Importantly, all subjects carrying I164T in the present study including CAD and non-CAD subjects had at least one or more metabolic disorders including diabetes mellitus, hypertension, and dyslipidemia. Among CAD patients, the prevalence of the metabolic syndrome was significantly higher in I164T mutation than that in wild type. These findings suggest that the I164T mutation of adiponectin gene is associated with the development of the metabolic syndrome-linked CAD. Importantly, the severe hypoadiponectinemia in subjects with the I164T mutation was independent of BMI. Recently, we have demonstrated that intimal thickening was accelerated in mechanically injured arteries of adiponectin knockout mice, and that adenovirus-mediated supplement of adiponectin completely abolished the enhanced neointimal formation (15). These results suggest that hypoadiponectinemia directly contributes to abnormal vascular remodeling. Therefore, the I164T mutation plays a pivotal role in the development of atherosclerosis.

We have reported that the plasma adiponectin levels were significantly low in subjects with obesity (27), diabetes mellitus (31), and hypertension (32). In addition, we reported that plasma adiponectin level was predictive of the development of type 2 diabetes in the Pima Indian population (33). These observations suggest that the plasma adiponectin levels might be closely associated with the development of the metabolic syndrome. In adiponectin knockout mice, glucose metabolism was normal under standard diet, and severe insulin resistance, hyperglycemia, and hypertension were developed after two weeks' feeding of atherogenic diet (18,34). In the present study, all subjects carrying I164T had at least one or more coronary risk factors. However, HOMA-IR levels of nondiabetic I164T mutation were no different than those of control subjects. These results suggest that the hypoadiponectinemia caused by I164T mutation might lead to diabetes mellitus, hypertension, and atherosclerosis only under overnutrition in the modern industrialized countries.

A recent study demonstrated that the I164T mutation was not found in the type 2 diabetic and obese French Caucasian subjects and that the genotypes of SNP94 and SNP276 affected plasma adiponectin levels (23). Higher plasma adiponectin levels were associated with the T allele of SNP94 and the G allele of SNP276 in Caucasians (23). We and others demonstrated that the I164T mutation was observed in the Japanese population (19,21). In the present study, the G allele of SNP94 tended to be associated with lower plasma adiponectin levels, and SNP276 did not correlate with plasma adiponectin levels in CAD and non-CAD Japanese subjects whose mean BMI were approximately 24 kg/m^2. Recently, the genotypes of SNP276 were reported to be associated with plasma adiponectin levels only in the obese subgroup of Japanese subjects (21). These differences between the French and Japanese populations may be due to ethnic background, although a larger population study is required to elucidate the discrepancy.

In the current study, three of the 14 subjects with the I164T mutation did not suffer from CAD, although they had at least one coronary risk factor and markedly low plasma adiponectin level. The follow-up study will be necessary to clarify whether the non-CAD subjects with I164T mutation develop CAD in the future.

In summary, we demonstrated that the I164T mutation of adiponectin gene affects CAD prevalence and the clustering of multiple risk factors for atherosclerosis. Our results indicate that screening the common genetic background of hypoadiponectinemia is helpful in evaluating the risk of the metabolic syndrome and CAD.

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Reprints requests and correspondence: Dr. Shinji Kihara, Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: kihara@imed2.med.osaka-u.ac.jp.

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Hypoadiponectinemia Is an Independent Risk Factor for Hypertension

Yoshio Iwashima, Tomohiro Katsuya, Kazuhiko Ishikawa, Noriyuki Ouchi, Mitsuru Ohishi, Ken Sugimoto, Yuxiao Fu, Masaharu Motone, Kouichi Yamamoto, Akiko Matsuo, Koji Ohashi, Shinji Kihara, Tohru Funahashi, Hiromi Rakugi, Yuji Matsuzawa, Toshio Ogihara

Abstract—Adiponectin is one of the key molecules in the metabolic syndrome, and its concentration is decreased in obesity, type-2 diabetes, and coronary artery disease. Genetic investigation has revealed that 2 polymorphisms (I164T and G276T) are related to adiponectin concentration and diabetes. To examine whether adiponectin affects hypertension genetically or biologically, we performed a case-control study. A total of 446 diagnosed cases of hypertension (HT) in men and 312 normotensive (NT) men were enrolled in this study. Plasma adiponectin concentration was measured using an enzyme-linked immunosorbent assay system. Single nucleotide polymorphisms were determined by TaqMan polymerase chain reaction method. After adjustment for confounding factors, adiponectin concentration was significantly lower in HT (HT: 5.2±0.2 μg/mL; NT: 6.1±0.2 μg/mL; $P<0.001$). Furthermore, multiple regression analysis indicated that hypoadiponectinemia was an independent risk factor for hypertension ($P<0.001$). Blood pressure was inversely associated with adiponectin concentration in normotensives regardless of insulin resistance. In subjects carrying the TC genotype of the I164T polymorphism, adiponectin concentration was significantly lower (TC: 2.6±0.9 μg/mL; TT: 5.5±0.1 μg/mL; $P<0.01$), and most of them had hypertension. In contrast, the G276T polymorphism was not associated with adiponectin concentration or hypertension. In conclusion, hypoadiponectinemia is a marker for predisposition to hypertension in men. (***Hypertension.* 2004;43:1318-1323.**)

Key Words: blood pressure ■ genetics ■ hypertension, genetic ■ men ■ mutation

Adipose tissue participates in the regulation of a variety of homeostatic processes as an endocrine organ that secretes many biologically active molecules such as leptin, tumor necrosis factor-α, and plasminogen-activator inhibitor type 1, which contribute to the development of cardiovascular disease.[1–5] Furthermore, some of these molecules, such as leptin and plasminogen-activator inhibitor type 1, are known to contribute to the development of hypertension.[6–8] Adiponectin is an adipose tissue-specific collagen-like factor, which is abundant in plasma, and a decrease of adiponectin is associated with obesity[9] and type-2 diabetes.[10] Adiponectin modulates the endothelial inflammatory response in vitro, and its concentration is decreased in patients with coronary artery disease.[10–12] Furthermore, adiponectin has been reported to be associated with lipid metabolism,[13,14] glucose metabolism,[15] and insulin resistance.[13,14,16] It was recently reported that treatment of diabetic animals with adiponectin markedly improved insulin sensitivity via reducing triglyceride accumulation in skeletal muscle.[17] These results suggest that adiponectin is one of the key molecules in the metabolic syndrome.

Hypertension is a common disease that increases the risk for cardiovascular disease, and it is also a component of the metabolic syndrome, which is defined as the combination of obesity, insulin resistance, glucose intolerance, and hyperlipidemia. Hypertensive patients are known to have higher body mass index (BMI), triglyceride level, and insulin resistance compared with normotensive subjects.[18] Even though an association between hypertension and serum adiponectin concentration has been reported by several groups using a small number of subjects,[19–22] the obtained results were not identical. Mallamaci et al[19] reported an increased plasma adiponectin concentration in hypertensive patients with renal dysfunction, but Adamczak et al[20] reported decreased adiponectin in hypertensive subjects. Kazumi et al[21] reported that young Japanese men with high-normal blood pressure had lower adiponectin. Recently, Furuhashi et al[22] reported that only hypertensive patients with insulin resistance showed lower adiponectin concentration. Furthermore, in these studies, the association between plasma adiponectin and hypertension was evaluated without adjusting for confounding factors or without dividing the subjects by sex. It is well known that normal women have a higher adiponectin concentration than men,[23] so sex is a potential confounding factor. Thus, the clinical importance of hypoadiponectinemia in hypertension has not been fully elucidated.

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From the Departments of Geriatric Medicine (Y.I., T.K., K.I., M.O., K.S., Y.F., M.M., K.Y., A.M., H.R., T.O.) and Internal Medicine and Molecular Science (N.O., K.O., S.K., T.F., Y.M.), Osaka University Graduate School of Medicine, Japan.

Correspondence to Dr Tomohiro Katsuya, Department of Geriatric Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan. E-mail katsuya@geriat.med.osaka-u.ac.jp

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On the other hand, a genetic investigation revealed that subjects with the I164T polymorphism (T-to-C substitution at nucleotide 517 leading to amino acid substitution from isoleucine to threonine at position 164) more frequently had diabetes and had lower concentrations of adiponectin. It was interesting that all 9 patients with the I164T polymorphism had hypertension.[16] In addition, another report showed that the G276T polymorphism in intron 2 was also associated with type-2 diabetes, partially through affecting plasma adiponectin concentration.[24]

To examine whether adiponectin affects blood pressure genetically or biologically, we performed a case-control study using a large number of subjects. In addition, we confirmed the hypothesis that hypoadiponectinemia is correlated with increased insulin resistance.

Methods

Subjects

A total of 758 male subjects (mean age 58.4±0.4 years, BMI 23.9±0.1 kg/m^2) were selected from people who were admitted and underwent medical investigation at Osaka University Hospital or its affiliated hospitals. The numbers of normotensive subjects and hypertensive subjects were 312 and 446, respectively. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg on repeated measurements, or receiving antihypertensive treatment. Diabetes was defined as fasting plasma glucose of ≥7.0 mmol/L or receiving treatment for diabetes. All subjects enrolled were Japanese, and subjects with ischemic heart disease including myocardial infarction, congestive heart failure, abnormal electrocardiogram results, valvular heart disease, atrial fibrillation, arteriosclerosis obliterans, or renal failure were excluded. The study protocol was approved by the Ethical Committee of Osaka University, and subjects gave informed consent to participate in the present study, including genetic analysis.

Clinical Features

Blood pressure was measured with an appropriate arm cuff and a mercury column sphygmomanometer on the left arm after a resting period of at least 10 minutes in the supine position. Blood pressure was measured by well-trained physicians who were blinded during the study, and 3 measurements at 1 visit were averaged to evaluate the systolic and diastolic blood pressures. After blood pressure measurements, venous blood sampling from all subjects was performed after fasting overnight. Height and body weight were measured, and BMI was calculated. Plasma samples for subsequent assay were stored at −80°C. Insulin sensitivity was estimated using the homeostatic model assessment (HOMA) index (ie, plasma glucose level×[plasma insulin level/22.5]). Insulin resistance was defined as HOMA ≥3. Plasma concentration of adiponectin was determined by a sandwich enzyme-linked immunosorbent assay system (adiponectin ELISA kit; Otsuka Pharmaceutical Co. Ltd.) as previously reported.[9]

The following parameters were also determined: total cholesterol (T-chol), triglyceride (TG), high-density lipoprotein cholesterol (HDL-chol), and serum creatinine (Cr) levels.

Genotype Determination of Adiponectin Polymorphisms

To investigate the association between adiponectin polymorphisms and hypertension, we selected 2 polymorphisms (I164T and G276T) that were previously reported to be related to plasma adiponectin concentration.[16,24] Genomic DNA was prepared from the buffy coat using a QIAmp DNA blood kit (QIAGEN, Valencia, Calif). The genotypes of the I164T and G276T polymorphisms were determined by the TaqMan polymerase chain reaction (PCR) method.[25] The following primers and probes were included in the reactions: I164T, forward primer, 5′-AAC ATT CCT GGG CTG TAC TAC TTT G-3′; reverse primer, 5′-GGC TGA CCT TCA CAT CCT TCA TA-3′; probes, 5′-FAM-CCA CAC CAC AGT CT-3′, 5′-VIC-ACC ACA TCA CAG TCT A-3′; G276T, forward primer, 5′-AGA ATG TTT CTG GCC TCT TTC ATC-3′; reverse primer, 5′-TTC TCC CTG TGT CTA GGC CTT AGT-3′; probes, 5′-FAM-AAA CTA TAT GAA GTC ATT CAT TA-3′, 5′-VIC-CTA TAT GAA GGC ATT CAT TA-3′. The fluorescence level of PCR products was measured using an ABI PRISM 7900 HT Sequence Detector (Applied Biosystems).

TABLE 1. Clinical Characteristics of Study Subjects

Characteristics	HT (n=446)	NT (n=312)
Age, y	59.4±0.5	57.1±0.6*
BMI, kg/m^2	24.4±0.1	23.1±0.2*
Systolic BP, mm Hg	138±1	119±1*
Diastolic BP, mm Hg	83±1	72±1*
Adiponectin, μg/mL	5.2±0.2	6.4±0.2*
T-chol, mmol/L	5.34±0.06	5.17±0.05†
TG, mmol/L	1.77±0.05	1.65±0.07
HDL-chol, mmol/L	1.32±0.02	1.32±0.03
FPG, mmol/L	6.24±0.11	5.98±0.13
HbA1c, %	5.7±0.1	5.7±0.1
HOMA	2.4±0.2	2.1±0.2
Cr, μmol/L	84.6±3.2	90.6±4.2

Values are given as mean±SE. FPG, indicates fasting plasma glucose; other definitions are provided in the text.

*P<0.01 and †P<0.05 compared with hypertensive subjects for each parameter.

Statistical Analysis

Values are expressed as mean±SE. Associations between hypertension and all other parameters were first analyzed by simple logistic regression and then by multivariate analysis. Differences in genotypes and alleles were examined by χ^2 analysis. The association between polymorphisms and clinical variables was examined by multivariate analysis. The quantitative effects of covariates were assessed by multiple regression analysis. P<0.05 was considered statistically significant. All calculations were performed using a standard statistical package (JMP 4.0; SAS Institute Inc).

Results

Plasma Adiponectin Concentration and Hypertension

The average length of time since the first diagnosis of hypertension was 12.5±0.6 years. Furthermore, 342 of 758 hypertensive subjects also had close relatives (parents, brothers, and sisters) who were hypertensive. To assess whether adiponectin was related to hypertension, we compared the clinical characteristics of hypertensive male subjects (HT) and normotensive male subjects (NT) (Table 1). Plasma adiponectin concentration was significantly lower in hypertensive subjects than in normotensive subjects. Age, BMI, and T-chol were also significantly higher in hypertensive men than in normotensive men. Consequently, we selected these parameters as confounding factors. After adjustment for confounding factors (age, BMI, and T-chol), adiponectin concentration was significantly lower in HT (HT: 5.2±0.2 μg/mL; NT: 6.1±0.2 μg/mL; P<0.001). Multiple regression analysis revealed that each confounding factor, age, BMI,

TABLE 2. Multiple Logistic Regression Analysis for Hypertension

Term	Estimate	SE	*P*
Age	−0.0497	0.0086	<0.0001
BMI	−0.1144	0.0293	<0.0001
Adiponectin	0.1017	0.0278	0.0003
T-chol	−0.0048	0.0023	0.0374
Intercept	3.7284	1.0341	0.0003

R^2=0.0754 (n=758).

T-chol, and adiponectin concentration, independently affected the risk for hypertension (Table 2).

We examined simple correlations between plasma adiponectin concentration and clinical variables. The hypertensive subjects were divided into 2 groups: with and without antihypertensive medication; the normotensive subjects were divided into 3 subgroups: with diabetes, with insulin resistance (HOMA≥3) but without diabetes, and without insulin resistance or diabetes. Thus, we compared the clinical variables among 5 subgroups (Table 3). Adiponectin concentration significantly increased with age (in hypertensives using medication and normotensives without diabetes or insulin resistance, $P<0.01$, respectively) and HDL-chol (in hypertensives using medication and normotensives without diabetes, $P<0.01$, respectively), and decreased with BMI (in hypertensives using medication and normotensives, $P<0.01$, respectively) and TG (in hypertensives using medication and normotensives with diabetes, $P<0.01$, respectively). Systolic blood pressure was inversely associated with adiponectin concentration in normotensive subjects without diabetes ($P<0.01$). Diastolic blood pressure was inversely associated with adiponectin concentration in normotensive subjects ($P<0.01$). The association between plasma adiponectin concentration and blood pressure in normotensive subjects without diabetes is shown in Figure 1. However, adiponectin concentration was not associated with blood pressure in hypertensives without medication (Table 3).

TABLE 3. Simple Correlations Between Plasma Adiponectin Concentration and Clinical Characteristics

	Hypertensives		Normotensive		
	Medication		Diabetes	Insulin Resistance	
Characteristics	(+) (n=367)	(−) (n=79)	(+) (n=67)	(+) (n=93)	(−) (n=152)
Age	0.21*	0.26†	0.22	0.17	0.44*
BMI	−0.19*	−0.12	−0.36*	−0.36*	−0.37*
T-chol	−0.05	−0.09	−0.20	−0.11	−0.09
TG	−0.21*	−0.18	−0.43*	−0.19	−0.20†
HDL-chol	0.18*	0.29†	0.11	0.27*	0.34*
FPG	−0.06	−0.15	−0.15	−0.32*	−0.10
HbA1C	−0.03	−0.04	−0.18	−0.04	−0.03
HOMA	−0.21†	−0.13	−0.18	−0.25†	−0.25†
Cr	0.15†	0.17	0.48†	0.03	0.07
SBP		−0.02	−0.32†	−0.35*	−0.31*
DBP		−0.05	−0.44*	−0.38*	−0.38*

Data indicates correlation coefficient. FPG indicates fasting plasma glucose; other definitions are defined in the text.

*$P<0.01$ and †$P<0.05$.

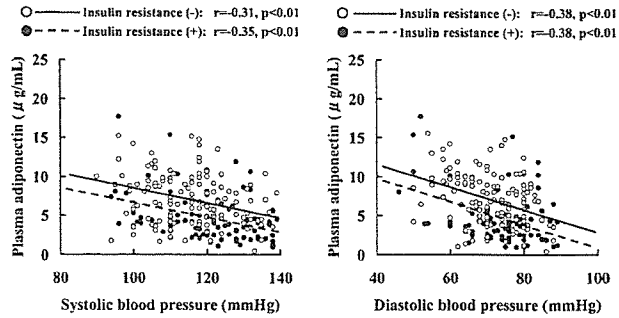

Figure 1. Correlation between plasma adiponectin concentration and blood pressure in normotensives without diabetes. ● indicates subjects with insulin resistance (n=93); ○, subjects without insulin resistance (n=152).

Polymorphisms of Adiponectin and Hypertension

We examined the association between the I164T and G276T polymorphisms and plasma adiponectin concentration. After adjustment for confounding factors (age, BMI, TG, HDL-chol, and HOMA), plasma adiponectin concentration was significantly lower in subjects with the TC genotype of the I164T polymorphism compared with those with the TT genotype (TC: 2.6±0.9 μg/mL; TT: 5.5±0.1 μg/mL; $P<0.01$). No subject with the CC genotype was found in this study. The G276T polymorphism was not significantly related to plasma adiponectin concentration (GG: 5.4±0.2 μg/mL; GT: 5.8±0.2 μg/mL; TT: 4.9±0.4 μg/mL; NS) (Figure 2). We also examined the influence of these polymorphisms on the prevalence of hypertension by case-control study. The G276T polymorphism showed no association with hypertension. Table 4 shows that the TC genotype of the I164T polymorphism was significantly associated with hypertension.

Discussion

The initial finding of the present study was that plasma adiponectin concentration was significantly lower in men

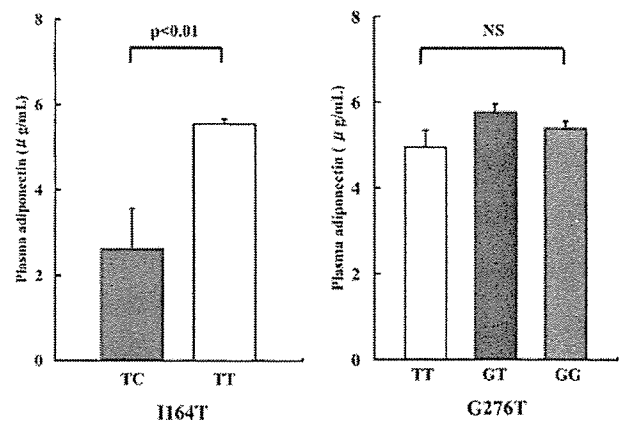

Figure 2. Plasma adiponectin concentration in subjects with I164T and G276T polymorphisms, after adjustment for confounding factors (age, BMI, triglyceride, HDL cholesterol, and homeostatic model assessment index). Data represent mean±SEM.

TABLE 4. Frequencies of Genotypes of Adiponectin Polymorphisms

Polymorphisms		HT	NT	χ^2	P
I164T, n	TT	433	311	6.815	0.009
	TC	13	1		
	GG	225	165		
G276T, n	GT	180	124	0.950	0.622
	TT	41	23		

with hypertension than in normotensive men and was negatively correlated with blood pressure in subjects without hypertension. Furthermore, multiple regression analysis clearly showed that hypoadiponectinemia is an independent risk factor for hypertension. Even though several studies have examined plasma adiponectin level, most of them focused on insulin resistance or diabetes and not on hypertension.

Our results were in accordance with the previous report that HOMA was significantly related to adiponectin concentration.[24] Recently, Furuhashi et al[22] reported that only hypertensive patients with insulin resistance showed a decreased adiponectin concentration. However, the cause–effect relationship among hypoadiponectinemia, insulin resistance, and hypertension has not been clearly elucidated. Even though the consensus has been that insulin resistance is correlated with hypertension,[26,27] the association between insulin and hypertension is controversial.[28–31] In fact, HOMA was not significantly different between hypertensive and normotensive subjects in the present study. As a specific finding of this study, plasma adiponectin level significantly decreased with an increase in blood pressure, even in the normotensives without insulin resistance or diabetes. These results indicate that hypoadiponectinemia may affect the pathogenesis of hypertension at a very early stage without involving insulin resistance. Recently, Lindsay et al[32] reported that there were loci on chromosomes 2, 3, 9, and 10 affecting the circulating adiponectin concentration in the Pima population, suggesting the possibility of an unknown modulator of adiponectin level. However, further investigation is required to examine this hypothesis.

There are 4 possible reasons for the negative correlation between hypertension and plasma adiponectin concentration. First, as Ouchi et al[33] recently reported that plasma adiponectin concentration was independently correlated with the vasodilator response to reactive hyperemia, adiponectin concentration could be an independent parameter of endothelial function. Endothelial dysfunction is an important feature of the early stage of atherosclerosis, which is related to pathogenic conditions including hypertension.[34,35] Furthermore, in adiponectin-knockout mice, hypoadiponectinemia causes diet-induced hypertension. Second, an increase in sympathetic nerve activity, which is common in hypertensives,[36] may inhibit adiponectin gene expression via β-adrenergic stimulation.[37] Third, the reciprocal association of adiponectin and high-sensitive C-reactive protein or increased risk of arteriosclerosis suggests that a low adiponectin concentration might enhance the predisposition to hypertension via vascular injury.[10,11] Fourth, activation of the renin-angiotensin system may be induced in adipose tissue by hypoadiponectinemia, resulting in an increase in fat mass and blood pressure.[38,39] However, further investigation is required to examine these hypotheses.

Another important finding of this study was the positive association between plasma adiponectin concentration and age. There is a supportive report that adiponectin was decreased by sex hormones like androgens, which are suppressed with aging.[23] A reduction in adiponectin clearance in older men is another possible reason for the age-related increase in adiponectin concentration. Furthermore, a previous report also suggested that age is an independent regulating factor for adiponectin concentration.[40] However, it is well known that the prevalence of hypertension, insulin resistance, and diabetes increases with age. There may appear to be a discrepancy, but these results lead to the hypothesis that the implication of hypoadiponectinemia in youth is different from that in old age, and adiponectin may exert an insufficient effect without increasing sufficiently with age. The finding of a lower adiponectin concentration in elderly subjects may indicate the existence of a metabolic disorder like "adiponectin resistance." Further investigation is required to examine these hypotheses.

The final finding of our study was related to adiponectin gene polymorphism. We examined 2 polymorphisms that were previously reported to be related to plasma adiponectin concentration in the Japanese population. Subjects with the TC genotype of the I164T polymorphism showed a significantly lower plasma adiponectin concentration, and most of the C allele carriers had hypertension. Furthermore, we also found a significant association between the TC genotype of the I164T polymorphism and hypertension. It seems to be a novel finding that >80% of C164 carriers were hypertensive in a previous study[16] and in the present study. In contrast, we could not find an association between the G276T polymorphism and adiponectin concentration or hypertension. A previous study has shown an association between theG276T polymorphism and adiponectin concentration only in obese subjects (BMI $\geq$26.7 kg/m^2).[24] Because few obese subjects were included in the present study, we could not conclude a lack of association between the G276T polymorphism and adiponectin.

Study Limitations

This study was designed to be cross-sectional and case-controlled, but not prospective. Several important determinants of plasma adiponectin level, such as body fat content and waist circumference, were not measured in our study. Instead of these measurements, we used HOMA to evaluate insulin resistance. In addition, verification of the cause–effect relationship between hypertension and hypoadiponectinemia would require a study design with a cohort base.

It has been reported that renal function, as indicated by creatinine clearance (Ccr), is an independent regulator of adiponectin concentration in hypertensive subjects.[19] In our study, also, adiponectin concentration was significantly associated with Ccr ($r=-0.38$, $P<0.01$). However, the number of subjects whose Ccr was measured was small (n=102) compared with the total number of study subjects (n=758). The mean Ccr was almost the same in normotensive and hypertensive subjects. Therefore, Ccr was not included in the

discussion of the association between adiponectin and hypertension in this study. However, it was revealed that adiponectin concentration was significantly associated with creatinine in hypertensives using medication and normotensives with diabetes (Table 3), suggesting that hyperadiponectinemia is also involved in the progression of renal damage.

In conclusion, the present findings suggest that a lower plasma adiponectin concentration is significantly associated with hypertension. Interestingly, hypoadiponectinemia is one of the risk factors for hypertension and could be a possible target for antihypertensive treatment.

Acknowledgments

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Intrarenal and Carotid Hemodynamics in Patients With Essential Hypertension

Takafumi Okura, Sanae Watanabe,
Ken-ichi Miyoshi, Tomikazu Fukuoka, and Jitsuo Higaki

Background: The pulsatility index (PI) and resistive index (RI) are used as markers of peripheral vascular resistance. Recently intrarenal PI and RI were introduced for the evaluation of the severity of acute and chronic renal failure, as well as for the diagnosis of renal artery stenosis and kidney graft rejection. In the present study, we evaluated intrarenal PI and RI in patients with essential hypertension.

Methods: Fifty-one patients with essential hypertension participated. The intima–media thickness (IMT) and mean diastolic (Vd) and systolic velocity (Vs) in the common carotid artery (CCA) were measured using ultrasound and Doppler flow methods. Relative diastolic flow velocity (Vd/Vs) was calculated as an assessment of CCA hemodynamics. Renal Doppler flow was obtained from the interlobar arteries in each of two kidneys. The mean PI ([peak systolic velocity − end-diastolic velocity]/mean velocity) and mean RI ([peak systolic velocity − end-diastolic velocity]/peak systolic velocity) were calculated.

Results: Intrarenal PI and RI were positively correlated with IMT and negatively correlated with Vd/Vs in CCA, indicating that renal vascular resistance is related to carotid stiffness. A stepwise regression analysis revealed that age and pulse pressure were independently associated with intrarenal PI and RI.

Conclusions: These results suggest that the measurement of PI and RI is useful for the evaluation of arterial stiffness in patients with essential hypertension. Am J Hypertens 2004;17:240–244 © 2004 American Journal of Hypertension, Ltd.

Key Words: Pulsatility index, resistive index, intima–media thickness, Doppler ultrasound, essential hypertension.

The pulsatility index (PI) and the resistive index (RI) are different indices calculated from the blood flow velocities in vessels during the cardiac cycle by a pulsed-wave Doppler ultrasound.[1,2] Originally, PI and RI were introduced to detect peripheral vascular disease. The measurement of PI and RI in renal arteries has been reported as a reliable marker of downstream renal resistance.[3,4] Furthermore, PI and RI are useful for the diagnosis of renal artery stenosis[5] and kidney graft rejection.[6] Recently the assessment of PI and RI of intrarenal arteries has been used to assess the severity of target organ damage in patients with hypertension and diabetes mellitus, as well as chronic renal failure.[7–9]

B-mode ultrasound imaging of the common carotid artery (CCA) has been developed for the in vivo evaluation of early atherosclerotic lesions.[10] Hypertensive patients exhibit a greatly increased intima–media thickness (IMT) and a higher prevalence of plaques in the CCA than normotensive individuals.[11] We have previously evaluated the hemodynamic changes in the CCA using Doppler ultrasound and demonstrated that the diastolic perfusion rate of the CCA in hypertensive patients with insulin resistance (IR) is lower than that of normotensive subjects and hypertensive patients without IR.[12]

In the present study, we evaluated pulse-Doppler PI and RI of intrarenal vasculature in hypertensive patients and noted a significant relation between renal hemodynamics and CCA hemodynamics.

Methods

Patients

Patients with essential hypertension participated in the present study. They were recruited from consecutive cases admitted to Ehime University Hospital from July 1999 to January 2003. Hypertension was defined as a systolic

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From the The Second Department of Internal Medicine, Ehime University School of Medicine, Onsen-gun, Ehime, Japan.

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Address correspondence and reprint requests to Dr. Takafumi Okura, The Second Department of Internal Medicine, Ehime University School of Medicine, Onsen-gun, Ehime 791-0295, Japan; e-mail: okura@m.ehime-u.ac.jp

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blood pressure (BP) ≥140 mm Hg or a diastolic BP ≥90 mm Hg measured three times in the sitting position using a brachial sphygmomanometer. Patients with diabetes mellitus and renal failure (creatinine >124 μg/mL) were excluded from the study. All patients received a diet containing 7 g of NaCl per day and all medications were discontinued at least 1 week before the investigation. Informed consent to the procedures was obtained from each patient.

Blood Sampling

Measurement of serum creatinine, total cholesterol, HDL-cholesterol, and triglyceride levels was performed using an automatic analyzer (model TBA-60S, Toshiba Inc., Tokyo, Japan).

Ultrasound Analysis of the CCA

Carotid arteries were evaluated using an SSD-2000 (Aloka Co., Tokyo, Japan) and a 7.5-MHz probe as previously described.[13] After the subject had rested for at least 10 min in the supine position with his or her neck in slight hyperextension, we examined an optimal visualization of the CCA, carotid bulb, and extracranial internal and external carotid arteries bilaterally. The IMT of the far wall was measured in the CCA at both 1 and 2 cm proximal to the bulb from the anterior, lateral, and posterior approaches. The data were then averaged to obtain the mean IMT. Measurements were never taken at the level of discrete plaque. Doppler evaluation was performed by scanning the right CCA in the anterior projection. Under guidance using color flow mapping, the sample volume was located at the center of the vessel. Flow velocity–time integrals of systolic and diastolic phases were computed automatically by electronic integration of the instantaneous flow velocity curves. Furthermore, systolic (Vs) or diastolic flow velocity (Vd), mean velocity, and relative diastolic flow velocity (Vd/Vs) were calculated to assess the hemodynamics in the CCA.

Ultrasound Analysis of the Kidney

Renal Doppler flow was obtained from the interlobar arteries by placing the sample at three different positions (superior, mid, and inferior) in each of two kidneys, guiding with color flow mapping similar to the CCA. The mean PI ([peak systolic velocity − end-diastolic velocity]/mean velocity) and mean RI ([peak systolic velocity − end-diastolic velocity]/peak systolic velocity) were calculated.[1,2]

Determination of Left Ventricular Mass Index

Echocardiographic studies were carried out using an SSD-6500 echocardiograph with a 3.5-MHz transducer (Aloka) according to the recommendations of the American Society of Echocardiography.[14] Left ventricular mass (LVM) was estimated using the formula of Devereux and Reichek (Penn convention)[15] and was adjusted for the body surface area to obtain the LVM index (LVMI).

Table 1. Clinical characteristics of the participants

Characteristic	Value
Number (M/F)	51 (29/22)
Age (y)	59 ± 14
Body mass index	25.2 ± 3.9
24-h systolic blood pressure (mm Hg)	155 ± 18
24-h diastolic blood pressure (mm Hg)	91 ± 12
Mean blood pressure (mm Hg)	112 ± 11
Pulse pressure (mm Hg)	64 ± 19
Heart rate (beats/min)	73 ± 13
Total cholesterol (mg/dL)	207 ± 35
HDL-cholesterol (mg/dL)	54 ± 21
Triglyceride (mg/dL)	143 ± 67
Creatinine (mg/dL)	0.8 ± 0.2
Intima–media thickness (mm)	0.81 ± 0.16
Left ventricular mass index	123 ± 32
Pulsatility index	1.30 ± 0.29
Resistive index	0.65 ± 0.08

Twenty-four-hour BP Determination

Twenty-four-hour systolic and diastolic BP (24h systolic BP and diastolic BP) was measured by a cuff-oscillometric method using an FB-250 oscillometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). Blood pressure was measured every 30 min from 6:00 AM to 10:00 PM and every 60 min from 10:00 PM to 6:00 AM of the following day.[16] Pulse pressure was calculated (mean 24h systolic BP − mean 24h diastolic BP).

Statistical Analysis

All values are expressed as mean ± SD. Pearson's correlation coefficient was used to determine the significance of associations. A stepwise regression analysis was applied to evaluate the determinant factor of PI and RI. A P value < .05 was considered statistically significant.

Results

Fifty-one patients with essential hypertension were enrolled in this study. Clinical characteristics of the subjects are shown in Table 1. Intrarenal hemodynamic data were positively correlated with morphologic and hemodynamic alteration of the CCA. Both PI and RI were positively correlated with the IMT of the CCA ($r = 0.532$, $P < .0001$ and $r = 0.564$, $P < .0001$, respectively; Fig. 1) and negatively correlated with the relative diastolic flow velocity Vd/Vs ($r = -0.559$, $P < .0001$ and $r = -0.571$, $P < .0001$, respectively; Fig. 2). Furthermore, PI and RI were positively correlated with age ($r = 0.682$, $P < .0001$ and $r = 0.682$, $P < .0001$, respectively) and pulse pressure ($r = 0.628$, $P < .0001$ and $r = 0.679$, $P < .0001$,

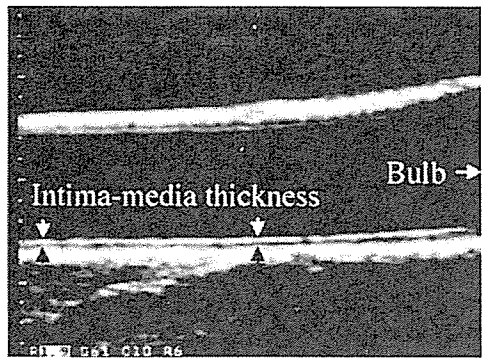

FIG. 1. Measurement of intima–media thickness of common carotid artery. The intima–media thickness of the far wall was measured in the common carotid artery at both 1 and 2 cm proximal to the bulb.

respectively; Fig. 3). However, there was no relationship between intrarenal hemodynamic data and LVMI. Both PI and RI were not associated with total cholesterol, HDL cholesterol, and triglyceride levels. The RI was significantly correlated with body mass index (r = 0.312, P = .0257) but not PI (r = 0.246, P = .0817). A stepwise regression analysis for PI or RI was performed with age, body mass index, pulse pressure, and total cholesterol as independent variables. Age and pulse pressure were independently associated with PI and RI (Table 2).

Discussion

The echo-Doppler technique in renal arteries is highly effective in the diagnosis of several pathologic renal conditions such as arterial stenosis,[5] urinary tract obstruction,[17] and acute renal transplant rejection.[6] The PI and RI were introduced by Gosling et al[1] in 1971 and Pourcelot[2] in 1974, respectively, to detect peripheral vascular disease. A high index of PI and RI is associated with a high difference in velocity between the systolic and the diastolic phase. This difference in flow velocities reflects downstream resistance, which could at least in part depend on the degree of peripheral arterial stiffness.[3,4] Recently, PI and RI in intrarenal arteries have been evaluated in patients with hypertension.[7,8] Petersen et al[7] reported that both PI and RI were significantly higher in hypertensive patients than normotensive subjects and both PI and RI were correlated with renal plasma flow, renal vascular resistance, and creatinine clearance. The increased PI and RI measured at the level of the intrarenal arteries are also associated with end organ damage of patients with hypertension[8] or diabetes mellitus.[10] Pontremoli et al[8] reported that RI was positively correlated with the albumin-to-creatinine ratio and IMT in hypertensive patients. In patients with non–insulin-dependent diabetes, Boeri et al[10] reported that patients with macroangiopathy exhibited a significantly higher RI. In the present study, we have

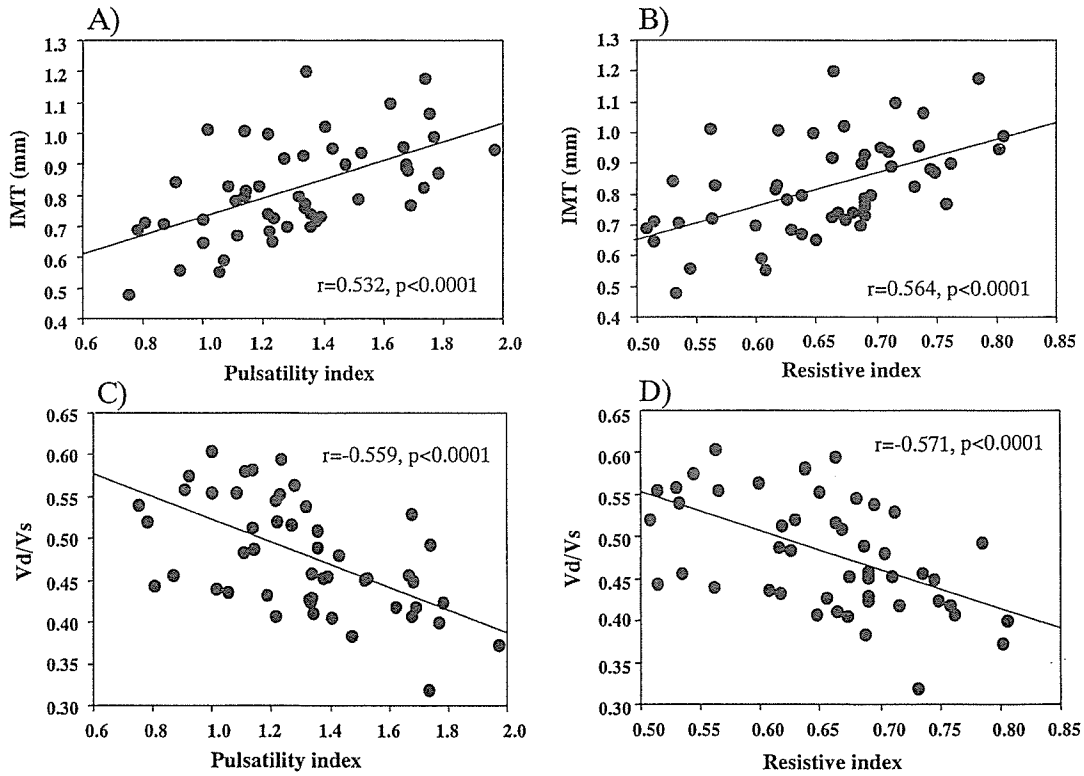

FIG. 2. Correlation between intrarenal hemodynamic data and carotid morphologic and hemodynamic data. (**A**) Relation between pulsatility index and intima–media thickness. (**B**) Relation between resistive index and intima–media thickness. (**C**) Relation between pulsatility index and Vd/Vs. (**D**) Relation between resistive index and Vd/Vs. IMT = intima–media thickness; Vd/Vs = relative diastolic flow velocity.

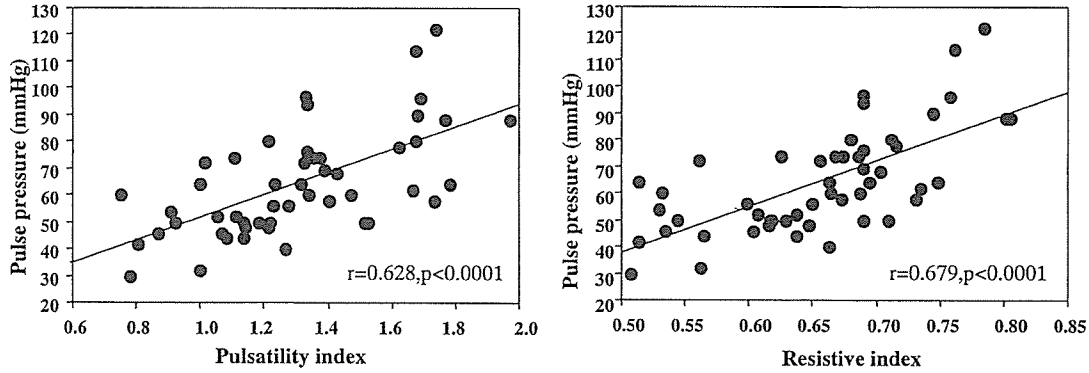

FIG. 3. Correlation between intrarenal hemodynamic data and pulse pressure. (**Left**) Relation between pulsatility index and pulse pressure. (**Right**) Relation between resistive index and pulse pressure.

demonstrated that intrarenal PI and RI were associated with carotid arteriosclerosis and hemodynamic alteration.

Hypertensive patients have an increased IMT of the CCA and this pathologic change is related to cardiovascular complications and future cerebrovascular events.[11] In this study, we have demonstrated that the PI and RI of intrarenal arteries are positively correlated with the IMT of CCA in hypertensive patients thereby, indicating that measurement of PI and RI is useful for the evaluation of atherosclerosis. Previously, we evaluated the hemodynamic changes in the CCA using Doppler ultrasound and demonstrated that the diastolic perfusion rate (Vd/Vs) of the CCA in hypertensive patients with insulin resistance was significant lower than that of both normotensive subjects and hypertensive patients without insulin resistance.[12] This previous report showed that hypertensive patients, especially those with insulin resistance, exhibit an increased arterial stiffness of the CCA by hemodynamic criteria. In the present study, we showed that Vd/Vs was also associated with the PI and RI of intrarenal arteries, indicating that abnormal hemodynamic alterations occurred in different organs to a comparable degree in hypertensive patients.

We were unable to demonstrate the positive relationship between LVH and intrarenal PI or RI. Pontremoli et al[8] reported that hypertensive patients with an elevated RI showed a significantly higher prevalence of LVH, but they were also unable to demonstrate a positive correlation between RI and LVMI. These results suggest that the mechanism of hypertension-mediated progressive damage and injury differ between vessels and the myocardium.

In stepwise regression analysis, both PI and RI were independently associated with age and pulse pressure. Increased pulse pressure and increased stiffness and thickness of the CCA wall were shown to be significant and independent predictors of cardiovascular complications,[18–21] mainly for myocardial infarction but also for stroke.[22] Our results in the present study suggest that the PI and RI of intrarenal arteries could be a useful marker of end organ damage and might be a predictor of future cardiovascular complications in hypertensive patients.

In conclusion, we have demonstrated that intrarenal PI and RI are positively correlated with both morphologic and hemodynamic alteration of the CCA, indicating that renal vascular resistance is related to carotid stiffness. Both PI and RI were independently associated with age and pulse pressure. Measurement of PI and RI may well be useful for the evaluation of arterial stiffness in patients with essential hypertension.

Table 2. Stepwise regression analysis for intrarenal pulsatility index and resistive index

	Partial Correlation Coefficient	*P*
Pulsatility index		
Age	0.544	< .001
Pulse pressure	0.420	< .001
Resistive index		
Age	0.517	< .001
Pulse pressure	0.503	< .001

Stepwise regression analysis for pulsatility index and resistive index were performed with the following parameters: age, body mass index, pulse pressure, and total cholesterol.

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Prediction of Stroke by Self-Measurement of Blood Pressure at Home Versus Casual Screening Blood Pressure Measurement in Relation to the Joint National Committee 7 Classification

The Ohasama Study

Kei Asayama, MD; Takayoshi Ohkubo, MD, PhD; Masahiro Kikuya, MD, PhD; Hirohito Metoki, MD; Haruhisa Hoshi, MD, PhD; Junichiro Hashimoto, MD, PhD; Kazuhito Totsune, MD, PhD; Hiroshi Satoh, MD, PhD; Yutaka Imai, MD, PhD

Background and Purpose—To compare the predictive power of self-measured home blood pressure (HBP) and casual blood pressure (CBP) for stroke risk in relation to the Joint National Committee 7 (JNC-7) classification.

Methods—HBP and CBP measurements were taken in 1702 subjects (≥40 years) without a history of stroke, who were followed up for an average of 11 years. Subjects were classified into 4 groups on the basis of either HBP or CBP, according to the JNC-7 criteria: group 1 (HBP <115/75 mm Hg; CBP <120/80 mm Hg); group 2 (115/75≤HBP<135/85 mm Hg; 120/80≤CBP<140/90 mm Hg); group 3 (135/85≤HBP<150/95 mm Hg; 140/90≤CBP<160/100 mm Hg); and group 4 (HBP≥150/95 mm Hg; CBP ≥160/100 mm Hg). Groups 2, 3, and 4 were further divided into 2 subgroups (a and b): those without and with cardiovascular disease risks, respectively. The risk of the first stroke in these groups was examined by the Cox hazards model adjusted for age and sex.

Results—The stroke risk in groups 3b and 4b (defined by HBP and CBP) was 2 to 5× higher than that in group 1 with significant differences. The risk in groups 2a, 3a, and even 4a was not significantly different from that in group 1 by the CBP-based classification, but the risk in group 4a was significantly higher than that in group 1 by the HBP-based classification, which also showed a stepwise increase in risk from groups 2a to 4a.

Conclusions—The JNC-7 classification had a stronger predictive power using HBP-based classification compared with CBP-based classification, suggesting the usefulness of HBP in the management of hypertension. (***Stroke*. 2004;35:2356-2361.**)

Key Words: blood pressure ■ hypertension ■ prospective studies ■ stroke

Hypertension is a major risk factor for stroke in developed and developing countries. Accurate diagnosis and treatment of hypertension are necessary for better stroke prevention in the Asia-Pacific region because a high frequency of ischemic and hemorrhagic stroke related to blood pressure (BP) is observed in this region.[1]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Joint National Committee 7 [JNC-7]) is based on recent, up-to-date evidence for handling hypertension.[2] The JNC-7 classification has 2 distinctive features compared with past JNC-VI[3] and the 1999 World Health Organization–International Society of Hypertension Guidelines:[4] risk stratification is simplified to 4 grades on the basis of BP; a new category, 120 to 139 mm Hg systolic BP (SBP) or 80 to 89 mm Hg diastolic BP (DBP), is defined as prehypertension. The JNC-7 recommended that subjects who had a past history of cerebrovascular disease should be treated intensively to prevent the recurrence of stroke. However, there was no specific description of strategies to prevent the first stroke. Although the applicability of JNC-VI was demonstrated in the Japanese population,[5] it is still uncertain whether the newer classification could be similarly useful in Asian populations.

We reported that self-measurement of home BP (HBP) was more likely to reflect an individual's "true" BP and thus has a stronger predictive power for mortality compared with conventional casual BP (CBP).[6–8]

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From the Departments of Clinical Pharmacology and Therapeutics (K.A., H.M., K.T., Y.I.) and Drug Development and Clinical Evaluation (T.O., M.K., J.H.), Environmental Health Sciences (H.S.), Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai; and Ohasama Hospital, Iwate (H.H.), Japan.

Correspondence to Dr Yutaka Imai, Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Science and Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai, 980-8574, Japan. E-mail imai@tinet-i.ne.jp

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TABLE 1. Classification of Groups According to Home (HBP) or Casual BP (CBP) Values and Cardiovascular Risks

Groups	Category Definitions	Systolic BP, mm Hg		Diastolic BP, mm Hg	Cardiovascular Disease Risks*
HBP					
Group 1	Normotension	<115	and	<75	Yes or No
Group 2a	Prehypertension	115–134	or	75–84	No
Group 2b					Yes
Group 3a	Stage 1 hypertension	135–149	or	85–94	No
Group 3b					Yes
Group 4a	Stage 2 hypertension	≥150	or	≥95	No
Group 4b					Yes
CBP					
Group 1	Normotension	<120	and	<80	Yes or No
Group 2a	Prehypertension	120–139	or	80–89	No
Group 2b					Yes
Group 3a	Stage 1 hypertension	140–159	or	90–99	No
Group 3b					Yes
Group 4a	Stage 2 hypertension	≥160	or	≥100	No
Group 4b					Yes

The higher category was used when a subject's systolic and diastolic blood pressures (BPs) fell into different categories.

*Cardiovascular disease risks: diabetes mellitus, hypercholesterolemia, smoking habit, or history of cardiovascular disease.

An objective of this study is to examine whether the JNC-7 classification is applicable in predicting the first-stroke risk among Japanese. Another objective is to compare the predictive power of HBP and CBP for stroke risk in relation to the CBP-based JNC-7 classification.

Methods

Study Population

The present study is part of a longitudinal observational study of subjects who have been participating since 1987 in HBP measurement in Ohasama, which is a rural community in Japan. The socioeconomic and demographic characteristics of this region and the details of the selection of the study subjects have been described previously.[9] Briefly, HBP measured 3× or more and CBP measurements were obtained from 1789 representative individuals of the 1989 eligible individuals aged ≥40 years. Eighty-seven individuals had a previous history of stroke, so they were excluded from the present analysis to show the relationship between the first onset of stroke and BP. Therefore, the study sample consisted of 1702 individuals. The mean (SD) age was 60.6 (10.7) years, and the ratio of men to women was 39:61. The reasons for the disproportionate ratio of men and women were described previously.[9]

The study protocol was approved by the institutional review board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. Informed consent was obtained from each subject.

BP Measurements

Annual health check-ups are available to all Japanese citizens ≥40 years, where CBP is measured. Subjects are seated at rest for ≥2 minutes, and then CBP is measured by well-trained nurses or technicians. In Ohasama, BPs were measured twice consecutively during the health check-up, using a semiautomatic BP measuring device (USM700F; Ueda Electronic Work Co, Ltd) based on the microphone method. For CBP, we used data measured at an annual check-up that occurred within the same time period when HBP was first initiated as part of the study protocol.

We used the following procedure to ascertain the accuracy of HBP. Briefly, health education classes were conducted by physicians and well-trained public health nurses to inform the population of the significance of HBP recording and to teach them how to measure their own BP. Approximately 80% of household members living in Ohasama town attended the classes; public health nurses visited all of the remaining households to provide instruction on HBP measurement. All subjects were asked to hold their cuff-covered arms at heart level during HBP measurements. The subjects were asked to perform each step in the procedure while being observed by a nurse. Individuals attended education class for systematic retraining only once during HBP measurement; however, we emphasize that procedure is comparably easy for individuals with an average educational background in Japan. After their ability to measure HBP was verified, subjects were asked to measure their own HBP in a sitting position every morning within 1 hour after awaking and after ≥2 minutes of rest, and to record the measurements for 4 weeks. If individuals were taking antihypertensive drugs, HBP was measured before medication was taken. These procedures are described in detail in our previous report.[10] HBP was measured with a semiautomatic BP measuring device (HEM401C; Omron Healthcare Co, Ltd) based on the cuff-oscillometric principle, which generates a digital display of systolic and diastolic BP.

The devices for measurement of CBP and HBP were calibrated before the start of the study.[10] The mean difference (SD) between HEM401C and USM700F was −0.4 (6.0) mm Hg for SBP and +1.2 (5.8) mm Hg for DBP. All devices met the criteria set by the Association for the Advancement of Medical Instrumentation.[11]

Classification of Groups

According to the JNC-7 criteria, subjects were classified into 4 groups on the basis of either HBP or CBP, as shown in Table 1. When a systolic or diastolic BP was in a different category, the subject was assigned to the higher category. The CBP classification was equal to JNC-7 criteria. In the present analysis, 135/85 mm Hg HBP was defined as hypertension according to the JNC-VI and

JNC-7 guidelines.[2,3] To define stage 2 hypertension and normotension based on HBP, we postulated that 95 mm Hg and 75 mm Hg diastolic HBP are equivalent to 100 mm Hg and 80 mm Hg diastolic CBP (ie, parallel shift of CBP to HBP). Then SBP levels of HBP were introduced from the rate of subjects with normotension (group 1), prehypertension (group 2), stage 1 hypertension (group 3), and stage 2 hypertension (group 4) of CBP classification. According to this classification method for HBP, HBP in group 1 was defined as SBP<115 mm Hg and DBP<75 mm Hg, group 2 as 115 ≤SBP<135 mm Hg or 75 ≤DBP<85 mm Hg, group 3 as 135≤SBP <150 mm Hg or 85≤DBP<95 mm Hg, and group 4 as 150≤SBP or 95≤DBP.

After classification on the basis of either CBP or HBP, groups 2 to 4 were further divided into 2 subgroups (a and b): those without and with cardiovascular disease risks (diabetes mellitus, hypercholesterolemia, habitual smoking, or history of cardiovascular diseases), respectively. According to JNC-7 criteria, these cardiovascular disease risks prescribe a compelling indication for antihypertensive drugs. Therefore, all subjects were assigned to 1 of 7 categories (groups 1, 2a, 3a, 4a, 2b, 3b, and 4b). Subjects classified according to CBP and HBP were analyzed separately (Table 1).

Follow-Up and Risk Ascertainment

In the present study, we accumulated follow-up data until December 31, 2001. The incidence and past history of stroke and transient ischemic attack (TIA) were investigated by use of the Stroke Registration System of Iwate Prefecture, death certificates, receipt of National Health Insurance, and questionnaires sent to each household at the time of HBP measurement. This was then confirmed by checking the medical records of Ohasama Hospital, which is the only hospital in the town. Computed tomography (CT) scan and MRI of the brain are available, and >90% of the subjects have their regular check-ups at this facility. We defined stroke and TIA as clinical disorders with focal brain dysfunction. The diagnostic criteria of stroke, TIA, and their subtypes were based on the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke.[12] We used CT scan and MRI to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. The analysis in the present study included only the first event for those who had multiple nonfatal events, whereas subarachnoid hemorrhage (SAH) was excluded as an incident of stroke. Cardiovascular disease risks were obtained from the questionnaires and medical records at Ohasama Hospital.

Data Analysis

CBP of each subject was the average of 2 consecutive CBP readings. HBP values were the average of all home measurements per subject.

The risk of first stroke or TIA was examined by using the Cox proportional hazards model. The dependent variable was the number of days from the measurement of the first BP to death or censoring for survivors until December 31, 2001. The independent variables were age, sex, and subgroups of HBP or CBP classifications.

The estimated relative hazard (RH) and the 95% CI of variables were derived from the coefficient and its SE determined by the Cox model. The RH is expressed relative to group 1 (normotensives; RH, 1). All data were expressed as mean (SD) unless otherwise stated. $P<0.05$ (2-sided test) was considered statistically significant. The SAS system (version 8.02; SAS Institute) was used for all statistical calculations.

Results

Subjects were followed up for a mean of 10.6±3.0 years (maximum of 13.9 years). There were 141 incident cases of first stroke or TIA among the 1702 individuals: 106 (75%) resulting from cerebral infarction, 28 (20%) resulting from intracerebral hemorrhage, 4 (3%) TIA, and 3 (2%) of unknown causes. Twelve events of SAH were observed and excluded from the 141 incident cases.

Characteristics of subjects are shown in Table 2. Of the 1702 study subjects, 370 (22%) were classified as current or ex-smokers; 507 (30%) were treated with antihypertensive medication at baseline; 16 (1%) had a history of heart disease; 218 (13%) of diabetes mellitus; and 207 (12%) of hypercholesterolemia. The mean number of HBP measurements from each individual was 23.0 (7.1). The mean SBP and DBP of all subjects were 125.2 (15.0) and 74.9 (10.1) mm Hg, respectively.

Preliminarily, we analyzed the risk of first onset of stroke or TIA among the 4 groups of BP stratification (Figure 1). The cardiovascular disease risks were used for adjustment of the Cox model instead of risk stratification ("a" and "b"). Linear increases in the risk of stroke or TIA for CBP-based and HBP-based classifications were observed in this sample. The predictive value of HBP was higher than that of CBP; the risk in group 3 was not significantly higher by the CBP-based classification (RH, 1.62; CI, 0.90 to 2.91; $P=0.1$), but it was significantly higher by the HBP-based classification (RH, 4.07; CI, 1.99 to 8.31; $P=0.0001$). The statistically significant linearity among the groups was observed for CBP-based (trend $P=0.0009$) and HBP-based (trend $P<0.0001$) classifications.

Figure 2 shows the risk of first stroke or TIA of the 7 groups in each CBP-based and HBP-based classification. The RHs in subgroup b, with cardiovascular disease risks on the basis of HBP and CBP, increased linearly with the elevation of BP grade. In group 4b and 4a, the predictability of HBP (4b RH, 6.41; CI, 2.81 to 14.6; $P<0.0001$; 4a RH, 2.88; CI, 1.09 to 7.60; $P=0.03$) in terms of magnitude of RH was higher than that of CBP (4b RH, 2.94; CI, 1.32 to 6.55; $P=0.009$; 4a RH, 2.06; CI, 1.02 to 4.15; $P=0.04$). On the other hand, the risk in groups 2a and 3a was not significantly different from that in group 1 by the CBP-based classification (group 2a RH, 0.94; CI, 0.50 to 1.77; $P=0.8$; group 3a RH, 0.75; CI, 0.35 to 1.62; $P=0.5$), and no stepwise increase in risk was observed (trend $P=0.1$). However, when based on HBP classification, a significant increase in risk was clearly observed even in group 3a (RH, 2.40; CI, 1.09 to 5.29; $P=0.03$), and the stroke or TIA risk was increased linearly (trend $P=0.01$).

The same results were obtained when SAH was included in the stroke incidence (data not shown). The relationships between cerebral infarction and JNC-7 classification or cerebral hemorrhage and JNC-7 classification were analyzed separately. In cerebral infarction, the same results were observed, whereas in cerebral hemorrhage, such tendency was not observed (group 4a and 4b $P>0.05$). There was no interaction between use of antihypertensive medication and BP category (CBP $P=0.4$; HBP $P=1.0$).

Discussion

We found that JNC-7 classification by HBP had stronger predictive power than by CBP for stroke or TIA risk in this prospective cohort study. We also showed that risk for stroke was apparently predicted when HBP was used for classification irrespective of the presence of cardiovascular disease risks but not necessarily when CBP was used. These results were based on a comprehensive follow-up system in the

TABLE 2. Clinical Characteristics Among Groups*

Variables	Group 1	Group 2a	Group 2b	Group 3a	Group 3b	Group 4a	Group 4b
HBP Based Groups							
No. of subjects	432	452	316	210	152	62	78
Age (y)	55.8±10.0	59.8±9.9	60.9±9.8	66.4±10.4	61.9±10.0	68.6±10.6	65.4±10.7
Male (%)	25.2	24.6	60.1	31.4	64.5	58.1	76.9
Body mass index (kg/m^2)	22.7±2.8	23.5±3.0	23.5±3.2	23.6±3.2	24.4±3.2	23.0±2.9	24.8±3.8
PH of cardiovascular diseases (%)	0	N/A	2.8	N/A	3.9	N/A	1.3
Diabetes (%)	10.4	N/A	30.4	N/A	35.5	N/A	29.5
Smoking (%)	13.9	N/A	55.7	N/A	54.6	N/A	65.4
Hypercholesterolemia (%)	6.9	N/A	31.3	N/A	34.2	N/A	33.3
Use of antihypertensive medication (%)	10.4	22.3	28.2	50.0	55.3	58.1	60.3
Home SBP (mm Hg)	107.7±5.4	123.0±5.8	123.9±5.8	138.9±5.6	138.1±6.8	155.0±10.1	154.0±9.9
Home DBP (mm Hg)	65.0±5.8	73.8±5.8	74.3±5.6	80.6±7.4	84.5±6.1	90.5±8.4	92.5±11.0
Casual SBP (mm Hg)	120.9±15.3	132.5±16.8	132.1±14.3	143.9±18.2	141.4±19.6	148.9±22.1	148.4±18.9
Casual DBP (mm Hg)	69.6±9.4	75.6±10.6	74.8±10.2	80.3±12.1	80.7±12.0	85.3±11.9	83.1±14.2
CBP Based Groups							
No. of subjects	370	458	325	220	155	106	68
Age (years)	57.2±8.9	59.3±11.1	60.8±9.8	63.0±11.2	63.1±10.3	65.9±11.7	63.7±11.1
Male (%)	28.9	25.8	58.8	32.3	61.9	34.9	73.5
Body mass index (kg/m^2)	22.6±2.8	23.4±2.9	23.7±3.2	23.7±3.4	24.0±3.7	23.5±3.2	24.6±2.8
PH of cardiovascular diseases (%)	1.1	N/A	2.2	N/A	2.6	N/A	1.5
Diabetes (%)	9.2	N/A	32.9	N/A	31.6	N/A	41.2
Smoking (%)	19.5	N/A	55.1	N/A	54.2	N/A	51.5
Hypercholesterolemia (%)	7.6	N/A	31.4	N/A	31.6	N/A	41.2
Use of antihypertensive medication (%)	15.9	24.0	28.6	35.9	56.1	42.5	50.0
Home SBP (mm Hg)	114.7±12.1	122.4±12.9	125.7±12.4	130.6±13.0	134.1±14.1	138.1±14.9	141.4±14.4
Home DBP (mm Hg)	69.7±9.0	73.0±8.7	76.4±9.5	77.1±8.9	79.6±10.4	79.9±10.3	84.0±11.4
Casual SBP (mm Hg)	109.9±7.0	129.2±6.0	129.3±6.0	146.3±6.8	146.8±5.8	169.7±14.6	171.0±11.1
Casual DBP (mm Hg)	64.9±7.0	73.6±7.5	74.2±8.1	83.1±9.8	81.7±9.6	90.6±11.8	94.0±11.4

*See Table 1 for the definitions of groups.
Values are expressed as mean±SD.
PH indicates past history.

Ohasama cohort. First, our investigators repeatedly checked the medical records in Ohasama hospital with the radiologists' interpretations of CT/MRI and were convinced that the diagnoses of stroke and subtypes were highly reliable. Second, the determination of stroke incidence by death certificates only was limited to 3% of the total cases, therefore, bias in the findings attributable to unidentified cases would be unlikely.

Japanese mortality resulting from stroke is 3× higher than that in the United States,[13] and the mortality from coronary heart disease in Japan is one third of that in the United States.[14] Such differences may be explained by differential environmental and genetic risk factors, and thus guidelines for treating hypertension would depend on the properties of each population. JNC-7 is essentially the guideline for the US population. However, our results demonstrate that JNC-7 criteria are valuable for prediction of stroke risk even in the general Japanese population. The incidence of first cerebral hemorrhage, contrary to that of cerebral infarction, was not associated with JNC-7 classification; this may be attributable to the low incidence of cerebral hemorrhage (n=28).

In addition, the criteria categorized by CBP are not equivalent to those categorized by HBP. It should be emphasized that HBP was a better predictor of stroke and TIA than CBP. Thus, the usefulness of HBP should be higher in countries with high incidences of stroke and TIA, including Japan.

The JNC-VI and JNC-7 set the reference value of hypertension as HBP of 135/85 mm Hg.[2,3] In the present study, HBP was classified on the basis of the percentage distribution of subjects according to the corresponding ratio of CBP. The HBP group 2 would be equivalent to prehypertension by JNC-7 on the basis of CBP because a stepwise increase of stroke risk occurred from group 1 to groups 3a and 3b. Such stepwise increase in stroke risk supports the concept of the JNC-7 recommendation that prehypertensive individuals have a relatively higher cardiovascular disease risk when compared with individuals with normal or "optimal"[15] BP. These data also support the

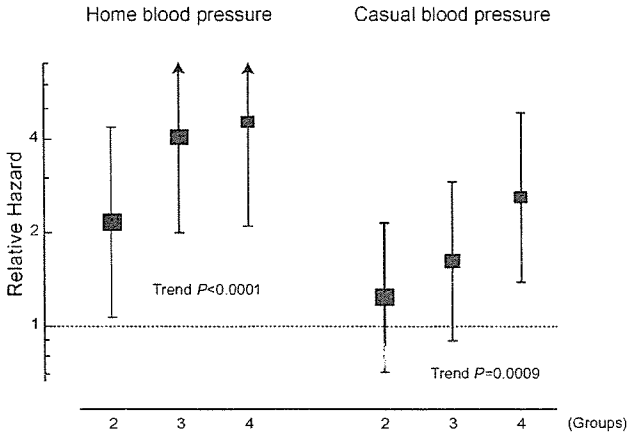

Figure 1. Risk of first stroke among 4 groups defined on the basis of HBP or CBP values. Right and left panels demonstrate RH and 95% CIs for first stroke adjusted for age, sex, and cardiovascular disease risks (diabetes mellitus, hypercholesterolemia, habitual smoking, or history of cardiovascular diseases) plotted on a log scale among groups classified by CBP and HBP values, respectively. Group 2, Prehypertension; group 3, stage 1 hypertension; group 4, stage 2 hypertension. Criteria are shown in Table 1. Group 1, normotension, is treated as the reference category. Solid squares are centered on the RH point and are sized in proportion to the number of events observed. Vertical lines extending from squares represent 95% CI. Trend probability values express the linearity among groups.

intervention strategy for primary prevention of cardiovascular disease in prehypertensive individuals. This intervention might be based on HBP information because stroke risk in patients without cardiovascular disease risks is predictable only when based on HBP not on CBP.

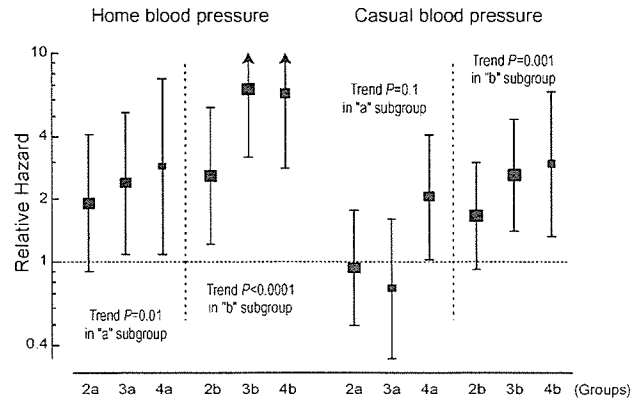

Figure 2. Risk of first stroke among groups defined on the basis of HBP or CBP values and cardiovascular risks. Right and left panels demonstrate RH and 95% CIs for first stroke adjusted for age and sex plotted on a log scale among groups classified by CBP and HBP values. Group 2, Prehypertension; group 3, stage 1 hypertension; group 4, stage 2 hypertension. Groups 2 through 4 were divided into 2 subgroups (a and b): those without and with high cardiovascular disease risks, respectively. Criteria are shown in Table 1. Group 1, normotension, is treated as the reference category. Solid squares are centered on the RH point and are sized in proportion to the number of events observed. Vertical lines extending from squares represent 95% CI. Trend probability values express the linearity among each subgroup (both with group 1).

In this and previous studies, we report repeatedly that HBP is superior to CBP at predicting prognosis of hypertension.[6-10] Such beneficial characteristics of HBP may be derived from increased BP information obtained in relation to time of day. If HBP is measured once every morning and once every evening, this provides at least 60 measurements per month linked to specific times. Information on BP as a function of clock time, as well as an increased number of measurements, improves the quality of data. Furthermore, HBP is usually measured under more controlled conditions than CBP. The measurement conditions described here accord with the Japanese Society of Hypertension Guidelines for Self-Monitoring of Blood Pressure at Home,[8] which may give high reproducibility and reliability of BP information without biases such as white-coat effect, regression dilution biases, and time effect. It is clinically difficult to exclude such biases using CBP. As a result, the CBP-based evaluation of individual risk was unstable (ie, in the present study, the number of subjects in each group using HBP was not matched to a comparable number of CBP subjects in relation to JNC-7). We postulate that such characteristics of HBP provide higher predictability of cardiovascular morbidity and mortality than those of CBP.

We validated the JNC-7 criteria for prediction of stroke risk in the general Japanese population and demonstrated that JNC-7 classification based on HBP measurements is a valuable tool for predicting morbidity and mortality of stroke and TIA. We conclude that HBP measurements should be used more extensively in clinical and epidemiological settings for the primary prevention of cerebrovascular diseases.

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How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study

Takayoshi Ohkubo[a], Kei Asayama[b], Masahiro Kikuya[a], Hirohito Metoki[b], Haruhisa Hoshi[c], Junichiro Hashimoto[a], Kazuhito Totsune[b], Hiroshi Satoh[d] and Yutaka Imai[b]

Objective To determine the optimum number of blood pressure self-measurements taken at home (home blood pressure) in relation to their predictive value for stroke risk.

Methods We obtained more than 14 measurements of home blood pressure from 1491 people aged ≥ 40 years without a history of stroke in the general population in Japan, and followed them up after a mean period of 10.6 years. The prognostic significance of blood pressure for stroke risk was examined using the Cox proportional hazards regression model, which was adjusted for possible confounding factors.

Results The predictive value of home blood pressure increased progressively with the number of measurements, showing the highest predictive value with the average of whole measurements (mean = 25 measurements, 35% increase in the risk of stroke per 10 mmHg elevation in blood pressure). The initial home blood pressure values (one measurement) showed a significantly greater relation with stroke risk than conventional blood pressure values (mean of two measurements) (19/8% increase in the risk of stroke per 10 mmHg elevation in initial home/conventional systolic blood pressure values, respectively).

Conclusions There was no threshold for the number of home blood pressure measurements within the range of 1–14 measurements for increasing the predictive power of stroke risk, suggesting that as many measurements as possible, preferably more than 14 measurements, is recommended for better prediction of stroke risk. It should be emphasized that home blood pressure has a stronger predictive power than does conventional blood pressure, even for a lower number of measurements. *J Hypertens* 22:1099–1104 © 2004 Lippincott Williams & Wilkins.

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Keywords: home blood pressure, conventional blood pressure, stroke, general population, prospective study

[a]Department of Planning for Drug Development and Clinical Evaluation, [b]Department of Clinical Pharmacology and Therapeutics, and [d]Department of Environmental Health Sciences, Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai, Japan and [c]Ohasama Hospital, Iwate, Japan.

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Correspondence and requests for reprints to Takayoshi Ohkubo, MD, Department of Clinical Pharmacology and Therapeutics, Tohoku University Hospital, Sendai, 980-8574, Japan.
Tel: +81 22 717 8590; fax: +81 22 717 8591;
e-mail: tohkubo@mail.tains.tohoku.ac.jp

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Introduction

Self-measured blood pressure at home (home blood pressure), a technique that makes it possible to obtain multiple measurements under well-controlled conditions, has been reported to be more reliable than conventional blood pressure measurement because it avoids both observer and regression dilution biases and eliminates the white-coat effect [1–3]. Cross-sectional studies have also shown that left ventricular hypertrophy is more strongly correlated with home blood pressure measurement than with conventional blood pressure measurement [4–6]. However, no study has yet examined the optimum number of home blood pressure measurements in relation to prognostic significance.

Stroke is a major cause of mortality and disability [7]. Hypertension is a major risk factor for stroke, especially in Asian countries [8–10], and therefore its accurate diagnosis and treatment is necessary for better stroke prevention.

In 1987 we established a project of home blood pressure measurement in the general population of a rural Japanese community, Ohasama [11], and have since monitored the mortality and morbidity of these

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