with HCM are mainly those of the sarcomere components of the myocyte. Although the mechanism of myocardial hypertrophy in these patients is not fully understood, increased Ca^{2+} sensitivity has been reported in various types of mutations[29,30] In addition, calcineurin, a Ca^{2+}/calmodulin-dependent phosphatase, is reported to play an important role in the development of cardiac hypertrophy[31] Insulin activates insulin receptor substrate-1 (IRS-1) by tyrosine phosphorylation and then phosphatidylinositol 3-kinase within the cytoplasm, resulting in various insulin actions such as enhancing glucose uptake and glycogen synthesis. Recently, Hallak et al reported that dephosphorylation of IRS-1 was calcium dependent and inhibited by the calcineurin inhibitor, cyclosporin, in primary cultured rat cerebellar granule neurons, suggesting the importance of calcineurin in the regulation of IRS-1 tyrosine phosphorylation[32] Naya et al reported that calcineurin activation induced slow muscle fiber gene expression of skeletal muscles in transgenic mice[33] In fact, microscopic examinations of biopsy specimens of the soleus muscle from patients with HCM caused by β-myosin mutations have demonstrated a skeletal myopathy similar to central core disease, characterized by a predominance of type I slow fibers and absence of mitochondria in the center of many type I fibers[34] Musaro et al[35] and Semsarian et al[36] also reported that calcineurin and transcription factor NF-ATc1 mediated the hypertrophic effects of IGF-1 in skeletal muscles. How insulin sensitivity is diminished in patients with HCM remains unknown. However, in the light of these reports, it is possible that increased systemic calcineurin activity in patients with HCM suppresses the intracellular signal transduction of insulin receptors in the skeletal muscles, which results in IR.

Relationship Between IR and Prognosis in HCM

The natural history of HCM is not yet fully understood. In the clinical setting, we sometimes encounter sudden cardiac death and congestive heart failure in patients with HCM. Four of the present HCM patients died suddenly during the follow-up period and all of them had high HOMA-IR values. The multiple regression analyses determined that LVPG was the most powerful independent determinant of the HOMA-IR values in HCM. In addition, there is only a suggested association but neither clinical relevance nor independent linkage between sudden cardiac death and left ventricular outflow obstruction[37] Therefore, our findings regarding the association between IR and sudden cardiac death in patients with HCM may be mediated through the LVPG without provocation.

On the other hand, Hecht et al indicated that end-stage heart failure, characterized by left ventricular enlargement, wall thinning and decreased wall motion, was an important cause for death, especially in older patients with familial HCM[38] In addition, heart failure was associated with IR in dilated cardiomyopathy[39] Of the present patients with HCM, 9 had congestive heart failure during the follow-up period, but there was no significant association between the incidence of heart failure and IR. Unfortunately, we could not assess the follow-up data regarding left ventricular size, wall thickness and wall motion.

Conclusions

We have shown that patients with HCM without apparent diabetes mellitus and hypertension have significant IR in comparison with hypertensive patients or normotensive control subjects. Our findings also suggest that IR may be related to sudden cardiac death mediated through the LVPG in patients with HCM. Further more extensive and long-term follow-up studies of large number of patients with HCM are needed to evaluate the exact mechanisms by which patients with HCM develop IR and the association between IR and the clinical manifestations of HCM.

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Intrarenal and Carotid Hemodynamics in Patients With Essential Hypertension

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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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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 $r = 0.679$, $P < .0001$,

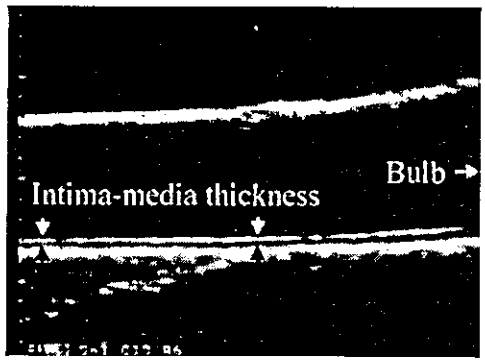

FIG. 1. Measurement of intima–media thickness of common carotid artery. The intima–media thickness of the far wall was measured in the common carotid artery at both 1 and 2 cm proximal to the bulb.

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

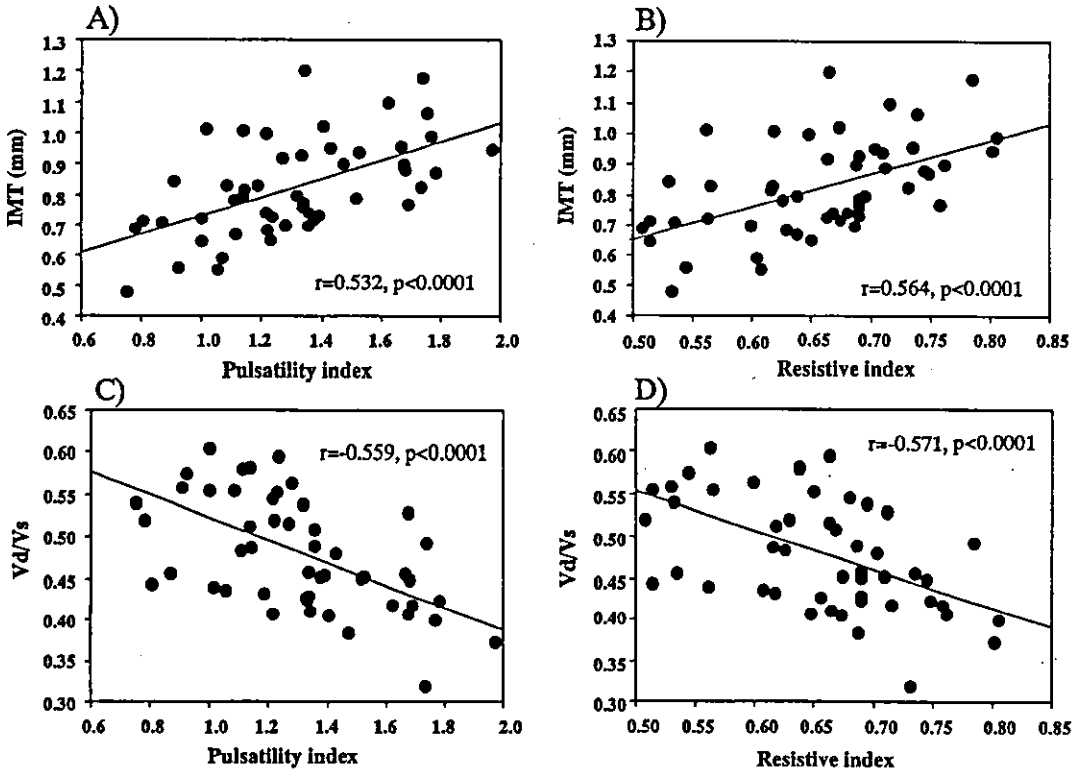

FIG. 2. Correlation between intrarenal hemodynamic data and carotid morphologic and hemodynamic data. **(A)** Relation between pulsatility index and intima–media thickness. **(B)** Relation between resistive index and intima–media thickness. **(C)** Relation between pulsatility index and Vd/Vs. **(D)**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

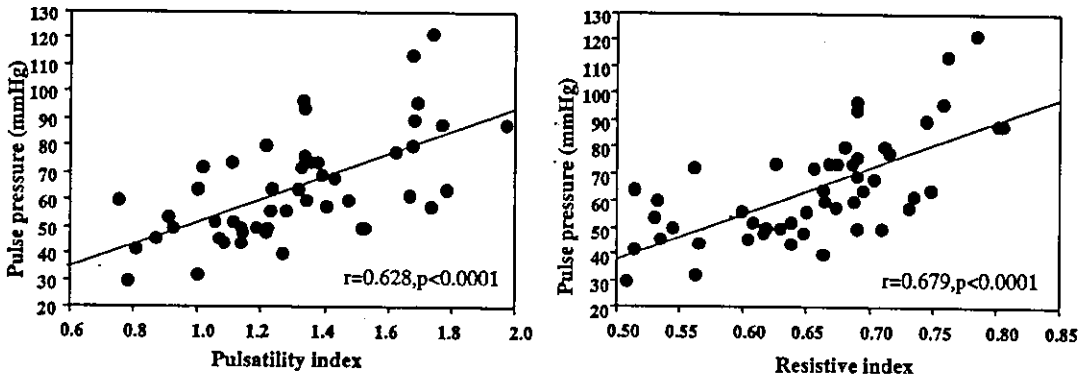

FIG. 3. Correlation between intrarenal hemodynamic data and pulse pressure. **(Left)** Relation between pulsatility index and pulse pressure. **(Right)** Relation between resistive index and pulse pressure.

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

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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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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

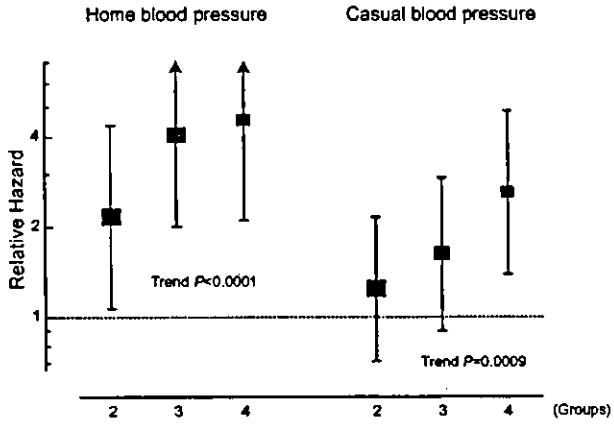

Figure 1. Risk of first stroke among 4 groups defined on the basis of HBP or CBP values. Right and left panels demonstrate RH and 95% CIs for first stroke adjusted for age, sex, and cardiovascular disease risks (diabetes mellitus, hypercholesterolemia, habitual smoking, or history of cardiovascular diseases) 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.

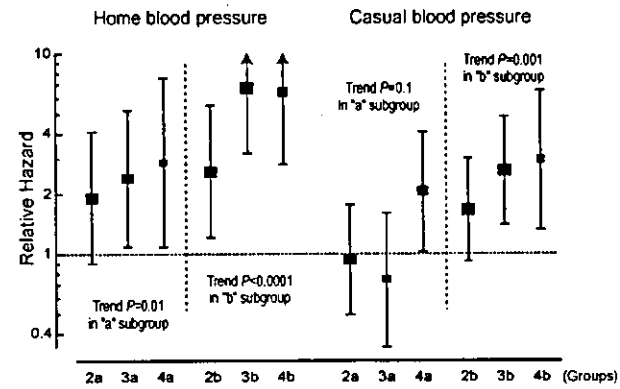

Figure 2. Risk of first stroke among groups defined on the basis of HBP or CBP values and cardiovascular risks. Right and left panels demonstrate RH and 95% CIs for first stroke adjusted for age and sex plotted on a log scale among groups classified by CBP and HBP values. Group 2, Prehypertension; group 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

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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

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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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individuals [12,13]. The primary objective of the present study was to determine the optimum number of home blood pressure measurements in relation to their predictive value for stroke risk. The secondary objective was to compare the predictive value of conventional (screening) and home blood pressure values for the same or less number of measurements (one or two measurements).

Methods

Design

The present report is based on a longitudinal observation of subjects who have been participating in our home blood pressure measurement project in Ohasama, Iwate Prefecture (Japan) since 1987. Ohasama, a rural community, had a total population of 8040 in 1991. The socio-economic and demographic characteristics of this region and the details of the study project have been previously described [11–13]. 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.

Study population

Details of the selection of the study population have been reported previously [12,13]. In brief, of the 1989 eligible individuals aged 40 years and older, more than three measurements (3 days) of home blood pressure data and screening blood pressure data were obtained from 1789 representative individuals [12,13]. Of these, 87 had a previous history of stroke and these subjects were therefore excluded from the present analysis of the relationship between the first onset of stroke and blood pressure values. Of the remaining 1702 subjects, 211 measured their home blood pressure for a period of less than 2 weeks. Therefore, the study population consisted of 1491 individuals. The mean age was 60.6 years and the ratio of men to women was 37 : 63.

Home blood pressure measurements

Physicians and/or public health nurses instructed subjects on how to perform home blood pressure measurements. Subjects were asked to measure their blood pressure every morning within 1 h of waking, in the sitting position after more than 2 min of rest, and to record the results over a period of 4 weeks. The initial 1-day, 2-day, 1-week, 2-week (mean of one, two, seven and 14 measurements, respectively) and multiple (mean of more than 14 measurements; average number of measurements = 25) home blood pressure values were calculated for each individual.

Screening blood pressure measurements

Annual health check-ups, including blood pressure measurements, are available to all Japanese citizens aged 40 years or older. Blood pressure is measured twice consecutively in the sitting position after a rest of at least 2 min by nurses or technicians using a semi-automatic device. The average of the two readings is defined as a screening blood pressure value.

Blood pressure measuring device

Home blood pressure was measured using the HEM 401C (Omron Healthcare Co. Ltd, Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric method [14], which generates a digital display of both systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Screening blood pressure was measured using a USM-700F (UEDA Electronic Works Co. Ltd, Tokyo, Japan), an automatic device based on the Korotkoff sound technique (microphone method).

The average arm circumference for subjects was usually less than 34 cm, so we used a standard arm cuff for both ambulatory and screening blood pressure measurements. Both the home blood pressure measuring device and the screening blood pressure measuring device used in the present study have been previously validated [14,15] and meet the criteria of the Association for the Advancement of Medical Instrumentation [16].

Data analysis

The incidence of stroke and transient ischemic attack (TIA) until 31 December 2001 was investigated through: the Stroke Registration System of the Iwate Prefecture; by tracking death certificates and receipt of National Health Insurance; and by sending questionnaires to each household at the time of home blood pressure measurement. This was then confirmed by checking the medical records of Ohasama Hospital, the only hospital in the town with the facilities for computed tomography and/or magnetic resonance imaging of the brain, where more than 90% of the subjects have their regular check-ups. For 3% of stroke cases, death certificates were the only source of information.

The diagnostic criteria for these subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke [17]. The analysis included only the first event for those subjects who had multiple non-fatal events.

Residence in Ohasama as at 31 December 2001 was confirmed by the residents' registration cards. These cards in Japan are accurate and reliable because they are used for pensions and social security benefits. Twenty-seven subjects (1.8%) had moved away and could not be followed up, and 209 deaths (14.0%) were identified from the residents' registration cards.

The association between baseline blood pressure levels

and the incidence of first stroke or TIA was examined using the Cox proportional hazards regression model, which was adjusted for age, sex and smoking status, for the use of antihypertensive medication at baseline, and for history of heart disease, diabetes mellitus or hypercholesterolemia. The dependent variable in these analyses was the number of days from the date of home blood pressure measurement to the date of stroke or TIA, or censoring. Stroke-free and TIA-free survivors as at 31 December 2001 were censored. When examining the incidence of stroke and TIA, we censored cases of death from causes other than fatal stroke events. The mean duration of follow-up was 10.6 years (standard deviation, 2.9; maximum, 13.9 years).

The information on smoking status, on the use of antihypertensive medication at baseline, and on history of heart disease, diabetes mellitus or hypercholesterolemia was obtained from questionnaires sent to each household at the time of home blood pressure measurements and from medical records at Ohasama Hospital. Of the 1491 study subjects, 299 (20%) were classified as current or ex-smokers and 456 (31%) were treated with antihypertensive medication at the baseline, while 15 (1%), 200 (13%) and 189 (13%) subjects were classified as having a history of heart disease, diabetes mellitus or hypercholesterolemia, respectively.

The estimated relative hazard (RH) and the 95% confidence interval (95% CI) of variables were derived from the coefficient and its standard error as determined by the Cox proportional hazards model. Data are shown as mean ± standard deviation. $P < 0.05$ was accepted as indicative of statistical significance. All statistical analyses were conducted using the SAS package (version 8.2; SAS Institute Inc., Cary, North Carolina, USA).

Results

Of the 1491 subjects, 136 had a first onset of stroke or TIA. This was due to cerebral infarction in 95 (69.9%) subjects, intracerebral hemorrhage in 25 (18.4%) subjects, subarachnoid hemorrhage in 10 (7.4%) subjects, TIA in three (2.2%) subjects, and unknown causes in three (2.2%) subjects.

Home and screening blood pressure values

The initial 1-day, 2-day, 1-week, 2-week and multiple home blood pressure values were significantly lower than the screening blood pressure for SBP (Table 1). All home and screening blood pressure values for those patients who developed stroke over the follow-up period were significantly higher than those who did not develop stroke (screening diastolic, $P = 0.02$; other, $P < 0.001$) (Table 1).

Screening blood pressure was significantly correlated with home blood pressure values (SBP: 1-day, $r = 0.45$; 2-day, $r = 0.49$; 1-week, $r = 0.51$; 2-week, $r = 0.52$; multiple, $r = 0.52$; DBP: 1-day, $r = 0.39$; 2-day, $r = 0.43$; 1-week, $r = 0.47$; 2-week, $r = 0.48$; multiple, $r = 0.49$) (all $P < 0.001$), although the correlation coefficient was not very high.

Association between 2-day, multiple home and screening blood pressure values and stroke risk

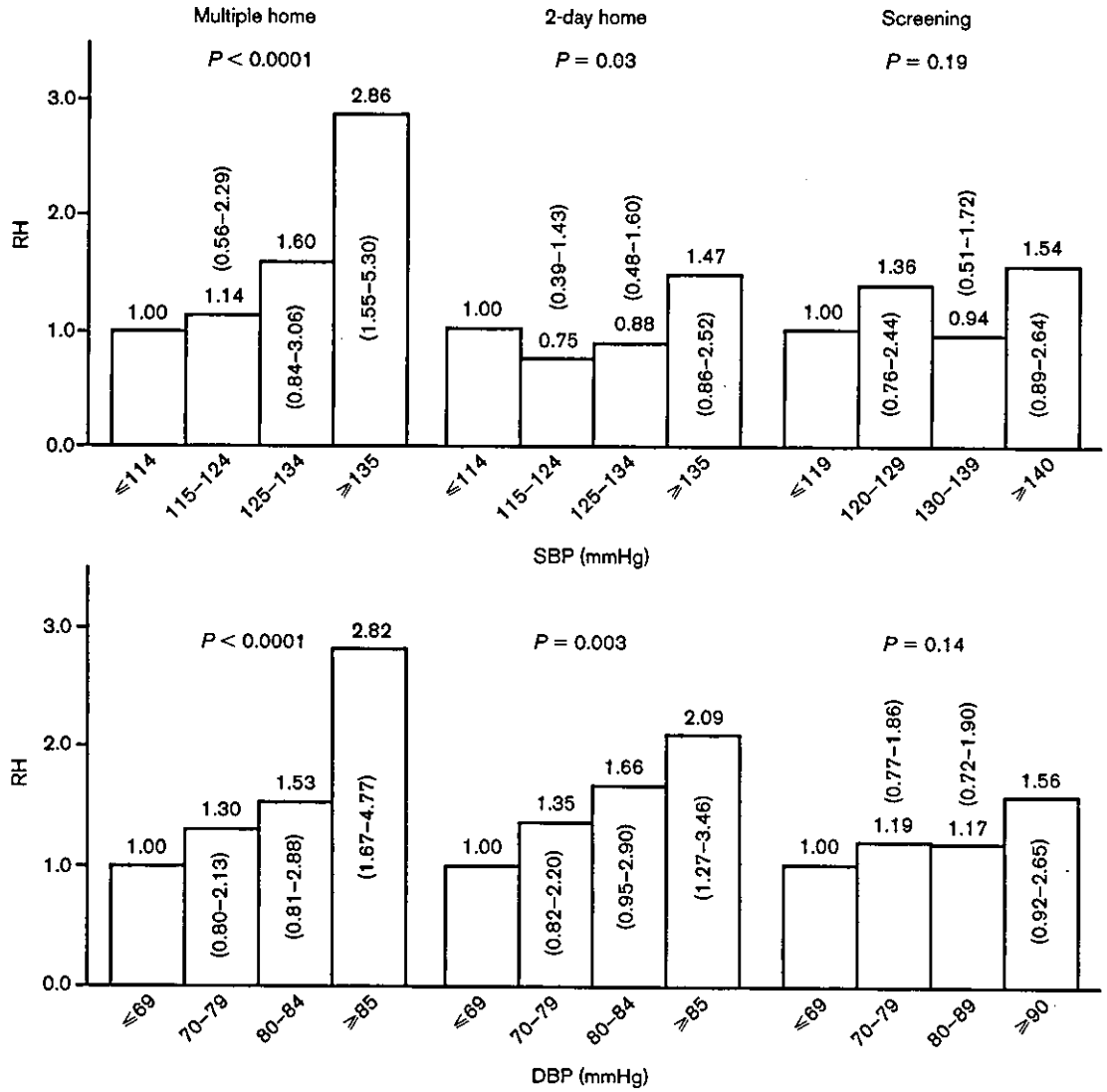
We subdivided the subjects into four groups according to each blood pressure value, and then compared their risk of stroke and TIA (Fig. 1). In the analysis, we treated the lowest group as the reference group. For multiple home SBP measurements, the risk among those with SBP ≥ 135 mmHg (RH = 2.86, $P = 0.0008$) was significantly higher than that among those with SBP < 115 mmHg (reference category), with a significant observable linear trend ($P < 0.0001$). Similarly, multiple home DBP, and 2-day home SBP and DBP values were significantly related to stroke risk (for linear trend, all $P < 0.05$) (Fig. 1). There was a non-significant linear trend between screening SBP, DBP

Table 1 Blood pressure values of the subjects

			Stroke and transient ischemic attack	
		Whole	Developed	Not developed
Systolic blood pressure	Screening	132.9 (19.1)	138.9 (19.3)*	132.3 (19.0)
	Home			
	1-day	127.8 (18.6)	137.8 (20.9)*	126.8 (18.0)
	2-day	127.0 (17.1)	136.2 (18.2)*	126.0 (16.7)
	1-week	126.1 (15.8)	135.6 (17.4)*	125.1 (15.3)
	2-week	125.4 (15.4)	135.3 (16.4)*	124.4 (14.9)
	Multiple	125.1 (15.0)	135.2 (16.0)*	124.1 (14.5)
Diastolic blood pressure	Screening	75.5 (11.7)	77.8 (11.1)**	75.2 (11.7)
	Home			
	1-day	76.4 (12.5)	80.5 (13.3)*	76.0 (12.4)
	2-day	75.9 (11.5)	79.6 (11.2)*	75.5 (11.4)
	1-week	75.4 (10.4)	79.2 (10.2)*	75.0 (10.3)
	2-week	75.0 (10.1)	79.1 (10.1)*	74.6 (10.0)
	Multiple	74.8 (9.9)	79.0 (10.1)*	74.4 (9.8)

t test: * $P < 0.001$, ** $P = 0.02$ versus those who did not develop stroke.

Fig. 1



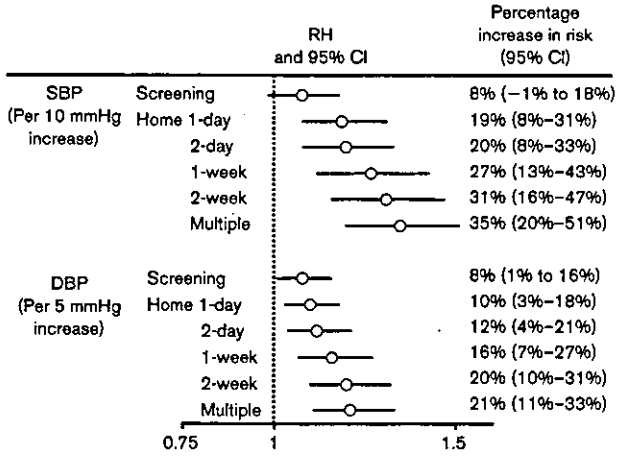
Association between multiple home, 2-day home and screening blood pressure values and stroke risk. Relative hazard (RH) and 95% confidence intervals (CI) of multiple home, 2-day home, and screening systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels adjusted for age, gender, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolemia, and diabetes for first symptomatic stroke. *P* for linear trend indicated above the bars. Numbers inside the bars indicate 95% CI. The lowest group was treated as the reference category.

and stroke risk (both $P > 0.1$) (Fig. 1). The initial 1-day, 1-week and 2-week home SBP and DBP values showed a significant linear relationship with stroke risk (all $P < 0.05$) (data not shown).

Predictive values of home and screening blood pressures

As continuous variables, screening blood pressure values showed a linear association with the risk of stroke and TIA (Fig. 2). A 10 mmHg elevation of screening SBP and a 5 mmHg elevation of screening DBP were associated with 8% increases in both the risk of stroke and TIA, respectively (screening SBP $P = 0.07$, screening DBP $P = 0.03$) (Fig. 2). All home blood pressures showed a linear association with the risk of stroke and TIA (Fig. 2). The predictive value of home blood pressure increased progressively with the number of measurements, showing the highest predictive value with multiple home blood pressure measurements: 10 mmHg elevations of 1-day, 2-day, 1-week, 2-week and multiple home SBP values were associated with respective 19, 20, 27, 31 and 35% increases in the risk of stroke and TIA (all $P < 0.01$) (Fig. 2). Similarly, 5 mmHg elevations of 1-day, 2-day, 1-week, 2-week and multiple home DBP values were associated with

Fig. 2



Predictive values of home and screening blood pressures. Relative hazard (RH) and 95% confidence intervals (CI) of 1-day home, 2-day home, 1-week home, 2-week home, multiple home, and screening systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels adjusted for age, gender, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolemia, and diabetes for first symptomatic stroke. Open circles are RH expressed as an increase in stroke risk per 10 mmHg elevation of SBP and per 5 mmHg elevation of DBP. Horizontal lines represent 95% CI.

respective 10, 12, 16, 20 and 21% increases in the risk (all $P < 0.01$) (Fig. 2). A similar association was observed for the risk of hemorrhagic stroke (intracerebral and subarachnoid hemorrhage) and for the risk of ischemic stroke (cerebral infarction) (data not shown).

Comparison of predictive values between home and screening blood pressures

When 1-day home and screening blood pressure values were simultaneously included in a Cox model, only 1-day home blood pressure was significantly related with stroke/TIA risk as follows: 1-day home SBP, RH per 10 mmHg elevation = 1.18, $P = 0.002$; screening SBP, RH = 1.02, $P = 0.6$; 1-day home DBP, RH per 5 mmHg elevation = 1.09, $P = 0.03$; screening DBP, RH = 1.05, $P = 0.3$. The model including both 1-day home and screening blood pressure lost 'goodness of fit' when 1-day home blood pressure was removed (SBP likelihood ratio = 9.70, $P < 0.01$; DBP likelihood ratio = 4.91, $P < 0.03$). However, the goodness of fit of the model including both 1-day home and screening blood pressure did not change significantly when screening blood pressure was removed (SBP likelihood ratio = 0.21, $P > 0.5$; DBP likelihood ratio = 1.31, $P > 0.1$). Similarly, the 2-day, 1-week, 2-week and multiple home blood pressure values showed a significantly greater relation with the risk of stroke and TIA than the screening blood pressures (all $P < 0.03$).

Discussion

The present study was based on a longitudinal observation of a representative sample of the general population in a rural Japanese community. Although home blood pressure values showed a linear association with the risk of stroke, the predictive value increased progressively with the number of measurements. 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. Goodness of fit of the model including home and screening blood pressures significantly decreased when home blood pressure was removed, but not screening blood pressure. Importantly, even though the number of measurements was the same or less, the 1-day as well as the 2-day home blood pressure values showed a significantly greater relationship with stroke risk than screening blood pressure values.

Home blood pressure is generally self-measured several times over a particular period, but it has not to date been determined how many measurements are needed to provide reliable information in terms of the prognostic significance. Although previous studies of short duration proposed the optimum schedule of home blood pressure measurements as an average of at least 3 days, these studies were based merely on the repeatability and the stability of home blood pressure measurements [18,19]. In this study, multiple home blood pressure measurement (average of 25) was the strongest predictor of stroke or TIA, indicating that the predictive power of home blood pressure was partly dependent upon the number of measurements. We could not determine a threshold for the minimum 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, would be recommended for adequate prediction of stroke risk. Initial 1-day home blood pressure was a stronger predictor of stroke or TIA risk than screening blood pressure, even for less number of measurements. These results suggest that, in addition to the number of measurements, other factors such as the lack of the white-coat effect may be associated with superior predictive power. These results also suggest that the view that "the measurement of the initial-single day should be excluded" [19] could not necessarily be applicable from the view point of the prognostic significance.

Previous researchers have reported a stronger correlation of left ventricular hypertrophy determined by electrocardiogram [4] or echocardiography [5,6] with home blood pressure measurements than with conventional measurements. In these studies, home blood pressure was measured for 3 weeks (an average total of more than 20 measurements). In contrast, one study

reported that neither conventional nor home blood pressure was significantly correlated with left ventricular hypertrophy and its treatment-induced regression [20]. In this study, home blood pressure was measured only twice. These results were consistent with our findings that multiple blood pressure measurement at home has a stronger predictive power. It remains to be investigated whether the prognostic value can be improved and a shorter period of home blood pressure measurements may be required if more measurements are obtained on each day.

Compared with those who developed stroke, the difference between screening and home blood pressure (i.e. the magnitude of the white-coat effect) was larger in subjects who did not develop stroke, whose home blood pressure levels were lower than those who developed stroke. These results are consistent with our previous findings that lower home blood pressure levels are associated with larger white-coat effect [21]. These results also suggest that a larger white-coat effect might be a favorable condition for developing stroke.

Although home blood pressure measurement is now widely practised in developed countries, a lack of information on its prognostic significance has partly limited its effective use [22–24]. In this study, we first demonstrated that home blood pressure measurement provides more useful prognostic information for stroke than conventional blood pressure measurement, and that multiple home blood pressure measurements have the strongest predictive power of stroke risk. Although the external validity of the present findings, especially to non-Asian population, would need to be clarified by further studies, in view of these results, we recommend that home blood pressure measurements should be used more effectively in clinical and epidemiological settings for better prediction of individual risk.

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Prediction of ischaemic and haemorrhagic stroke by self-measured blood pressure at home: the Ohasama study

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Objective To examine the predictive value of self-measured blood pressure values taken at home (home blood pressure) for risk of stroke and subtypes.

Methods We obtained home blood pressure measurements from 1702 people, aged ≥ 40 years, without a history of stroke, in the general population in Japan, and continued follow-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 There was a linear relationship between home blood pressure and risk of stroke and subtypes. On average, each 10/5 mmHg elevation in home systolic/diastolic blood pressure respectively, was associated with an approximately 30/20% respectively, higher risk of total stroke. A similar relationship was observed for the risk of haemorrhagic stroke (intracerebral and subarachnoid haemorrhage), and the risk of ischaemic stroke [cerebral infarction and transient ischaemic attack (TIA)]. The risk of stroke and subtypes showed a significantly greater relation with home blood pressure values compared to conventional blood pressure values.

Conclusions This is the first study to demonstrate that home blood pressure is an independent predictor for haemorrhagic and ischaemic stroke, in the general population. *Blood Press Monit* 9:315–320 © 2004 Lippincott Williams & Wilkins.

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

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Introduction

Stroke is a major and worldwide cause of mortality and disability [1]. Hypertension is a major risk factor for stroke, especially in Asian countries [2–4], and therefore accurate diagnosis and treatment is necessary for better stroke prevention.

Self-measured blood pressure (BP) at home (home BP), is a technique that makes it possible to obtain multiple measurements under well-controlled conditions. It has been reported to be more reliable than conventional BP measurement because it avoids both observer and regression dilution biases and eliminates the white-coat effect [5–7]. Cross-sectional studies have also shown that left ventricular hypertrophy is more strongly correlated with home BP measurement than with conventional BP measurement [8–10]. However, its prognostic significance for stroke and subtypes has not been fully investigated.

In 1987, we established a project of home BP measurement in the general population of a rural Japanese community, Ohasama [11], and have since monitored the mortality and morbidity among this group [12–14]. In a previous report, we demonstrated that home BP had a stronger predictive power for risk of total stroke than conventional (screening) BP [14]. The objective of the present study was to clarify the applicability of the previous findings to the risk of stroke subtypes, i.e., haemorrhagic stroke and ischaemic stroke.

Methods

Design

The present report is based on a longitudinal observation of subjects who have been participating in our home BP measurement project in Ohasama, Iwate Prefecture (Japan) since 1987. The socio-economic and demographic characteristics of this region and the details of the study project have been previously described [11]. 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.

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