Study population

Details of the selection of the study population have been reported previously [12,13]. Briefly, of the 1989 eligible individuals aged 40 years and over, more than three measurements (three days) of home BP data and screening BP 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 BP values. Therefore, the study population consisted of 1702 individuals.

Home BP measurements

Physicians and/or public health nurses instructed subjects on how to perform home BP measurements. Subjects were asked to measure their BP 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 mean of the home BP values was calculated for each individual (average number of measurements = 25).

Screening BP measurements

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

BP measuring device

Home BP was measured using the HEM 401C (Omron Life Science Co. Ltd., Tokyo, Japan), a semi-automatic device based on the cuff-oscillometric method [15], which generates a digital display of both systolic BP (SBP) and diastolic BP (DBP).

Screening BP was measured using an 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 BP measurements. Both the home BP measuring device and the screening BP measuring device used in the present study have been previously validated [15,16] and meet the criteria of the Association for the Advancement of Medical Instrumentation [17].

Follow-up and outcome

The residents' registration cards confirmed residence in Ohasama as of 31 December 2001. The incidence of stroke and transient ischaemic attack (TIA) up until 31 December 2001 was investigated through the Stroke Registration System of the Iwate Prefecture by tracking death certificates, receipt of National Health Insurance, and by sending questionnaires to each household at the time of home BP 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, and 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.

Outcomes were determined as incidence of: (1) total stroke and transient ischaemic attack (TIA); (2) haemorrhagic stroke that included intracerebral haemorrhage and subarachnoid haemorrhage (SAH), and (3) ischaemic stroke that included cerebral infarction and TIA. The diagnostic criteria for stroke and the subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke [18].

Data collection and statistical analysis

The association between baseline BP levels and the risk of 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 hypercholesterolaemia. The dependent variable in these analyses was the number of days from the date of the first home BP measurement to the date of stroke or TIA, or censoring. Stroke-free and TIA-free survivors as of 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 analysis included only the first event for those subjects who had multiple non-fatal events.

The estimated relative hazard (RH) and the 95% confidence interval (95% CI) of variables were derived from the coefficient and standard error as determined by the Cox proportional hazards model. Data are shown as mean ± SD. A P value less than 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

Baseline characteristics

The mean age was 61 ± 11 years and the ratio of men to women was 37 : 63. Of the 1702 study subjects, 370 (22%) were classified as current or ex-smokers and 507 (30%) were treated with antihypertensive medication at the baseline, while 16 (1%), 218 (13%) and 207 (12%) were

classified as having a history of heart disease, diabetes mellitus or hypercholesterolaemia, respectively.

Home and screening BP values

The home BP values were significantly lower than the screening BP for SBP (Table 1). All home and screening BP values for those patients who developed stroke over the follow-up period were significantly higher than those who did not develop stroke (casual diastolic: $P = 0.02$, other: $P < 0.001$) (Table 1).

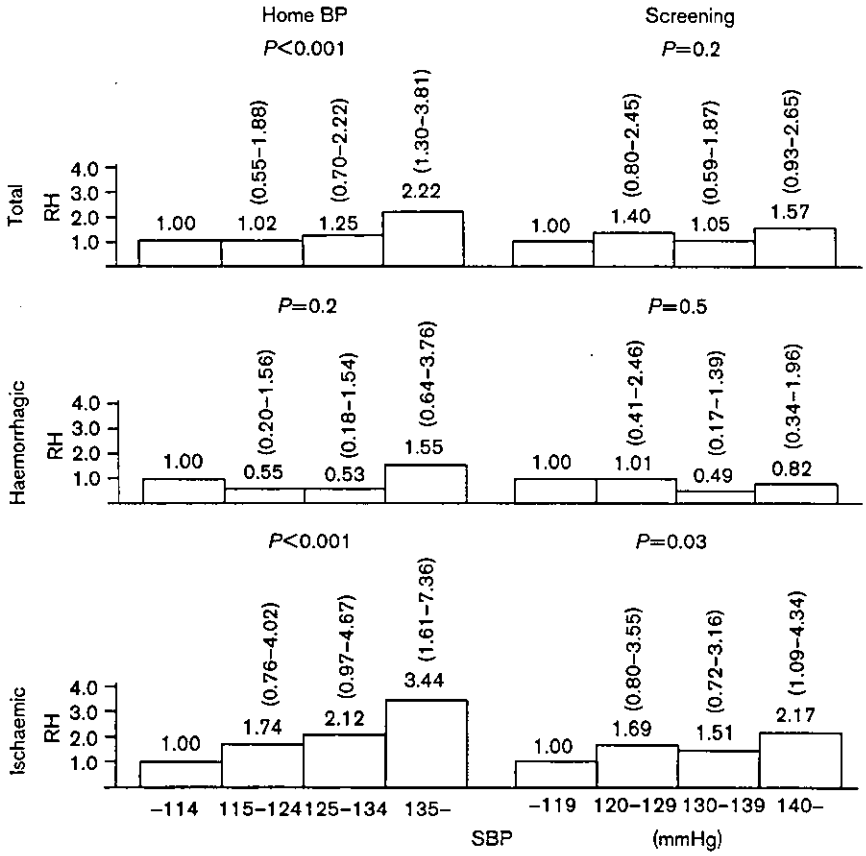
Screening BP was significantly correlated with home BP values (SBP: $r = 0.45$; DBP: $r = 0.39$) (all $P < 0.001$), although the correlation coefficient was not very high.

Table 1 Mean (SD) of blood pressure values at baseline among the whole, those who developed and who did not develop stroke during the follow-up period (n=1702)

		Developed stroke or TIA (n=150)				Not developed any stroke or TIA (n=1549)	P value (ANOVA)
		All subjects (n=1702)	Ischemic stroke/TIA (n=110)	Haemorrhagic stroke (n=40)	Unknown (n=3)		
Systolic blood pressure	Screening	133 (19)	140 (18)	135 (20)	162 (32)	132 (19)	<0.0001
	Home	125 (15)	135 (15)	133 (19)	133 (24)	124 (15)	<0.0001
Diastolic blood pressure	Screening	76 (12)	78 (11)	76 (11)	88 (7)	76 (12)	0.09
	Home	75 (10)	78 (11)	79 (10)	76 (6)	75 (10)	<0.0001

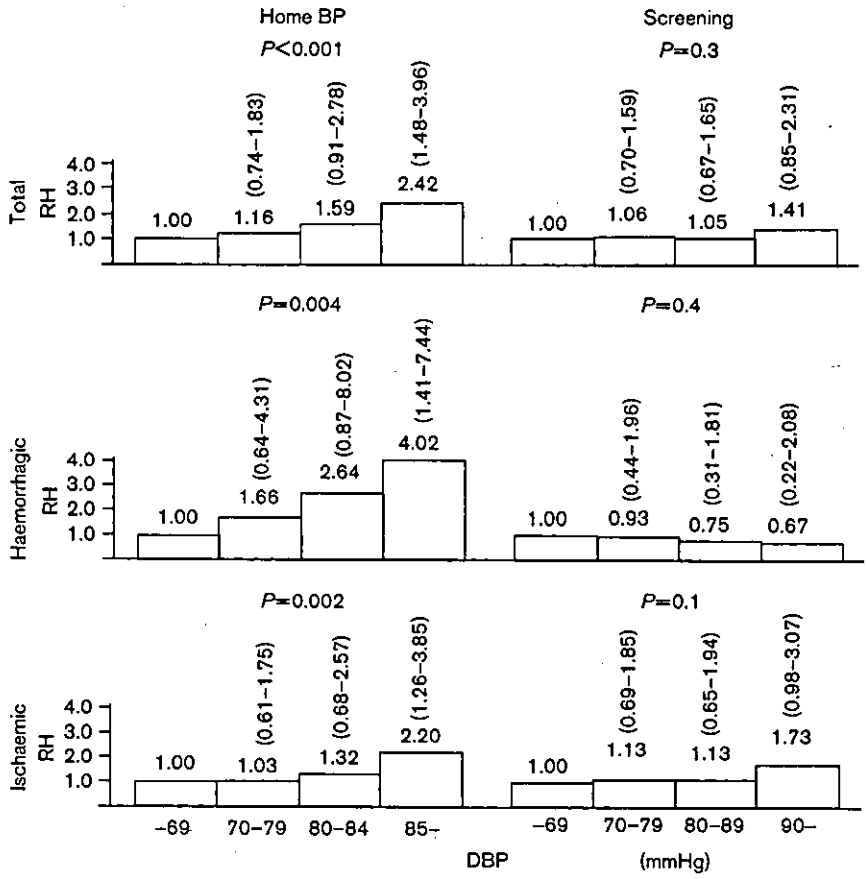
TIA, transient ischaemic attack.

Fig. 1



Association between home and screening systolic blood pressure (SBP) values and the risk of stroke and subtypes. Relative hazard (RH) and 95% confidence intervals (CI) of home and screening SBP levels adjusted for age, gender, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolaemia, and diabetes for the risk of total [total stroke or transient ischaemic attack (TIA)], haemorrhagic (cerebral haemorrhage or subarachnoid haemorrhage) and ischaemic (cerebral infarction or TIA) stroke. The '*P* ' for linear trend is indicated above the bars. Numbers inside the bars indicate 95% CI. The group with the lowest BP values was treated as the reference category.

Fig. 2



Association between home and screening diastolic blood pressure (DBP) values and the risk of stroke and subtypes. Relative hazard (RH) and 95% confidence intervals (CI) of home and screening DBP levels adjusted for age, gender, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolaemia, and diabetes for the risk of total [total stroke or transient ischaemic attack (TIA)], haemorrhagic (cerebral haemorrhage or subarachnoid haemorrhage) and ischaemic (cerebral infarction or TIA) stroke. The '*P* ' for linear trend is indicated above the bars. Numbers inside the bars indicate 95% CI. The group with the lowest BP values was treated as the reference category.

Follow-up and outcomes

Mean duration of follow-up was 10.6 ± 3.0 years. A total of 32 subjects (2%) moved away and were lost to follow-up, while 79 cardiovascular deaths (5%) and 180 non-cardiovascular deaths (11%) were recorded.

Of the 1702 subjects, 153 (9%) had a first onset of stroke or TIA. This was due to cerebral infarction in 106 (69%), intracerebral haemorrhage in 28 (18%), subarachnoid haemorrhage in 12 (8%), TIA in four (3%), and unknown causes in three (2%).

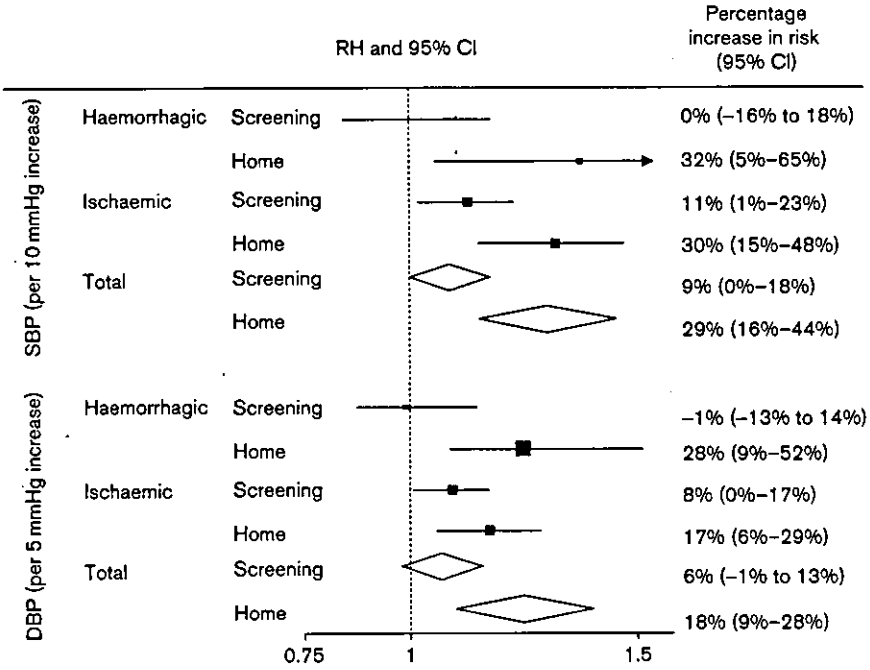
Association between home and screening BP values and stroke risk

We subdivided the subjects into four groups according to individual home BP values, and then compared their risk for total, haemorrhagic, and ischaemic stroke and TIA (Fig. 1 for SBP and Fig. 2 for DBP). In the analysis, we treated the group with the lowest BP values as the reference group. For home SBP measurements, the risks for total and ischaemic stroke among those with SBP ≥ 135 mmHg were significantly higher than amongst those with SBP < 115 mmHg (both $P < 0.004$), with a significant observable linear trend (all $P < 0.001$) (Fig. 1). Higher SBP category also tended to be associated with the risk of haemorrhagic stroke, although there was no statistically significant difference (Fig. 1). Similarly, home DBP values were significantly related to stroke risk (all *P* for linear trend < 0.005) (Fig. 2). There were non-significant linear trends between screening SBP, DBP and the risk for total, ischaemic, and haemorrhagic stroke, except for a significant association between screening SBP and the risk of ischaemic stroke ($P = 0.03$) (Figs 1 and 2).

Comparison of predictive values between home and screening BP

As continuous variables, home BP values showed a linear association with risks for total, haemorrhagic, and

Fig. 3



Predictive values of home and screening blood pressure (BP) for the risk of stroke and subtypes. Relative hazard (RH) and 95% confidence intervals (CI) of home and screening systolic BP (SBP) (above) and diastolic BP (DBP) (below) levels adjusted for age, gender, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolaemia, and diabetes for the risk of total (total stroke or transient ischaemic attack [TIA]), haemorrhagic (cerebral haemorrhage or subarachnoid haemorrhage) and ischaemic (cerebral infarction or TIA) stroke. Relative hazard is expressed as an increase in stroke risk per 10 mmHg elevation of SBP and per 5 mmHg elevation of DBP. Boxes are centred on the point estimates of RH in the relevant stroke subtypes and are sized in proportion to the number of events recorded. The diamond represents the results for total stroke and is centred on the point estimate of the RH. The horizontal lines and the tips of the diamond represent 95% CI.

ischaemic stroke (Fig. 3). A 10 mmHg elevation of home SBP values was significantly associated with 29, 32 and 30% increases in the risk for total, haemorrhagic, and ischaemic stroke, respectively (Fig. 3). A 5 mmHg elevation of home DBP was also significantly associated with 18, 28 and 17% increases in the risk for total, haemorrhagic, and ischaemic stroke, respectively (Fig. 3). Although all screening SBP and DBP values showed a tendency of linear association with the risk of stroke and subtypes, the predictive power was less remarkable compared with those of home BP values (Fig. 3).

When home and screening BP values were simultaneously included in a Cox model, only home BP was significantly related with total stroke risk (data not show). The model including both home and screening BP lost 'goodness of fit' when home BP was removed (SBP likelihood ratio = 16.4; DBP likelihood ratio = 11.9, both $P < 0.001$). However, the goodness of fit of the model including both home and screening BP did not change significantly when screening BP was removed (SBP likelihood ratio = 0.035; DBP likelihood ratio = 0.001, both $P > 0.8$). Similarly, home BP values showed a significantly greater relation with the risk of haemorrhagic and ischaemic stroke than the screening BP values (all $P < 0.02$).

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 and screening BP values showed a linear association with the risk of stroke and subtypes, the predictive value was significantly higher for home BP. Broadly, a 10 mmHg elevation of home SBP and a 5 mmHg elevation of DBP were associated with 30 and 20% increases, respectively, for the risk of stroke and subtypes. This finding is the first demonstration that home BP has a stronger predictive power of ischaemic and haemorrhagic strokes than conventional BP.

Previous meta-analysis that used conventional BP adjusted for regression dilution bias showed a steeper association of BP values with haemorrhagic stroke than ischaemic stroke [2,4]. In the present study we also found that, in terms of the magnitude of the RH, home

DBP values tended to be more strongly associated with the risk of haemorrhagic stroke than with the risk of ischaemic stroke (28% increase and 17% increase in the risk of haemorrhagic and ischaemic stroke, respectively). These results confirmed the importance of BP control particularly in the prevention of haemorrhagic stroke.

Although home BP measurement is now widely practised in developed countries, a lack of information on the prognostic significance has partly limited its effective use [19–21]. In this study, we first demonstrated that home BP measurement provides more useful prognostic information for stroke than conventional BP measurement. Although the external validity of the present findings, especially to non-Asian population, would need to be clarified by further studies, we recommend that home BP measurements should be used more effectively in clinical and epidemiological settings for better prediction of individual risk.

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Original Contributions

Prognostic Value of Home Heart Rate for Cardiovascular Mortality in the General Population

The Ohasama Study

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Background: Recently, the advantages of self-measurement of blood pressure (BP) at home have been recognized. The same advantages could also be applicable to resting heart rate (HR) values assessed at home using a device designed for home BP measurement. However, there have been no studies investigating whether home HR values predict the risk of cardiovascular disease mortality. We therefore investigated the usefulness of HR values in predicting cardiovascular mortality using a device that allowed self-measurement of BP and HR at home.

Methods: The association between the home-measured resting HR and the 10-year risk of cardiovascular mortality was examined in 1780 Japanese individuals ≥40 years of age who had no significant arrhythmias. A Cox proportional hazards model that adjusted for major risk factors was used.

Results: An increase of 5 beats/min in the morning home HR measurement was associated with a 17% increase in the risk of cardiovascular mortality (95% confidence interval 5% to 30%). This relationship was also statistically significant after adjustment for home BP values. Even when home-measured systolic BP was within the normal range (<135 mm Hg), subjects with HR ≥70 beats/min had a higher risk of cardiovascular mortality (relative hazard 2.16, 95% confidence interval 1.21 to 3.85) than those with normal systolic BP and HR values.

Conclusions: Self-measurement of HR at home, together with self-measurement of BP, is a simple method of providing useful clinical information for assessing cardiovascular risk. Am J Hypertens 2004;17:1005–1010

Key Words: Heart rate, blood pressure, cardiovascular disease, mortality, population.

Recently, the usefulness of self-measurement of blood pressure (BP) at home (home BP) has been recognized. It has also been found that multiple measurements lead to a better reproducibility of home BP values.[1,2] This better reproducibility, together with the absence of environmental influences such as the so-called white coat effect[3] and observer bias, diminish regression dilution bias, which results in a better predictive power of home BP measurements having greater predictive power than conventional BP measurements.[4–6] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation,

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and Treatment of High Blood Pressure (JNC VII)[7] and the European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension[8] have also emphasized the usefulness of home BP measurements. The same advantages could also be applicable to resting heart rate (HR) values assessed at home (home HR) using a device designed for home BP measurement.

To date, however, there have been no studies investigating whether home HR values predict the risk of cardiovascular disease (CVD) mortality and what value should be made into the reference values. For this reason, we carried out a population-based prospective study to clarify the predictive value of home HR values.

Methods

Design

The present study was a part of a longitudinal observational study of subjects who had been participating in a BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987.[2–5,9–11] The socioeconomic and demographic characteristics of this region and full details of the project have been described elsewhere.[9,10] 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

The selection of study subjects has been described previously.[11] Briefly, the subjects were ≥40 years of age and were residents of three of the four regions of Ohasama (n = 2716). Hospitalized persons (n = 121) as well as persons who had dementia or who were bedridden (n = 31) were excluded. Individuals who worked out of town (n = 575) were also excluded because the project involved ambulatory BP monitoring. Informed consent to participate in the study was given by 1957 of the 1989 eligible individuals. We have previously confirmed the representativeness of the 1913 subjects who measured their morning home BP on more than three occasions (3 days).[11] For the current analysis, we also excluded 92 more of these subjects from the group of 1913 subjects, because they did not measure their home BP and home HR in both the morning and the evening for at least 3 days. This criterion was based on our previous observation that the average BP value for the first 3 days did not differ significantly from values obtained over the entire study period,[9] and also on the observation that the average home HR value for the first 3 days (morning HR [mean ± SD]: 67.8 ± 8.7 beats/min) did not differ from the value obtained over the entire study period (67.8 ± 7.9 beats/min); indeed, there was a significant correlation between the latter two values (r = 0.87, P = .0001).

We also excluded subjects (n = 41) with a history of significant arrhythmias (such as atrial fibrillation), sick sinus syndrome, or permanent pacemaker implantation. Therefore, the study population comprised of 1780 individuals (mean age, 60.6 years; men:women, 40:60), representing almost 90% of the total eligible population.

Home BP and Heart Rate Measurements

Physicians and public health nurses conducted a health education class to inform the population about home BP and HR recording, taught them how to measure their own BP and HR, and assessed whether the participants were able to measure their own BP correctly. Of the households in the town, 80% attended the class, and public health nurses visited all of the remaining households to provide similar information.[9,10]

The subjects were then asked to measure and record their BP and HR once every morning and evening for 4 weeks. Morning measurements of BP and HR were made within 1 h of awakening, before breakfast or taking any drugs, with the subjects seated and having rested for at least 2 min. Evening measurements of BP and HR were made similarly just before going to bed. Home BP and HR were measured using HEM401C automatic devices (Omron Healthcare Co., Kyoto, Japan), which use the cuff-oscillometric method[12] to generate a digital display of systolic/diastolic BP and HR values. These devices have been validated previously[12] and satisfy the criteria of the Association for the Advancement of Medical Instrumentation.[13] The circumference of the arm was <34 cm in most cases, so we used a standard arm cuff.

The pulse interval was calculated from the pulse wave, which was detected by a manometer incorporated in the equipment. The HR was calculated as follows: HR (beats/min) = 60/average pulse interval. The home BP and HR values for each individual were defined as the means of all measurements obtained for that person.

Follow-Up and Data Collection

Residence in Ohasama Town on December 31, 2001, was confirmed from the residents' registration cards, which were considered accurate and reliable because they are the basis for the payment of pensions and social security benefits in Japan. The underlying cause of any death was determined from the death certificates and classified according to the recommendations of the *International Classification of Diseases, 10th revision* (ICD-10). The primary outcome was mortality from CVD, defined as death from disease of the circulatory system (ICD-10: I00 to I99). Secondary outcomes were mortality from cerebrovascular disease (ICD-10: I60 to I69) or heart disease (ICD-10: I00 to I52 or I70 to I99), respectively.

Information on possible confounding variables (such as smoking status, overweight, use of antihypertensive medication, and history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus) was obtained from questionnaires sent to each subject at the time of starting

Table 1. Characteristics among quintiles of morning home heart rate (HR)

Morning Home HR (beats/min)	≤59	60–64	65–69	70–73	≥74	*P* Value
Number of subjects	371	312	489	282	326	
Age, (ys)	63	61	60	58	59	<.01
Sex (male, %)	51	38	37	35	40	<.01
Smoking status (ever smoker, %)	24	23	22	24	30	.12
Overweight, (BMI >25 kg/m^2), %	34	27	27	34	29	.14
Antihypertensive medication, %	38	32	25	26	29	<.01
Previous history, (%)						
Diabetes	9	13	10	10	12	.42
Hypercholesterolemia	15	13	17	16	17	.48
CVD	8	6	7	7	9	.78
Home BP, (mm Hg)						
Systolic	128	125	124	124	125	<.01
Diastolic	75	75	74	75	77	<.01

BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease.
Continuous variables were tested by ANOVA; categorical variables were tested by χ^2 test.

home BP measurement, from records of annual health check-ups, and from medical records held at the Ohasama Prefectural Hospital.

Statistical Analysis

The association between home HR and BP values and mortality risks were estimated from Cox proportional hazards models[14] adjusted for major CVD risk factors (smoking status, overweight, use of antihypertensive medication, and history of cardiovascular disease, hypercholesterolemia, or diabetes). Subjects who died of other causes were treated as censored. Variables were compared using the χ^2 test or analysis of variance, as appropriate. Differences with a two-tailed P value <.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, NC).

Results

Home Heart Rate Measurement

The mean home HR values were 67.3 ± 7.8 beats/min for the morning and 69.1 ± 7.9 beats/min for the evening, whereas mean home systolic/diastolic BP values were 125.2 ± 15.1/75.1 ±10.0 mm Hg for the morning and 123.2 ± 14.5/73.4 ± 9.5 mm Hg for the evening. A mean of 23.1 ± 6.9 morning and 23.8 ± 6.9 evening home BP measurements were obtained; similarly, a mean of 22.9±7.0 for morning and 23.6 ± 6.7 evening home HR measurements were recorded. Of the 1780 study subjects, 24% were current or ex-smokers, 30% were overweight (body mass index >25 kg/m^2), and 30% were taking antihypertensive medication. Of the latter, 297 (56%) were receiving calcium antagonists, 107 (20%) were receiving β-blockers, 111 (21%) were receiving diuretics, and 44 (8.2%) were receiving angiotensin-converting enzyme inhibitors. A history of CVD, hypercholesterolemia, or diabetes was recorded in 131 (7%), 283 (16%), and 186 (10%) subjects, respectively.

Table 1 shows the characteristics of the subjects in each quintile, classified on the basis of morning home HR values. The proportion of smokers was higher in the fifth quintile, whereas the values for mean age and mean systolic BP were higher in the first quintile. No significant association was observed between HR values and a history of diabetes, hypercholesterolemia, or cardiovascular disease. The proportion of subjects who were taking antihypertensive medication was higher in the first quintile, although no specific class of antihypertensive drug could account for this difference (data not shown). A similar pattern of characteristics was observed when the quintiles of evening values were examined (data not shown).

Home Heart Rate and Cardiovascular Disease Mortality Risk

The mean duration of follow-up was 10.5 years (maximum 13.9 years). There were 104 CVD deaths (5.8%) and 178 non-CVD deaths (10.0%). Of the 104 CVD deaths, 60 (60%) were due to cerebrovascular disease and 44 (40%) to heart disease. In addition, 35 subjects (2.0%) moved away from the region and were lost to follow-up.

Table 2 shows the relationship between home HR values and the CVD mortality risk. The fifth quintile (≥74 beats/min; relative hazard [RH] = 2.61, P = .008), the fourth quintile (70 to 74 beats/min; RH 2.54, P = .02) of morning HR values were associated with a significantly higher risk of CVD mortality (for linear trend, P < 0.001). When analyzed as a continuous variable, an increase of 5 beats/min in morning home HR as a continuous variable was associated with a 17% increase in the overall CVD mortality risk (95% confidence interval [CI] 5% to 30%, P = .003) after adjustment for major risk factors. Similar tendencies were also observed for the cerebrovascular mortality risk (20% risk increase per increase of 5 beats/min in morn-

Table 2. Relationship between home heart rate (HR) and mortality in all subjects

	No. of Subjects	No. of Events	CVD Mortality RH	95% CI
Morning HR, beats/min				
≤60	371	23	1.12	(0.54–2.33)
61–64	312	11	1.00	
65–69	489	29	1.63	(0.81–3.29)
70–73	282	15	2.54	(1.16–5.58)
≥74	326	26	2.61	(1.29–5.31)
Continuous variable	1780	104	1.17	(1.05–1.30)
Continuous variable*	1780	104	1.17	(1.05–1.30)
Evening HR, beats/min				
≤62	372	17	1.00	
63–66	354	20	1.47	(0.77–2.82)
67–69	270	10	1.14	(0.51–2.52)
70–74	417	30	3.20	(1.73–5.91)
≥75	367	27	2.25	(1.21–4.21)
Continuous variable	1780	104	1.17	(1.05–1.30)
Continuous variable*	1780	104	1.16	(1.04–1.29)

CI = confidence interval; CVD = cardiovascular disease; RH = relative hazards for increase of 5 beats/min in HR.
Relative hazards were calculated by Cox proportional hazard model adjusted for age, sex, smoking status (current v ever), overweight, use of antihypertensive medication, history of CVD, diabetes, hypercholesterolemia.
* Further adjustment for systolic blood pressure.

ing HR, 95% CI 4% to 37%, $P = .01$) and the heart disease mortality risk (16%; 95% − 2% to 37%, $P = .09$).

Similarly, evening HR was linearly associated with an increased risk of CVD mortality (17% risk increase per increase of 5 beats/min in HR: 95% CI 5% to 30%, $P = .004$), cerebrovascular mortality (22%; 95% CI 6% to 39%; $P < .01$). However, only weak trends were observed for heart disease mortality (12%; 95% CI −6% to 33%; $P = .21$).

Because we have previously reported that, in this population, home systolic BP had a stronger predictive power for CVD mortality than home diastolic BP,[5] we further examined the effect of home systolic BP on the relationship between home HR and CVD mortality risk. The relationship was essentially unchanged after adjustment for home systolic BP as well as other major risk factors: increases of 5 beats/min in morning and evening HR were associated with 17% (95% CI 5% to 30%, $P < .01$) and 16% (95% CI 4% to 29%, $P < .01$) increases in the CVD mortality risk, respectively.

As the mean age and the proportions of men, smokers, and individuals receiving antihypertensive treatment differed significantly among the quintiles of home HR values (Table 1), we conducted a subgroup analysis based on these characteristics (Table 3). Both morning HR and evening HR values were positively related to the CVD mortality risk without significant interactions with age, sex, smoking status, and antihypertensive treatment.

Home Heart Rate and BP Values and the Risk of Cardiovascular Disease Mortality

Figure 1 indicates the CVD mortality risks among groups defined on the basis of the combined parameters (that is, morning home HR and morning home systolic BP values). We defined a home HR value of ≥70 beats/min as a "high home HR" and a value of <70 beats/min as "normal home HR," given that the fourth and fifth quintiles of both morning and evening home HR values were associated with significantly higher risks than that in the reference category (Table 2). "Systolic home hypertension" was defined according to established reference values of home BP (≥135 mm Hg).[7,8] Hypertensive subjects with a normal HR (RH 1.65; $P = .06$) and normotensive subjects with high HR (RH 2.16, $P < .01$) had significantly higher CVD risk than normotensive subjects with a normal HR (RH 1.00 for reference group). Furthermore, hypertensive subjects with a high HR (RH 3.16, $P < .01$) had the highest CVD risk among the four subgroups. No significant interaction was observed between BP and HR. A similar association was observed among groups defined according to evening values (data not shown).

Discussion

This prospective cohort study demonstrated an independent association between home-measured HR values and CVD mortality in a representative sample of the general population in Japan. On average, each increase of 5 beats/min in home HR was associated with an approximately 17% higher risk of CVD mortality, which was independent of home BP values and other possible confounding factors. This association was also observed for the risks of mortality due to stroke and heart disease. Furthermore, individuals with high home-measured BP and high home-measured HR had a threefold higher risk of CVD mortality than did individuals with normal levels of both variables. These results suggest that self-measured resting HR and

Table 3. Relationship between morning home heart rate (HR) and cardiovascular disease (CVD) mortality by baseline subgroups

	Morning			Evening		
	RH	95% CI	*P* for Interaction	RH	95% CI	*P* for Interaction
Age						
Younger (40–69 y)	1.11	0.94–1.31	.39	1.11	0.94–1.30	.49
Older (≥70 y)	1.20	1.04–1.38		1.19	1.03–1.38	
Sex						
Male	1.16	1.02–1.33	.94	1.13	0.99–1.29	.69
Female	1.13	0.95–1.35		1.16	0.96–1.40	
Smoking status						
Never	1.20	1.04–1.39	.45	1.16	0.99–1.36	.74
Ever	1.12	0.94–1.32		1.13	0.96–1.34	
Antihypertensive medication						
Absent	1.31	1.09–1.57	.09	1.32	1.09–1.60	.06
Present	1.12	0.98–1.28		1.12	0.98–1.28	

Abbreviations as in Table 2

Relative hazards were calculated by Cox proportional hazard model adjusted for age, sex, smoking status, overweight, use of antihypertensive medication, history of CVD, diabetes, hypercholesterolemia and home systolic BP.

BP at home are useful parameters for predicting the CVD risk in the general population.

The present results clearly demonstrated that home HR was an independent predictor of the CVD mortality risk. Home HR measurements are usually taken more frequently under more controlled conditions and with less psychological stress than those obtained in a clinical setting. Several studies[15–21] have reported a positive relationship between clinic HR measurements and CVD mortality after adjustment for BP values, and our results were consistent with those data. However, as we did not measure clinic HR values in the present study population, we could not compare the predictive power of home HR with that of casually measured HR. Nonetheless, in previous studies that treated HR as a continuous variable, an increase of 10 beats/min and an increase of 20 beats/min in clinic HR was reported to be associated with a 23% and a 63% increase in CVD mortality risk,[20,21] respectively, whereas in the present study an increase of 10 beats/min and an increase of 20 beats/min in morning home HR was more strongly associated with CVD mortality risk (37% and 87%, respectively). These results may reflect the possibility that home HR can detect a high risk of CVD mortality more effectively than clinic HR, probably through its better reproducibility resulting from multiple measurements under stable conditions at home.

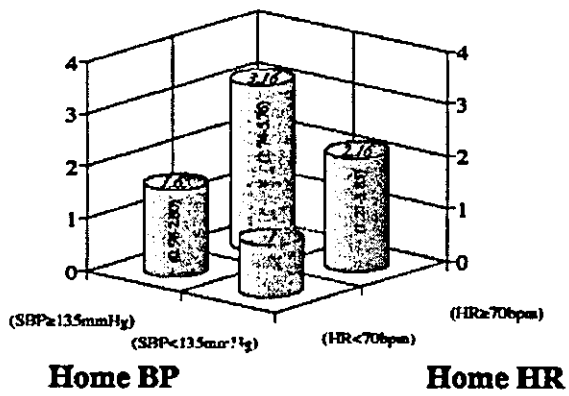

FIG. 1. Home-measured heart rate (HR) and blood pressure (BP) values and the risk of cardiovascular mortality. The relative hazard and 95% confidence interval for cardiovascular mortality associated with each of four groups, defined by a combination of systolic blood pressure (SBP) and HR (in beats/min [bpm]) measured at home in the morning, are shown. The values have been adjusted for age, sex, smoking status, overweight, use of antihypertensive medication, and history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus. **Numbers inside the columns** indicate 95% confidence intervals.

Home-measured HR could be lower than office HR because of the absence of the white coat effect. In fact, some studies that have provided both office HR and home HR values have shown that office HR is higher than home HR.[6,22] Therefore, it is necessary to define the original reference value for home HR. In our study, we found that home HR values ≧70 beats/min were associated with a higher risk of CVD mortality. Therefore, this value could be used as a reference value of home HR to define individuals at high risk when monitoring home HR in this population. However, to generalize these values, further follow-up studies will be needed.

When we estimated the CVD risks among groups defined on the basis of combined parameters, even if home-measured systolic BP was within the normal range (<135 mm Hg), subjects with HR ≧70 beats/min had a higher risk of CVD mortality (RH 2.16, 95% CI 1.21 to 3.85) than those with normal systolic BP and HR values. These results confirmed that a certain proportion of subjects who had higher CVD risk were neglected when HR values were overlooked. Therefore, we consider that the informa-

tion on home HR values should be considered just as important as home BP values.

Our observational study was unable to resolve the issue of whether HR lowering treatments such as β-blocker therapy should be implemented for patients with high HR. The answers to such questions must await large scale, randomized trials of the effects of HR lowering therapy on major causes of morbidity and mortality.

In conclusion, home-measured HR is a strong predictor of the risk of CVD mortality in the general population, and the CVD risk associated with a particular HR value is independent of the home-measured BP value. In this study, a high home HR value was associated with a high risk of CVD, even in normotensive individuals. Moreover, subjects with high home-measured values of both BP and HR showed an extremely high risk of CVD. The HR values obtained at home should be considered just as important as home BP values.

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Patient characteristics and factors associated with inter-arm difference of blood pressure measurements in a general population in Ohasama, Japan

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Objectives **To assess whether there is a natural difference in blood pressure (BP) measurements between the right and left arms, and to identify what factors are associated with this difference in a general population.**

Methods **The study subjects were 1090 individuals who participated in a medical check-up in Ohasama, Japan. The BP was measured simultaneously in both arms, using an automated device. The inter-arm BP difference was expressed as the relative difference [right-arm BP (R) minus left-arm BP (L): R − L] and the absolute difference (|R − L|). The relationship between inter-arm difference and various factors was analyzed using univariate analysis. The characteristics of subjects in whom the absolute systolic BP (SBP) difference was greater than 10 mmHg were analyzed using multivariate logistic analysis.**

Results **The relative differences in SBP and diastolic BP (DBP) were −0.6 ± 6.6 (mean ± SD) and 1.1 ± 4.7 mmHg, while the absolute differences were 4.9 ± 4.4 and 3.7 ± 3.0 mmHg. The absolute SBP difference was found to correlate significantly with age, body mass index, ankle–brachial index (ABI), and hypertension. Subjects with hypertension, hypercholesterolemia, obesity, elevated hemoglobin A_{1c} (HbA_{1c}) and low ABI had a significant and independent increase in the risk of an absolute SBP difference greater than 10 mmHg.**

Conclusions **The results suggest that there is considerable difference in the measured BP in the right and left arms and that large differences in the absolute SBP are associated with risk factors for arteriosclerosis such as hypertension, hypercholesterolemia, obesity, metabolic abnormalities and low ABI.** *J Hypertens* **22:2277–2283 © 2004 Lippincott Williams & Wilkins.**

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Introduction

In the European Society of Hypertension–European Society of Cardiology guidelines for the management of hypertension, it is recommended that the blood pressure (BP) be measured in both arms at the first visit, and the arm with the higher values be used [1]. In previous studies it has been shown that aneurysm [2], syphilitic aortitis [3], coarctation [4,5] and aortitis syndrome (Takayasu's disease) [6] can lead to an inter-arm BP difference. Other authors have reported that inter-arm BP differences can be observed in patients with no apparent unilateral pathologic changes in the arteries [2,7,8], as well as in a large proportion of apparently healthy individuals [3,9,10]. In addition, the incidence and the magnitude of this BP imbalance are increased in hypertensive subjects [2]. These studies were based on considerably different patient populations and methodology. In order to accurately evaluate a BP difference between the two arms, it is necessary to measure the BP simultaneously, using the same measuring device. However, in some of these previous studies the measurement of BP was not standardized and was performed by various observers using different sphygmomanometers. Therefore it remains unclear whether there is true inter-arm BP difference in a general population. In this study we have examined the distribution of inter-arm BP difference in a general population, using an automated device that can record the BP in both arms simultaneously. We have also assessed the factors that are associated with inter-arm difference.

Methods

Study subjects

The study population comprised 1090 subjects who were participating in a medical check-up for arterio-

sclerosis. Subjects were excluded if they had thoracic aortic dissection, aneurysm, syphilitic aortitis, coarctation or aortal syndrome (Takayasu's disease). The study was conducted in Ohasama, Japan, and the geographic and demographic characteristics of the Ohasama population have been reported previously [11–13].

Blood pressure measurement

A casual BP reading was measured twice in a sitting position after a 2-min rest, using an automated cuff-oscillometric device (Omron HEM-907; Omron Life Science, Kyoto, Japan).

With subjects in a supine position, simultaneous BP measurements in all four limbs were recorded using an automatic device (Form PWV/ABI; Colin Co. Ltd., Komaki, Japan). This device can measure the electrocardiogram, phonocardiogram, ABI and pulse wave velocity (PWV) as well as the BP, and is based on the cuff-oscillometric method. It utilizes four cuffs that are wrapped on the upper arms and the ankles, and it can measure the BP simultaneously in all four limbs. The use of this device has been validated previously [14].

Data collection

Informed consent was obtained from all subjects. Trained public health nurses interviewed the subjects and collected data on current smoking habits, hypercholesterolemia, diabetes and previous history of cardiovascular disease. Blood samples were taken and the levels of plasma cholesterol, high-density lipoprotein cholesterol (HDL cholesterol), hemoglobin A_{1c} (HbA_{1c}) and serum creatinine were measured.

Definition of the inter-arm blood pressure difference

An inter-arm BP difference was expressed as both the relative difference and the absolute difference, and these differences were determined for each subject. The relative BP difference was calculated by subtracting the left-arm BP (L) from the right-arm BP (R), i.e. R minus L (R – L). We also calculated the absolute BP difference as the absolute value of R – L (|R – L|) to investigate the difference in BP between the right and left arms regardless of which arm showed the higher BP value. Where the absolute inter-arm SBP difference was greater than 10 mmHg, this was defined as an abnormal inter-arm BP difference [15].

Statistical analysis

The Student's *t*-test was used to compare the continuous variables in the two groups, and the χ^2-test was used to compare the categorical variables. The correlation between the BP in the right and left arms was evaluated using a correlation coefficient, and the variability in inter-arm difference was analyzed using Bland–Altman plots [16]. The relationship between the absolute BP difference and potentially related variables, such as age, gender, body height, body weight, body mass index (BMI), current smoking status, SBP, DBP, mean arterial pressure (MAP), pulse pressure (PP), total cholesterol, HDL cholesterol, serum creatinine, HbA_{1c}, ankle–brachial index (ABI), hypertension (SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg, or use of antihypertensive drugs), diabetes (fasting blood glucose $\geq$ 126 mg/dl or postprandial glucose $\geq$ 200 mg/dl, or medication for diabetes), hypercholesterolemia (total plasma cholesterol $\geq$ 240 mg/dl or medication for hyperlipidemia) and a previous history of cardiovascular disease, was also assessed using univariate analysis. Multiple stepwise logistic regression analysis was used to clarify the relevant importance of factors that might be associated with an abnormal inter-arm BP difference. In subjects where the inter-arm SBP difference was greater than 10 mmHg, the adjusted-odds ratio (OR) and 95% confidence intervals (CI) were calculated for a number of possibly independent categorical variables, including age, defined as young and middle age (< 65 years old) or elderly ($\geq$ 65 years old); gender; the presence of obesity (BMI $\geq$ 25 kg/m^2); the presence of a smoking history; low ($\leq$ 1.0) or normal (> 1.0) ABI; normal (< 5.8%) or raised ($\geq$ 5.8%) HbA_{1c}; the presence of hypertension; the presence of diabetes; the presence of hypercholesterolemia; or a previous history of cardiovascular disease. All the statistical analyses were performed using SPSS software version 11.0 (SPSS Inc., Chicago, Illinois, USA). Data are expressed as mean ± SD. Differences were considered to be statistically significant where $P < 0.05$.

Results

The clinical characteristics of the subjects are shown in Table 1. The mean age was 62.4 ± 11.1 years (range 34–88); 51 subjects were younger than 40 years, 112 subjects between 40 and 49 years, 200 between 50 and 59 years, 432 between 60 and 69 years, 256 between 70 and 79 years, and 39 were aged 80 years or older.

The relative BP difference

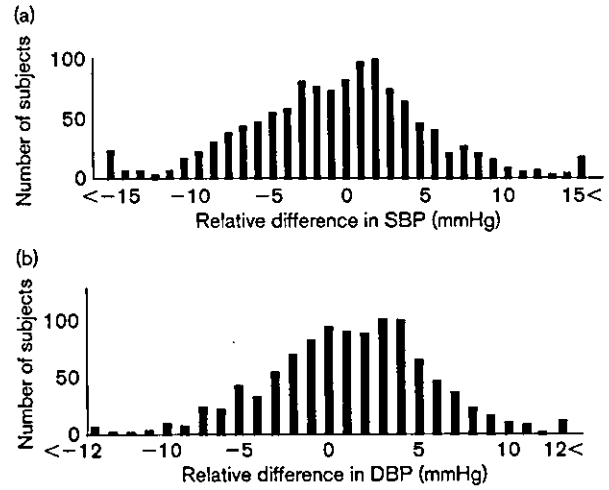
When measured with the subject in a supine position, the mean SBP/DBP readings in the right arm were 143.4 ± 20.3/84.9 ± 10.3 mmHg. In the left arm these measurements were 143.9 ± 20.1/83.8 ± 11.1 mmHg. Overall, the relative SBP difference was −0.6 ± 6.6 mmHg, with the SBP in the right arm being slightly but significantly lower than that in the left. The relative DBP difference was 1.1 ± 4.7 mmHg, with the DBP in the right arm being significantly higher than in the left. The mean right and left pulse pressures (PP) were 58.5 ± 13.6 and 60.1 ± 13.2 mmHg, respectively. The relative inter-arm difference in PP was −1.6 ± 6.4 mmHg, with the right PP being significantly lower than in the left. The distribution of these relative differences is shown in Figure 1. In 45.1% of the subjects the right SBP was higher than in the left, in

Table 1 The clinical characteristics of the subjects

	Male ($n = 388$)	Female ($n = 702$)	Total ($n = 1090$)
Age (years)	63.2 ± 11.5	62.0 ± 10.9	62.4 ± 11.1
BMI (kg/m^2)	24.0 ± 2.9	24.1 ± 3.4	24.0 ± 3.2
Total cholesterol (mg/dl)	193.3 ± 32.3	208.0 ± 32.0***	202.7 ± 32.8
HDL cholesterol (mg/dl)	57.5 ± 16.5	62.4 ± 14.8***	60.6 ± 15.6
HbA_{1c} (%)	5.1 ± 0.78	5.0 ± 0.7	5.1 ± 0.7
Serum creatinine (mg/dl)	0.8 ± 0.2	0.6 ± 0.1***	0.7 ± 0.2
Casual SBP (mmHg)	138.6 ± 17.2	134.2 ± 20.1**	135.4 ± 19.2
Casual DBP (mmHg)	76.3 ± 11.1	73.9 ± 11.0**	74.8 ± 11.1
Casual PP (mmHg)	61.3 ± 13.4	60.3 ± 14.9	60.6 ± 14.4
Casual HR (bpm)	71.8 ± 13.6	74.8 ± 11.0***	73.7 ± 12.0
Right ABI	1.10 ± 0.09	1.10 ± 0.08	1.10 ± 0.08
Left ABI	1.11 ± 0.09	1.09 ± 0.08***	1.10 ± 0.08
Smoking (%)	35.1	2.6***	14.1
Hypertension (%)	54.0	48.0	50.1
Hypercholesterolemia (%)	9.3	22.6***	17.9
Diabetes (%)	8.8	6.1	7.1
Previous history of CVD (%)	6.4	4.3	5.0

BMI, body mass index; HDL, high-density lipoprotein; HbA_{1c}, hemoglobin A_{1c}; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate; bpm, beats per minute; ABI, ankle–brachial index; CVD, cardiovascular disease; $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$.

Fig. 1



Relative differences in (a) systolic blood pressure (SBP) and (b) diastolic blood pressue (DBP) in 1090 subjects.

48.2% it was lower than in the left, and in the remaining 6.7% of subjects the SBP was the same in both arms. In 56.8% of the subjects the right DBP was higher than in the left, in 34.3% it was lower than in the left, and in the remaining 8.9% of subjects there was no difference between the two arms. There was a high degree of correlation between the measured value of both the SBP and the DBP in the right and left arms, and this was statistically significant ($r = 0.95$ for SBP, $r = 0.91$ for DBP). The Bland–Altman plots showed considerable inter-individual difference, with this variability being greater in the SBP than in the DBP (mean ± 2SD: −0.6 ± 13.2 mmHg for SBP; 1.1 ± 9.4 mmHg for DBP). On a univariate analysis, the relative difference in the SBP and DBP were shown to be significantly and negatively correlated with BMI ($P = 0.005$ for SBP, $P = 0.001$ for DBP), but not with age, total cholesterol, HDL cholesterol, serum creatinine or HbA_{1c}.

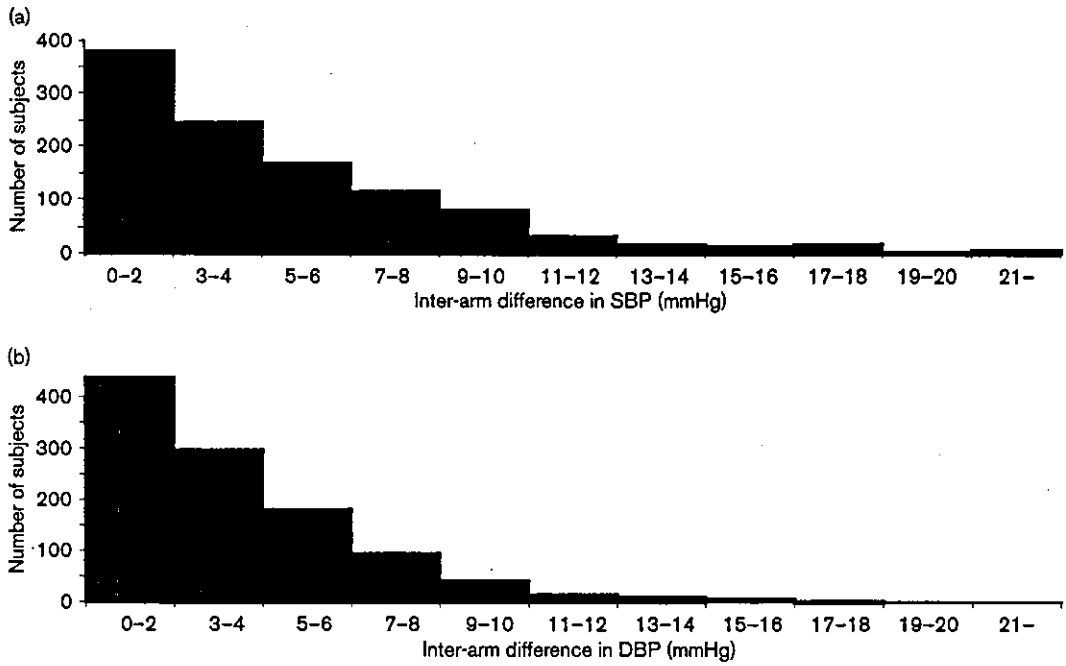
The absolute BP difference

The absolute inter-arm difference in the SBP was 4.9 ± 4.4 mmHg and 3.7 ± 3.0 mmHg for DBP. In 9.1% of the subjects the absolute inter-arm SBP difference was greater than 10 mmHg (Fig. 2). On a univariate analysis the absolute SBP difference was found to be significantly and positively correlated with age, weight, BMI, total cholesterol and SBP, and negatively correlated with ABI (Table 2). Hypertensive subjects ($n = 546$) had a significantly greater inter-arm SBP difference than normotensive subjects ($n = 544$, Table 3). Subjects with a previous history of cardiovascular disease also had a greater inter-arm SBP difference. However, no correlation was found between these characteristics and the inter-arm DBP difference. On the basis of multivariate logistic regression analysis, hypertension, hypercholesterolemia, obesity (BMI ≥ 25 kg/m^2), elevated HbA_{1c} (≥ 5.8%) and low ABI (≤ 1.0) were found to be significant and independent risk factors for an abnormal inter-arm SBP difference (> 10 mmHg) (Table 4).

Discussion

The present study, performed in a general population, has shown that there is a difference between the BP measured in the right and left arms, and that a large absolute inter-arm SBP difference is associated with risk factors for arteriosclerosis, such as hypertension, hypercholesterolemia, obesity, metabolic abnormalities and low ABI.

Fig. 2



Inter-arm differences in (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) in 1090 subjects.

Table 2 The correlation coefficients between the absolute inter-arm blood pressure difference and various parameters

	SBP |R – L|		DBP |R – L|	
	r	*P*	*r*	*P*
Age (years)	0.069	0.022*	−0.024	0.422
Body height (cm)	−0.038	0.207	< 0.001	0.988
Weight (kg)	0.066	0.028*	−0.013	0.665
BMI (kg/m^2)	0.119	< 0.001***	−0.022	0.477
Total cholesterol (mg/dl)	0.063	0.038*	−0.015	0.630
HDL cholesterol (mg/dl)	−0.036	0.238	−0.032	0.291
HbA_{1c} (%)	0.015	0.614	0.029	0.340
Serum creatinine (mg/dl)	0.016	0.605	−0.009	0.759
Mean SBP (mmHg)	0.177	< 0.001***	0.100	0.001**
Mean DBP (mmHg)	0.120	< 0.001***	0.019	0.532
Mean MAP (mmHg)	0.160	< 0.001***	0.890	0.003**
Mean PP (mmHg)	0.174	< 0.001***	0.137	< 0.001***
Right ABI	−0.217	< 0.001***	0.012	0.688
Left ABI	−0.226	< 0.001***	0.002	0.951

|R – L|, absolute difference; *r*, Pearson correlation coefficient; MAP, mean arterial pressure.
Mean SBP (DBP, MAP, PP), the average value of right SBP (DBP, MAP, PP) and left SBP (DBP, MAP, PP).
Other abbreviations are as defined in Table 1. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

A previous study [17] has demonstrated that a relative inter-arm BP difference is unrelated to age, gender, ethnicity, arm circumference, handedness, hypertension, diabetes or previous history of cardiovascular disease. The results of this present study are consistent with those of previous studies in that relative BP differences were unrelated to age, gender, hypercholesterolemia or diabetes. In previous studies, the relative SBP/DBP differences, as measured by an indirect method, were 0.5/−1.3 mmHg [18], 1.3/−1.1 mmHg [19], 1.1/0 mmHg [20], and 1.8/−0.2 mmHg [17]. In these studies, the SBP was slightly higher and the DBP was slightly lower in the right arm when compared with the left arm (Table 5). By contrast, in our study we have found that the relative difference was −0.6/1.1 mmHg, with the SBP being slightly lower and the DBP higher in the right arm when compared with the left. This result is similar to that reported from a study

Table 3 Univariate analysis of the absolute inter-arm blood pressure difference

	SBP |R − L|	*P*	DBP |R − L|	*P*
Gender				
male	4.89 ± 4.13	0.917	3.70 ± 2.93	0.739
female	4.92 ± 4.50		3.76 ± 3.07	
Smoking				
(+)	4.58 ± 3.43	0.305	3.53 ± 3.14	0.344
(−)	4.97 ± 4.50		3.77 ± 3.00	
Hypertension				
(+)	5.29 ± 4.67	0.004**	3.69 ± 3.02	0.620
(−)	4.53 ± 4.02		3.78 ± 3.03	
Hypercholesterolemia				
(+)	5.46 ± 4.65	0.053	3.88 ± 3.41	0.467
(−)	4.79 ± 4.30		3.71 ± 2.93	
Diabetes				
(+)	5.61 ± 4.84	0.146	3.74 ± 2.70	0.998
(−)	4.86 ± 4.33		3.74 ± 3.05	
Previous history of CVD				
(+)	6.23 ± 6.56	0.043*	3.93 ± 3.32	0.673
(−)	4.86 ± 4.25		3.73 ± 3.01	

|R − L|, absolute difference; (+), yes; (−), no; CVD, cardiovascular disease; $^{**}P < 0.01$, $^{*}P < 0.05$.

Table 4 Multiple stepwise logistic regression analysis

	Odds ratio (95%CI)	*P*
Hypertension	2.19 (1.37–3.48)	0.001
Obesity	1.90 (1.22–2.94)	0.004
ABI ⩽ 1.0	3.85 (2.28–6.49)	< 0.001
HbA_{1c} ⩾ 5.8%	2.00 (1.03–3.87)	0.039
Hypercholesterolemia	1.79 (1.10–2.91)	0.019

Factors excluded from the model were: age, gender, smoking, diabetes and previous history of cardiovascular disease.

by Harrison *et al.* [18] (−0.3/0.4 mmHg) in which the relative difference was evaluated using simultaneous and direct intra-arterial BP measurements. In our present study, the BP measurements were synchronized in both arms using an automatic device, and it is likely that this more accurately reflects the real inter-arm BP difference, since previous studies have been based on non-simultaneous BP measurement by a number of different observers using varied sphygmomanometers. The reason why there is a BP difference between the right and the left arms remains unclear. However, it seems unlikely that this relative BP difference has much clinical significance in the general population. As shown in Figure 1, the distribution as to which arm had the higher pressure is bell-shaped, and the mean difference is very small for the overall population. The clinical relevance of this is that clinicians must determine which is the higher-pressure arm, and then use this arm to obtain readings for each individual subject.

On the other hand, the absolute inter-arm BP difference was larger than the relative difference. If an assessment of hypertension is made on the basis of a measurement in the right or left arm alone, a large difference in the absolute BP between the two arms

Table 5 Summary of previous studies on differences in inter-arm blood pressure

Year	1940	1960		1985	1993	1998		1999	2001	2002	2004
Reference	[9]	[18]		[19]	[21]	[22]		[20]	[28]	[17]	our study
Number of subjects	102	447	53	91	80	300	310	462	273	400	1090
Character of subjects	NA	Clinical PT		HT	In-PT and out-PT	Emergency-room PT		Ward visitor, PT, workforce	PT	Staff, PT	General population
Mean age (years) ± SD	NA	48 ± 14.4	NA	50	31 (young) 74 (elderly)	35		NA	NA	56.3 ± 19.7	62.4 ± 11.1
Number of readings	48	3	NA	8	8	1	1	4	1	2	1
Method	NA	M (indirect)	direct	M	AT (Spacelabs 90207)	AT	AT	AT	M	AT	AT
*Observers/devices (*n*)	3	2	NA	2	NA	1 (sequential)	2	2	1 (sequential)	2	1 (simultaneous)
Right SBP (mmHg)	NA	168	179	NA	125.8 148.4	NA	NA	134	NA	131.2	143.4
Left SBP (mmHg)	NA	167	179	NA	125.5 149.2	NA	NA	133	NA	129.4	143.9
Right DBP (mmHg)	NA	98	91	NA	77.7 83.9	NA	NA	74	NA	76.8	84.9
Left DBP (mmHg)	NA	99	90	NA	77.8 84.6	NA	NA	74	NA	77.1	83.8
|R − L| in SBP (mmHg)	3.1	NA	NA	NA	3.3 4.2	10.7	10.4	NA	NA	6.3	4.9
|R − L| in DBP (mmHg)	1.5	NA	NA	NA	2.7 3.6	8.5	6.7	NA	NA	5.1	3.7
R − L in SBP (mmHg)	1.8	0.5	−0.3	1.3	NA NA	NA	NA	1.1	4.8	1.8	−0.6
R − L in DBP (mmHg)	0.4	−1.3	0.4	−1.1	NA NA	NA	NA	0	3.7	−0.2	1.1
SBP > 10 mmHg (%)	NA	5.3	6	0	0 10	41.7	38.7	NA	NA	20	9.1

|R−L|, absolute difference; R−L, relative difference; NA, not available or not applicable; HT, hypertensive patients; PT, patients; M, manual (mercury sphygmomanometer); AT, automatic; * the number of observers for manual sphygmomanometric measurements or the number of devices for automatic measurements; SBP, systolic blood pressure; DBP, diastolic blood pressure.

could significantly affect diagnostic accuracy, particularly if a subject has borderline hypertension. For this reason, it is important to consider the clinical implications of the absolute inter-arm difference in an individual patient. Previous studies have demonstrated that age is the only significant predictor for an absolute difference in both SBP and DBP [21]. In this present study we have found that the absolute difference in the SBP was significantly associated not only with age but also with BMI, total cholesterol and ABI. The inter-arm SBP difference was also significantly increased in subjects with hypertension or a previous history of cardiovascular disease.

In this study the prevalence of an abnormally large inter-arm difference was lower than in previous studies [17,22]. The difference between current and previous findings could be due to differences in methodology. For example, in our study the BP determination in both arms was synchronized using an automatic device, whereas in some previous studies the BP measurement was made by a number of observers using various sphygmomanometers. Another reason might be differences in study populations. For example, our subjects were from the general Japanese population, whereas the subjects of the study by Singer and Hollander [22] were emergency outpatients. In the current study we have shown that a large inter-arm absolute SBP difference is associated with hypertension, hypercholesterolemia, obesity, metabolic abnormalities and low ABI. Hypertension, hypercholesterolemia, obesity and metabolic abnormalities are widely recognized as risk factors for arteriosclerosis. A low ABI has also been reported to be associated with increased mortality, total cardiovascular disease (CVD), coronary heart disease (CHD), congestive heart failure, symptomatic peripheral arterial disease, and stroke or transient ischemic attack (TIA) in middle-aged adults, and a low ABI level is associated with generalized arteriosclerosis [23–27]. Therefore, there appears to be a link between general atheroma or arteriosclerosis and a large difference in inter-arm absolute BP. An asymmetrical atheromatous narrowing of the subclavian or brachial arteries may be related to a large absolute difference [8].

Based on the results of this present study, we suggest that routine BP measurements should be taken in both upper arms. Specifically, the presence of latent arteriosclerosis should be considered if the absolute SBP difference is greater than 10 mmHg. For this reason, routine measurement of the inter-arm BP difference may provide a simple and effective screening method for arteriosclerosis.

In this present study, BP was not determined using a direct intra-arterial recording but through the use of an indirect cuff-oscillometric method, and the readings were made in a supine position rather than in the more standard seated position. In addition, most of the study subjects were elderly, and the distribution of inter-arm difference may differ in other age groups, such as the young and the middle aged, so the results of this study may not be generalizable to these groups.

In conclusion, we have demonstrated that BP measurements in an individual in a general population vary between the right and the left arms. It is therefore important to measure the BP in both arms, and if an inter-arm BP difference of more than 10 mmHg is found, it may be associated with risk factors for arteriosclerosis. A further prospective study is needed in order to evaluate the applicability of measured absolute differences in the inter-arm BP as a screening tool in the initial assessment of arteriosclerosis.

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Carboxy Terminus of Glucose Transporter 3 Contains an Apical Membrane Targeting Domain

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We previously demonstrated that distinct facilitative glucose transporter isoforms display differential sorting in polarized epithelial cells. In Madin-Darby canine kidney (MDCK) cells, glucose transporter 1 and 2 (GLUT1 and GLUT2) are localized to the basolateral cell surface whereas GLUTs 3 and 5 are targeted to the apical membrane. To explore the molecular mechanisms underlying this asymmetric distribution, we analyzed the targeting of chimeric glucose transporter proteins in MDCK cells. Replacement of the carboxy-terminal cytosolic tail of GLUT1, GLUT2, or GLUT4 with that from GLUT3 resulted in apical targeting. Conversely, a GLUT3 chimera containing the cytosolic carboxy terminus of GLUT2 was sorted to the basolateral membrane. These findings are not attributable to the presence of a basolateral signal in the tails of GLUTs 1, 2, and 4 because the basolateral targeting of GLUT1 was retained in a GLUT1 chimera containing the carboxy terminus of GLUT5. In addition, we were unable to demonstrate the presence of an autonomous basolateral sorting signal in the GLUT1 tail using the low-density lipoprotein receptor as a reporter. By examining the targeting of a series of more defined GLUT1/3 chimeras, we found evidence of an apical targeting signal involving residues 473–484 (DRSGKDGVMEMN) in the carboxy tail. We conclude that the targeting of GLUT3 to the apical cell surface in MDCK cells is regulated by a unique cytosolic sorting motif. (*Molecular Endocrinology* 18: 339–349, 2004)

THE DELIVERY SYSTEM for the targeting of membrane proteins to different cell surfaces in polarized cells has been a subject of considerable interest. Many studies have concentrated on identifying the determinants of basolateral and apical sorting signals at the molecular level (1, 2). A number of basolateral sorting signals described to date have been found to reside in the cytoplasmic domain of membrane proteins (3, 4). Most belong to two classes characterized by either a critical tyrosine-containing motif (YXXØ) (5) or a dileucine or leucine residue adjacent to another bulky hydrophobic amino acid (a.a.) (6, 7). These signals have been demonstrated to associate with adaptor protein 1 (8) and adaptor protein 2 (9, 10), which regulate clathrin assembly at the trans-Golgi network and the plasma membrane, respectively. These signals appear to mediate both efficient delivery to the basolateral membrane and endocytic recycling. Conversely, most of the apical signals that have been characterized to date are found in luminal or transmembrane domains. Although relatively little is known about apical sorting signals, both N-linked (11, 12) and O-linked glycosylation (13, 14) have been shown to play an important role.

Facilitative hexose transporters constitute a family of integral membrane proteins that mediate the transport of sugars across cellular membranes (15). These isoforms share a high level of a.a. sequence homology, and their predicted three-dimensional structure is conserved. Considerable evidence suggests that they contain 12 transmembrane domains with both the N and C termini located on the cytosolic side (15). Despite these similarities, major differences in intracellular trafficking have been noted between individual GLUTs. These differences are best demonstrated in polarized cell types in which different transporters have been localized to discrete surfaces. Glucose transporter 1 and 2 (GLUT1 and GLUT2) are principally found on the basolateral surface in epithelial cells whereas GLUT3 and GLUT5 are mainly targeted to the apical domain (16–19). Similar results are obtained when these transporter isoforms are transfected into Madin-Darby canine kidney (MDCK) cells indicating that this is a universal feature of these proteins that can be recapitulated in a heterologous system (20). These results also demonstrate that MDCK cells provide a useful model for studying the vectorial membrane trafficking of facilitative hexose transporters.

Abbreviations: a.a., Amino acid(s); GLUT, glucose transporter; LDL-R, low-density lipoprotein receptor; MDCK, Madin-Darby canine kidney.

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The asymmetric distribution of GLUTs in polarized cell types has physiological relevance. For example, with respect to the intestinal absorption of fructose, the apically targeted GLUT5 exhibits a high affinity for fructose [low Michaelis-Menten constant (K_m)] (21), whereas the basolaterally targeted GLUT2 exhibits a high V_{max} for fructose (22). Hence, these two facilitative transporters cooperate to achieve efficient absorption of fructose across the gut epithelium.

The molecular mechanisms by which GLUTs are differentially targeted in polarized cells remain to be clarified. Therefore, we attempted to characterize the structural determinants of GLUTs required for this differential targeting. We have expressed a panel of chimeric transporters utilizing various portions of GLUTs 1–5 in MDCK cells and assessed their differential distribution. Our data show that the carboxy-terminal tail of human (h)GLUT3 contains a dominant apical sorting signal that is capable of rerouting both GLUT1 and GLUT2 from the basolateral to the apical cell surface in MDCK cells.

RESULTS

Expression and Analysis of GLUT1/3 Chimeras in MDCK Cells

To clarify the molecular basis for the differential targeting of GLUTs in polarized epithelial cells, we undertook a chimeric strategy whereby different portions of a basolateral transporter and an apical transporter were spliced together and expressed in MDCK cells. Initially, we focused on hGLUT1 and hGLUT3, which are targeted to the basolateral and apical cell surfaces, respectively, in MDCK cells (20). MDCK cells express GLUT1 endogenously but not GLUT3 (20). Initially, we studied the targeting of recombinant hGLUT1 when overexpressed in MDCK cells. Stable cell lines were selected and screened for hGLUT1 expression using a monoclonal antibody that is specific for hGLUT1 (23). This antibody recognizes an epitope in the central loop of hGLUT1 and provides a useful tool for comparing relative expression levels between individual constructs and clones. To verify that this expression system did not result in marked overexpression, we analyzed the glucose transport activities of these clones. In wild-type cells, we observed glucose transport rates of 0.77 ± 0.16 nmol/mg·min and 0.04 ± 0.06 nmol/mg·min across the basolateral and apical membranes, respectively (n = 5, mean ± SD). The glucose transport rates across the basolateral membranes in GLUT1-expressing cell lines were increased at most by 1.5-fold as compared with that observed in wild-type cells. Moreover, we did not observe a significant change in apical transport in clones expressing GLUT1 at this expression level. On the other hand, in clones expressing GLUT3 over a broad range of expression levels, we observed a highly significant increase in transport across the apical membrane (0.56 ± 0.10 nmol/mg·min). Thus, these data provide a good indication that we have performed our studies using non-saturating expression levels of recombinant transporters. As shown in Fig. 1C (*left upper panel*), at this level of expression the targeting of hGLUT1 was restricted to the basolateral surface as was the case for the endogenous protein. Also shown in Fig. 1C (*right upper panel*) is the distribution of hGLUT3 expressed in MDCK cells. Consistent with our previous findings (20), this protein was highly enriched at the apical cell surface. Whereas these transporters localize to either basolateral or apical membranes, intracellular labeling is also evident. Our focus in this study was the contribution of the cytosolic carboxy terminus to domain-specific cell surface localization and as such we did not characterize the intracellular vesicular compartments through which these chimeras traffic.

The above data provided the basis for our initial studies using hGLUT1/3 chimeras expressed in MDCK cells. We first designed two GLUT1/3 chimeras comprised of different portions of both proteins: hGLUT1/3CT290 contains the N-terminal half of hGLUT1 and the C-terminal half of GLUT3; and hGLUT1/3CT36 is comprised of hGLUT1 in which the carboxy-terminal tail (32 a.a.) has been replaced with that of hGLUT3 (36 a.a.). A scheme of these and other constructs is shown in Fig. 1A. As was the case for all of the constructs described in this study, we selected at least 12 different stable cell lines expressing the recombinant protein of interest and performed detailed analyses on at least three to four different clones for each construct covering a range of expression levels. The targeting of endogenous GLUT1, as well as inulin exclusion, was analyzed in each clone to verify polarity at the time of study (data not shown). Figure 1B shows a Western blot of cell lysates from cells expressing either full-length GLUT3 or the relevant chimeras using an antibody raised against the C-terminal domain of hGLUT3. This antibody did not detect a specific signal in non-transfected MDCK cells, but clearly detected the exogenous hGLUT3 epitope. The chimeras yielded proteins of the appropriate molecular size, *i.e.* similar to that observed for full-length GLUT3. Figure 1C shows the immunolocalization of the hGLUT1/3CT290 (*left lower panel*) and hGLUT1/3CT36 (*right lower panel*) chimeras in MDCK cells as compared with both GLUT1 and GLUT3. Both chimeras were concentrated on the apical domain, similar to the targeting observed for the full-length GLUT3 protein. We also observed labeling of intracellular structures (Fig. 1). This is consistent with our previous studies in which even GLUT1, which is highly concentrated on the basolateral surface (Fig. 1), was also found in intracellular vesicles in MDCK cells (20). These results suggest that the carboxy tails of these transporter proteins determine basolateral *vs.* apical delivery.