため，ラクナ梗塞の発症頻度の高い本邦では，これまでの TIA の診断に軽症のラクナ梗塞が含まれていた可能性が高く，高血圧の関与が大きい small vessel disease としての側面にも留意を要する。

3. 脳　梗　塞

心原性脳塞栓症，アテローム血栓性脳梗塞，ラクナ梗塞の3病型に分けられる。高血圧が危険因子となるのは後2者であり，アテローム血栓性脳梗塞は頭蓋内・外の比較的大きな動脈のアテローム硬化病変を原因とし，脳梗塞の約30%を占める。一方，ラクナ梗塞は，脳深部や脳幹を灌流する小動脈（穿通枝）の病変を基盤とした血栓性閉塞により，ラクナ症候群を呈し，脳梗塞の30～40%を占める。前者は large vessel disease，後者は small vessel disease の病態とされ，後者では高血圧の関与が最も大きく，前者では高血圧に加えて，糖尿病，高脂血症などのアテローム性動脈硬化の危険因子の関与が大きい。

4. 脳　出　血

高血圧性と非高血圧性に大別され，前者は好発部位により被殻出血，視床出血，橋出血，小脳出血，皮質・皮質下出血に分けられ，後者は原因疾患（動静脈奇形，アミロイドアンギオパチーなど）により分けられ好発部位もそれぞれ異なる。高血圧性脳出血では，高血圧の持続による穿通枝動脈の類線維素性壊死による微小動脈瘤の形成があり，これに血圧上昇が加わり発症すると考えられている。small vessel disease に属する病態であり，脳出血に至らなかった例がラクナ梗塞を発症することも多いと考えられている。ただし，非高血圧性脳出血ではその発症に血圧の関与が殆ど無いことに留意を要する。

5. 高血圧性脳症

脳循環の自動調節能（図1）の上限値 (breakthrough point) を超える高血圧状態により，急性または亜急性に発症する意識障害（傾眠，昏迷など），頭痛，視覚障害，痙攣などを来たす状態をいう。適切な治療が実施されない場合は脳出血や昏睡状態を来たし，死に至る場合もある。その病態の詳細はなお充分には解明されていないが，高度の高血圧により脳血管内皮細胞の機能不全が招来され，血液・脳関門 (BBB) の破綻による透過性亢進や，浮腫，微小出血などの形成に至ると考えられている[6]。MRI (T2 強調画像) などの画像診断により頭頂・後頭葉領域の白質に可逆性の病変が捉えられることが多く，より包括的な診断名である hypertensive reversible posterior leukoencephalopathy syndrome (PLS) もよく用いられるようになってきている。なぜ，この部分に病変が好発するのかについては，現在のところ明確な答えはないが，この領域の血管周囲の交感神経終末が少なく，breakthrough point が他領域に比し低値となりやすいためではないかと考えられている。

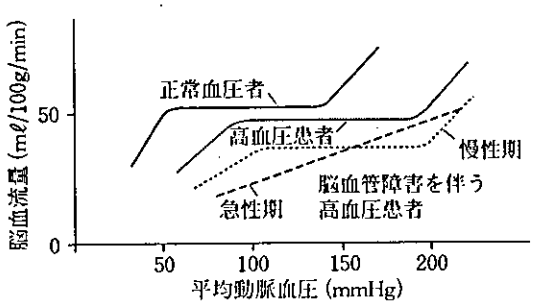

図 1　脳血流の自動調節能の変化（文献5より引用）

6. 脳血管性痴呆

脳血管障害が原因となって生じる痴呆を総称して脳血管性痴呆という。診断基準については各種のものが提唱されているが，わが国で高頻度にみられる脳血管性痴呆の診断には California ADDTC による診断基準[7]が有用である。また，脳血管性痴呆は各種病型に分類 (ICD-10) されているが，これらの内，本邦では大脳皮質の多発性梗塞による多発梗塞性痴呆は少なく，大脳皮質下性痴呆である Binswanger 型や多発性皮質下梗塞型などの小血管病変に伴う痴呆 (small vessel disease with dementia) が多くみられる。多発梗塞性痴呆は心原性脳塞栓症やアテローム血栓性脳梗塞により，大脳皮質を含む多発性脳梗塞を生じ痴呆の発症に至る皮質性痴呆であり，虚血性神経症候と痴呆発症との関連が明らかである。一方，Binswanger 型痴呆は病理学的に大脳白質の広範な脱髄，皮質下の多発ラクナ，白質や深部の小動脈硬化を特徴とし，CT や MRI (T2 強調画像) 上 leukoaraiosis と総称される PVL (periventricular lucency) や PVH (periventricular hyperintensity) などの特徴的所見を呈する。痴呆症候としては，意欲・自発性低下などの前頭葉性痴呆の病像をとることが多く，特徴的な歩行障害や尿失禁も見られる。また，多発性皮質下梗塞型痴呆は白質や基底核，視床に多発するラクナを有し，小歩症，筋強剛などのパーキンソニズム，仮性球麻痺，感情失禁などの神経症状を合併することが多い。画像診断上は，多発

性ラクナが存在し顕著な leukoaraiosis を認めないことで Binswanger 型痴呆と区別される。small vessel disease with dementia は高血圧との関わりが大きく，その発症抑制のためには，軽度な認知機能障害の存在が報告されている無症候性脳梗塞の段階で適切な降圧療法などによりその進展を阻止する必要がある。

Ⅱ．脳卒中および痴呆発症の予防と降圧療法

脳卒中の発症が高血圧治療により抑制できることは，既に各種の大規模臨床試験により確認されている[8]。主に成壮年者軽・中等症高血圧を対象とした臨床試験（VA，VA-NHLBI，USPHS，Oslo，ANBPS，MRC 研究など）では，メタアナリシスにより収縮期血圧を10mmHg，拡張期血圧を5～6 mmHg 下降させると脳血管障害の発症を約40％抑制できることが判明しており，ほぼ疫学データより期待される効果が確認されている。また，脳血管障害を発症しやすい老年者高血圧患者を対象とした大規模臨床試験（EWPHE，STOP-Hypertension，MRC，SHEP，MRC，Syst-Eur，Syst-China，STONE，INSIGHT，NICS-EH 研究など）の結果も報告されており，メタアナリシスにより収縮期血圧を12～14mmHg，拡張期血圧を5～6 mmHg 下降させると脳血管障害の発症を34％減少させ得ることが報告されている。すなわち，脳梗塞を含む脳血管障害の1次予防に関しては，上記の臨床試験により降圧薬療法の有効性は実証されている。また，Blood Pressure Lowering Treatment Trialists' Collaboration によるメタアナリシス[9]では，長時間作用型の Ca 拮抗薬や ACE 阻害薬が降圧利尿薬やβ遮断薬などの従来の降圧薬に勝るとも劣らない脳心血管疾患抑制効果があることを示すとともに，特に脳卒中予防に関しては従来の降圧薬に比し Ca 拮抗薬が優位に優れる（相対危険度を13％低下させる）ことが実証されている（図2）。このメタアナリシスでは ACE 阻害薬が脳卒中について特に優れた効果を示すとの結果は得られていないが，最近報告された HOPE 試験[10]，LIFE 試験[11]，SCOPE 試験[12]などの結果によれば ACE 阻害薬や AⅡ受容体拮抗薬には有意な脳卒中発症抑制効果が示されており，脳卒中抑制におけるクラス効果はレニンアンジオテンシン系阻害薬についてもエビデンスの集積により明らかになると思われる。

また，欧米における各種の追跡観察研究[13)－15)]の結果から，高血圧が痴呆発症の危険因子とされ，降圧療法による痴呆発症抑制効果が以前より期待されていた。事実，高齢者高血圧患者を対象として利尿薬やβ遮断薬を用いた大規模臨床試験（SHEP 試験[16]，MRC 試験[17]など）により降圧による痴呆発症抑制に関する検討も実施されたが，これらの降圧薬による痴呆発症抑制効果は証明されるには至らなかった。しかしながら，その後に実施された Ca 拮抗薬を用いた Syst-Eur 試験[18]（図3）や最近の ACE 阻害薬，AⅡ受容体拮抗薬などを用いた臨床試験（HOPE 試験，SCOPE 試験など）では脳卒中発症の有無にかかわらず認知機能障害の発現や進展を有意に抑制する効果も報告されており，脳血管障害や痴呆症の激増が予想されている高齢化社会において，極めて有用な降圧薬になるものと思われる。

Ⅲ．脳卒中急性期の降圧療法

脳血管障害急性期（発症後2週以内）には病型を

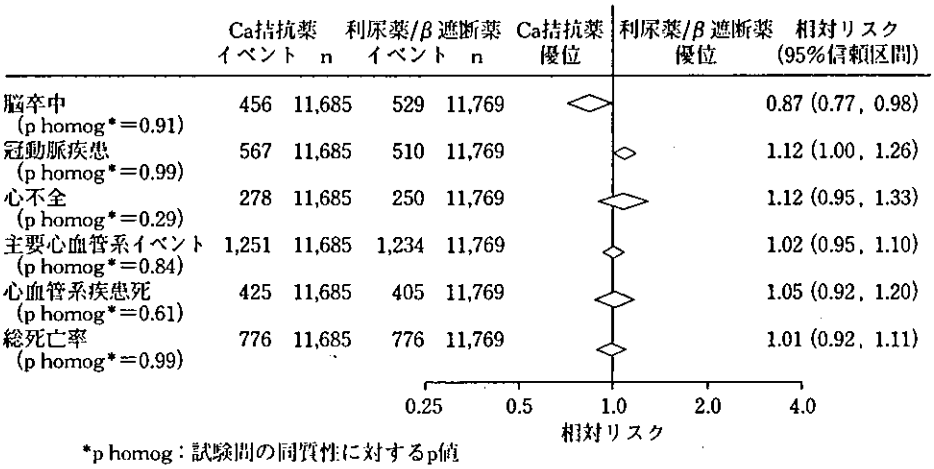

図　2　Ca 拮抗薬と利尿薬/β遮断薬の比較（INSIGHT，NICS-EH，STOP-2，NORDIL，VHAS）（文献9より引用）

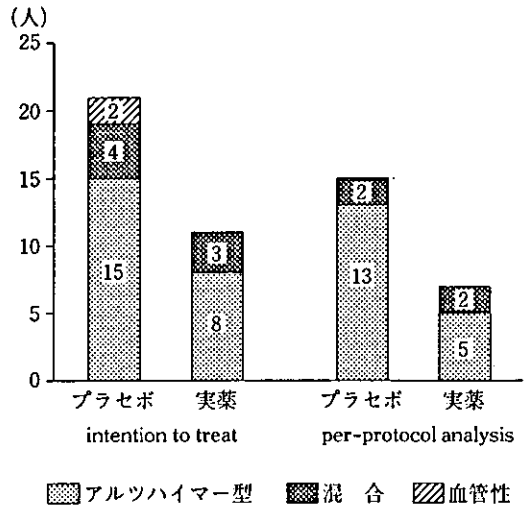

図 3　痴呆症のタイプ別発生数（文献18より引用）

問わず血圧上昇を来すことが多いが，その殆どが1～2週で発症前のレベルまで自然下降する[19]ため原則として積極的な降圧療法は行わない。この急性期の昇圧機序としては，脳卒中発症にともなうストレスや頭蓋内圧亢進に対する一種の防御機構としての反応性の血圧上昇などが関わるとされており，むしろ脳浮腫の治療や鎮静などにより昇圧要因の除去を図る必要がある。また，脳血流自動調節能の障害のために，降圧により脳血流低下を来し易いこともその理由とされている。ただし，脳出血の超急性期（発症3～6時間以内）では，血腫の増大や再出血を避ける意味で収縮期血圧で160～180mmHg を目標に治療前値の80％程度までの降圧を図ることが望ましい[20]。虚血性脳血管障害の場合も，発症後1～2日経過しても収縮期血圧で220mmHg あるいは平均動脈血圧で130mmHg 以上の状態が続く時には降圧を考慮する必要がある[21][22]。さらに，Brain Attack（脳発作）として発症3から6時間以内に t-PA (tissue plasminogen activator) やウロキナーゼによる血栓溶解療法が実施される場合には，出血性脳梗塞を避けるためにより厳格な血圧コントロール（180/105mmHg 以下）が必要とされており，表1に米国 AHA による血圧管理のガイドライン[22][23]を参考とした治療指針[24]を提示する。

Ⅳ. 脳卒中慢性期の降圧療法

脳卒中を既往に有する症例は有さない例に比しはるかに高率に脳卒中を発症することが知られており，脳卒中の最大の危険因子である高血圧を如何にコントロールするかは慢性期の脳卒中患者の治療上きわめて重要な問題である。したがって，これまで

表 1　脳梗塞急性期の血圧治療のガイドライン（橋本，岡田，峰松による）（文献24より引用）

降圧基準と使用薬剤
①拡張期血圧140mmHg 以上の場合（5分以上の間隔で2回測定）：微量点滴静注できる薬剤（ジルチアゼム，ニカルジピン）で降圧
②収縮期血圧220mmHg 以上，または拡張期血圧121～140mmHg，または平均血圧130mmHg 以上の場合（20分以上の間隔で2回測定）：微量点滴静注，経口薬（Ca 拮抗薬，ACE 阻害薬），湿布薬（亜硝酸薬）にて降圧，Ca 拮抗薬の舌下投与は避ける
③収縮期血圧185～220mmHg，または拡張期血圧105～120mmHg の場合では，左心不全，大動脈解離，急性心筋梗塞の合併がなければ緊急治療の必要がない（血栓溶解療法を行う際を除く）
④収縮期血圧185mmHg 以下，かつ拡張期血圧105mmHg 以下の場合は原則として降圧しない

降圧目標
①合併症がなければ収縮期血圧185～220mmHg/拡張期血圧105～120mmHg
②左心不全，心筋梗塞，大動脈解離を合併する場合：収縮期血圧185mmHg 以下，かつ拡張期血圧105mmHg 以下
③血栓溶解療法中と投与後24時間：収縮期血圧180mmHg 以下，かつ拡張期血圧105mmHg 以下

にもこの問題についていくつかの研究結果が報告されているが，その結果は必ずしも一致していなかった[25][26]。これには，脳出血と脳梗塞の区別などの脳卒中の病型分類すら充分にはなされてこなかったことが関わっているものと思われる。また，脳梗塞の場合も臨床病型により脳卒中発症率や同じ臨床病型での再発率が大きく異なることも知られており[27]，降圧の意義も病型ごとに異なるものと予想される[28]。事実，Irie ら[29]は後ろ向き研究ではあるが，脳卒中後の血圧と再発率との関係には，病型による違いが顕著であることを報告している。しかしながら，つい最近まで，この問題に明確な解答を与える前向きの大規模臨床試験は殆ど報告されておらず，脳卒中既往例の血圧コントロールの効果について9つの臨床試験（Carter，HSCSG，EWPHE，Coope，HDFP，MRFIT，SHEP，STOP，PATS）をまとめた INDANA Project Collaborators によるメタアナリシス[30]による有意な28％の再発抑制効果が示唆されていたのみであり，この際にも脳卒中の統一した病型分類がなされていないことが問題であった。その意味で，著者らを含む我が国の研究者も多数参加して，この問題に正面から取り組んだ初の大規模臨床試験である PROGRESS（Perindopril Protection Against Recurrent Stroke Study）試験[31]の結果はきわめてインパクトの強いものと言える。すなわち，1次評価項

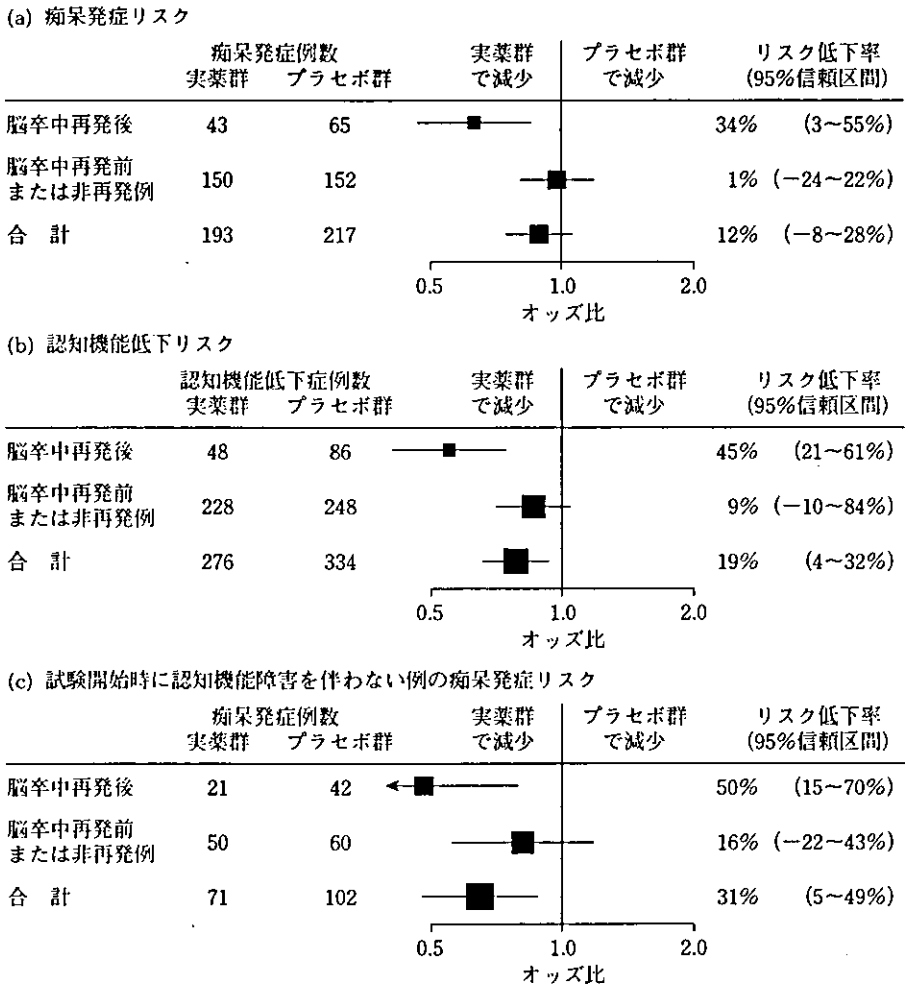

図　4　PROGRESS サブ解析の主な結果（文献32より引用）

目である脳卒中の再発については，ペリンドプリル群ではプラセボ群に比し28％もの有意な脳卒中発症抑制および26％の心血管系事故発症抑制効果が観察されている。また，興味深いことに脳卒中発症例における痴呆・高度の認知機能障害，ADL 障害の発現頻度や，試験開始時に認知機能障害を伴わない例の痴呆発症は脳卒中再発の有無にかかわらず有意に抑えられることが示されている（図4）。さらに，PROGRESS 試験ではエントリー時の 147/86mmHg からペリンドプリルや降圧利尿薬であるインダパミドの追加投与により血圧を 138/82mmHg 程度に持続的に降下させることにより，平均年齢64歳の患者で4～5年間で28％ものさらなる再発抑制効果が得られることを実証し，慢性期の脳卒中患者における降圧の重要性を示している。ただし，個々の降圧薬の特徴を把握し[33)34)]，個々の患者の血圧日内変動[35)36)]や臨床病型に配慮した緩徐な降圧を心がけることの重要性[8)33)36)]は変わらないものと思われる。

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2. 抗血小板薬と抗凝固薬

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動　向

2002年にAntithrombotic Trialists' Collaboration(ATT)により血栓性疾患の高リスク患者における抗血小板療法の無作為化比較試験 randomized controlled trial（RCT）のメタ分析の結果が報告された．抗血小板療法は，脳卒中あるいは一過性脳虚血発作 transient ischemic attack（TIA）の既往のある患者において，重大な血管事象（脳卒中，心筋梗塞または血管死）の発生を22%有意に減少させることが確認され，非心原性脳梗塞の再発予防のために抗血小板薬の有効性が確立されている．長期投与においてアスピリン75～150mg/日の低用量は，500～1,500mgの高用量や160～325mgの中用量と同等の有効性が示された．しかし，75mg/日未満の超低用量では有意の効果がなかった．このことから高リスク患者における血管事象の長期予防においては75～150mg/日の低用量のアスピリンの投与が有用である．急性期脳卒中を除く高リスク患者における血管事象の発生はアスピリンで23%，チクロピジンで32%の有意の抑制がみられた．シロスタゾールは脳梗塞慢性期患者において血管事象の発生を39%有意に減少させた．抗血小板薬のラクナ梗塞に対する予防効果に関しては議論のあるところであるが，シロスタゾールによりラクナ梗塞の再発が43%有意に減少することが示された．

発症48時間以内の虚血性脳卒中患者に対するアスピリンの効果を検討する2つの大規模抗血小板療法のメタ分析において，アスピリン160～300mg/日の経口投与が虚血性脳卒中の再発を抑制し，長期予後も改善することが示された．このことから，発症48時間以内の虚血性脳卒中患者に対して，アスピリンに対する禁忌がないかぎり，160～300mg/日のアスピリンの投与が推奨されている．

心房細動患者における抗血栓療法のメタ分析において，用量を調節したワルファリンにより脳卒中の発症は62%減少した．一方，アスピリンにより脳卒中は22%減少した．このように用量を調節したワルファリンはアスピリンより36%効果が上回っていた．非弁膜症性心房細動 non-valvular atrial fibrillation（NVAF）患者の脳塞栓症の発症予防において治療域INR (international normalized ratio: 国際標準化比) 2.0～3.0のワルファリンのコントロールが推奨されている．しかし，70歳以上の高齢者においては，NVAFによる心原性脳塞栓症の再発予防において低用量のワルファリン療法（治療域INR 1.5～2.1）が安全であり，