Original Article

Factors Affecting Heart Rate as Measured at Home among Treated Hypertensive Patients: The Japan Home *versus* Office Blood Pressure Measurement Evaluation (J-HOME) Study

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We previously reported that a resting heart rate measured at home (home HR) of ≥70 beats per minute was a powerful predictor of the risk of cardiovascular disease mortality, and identified factors affecting home HR in the general Japanese population. The present study examines factors affecting home HR in hypertensive patients treated with antihypertensive medications. Home HR was measured using a home blood pressure (BP) device. Information about the characteristics of the patients was collected using questionnaires administered by a physician. Among 3,400 patients, 3,086 measured home HR both in the morning and evening. The mean values of home HR in the morning and evening were 67.2±9.1 and 69.6±9.2 beats per minute, respectively. Multivariate linear regression analysis showed that lower age, diabetes mellitus, habitual smoking, higher diastolic BP, and the lack of β-blocker or angiotensin-converting enzyme inhibitor use were determinants of elevated morning or evening home HR. These results suggest that adequate control of risk factors for cardiovascular disease such as smoking and diabetes mellitus or use of heart rate–lowering agents might help to decrease home HR in treated hypertensive patients. (*Hypertens Res* 2007; 30: 1051–1057)

***Key Words*: home heart rate, life-style modifications, β-blockers**

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Introduction

Self-measured blood pressure (BP) at home (home BP) and ambulatory BP monitoring have both been proven effective and widely adopted (*1–3*). Home BP measurement eliminates the white coat effect, is highly reproducible and is useful in assessing the effect of antihypertensive strategies (*4*, *5*). Home BP is a more powerful predictor of mortality and morbidity than casual-clinic BP (*6*, *7*). On the other hand, the clinical significance of home measurements of heart rate (home HR) has not yet been elucidated. Resting clinic-casual heart rate (HR) is associated with all-cause and cardiovascular disease mortality in the general population (*8–10*). A previous study found that resting home HR is a powerful predictor of the risk of cardiovascular disease mortality independently of home BP and other possible confounding factors in the general population (*11*). Thus, understanding which factors affecting home HR can be modified might help to prevent cardiovascular disease. We previously identified factors affecting home HR, including lifestyle-related factors, in the general Japanese population (*12*). However, the factors affecting home HR among patients treated with antihypertensive drugs remain unknown.

In the present study, we examined the factors affecting home HR in hypertensive Japanese patients treated with antihypertensive medications in a large-scale, nationwide study.

Methods

Study Population

The Japan Home *versus* Office BP Measurement Evaluation (J-HOME) study was conducted to measure BP control as evaluated by home and office BP measurements among Japanese patients with essential hypertension who were undergoing antihypertensive therapy in primary care settings (*13*, *14*). In March 2003, 7,354 physicians randomly selected from all over Japan were invited to participate in this project. Of the 1,477 who agreed to participate, 751 collected data for the study. By the end of August 2003, 3,586 patients who provided written, informed consent to participate in the study were enrolled. Specific exclusion criteria were not defined. Most doctors (79.3%) enrolled 5 patients or less. The proportions of doctors who enrolled 1 or 2, 3 or 4, 5, 6 or 7, or at least 8 patients were 11.1%, 21.3%, 46.9%, 19.7%, and 0.9%, respectively. Sixty-six patients were excluded since their BP levels were within the normal range when they were not medicated with antihypertensive drugs. A further 120 were excluded since insufficient data on BP values or on patients' characteristics were provided. The study population thus consisted of 3,400 treated patients with essential hypertension. Of those, 306 were excluded because of insufficient morning or evening home HR data and 8 were excluded because of an inadequate number of home HR measurements in the morning or in the evening (*i.e.*, less than 3 measurements). Therefore, the final study population comprised 3,086 patients with complete morning and evening data. The Institutional Review Board of Tohoku University School of Medicine approved the study protocol.

Table 1. Characteristics of the Study Subjects

Characteristics (n=3,086)	
Age (years)	66.1±10.5
Men (%)	44.9
Body mass index (kg/m^2)	23.8±3.3
Morning home BP (mmHg)	
Systolic	139.7±13.9
Diastolic	81.8±9.5
Morning home HR (bpm)	67.2±9.1
Evening home BP (mmHg)	
Systolic	133.5±13.4
Diastolic	76.9±9.2
Evening home HR (bpm)	69.6±9.2
Family history of hypertension (%)	56.7
Family history of cerebrovascular disease (%)	28.0
History of ischemic heart disease (%)	8.5
History of cerebrovascular disease (%)	16.7
Diabetes (%)	13.6
Hypercholesterolemia (%)	40.6
High uric acid (%)	11.4
Renal disease (%)	4.9
Current smoker (%)	13.9
Current drinker (%)	34.7
Antihypertensive medication	
Duration of treatment (months)	29.2±42.5
Number of drugs, mean (n)	1.7±0.9
1 (%)	49.1
2 (%)	34.9
3 (%)	12.4
4 or more (%)	3.6
Class of drugs (including combination therapy) (%)	
Calcium channel blockers	68.9
Amlodipine	38.6
Dyhydropyridine calcium channel blockers except for amlodipine	29.8
Non dihydropyridine calcium channel blockers	1.7
Angiotensin II receptor blockers	43.6
Angiotensin converting enzyme inhibitors	17.0
α-Blockers	13.4
β-Blockers*	15.6
Diuretics	9.1

BP, blood pressure; HR, heart rate; bpm, beats per minute. *Including α,β-blockers.

Table 2. Multivariate Regression Analysis of Factors Affecting Home HR Value

	All subjects (n=3,086)		Men (n=1,386)		Women (n=1,700)	
	Coefficient	p	Coefficient	p	Coefficient	p
Morning variable						
Age (per year)	−0.06	0.0002	−0.09	0.0002	−0.03	0.23
Home diastolic BP (per mmHg)	0.13	<0.0001	0.17	<0.0001	0.11	<0.0001
Smoking (current=1)	2.21	<0.0001	2.77	<0.0001	0.81	0.44
Diabetes (present=1)	1.43	0.002	2.06	0.002	1.01	0.13
Number of drugs (2 or more=1)	−0.42	0.21	−0.27	0.60	−0.50	0.26
β-Blockers (user=1)	−3.92	<0.0001	−3.94	<0.0001	−3.88	<0.0001
r^2	0.07		0.10		0.05	
Evening variable						
Gender (male=0, female=1)	−0.33	0.40				
Age (per year)	−0.05	0.002	−0.15	<0.0001	0.03	0.21
Body mass index (per kg/m^2)	0.09	0.08	0.02	0.78	0.10	0.08
Home diastolic BP (per mmHg)	0.17	<0.0001	0.14	<0.0001	0.20	<0.0001
Smoking (current=1)	2.35	<0.0001	2.41	<0.0001	1.03	0.33
Diabetes (present=1)	1.67	0.0004	1.81	0.008	1.56	0.02
Alcohol consumption (current=1)	0.79	0.053	1.37	0.01	−0.46	0.49
Number of drugs (2 or more=1)	−0.14	0.68	−0.04	0.94	−0.39	0.37
β-Blockers (user=1)	−5.09	<0.0001	−5.54	<0.0001	−4.58	<0.0001
r^2	0.10		0.13		0.09	

BP, blood pressure; HR, heart rate.

Measurement of Home BP and Home HR

The patients used the following procedures specified in the Japanese guidelines for home BP measurements (*15*). They measured their own BP and HR once every morning while seated, within 1 h of waking, after at least 2 min of rest, but before ingesting medications and breakfast, and once every evening just before bedtime and recorded the results for a 2-week period (*15*). The patients applied the cuff-oscillometric method using electronic arm-cuff devices from Omron Healthcare Co. Ltd., (Kyoto, Japan), A&D Co., Ltd., (Tokyo, Japan), Terumo Co. Ltd. (Tokyo, Japan) and Matsushita Electric Works, Ltd. (Osaka, Japan). The Ministry of Health, Labour and Welfare, Japan has validated and approved all such devices available in this country (*16*). The actual models were not described by the doctors who participated in the study, but all devices for measuring BP and HR used in the present study were certified as having been adjusted to the Association for the Advancement of Medical Instrumentation (AAMI) standard (*16*, *17*). The mean of all measurements recorded over the 2-week period was calculated for each patient and further analyzed.

Data Collection and Statistical Analysis

Information about patient characteristics and antihypertensive treatment was collected from a questionnaire administered by the attending physician at the time of patient recruitment. We applied an initial bivariate analysis to determine which factors affected home HR. We then performed a multivariate linear regression analysis including gender and other factors that were significantly associated with home HR in the bivariate analysis. Variables were compared using Pearson's regression analysis, Student's t-test, and the χ^2 test where appropriate. Data are shown as the means±SD. A p value below 0.05 was accepted as indicating statistical significance. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, USA).

Results

Patients

Table 1 shows the characteristics of patients who measured HR (n=3,086). Mean morning and evening home HR were 67.2±9.1 (range: 40–101) and 69.6±9.2 (range: 41–105) beats per minute (bpm), respectively, and approximately 2% and 1% of the patients had relatively low morning and evening home HR (HR <50 bpm), respectively. The mean numbers of morning and evening home HR measurements were 13.3±5.0 and 12.8±5.0, respectively. The SD of home HR was 9 bpm at both times and the coefficient of variation (CV) was 6.6% in the morning and 7.1% in the evening. Of the 3,086 patients who measured HR, 68.9% were taking calcium channel blockers (CCBs), 43.6% angiotensin II receptor blockers (ARBs), 17.0% angiotensin-converting enzyme

Table 3. Effect of Each Antihypertensive Drugs except for β-Blockers on Home HR Value

	Model 1		Model 2	
	Coefficient	*p*	Coefficient	*p*
Morning HR (*n*=3,086)				
Calcium channel blockers (present=1)	−0.24	0.49	−0.48	0.19
Amlodipine	0.01	0.97	—	—
Dyhydropyridine calcium channel blockers except for amlodipine	−0.09	0.80	—	—
Non-dihydropyridine calcium channel blockers	−0.33	0.79	—	—
Angiotensin II receptor blockers (present=1)	−0.30	0.35	−0.61	0.09
Angiotensin converting enzyme inhibitors (present=1)	−0.50	0.24	−0.77	0.09
α-Blockers (present=1)	0.14	0.76	0.17	0.71
Diuretics (present=1)	−0.64	0.25	−0.64	0.24
Evening HR (*n*=3,086)				
Calcium channel blockers (present=1)	−0.14	0.68	−0.20	0.57
Amlodipine	0.13	0.69	—	—
Dyhydropyridine calcium channel blockers except for amlodipine	−0.10	0.78	—	—
Non-dihydropyridine calcium channel blockers	−1.33	0.28	—	—
Angiotensin II receptor blockers (present=1)	0.19	0.55	−0.09	0.80
Angiotensin converting enzyme inhibitors (present=1)	−0.91	0.03	−0.96	0.03
α-Blockers (present=1)	−0.07	0.88	−0.06	0.90
Diuretics (present=1)	−0.10	0.85	−0.08	0.88

HR; heart rate, BP; blood pressure. Model 1: adjusted for age, home diastolic BP, smoking status, diabetes mellitus, β-blockers, and each antihypertensive drug. Model 2: adjusted for age, home diastolic BP, smoking status, diabetes mellitus, β-blockers, and antihypertensive drugs simultaneously.

(ACE) inhibitors, 13.4% α-blockers, 15.6% β-blockers, and 9.1% diuretics. The mean number of antihypertensive drugs was 1.7±0.9. About half of the patients were prescribed more than two antihypertensive agents. The most common treatment regimen was CCBs alone (26.0%), followed by ARBs alone (15.1%), CCBs plus ARBs (14.0%), CCBs plus ACE inhibitors (6.5%), and ACE inhibitors alone (3.9%). The mean duration of the current antihypertensive regimen was 29.2 months.

Bivariate Analysis of Factors Affecting Home HR

We applied a bivariate analysis to determine which factors among age, gender, body mass index (BMI), home BP, smoking, alcohol consumption, and history of complications affect home HR values. Home HR in the morning correlated negatively with age ($r=-0.12$, $p<0.0001$) and positively with morning home diastolic BP ($r=0.16$, $p<0.0001$). Home HR in the morning differed significantly between smokers (69.5±9.9 bpm) and non-smokers (66.8±8.9 bpm, $p<0.0001$), between patients with β-blockers (63.8±8.8 bpm) and those without β-blockers (67.8±9.0 bpm, $p<0.0001$), and between patients administered two or more antihypertensive drugs (66.6±9.5 bpm) and those receiving monotherapy (67.8±8.6 bpm, $p<0.0001$). Home HR in the evening was associated negatively with age ($r=-0.12$, $p=0.0002$) and positively with home diastolic BP in the evening ($r=0.20$, $p<0.0001$) and BMI ($r=0.07$, $p<0.0001$). Home HR in the evening was significantly higher in men (70.4±9.9 bpm), smokers (72.5±9.8 bpm), drinkers (70.9±8.9 bpm), and patients with diabetes mellitus (70.6±9.8 bpm) than in women (69.0±8.5 bpm, $p<0.0001$), non-smokers (69.1±9.0 bpm, $p<0.0001$), non-drinkers (68.9±8.9 bpm, $p<0.0001$), and patients without diabetes mellitus (69.4±9.1 bpm, $p=0.02$), respectively. Compared to patients with β-blockers (65.3±8.8 bpm) or those receiving two or more antihypertensive drugs (69.1±9.5 bpm), patients without β-blockers (70.4±9.1 bpm, $p<0.0001$) or those receiving monotherapy (70.1±8.9 bpm, $p=0.001$), respectively, had significantly lower levels of home HR in the morning and in the evening. Other disease histories were not significantly associated with home HR.

Multivariate Regression Analysis of Factors Affecting Home HR

Table 2 shows the findings from the multivariate regression analysis of factors affecting home HR. Elevated home HR in the morning was significantly associated with lower age, habitual smoking, higher home diastolic BP, presence of diabetes mellitus, and nonuse of β-blockers. Home HR in the evening was also significantly associated with variables similar to those for home HR in the morning. Although gender did not significantly correlate with the home HR of all patients, home HR was significantly associated with age, smoking or alcohol consumption only in men (Table 2). Ele-

vated average of home HR in the morning and in the evening was significantly associated with lower age, higher home diastolic BP, habitual smoking, presence of diabetes mellitus, and nonuse of β-blockers.

Effects of Antihypertensive Medication Except for β-Blockers on Home HR

Multiple linear regression analysis adjusted for age, morning home diastolic BP, smoking status, presence of diabetes mellitus, and use of β-blockers revealed no antihypertensive drugs that were significantly associated with home HR in the morning (Table 3, Model 1 and Model 2). On the other hand, the use of ACE inhibitors was significantly and inversely associated with home HR in the evening (Table 3, Model 1). Because some patients were taking these antihypertensive drugs simultaneously, we included all of these drugs in a multivariate model. The model also showed that the use of ACE inhibitors was inversely and independently associated with home HR in the evening (Table 3, Model 2).

Discussion

We here identified the determinants of elevated home HR among hypertensive Japanese patients medicated with antihypertensive drugs. Elevated home HR in the morning was associated with lower age, habitual smoking, higher morning home diastolic BP, presence of diabetes mellitus, and nonuse of β-blockers. Elevated home HR in the evening was associated with variables similar to those for elevated home HR in the morning, in addition to nonuse of ACE inhibitors. The present study is the first large scale, nationwide study clarifying the factors affecting home HR determined under stable conditions in general hypertensive patients undergoing treatment. Determinants of elevated home HR in the present study were comparable to those in the general population (*12*). Yamaguchi *et al*. demonstrated in the Ohasama study population that lower age ($\beta = -0.08$, $p \leq 0.01$), current smoking ($\beta = 3.22$, $p \leq 0.01$), female gender ($\beta = 2.07$, $p \leq 0.01$) and a sedentary lifestyle (walking < 1 h/day) ($\beta = 2.43$, $p \leq 0.01$) are determinants of elevated morning home HR (*12*).

The present study found that presence of diabetes mellitus was significantly associated with elevated morning and evening home HR. It has been reported that a high HR may be associated with more advanced diabetic retinopathy and insulin resistance (*18*, *19*). These results suggest that a high HR may represent diabetic disorder of the sympathetic nervous system (*20*, *21*). In addition, a high HR could also be considered an indicator of autonomic neuropathy (*22*).

Home HR was significantly associated with smoking or alcohol consumption only in men in the present study. However, this gender difference might be affected by the gender-related differences in the proportion of smokers and drinkers (proportion of smokers and drinkers in men: 26.0% and 63.9%; in women: 4.0% and 11.0%) and in the amount of smoking or alcohol consumption. Therefore, controlling all risk factors is important in both genders, but smoking cessation and alcohol restriction need to be emphasized in men. Kawano *et al*. reported that alcohol restriction lowers HR in hypertensive men ($n = 34$) who habitually consume alcohol. After alcohol restriction, daytime, nighttime, and 24-h HR significantly decreased during the period of reduced alcohol consumption (*23*). Minami *et al*. evaluated the effects of stopping smoking on ambulatory BP and HR in 39 normotensive habitual male smokers. They found that 24-h, daytime HR, and nighttime HR were significantly lower during the nonsmoking than during the smoking period (*24*). These findings together with the present results suggest that lifestyle modifications would help to reduce home HR.

The present study showed that home HR was significantly lower in patients taking β-blockers than in those who were not. A recent meta-analysis has suggested that β-blockers should not remain a first treatment choice for primary hypertension (*25–27*). In response, the British Hypertension Society (BHS) recommend re-appraisal of the role of β-blockers (*28*). Two prospective, randomized and double-blind trials with β-blockers have shown that a reduction in HR brings about a reduction in mortality among patients after myocardial infarction (*29*, *30*). Further trials targeting HR are necessary to clarify whether reducing HR also benefits hypertensive patients. In the present study, the use of ACE inhibitors was found to be a factor decreasing evening home HR. It is possible that this result was attributable to the decrease in plasma norepinephrine concentration caused by chronic administration of ACE inhibitors, as reported in previous studies (*31–33*). However, because of the cross-sectional design of the present study, the causality of this association remains to be investigated.

Although the relationship between casual-clinic HR and mortality has been investigated in several studies (*34–38*), the relationship between home HR and cardiovascular disease mortality was examined only in the Ohasama study (*11*). The results suggested that a resting home HR (obtained using a self-monitored BP measuring device) of ≥70 bpm is associated with a higher risk of cardiovascular disease mortality than a home HR < 70 bpm (*11*). However, a treatment goal for home and casual-clinic HR levels has not been established, and must await the results of large-scale intervention studies.

Several possible limitations are associated with the present study. First, we did not collect information about physical fitness. One population-based study has shown that walking frequency is negatively associated with home HR (*12*). Thus the possibility cannot be excluded that some factors found in the present study were confounded by the effect of exercise on home HR. In addition, we did not have information about the amount of alcohol consumed. The effect of alcohol consumption on HR might not be linear, since a small amount of alcohol might have a relaxing effect. We also did not collect information about caffeine consumption, an important variable affecting home HR. However, we previously found no

association between green tea or coffee consumption and home HR in the general population (*12*). Thus, tea consumption might not have substantially altered the present findings. Hemodynamic parameters apparently differ among those who never, previously, and currently smoke. However, our information about smoking was limited to a questionnaire item asking whether the respondent was a "current-" or "non-" smoker, with the latter category including both "never-" and "ex-" smokers. Thus we could not precisely analyze the effect of smoking status. We also did not collect information on airway disease and did not estimate stress or anxiety, although bronchodilators and psychological issues might increase HR. Our study lacked data about biochemical parameters such as catecholamine levels, and the r^2 values in the multiple regression analyses were relatively small. Because of these limitations, further studies will be needed to detect other unmeasured or unknown factors that could affect home HR in hypertensive patients receiving antihypertensive drugs.

In conclusion, the present results suggest that adequate control of risk factors for cardiovascular disease such as smoking and diabetes mellitus or the use of HR-lowering agents might help to decrease home HR among treated hypertensive patients.

Appendix

This study was designed, conducted, and interpreted by the J-HOME study group, independently of the sponsors.

Members of the J-HOME Study Group

Principal Investigator: Yutaka Imai.
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All names of participating practitioners have been previously mentioned (*13*).

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