Original Article

Risk Factors and Predictors of Coronary Arterial Lesions in Japanese Hypertensive Patients

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The morbidity rate of coronary artery disease has recently increased in Japan. This is attributable to changes from traditional to more westernized lifestyles. In this study, we therefore examined the risk factors and predictors of coronary arterial lesions in Japanese patients with essential hypertension. Coronary angiography was performed in 109 consecutive essential hypertension patients (57 men and 52 women; 66 ± 8.0 years of age) with either angina pectoris or atypical chest pain, who were chosen from 485 consecutive hypertensive patients in a hypertension clinic in Sendai, Japan. Coronary arterial stenosis of greater than 50% was defined as significant and used as a dependent variable for the multiple regression analysis. Risk factors were defined as factors confirmed to have a causal relationship with coronary arterial lesions, whereas arteriosclerotic complications and hypertensive target organ damage were defined as predictors. Multiple logistic regression analysis was performed using these parameters as independent variables. Of 109 patients, 25 had a coronary arterial stenosis greater than 50%. A smoking habit (odds ratio (OR): 4.48; 95% confidence interval (CI): 1.13-17.82; $p < 0.05$), hypercholesterolemia (OR: 5.34; 95% CI: 1.52-18.73; $p < 0.05$), and 24-h diastolic blood pressure (OR: 2.33; 95% CI: 1.06-5.16; $p < 0.05$) were significant risk factors, whereas carotid intima-media thickness (OR: 5.85; 95% CI: 1.48-23.2; $p < 0.05$) was a significant predictor of coronary arterial lesion. When two of the major risk factors (a smoking habit, hypercholesterolemia, or impaired glucose tolerance including diabetes mellitus) were clustered in addition to the hypertension, the risk of coronary arterial lesions increased by 6.7 to 10.1 times. These findings indicate that the major risk factors established in Caucasians, *i.e.*, a smoking habit, hypercholesterolemia and blood pressure level, are also risk factors for coronary arterial lesions in Japanese with essential hypertension. The presence of two or more risk factors increases the risk of coronary arterial lesions synergistically in the presence of hypertension. (*Hypertens Res* 2001; 24: 3-11)

Key Words: essential hypertension, coronary artery lesion, risk factors, predictors

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Introduction

Treatment of hypertension is aimed at reducing the risk of future cardiovascular morbidity and mortality. In Japan, age-adjusted cardiovascular mortality rates are lower than those in other industrialized countries (1). Recently, the lifestyles in Japanese have changed from traditional to more westernized. At the same time, the prevalence of hypercholesterolemia has rapidly increased in the past several decades (2). The 90th percentile values for serum total cholesterol level in the population of 5- to 18-year-olds in Japan is 5.17 mmol/l (200 mg/dl), which is similar to the 95th percentile values of serum total cholesterol level in 5- to 18-year-olds in the United States (3). Thus, the morbidity of coronary arterial disease is predicted to increase in Japan.

In Western countries, elevated blood pressure, high blood cholesterol levels, and cigarette smoking have all been indicated to be risk factors of coronary arterial disease (CAD) (4). It is uncertain, however, whether such risk factors also affect CAD in Japanese. Almost 33 million Japanese have a blood pressure of at least 140/90 mmHg or are taking antihypertensive medication. The Framingham Study indicated that hypertension contributes to development of CAD, with hypertension mediating a 2- to 3-fold increase in CAD among subjects (5). A Glasgow hypertension clinic recently reported that approximately 40% of mortality of the hypertensive population was due to CAD (6). Clearly, CAD is an important issue for hypertensive patients. Moreover, high blood cholesterol levels (≥ 6.21 mmol/l; ≥ 240 mg/dl) have been shown to accompany more than 40% of the cases of hypertension in western populations (7). There is a clustering of risk factors in hypertensive patients when compared to normotensive subjects, and various risk factors for CAD exist simultaneously in hypertensive patients (8). In the present study, risk factors and predictors of CAD were examined in Japanese subjects with essential hypertension. To determine the presence of CAD, coronary angiography, the "gold-standard" for identifying coronary arterial lesions, was performed. The angiographic findings provide an opportunity to estimate the relationship between risk factors and actual stenotic or occlusive lesions.

Methods

Study Population

The study population consisted of 485 hypertensive patients who were examined in a hypertension clinic in Sendai, a capital city of northern Japan, from 1991 to 1997. All 485 patients were diagnosed with essential hypertension on the basis of a clinic systolic blood pressure (SBP)

of 160 mmHg or higher and/or clinic diastolic blood pressure (DBP) of 95 mmHg or higher on at least two clinic visits while off all medications. Patients with secondary hypertension, including renal hypertension, were excluded by routine biochemical and radiological examinations, including measurement of plasma renin activity and plasma aldosterone concentration. Of 485 patients, 119 consecutive patients who were suspected to have CAD underwent coronary angiography. Informed consent was obtained from each patient before coronary angiography. Of the 119 patients, 10 were excluded due to presence of valvular disease, prior myocardial infarction, or secondary hypertension (renovascular hypertension, primary aldosteronism, or chronic glomerulonephritis). The duration of hypertension in the remaining 109 consecutive hypertensive subjects (57 men and 52 women; 66 ± 8.0 years of age) was 18.3 ± 1.38 years. As a first-choice drug, these patients were prescribed antihypertensive medications from any one of four classes of drugs — *i.e.*, diuretics, calcium antagonists, β -blockers and angiotensin-converting enzyme inhibitors. Different classes of drugs were sequentially added in cases in which the target BP was not achieved. In total, 109 consecutive hypertensive subjects with either angina pectoris or atypical chest pain with or without ischemic change in electrocardiogram (ECG) or with ischemic change in ECG but without anginal pain were enrolled. The criteria for ischemia on standard 12-lead ECGs were based on a modification of the Minnesota code 5-1 or, in the case of isolated T-wave abnormalities, 5-2. Of the 109 subjects, 39 had anginal pain with ischemic changes in ECG under resting conditions or exercise load (Group 1), 43 had anginal pain and were highly suspected as having angina pectoris based on their history but had no ischemic changes in ECG (Group 2), 20 showed ischemic changes in ECG, but no anginal pain (Group 3), 5 had atypical chest pain and ischemic changes in ECG (Group 4), and 2 had strong anxiety due to low grade chest pain without any ischemic changes in ECG (Group 5).

Coronary Angiography

Coronary angiography was performed *via* the percutaneous radial artery approach (9). Multiple views of the right and left coronary arteries were recorded. The angiograms were reviewed and coded by two cardiologists without knowledge of the patients' data. In accordance with the American Heart Association categories, patients who had one or more coronary arterial luminal stenosis of more than 50% on angiography were defined as having significant coronary stenosis (10). Because coronary arterial stenosis of more than 50% would not necessarily induce reactive hyperemia, severity of the stenosis is generally considered to have clinical significance.

Risk Factors and Predictors

We defined the risk factors of coronary arterial lesion as those confirmed to have a causal relationship with coronary arterial lesions, and then, arteriosclerotic complications (except coronary arterial lesions) and hypertensive target organ damage were defined as predictors. The following parameters were examined as risk factors: gender, age, family history of hypertension, antihypertensive drug treatment, casual BP level, ambulatory BP levels, circadian BP variation (dippers and non-dippers), a smoking habit (more than 10 cigarettes daily for a year or more), alcohol intake, body mass index [BMI: weight/(height)², kg/m²], platelet count, fibrinogen, hematocrit (Hct), lipoprotein (a) [Lp (a)], hypercholesterolemia, impaired glucose tolerance (IGT), diabetes mellitus (DM), and hyperuricemia. The following were taken as predictors: left ventricular hypertrophy (LVH) in electrocardiography, LVH in echocardiography (11), albuminuria, fundoscopic finding (hypertonic and sclerotic change), lacunar infarction on brain magnetic resonance imaging (MRI), and carotid intima-media thickness (IMT) by B-mode ultrasonography. Subjects who were administered lipid-lowering drugs or who had serum total cholesterol levels higher than 5.68 mmol/l (220 mg/dl) were considered to have hypercholesterolemia. Of the 109 subjects, 40 were administered pravastatin or simvastatin. The result of the glucose tolerance test was defined on the basis of the World Health Organization criteria (12); *i.e.*, those with a fasting glucose of ≥ 77 mmol/l (140 mg/dl) and 2-h glucose of ≥ 11.11 mmol/l (200 mg/dl) were defined as having newly recognized diabetes mellitus; those with a fasting glucose < 7.77 mmol/l (140 mg/dl) or 2-h glucose of ≥ 7.77 mmol/l (140 mg/dl) and < 11.11 mmol/l (200 mg/dl) were defined as having impaired glucose tolerance. Patients who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus. Patients with a uric acid level higher than 0.48 mmol/l (8 mg/dl) in men and 0.36 mmol/l (6 mg/dl) in women, or who were treated with uric acid-lowering drugs were defined as having hyperuricemia.

Blood Pressure Measurements

Casual (clinic) BP was measured with patients in a seated position twice consecutively after an at least 5-min interval by nurses using an automatic BP measuring device (Nippon Colin 203 I, Nippon Colin, Komaki, Japan). The average of the two readings was used for analysis.

Ambulatory BP was measured every 30 min for 24 h using an A & D TM-2421 (Takeda Medical, Tokyo, Japan). Daytime and nighttime ambulatory BPs were analyzed separately. Subjects were classified as either dippers or non-dippers. Dippers were defined as those with a nocturnal decline in BP (daytime ambulatory BP — night-

time ambulatory BP) greater than 10% of the daytime BP and non-dippers were defined as those with a less than 10% decline.

Echocardiography

M-mode echocardiograms were recorded using an SSA-240A (Toshiba, Tokyo, Japan) under the guidance of two-dimensional echocardiographic imaging in a supine position. Measurements were taken according to the American Society of Echocardiography recommendations (11). The left ventricular posterior wall thickness and interventricular septal thicknesses were measured. Left ventricle mass (LVM) was calculated using Devereux's formula, and corrected by body surface area (LVM index: LVMI, g/m²). Those with an LVMI of more than 110 g/m² in women and 120 g/m² in men were defined as having LVH.

Lacunar Infarction on Brain Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed with a super conducting magnet that had a main field strength of 0.5 T (Toshiba 50-A). The brain was imaged in the axial plane in 10 mm-thick slices. A lacunar infarction was defined as an area of low signal intensity lesion < 10 mm and > 3 mm on T_1 -weighted images and was visible as a hyperintense lesion on T_2 -weighted images. MRIs were evaluated in a blinded manner by two physicians. All data were measured within 6 months of coronary angiography.

Ultrasonographic Assessment of Carotid Artery

The ultrasonographic assessment of carotid arteries was performed while the subject was sitting. The B-mode scanning protocol includes scanning of the bilateral common carotid arteries and the carotid bifurcation-bulb area. The sites of predilection for the development of arteriosclerosis were determined by three projections: lateral oblique, anterior oblique, and posterior oblique. In all subjects, the intima-media thickness (IMT) of the common carotid arteries was measured. We classified the findings into four categories (13): 1) no atherosclerotic lesion; 2) intima-media thickening; 3) nonstenotic plaque; and 4) large stenotic plaque. The classification was based on the findings of the most severely affected site on either the left or right side. Intima-media thickening (category 2) of the arterial wall was defined as a distance of more than 1.0 mm between the intima-lumina interface and the media-adventitia interface in the common carotid arteries below the carotid bulb. Atherosclerotic plaque (category 3) was considered to exist when a distinct area with mineralization (a bright echo, often producing a typical echogenic shadow) or with focal protrusion into the lu-

Table 1. Comparison of Risk Factors and Predictors between Controls and Cases

	Controls	Cases	<i>p</i> -value	Test
Gender (% male)	46	72	<0.05	<i>t</i>
Age (years)	65.2±8.3	66.9±7.2	N.S.	<i>t</i>
Fibrinogen (mg/dl)	277.2±43.9	297±73.6	N.S.	<i>t</i>
Lipoprotein (mg/dl)	19.8±19.2	26.9±18.5	N.S.	<i>t</i>
A smoking habit (%)	21	60	<0.01	χ^2
Hypercholesterolemia (%)	43	76	<0.01	χ^2
IGT including DM (%)	27	44	<0.05	χ^2
Hyperuricemia (%)	33	40	N.S.	χ^2
ECG—LVH+ST-T changes (%)	45	76	<0.05	χ^2
Echocardiograph—LVH (%)	42	75	<0.01	χ^2
Albuminuria (mg/day)	22.6±739.0	69.8±118.9	N.S.	<i>t</i>
FD≥S2 (%)	40	68	<0.05	χ^2
Lacunar infarction (%)	25	49	<0.05	χ^2
IMT (mm)	0.84±0.16	0.99±0.19	<0.01	<i>t</i>

Values are expressed as means±SD; IGT, impaired glucose tolerance; DM, diabetes mellitus; ECG, electrocardiographic; LVH, left ventricular hypertrophy; FD, funduscopic finding; IMT, intima-media thickness. Controls: without coronary arterial lesion, Cases: without coronary arterial lesion.

men was identified. A stenotic lesion (category 4) was considered to exist when there was a more than 20% decrease in the luminal diameter in the greatest diameter of the common carotid artery.

Statistical Methods

The relationships between coronary arterial lesions and potential risk factors or between coronary arterial lesions and predictors were examined using both univariate and multivariate methods. The univariate analyses consisted of *t*-tests for CAD status for continuous factors and χ^2 tests for CAD status for dichotomous factors. Multiple logistic regression analyses were performed using the parameters mentioned above as independent variables to obtain adjusted odds ratios (OR) and 95% confidence intervals (CI) from the coefficients (maximum likelihood estimates). All statistical procedures were performed using Statistical Analysis System programs (14). Values are expressed as the means±SD. A *p* value less than 0.05 was considered to indicate statistical significance.

Results

Of the 109 patients, 25 had a coronary arterial stenosis greater than 50%. Of those with significant coronary arterial stenosis, 21 underwent percutaneous transluminal coronary angioplasty, while the remaining four underwent coronary artery bypass grafts. Rates of medication of each antihypertensive drug in cases (*n*=25) and controls (*n*=84) were 16.0% and 15.5% for diuretics, 64.0% and 49.0% for β -blockers, 88.0% and 81.0% for calcium entry blockers and 36.0% and 31.0% for angiotensin I convert-

ing enzyme inhibitors, respectively. In control subjects (*n*=84), 27.4% was medicated by statin derivatives while 44% in case subjects (*n*=25).

Univariate Analyses

The casual BP (SBP: 164.8±18.6 mmHg; DBP: 99.8±13.0 mmHg) in those with CAD also tended to be higher than that in those without CAD (SBP: 156.8±19.4 mmHg; DBP: 95.9±10.9 mmHg; N.S. for SBP; N.S. for DBP). The 24-h ambulatory BP (SBP: 145.1±11.8 mmHg; DBP: 91.9±7.8 mmHg) in those with CAD was significantly higher than that in those without CAD (SBP: 139.1±11.5 mmHg; DBP: 86.9±8.1 mmHg; *p*<0.05 for SBP; *p*<0.01 for DBP) and the daytime BP (SBP: 153.3±12.6 mmHg; DBP: 97.3±8.6 mmHg) in those with CAD was significantly higher than that in those without CAD (SBP: 146.3±11.7 mmHg; DBP: 92.8±9.6 mmHg; *p*<0.05 for SBP and DBP). The remaining BP parameters also tended to be higher in those with CAD than in those without CAD. The coronary risk factors and predictors are shown in Table 1. The frequency of male gender, a smoking habit, hypercholesterolemia, and IGT including DM were significantly higher in those with CAD than in those without. LVH, as determined by both ECG and echocardiogram, was observed more frequently in those with CAD than in those without. Sclerotic changes in funduscopic findings were more accelerated and the presence of lacunar infarction on brain MRI was more frequent in those with CAD than in those without. The average IMT in patients with CAD was 0.99±0.19 mm, and that in those without CAD was 0.84±0.16 mm (*p*<0.05).

Table 2. Multiple Logistic Regression Analysis of Coronary Arterial Lesion, Where BP Levels Were Excluded from the Independent Variables

Independent variables		Adjusted odds ratio (95% CI)	p-value
Gender	(Male/Female)	1.29 (0.31-5.34)	N.S.
Age	(Per year)	1.05 (0.98-1.13)	N.S.
A smoking habit	(Yes/No)	4.48 (1.13-17.82)	<0.05
Hypercholesterolemia	(Yes/No)	5.34 (1.52-18.73)	<0.01
IGT including DM	(Yes/No)	2.69 (0.81-8.97)	N.S.

The multivariate model includes all variables listed above. CI, confidence interval; IGT, impaired glucose tolerance; DM, diabetes mellitus.

Fig. 1. Multiple logistic regression analysis for coronary arterial lesion using a smoking habits and/or those with hypercholesterolemia as risk factors. Comparison between those with these risk factors and those without these risk factors. Data were adjusted for gender and age. SM (-) and HC (-); odds ratio 1, * $p < 0.005$. SM, a smoking habit.; HC, hypercholesterolemia.

Fig. 2. Multiple logistic regression analysis for coronary arterial lesion using hypercholesterolemia and/or those with IGT including DM as risk factors. Comparison between those with these risk factors and those without these risk factors. Data were adjusted for gender and age. * $p < 0.01$. HC (-) and IGT DM (-); odds ratio 1. HC, hypercholesterolemia; IGT DM, IGT including DM.

Multiple Logistic Regression Analyses

The results of multiple logistic regression analyses for coronary arterial lesions using age, gender, a smoking habit, hypercholesterolemia, and IGT including DM as independent variables, are shown in Table 2. A smoking habit and hypercholesterolemia were determined as significant and independent variables as risk factors of coronary arterial lesions (a smoking habit: OR, 4.48; 95% CI, 1.13-17.82; $p < 0.05$; hypercholesterolemia: OR, 5.34; 95% CI, 1.52-18.73; $p < 0.05$). Multiple logistic regression analysis for coronary arterial stenosis using blood pressure parameters, gender, a smoking habit, hypercholesterolemia, and IGT including DM as independent variables demonstrated that only high 24-h DBP (OR: 2.33; 95% CI: 1.06-5.16; $p < 0.05$) was a significant independent risk factor. Multiple logistic regression analysis for coronary arterial lesions vs. each predictor after adjustment by age, gender, a smoking habit, hypercholesterolemia, high 24-h DBP and IGT including DM demonstrated that IMT (OR: 5.85; 95% CI: 1.48-23.2; $p < 0.05$) was the only sig-

nificant independent variable to predict coronary arterial lesions.

Clustering of Risk Factors

The risk of coronary arterial lesions was estimated when two of the three major risk factors (a smoking habit, hypercholesterolemia, and IGT including DM) were clustered in addition to the hypertension. Multiple logistic regression analyses for coronary arterial stenosis were performed to evaluate the risk of clustering of a smoking habit and hypercholesterolemia after adjustment for age and gender. The subjects were classified into four groups. Of the 109 patients, 19 (17%) had a smoking habit and hypercholesterolemia. Of these 19 patients, 10 had coronary arterial stenosis. The OR of coronary arterial stenosis was 10.1 times higher in those with both a smoking habit and hypercholesterolemia than in those without both risk factors (Fig. 1). Of the 109 patients, 35 (32%) had hypercholesterolemia and IGT including DM. Of these 35 patients, 14 had coronary arterial stenosis. The OR of

Fig. 3. Multiple logistic regression analysis for coronary arterial lesion using a smoking habit and/or those with IGT including DM as risk factors. Comparison between those with these risk factors and those without these risk factors. Data were adjusted for gender and age. * $p < 0.01$. SM (-) and IGT DM (-); odds ratio 1. SM, a smoking habit; IGT DM, IGT including DM.

coronary arterial stenosis was 9.3 times higher in patients with hypercholesterolemia and IGT including DM than in those without both risk factors (Fig. 2). Of these 109 patients, 23 (21%) had a smoking habit and IGT including DM. Of these 23 patients, 10 had coronary arterial stenosis. The OR of coronary arterial stenosis was 6.7 times higher in patients with a smoking habit and IGT including DM than in those without both risk factors (Fig. 3).

Discussion

Hypertension, hypercholesterolemia, and a smoking habit have been confirmed to be major risk factors for CAD (4). Such risk factors have been studied not only in relation to coronary arterial lesions in autopsy specimens, but also in relation to lesions in coronary angiography (15). The prevalence of CAD is high in Western countries, and thus, epidemiological surveys of this disease have been widely performed. A few epidemiological surveys of CAD in Japanese population have been reported. In the Honolulu Heart Program (16), which examined risk factors of CAD in Japanese-Americans in Hawaii, and in the Hiroshima-Nagasaki Study (17), which examined risk factors of CAD in Japanese exposed to the atomic bomb, these three factors were also confirmed to be major risk factors for CAD. In the Hisayama Study of Japan (18), serum cholesterol levels were associated with CAD, and it has also been reported that hypertension and a smoking habit were risk factors of CAD (19). Konishi *et al.* also reported that hypercholesterolemia, hypertension, and a smoking habit were risk factors for CAD in a population of Osaka, Japan (20).

Risk Factors

The present results indicate that hypercholesterolemia, a smoking habit, and a high 24-h DBP are independent risk factors for coronary arterial lesions in patients with hypertension. Hypercholesterolemia was the strongest risk factor for coronary arterial lesions, followed by a smoking habit. High 24-h DBP was also significantly associated with coronary arterial lesions. Hypertension has long been recognized as a major risk factor for stroke and coronary arterial disease. A meta-analysis of 17 major interventional studies demonstrated that the treatment of mild to moderate hypertension reduced the risk for stroke by 38%, whereas risk reduction for CAD was only 16% (21). In Japan, the screening for and treatment of hypertension have dramatically reduced stroke mortality. Since 1990, however, the crude mortality rate of coronary heart disease has gradually increased, although the age-adjusted mortality rate of coronary heart disease has slightly decreased. Thus, the increase in the crude mortality rate of coronary heart disease is mediated by an increase in the elderly population (22). In fact, according to a report by the Japanese Ministry of Health and Welfare, the visit rate for outpatient care and the hospitalization rate for inpatient care for CAD increased 4-fold between 1970 and 1990 (23). Thus, in the present study, risk factors for coronary arterial lesions were examined in Japanese hypertensive patients.

Blood Pressure

In the present study, BP parameters tended to be higher in those with CAD than in those without CAD. The 24-h ambulatory BP values were significantly higher in those with CAD than in those without in a univariate analysis. In the multiple logistic regression analysis, high 24-h DBP was determined to be an independent risk factor. DBP is widely recognized as a risk factor for CAD (24-26). The present study clearly demonstrated that ambulatory BP was more closely associated with coronary arterial lesions than casual BP. Such results have been confirmed by several studies in which target organ damage and prognosis of hypertension were more closely correlated to ambulatory BP than to casual BP (27-29).

Clustering of Risk Factors

The present study clearly demonstrated that clustering of risk factors (a smoking habit, hypercholesterolemia, and IGT including DM) synergistically increased the risk of coronary arterial lesions in patients with hypertension. It is widely recognized that clustering of such risk factors as hypertension, hypercholesterolemia, a smoking habit, IGT including DM, and so on, significantly increases the OR for coronary arterial lesion (8, 30), indicating an in-

teraction among risk factors. In particular, the combination of hypercholesterolemia and a smoking habit or the combination of a smoking habit and IGT including DM have been shown to increase the OR synergistically (8, 30). A synergistic increase in the OR, however, was not observed when hypercholesterolemia and IGT including DM were combined, indicating that these risk factors are independently associated with CAD (30). In the Hisayama Study (19), the risk ratio of ischemic heart disease in the general population increased by 1.3 times, 1.5 times, and 3.9 times when subjects had hypercholesterolemia, a smoking habit, or both, respectively, when compared to those without such risk factors. In the present study, in which hypertensive subjects were examined after adjustment by age and gender, the risk ratio in subjects with hypercholesterolemia was 2.4 times higher than in those without risk factors. The risk ratio in those with a smoking habit was 2.1 times higher than that in those without risk factors. In those with both risk factors, the risk ratio was 10.1 times higher than that in those without risk factors (Fig. 1). The Hisayama Study examined the risk for incidence of CAD, whereas the present study examined the risk for the presence of coronary arterial lesions. The presence of coronary arterial lesions is not necessarily equivalent to the incidence of CAD. In the present study, however, coronary intervention was necessary for significant coronary arterial lesions. Therefore, it seemed that the occurrence of significant coronary arterial lesions could be equated with the incidence of CAD in our study. Thus, it is concluded that the risk of hypercholesterolemia and a smoking habit can be enhanced by the presence of hypertension. In the present study, age and gender were not independent risk factors. This may be due, at least in part, to the small scale of samples in this case-controlled study.

Predictors

As a predictor for coronary arterial stenosis, only a carotid IMT measured by B-mode ultrasound was adopted. B-mode ultrasound of the carotid artery provides an image of atherosclerosis within the arterial wall. Carotid IMT measured by ultrasonography correlates well with pathological findings of the carotid artery (31). Previous studies have assessed the relationship between carotid IMT measured by B-mode ultrasonography and coronary arterial stenosis as documented by coronary angiography (32). Geroulakos *et al.* (32) compared subjects who had coronary arterial stenosis of 50% or more in one or more coronary arteries with those who had normal coronary arteries, and found that IMT was higher in the former than in the latter. Salonen and Salonen reported that carotid IMT was associated with future coronary events (13). Adams *et al.* (33), however, reported that carotid IMT was weakly correlated with the extent and severity

of coronary arterial stenosis. Based on these results, we postulate that there are differential underlying processes of atherosclerosis between the carotid and coronary arteries. On the other hand, many studies have demonstrated that there are traditional risk factors in common between the development of carotid and coronary atherosclerosis (34). In a previous autopsy study (35), a close relationship was observed between carotid and coronary atherosclerosis. Thus, noninvasive assessment of carotid atherosclerosis is useful for predicting coronary arterial lesions.

On the other hand, lacunar infarction on MRI was not associated with coronary arterial stenosis in the present study. This finding suggests that extracranial carotid arterial change is more closely associated with changes in the coronary artery than with changes in the intracranial small vessels.

In the present study, 25 significant coronary arterial lesions were found in 482 consecutive hypertensive patients over a 6-year follow-up period. Komachi *et al.* reported that the incidence of CAD was 0.8, 0.9, and 1.7 per 1,000 persons/year in a rural community in northern Japan, in urban office workers and in urban oil refinery workers, respectively (36). Although the incidences of CAD and coronary arterial lesions are not necessarily equivalent, in the present study the prevalence of significant coronary arterial lesions was estimated to be 8 per 1,000 persons/year. This value is remarkably high when compared to that of the incidence of CAD in the general Japanese population (36). Such an effect of hypertension on CAD has also been confirmed in the Hisayama Study (18).

Study Limitations

Among the subjects who were deemed not to have coronary arterial stenosis in the present study, only a portion had been examined angiographically. It is possible that some asymptomatic individuals also had coronary artery stenosis. If all subjects had received coronary angiography and asymptomatic coronary stenosis had been included in the analyses, the association between coronary artery stenosis and risk factors or between the former and predictors might have been altered. In addition, although the hypertensive patients in the present study were consecutively registered, thereby omitting selection bias, the resulting number of hypertensive subjects was limited. It is thus difficult to generalize the present results to the general population. Further large scale studies will be needed to generalize to the Japanese hypertensive population.

Conclusions

The present results indicate that hypercholesterolemia, a smoking habit, and a high 24-h DBP are risk factors for coronary arterial lesions, and that clustering of risk fac-

tors (a smoking habit, hypercholesterolemia, IGT including DM) synergistically increased the risk of coronary arterial disease under the presence of hypertension, even in Japanese. They thus suggest that noninvasive assessment of carotid atherosclerosis is useful for predicting coronary arterial stenosis.

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