As summarized in review articles [24,25], many investigators have demonstrated the crucial role of PAI-1 in human atherothrombosis. High plasma PAI-1 concentrations are associated with various thrombotic diseases and are independent risk factors for myocardial infarction, as has been proven by epidemiological studies. Animal experiments using PAI-1 transgenic mice and PAI-1 knock-out mice also support the role of PAI-1 in the progression of atherosclerosis [26–28]. These previous findings suggest that an increased PAI-1 level in the plasma is closely associated with the progression of atherosclerotic conditions. Here, we have demonstrated that this relationship could also be observed in early atherosclerotic conditions in a general population.

We have previously reported that the mean IMT value of both sexes increased stepwise with the number of major coronary risk factors, namely hypertension, smoking, and hypercholesterolemia [5]. It has also been reported that PAI-1 levels were increased in patients with early hypertension, and that these elevated PAI-1 levels were improved by treatment with angiotensin-converting enzyme inhibitor [29]. Recently, it has been reported that PAI-1 deficiency prevents hypertension and vascular fibrosis in response to long-term nitric oxide synthase inhibition [30]. Taken together, these data indicate that early atherosclerotic conditions or endothelial cell dysfunction are induced by hypertensive conditions, resulting in elevation of the plasma levels of free TFPI and PAI-1. Therefore, it is thought that the close association between elevation of the plasma levels of free TFPI and PAI-1 and hypertensive conditions probably diminished the statistically independent association between plasma levels of free TFPI and PAI-1 and the degree of IMT.

In conclusion, we have demonstrated that the levels of free TFPI and PAI-1 in men increased with the degree of IMT. Therefore, we propose that free TFPI and PAI-1 are potentially useful markers for detecting early atherosclerosis. However, prospective studies are necessary to clarify whether these markers are predictive of the onset of atherosclerotic diseases in Japanese people.

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References

[1] Hodis HN, Mack WJ. Risk factor assessment, treatment strategy and prevention of coronary artery disease: the need for a more rational approach. J Intern Med 1994;236:111–3.
[2] Blankenhorn DH, Hodis HN. Arteial imaging and atherosclerosis reversal. Arterioscler Thromb 1994;14:177–92.
[3] Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan GJ, Nicolaides AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. Eur Heart J 1994;15:781–5.
[4] Crouse III JR, Craven TE, Hagaman AP, Bond MG. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 1995;92:1141–7.
[5] Mannami T, Baba S, Ogata J. Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: the Suita Study. Arch Intern Med 2000;160:2297–303.
[6] Hunt KJ, Pankow JS, Offenbacher S, et al. B-mode ultrasound-detected carotid artery lesions with and without acoustic shadowing and their association with markers of inflammation and endothelial activation: the atherosclerosis risk in communities study. Atherosclerosis 2002;162:145–55.
[7] Wu KK, Folsom AR, Heiss G, et al. Association of coagulation factors and inhibitors with carotid artery atherosclerosis; early results of the athrosclerosis risk in communities (ARIC) study. Ann Epidemiol 1992;2:471–80.
[8] Folsom AR, Wu KK, Shahar E, Davis CE. For the athrosclerosis risk in communities (ARIC) study investigators. Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. Arterioscler Thromb 1993;13:1829–36.
[9] Salomaa V, Stinson V, Kark JD, et al. Association of fibrinolytic parameters with early atherosclerosis. The ARIC study. Circulation 1995;91:284–90.
[10] Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Engl J Med 1995;332:635–41.
[11] Kumari M, Marmot M, Brunner E. Social determinants of von Willebrand factor: the Whitehall II study. Arterioscler Thromb Vasc Biol 2000;20:1842–7.
[12] Bajaj MS, Birktoft JJ, Steer SA, Bajaj SP. Structure and biology of tissue factor pathway inhibitor. Thromb Haemost 2001;86:959–72.
[13] Kato H. Regulation of functions of vascular wall cells by tissue factor pathway inhibitor: basic and clinical aspects. Arterioscler Thromb Vasc Biol 2002;22:539–648.
[14] Morange PE, Renucci JF, Charles MA, et al. Plasma levels of free and total TFPI, relationship with cardiovascular risk factors and endothelial cell markers. Thromb Haemost 2001;85:999–1003.
[15] Kokawa T, Enjyoji K, Kumeda K, et al. Measurement of the free form of TFPI antigen in hyperlipidemia: relationship between free

and endothelial cell-associated forms of TFPI. Arterioscler Thromb Vasc Biol 1996;16:802–8.
[16] Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: The Suita Study. Stroke 1997;28:518–25.
[17] Abumiya T, Enjyoji K, Kokawa T, Kamikubo Y, Kato H. An anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody recognized the third Kunitz domain (K3) of free-form of TFPI but not liporotein-associated forms in plasma. J Biochem 1995;118:178–82.
[18] Caplice NM, Mueske CS, Kleppe LS, Simari RD. Presence of tissue factor pathway inhibitor in human atherosclerotic plaques is associated with reduced tissue factor activity. Circulation 1998;98:1051–7.
[19] Kaikita K, Takeya M, Ogawa H, et al. Co-localization of tissue factor and tissue factor pathway inhibitor in coronary atherosclerosis. J Pathol 1999;188:180–8.
[20] Crawley J, Lupu F, Westmuckett AD, et al. Expression, localization, and activity of tissue factor pathway inhibitor in normal and atherosclerotic human vessels. Arterioscler Thromb Vasc Biol 2000;20:1362–73.
[21] Kamikura Y, Wada H, Yamada A, et al. Increased tissue factor pathway inhibitor in patients with acute myocardial infarction. Am J Hematol 1997;55:183–7.
[22] Soejima H, Ogawa H, Yasue H, et al. Heightened tissue factor associated with tissue factor pathway inhibitor and prognosis in patients with unstable angina. Circulation 1999;99:2908–13.
[23] Sakkinen PA, Cushman M, Psaty BM, et al. Correlates of antithrombin, protein C, protein S, and TFPI in a healthy elderly cohort. Thromb Haemost 1998;80:134–9.
[24] Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. N Engl J Med 2000;342:1792–801.
[25] Folsom AR. Hemostatic risk factors for atherothrombotic disease: an epidemiologic view. Thromb Haemost 2001;86:366–73.
[26] Eitzman DT, Westrick RJ, Xu Z, Tyson J, Ginsburg D. Plasminogen activator inhibitor-1 deficiency protects against atherosclerosis progression in the mouse carotid artery. Blood 2000;96:4212–5.
[27] Hasenstab D, Lea H, Clowes AW. Local plasminogen activator inhibitor type 1 overexpression in rat carotid artery enhances thrombosis and endothelial regeneration while inhibiting intimal thickening. Arterioscler Thromb Vasc Biol 2000;20:853–9.
[28] Eren M, Painter CA, Atkinson JB, Declerck PJ, Vaughan DE. Age-dependent spontaneous coronary arterial thrombosis in transgenic mice that express a stable form of human plasminogen activator inhibitor-1. Circulation 2002;106:491–6.
[29] Tomiyama H, Kimura Y, Mitsuhashi H, et al. Relationship between endothelial function and fibrinolysis in early hypertension. Hypertension 1998;31:321–7.
[30] Kaikita K, Fogo AB, Ma L, et al. Plasminogen activator inhibitor-1 deficiency prevents hypertension and vascular fibrosis in response to long-term nitric oxide synthase inhibition. Circulation 2001;104:839–44.

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Editorial

Blood Pressure Variability in Hypertension

A Possible Cardiovascular Risk Factor

Kazuomi Kario

There is consensus that an increased blood pressure (BP) level increases the risk for cardiovascular disease. The ambulatory BP level during a 24-h period is more closely associated with advanced hypertensive target organ damage and a poorer cardiovascular prognosis than the clinic BP level. On the other hand, the clinical implication of ambulatory BP variability has not been established as an independent cardiovascular risk predictor.[1] Some studies have found that ambulatory BP variability is a significant and independent determinant of target organ damage,[2,3] and poor cardiovascular prognosis, whereas other investigators have not found an independent association.[4] In population studies, 24-h BP variability and daytime BP variability have been independently associated with left ventricular hypertrophy[3] and cardiovascular mortality,[4] respectively.

Recently, Gómez-Angelats et al[5] demonstrated that in middle-aged untreated hypertensive patients, ambulatory systolic BP variabilities (SD of 24-h BP) assessed by intermittent ambulatory BP monitoring and by noninvasive continuous (beat-to-beat) BP monitoring were significantly associated with brain deep white matter lesion detected by brain magnetic resonance imaging. This deep white matter lesion, a silent cerebral disease, is a predisposing condition of clinical stroke, dementia, depression, and falls in the elderly.[6] In older subjects, increased ambulatory systolic BP variability was also significantly associated with brain atrophy.[7]

The two major determinants of BP variability are age and a high BP level, which are also major cardiovascular risk factors. Thus, the significant impact of BP variability on cardiovascular disease seems to depend partly on age and high BP level. In fact, in a previous study, the significant association between BP variability and cardiovascular risk disappeared after controlling for confounding factors including age and ambulatory BP level.[4] In the study by Gómez-Angelats et al,[5] after adjusting for 24-h BP level, the positive association between BP variability and deep white matter lesion disappeared.

The 24-h ambulatory BP variability includes behavior-induced BP changes[8,9] and specific components of diurnal BP variation, which is a potential risk for cardiovascular disease (Fig. 1).[10–16] These specific components may be more closely associated with hypertensive target organ damage and subsequent cardiovascular events than overall 24-h ambulatory BP variability. Abnormal diurnal BP variation, such as marked nocturnal BP decreases (extreme dippers)[10,11] or exaggerated morning BP surge,[12–14] and reverse diurnal BP variation patterns with higher sleep BP than awake BP (risers), are risks for target organ damage and cardiovascular events. These phenotypes of ambulatory BP variability are associated with each other and with 24-h ambulatory BP variability.[14,15] Abnormal diurnal BP variability is associated with other relatively shorter BP variability such as orthostatic BP variability in elderly hypertensives.[15]

Various mechanisms may be involved in the association between BP variability and cardiovascular disease. In addition to augmented mechanical stress on the cardiovascular system (which leads to cardiovascular remodeling), increased variability of blood flow by augmented BP variability increases sheer stress on endothelial cells advancing atherosclerosis. Sheer stress-induced platelet activation at atherosclerotic stenotic sites,[17] and subsequent hypercoagulability may lead to cardiovascular events. Neurohumoral activation, which is increased in those with increased BP variability,[18] may also increase the risk for cardiovascular disease.

Clinically, current cardiovascular risk stratification depends on the ambulatory BP level and the status of the target organ damage. In addition to these two major predictors, BP variability may be the possible third axis of risk stratification. Development of a BP monitoring device to detect the specific component of BP variability, reproducibility, and further prospective and interventional studies are necessary to establish the clinical impact of BP variability on target organ damage and cardiovascular events in hypertensive patients.

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From the Division of Cardiology, Department of Medicine, Jichi Medical School, Tochigi, Japan.

Address correspondence and reprint requests to Dr. Kazuomi Kario, Division of Cardiology, Department of Medicine, Jichi Medical School, 3311-1, Yakushiji, Minamikawachi, Kawachi, Tochigi, 329-0498 Japan; e-mail: kkario@jichi.ac.jp

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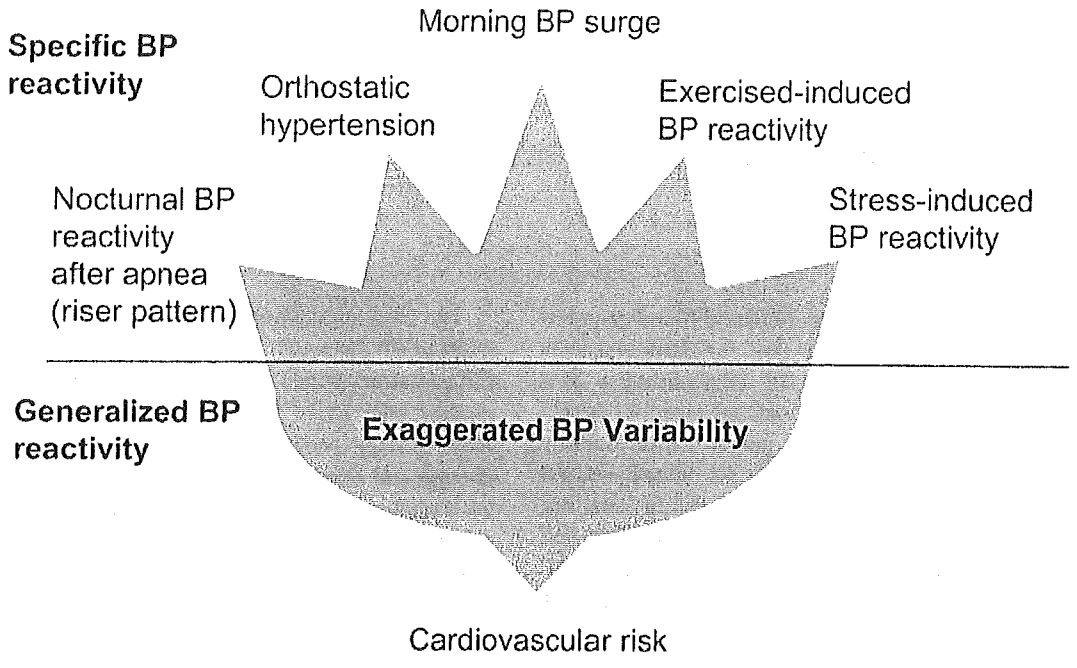

FIG. 1. Phenotypes of ambulatory blood pressure (BP) variability for cardiovascular risk in hypertension.

References

1. Parati G: Blood pressure variability, target organ damage and antihypertensive treatment. J Hypertens 2003;21:1827–1830.
2. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y: Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. Hypertension 2000;36: 901–906.
3. Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G, Ferrario M, Mancia G: Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). Hypertension 2002;39:710–714.
4. Verdecchia P, Borgioni C, Ciucci A, Gattobigio R, Schillaci G, Sacchi N, Santucci A, Santucci C, Reboldi G, Porcellati C: Prognostic significance of blood pressure variability in essential hypertension. Blood Press Monit 1996;1:3–11.
5. Gómez-Angelats E, de la Sierra A, Sierra C, Parati G, Mancia G, Coca A: Blood pressure variability and silent cerebral damage in essential hypertension. Am J Hypertens 2004;17:696–700.
6. Kario K, Pickering TG: Blood pressure variability in elderly patients. Lancet 2000;355:1645–1646.
7. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D: Ambulatory blood pressure and brain atrophy in the healthy elderly. Neurology 2002;59: 713–719.
8. Kario K, Schwartz JE, Gerin W, Robayo N, Maceo E, Pickering TG: Psychological and physical stress-induced cardiovascular reactivity and diurnal blood pressure variation in women with different work shifts. Hypertens Res 2002;25:543–551.
9. Kario K, James GD, Marion R, Ahmed M, Pickering TG: The influence of work- and home-related stress on the levels and diurnal variation of ambulatory blood pressure and neurohumoral factors in employed women. Hypertens Res 2002;25:499–506.
10. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K: Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension 2001;38:852–857.
11. Hoshide Y, Kario K, Schwartz JE, Hoshide S, Pickering TG, Shimada K: Incomplete benefit of antihypertensive therapy on stroke reduction in older hypertensives with abnormal nocturnal blood pressure dipping (extreme-dippers and reverse-dippers). Am J Hypertens 2002;15:844–850.
12. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003;107:1401–1406.
13. Kario K, Pickering TG, Hoshide S, Eguchi K, Ishikawa J, Morinari M, Hoshide Y, Shimada K: Morning blood pressure surge and hypertensive cerebrovascular disease: role of the α-adrenergic sympathetic nervous system. Am J Hypertens 2004;17:668–675.
14. Gosse P, Lasserre R, Minifie C, Lemetayer P, Clementy J: Blood pressure surge on rising. J Hypertens 2004;22:1113–1118.
15. Kario K, Eguchi K, Hoshide S, Hoshide Y, Umeda Y, Mitsuhashi T, Shimada K: U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol 2002;40:133–141.
16. Hoshide S, Kario K, Hoshide Y, Umeda Y, Hashimoto T, Kunii O, Ojima T, Shimada K: Associations between nondipping of nocturnal blood pressure decrease and cardiovascular target organ damage in strictly selected community-dwelling normotensives. Am J Hypertens 2003;16:434–438.
17. Ikeda Y, Handa M, Kawano K, Kamata T, Murata M, Araki Y, Sakai K, Ruggeri ZM: The role of von Willebrand factor and fibrinogen in platelet aggregation under varying shear stress. J Clin Invest 1991;87:1234–1240.
18. Kario K, Mitsuhashi T, Shimada K: Neurohumoral characteristics of older hypertensive patients with abnormal nocturnal blood pressure dipping. Am J Hypertens 2002;15:31–537.

Original Article

Smoking Is Associated with Silent Cerebrovascular Disease in a High-Risk Japanese Community-Dwelling Population

Kazuo EGUCHI*,**, Kazuomi KARIO**, Satoshi HOSHIDE**, Yoko HOSHIDE**, Joji ISHIKAWA**, Masato MORINARI**, Toru HASHIMOTO**, and Kazuyuki SHIMADA**

We aimed to investigate the relationships between smoking and silent cerebrovascular damage. We performed brain MRI to evaluate silent cerebral infarct (SCI) and periventricular hyperintensity (PVH), and carotid-ultrasonography to investigate carotid atherosclerotic plaque in 170 high-risk community-dwelling subjects (mean age: 67.2 years; men: 28.7%) who met more than 3 of the following 9 criteria: 1) high blood pressure (BP); 2) hypercholesterolemia; 3) left ventricular hypertrophy; 4) high hemoglobin A_{1c}; 5) proteinuria; 6) high waist-to-hip ratio; 7) smoking ≥30 cigarettes/day; 8) heavy alcohol intake; 9) family history of stroke. The subjects with SCI (SCI group) were older (70 years *vs.* 66 years, $p=0.004$) and had higher systolic BP (SBP) (160 *vs.* 148 mmHg, $p<0.001$) and higher carotid plaque score (2.3 *vs.* 1.5/person, $p<0.05$) than those without SCI. Among the variables, smoking status ($r=0.34$, $p<0.001$), SBP ($r=0.28$, $p<0.001$), male gender ($r=0.29$, $p<0.001$), left ventricular mass index ($r=0.25$, $p=0.001$), and serum creatinine ($r=0.20$, $p=0.006$) were significantly correlated with the number of SCIs. Among smokers, the number of SCIs was significantly higher in current smokers than in past smokers (1.9±2.2 *vs.* 0.5±0.8, $p<0.01$). In multiple regression analysis, smoking status ($\beta=0.183$, $p=0.045$) and SBP ($\beta=0.196$, $p=0.011$) were independent determinants of the increased number of SCIs. In conclusion, smoking status was an independent determinant of multiple SCIs in a high-risk Japanese community-dwelling population.

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***Key Words*: smoking, silent cerebral infarct, periventricular hyperintensity, high-risk community-dwelling subjects, carotid plaque**

Introduction

Cigarette smoking is associated with increased risk of stroke (*1–4*) and nearly doubles the risk of ischemic stroke: the greatest risk is subarachnoid haemorrhage, followed by cerebral infarction (*5*). Smoking acts synergistically with other risk factors (*6*, *7*), and the relative risk of stroke among hypertensive smokers is five times that among normotensive smokers, but 20 times that of normotensive non-smokers (*5*). Cigarette smoking is associated with a higher serum level of cholesterol, coronary vasomotor activity, platelet aggregation, and prothombotic state (*8*). Relationships between smoking and carotid atherosclerosis (*9*, *10*) and cardiac hypertrophy (*11*) have also been reported.

Early detection of silent cerebral infarct (SCI) is important because SCI is associated with higher rates of mortality and subsequent clinical cerebral infarctions (*12–14*). SCI has been reported to be associated with many "traditional" cerebrovascular risk factors, including age, hypertension, atrial

From the *Department of Cardiology, Shioya General Hospital, Tochigi, Japan, and **Department of Cardiology, Jichi Medical School, Tochigi, Japan.

Address for Reprints: Kazuo Eguchi, M.D., Ph.D., Department of Cardiology, Shioya General Hospital, Tomita 77, Yaita 329-2145, Japan. E-mail: kazuo-eg@jichi.ac.jp

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fibrillation and diabetes (*15*). However, conflicting results about the relationship between smoking and silent cerebrovascular disease were obtained in previous studies (*16–20*). In this study, we investigated the relationship between smoking and silent cerebrovascular damage in a high-risk Japanese general population.

Methods

Study Population

We studied 170 older asymptomatic patients (mean age: 67.2±9.5 years, ranging from 42 to 89 years; 48 men and 122 women). We enrolled the subjects into our study from the annual health screening in Nishiarita Town, Saga Prefecture, Japan. The number of town residents aged over 40 years was 5,323. Those who underwent their company's health check, or were unwilling to have this health check were excluded in advance as potential subjects. Of the 2,784 residents invited, 1,511 subjects participated in the '01 conventional health check. Two hundred eighty-three high-risk subjects (187 female and 96 male) were identified, and 170 subjects who visited the hospital to undergo further examinations (65.2% for females and 50.0% for males) were finally recruited. High-risk subjects were defined as meeting more than 3 of the following 9 criteria: 1) blood pressure (BP) ≥140/90 mmHg; 2) total cholesterol ≥250 mg/dl; 3) left ventricular hypertrophy by electrocardiogram who met either the Cornel voltage criteria ($RaVL+SV_3$ >28 mm in men and 20 mm in women) or Sokolow and Lyon criteria (SV_1+RV_5 or RV_6 >35 mm, RaVL >11 mm, RaVF >20 mm); 4) hemoglobin A_{1c} ≥6.5%; 5) proteinuria; 6) high waist-to-hip ratio (men ≥0.95, women ≥0.80); 7) current heavy smoker (≥30 cigarettes/day); 8) heavy alcohol intake (ethanol ≥84 ml/day); 9) family history of stroke. We excluded patients with renal failure, hepatic damage, secondary or malignant hypertension, ischemic or other cardiac disease, congestive heart failure, arrhythmia (including atrial fibrillation or other arrhythmia), stroke (including transient ischemic attacks), or other severe concomitant diseases. The duration of hypertension, smoking status, alcohol intake and family history of stroke were based mainly on the self-reported information.

This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan. All of the subjects studied were ambulatory and all gave informed consent for the study.

Brain MRI

Brain MRI was carried out in all 170 participants using a superconducting magnet with a main strength of 0.5 T (MRT50GP, Toshiba, Tokyo, Japan). The brain was imaged in the axial plane at a 7-mm slice thickness. T_1-weighted images were obtained using a short spin-echo pulse sequence with a repetition time of 470 ms and an echo time of 15 ms. T_2-weighted images were obtained using a long spin-echo pulse sequence with a repetition time of 4,000 ms and echo time of 120 ms. The matrix size was 256×256 pixels. An SCI was defined exclusively as a low signal intensity area (≥3 mm, but all were <15 mm in size) on T_1-weighted images that was also visible as a hyperintense lesion on T_2-weighted images, as described previously (*21*). The MRI images of the subjects were randomly stored and interpreted by reviewers blind to the subjects' names and characteristics.

Periventricular hyperintensity (PVH) on T_2-weighted images was classified into four groups, as described and illustrated previously (*22*). Briefly, grade 1, PVH was defined as no abnormality or minimal periventricular signal hyperintensity in the form of caps confined exclusively to the anterior horns or rims lining the ventricle; grade 2, as caps in both the anterior and posterior horns of lateral ventricles or periventricular unifocal patches; and grade 3, as multiple periventricular hyperintense punctate lesions and their early confluent stages. Multiple areas of high signal intensity that reached confluence in the periventricular region were defined as grade 4. The neuropathological significance of these MRI findings has been discussed in a previous report (*22*).

Other Measurements

Left ventricular mass index (LVMI) detected by echocardiography (SSD 2200; Aloka, Tokyo, Japan) was calculated by the method described previously (*23*). Carotid plaque was assessed by carotid-ultrasonography (LOGIQ500; GE Yokogawa Medical Systems, Tokyo, Japan). Carotid plaque score was calculated by the method reported previously (*24*). Urinary microalbumin was measured by a latex agglutination photometric immunoassay with an automated immunochemistry analyzer (LX-6000; Eiken Chemical Co., Tokyo, Japan).

Statistical Analysis

All statistical analyses were carried out with SPSS/Windows, version 11.0J (SPSS Inc., Chicago, USA). The χ^2 test was used to calculate proportions. One-way analysis of variance (ANOVA) was performed to detect differences of mean values among groups, and unpaired *t*-tests were used for comparison of variables between the SCI group and the non-SCI group. The data are expressed as the mean±SD or percentages. Spearman's correlation was used for bivariate analysis. Multivariate linear regression analysis was performed to analyze factors associated with the number of SCIs, advanced PVH and carotid plaque. Factors associated with SCI in the bivariate analysis or confirmed associating factors were entered as independent variables in this model. A two-sided p value <0.05 was considered statistically significant.

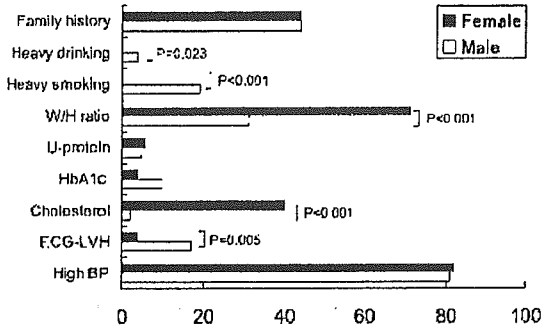

Fig. 1. *The frequency of the risk factors used for the screening of high-risk population divided according to gender. LVH, left ventricular hypertrophy; ECG, electrocardiogram; HbA1c, hemoglobin A1c.*

Table 1. Baseline Characteristics of the Subjects Studied

Variable	SCI (n=75)	Non-SCI (n=95)
Age (years)	70±7.6**	66±9.9
Male gender (%)	26 (35)	22 (23)
Body mass index (kg/m^2)	23.6±3.1	23.3±2.9
Hypertension history (%)	43 (37)	28 (45)
Diabetes (%)	9 (12)	6 (6)
Smoking (%)	16 (21)	11 (12)
Serum creatinine (mg/dl)	0.97±0.2	0.92±0.20
Total cholesterol (mg/dl)	219±37	227±40
Triglyceride (mg/dl)	117±57	127±90
Hematocrit (%)	40.3±3.8	40.5±3.3
Urinary microalbumin (mg/g•Cr)	58±148	43±163
Systolic BP (mmHg)	160±21***	148±19
Diastolic BP (mmHg)	90±9.9*	86±11
LV mass index (g/m^2)	138±44**	123±33
Plaque score (/person)	2.3±2.8*	1.5±2.9

Data are shown as the number (%) or mean±SD. *p<0.05, **p<0.01, ***p<0.001 *vs.* non-SCI. SCI, silent cerebral infarct; Cr, creatinine; BP, blood pressure; LV, left ventricular.

Results

Baseline Characteristics of the Population

The frequencies of the risk factors used for the screening of the high-risk population divided according to gender are shown in Fig. 1. High BP, high waist-to-hip ratio, family history of stroke, and hypercholesterolemia were the 4 most commonly met of the 9 criteria. Although the percentages of heavy drinking and heavy smoking were higher in men, higher waist-to-hip ratio and hypercholesterolemia were more common in women.

Table 1 shows the characteristics of the 170 subjects separated into two groups: an SCI group (n=75) and a non-SCI group (n=95). Gender, body mass index (BMI), prevalence of smokers, hypertension history, diabetes, serum creatinine, total cholesterol, triglyceride, hematocrit, and urinary microalbumin were comparable between the two groups, but age, systolic BP (SBP), diastolic BP (DBP), LVMI and plaque score were higher in the SCI group than in the non-SCI group. We used the terms "hypertension" and "high BP" separately, because BP in the health screening check tends to be very high. "Hypertension" referred to hypertensive patients who had been found to have hypertension previously in a clinic or hospital, whereas "high BP" means simply that high BP was recorded in the health screening check. In all 170 subjects screened, high-density lipoprotein (HDL) cholesterol was 58.7±13 mg/dl for women (n=122) and 52.2±14 mg/dl for men (n=48) (p< 0.01), but the prevalence of low HDL cholesterol (<40 mg/dl) was similar between women (26%) and men (21%).

Silent Cerebral Infarcts

Age (r=0.22, p=0.003), male gender (r=0.29, p<0.001), smoking status (r=0.34, p<0.001), SBP (r=0.28, p<0.001), LVMI (r=0.25, p=0.001), and serum creatinine (r=0.20, p=0.006) were significantly correlated with the number of SCIs.

Table 2. Multiple Regression Model for the Number of Silent Cerebral Infarct

Independent variable	Regression coefficient	SEM	β	p
Constant	−2.447	1.637		
Age (years)	0.002	0.011	0.115	0.135
Male gender	0.285	0.304	0.097	0.350
Body mass index (kg/m^2)	−0.001	0.032	−0.021	0.780
Systolic BP (mmHg)	0.001	0.005	0.196	0.011
Total cholesterol (mg/dl)	0.000	0.003	0.001	0.990
Serum creatinine (mg/dl)	0.494	0.635	0.070	0.438
HbA1c (%)	−0.003	0.157	−0.016	0.839
Smoking	0.663	0.328	0.183	0.045

Coding for gender: 0, women; 1, men. "Smoking" was defined present, if the subjects smoke at least one cigarette per day. BP, blood pressure.

Table 3. Characteristics of Subjects Divided by Smoking Status

	Non-smoker	Past smoker	Current smoker
n	126	20	28
Male gender (%)	8	75***	89***
Age (years)	67.0±9.4	62.7±9.1	71.7±8.4*
Duration of smoking (years)	0	37±14	27±15***,†††
Diabetes mellitus (%)	7	15	11
Systolic BP (mmHg)	154±20	140±17*	163±21†††
Diastolic BP (mmHg)	88±10	84±10	90±11
Pulse pressure (mmHg)	66±16	57±18	73±16†
Total cholesterol (mg/dl)	232±36	209±43†	192±27***
Hematocrit (%)	40±3.3	42±3.7*	43±3.8***
Serum creatinine (mg/dl)	0.9±0.2	1.0±0.2	1.1±0.2***,†
Blood sugar (mg/dl)	86±13	81±14	90±25
Hemoglobin A_{1c} (%)	5.3±0.6	5.6±0.8	5.5±0.7
LVMI (g/m^2)	123±34	147±50*	146±42*
Urinary albumin (mg/g·Cr)	52±168	62±162	25±47
Plaque score (/person)	1.4±2.2	2.6±2.7	3.0±4.7*
Number of SCI (/person)	0.7±1.0	0.5±0.8	1.9±2.2***,††
SCI (%)	42	37	59
Multiple SCI (%)	21	16	52**,†
PVH grade	1.3±0.7	1.4±0.6	1.8±0.8

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ *vs.* non-smoker, † $p<0.05$, †† $p<0.01$, ††† $p<0.001$ *vs.* past smoker. BP, blood pressure; LVMI, left ventricular mass index; Cr, creatinine; SCI, silent cerebral infarct; PVH, periventricular hypertintensity.

Factors associated with SCI in bivariate analyses were entered into a multiple linear regression model (Table 2). Smoking and SBP were independently correlated with the number of SCIs in this model. Despite the significant bivariate associations, age, gender, total cholesterol and LVMI were not independent predictors of SCI in this model.

Smoking Status and SCI

The percentage of heavy smokers (>30 cigarettes/day) was only 6/27 (22%). Of the overall 170 patients, 28 (16.5%) were current smokers, 20 (11.8%) were past-smokers, and 126 (74.1%) were non-smokers (Table 3). The percentage of males was higher in current smokers and past smokers than in non-smokers. Current smokers were older than non-smokers. SBP and pulse pressure were higher in current smokers than in past smokers. Although the prevalence of SCIs was similar among the 3 groups, the number of SCIs (Fig. 2) and the prevalence of multiple SCIs were higher in current smokers than in past smokers and non-smokers. However, the total duration of smoking was shorter in current smokers than in past smokers (27±15 years *vs.* 37±14 years, $p<0.01$).

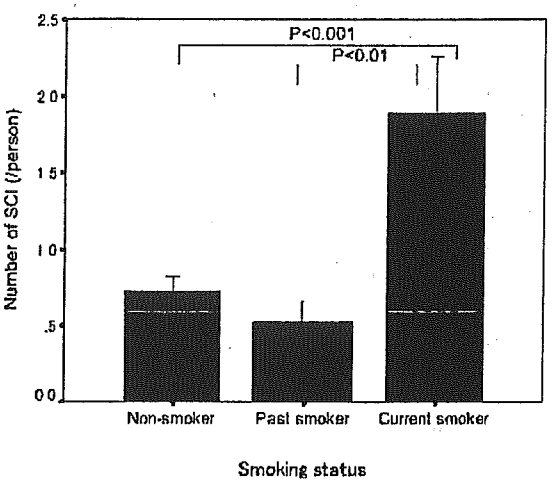

Fig. 2. *Comparison of the number of SCIs divided by non-smokers, past smokers and current smokers. Values are the means±SEM.*

PVH and Carotid Plaque

As shown in Fig. 3a, the grade of PVH was significantly correlated with the number of cigarettes ($r=0.201$, $p=0.009$). The prevalence of advanced PVH (grade 3 or 4) was significantly higher in current smokers (59%) than in past smokers (21%, $p=0.02$) and non-smokers (25%, $p=0.001$) (Fig. 3b). In multiple linear regression analysis, the only factor related to advanced PVH was SBP ($\beta=0.189$, $p=0.015$) (Table 4).

As shown in Fig. 4a, the carotid plaque score was significantly associated with the number of cigarettes ($r=0.224$,

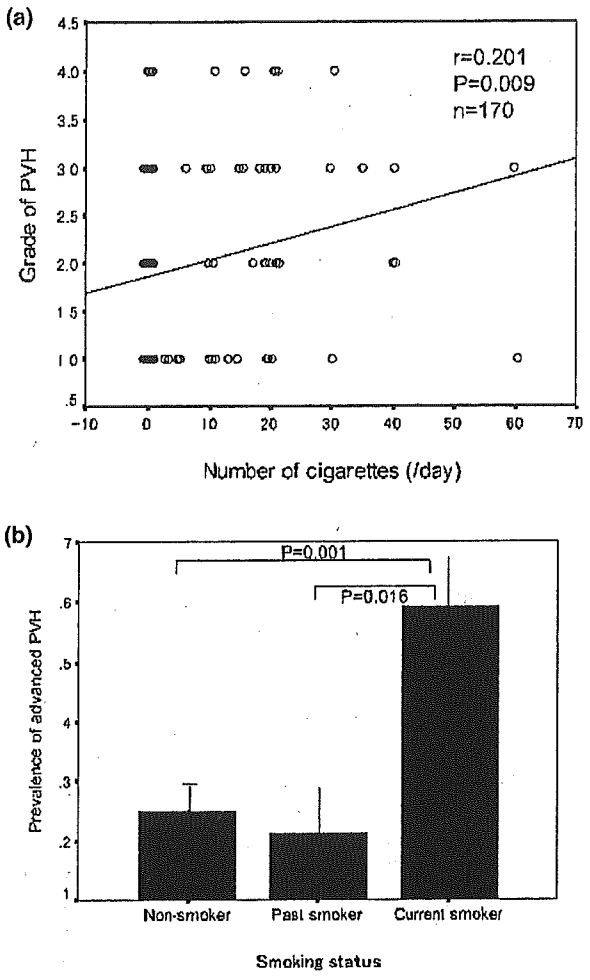

Fig. 3. *a: Relationships between number of cigarettes and grade of PVH. Correlation coefficient of overall patients was* r=*0.201,* p=*0.009. Straight bar shows regression line. b: Comparison of the prevalence of advanced PVH divided according to non-smokers, past smokers and current smokers. Values are the means*±*SEM.*

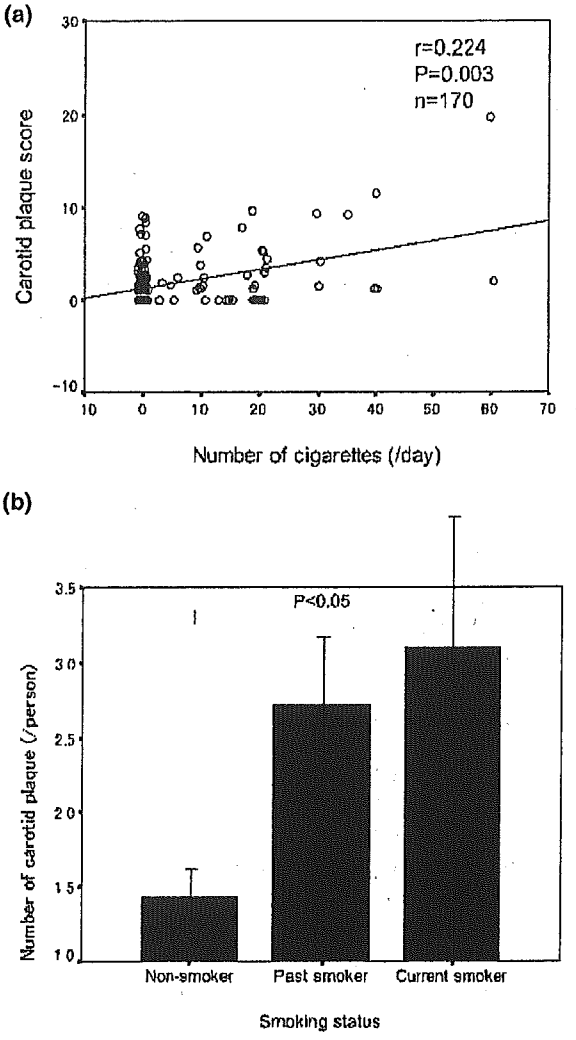

Fig. 4. *a: Relationships between number of cigarettes and carotid plaque score. Correlation coefficient of overall patients was* r=*0.224,* p=*0.003. Straight bar shows regression line. b: Comparison of the number of carotid plaque divided according to non-smokers, past smokers and current smokers. Values are the means*±*SEM.*

Table 4. Multiple Regression Model for Advanced PVH

Independent variable	Regression coefficient	SEM	β	p
Constant	−0.620	0.568		
Age (years)	0.007	0.004	0.150	0.054
Male gender	−0.033	0.105	−0.032	0.757
Body mass index (kg/m²)	−0.011	0.011	−0.072	0.328
Systolic BP (mmHg)	0.004	0.002	0.189	0.015
Total cholesterol (mg/dl)	−0.001	0.001	−0.076	0.382
Serum creatinine (mg/dl)	0.420	0.220	0.172	0.058
HbA1c (%)	−0.035	0.054	−0.050	0.525
Smoking	0.164	0.114	0.131	0.151

Coding for gender: 0, women; 1, men. "Smoking" was defined present, if the subjects smoke at least one cigarette per day. Advanced PVH was defined as PVH grade 3 or 4. PVH, periventricular hypertintensity; BP, blood pressure.

Table 5. Multiple Regression Model for Carotid Plaque Score

Independent variable	Regression coefficient	SEM	β	p
Constant	−6.915	3.521		
Age (years)	−0.079	0.024	0.254	0.001
Male gender	2.144	0.654	0.340	0.001
Body mass index (kg/m^2)	−0.115	0.069	−0.123	0.098
Systolic BP (mmHg)	−0.003	0.011	0.025	0.747
Total cholesterol (mg/dl)	−0.002	0.006	0.212	0.015
Serum creatinine (mg/dl)	−1.269	1.367	−0.084	0.354
HbA$_{1c}$ (%)	0.507	0.337	0.119	0.134
Smoking	0.170	0.706	0.022	0.810

Coding for gender: 0, women; 1, men. "Smoking" was defined present, if the subjects smoke at least one cigarette per day. BP, blood pressure.

$p=0.003$). The carotid plaque score was similar between current smokers and past smokers (3.0±4.7 *vs.* 2.6±2.7, n.s.) (Fig. 4b). In multiple linear regression analysis, factors related to the carotid plaque score were age ($\beta=0.254$, $p=0.001$), male gender ($\beta=0.340$, $p=0.001$) and total cholesterol ($\beta=0.212$, $p=0.015$) (Table 5).

Discussion

In the present study, the overall prevalences of single SCI and multiple SCIs were 75/170 (44%) and 43/170 (25%), respectively, in the subjects aged 42 to 89 years old. The prevalence of SCI was higher than those in previous population-based studies: 11% (*16*) or 20% (*17*).

In the present study, smoking and SBP at the health screening examination were found to be independent risk factors for SCI among the high-risk community-dwelling Japanese population. In a previous Japanese epidemiological study (the Hisayama study), the determinants of SCI were higher BP as well as age, history of coronary heart disease, diabetes and atrial fibrillation (*25*). The present study design was different from the design of the Hisayama study, but both studies indicate that BP at the health screening might be an important factor related to SCI.

There is controversy about smoking as a risk factor for SCI. Two reports (*16*, *26*) showed that cigarette smoking was related to the prevalence of SCI, but other reports failed to find this relationship (*17–19*). In the present study, the results were consistent with the former reports. The major differences between our study and these previous studies were the study population: our high-risk population was selected from the general population based on having more than 3 risk factors but no prior cardiovascular events. The impact of each risk factor on SCI in the present study was different from that in previous studies, because SCI was not determined by older age. On the other hand, the history of hypertension (nearly 40% *vs.* 30%) and BP level (nearly 150/88 mmHg *vs.* 125/75 mmHg) were higher in our population than in the report of Yamashita *et al.* (*18*). Although the rate of smokers was not different between the SCI group and non-SCI group, presence of smoking was related to the increased number of SCIs. This may indicate that smoking can cause extensive atherosclerotic changes in the brain arteries.

Generally, in smokers, cardiovascular risk factors tend to cluster (*27*). Furthermore, smoking itself has both acute and chronic effects of raising BP levels (*28*). The mechanisms of the acute increase of BP may be due partly to the elevation of plasma endothelin-1 levels (*29*) or associated with oxidative stress (*30*). Plasma endothelin-1 concentrations also showed significant positive association with the number of asymptomatic SCIs in a previous report (*31*).

The number of SCIs was significantly higher in current smokers than in past smokers; however, LVMI and plaque score were similar between current and past smokers. This may indicate that smoking has different impacts on hypertensive damage of different target organs by different mechanisms. Because smoking can cause hypertension even in young people (*32*), relationships between smoking, hypertension and arterial stiffness might be a key factor. In a previous study, smoking caused short-term increases in arterial wall stiffness in habitual smokers, while no obvious long-term effect was observed on arterial stiffness (*33*). In the present study, pulse pressure was significantly greater in current smokers than in past smokers. Pulse pressure was reported to have greater prognostic value and to be associated with cardiovascular risk factors, including smoking (*34*), and may be a marker of systemic atherosclerosis (*35*). The difference of the number of SCIs between current and past smokers is partly explainable by pulse pressure. Cessation of smoking before developing atherosclerotic change can prevent further deterioration of atherosclerosis. Synergistic effects of aging and smoking might be responsible for causing multiple atherosclerotic effects on brain arteries: namely, the impact of smoking on silent cerebrovascular damage might be amplified when smokers continued to smoke after middle age.

In the present study, the prevalence of advanced PVH was higher in current smokers than in past smokers or non-smokers. In multiple regression analysis, only SBP was a signifi-

cant determinant of advanced PVH, but age and serum creatinine tended to be associated with advanced PVH. In other words, advanced PVH might be determined mainly by hypertensive (hypertension and silent renal damage) factors.

The number of carotid plaques was also higher in current smokers than in non-smokers. However, in multiple linear regression analysis, the number of carotid plaques was significantly associated with age, male gender and cholesterol, but not with smoking. Previous reports have shown that smoking was associated with carotid atherosclerosis (*10*, *36*) and atherosclerotic peripheral arterial disease (*37*), but not pulse wave velocity (*38*). In a report about a male working population, only total cholesterol level was associated with the progression of early carotid atherosclerosis (*39*). In the present study, we failed to find any association between smoking and carotid plaque. This may be because the impact of aging, gender, and lipids on carotid plaque was stronger than that of smoking.

In conclusion, current smoking was shown to be an independent determinant of SCI in a Japanese community-dwelling high-risk population.

References

1. Ockene IS, Miller NH: Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association: American Heart Association Task Force on Risk Reduction. *Circulation* 1997; **96**: 3243–3247.
2. Tanizaki Y, Kiyohara Y, Kato I, *et al*: Incidence and risk factor for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke* 2000; **31**: 2616–2622.
3. Hata Y, Kimura Y, Muratani H, *et al*: Office blood pressure variability as a predictor of brain infarction in elderly hypertensive patients. *Hypertens Res* 2000; **23**: 553–560.
4. Yamagishi K, Iso H, Kitamura A, *et al*: Smoking raises the risk of total and ischemic strokes in hypertensive men. *Hypertens Res* 2003; **26**: 209–217.
5. Shinton R, Beevers G: Meta-analysis of relation between cigarette smoking and stroke. *BMJ* 1989; **298**: 789–794.
6. Kato J, Aihara A, Kikuya M, *et al*: Risk factors and predictors of coronary arterial lesions in Japanese hypertensive patients. *Hypertens Res* 2001; **24**: 3–11.
7. Kannel WB: Framingham study insights into hypertensive risk of cardiovascular disease. *Hypertens Res* 1995; **18**: 181–196.
8. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK: Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med* 2003; **138**: 891–897.
9. Liang YL, Shiel LM, Teede H, *et al*: Effects of blood pressure, smoking, and their interaction on carotid artery structure and function. *Hypertension* 2001; **37**: 6–11.
10. Crouse JR, Toole JF, McKinney WM, *et al*: Risk factors for extracranial carotid artery atherosclerosis. *Stroke* 1987; **18**: 990–996.
11. Verdecchia P, Schillaci G, Borgioni C, *et al*: Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in essential hypertension. *J Hypertens* 1995; **13**: 1209–1215.
12. Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S: Subcortical silent brain infarction as a risk factor for clinical stroke. *Stroke* 1997; **28**: 1932–1939.
13. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K: Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38**: 852–857.
14. Bernick C, Kuller L, Dulberg C, *et al*, for Cardiovascular Health Study Collaborative Research Group: Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology* 2001; **57**: 1222–1229.
15. Uehara T, Tabuchi M, Mori E: Risk factor for silent cerebral infarcts in subcortical white matter and basal ganglia. *Stroke* 1999; **30**: 378–382.
16. Howard G, Wagenknecht LE, Cai J, Cooper L, Kraut MA, Toole JF: Cigarette smoking and other risk factors for silent cerebral infarction in the general population. *Stroke* 1998; **29**: 913–917.
17. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB: Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam scan study. *Stroke* 2002; **33**: 21–25.
18. Yamashita K, Kobayashi S, Yamaguchi S, Koide H: Cigarette smoking and silent brain infarction in normal adults. *Intern Med* 1996; **35**: 704–706.
19. Lee SC, Park SJ, Ki HK, *et al*: Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertension* 2000; **36**: 73–77.
20. Fukuda H, Kitani M: Cigarette smoking is correlated with the periventricular hyperintensity grade on brain magnetic resonance imaging. *Stroke* 1996; **27**: 645–649.
21. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K: Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients: advanced silent cerebrovascular damage in extreme dippers. *Hypertension* 1996; **27**: 130–135.
22. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T: Silent cerebrovascular disease in the elderly: correlation with ambulatory pressure. *Hypertension* 1990; **16**: 692–699.
23. Devereux RB, Alonso DR, Lutas EM, *et al*: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450–458.
24. Handa N, Matsumoto M, Maeda H, *et al*: Ultrasonic evaluation of early carotid atherosclerosis. *Stroke* 1990; **21**: 1567–1572.
25. Shinkawa A, Ueda K, Kiyohara Y, *et al*: Silent cerebral infarction in a community-based autopsy series in Japan: the Hisayama study. *Stroke* 1995; **26**: 380–385.
26. Herderscheê D, Hijdra A, Algra A, Koudstaal PJ, Kappelle LJ, van Gijn J: Silent stroke in patients with transient ischemic attack or minor ischemic stroke: the Dutch TIA Trial Study Group. *Stroke* 1992; **23**: 1220–1224.
27. Muratani H, Kimura Y, Fukiyama K, *et al*: Control of blood pressure and lifestyle-related risk factors in elderly Japanese hypertensive subjects. *Hypertens Res* 2000; **23**: 441–449.
28. Groppelli A, Giorgi DM, Omboni S, Parati G, Mancia G:

Persistent blood pressure increase induced by heavy smoking. *J Hypertens* 1992; **10**: 495–499.
29. Haak T, Jungmann E, Raab C, Usadel KH: Elevated endothelin-1 levels after cigarette smoking. *Metabolism* 1994; **43**: 267–269.
30. Tomiyama H, Kushiro T, Okazaki R, Yoshida H, Doba N, Yamashina A: Influences of increased oxidative stress on endothelial function, platelets function, and fibrinolysis in hypertension associated with glucose intolerance. *Hypertens Res* 2003; **26**: 295–300.
31. Minami S, Yamano S, Yamamoto Y, *et al*: Associations of plasma endothelin concentration with carotid atherosclerosis and asymptomatic cerebrovascular lesions in patients with essential hypertension. *Hypertens Res* 2001; **24**: 663–670.
32. Kawasaki T, Uezono K, Sanefuji M, *et al*: A 17-year follow-up study if hypertensive and normotensive male university students in Japan. *Hypertens Res* 2003; **26**: 445–452.
33. Kool MJ, Hoeks AP, Struijker Boudier HA, Reneman RS, Van-Bortel LM: Short- and long-term effects of smoking on arterial wall properties in habitual smokers. *J Am Coll Cardiol* 1993; **22**: 1881–1886.
34. Inoue T, Matsuoka M, Nagahama K, *et al*: Cardiovascular risk factors associated with pulse pressure in a screened cohort in Okinawa, Japan. *Hypertens Res* 2003; **26**: 153–158.
35. Miyagi T, Muratani H, Kimura Y, *et al*: Increase in pulse pressure relates to diabetes mellitus and low HDL cholesterol, but not to hyperlipidemia in hypertensive patients aged 50 years or older. *Hypertens Res* 2002; **25**: 335–341.
36. Howard G, Wagenknecht LE, Burke GL, *et al*: Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA* 1998; **279**: 119–124.
37. Cui R, Iso H, Yamagishi K, *et al*: Ankle-arm blood pressure index and cardiovascular risk factors in elderly Japanese men. *Hypertens Res* 2003; **26**: 377–382.
38. Okamura T, Moriyama Y, Kadowaki T, Kanda H, Ueshima H: Non-invasive measurement of brachial-ankle pulse wave velocity is associated with serum C-reactive protein but not with α-tocopherol in Japanese middle-aged male workers. *Hypertens Res* 2004; **27**: 173–180.
39. Fujii K, Abe I, Ohya Y, *et al*: Risk factors for the progression of early carotid atherosclerosis in a male working population. *Hypertens Res* 2003; **26**: 465–471.

Original Article

Reproducibility of Arterial Stiffness Indices (Pulse Wave Velocity and Augmentation Index) Simultaneously Assessed by Automated Pulse Wave Analysis and Their Associated Risk Factors in Essential Hypertensive Patients

Yoshio MATSUI, Kazuomi KARIO*, Joji ISHIKAWA*, Kazuo EGUCHI*, Satoshi HOSHIDE*, and Kazuyuki SHIMADA*

Arterial stiffness is a strong determinant of cardiovascular risk. Pulse wave velocity (PWV) and the augmentation index (AIx) are widely used as arterial stiffness indices. We studied the reproducibility of these indices and their association with cardiovascular risk factors in hypertensives. We measured brachial blood pressure (BP), brachial-ankle PWV (baPWV) and carotid AIx (cAIx) twice (at the baseline and 4 weeks after the baseline) using an automatic device in 103 hypertensives. The mean intraobserver-intersession difference was 29.0 cm/s with an SD of 201.6 cm/s for baPWV, and 0.5% with an SD of 5.9% for cAIx, and the Bland-Altman plots demonstrated the good reproducibility of baPWV and cAIx. Both baPWV and cAIx (the average of the 1st and the 2nd measurements) were significantly correlated with age, systolic BP (SBP), and pulse pressure (all, $p<0.005$); however, these factors were not correlated with each other ($r=0.06$, NS). cAIx was correlated with height, heart rate (HR), total cholesterol, and low density lipoprotein cholesterol (LDL-C) (all, $p<0.05$). In multiple regression analysis, age, SBP, and HR emerged as significant independent predictors of baPWV (adjusted $R^2=0.43$, $p<0.0001$), while height, SBP, HR, and LDL-C emerged as significant independent predictors of cAIx (adjusted $R^2=0.58$, $p<0.0001$). Both PWV and AIx measured using an automatic device were fairly reproducible, and their associated risk factors appeared to be different. Automated simultaneous measurement of these arterial stiffness indices may be useful for risk stratification of hypertensives. (*Hypertens Res* 2004; 27: 851–857)

***Key Words*: automated pulse wave analysis, pulse wave velocity, augmentation index, reproducibility, hypertension**

Introduction

Pulse wave velocity (PWV) and the augmentation index (AIx: augmentation expressed as percentage of the pulse pressure [PP]) have recently been recognized as arterial stiffness indices (*1–3*). Recent reports have shown that PWV is a prognostic predictor in patients with hypertension or end-stage renal failure, independently of classical risk factors and PP (*1*, *2*, *4*). On the other hand, it has been reported that AIx was an independent predictor of all-cause and cardiovascular mortality in end-stage renal failure patients (*3*), and also, recently, that increased AIx was associated with the presence and severity of coronary artery disease (CAD), particularly

From the Department of Internal Medicine, Miwa Municipal Hospital, Yamaguchi, Japan, and *Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical School, Tochigi, Japan.

Address for Reprints: Yoshio Matsui, M.D., Department of Internal Medicine, Miwa Municipal Hospital, 1776 Shibukuma, Miwa-cho, Kuga-gun, Yamaguchi 740-1225, Japan. E-mail: matsui.yoshio@town.miwa.yamaguchi.jp

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Table 1. Clinical Characteristics and Arterial Stiffness Indices in Study Patients

Variable	Mean±SD (or %)
Age (years)	69.4±8.3
Men (%)	39.8
Height (cm)	152.5±8.5
Body mass index (kg/m²)	23.9±3.3
Duration of hypertension (years)	7.5±6.5
Treated hypertensives (%)	56.3
SBP (mmHg)	157.7±16.3
DBP (mmHg)	87.5±10.6
MAP (mmHg)	110.9±11.3
PP (mmHg)	70.2±12.9
Heart rate (beats/min)	65.6±9.1
Total cholesterol (mg/dl)	210.3±30.6
HDL cholesterol (mg/dl)	57.4±16.6
LDL cholesterol (mg/dl)	126.3±30.0
Triglyceride (mg/dl)	133.2±62.3
Fasting plasma glucose (mg/dl)	97.9±24.0
HbA1C (%)	5.2±0.8
Serum creatine (mg/dl)	0.8±0.2
Risk factors	
Diabetes mellitus (%)	18.6
Hyperlipidemia (%)	46.1
Smokers (%)	21.6
Coronary artery disease (%)	3.9
Cerebrovascular disease (%)	16.7
Arterial indices*	
baPWV (cm/s)	2,143.7±409.0
cAIx (%)	32.1±8.3
ABI	1.1±0.2

Data are shown as the mean±SD or prevalences. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, calculated as DBP+PP/3; PP, pulse pressure, calculated as SBP−DBP; baPWV, brachial-ankle pulse wave velocity; cAIx, carotid augmentation index; ABI, ankle/brachial blood pressure index. * The average of the 1st and the 2nd measurements.

in younger and middle-aged male patients (*5*). However, in hypertensive patients the impact of AIx on the prognosis remains unclear.

Arterial stiffness is determined by functional and structural components related to the intrinsic elastic properties of the artery (*6*). Persistently elevated blood pressure (BP) accelerates arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby increasing arterial stiffness (*6*). On the other hand, arterial stiffening increases systolic BP (SBP) and PP directly by increasing the PWV generated by ventricular ejection and by an early return of arterial wave reflections, which augment central aortic and left ventricular pressure in late systole, resulting in increased systolic work and thus left ventricular hypertrophy and increased myocardial oxygen demand (*6*). Although the timing of the arrival of the reflected wave at the proximal aorta is largely determined by large artery PWV, AIx and PWV are not simply interchangeable indices of arterial stiffness, because AIx is influenced by vasoactive drugs independently of PWV (*7*). Although it might be presumed that these arterial stiffness indices are useful for following up hypertensive patients, it remains to be determined whether there are significant differences in the reproducibility and related cardiovascular risk factors between these indices.

We therefore studied the reproducibility of PWV and AIx determined using a recently developed automatic device and the association between these indices and cardiovascular risk factors in hypertensive patients.

Methods

Study Population

One hundred and three consecutively recruited outpatients (41 men and 62 women; mean age, 69.4 years) with essential hypertension were enrolled in this study. Characteristics of the study population are shown in Table 1. Hypertension was defined as SBP≥140 mmHg, diastolic BP (DBP)≥90 mmHg, or use of antihypertensive medication. Of the total population, 56.3% were treated hypertensives (diuretics: 24.1%; β-blockers: 12.1%; calcium channel blockers: 31.0%; angiotensin-converting enzyme [ACE] inhibitors: 15.5%; angiotensin receptor blockers: 44.8%). Hyperlipidemia was defined as total cholesterol (TC)≥220 mg/dl, triglyceride (TG)≥150 mg/dl, or use of antihyperlipidemic medication. Diabetes mellitus was defined as a fasting blood glucose ≥126 mg/dl or the current use of antidiabetic medication. Smoking status was defined as current or past *vs.* never. Exclusion criteria were as follows: secondary hypertension, complicated hypertension with recent cardiovascular events, atrial fibrillation, and arteriosclerosis obliterance (ASO; defined as an ankle/brachial blood pressure index [ABI]<0.9). According to these criteria, we excluded 4 patients (3 men and 1 woman) who had ASO by measuring ankle/brachial blood pressure. Medications were not changed for any of the patients during the study period. The study was approved by the Research Ethics Committee of Miwa Municipal Hospital, and informed consent was obtained from all patients.

Risk Factor Evaluation

A detailed history of risk factors and medical conditions was obtained. The patients were scheduled to fast in the morning without medication. Venous blood was drawn for analysis of fasting plasma glucose (FPG) and serum concentrations of TC, TG, high-density lipoprotein cholesterol (HDL-C), serum creatinine (Cre), and HbA1C by standard laboratory methods. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation. None of the patients had

a TG value>400 mg/dl, which would have made the use of this equation inappropriate. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2).

Pulse Wave Analysis

Patients were examined in a quiet and temperature-controlled laboratory (23 °C) after 5 min of lying supine at 9:00–11:00 AM. Brachial-ankle PWV (baPWV) was used as a substitute for aortic PWV in the study because of the good correlation between baPWV and aortic PWV ($r=0.87$, $p<0.01$), which was obtained by invasive measurements of the aorta across a distance of 50 cm using a catheter tip manometer (*8*). baPWV was measured as reported previously (*8–10*), using a volume-plethysmographic device (form PWV/ABI; Colin Co., Ltd., Komaki, Japan) with four cuffs matched with oscillometric sensors, which were wrapped around the upper arms and ankles, and then the pulse volume records of the bilateral brachial and tibial arteries were monitored during a continuous deflation of the cuffs. The BP of each lesion can be obtained by this oscillometric method. Electrodes of the electrocardiograph were placed on both wrists, and a microphone was placed on the left edge of the sternum to detect heart sounds. Transit time (ΔT_{ba}) between the brachial and ankle pulse waves was automatically measured from the time delay between the feet (sharp initial systolic upstroke) of the wave at the 2 sites. The distance between the 2 recording sites of baPWV was calculated automatically based on the height of the patient and anthropomorphic data for the Japanese population. The path length from the suprasternal notch to the brachium (L_b) and ankle (L_a) was indicated using the following equation: $L_b=0.2195\times$height of the patient (cm)-2.0734, $L_a=0.8129\times$height of the patient (cm)$+12.328$. baPWV was then calculated using the following equation: baPWV$=(L_a-L_b)/\Delta T_{ba}$. Since there was a significant positive correlation between left and right baPWV ($r=0.93$, $p<0.0001$), we used the right baPWV value in this study.

Measurement of carotid AIx (cAIx) was performed using a multi-element applanation tonometry sensor for the left common carotid artery. A multi-element tonometry sensor, which consists of 15 pressure-sensitive small elements aligned side-by-side, is coupled to the device. The carotid tonometry sensor is compact and lightweight and can be easily attached around the neck. The sensor element manually located at the center of the carotid artery can be identified by screening the pulse pressure levels of the 15 elements, provided that the sensor element size is sufficiently small compared to the vessel diameter. The investigator can apply the sensor easily with one hand by holding the handle of the sensor, and adjust the pressure and position so as to record the best signals while palpating the carotid artery with the other hand. The quality of the carotid pulse wave and the downward force were checked visually on tonography, and pulse waves were recorded and stored over a 30-s period. The validity and reliability of this tonometry sensor have been reported previously (*11*).

In this study, we evaluated the intraobserver-intersession reproducibility to confirm whether baPWV and cAIx obtained using this device were suitable for longitudinal clinical studies. All measurements were therefore made by the same investigator, and obtained on two separate visits with a time interval of 4 weeks. The mean value of baPWV and cAIx between the different visits was applied in evaluating related factors. Table 1 shows the hemodynamic parameters obtained using this device in the study population.

Statistical Analysis

All parameters are given as the mean±SD or percentage (%). Paired *t*-test was used to determine the significance of differences between visit 1 and visit 2 for hemodynamic parameters. The reproducibility of arterial stiffness indices was analyzed using Bland-Altman plots (*12*). Relationships between arterial stiffness indices and clinical/hemodynamic parameters were analyzed by simple and multiple regression analysis. A value of $p<0.05$ was considered to indicate statistical significance.

Results

Reproducibility of Arterial Stiffness Indices

There were no significant differences between visit 1 and visit 2 in SBP ($p=0.06$), HR ($p=0.96$), baPWV ($p=0.17$), or cAIx ($p=0.40$). Figures 1 and 2 show the agreement between the two measurements of baPWV and cAIx. The correlation coefficients of SBP, heart rate (HR), baPWV, and cAIx between visit 1 and visit 2 were 0.67 ($p<0.0001$), 0.78 ($p<0.0001$), 0.89 ($p<0.0001$), and 0.87 ($p<0.0001$), respectively. The coefficients of variation (CV) of SBP, HR, baPWV, and cAIx were 3.9%, 3.6%, 3.8%, and 9.7%, respectively. As shown by the Bland-Altman plots, the mean intraobserver-intersession difference was 29.0 cm/s, with an SD of 201.6 cm/s, for baPWV (Fig. 1), and 0.5%, with an SD of 5.9%, for cAIx (Fig. 2). As can be seen, in each graph most of the data points fell well within the 2SD range.

Associated Risk Factors

baPWV and cAIx were not significantly correlated with each other ($r=0.06$, NS). In simple regression analysis, baPWV was significantly correlated with age ($r=0.40$, $p<0.0001$), SBP ($r=0.39$, $p<0.0001$), mean arterial pressure (MAP; $r=0.29$, $p<0.01$), and PP ($r=0.30$, $p<0.005$) (Table 2), while cAIx was significantly correlated with age ($r=0.38$, $p<0.0005$), height ($r=-0.47$, $p<0.0001$), SBP ($r=0.29$, $p<0.005$), PP ($r=0.31$, $p<0.005$), HR ($r=-0.52$, $p<0.0001$), TC ($r=0.23$, $p<0.05$), and LDL-C ($r=0.29$, $p<0.005$) (Table 3). In the multiple regression analysis, age,

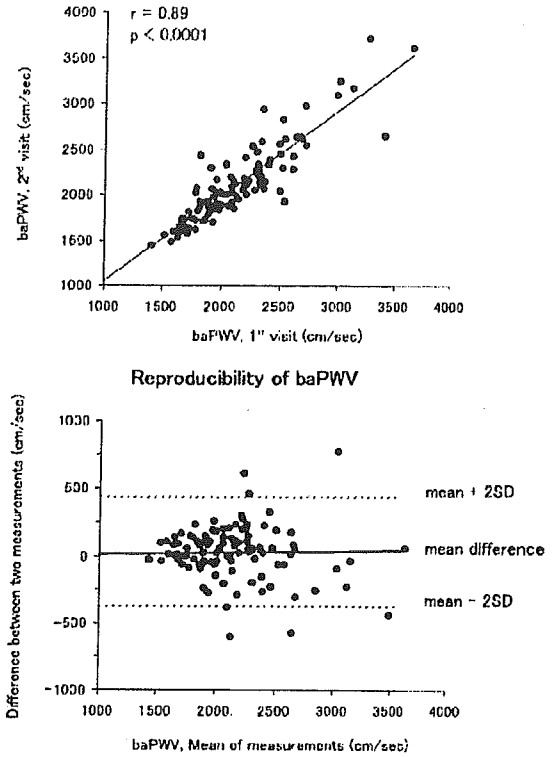

Fig. 1. *Correlation between the two measurements of baPWV (upper panel). Difference between baPWV at the 1st visit and 2nd visit plotted against their mean. The lines represent the mean difference and the limits of agreement, that is, ±2SD (lower panel). baPWV, brachial-ankle pulse wave velocity.*

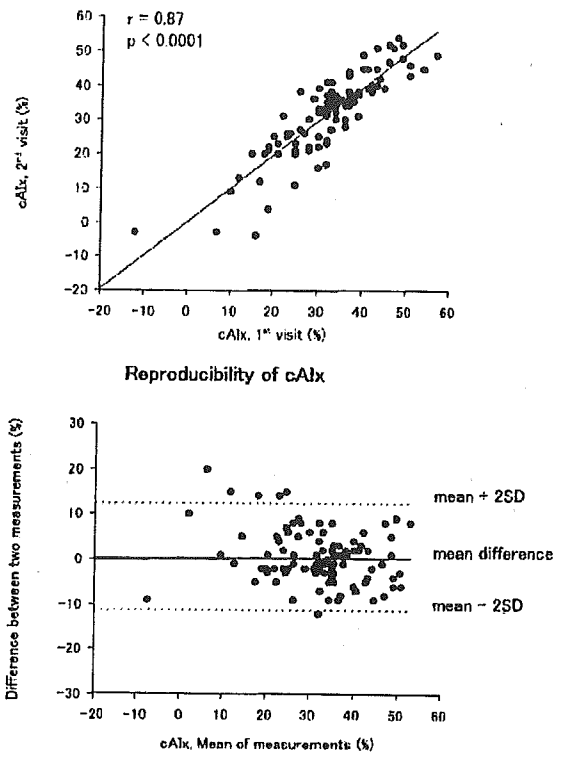

Fig. 2. *Correlation between the two measurements of cAIx (upper panel). Difference between cAIx at the 1st visit and 2nd visit plotted against their mean. The lines represent the mean difference and the limits of agreement, that is, ±2SD (lower panel). cAIx, carotid augmentation index.*

SBP, and HR remained independent determinants of baPWV (adjusted R^2=0.43, p<0.0001), while height, SBP, HR, and LDL-C remained independent determinants of cAIx (adjusted R^2=0.58, p<0.0001).

Discussion

This study demonstrated that both PWV and AIx measured using an automatic device are fairly reproducible, as indicated by high correlation coefficients, small coefficients of variation, and small mean differences observed in the Bland-Altman plots. The cardiovascular risk factors associated with these simultaneously measured arterial stiffness indices appear to be different in hypertensive patients.

Carotid-femoral PWV (cfPWV) has been used as an established method for measuring PWV (*13*, *14*), but the use of the femoral artery requires a transducer to be attached to the inguinal region, which has a strong psychological impact on the patients. As the PWV is closely determined by BP level *per se*, the psychological pressor effect may increase cfPWV, leading to lower reproducibility. This disadvantage might make the conventional technique for cfPWV measurement unsuitable for routine use. Measurement of baPWV minimizes the psychological stress by simply using exposed extremities. In this study, the good reproducibility of baPWV may have resulted from the stability of BP, which was obtained by measuring these parameters under the same conditions. Reproducible results could also be obtained irrespective of the operator's technical skill. Recently, it has been reported that the validity and reproducibility of baPWV measurement are as good as those of aortic PWV or cfPWV, as shown using Bland-Altman analysis (*8*, *9*). Yamashina *et al.* reported that the intraobserver correlation coefficient (r) was 0.87, and the CV was 10.0% (*8*), while Munakata *et al.* reported that the CV was 6.5% (*9*). Although the present study had a much longer interval between the successive measurements than those studies, the reproducibility in this study (CV= 3.8%) was much better. While cfPWV principally reflects the elastic properties of central arteries, baPWV also includes peripheral arterial components, which contain more muscular

Table 2. Simple and Multiple Regression Analysis of baPWV

Variable	Simple regression		Multiple regression	
	r	*p*	*β*	*p*
Age (years)	0.40	<0.0001	0.49	<0.0001
Men gender	0.09	NS		
Height (cm)	0.02	NS		
Body mass index (kg/m^2)	−0.14	NS		
Duration of hypertension (years)	0.05	NS		
SBP (mmHg)	0.39	<0.0001	0.37	0.024
DBP (mmHg)	0.17	NS		
MAP (mmHg)	0.29	0.006		
PP (mmHg)	0.30	0.002		
Heart rate (beats/min)	0.24	0.017	0.23	0.012
Total cholesterol (mg/dl)	0.11	NS		
HDL cholesterol (mg/dl)	−0.07	NS		
LDL cholesterol (mg/dl)	0.13	NS		
Triglyceride (mg/dl)	0.05	NS		
Serum glucose (mg/dl)	0.08	NS		
HbA1C (%)	0.10	NS		
Serum creatinine (mg/dl)	0.09	NS		
cAIx (%)	0.06	NS		
ABI	−0.05	NS		
Adjusted R^2			0.43	

Correlation coefficients of simple regression analysis (r), multiple regression analysis (β), and level of significance are shown. NS, not significant; HDL, high-density lipoprotein; LDL, low-density lipoprotein; R^2, multiple coefficient of determination; other abbreviations are as in Table 1.

Table 3. Simple and Multiple Regression Analysis of cAIx

Variable	Simple regression		Multiple regression	
	r	*p*	*β*	*p*
Age (years)	0.38	0.0002		
Men gender	−0.21	NS		
Height (cm)	−0.47	<0.0001	−0.26	0.021
Body mass index (kg/m^2)	0.08	NS		
Duration of hypertension (years)	0.04	NS		
SBP (mmHg)	0.29	0.0032	0.32	0.038
DBP (mmHg)	0.06	NS		
MAP (mmHg)	0.10	NS		
PP (mmHg)	0.31	0.0014		
Heart rate (beats/min)	−0.52	<0.0001	−0.43	<0.0001
Total cholesterol (mg/dl)	0.23	0.02		
HDL cholesterol (mg/dl)	−0.02	NS		
LDL cholesterol (mg/dl)	0.29	0.0038	0.28	0.031
Triglyceride (mg/dl)	−0.18	NS		
Serum glucose (mg/dl)	0.17	NS		
HbA1C (%)	0.18	NS		
Serum creatinine (mg/dl)	0.18	NS		
baPWV (cm/sec)	0.06	NS		
ABI	0.03	NS		
Adjusted R^2			0.58	

Correlation coefficients of simple regression analysis (r), multiple regression analysis (β), and level of significance are shown. Abbreviations are the same as those in Tables 1 and 2.

components (*15*). Considering that baPWV is a highly reproducible parameter of arterial stiffness, however, baPWV may be better suited for routine examinations and large clinical trials.

Chen *et al.* demonstrated that cAIx measured by the applanation tonometric method provides a waveform closest to that of the central aorta, and its value is reliable enough for use in the clinical field (*16*). Liang *et al.* studied the intraobserver reproducibility of cAIx using applanation tonometry, and gave the CV of cAIx as 1.3% (*17*), while we gave it as 9.7%. These discrepancies are due to the differences in measurement interval (Liang *et al.* (*17*): mean, 2.5 weeks; our study: mean, 4 weeks). Moreover, they studied cAIx in healthy volunteers, while we targeted hypertensive patients. Therefore, we cannot simply compare their results with our results; however, considering our interval, we speculate that our CV is preferable. Cortez-Cooper *et al.* reported the reliability of this automatic device for measuring cAIx, as indicated by the relatively small CV (13.0%) (*11*). In our study, however, it is noteworthy that the measurement of cAIx was less reproducible than that of baPWV, probably because carotid tonometric measurement requires more technical skill than the measurement of baPWV. Thus, the recent development of user-independent tonometer systems, *i.e.*, automated sensors that do not require hand-held operation, may have improved the reliability and reproducibility of the measurements of cAIx.

As shown recently (*9*, *10*, *18*, *19*), baPWV was correlated with age and SBP. Aging induces functional and structural changes such as arterial wall remodeling and degeneration of elastic fibers or disorganization of the medial layer (*20*). With advancing age, therefore, arteries progressively stiffen, and increased arterial stiffness has been reported to lead to an age-related rise in PWV (*21*). Arterial stiffening, moreover, induces an increase of SBP concomitant with a decrease of DBP, resulting in an increase of PP, which reflects arterial pulsatile hemodynamics (*22*). When we conducted the same analysis using MAP, the distended pressure, instead of SBP, the results were essentially the same. The present study showed a positive relationship between PWV and HR, as previously shown by Lantelme *et al.* (*23*). Moreover, by using multiple regression analysis, we demonstrated that HR may have an effect on baPWV, independent of SBP level, in the observational data. This is supported by the fact that increasing HR by pacing causes a marked reduction of arterial distensibility (*24*), which is inversely related to PWV, without HR-dependent changes in BP.

While in this study cAIx was correlated with SBP and PP, but not DBP, Nürnberger *et al.* reported that DBP was an important determinant of cAIx (*25*). This phenomenon was probably due to the differences of age distribution (mean age: 69.4 years for this study *vs.* 27.8 years for Nürnberger *et al.* (*25*)). In the elderly, the reflected pulse wave returns to the aorta in the systole, thereby increasing SBP and PP. cAIx was correlated with LDL-C apart from baPWV, and this relationship was not lost after multiple regression analysis. It has been shown that patients with hypertension and elevated LDL-C have endothelial damage and progressing atherosclerosis (*26*). Increased AIx has been reported in hypercholesterolemic patients (*27*). AIx may depend on the pattern of ventricular ejection and on the arterial properties determining the amount and site of wave reflection (*28*). These reflection sites may be influenced by the vascular tone of the small muscular arteries (*7*). Megnien *et al.* showed that arterial stiffening does not predict atherosclerotic disease in asymptomatic men at cardiovascular risk (*29*). In contrast, Weber *et al.* have recently shown that AIx as an index of arterial stiffening is an independent risk marker for premature coronary atherosclerosis (*5*). Further studies are needed to evaluate whether AIx could be considered a useful surrogate marker for assessing early-stage (preclinical) atherosclerosis.

cAIx was also significantly correlated with height. We considered that this reflected the earlier arrival of the reflected waveform due to the reduced length of the arterial tree. Smulyan *et al.* demonstrated the early systolic arrival of reflected waves in short people, and suggested that this fact could explain the inverse relationship between height and cardiovascular risk (*30*). Contrary to the findings with baPWV, this study showed a negative relationship between AIx and HR, as shown by Wilkinson *et al.* (*31*) and Gatzka *et al.* (*32*). Arteries also display viscoelasticity, which means that their stiffness itself depends on the rate at which they are stretched by the pulse, and is thus dependent on HR. In addition, ejection times are prolonged and reflections return during the systolic interval, merging with the incident pressure wave and increasing the peak systolic pressure. Similarly to baPWV, cAIx must therefore be evaluated after considering HR differences as a confounding factor. Standardizing AIx for these physiologic factors, including height and HR, seems mandatory if one wants to interpret these changes in interventional clinical trials. In the present study, contrary to our expectation but in agreement with the findings of Kelly *et al.* (*7*), PWV and AIx could not be used interchangeably as an index for arterial stiffness. This may be explained by the fact that AIx is also determined by the pattern of ventricular ejection and the intensity of wave reflection which, in turn, is determined by the diameter and elasticity of small arteries and arterioles (*33*).

In conclusion, this study demonstrated good intraobserver-intersession reproducibility of these arterial stiffness indices under controlled experimental conditions, provided that the measurements are done by a single investigator. Since these simultaneously measured arterial stiffness indices seem to contribute to the more precise assessment of cardiovascular risk, this apparatus would greatly facilitate the analysis of pulse waveforms in large longitudinal and interventional studies in hypertensive patients.

References

1. Laurent S, Boutouyrie P, Asmar R, *et al*: Aortic stiffness is

an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236–1241.
2. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**: 2434–2439.
3. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME: Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; **38**: 434–438.
4. Laurent S, Katsahian S, Fassot C, *et al*: Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke* 2003; **34**: 1203–1206.
5. Weber T, Auer J, O'Rourke MF, *et al*: Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* 2004; **109**: 184–189.
6. Nichols WW, O'Rourke MF: McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles, 4th ed. London, Edward Arnold, 1998.
7. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ: Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. *Hypertension* 2001; **37**: 1429–1433.
8. Yamashina A, Tomiyama H, Takeda K, *et al*: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
9. Munakata M, Ito N, Nunokawa T, Yoshinaga K: Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. *Am J Hypertens* 2003; **16**: 653–657.
10. Kubo T, Miyata M, Minagoe S, Setoyama S, Maruyama I, Tei C: A simple oscillometric technique for determining new indices of arterial distensibility. *Hypertens Res* 2002; **25**: 351–358.
11. Cortez-Cooper MY, Supak JA, Tanaka H: A new device for automatic measurements of arterial stiffness and ankle-brachial index. *Am J Cardiol* 2003; **91**: 1519–1522.
12. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
13. van Popele NM, Grobbee DE, Bots ML, *et al*: Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001; **32**: 454–460.
14. Blacher J, Asmar R, Djane S, London GM, Safar ME: Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; **33**: 1111–1117.
15. Aso K, Miyata M, Kubo T, *et al*: Brachial-ankle pulse wave velocity is useful for evaluation of complications in type 2 diabetic patients. *Hypertens Res* 2003; **26**: 807–813.
16. Chen CH, Ting CT, Nussbacher A, *et al*: Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension* 1996; **27**: 168–175.
17. Liang YL, Teede H, Kotsopoulos D, *et al*: Non-invasive measurements of arterial structure and function: repeatability, interrelationships and trial sample size. *Clin Sci* 1998; **95**: 669–679.
18. Tomiyama H, Yamashina A, Arai T, *et al*: Influence of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement: a survey of 12,517 subjects. *Atherosclerosis* 2003; **166**: 303–309.
19. Yamashina A, Tomiyama H, Arai T, *et al*: Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. *Hypertens Res* 2003; **26**: 801–806.
20. Tanaka H, Dinenno FA, Monahan KD, DeSouza CA, Seals DR: Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men. *Arterioscler Thromb Vasc Biol* 2001; **21**: 82–87.
21. Asmar R, Benetos A, Topouchian J, *et al*: Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension* 1995; **26**: 485–490.
22. London GM, Guerin AP: Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J* 1999; **138**: 220–224.
23. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H: Heart rate: a important confounder of pulse wave velocity assessment. *Hypertension* 2002; **39**: 1083–1087.
24. Giannattasio C, Vincenti A, Failla M, *et al*: Effects of heart rate changes on arterial distensibility in humans. *Hypertension* 2003; **42**: 253–256.
25. Nürnberger J, Dammer S, Opazo Saez A, Philipp T, Schafers RF: Diastolic blood pressure is an important determinant of augmentation index and pulse wave velocity in young, healthy males. *J Hum Hypertens* 2003; **17**: 153–158.
26. Sun P, Dwyer KM, Merz CN, *et al*: Blood pressure, LDL cholesterol, and intima-media thickness: a test of the "response to injury" hypothesis of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2000; **20**: 2005–2010.
27. Wilkinson IB, Prasad K, Hall IR, *et al*: Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol* 2002; **39**: 1005–1011.
28. O'Rourke MF, Kelly RP: Wave reflection in the systemic circulation and its implications in ventricular function. *J Hypertens* 1993; **11**: 327–337.
29. Megnien JL, Simon A, Denarie N, *et al*: Aortic stiffening does not predict coronary and extracoronary atherosclerosis in asymptomatic men at risk for cardiovascular disease. *Am J Hypertens* 1998; **11**: 293–301.
30. Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM: Influence of body height on pulsatile arterial hemodynamic data. *J Am Coll Cardiol* 1998; **31**: 1103–1109.
31. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ: The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol (Lond)* 2000; **525**: 263–270.
32. Gatzka CD, Cameron JD, Dart AM, *et al*: Correction of carotid augmentation index for heart rate in elderly essential hypertensives: ANBP2 Investigators: Australian Comparative Outcome Trial of Angiotensin-Converting Enzyme Inhibitor- and Diuretic-Based Treatment of Hypertension in the Elderly. *Am J Hypertens* 2001; **14**: 573–577.
33. Oliver JJ, Webb DJ: Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thromb Vasc Biol* 2003; **23**: 554–566.

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Type 2 Diabetes Is Associated With Left Ventricular Concentric Remodeling in Hypertensive Patients

Kazuo Eguchi, Kazuomi Kario, Satoshi Hoshide, Joji Ishikawa, Masato Morinari, and Kazuyuki Shimada

Background: Left ventricular (LV) geometric remodeling is associated with cardiovascular prognosis in hypertensive patients. It is uncertain how LV remodeling is modulated by diabetes in hypertensive patients. In this study, we investigated the impact of diabetes and ambulatory blood pressure (BP) on LV geometric remodeling in hyptensives with/without diabetes.

Methods: Ambulatory BP monitoring and echocardiography were performed to compare 24-h BP levels and LV measurements in 400 uncomplicated hypertensives (mean age, 67 years, 152 men and 248 women) between diabetic (n = 161) and nondiabetic (n = 239) patients.

Results: The age (67 *v* 68 years), percentage of men (43% *v* 34%), body mass index (24.5 *v* 24.0 kg/m^2), 24-h systolic BP (144/80 *v* 144/82 mm Hg), LV mass index (128 *v* 130 g/m^2) were similar between the groups. Diabetic patients had higher relative wall thickness (0.50 *v* 0.44, $P < .001$) and higher prevalence of concentric LV hypertrophy (39.4% *v* 26.8%, $P < .001$) than nondiabetic patients. The presence of diabetes (odds ratio [OR] = 2.76; 95% confidence interval [CI] = 1.73–4.41, $P < .001$) and 24-h systolic BP (OR for 10 mm Hg increase = 1.17; 95% CI = 1.01–1.37, $P < .05$) were independently associated with the higher relative wall thickness (≥0.45). On the other hand, 24-h systolic BP was independently associated with LV hypertrophy (OR for 10 mm Hg increase = 1.32; 95% CI = 1.14–1.52, $P < .05$).

Conclusions: Among hypertensive patients, type 2 diabetes was associated with concentric LV geometry independent of ambulatory BP. Am J Hypertens 2005;18: 23–29 © 2005 American Journal of Hypertension, Ltd.

Key Words: Type 2 diabetes, hypertension, concentric hypertrophy, left ventricular geometric remodeling, ambulatory blood pressure monitoring.

Diabetes mellitus is one of the most important risk factors for cardiovascular disease.[1] Diabetes mellitus and hypertension frequently coexist and each pathologic condition exacerbates the other.[2] Several population studies have shown that diabetes is associated with left ventricular (LV) structural and functional abnormalities.[3–5] In the Hypertension genetic epidemiology network (HyperGEN) study[4] and the Strong Heart Study,[5] type 2 diabetes was associated with higher LV mass, more concentric LV geometry, and lower cardiac function. Because there is a strong relationship between LV hypertrophy and adverse cardiovascular outcomes in hypertensive patients,[6–8] early detection of LV structural changes in diabetic patients may be important.

The level of blood pressure (BP) using ambulatory BP monitoring correlates better than clinic BP measurements with hypertensive target organ damage.[9] Patients with white coat hypertension, defined as persistent clinic hypertension but normal 24-h BP with ambulatory BP monitoring, have smaller LV mass than patients with sustained hypertension. The LV mass of the former is similar to that of normotensive patients.[10] Although diabetes and hypertension both may be contributing factors to LV remodeling, there are few reports showing the impact of ambulatory BP on LV remodeling in diabetic patients.

Thus we performed a cross-sectional study to assess the association of diabetes and ambulatory BP with LV geometric remodeling in Japanese hypertensive patients with and without diabetes.

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From the Department of Cardiology, Shioya General Hospital, Tochigi, Japan (KE), and the Department of Cardiology, Jichi Medical School (KE, KK, SH, JI, MM, KS), Tochigi-Ken, Japan.

Address correspondence and reprint requests to Dr. Kazuo Eguchi, Jichi Medical School, Department of Cadiology, 3311-1 Yakushiji, Minamikawachi, Kawachi, Tochigi, 329-0490 Japan; e-mail: Kazuo-eg@jichi.ac.jp

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