Table 1. Characteristics of the Subjects at Baseline*

Risk Factor	All Subjects (N = 777)	Subjects With SNT (n = 649)	Subjects With WCHT (n = 128)	*P* Value†
Age, y	56.0 (8.7)	55.8 (8.5)	57.0 (9.5)	.13
Male	34.0	32.4	42.2	.03
History of smoking	19.4	19.9	17.2	.48
Obesity	20.1	19.0	25.8	.08
Family history of hypertension	34.9	33.6	41.4	.09
Hypercholesterolemia	7.2	7.7	4.7	.23
Diabetes mellitus	11.1	10.8	12.5	.57
Office BP, mm Hg				
Systolic	125.9 (15.8)	121.1 (11.3)	150.4 (12.2)	<.001
Diastolic	72.5 (10.3)	70.2 (8.5)	84.4 (10.5)	<.001
Home BP, mm Hg				
Systolic	116.0 (9.1)	114.9 (8.9)	121.5 (8.0)	<.001
Diastolic	70.4 (7.2)	69.8 (7.1)	73.5 (6.7)	<.001

Abbreviation: BP, blood pressure; SNT, sustained normotension; WCHT, white-coat hypertension.
*Data are given as mean (SD) or percentage of subjects unless otherwise specified.
†Statistical significance between normotensive subjects and subjects with WCHT was compared using the *t* test for continuous variables and the χ^2 test for categorical variables.

vey, 60 died or moved away from the town before the follow-up. Of the remaining 912 subjects, 777 (85%) took part in the follow-up home BP measurements. Mean duration of the period between the baseline and the follow-up home BP measurements was 8.2 (2.0) years. The mean number of follow-up home BP measurements was 23.7 (5.6).

BASELINE CHARACTERISTICS

The baseline characteristics of the subjects in each group are presented in **Table 1**. The mean (SD) age of the 777 subjects was 56.0 (8.7) years and the proportion of men was 34.0%. Mean (SD) office and home systolic/diastolic BP values were 125.9 (15.8)/72.5 (10.3) mm Hg and 116.0 (9.1)/70.4 (7.2) mm Hg, respectively. Of the 777 subjects, 649 (83.5%) were classified as having SNT, while the remaining 128 (16.5%) were classified as having WCHT. Office and home BP values and the proportion of men were significantly higher in subjects with WCHT than among subjects with SNT. Subjects with WCHT tended to be older and have higher proportions of obesity and a more prominent family history of hypertension than those with SNT.

RATE OF DEVELOPMENT OF HOME HYPERTENSION

Development of home hypertension was defined as either progression to high home BP or the start of treatment with antihypertensive medication. At baseline, 649 subjects had SNT and 128 subjects had WCHT. At the time of follow-up measurements, 144 subjects (22.2%) with SNT and 60 (46.9%) with WCHT developed home hypertension. The rate was significantly higher in subjects with WCHT ($P<.001$). The significantly higher rate of development of home hypertension in subjects with WCHT was observed for both hypertension defined by a home BP of 135/85 mm Hg or higher (71 [10.9%] of 649 subjects with SNT and 31 [22.7%] of 128 subjects with WCHT [$P<.001$]) and hypertension defined by the start of treatment with antihypertensive medication (73 [11.2%] of 649 subjects with SNT and 29 [24.2%] of 128 subjects with WCHT [$P<.001$]).

RATE OF DEVELOPMENT OF HOME HYPERTENSION BY BASELINE HOME BP LEVELS

Table 2 gives the rates of development of home hypertension, home BP values, and the magnitude of changes for home BP from baseline to follow-up. (Categories were divided according to baseline home systolic and diastolic BP values.) In subjects with WCHT, as well as those with SNT, rates for development of home hypertension showed a significant trend ($P<.001$), as the baseline home BP values increased across the categories (Table 2). Across a broad range of baseline home BP levels, compared with subjects with SNT, rates of development of home hypertension were higher in most subjects with WCHT (Table 2). In both groups, subjects with a baseline home systolic BP of 108 mm Hg or lower or a diastolic BP of 52 mm Hg or lower had a less than 5% chance of developing home hypertension (Table 2). Similar tendencies were observed regarding the rate for those who developed home hypertension defined by the start of treatment with antihypertensive medication (Table 2).

RISK OF DEVELOPMENT OF HOME HYPERTENSION

The odds ratio (OR) for WCHT to progress to home hypertension, adjusted for other factors, was significantly higher than that of SNT (OR, 2.86; $P<.001$) (**Table 3**). In this multivariate model, older age, male sex, and obesity also significantly predicted the development of home hypertension (Table 3). The significant OR of WCHT for progression to home hypertension was similarly observed for both hypertension defined by a home BP of 135/85 mm Hg or higher (OR, 3.09; 95% confidence interval [CI], 1.83-5.23 [$P<.001$]) and hypertension de-

Table 2. Rate of Development of Home Hypertension by Baseline Home BP Levels in Subjects With Sustained Normotension and White-Coat Hypertension

Home BP Categories	No. of Subjects (N=777)	Rate of Development of Home Hypertension, %		Baseline BP, mm Hg	Follow-up BP, mm Hg	ΔBP,† mm Hg
		Total	Treatment*			
Sustained Normotension						
Systolic BP, mm Hg						
≤108	143	3.5	1.4	102.7	109.4	6.7
109-114	170	15.3	10.6	111.6	117.3	5.7
115-119	141	26.2	12.1	117.0	121.8	4.8
120-124	97	32.0	15.5	122.0	125.7	3.7
125-129	63	41.3	20.6	126.6	129.2	2.6
130-134	35	54.3	22.9	131.6	134.2	2.6
Total	**649**	22.2	11.3	114.9	119.9	4.9
Diastolic BP, mm Hg						
≤52	9	0	0	50.6	61.9	11.4
53-64	140	9.3	5.0	60.5	68.1	7.6
65-69	140	15.0	9.3	67.3	71.5	4.2
70-74	190	23.7	13.2	71.7	74.1	2.4
75-79	108	36.1	19.4	76.7	78.1	1.4
80-84	62	41.9	11.3	81.3	80.6	-0.7
Total	**649**	22.2	11.3	69.8	73.4	3.6
White-Coat Hypertension						
Systolic BP, mm Hg						
≤108	6	0	0	103.7	110.2	6.5
109-114	22	18.2	13.6	111.4	118.6	7.2
115-119	21	52.4‡	23.8	117.4	125.8	8.4
120-124	25	44.0	16.0	121.8	131.5	9.6‡
125-129	34	58.8	23.5	127.0	132.3	5.3
130-134	20	70.0	45.0	132.4	131.3	-1.0
Total	**128**	46.9§	22.7§	121.5	127.5	6.0
Diastolic BP, mm Hg						
≤52	0	0	0	NA	NA	NA
53-64	13	30.8‡	23.1‡	61.5	65.7	4.1
65-69	23	34.8‡	13.0	66.6	73.6	7.1
70-74	29	41.4‡	24.1	72.2	74.5	2.3
75-79	38	50.0	21.1	77.2	79.3	2.2
80-84	25	68.0‡	32.0‡	81.9	83.2	1.3
Total	**128**	46.9§	22.7§	73.5	76.6	3.1

Abbreviations: BP, blood pressure; NA, not applicable.
*Rate of subjects defined as developed home hypertension by the start of treatment with antihypertensive medication in each home BP category.
†Follow-up home BP – baseline home BP.
‡$P<.05$ vs sustained normotension.
§$P<.01$ vs sustained normotension.

fined by the start of treatment with antihypertensive medication (OR, 2.71; 95% CI, 1.61-4.56 [$P<.001$]).

Because higher home BP values at baseline were associated with a significantly higher rate of development for home hypertension (Table 2), we adjusted for home systolic/diastolic BP values separately, in addition to the previously mentioned factors. Although higher home BP levels were significantly and independently associated with the risk of home hypertension in the multivariate model (home systolic BP: OR (per 1–mm Hg increase), 1.11; 95% CI, 1.08-1.14 [$P<.001$]; home diastolic BP: OR (per 1–mm Hg increase), 1.10; 95% CI, 1.07-1.13 [$P<.001$]), WCHT remained a significant predictor of home hypertension (adjusted home systolic BP: OR, 1.81; 95% CI, 1.16-2.82 [$P=.009$]; adjusted home diastolic BP: OR, 2.36; 95% CI, 1.55-3.61 [$P<.001$]). Subgroup analysis of home BP levels at baseline also showed similar results (in subjects with a home BP lower than 125/80 mm Hg[26]: OR of WCHT, 2.24; 95% CI, 1.25-4.01 [$P=.007$]; in subjects with a home BP of 125/80 mm Hg or higher and lower than 135/85 mm Hg: OR of WCHT, 1.84; 95% CI, 0.94-3.60 [$P=.08$]). There was no significant interaction between the subgroup of home BP levels and the presence of WCHT on the risk of development of home hypertension ($P=.90$).

COMMENT

This 8-year follow-up study demonstrated that WCHT was a significant predictor of the development of home hypertension, independent of other confounding factors and baseline home BP levels. The risk of developing home hypertension was consistently higher in subjects with WCHT than in those with SNT, starting at a threshold of 108/58 mm Hg and across a broad range of base-

line home BP levels. Our results indicate that WCHT could pose a greater risk for progression to hypertension outside medical settings even if home BP values were within completely normal range.

Some studies reported that WCHT is associated with hyperreactivity to stress and higher sympathetic nerve activity.[27-29] Because stress has been reported to be an independent risk factor in the development of hypertension,[30,31] it is possible that a higher reactivity to stress in medical environments leads to WCHT, which in turn contributes to higher rates of progression to home hypertension in subjects with WCHT.

Only 1 study has ever compared the risk of developing hypertension outside medical settings in subjects with WCHT with those with SNT[12]; results showed that the transition to ambulatory hypertension occurred in a similar way in subjects with SNT and in subjects with WCHT. Those results were inconsistent with our findings; however, in that study the follow-up period was shorter (3.5 years) and the sample size was too small (36 subjects with WCHT and 56 subjects with SNT) to reliably determine the risk of WCHT. In the present study, we followed 649 subjects with SNT and 128 subjects with WCHT for 8-years and found high risk in subjects with WCHT.

Although 3 prospective studies reported the prognostic significance of WCHT compared with normotensive control subjects, the results were controversial: 2 studies[7,10] with short duration follow-up periods (mean of <5 years) showed similar lower cardiovascular risk for subjects with WCHT compared with normotensive control subjects, but 1 study[2] with a longer follow-up (10 years) demonstrated higher risk in subjects with WCHT compared with normotensive controls. In a recent 3-year follow-up study[19] of hypertensive patients taking antihypertensive medication, cases of isolated uncontrolled hypertension at the office had a similar risk of cardiovascular events compared with subjects with sustained controlled hypertension. These results and the present 8-year follow-up results suggest that WCHT could potentially represent a cardiovascular risk after 10 or more years. We are pursuing follow-up with research subjects to find the answer to this hypothesis.

To define WCHT, BP information obtained outside medical settings (home BP measurements or ambulatory BP monitoring) is necessary. Ambulatory BP monitoring provides a wide variety of BP information outside medical settings, and thus it may offer a more reliable definition of WCHT. However, because ambulatory BP monitoring is not easily achieved in typical clinical settings, it is not necessarily practical as a method to determine WCHT. On the other hand, home BP measurements are now widely recommended by professionals who practice in clinical settings in most developed countries[15-17] (in Japan, 30 million devices for self BP measurement at home have been distributed[32]). For these reasons, we based the definition of WCHT on actual and practical home BP measurements. However, applicability of the present findings to WCHT using a definition based on ambulatory BP remains to be investigated.

Development of home hypertension was defined as either progression to high home BP or start of treatment with antihypertensive medication at follow-up. Because subjects with WCHT had a higher office BP level, it is possible that the higher risk of developing hypertension might be attributable to receiving antihypertensive medication according to high office BP levels. However, WCHT showed a significant risk for progression to home hypertension by the definition of home BP levels as well as the start of treatment with antihypertensive medication. Furthermore, the rate of developing home hypertension, defined by the start of treatment with antihypertensive medication, was consistently higher in subjects with WCHT than in those with SNT, across a broad range of baseline home BP levels. Therefore, these findings suggest that WCHT is a transitional condition leading to home hypertension irrespective of high office BP levels. The objective of this study was to investigate home BP, and therefore no office BP data were collected at the time of follow-up. We recommend that the evaluation of subjects with SNT who develop WCHT is a topic for future research.

The present 8-year follow-up study based on home BP measurements demonstrated that subjects with WCHT had an approximately 2-fold higher risk of eventually manifesting home hypertension compared with those who had SNT. Although the prognostic significance of WCHT remains unclear, these results suggest that WCHT is not a totally benign condition. Further follow-up studies targeting cardiovascular outcomes are needed to clarify whether WCHT is a potentially dangerous condition. In the meantime, patients with WCHT should be carefully monitored.

Table 3. Multiple Logistic Regression Analysis for Risk Factors for the Development of Home Hypertension

Variable	OR (95% CI)	*P* Value
Age (per 10 y)	1.32 (1.09-1.60)	<.005
Male	1.78 (1.12-2.82)	.01
History of smoking (present)	0.90 (0.53-1.52)	.69
Obesity* (present)	1.76 (1.14-2.72)	.01
Family history of hypertension (present)	0.80 (0.54-1.19)	.27
Diabetes (present)	0.67 (0.37-1.20)	.17
Hypercholesterolemia (present)	1.35 (0.70-2.63)	.37
White-coat hypertension (present)	2.86 (1.90-4.31)	<.001

Abbreviations: OR, odds ratio; CI, confidence interval.
*Obesity was defined as a body mass index of 25 kg/m^2 or greater.

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Clinical research

Use of 2003 European Society of Hypertension–European Society of Cardiology guidelines for predicting stroke using self-measured blood pressure at home: the Ohasama study

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Aims To evaluate the predictive power of the risk stratification system proposed in the 2003 European Society of Hypertension–European Society of Cardiology (2003 ESH–ESC) guidelines and to compare self-measured blood pressure at home (HBP) with casual-screening blood pressure (CBP) for prediction of first stroke among a general Japanese population.

Methods and results HBP and CBP were measured in 1702 subjects (≥40 years) who had no history of stroke and who were followed for an average of 11 years. The subjects were assigned to one of five groups with differential risk stratification according to the 2003 ESH–ESC criteria: average risk, low added risk, moderate added risk, high added risk, and very high added risk. Even in the low risk group a significantly high risk for stroke was observed, and there was a linear step up of stroke risk based on HBP, as well as on CBP. On the basis of HBP classification, a higher stroke incidence was observed in the high and very high groups compared with CBP classification.

Conclusion The risk stratification system proposed in the 2003 ESH–ESC guidelines is valid for the prediction of stroke in this Japanese study population, and has a stronger predictive power when based on HBP than on CBP. The results indicate the usefulness of HBP for the prediction of stroke risk in individuals.

Introduction

Hypertension is an important risk factor for cardiovascular disease (CVD), which is the second leading cause of death in Japan. Although overall reduction of absolute risk factors for CVD is the goal, blood pressure (BP) management remains a key factor. Thus, accurate diagnosis and treatment of hypertension is necessary for better individual prognosis.

High reproducibility and reliability of self-measurement of BP at home (HBP) have been reported. HBP monitoring is well accepted by patients[1,2] and encourages active participation in the management of personal health conditions. Adjustment of antihypertensive medication based on HBP instead of casual-screening BP (CBP) could lead to lower costs.[3] Moreover, our previous study showed the strong predictive power of HBP measurement for CVD mortality,[4] as HBP avoids observer and regression dilution biases and eliminates the white-coat effect.[2]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[5] emphasized simplified risk stratification. The 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension (2003 ESH–ESC) followed the concepts of the 1999 World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines,[6] stating that comprehensive risk stratification is the essential strategy for the management of hypertension. The

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2003 ESH-ESC guidelines emphasized the importance of individualized medications.

Although the 2003 ESH-ESC guidelines would possibly be applicable even for populations outside Europe,[7] the usefulness of the guidelines in non-European countries has not yet been established. Also, the advantages of HBP measurements when compared with CBP have not been established, especially in terms of predicting first onset of stroke.

One aim of the present study was to examine whether the 2003 ESH-ESC classification was applicable to predict the risk of first stroke incidence, particularly because there is a high incidence of stroke observed among the Japanese.[8] Another aim was to compare the predictive power of HBP and CBP for stroke risk with the stratification system of the 2003 ESH-ESC guidelines. Finally, we compared the prediction of first stroke based on the simplified risk stratification suggested by JNC-7[9] with prediction based on the comprehensive risk stratification from the 2003 ESH-ESC guidelines.

Methods

Study population

The present study was a part of the longitudinal observational study. Subjects have been participating in our HBP measurement project in Ohasama, a rural community in the northern part of Japan, since 1987. 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 and complies with the Declaration of Helsinki. Informed consent was obtained from each subject.

The socio-economic and demographic characteristics of this region and the details of the selection procedure of study populations have been previously described.[4,10-12] Briefly, HBP measured three times or more and CBP measurements were obtained from 1789 representative individuals of the 1989 eligible individuals aged 40 years or over. As 87 individuals had a previous history of stroke, they were excluded from the present analysis in order to examine the relationship between the first onset of stroke and the risk stratification system of the 2003 ESH-ESC guidelines. Therefore, the study population consisted of 1702 individuals. The mean (SD) age was 60.6 (10.7) years. The ratio of men to women was 39:61, and the reasons for this disproportionate ratio were previously described.[12]

Blood pressure measurements

Physicians and well-trained public health nurses conducted health education classes to inform the subjects on how to measure and record HBP. After their ability to measure HBP was verified, subjects were asked to measure their own HBPs in the sitting position every morning within 1 h after awaking and after ≥2 min of rest and to record the measurements for 4 weeks. All subjects were instructed to position their cuff-covered arms at heart level during HBP measurements. If individuals were taking antihypertensive medications, HBP was measured before taking medications. These procedures were described in detail in our previous report,[10] and were developed according to the guidelines for self-monitoring of HBP.[2] HBP was measured using the HEM 401C (Omron Healthcare Co. Ltd, Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric principle, which generates a digital display of both systolic and diastolic BP.[13]

Annual health check-ups are available to all Japanese citizens aged 40 or over. Subjects are seated at rest for at least 2 min, then CBP is consecutively measured two times by nurses or technicians. A semi-automatic BP measuring device (USM700F; Ueda Electronic Work Co., Ltd, Tokyo, Japan) based on the microphone method was used.

The average arm circumference for subjects was typically <34 cm, so we used a standard arm cuff for both HBP and CBP measurements. The devices for measurement of CBP and HBP were calibrated before the start of the study.[13] All devices met the criteria set by the Association for the Advancement of Medical Instrumentation.[14]

Classification of groups

On the basis of the 2003 ESH-ESC risk stratification system, the subjects were first classified into six BP categories as shown in *Table 1*. HBP-based and CBP-based criteria were defined as follows: optimal (HBP <115/75 mmHg, CBP <120/80 mmHg); normal (HBP 115/75-124/79 mmHg, CBP 120/80-129/84 mmHg); high normal (HBP 125/80-134/84 mmHg, CBP 130/85-139/89 mmHg); Grade 1 (mild hypertension: HBP 135/85-149/94 mmHg, CBP 140/90-159/99 mmHg); Grade 2 (moderate hypertension: HBP 150/95-164/104 mmHg, CBP 160/100-179/109 mmHg); Grade 3 (severe hypertension: HBP ≥165/105, CBP ≥180/110 mmHg). 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 the 2003 ESH-ESC criteria. In the present analysis, hypertension was defined as HBP ≥135/85 mmHg, according to the JNC-VI, JNC-7, and 2003 ESH-ESC guidelines; HBP of 135/

Table 1 Stratification of risk to quantify prognosis

Category definition	Optimal	Normal	High normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension
CBP-based	≤120/80 ($n = 370$)	120/80-129/84 ($n = 387$)	130/85-139/89 ($n = 396$)	140/90-159/99 ($n = 375$)	160/100-179/109 ($n = 136$)	≥180/110 ($n = 38$)
HBP-based	≤115/75 ($n = 432$)	115/75-124/79 ($n = 390$)	125/80-134/84 ($n = 378$)	135/85-149/94 ($n = 362$)	150/95-164/104 ($n = 111$)	≥165/105 ($n = 29$)
No other risk factors	Average	Average	Average	Low	Moderate	High
1-2 risk factors	Average	Low	Low	Moderate	Moderate	Very high
≥3 risk factors or DM	Low	Moderate	High	High	High	Very high
PHCVD	Moderate	High	Very high	Very high	Very high	Very high

DM, diabetes mellitus; PHCVD, past history of cardiovascular disease; Average, average risk; Low, low added risk; Moderate, moderate added risk; High, high added risk; Very high, Very high added risk.

85 mmHg is equivalent to CBP of 140/90 mmHg. To define other BP levels based on HBP, we postulated that 75, 80, 95, and 105 mmHg of diastolic HBP were equivalent to 80, 85, 100, and 110 mmHg of diastolic CBP, respectively. Then systolic BP levels for HBP were introduced from the rate of subjects from each level of CBP classification. In the present analysis, we did not include the concept of pure systolic hypertension.

The individuals were then stratified into four classes based on the extent of cardiovascular risks: Class 1 (no risk factors), Class 2 (one or two risk factors), Class 3 (more than two risk factors or diabetes mellitus), and Class 4 (past history of CVD). Risk factors were defined as follows: age >55 for males, age > 65 for females, body mass index (BMI) >25 kg/m^2, habitual smoking, and hypercholesterolaemia. Finally, study subjects were assigned to one of five groups, according to the 2003 ESH–ESC criteria: average risk, low added risk, moderate added risk, high added risk, and very high added risk (*Table 1*). Subjects with an optimal BP (optimal) who were not described in the risk stratification table of the original ESH–ESC guidelines were assigned to the average, low, or moderate risk group according to their classes. The average risk group was used as the reference group in the analysis. Subjects classified according to CBP and HBP were analysed separately.

In addition to these criteria, we also used the classification system based on the JNC-7 guidelines as previously reported.[9] Briefly, the subjects were classified into four groups based on HBP or CBP according to the JNC-7 criteria:[5] Group 1 (normotension: HBP <115/75 mmHg, CBP <120/80 mmHg); Group 2 (prehypertension: HBP 115/75–134/84 mmHg, CBP 120/80–139/89 mmHg); Group 3 (Stage 1 hypertension: HBP 135/85–149/94 mmHg, CBP 140/90–159/99 mmHg); Group 4 (Stage 2 hypertension: HBP ≥150/95 mmHg, CBP ≥160/100 mmHg). After classification of BP values, Groups 2–4 were divided into two subgroups—'a' and 'b'—indicating those without and those with CVD risks (diabetes, hypercholesterolaemia, habitual smoking, or history of CVD), respectively. All subjects were assigned to one of seven categories (Groups 1, 2a, 3a ... 4b) based on the JNC-7 classification.

Follow-up and risk ascertainment

We accumulated follow-up data until 31 December 2001. The subjects' residence status in Ohasama was confirmed by registration cards. These cards are accurate and reliable because they are used for pensions and social security benefits in Japan. Twenty-seven subjects (1.8%) had moved away and were eliminated from follow-up, and 209 deaths (14.0%) were identified from the residents' registration cards.

The incidence and past history of stroke were investigated through 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. The information was then confirmed by checking the medical records of Ohasama hospital where >90% of the subjects had their regular check-ups. We used computed tomography (CT) scans and magnetic resonance imaging (MRI) reports to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. The analysis included only the first event in those who had multiple non-fatal events. The diagnostic criteria of stroke and their subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke.[15]

Other information for individuals such as height, weight, habitual smoking, use of antihypertensive medication at baseline, history of heart disease, hypercholesterolaemia, or diabetes mellitus was obtained from questionnaires sent to each household at the time of HBP measurements, from records of annual health check-ups, and from medical records at Ohasama Hospital. Subjects using lipid-lowering drugs or those with serum cholesterol levels of ≥5.68 mmol/L (220 mg/dL) were considered to have hypercholesterolaemia. Subjects with a fasting glucose level of ≥7.77 mmol/L (140 mg/dL) or non-fasting glucose level of ≥11.11 mmol/L (200 mg/dL), or those using insulin or oral antihyperglycaemic drugs were defined as having diabetes mellitus. A past history of CVD included a history of myocardial infarction, angina pectoris, atrial fibrillation, or cardiac failure.

Data analysis

The HBP values were the average of all home measurements per subject. CBP of each subject was the average of two consecutive CBP readings taken at the beginning of the study.

The risk of the first stroke was examined using the Cox proportional hazards model. The dependent variable was the number of days from the initial HBP measurement to the date of stroke or censoring. Stroke-free survivors as of December 31, 2001 were censored. The independent variables were the groups of the risk stratification system using the 2003 ESH–ESC guidelines in which factors of age and sex were included. In further analysis, the risk in relation to the JNC-7 guideline-based classification was examined by the Cox model adjusted for age and sex. When we analysed the incidence of stroke, we censored cases of death from causes other than fatal stroke events.

The estimated relative hazard (RH) and the 95% confidence interval (95% CI) of variables were derived from the coefficient and standard error determined by the Cox proportional hazards model. The RH is expressed relative to Group 1 (average risk; RH = 1). Separate models were used for HBP classification and CBP classification after verification of the assumption of proportionality for the Cox proportional hazards models.[16] The predictive values of HBP classification and CBP classification were evaluated using the comparison of corresponding regression coefficients and log likelihoods in the Cox model. We also assessed the interaction between antihypertensive medication and the five risk groups using the Cox model with stroke as the endpoint. All data are shown as mean (SD) unless otherwise stated. A *P*-value <0.05 (two-sided test) was accepted as indicative of statistical significance. The SAS system (Version 8.2, SAS Institute Inc., Cary, NC, USA) was used for all statistical calculations.

Results

The subjects were followed up for a median of 10.9 (interquartile 8.9–13.9) years, to a maximum of 13.9 years. We obtained 149 incident cases of first stroke among the 1702 individuals: 106 (69%) cerebral infarction, 28 (18%) intracerebral haemorrhage, 12 (8%) subarachnoid haemorrhage, and 3 (2%) unknown causes. In addition to 149 stroke cases, four incidences of transient ischaemic attack were observed, and excluded from the analysis. There was no interaction between the use of antihypertensive medication and the five risk groups (HBP, $P = 0.7$; CBP, $P = 0.4$).

The characteristics of the 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%) had diabetes mellitus, and 207 (12%) had hypercholesterolaemia. The mean number of HBP measurements from each individual was 23.0 (7.1). The mean systolic and diastolic HBP of all subjects were 125.2 (15.0) and 74.9 (10.1) mmHg, respectively.

The risk of first stroke of the five groups in HBP classification and CBP classification is shown in *Figure 1A and B*. Stroke risk was increased linearly, with the increase in the grade of stratified risk based on HBP, as well as on CBP. Even in the low risk group, the risk for stroke was

Table 2 Clinical characteristics among groups

Variables	Average	Low	Moderate	High	Very high
Home blood pressure based groups					
Number of subjects	584	543	377	160	38
Age (years)	54.9 ± 9.1	61.5 ± 9.8	65.5 ± 10.6	64.5 ± 9.1	68.2 ± 11.0
Male (%)	23.8	42.2	52.5	50.0	63.2
BMI (kg/m^2)	22.4 ± 2.4	23.7 ± 3.1	23.6 ± 3.2	25.0 ± 3.3	24.1 ± 4.7
PH CVD (%)	0	0	0	3.8	26.3
Diabetes (%)	0	8.3	11.9	75.6	18.4
Smoking (%)	8.9	27.8	26.8	33.1	34.2
Hypercholesterolaemia (%)	3.1	12.7	11.9	43.1	15.8
Use of antihypertensive medication (%)	11.8	26.2	46.9	60.0	60.5
Home SBP (mmHg)	112.6 ± 8.8	123.5 ± 8.2	138.8 ± 11.5	137.2 ± 10.1	157.1 ± 16.8
Home DBP (mmHg)	68.0 ± 7.2	74.1 ± 6.9	82.0 ± 9.1	81.9 ± 9.1	92.3 ± 13.6
Casual SBP (mmHg)	124.3 ± 16.2	132.4 ± 17.1	142.2 ± 18.2	140.9 ± 18.5	151.1 ± 23.8
Casual DBP (mmHg)	72.0 ± 10.5	74.9 ± 10.8	80.0 ± 11.9	79.8 ± 12.7	83.4 ± 13.3
Casual blood pressure based groups					
Number of subjects	529	564	408	158	43
Age (years)	55.1 ± 8.5	61.3 ± 10.7	64.9 ± 10.7	63.6 ± 9.3	65.2 ± 12.3
Male (%)	24.0	45.2	46.1	51.3	44.2
BMI (kg/m^2)	22.3 ± 2.2	23.5 ± 3.1	24.0 ± 3.4	24.8 ± 3.5	24.0 ± 3.1
PH CVD (%)	0	0	1.0	1.3	23.3
Diabetes (%)	0	5.9	11.8	82.3	16.3
Smoking (%)	11.3	27.3	24.5	29.7	20.9
Hypercholesterolaemia (%)	2.6	11.2	15.4	36.1	23.3
Use of antihypertensive medication (%)	14.2	26.1	45.8	47.5	53.5
Home SBP (mmHg)	115.5 ± 11.2	124.8 ± 13.0	133.9 ± 14.3	132.3 ± 14.5	140.6 ± 15.1
Home DBP (mmHg)	70.1 ± 8.6	75.0 ± 8.9	78.9 ± 10.4	78.6 ± 10.2	82.0 ± 11.7
Casual SBP (mmHg)	117.0 ± 11.2	130.2 ± 10.0	148.0 ± 14.9	146.1 ± 15.1	176.9 ± 22.1
Casual DBP (mmHg)	68.5 ± 8.4	74.4 ± 9.4	82.5 ± 11.6	81.3 ± 10.2	94.3 ± 14.5

See *Table 1* for definitions of groups. Values are expressed as mean ± SD. CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

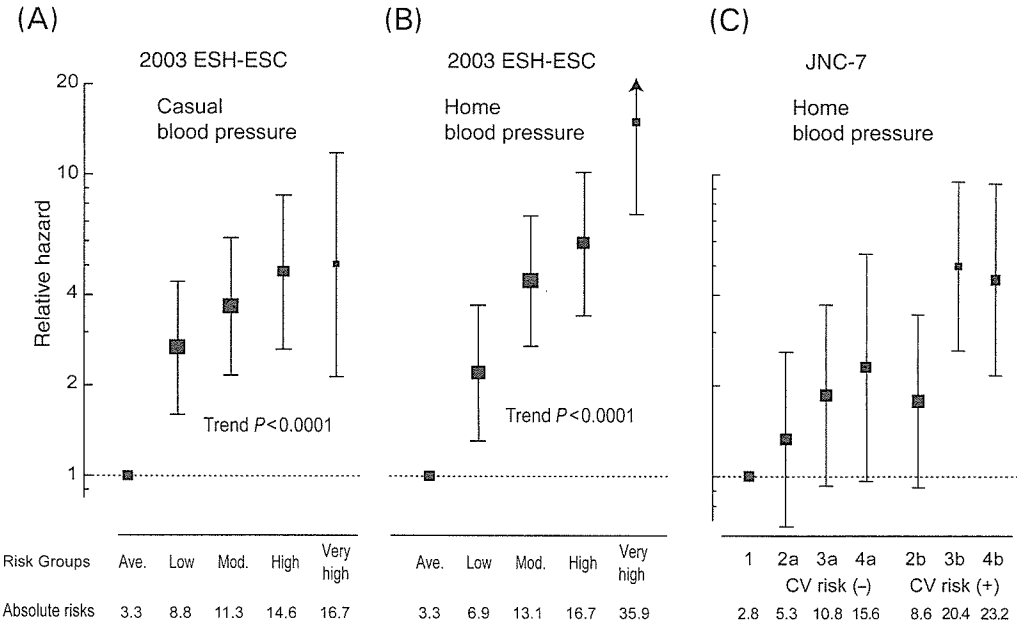

Figure 1 Risk of first stroke based on HBP or CBP values and cardiovascular risks. (*A*) and (*B*) demonstrate RH and 95% CI for first stroke plotted on a log scale among all groups classified by CBP (*A*) and HBP (*B*) values. Ave.: average risk group, Low: low added risk group, Mod.: moderate added risk group, High: high added risk group, Very High: very high added risk group. (*C*) demonstrates RH and 95% CI for first stroke according to JNC-7 classification based on HBP values. Absolute risks display incidence per 1000 person-years. Group definitions are shown in *Table 1* and in the Methods section. The average group (2003 ESH-ESC) or Group 1 (JNC-7) is treated as the reference category. Solid squares indicate the RH point and are sized in proportion to the number of events observed. Vertical lines extending from squares represent 95% CI. Trend *P*-values express the linearity among groups.

significantly higher than in the average risk group. In the low risk group, there was no difference in the stroke risk between HBP classification and CBP classification (HBP: RH = 2.24, 95% CI 1.32–3.80, $P = 0.003$; CBP: RH = 2.76, 95% CI 1.63–4.66, $P = 0.0001$). The stroke risk in the very high risk group was extremely high when subjects were classified by HBP (RH = 14.4, 95% CI 6.92–29.8, $P < 0.0001$). The predictive power decreased when subjects were classified by CBP (RH = 5.30, 95% CI 2.23–12.6, $P = 0.0002$). The statistically significant linearity among the groups was observed for both HBP and CBP classifications (trend $P < 0.0001$). When we designated the low risk group as a reference category in the Cox model, the stroke risk in the moderate risk group was significantly high for HBP (RH = 2.04, 95% CI 1.34–3.09, $P = 0.0009$), whereas the moderate risk group was not significantly different from the low risk group using the CBP classification (RH = 1.33, 95% CI 0.90–1.97, $P = 0.2$). When both classifications were treated as continuous variables and were simultaneously included in the model, only HBP classification was significantly related with stroke risk (HBP classification: RH = 1.88, 95% CI 1.55–2.28, $P < 0.0001$; CBP classification: RH = 0.98, 95% CI 0.81–1.20, $P = 0.9$). The model, including both HBP and CBP classifications, lost 'goodness of fit' when HBP was removed (likelihood ratio 40.2, $P < 0.001$), whereas no significant changes occurred when CBP was removed (likelihood ratio 0.028, $P = 0.9$). The same results were observed when transient ischaemic attack was included in the stroke incidence (data not shown).

We conducted further analysis by comparing the JNC-7 guideline-based classification (including subarachnoid haemorrhage and excluding transient ischaemic attack which was a modified analysis from our previous study[9]) and the 2003 ESH–ESC guideline-based classification (*Figure 1B and C* based on HBP). The stroke risk in Group 4b (highest) was significantly elevated for HBP classification (RH = 4.54, 95% CI 2.16–9.54, $P < 0.0001$) as well as for CBP (RH = 2.81, 95% CI 1.31–6.04, $P = 0.008$). However, for the magnitude of RH, the stroke risk based on the 2003 ESH–ESC classification was clearly more dramatic than that based on the JNC-7 classification.

Discussion

The 2003 ESH–ESC guidelines for treating hypertension emphasize a composite risk stratification system based on CBP categories and other risk factors. In this prospective cohort study, we found that the 2003 ESH–ESC classification was useful and applicable for a general Japanese population in predicting future stroke incidence. Furthermore, the risk stratification system became extremely powerful for the prediction of stroke incidence when HBP was used instead of CBP. These results were based on a comprehensive follow-up system in the Ohasama cohort as described previously and the high reliability of diagnoses of stroke and subtypes according to CT/MRI. Although some of the stroke cases were determined by death certificates only, these were limited to 3% of the total cases. Although some of the risk parameters from the 2003 ESH–ESC guidelines were not evaluated, it is a reasonable assumption that the predictive power of HBP as well as CBP would be emphasized if those unmeasured parameters were included in our analysis. Thus, the results support the usefulness of the 2003 ESH–ESC guidelines for the general Japanese population, especially when information on BP is based on HBP.

In comparison with the 2003 ESH–ESC guidelines, the JNC-7 classification adopts a simplified risk stratification that consists of four grades based on CBP.[5] Individuals who have hypertension and at least one risk factor are considered to be candidates for antihypertensive drugs and intensive treatment. Thus their cardiovascular risks are not thoroughly considered in JNC-7. We reported in the previous study that the JNC-7 classification is applicable for the general Japanese population.[9] However, when based on the risk stratification system proposed in the 2003 ESH–ESC guidelines, the measurements of HBP as well as CBP would predict the first stroke incidence more accurately than those based on the simplified risk stratification in JNC-7 as shown in the current study (refer to Asayama *et al.*[9]). It is a reasonable assumption that a comprehensive risk stratification system could be used for individualized BP management. Furthermore, we would like to emphasize that in this study, the stroke risk in the moderate risk group was significantly higher than that in the low risk group when based on HBP, whereas no significant differences were observed between two risk groups when based on CBP; these findings support the assertion that BP management should be based on HBP information.

The 2003 ESH–ESC guidelines set the reference value of hypertension using HBP at 135/85 mmHg. In the present study, hypertension was also defined as HBP at 135/85 mmHg, then HBP was classified by the percentage distribution of subjects according to the corresponding ratio of CBP. A stepwise increase of stroke risk in the stratification system was observed when based on HBP as well as CBP in the current study. It should be noted that high-normal individuals and prehypertension have relatively high CVD risk when compared with individuals with optimal[17] or normal BP.[18] Hypothetically speaking, the lower the BP, the better the stroke prevention.[19]

Approximately one-quarter of our subjects with high-normal BP (23.5% based on HBP and 22.5% based on CBP) were classified as average risk according to the 2003 ESH–ESC guidelines. There were 89 high-normal BP subjects among 584 (HBP-based) and 89 high-normal subjects among the 529 (CBP-based) average risk subjects. A major difference between the 2003 ESH–ESC and JNC-7 guidelines is that the latter advises pharmacological or non-pharmacological intervention in all prehypertensives (high-normal or normal BP), whereas the former suggests intervention only for those who are in the low added risk but not in the average risk' category.[20] According to our results, it was obvious that individuals in the low risk group needed treatment even though their BP was within normal limits, whereas treatment for the average risk individuals remains a matter for debate.

Although HBP measurement is now acknowledged worldwide in the major guidelines as a useful tool for clinical practice, lack of information on the prognostic significance has limited its use in clinical decision-making.[5,6,21–23] In the present study, we demonstrated that HBP measurements provide more useful prognostic information on cerebrovascular disease than CBP measurements. Information on BP in relation to the time of day, 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 average of multiple values of HBP obtained under controlled conditions provides individual BP information without biases such as white-coat effect, regression dilution biases, and time effect.[2]

In conclusion, the risk stratification system proposed in the 2003 ESH-ESC guidelines was valid for the prediction of stroke incidence in populations outside Europe, and we found that the stratification based on HBP measurements is a valuable tool for predicting the incidence of stroke. Guidelines based on individualized medications, such as the 2003 ESH-ESC guidelines, are more useful and applicable than those based on simple BP-oriented medications, such as the JNC-7. HBP measurement is a useful tool to improve awareness of hypertension and to predict future incidence of cerebrovascular disease.

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BP Measurement

Factors Affecting Home-Measured Resting Heart Rate in the General Population

The Ohasama Study

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Background: We recently demonstrated that a home-measured resting heart rate (HR) can predict cardiovascular disease mortality, and it is possible that the determinants of home HR are different from casual HR. Therefore, clarifying the determinants of home HR should be useful.

Methods: Home HR was obtained using a self-monitored blood pressure (BP) measuring device. The impact of factors including home-measured BP and lifestyle on home HR was examined in 1275 members of the general Japanese population aged ≥40 years.

Results: Multivariate linear regression analysis demonstrated that younger age ($\beta = -0.08$, $P \leq .01$), current smoking ($\beta = 3.22$, $P \leq .01$), female gender ($\beta = 2.07$, $P \leq .01$), and sedentary lifestyle (walking for ≤1 h/day) ($\beta = 2.43$, $P \leq .01$) were determinants of elevated morning home HR. No significant association was observed between home HR and home systolic BP, whereas casual HR was significantly and positively associated with casual systolic BP. The difference between casual and home HR was also significantly and positively associated with the difference between casual and home systolic BP, suggesting that positive association between BP and HR obtained in clinic settings would be a reflection of the so-called white-coat effect.

Conclusions: We observed that, with the exception of BP, most determinants of home HR were consistent with the determinants observed in previous studies using casual HR. These results suggest that reduction of home HR through modification of smoking habit or sedentary lifestyle may have a potential to decrease cardiovascular risk in addition to decreasing in these modifiable risk factor per se. Am J Hypertens 2005;18:1218–1225 © 2005 American Journal of Hypertension, Ltd.

Key Words: Heart rate, lifestyle, smoking, ambulatory blood pressure monitoring.

Heart rate (HR) varies widely depending on the degree of psychological stress experienced.[1] It has also been demonstrated that both blood pressure (BP) and HR values often rise immediately when measured during a physician's visit.[2] In contrast, self-measurement of BP at home (home BP) makes it possible to obtain multiple measurements over a long period in familiar, nonthreatening surroundings, thus avoiding the so-called white-coat effect.[3,4] As a result, home-measured BP has been found to have better predictive power than casual BP measurements taken by medical practitioners.[5–7] Such advantages could also apply to home measurements of heart rate (home HR) as assessed by a device used for home BP measurement. Accordingly, we first

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demonstrated that home HR is a strong predictor of the risk of cardiovascular disease (CVD) mortality, independent of BP values and other possible confounding factors.[8] Thus, it would be worthwhile to clarify modifiable factors that affect home HR for better prevention of CVD.

Although a few studies showed higher HR values in casual settings compared with HR measured at home,[9] no detailed information on the factors that affect home HR values has been published. Because our previous study demonstrated that modifiable lifestyle-related factors such as smoking habit, independently associated with the white-coat effect (defined based on the difference between casual BP and home BP),[10] HR might also be affected by differential factors between home and casual measurement. However, there have been no studies to clarify the determinants of home HR including lifestyle-related factors. Thus we conducted the present analysis to identify factors that might affect home HR values, including home BP and lifestyle-related factors, in the general Japanese population.

Methods

Study Population

This study was performed as a part of the Ohasama study, a community-based BP measurement project.[11,12] Ohasama is a town in Iwate prefecture, Japan. In February 1998, the total population of three of the four regions of the town numbered 4208. Of these individuals, 2769 were ≥40 years of age. Among this subgroup, 621 worked out of town and were considered ineligible for the study. This exclusion was necessary because our project also included ambulatory BP measurements; in order for us to attach the ambulatory BP-monitoring devices to the study subjects, they had to be in town on working days. Of the 2148 subjects remaining, those who were hospitalized (n = 124), mentally ill or bedridden (n = 40) were not invited to participate. Thus a total of 1984 subjects were eligible for the study. Of these, 1662 (84%) gave informed consent and participated in the BP-measuring program. We have previously confirmed that these subjects were representative of the total population.[13] In the present study, we measured HR on the basis of cuff-oscillation of the brachial pulse; therefore, the value could be called a pulse rate. However, because of previous studies that called such values HR values[8,9] we also used the term HR in this study. Home measurements of morning HR and BP were obtained from 1570 subjects who collected their own data on at least three occasions (3 days) during the 4-week study period. This inclusion criterion was based on our previous observation that the average HR and BP for the first three measurement occasions did not differ significantly from the mean for the entire study period.[8,11] We also excluded subjects with a history of chronic heart failure, ischemic heart disease, and significant arrhythmias, such as atrial fibrillation, sick sinus syndrome, and permanent pacemaker implantation (n = 107), and those who did not answer the questions about lifestyle and health (n = 188). Therefore, the study population consisted of 1275 individuals (77% of 1662 representative participants[13]). Age and home systolic blood pressure (SBP) were significantly lower in the 1275 study subjects compared with the 387 excluded subjects (age: 1275 subjects, 61.7±11.8; 387 subjects, 66.0±12.4, $P < .001$, SBP: 1275 subjects, 123.3±15.0 mm Hg; 387 subjects, 127.6±16.5 mm Hg, $P < .001$). Gender distribution was not significantly different (1275 subjects, 41% men and 59% women; 387 subjects, 47% men and 53% women, $P = .06$). Casual HR and BP measurements were obtained from 890 (70%) of these 1275 subjects.

Measurement of BP and HR

The procedures used for the casual and home HR and BP measurements and the measuring device have been described in detail in previous reports.[8,11,14,15] Briefly, physicians and public health nurses conducted health education classes to inform the participants about the home HR and BP recording method, to teach them how to measure their own HR and BP, and to validate their ability to perform these tasks on a consistent basis. The subjects were then asked to measure their HR and BP once every morning and evening and to record the results for 4 weeks. Measurements of morning HR and BP were made within 1 h of waking, before breakfast or taking any drugs, with the subject seated and having rested for at least 2 min. Measurements of evening HR and BP were obtained in a homologous way just before going to bed. Home HR and BP were measured using a HEM701C automatic device (Omron Healthcare Co. Ltd, Kyoto, Japan), which uses the cuff-oscillometric method to generate a digital display of HR and systolic/diastolic BP values. Pulse interval was calculated by pulse wave, which was differentiated by a microprocessor incorporated in the equipment. Pulse interval obtained between SBP and DBP were averaged and HR was calculated as follows: HR (beats/min) = 60 (sec) / average pulse interval (sec). The home HR and BP of an individual were defined as the mean of all measurements obtained for that person. The casual HR and BP were measured at screening settings using an USM-700F device (UEDA Electronic Works Co. Ltd, Tokyo, Japan), a fully automatic device that uses the Korotkoff sound technique (a microphone method). After the subject had been resting in a seated position for at least 2 min, two consecutive measurements of HR and BP were taken by a nurse or technician. The casual HR and BP were defined as the averages of the two readings. The devices used for the casual and home measurements were previously validated[14,15] and satisfied the criteria of the Association for the Advancement of Medical Instrumentation.[16]

Table 1. Characteristics of the study subjects

Characteristic	Morning (n = 1275)	Evening (n = 1133)
Age (y)*	61.7 ± 11.8	62.1 ± 11.7
Gender (men %)	41	38
Home HR (beats/min)*	66.1 ± 7.9	68.7 ± 7.8
Home SBP (mm Hg)*	123.3 ± 15.0	120.9 ± 14.6
Antihypertensive medication (%)	29	29
BMI (kg/m^2)*	23.6 ± 3.1	23.5 ± 3.1
Time spent walking (≥1 h/day %)	79	80
Smoking status (current smoker %)	20	18
Alcohol-drinking status (current drinker %)	40	38
Coffee intake (≥1 cup/week %)	76	75
History (%)		
Stroke	3	3
Diabetes mellitus	12	12
Hypercholesterolemia	13	14

BMI = body mass index; HR = heart rate; SBP = systolic blood pressure.
* Mean ± standard deviation.

Questionnaire Survey

Information on age, antihypertensive medication, smoking and alcohol drinking status, body mass index (BMI), activity levels (time spent walking per day), coffee intake, and any history of stroke, diabetes mellitus, or hypercholesterolemia was obtained from a questionnaire sent to each subject at the time of the first home HR and BP measurement. The information on antihypertensive medication was confirmed from medical records kept at Ohasama Hospital.

Statistical Analysis

All data are expressed as mean ± SD. Variables were compared using the Pearson regression analysis, Student t test, χ^2 test, multiple linear regression analysis, or analysis of variance (ANOVA) as appropriate. The threshold level for statistical significance was set at $P < .05$. All statistical analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC).

Results

Characteristics of the Study Subjects

Of the 1275 study subjects, 1133 (89%) measured their home HR and BP in both the morning and evening. Table 1 shows the characteristics of the study subjects who measured HR in the morning (n = 1275) and in the evening (n = 1133). The mean number of home HR measurements was 22.6 ± 6.5 for the morning and 22.8 ± 6.5 for the evening.

Of the 1275 subjects who measured HR in the morning, 365 (29%) were receiving antihypertensive medication. Of these, 232 (64%) were taking calcium (Ca) antagonists, 63 (17%) angiotensin-converting enzyme (ACE) inhibitors, 45 (12%) β-blockers, 34 (9%) α_1-blockers, 20 (5%) diuretics, 7 (2%) αβ-blockers, and 5 (1%) other drugs, respectively. The most common combinations of antihypertensive agents were Ca antagonists + ACE inhibitors (n = 46, 13%) and Ca antagonists + β-blockers (n = 40, 11%).

The characteristics of the subjects who measured HR in the evening were similar to those of the individuals who took measurements in the morning (Table 1).

Bivariate Analysis of Factors Affecting Home HR

An initial bivariate analysis was performed to determine which factors influenced home HR values. The factors investigated were age, gender, SBP, the use of antihypertensive medication, BMI, time spent walking, smoking, and alcohol-drinking status, coffee intake, and any history of stroke, diabetes mellitus or hypercholesterolemia (Table 2). Morning home HR levels showed significant negative correlation with age (r = −0.11, $P < .001$) and morning home SBP (r = −0.06, P = .02). There was also significant negative correlation between single home HR and home SBP in the morning obtained on the first day of the home measurement (r = −0.07 P = .014). There were significant differences in home HR values between subjects who were and were not taking antihypertensive medication (with antihypertensive medication, 65.3 ± 8.5 beats/min; without antihypertensive medication, 66.5 ± 7.8 beats/min, P = .01), between those who spent ≥1 h/day walking (≥1 h/day) and those who spent <h/day walking (<1 h/day) (≥1 h/day, 65.7 ± 7.9 beats/min; <1 h/day, 67.8 ± 7.8 beats/min, $P < .001$), and between current smokers and former or never smokers (current smokers, 67.8 ± 8.3 beats/min; former or never smokers, 65.8 ± 7.9 beats/min, $P < .001$). Similarly, evening home HR levels were associated with age, use of antihypertensive medication, time spent walking, and smoking. In addition, evening home HR levels were significantly as-

Table 2. Bivariate analysis of factors affecting home heart rate value

Continuous variable	Morning		Evening	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value
Age	−0.11	<.001	−0.15	<.001
Home SBP	−0.06	.02	−0.01	.75
BMI	−0.02	.39	0.05	.07

Categorical variable*		Morning		Evening	
		Mean value (beats/min)	*P* value	Mean value (beats/min)	*P* value
Gender	Men	65.8 ± 8.6	.20	69.1 ± 8.5	.07
	Women	66.4 ± 7.5		68.3 ± 7.4	
Antihypertensive medication	Present	65.3 ± 8.5	.01	67.2 ± 8.2	<.001
	Absent	66.5 ± 7.8		69.2 ± 7.6	
Time spent walking	≥ 1 h/day	65.7 ± 7.9	<.001	68.4 ± 7.9	.01
	< 1 h/day	67.8 ± 7.8		70.0 ± 7.5	
Smoking	Current smoker	67.8 ± 8.3	<.001	71.0 ± 8.1	<.001
	Former or never smoker	65.8 ± 7.9		68.1 ± 7.7	
Alcohol-drinking	Current drinker	66.4 ± 8.1	.31	69.6 ± 7.8	.001
	Former or never drinker	66.0 ± 8.0		68.1 ± 7.8	
Coffee-drinking	≥ 1 cup/week	66.5 ± 8.0	.19	69.1 ± 7.8	.14
	< 1 cup/week	65.8 ± 7.9		68.3 ± 8.1	
Stroke	Present	64.9 ± 10.2	.39	67.2 ± 9.6	.33
	Absent	66.3 ± 7.9		68.8 ± 7.7	
Diabetes mellitus	Present	66.7 ± 8.7	.43	69.2 ± 8.3	.44
	Absent	66.1 ± 7.7		68.6 ± 7.5	
Hypercholesterolemia	Present	66.4 ± 8.4	.93	68.8 ± 7.8	.86
	Absent	66.3 ± 7.9		68.7 ± 7.7	

Abbreviations as in Table 1.
Continuous variables were tested by Pearson's regression analysis. Categorical variables were tested by Student *t* test.
* Mean ± standard deviation.

sociated with alcohol drinking status (current drinkers, 69.6 ± 7.8 beats/min; former or never drinkers, 68.1 ± 7.8 beats/min, $P = .001$). The other variables were not significantly associated with home HR levels.

Multivariate Linear Regression Analysis of Factors Affecting Home HR

Because many of the previously mentioned factors might be interrelated, we performed a multivariate linear regression analysis including gender and the other factors that were significantly associated with home HR levels in the bivariate analysis. The results of this analysis are summarized in Table 3. When all subjects were included, the multivariate linear regression analysis revealed significant negative relation between morning home HR and age, time spent walking, male gender, and former smoking or never smoking status. Evening home HR was significantly associated with similar variables as the morning HR other than gender. No significant associations were observed between home HR levels and the other variables including home SBP. The associations between home HR and age and smoking status were greater in men than in women. Subjects who were not taking antihypertensive medication (untreated subjects) had similar morning and evening results with the overall study population.

Effects of Antihypertensive Medication on Home HR

Multiple linear regression analysis adjusted for age, time spent walking, gender, and smoking status showed a significant inverse association between the use of β-blocker and morning home HR (Model 1, Table 4). Similarly, the use of Ca antagonist and β-blocker were significantly and inversely associated with evening home HR, whereas diuretic use was positively associated with the evening home HR (Model 1, Table 4). Because these antihypertensive drugs were simultaneously used in some cases, we included all of these drugs simultaneously in a multivariate model (Model 2, Table 4). The model showed that β-blocker inversely and independently associated with both morning and evening home HR, whereas diuretic use was positively and independently associated with evening home HR values. In addition, even when we used each type of antihypertensive medication as a covariate, results that smoking and sedentary lifestyle effects home HR value were unchanged (data not shown).

Table 3. Multivariate regression analysis of factors affecting home heart rate value

Morning	All subjects (n = 1275)		Men (n = 523)		Women (n = 752)		Untreated subjects (n = 910)	
Variable	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Age (per 1 year)	−0.08	<0.001	−0.15	<.001	−0.02	.48	−0.09	<.001
Smoking (current = 1)	3.22	<0.001	3.01	<.001	2.63	.15	3.08	<.001
Time spent walking (≥1 h/day = 1)	−2.43	<0.001	−2.21	.01	−2.41	<.001	−2.06	.001
Gender (men = 1)	−2.07	<0.001	NA	NA	NA	NA	−1.90	.002
Antihypertensive medication (present = 1)	−0.32	0.57	−0.48	0.59	−0.26	0.72	NA	NA
Home SBP (per 1 mm Hg)	−0.005	0.80	0.04	0.22	−0.04	0.09	−0.003	0.88
R^2	0.052		0.095		0.025		0.050	
Evening	**All subjects (n = 1133)**		**Men (n = 432)**		**Women (n = 701)**		**Untreated subjects (n = 809)**	
Variable	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Age (per 1 year)	−0.07	.002	−0.18	<.001	0.003	.91	−0.08	.001
Smoking (current = 1)	3.09	<.001	2.77	<.001	0.96	.63	2.86	<.001
Time spent walking (≥1 h/day = 1)	−1.93	<.001	−1.56	.09	−1.65	.02	−1.44	.03
Gender (men = 1)	−0.91	.14	NA	NA	NA	NA	−0.18	.80
Antihypertensive medication (present = 1)	−1.04	.06	−1.23	.17	−1.24	.07	NA	NA
Alcohol-drinking (current = 1)	0.93	.10	1.48	.09	0.61	.42	0.61	.34
R^2	0.055		0.140		0.013		0.051	

NA = not analyzed; SBP = systolic blood pressure.

Table 4. Effect of each antihypertensive drugs on home heart rate (HR) value

	Morning HR (N = 1275)				Evening HR (N = 1133)			
	Model 1		Model 2		Model 1		Model 2	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
Ca antagonist (present = 1)	−0.34	.57	0.05	.94	−1.60	.01	−1.26	.07
ACE inhibitors (present = 1)	1.47	.15	1.58	.15	0.41	.71	0.97	.40
β-Blocker* (present = 1)	−2.50	.02	−2.64	.03	−3.23	.01	−2.60	.04
α-Blocker (present = 1)	−2.18	.11	−2.19	.12	−2.74	.07	−2.18	.17
Diuretics (present = 1)	2.67	.13	2.51	.17	3.69	.04	4.07	.03

ACE = angiotensin converting enzyme; Ca = calcium.
Model 1: adjusted for age, smoking status, time spent walking, gender. Model 2: Model 1 + each antihypertensive drug.
* Including α/β-blockers.

Effects of Casual HR and Casual BP on Home HR

Among the 890 individuals who underwent casual HR and BP measurements, casual HR and morning home HR showed significant correlation with casual SBP and home morning SBP, respectively (casual, $r = 0.08$ $P = .02$; home, $r = -0.09$, $P = .01$). This association persisted after adjustment for major confounding factors in casual measurements ($P = .003$), although it disappeared in home measurements ($P = .3$). The difference between casual and morning home HR (casual HR value − morning home HR value) was significantly and positively associated with the difference between casual and morning home SBP ($r = 0.11$, $P = .001$). Similar results were obtained even when the correlations were calculated by using data from single home measurement obtained on the first day. Correlation between casual and morning home HR was statistically significant ($r = 0.40$, $P \leq .0001$) although it was weaker than the correlation between morning home and casual BP values (SBP: $r = 0.52$, $P \leq .0001$; DBP: $r = 0.43$, $P \leq .0001$). Similar associations were observed for evening home HR (data not shown).

Discussion

We recently clarified the strong predictive value of resting HR for CVD mortality using home HR obtained by a self-monitored blood pressure measuring device,[8] which makes it possible to obtain reliable HR values at rest through multiple measurements under stable conditions. Knowledge of the factors that affect home HR values may be useful in the reduction of risk for CVD. However, no information on the determinants of elevated home HR values has been published. Therefore, we conducted a cross-sectional community survey to identify factors that might affect home HR.

In the present study, we first identified the factors that affect home-measured resting HR in the general population. Elevated home HR was found to be associated with younger age, current smoking, walking for <1 h/day, and female gender. Among these factors influencing home HR values, smoking status, and time spent walking were modifiable. Joint effects of modification of these two were correspond to approximately 5 beats/min, suggesting that these modification may lead to a 17% decrease in CVD mortality risk.[8] However, possibility of selection bias needs to be considered to generalize the present findings, as there were differences in age or systolic BP between the study subjects and those excluded.

The gender difference in HR (higher HR in women than in men) has already been reported in several studies.[17–21] A number of studies have also reported a negative association between HR and age,[18,20,22] whereas others have shown no association between alcohol consumption and HR.[17,19,22] A negative association between HR and physical activity has also been established by some au-

thors.[17,19–22] Our results are in agreement with those previous studies. Although younger age was the determinant of home HR, younger age is also established to be associated with lower CVD risks. The discrepancy may be explained by the clustering effect of other risk factors.

Heart rate is known to increase immediately after smoking a cigarette.[23] However, Gidding et al reported that HR level was higher in habitual smokers than in nonsmokers, even though in their study smokers were asked not to smoke at least for 2 h before examination.[24] They suggest that the effect is associated with the increased myocardial oxygen consumption at rest.[24] Some population-based studies have also found a positive association between smoking and HR.[19,22] These findings were consistent with ours. When we analyzed this association in men and women separately, home HR did not relate significantly to smoking in women. The lack of a significant association between home HR and smoking status in women might reflect the smaller number of women who were current smokers compared with men.

Most previous studies have demonstrated a strong positive correlation between casual HR and casual SBP values.[17,19–22] On the other hand, one study reported that HR was related to BP when measured in the clinic, but not when mean 24-h ambulatory HR and BP readings were compared.[21] This finding regarding 24-h ambulatory measurements is comparable to the results of our present study, in which no association between home HR and home SBP was observed after adjustment for other variables. Nevertheless, among the 890 subjects who underwent casual HR and BP measurements, casual HR showed significant positive correlation with casual SBP, whereas home HR was not positively correlated with home SBP. The difference between casual and home HR values was also significantly and positively correlated with the difference between casual and home SBP values. Similar results were obtained even when the correlations were calculated by using data from single home measurement obtained on the first day. These results suggest that the positive association HR and BP reported in previous studies was mainly attributable to the white coat effect that reflected an alarm reaction to the medical settings,[2] rather than some pressor effects associated with the first measurement.[17,21]

In conclusion, we observed most of determinants, except for BP, of home HR is consistent with the determinants observed in previous studies using casual HR. These results suggest that reduction of home HR through modifying smoking habit or sedentary lifestyle may have a potential to decrease cardiovascular risk in addition to decreasing in these modifiable risk factors per se.

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Expression of urocortin 3/stresscopin in human adrenal glands and adrenal tumors

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ABSTRACT

Urocortin 3 (Ucn 3)/stresscopin (SCP) is a novel peptide of the corticotropin-releasing factor (CRF) family and is a specific ligand for the CRF type 2 receptor. In the present study, we studied expression of Ucn3/SCP in the normal adrenal and adrenal tumors by radioimmunoassay and reverse transcriptase-polymerase chain reaction (RT-PCR). High concentrations of immunoreactive (IR)-Ucn3 were present in the normal portions of adrenal glands (4.2 ± 0.51 pmol/g wet weight, mean ± S.E.M., $n = 14$), and the levels were higher than those in the brain. IR-Ucn3 was also detected in the tumor tissues of aldosterone-secreting adenomas (6.2 ± 0.6 pmol/g wet weight, $n = 10$), cortisol-secreting adenomas (5.0 ± 1.2 pmol/g wet weight, $n = 4$), and pheochromocytomas (1.9 ± 0.4 pmol/g wet weight, $n = 7$). Reverse phase high performance liquid chromatography showed that IR-Ucn3 in normal portions of adrenal glands and aldosterone-secreting adenomas was eluted mainly in the positions of Ucn3 and SCP with several minor peaks eluting earlier. The RT-PCR showed expression of Ucn3 mRNA in normal portions of adrenal gland (positive ratio; 4/4), aldosterone-secreting adenomas (3/4), cortisol-secreting adenomas (1/3) and pheochromocytomas (6/7). These findings indicate that Ucn3 is produced in normal adrenal and adrenal tumors (both adrenocortical tumors and pheochromocytomas), and suggest that Ucn3 acts as an autocrine or paracrine regulator in normal adrenal and adrenal tumors.

1. Introduction

Urocortin 3 (Ucn3)/stresscopin (SCP) is a novel member of the CRF family and is a specific agonist for CRF type 2 receptor (CRF_2 receptor) [10,14]. Ucn3 and SCP were discovered independently by two research groups through the process of searching the public human genome databases. Post-translational processing sites were differently interpreteted by these two groups, and therefore, the amino acid number of these peptides is different: human Ucn 3 is a 38 amino acid

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peptide that corresponds to the sequence 3–40 of human SCP, a 40 amino acid peptide. Thus, the corticotropin-releasing factor (CRF) family now consists of CRF, urocortin 1 (Ucn1), Ucn2 (stresscopin-related peptide; SRP) and Ucn 3 (SCP) as well as fish urotensin I and frog sauvagine [10,14,17,29].

The actions of the CRF-family peptides are mediated by at least two types of G-protein coupled receptors: CRF type 1 receptor (CRF_1 receptor) and CRF_2 receptor [6,15]. CRF_1 receptor mediates ACTH responses to stress, whereas CRF_2 receptor mediates anxiolysis, anorexia, vasodilatation, a positive inotropic action on myocardium and dearousal. CRF and Ucn1 bind to both CRF_1 receptor and CRF_2 receptor, whereas Ucn2 and Ucn3 are specific ligands for CRF_2 receptor [10,14,17].

Ucn1 and Ucn3 are expressed in various human tissues including brain, pituitary, heart, gastrointestinal tract and kidney [2,7,10–12,14,16–19,24,25,27], whereas the presence of Ucn2 (SRP) has not been established in human tissues [10,14]. It is well known that adrenal medulla and pheochromocytomas express various types of neuropeptides and vasoactive peptides, such as neuropeptide Y (NPY), calcitonin gene-related peptide and adrenomedullin, and their receptors [1,13,26]. Moreover, there is accumulating evidence showing the production and secretion of some peptides, such as adrenomedullin and endothelin-1, from adrenal cortex and adrenocortical tumors [22,23]. We have recently shown expression of Ucn1, Ucn3 and CRF receptors in adrenal cortex and medulla, and adrenal tumors (adrenocortical tumors and pheochromocytomas) by immunocytochemistry and in situ hybridization, suggesting the presence of the adrenal CRF system [8]. Furthermore, Sirianni et al. have recently reported that CRF directly stimulated cortisol and the cortisol biosynthetic pathway in human fetal adrenal cells [20]. Immunoreactive (IR)-Ucn3 in the normal adrenal and adrenal tumors, however, has not been measured and has not been chromatographically characterized. We therefore studied IR-Ucn3 concentrations in normal portions of adrenal glands and adrenal tumors by radioimmunoassay, and Ucn3 mRNA expression by reverse transcriptase polymerase chain reaction (RT-PCR).

2. Methods

2.1. Samples

The present study has been approved by the Ethics Committee of Tohoku University School of Medicine. Adrenal tumor tissues were obtained at surgery from patients with aldosterone-secreting adenomas ($n = 10$), cortisol-secreting adenomas ($n = 4$), and pheochromocytomas ($n = 7$). Non-tumorous portions of adrenal glands containing both cortex and medulla were used as normal portions of adrenal glands ($n = 14$). Informed consent was obtained from each subject. Tumor tissues were stored at −80 °C until peptide extraction. Tumor tissues of four aldosterone-secreting adenomas, three cortisol-secreting adenomas and seven pheochromocytomas and four normal portions of adrenal glands were available also for RNA extraction. Total RNA samples prepared from cerebral cortex ($n = 2$) and hypothalamus ($n = 2$) obtained at autopsy [25] were used as positive controls for the RT-PCR analysis.

2.2. Peptide extraction and radioimmunoassay

Tissues were extracted, as reported previously [28]. Briefly, the tissue (approximately 750 mg) was boiled in 2 ml of 1 mol/l acetic acid for 10 min. Eight milliliters of 50% methanol in 0.5 mol/l acetic acid was added to each sample and the tissue was homogenized. The homogenate was centrifuged by 15,000 × *g* for 30 min. The supernatant was separated, dried by air, reconstituted in assay buffer [0.1 mol/l phosphate buffer, pH 7.5 containing 0.1% (w/v) bovine serum albumin (BSA), 0.2% (v/v) Triton X-100 and 0.1% (w/v) sodium azide] and assayed as previously described [25].

The radioimmunoassay of Ucn3 was previously reported in details [25]. Briefly, the antiserum against human Ucn 3 was raised in a rabbit by injecting tyrosyl-Ucn3 (Sawady Technology, Tokyo, Japan; Custom Synthesis) conjugated with BSA by carbodiimide, and was used at a final dilution of 1:24,000. This antiserum is the same as that used in our previous immunocytochemical studies [8,18,25]. Human Ucn3 (Phoenix Pharmaceuticals Inc., Belmont, CA) was used as a standard. ^{125}I-tyrosyl-Ucn3 prepared by the chloramine T method was used as a radioligand. The assay could detect changes of 4.7 ± 0.3 fmol/tube (mean ± S.D., $n = 8$) from zero at 95% confidence with duplicate tubes. The cross reactivity was 100% with human SCP (Peptide Institute), but less than 0.001% with other peptides including human CRF, Ucn1, human SRP (Peptide Institute), NPY, endothelin-1, arginine vasopressin, oxytoxin, substance P and vasoactive intestinal polypeptide. Intra and interassay coefficients of variation were 4.4% and 9.7%, respectively.

Chromatographic characterization of tissue extracts was performed by reverse phase high performance liquid chromatography (HPLC) using a μBondapak C18 column (3.9 mm × 300 mm, Waters). The tissue extract was re-extracted with a Sep-Pak C18 cartridge (Waters), reconstituted in 0.1% (v/v) trifluoroacetic acid (TFA) and loaded onto the column. The HPLC was performed with a linear gradient of acetonitrile containing 0.1% (v/v) TFA from 10% to 60% at a flow rate of 1 ml/(min fraction) over 50 min. Each fraction (1 ml) was collected, dried by air, reconstituted with assay buffer and assayed.

2.3. RNA extraction and RT-PCR

Total RNA was extracted from tissues by the guanidine thiocyanate-cesium chloride method. Total RNA (6 μg) was denatured at 65 °C for 5 min and transcribed at 37 °C for 60 min in a reaction mixture (20 μl) containing 0.75 μg oligo-dT, 0.5 mmol/l dNTP and 400 units of Moloney murine leukemia virus reverse transcriptase (BRL, Gaithersburg, MD, USA). The reaction was stopped by heating at 95 °C for 5 min, diluted with 30 μl of water and stored at −20 °C until PCR analysis. One microliter of the reaction mixture was subjected to PCR. The PCR was performed in a total volume of 20 μl containing 0.2 mmol/l of each dNTP, 0.25 μmol/l of each primer and 0.5 U Taq DNA polymerase (Pharmarcia, Piscateway, NJ).

The sense primer was 5′-CCGGAGCAGCCACAAGTTCAT-3′ (nucleotide numbers 112/132) and the anti-sense primer was 5′-CCAATTTGCGCCATCAGGTG-3′ (complementary to 678/697)(Genbank accession No.NM_053049) [14]. The primers