Higher Heart Rate Predicts the Risk of Developing Hypertension in a Normotensive Screened Cohort

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Background A higher heart rate (HR) is associated with cardiovascular morbidity and mortality. Hypertension is an important cardiovascular risk factor. The present study evaluated whether a higher HR was associated with the development of hypertension in normotensive, screened subjects.

Methods and Results Among normotensive participants of a 1-day health evaluation in 1997, we studied those who also participated in the program in 2000 (n=4,331; 2,823 men (65%), 1,508 women; mean age 47±9 years). Subjects were divided into 4 groups based on their HR in 1997: quartile 1 (HR ≤58, n=1,033), quartile 2 (59≤ HR ≤64, n=1,162), quartile 3 (65≤ HR ≤70, n=1,012), and quartile 4 (HR ≥71, n=1,124). The 3-year frequency of developing hypertension in 2000 was 4.5% for quartile 1, 6.8% for quartile 2, 6.0% for quartile 3, and 7.2% for quartile 4 (p=0.0424). Subjects with a higher HR were likely to have a greater number of metabolic syndrome components and a higher incidence of proteinuria. In a logistic regression analysis adjusted for gender, age, alcohol consumption, exercise, atherosclerotic risk factors, and lifestyle, the odds ratios (95% confidence intervals) for the development of hypertension were 1.53 (1.04–2.24) for quartile 2, 1.35 (0.90–2.02) for quartile 3, and 1.61 (1.10–2.37) for quartile 4, compared with quartile 1 as a reference.

Conclusion A higher HR was associated with the development of hypertension. Subjects with a higher HR should be followed carefully, even if they are normotensive. (Circ J 2007; 71: 1755–1760)

Key Words: Epidemiology; Heart rate; Hypertension; Screening

Hypertension is the most prevalent disorder that affects a vast majority of adults in Japan and is an important risk factor for myocardial infarction and cerebrovascular disease. Among the metabolic syndrome components, hypertension is the strongest predictor for cardiovascular events or carotid atherosclerosis. Moreover, high blood pressure (BP) is a useful predictor for excess medical costs. Therefore, the prevention of hypertension is an important public health issue. Patients with prehypertension are at an increased risk for progression to hypertension over a short period; those with a BP ranging 130–139/80–89 mmHg (systolic/diastolic) have twice the risk of developing hypertension as those with lower values. Accordingly, identifying subjects with a high risk of developing hypertension will enable us to better target cost-effective interventions.

The heart rate (HR) is easily obtained biologic information that requires no special instruments or techniques, in contrast to other recently developed biometric techniques. As HR fluctuates according to the method of measurement or condition, HR is an unreliable biometric marker to use for epidemiologic research. Furthermore, the significance of a higher HR tends to be underestimated in the clinical setting. Nonetheless, some studies report an association between HR and cardiovascular morbidity or mortality and all causes of mortality. A few studies report that HR is a predictor of developing hypertension.

We hypothesized that a high resting HR predicts the development of hypertension or BP progression, even after adjusting for risk factors such as metabolic syndrome or proteinuria. The aim of the present study was to evaluate whether a high HR predicts the development of hypertension and BP progression over a short period in normotensive, screened subjects.

Methods

Subjects

This was a retrospective longitudinal study. The subjects were the participants of a 1-day health evaluation held by the Okinawa General Health Maintenance Association (OGHMA), which is one of the largest screening centers in Okinawa, Japan. The OGHMA offers a 1-day health evaluation program throughout the year. This program provides thorough anthropometric measurements, a physical examination, laboratory tests and electrocardiography, both for individuals and health maintenance programs of companies and public organizations.

Of 9,914 participants in the health screening program in 1997, 5,923 participated in this program in 2000. In the present analysis, 1,592 participants were excluded for the following reasons: prevalent hypertension (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg), or use of anti-hypertensive medications; n=1,408), no electrocardiogram (ECG) recording, or a record of ectopic beats or atrial fibrillation (n=780) or heart disease (history of heart disease or the use of medication for heart disease; n=46). Particip-
pants with heart disease were excluded because the HR is directly affected by cardiac function or cardiac drugs. After the aforementioned exclusions, 4,331 participants (2,283 men and 1,058 women) remained eligible for the present analysis.

The subjects were divided into 4 groups for statistical analysis according to their initial HR. Quartile ranges for HR were as follows: quartile 1 (HR \( \leq 58 \) beats/min, \( n = 1,033 \)); quartile 2 (59 \( \leq \) HR \( \leq 64 \), \( n = 1,162 \)); quartile 3 (65 \( \leq \) HR \( \leq 70 \), \( n = 1,012 \)); and quartile 4 (HR \( \geq 71 \), \( n = 1,124 \)). Fujiura et al indicated in their population-based study that subjects with a HR greater than 90 beats/min had a significantly high mortality risk. Accordingly, we made an additional analysis indicating in their population-based study that subjects with a HR greater than 90 beats/min had a significantly high mortality risk. Accordingly, we made an additional analysis.

The present study was conducted in accordance with the principles of the Declaration of Helsinki 1975, as revised in 1993. Data for the present study were provided after approval from the ethics committee of the OGHMA. All data concerning privacy of the screened subjects were excluded from the original registry.

**Data Collection**

Individual histories of hypertension, diabetes mellitus, hyperlipidemia, smoking habits, alcohol consumption habits, and exercise habits were determined by self-administered questionnaires and confirmed by a physician’s interview. Data for the lifestyle-related factors were based on self-administered questionnaires collected in 1997. Blood sampling was performed after overnight fasting. Trained nurses measured systolic and diastolic BP twice, using a standard sphygmomanometer with an appropriate-sized cuff after the subject sat quietly for 15 min. In the present study, the lower BP value was used. Body mass index (BMI) was calculated as body weight (kg) divided by the height squared (m²). Obesity was defined as BMI \( \geq 25.0 \) kg/m². High BP was defined as systolic BP \( \geq 130 \) mmHg and/or diastolic BP \( \geq 85 \) mmHg. Hyperglycemia was defined as fasting blood glucose concentration \( \geq 110 \) mg/dl. Dyslipidemia was defined as serum triglyceride \( \geq 150 \) mg/dl and/or high-density lipoprotein-cholesterol (HDL-C) \( < 40 \) mg/dl. Obese subjects with 2 or more of the components described above were defined as having metabolic syndrome. As there was no waist circumference data, we used BMI instead of waist circumference for the definition of obesity. BMI correlated well with waist circumference for both genders. Proteinuria was defined as (+) or over using a dipstick. An ECG was recorded after the patient had been lying supine for 2 min. The HR was calculated from a 5-s average RR interval from the ECG recording.

**BP Outcomes on Follow-up**

We examined the relation of HR to 2 BP outcomes on follow-up: hypertension, defined as a systolic BP \( \geq 140 \) mmHg, diastolic BP \( \geq 90 \) mmHg; BP progression, defined as an increase in BP category on follow-up. For this purpose, participants without hypertension were assigned to 1 of 3 BP categories at baseline: (1) optimal; systolic BP \(< 120 \) mmHg and a diastolic BP of 80–84 mmHg; (2) normal; systolic BP 120–129 mmHg or diastolic BP 80–84 mmHg; and (3) high normal; systolic BP 130–139 mmHg or diastolic BP 85–89 mmHg.

**Statistical Methods**

We used multivariable logistic regression analysis to examine the association between HR and the risk of developing hypertension and BP progression. Odds ratios (ORs) and 95% confidence intervals (CI) were computed for incre-

**Table 1** Baseline Characteristics by HR Quartile

<table>
<thead>
<tr>
<th>HR quartile</th>
<th>Quartile 1 (n=1,033)</th>
<th>Quartile 2 (n=1,162)</th>
<th>Quartile 3 (n=1,012)</th>
<th>Quartile 4 (n=1,124)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 (9)</td>
<td>47 (9)</td>
<td>47 (9)</td>
<td>47 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73</td>
<td>64</td>
<td>64</td>
<td>60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>113 (11)</td>
<td>115 (11)</td>
<td>115 (11)</td>
<td>117 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 (8)</td>
<td>71 (8)</td>
<td>72 (8)</td>
<td>73 (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High normal</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 (2.7)</td>
<td>23.9 (2.9)</td>
<td>23.9 (3.0)</td>
<td>23.9 (3.2)</td>
<td>0.0034</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>202 (34)</td>
<td>205 (35)</td>
<td>206 (36)</td>
<td>207 (36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>57 (14)</td>
<td>56 (15)</td>
<td>56 (14)</td>
<td>55 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>129 (117)</td>
<td>130 (98)</td>
<td>148 (125)</td>
<td>151 (116)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>98 (11)</td>
<td>100 (14)</td>
<td>100 (15)</td>
<td>104 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of hypertension (%)</td>
<td>23</td>
<td>19</td>
<td>22</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CVD (%)</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are the mean ± SD or percentage. Screening was done during April 1997 to March 1998.

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; CVD, cerebrovascular disease.
ments of change in each category (i.e., for categorical variables). We used 2 logistic regression models to assess the OR and 95% CI for developing hypertension and BP progression; a model adjusted for age, gender, current smoking, current alcohol, and current exercise habits (Model 1); and a model adjusted for age, gender, smoking, alcohol consumption, exercise, metabolic syndrome, and proteinuria (Model 2). All analyses were performed with StatView 5.0 (SAS Institute, Cary, NC, USA). We used 1-factor ANOVA or chi-square test to analyze the association between HR and BP values. Two-tailed probability values of less than 0.05 were considered statistically significant.

Results

In 1997, the average HR of this cohort was 65±10 beats/min (Fig.1). The baseline characteristics of the study’s subjects categorized by initial HR are summarized in Table 1. Those subjects with a higher HR had significantly higher levels of systolic and diastolic BP, BMI, triglyceride, fasting blood glucose; higher frequencies of proteinuria and metabolic syndrome; and lower frequencies of males, current alcohol consumption, and habitual exercise. Age, HDL-C level, and incidence of current smoking habit were not associated with HR. Those subjects with a higher HR had a greater number of metabolic syndrome components (p<0.0001) (Fig 2) and higher frequencies of metabolic syndrome (p<0.0001) (Table 2).

Developing Hypertension

During the 3-year follow-up, a total of 4,064 subjects (93.8%) remained normotensive and 267 subjects (6.2%) developed hypertension. The 3-year frequency of developing hypertension increased according to the HR level. The frequency of developing hypertension after 3 years for each HR level was 4.5% in quartile 1, 6.8% in quartile 2, 6.0% in quartile 3, and 7.2% in quartile 4 (p<0.0424) (Table 3). Table 4 shows the results of multivariable logistic regression analyses that examined the risk of developing hypertension. The second through fourth HR quartiles had higher OR for developing hypertension compared with the first quartile. Both in Model 1 and Model 2, quartile 2 and quartile 4 had almost a 1.5 to 1.7-fold higher risk for developing hypertension compared with quartile 1 (p<0.05). When using 90 beats/min as the cut-off level, the OR (95% CI) for developing hypertension was 0.704 (0.253–1.954, p=0.499), which was not statistically significant (data are not shown).

BP Progression

During the follow-up period, 1,011 subjects (23%) pro-

Table 2 Frequencies of Initial BP Categories, Metabolic Syndrome Component and Proteinuria by Initial HR Quartile

<table>
<thead>
<tr>
<th>HR quartile</th>
<th>Quartile 1 (n=1,033)</th>
<th>Quartile 2 (n=1,162)</th>
<th>Quartile 3 (n=1,012)</th>
<th>Quartile 4 (n=1,124)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obesity</td>
<td>28</td>
<td>34</td>
<td>32</td>
<td>34</td>
<td>0.0173</td>
</tr>
<tr>
<td>High BP</td>
<td>14</td>
<td>17</td>
<td>18</td>
<td>22</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>29</td>
<td>32</td>
<td>38</td>
<td>38</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9</td>
<td>11</td>
<td>13</td>
<td>18</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Screening was done during April 1997 to March 1998. Dyslipidemia, triglyceride ≥150 mg/dl or HDL-C <40 mg/dl; hyperglycemia, fasting glucose concentration ≥110 mg/dl; obesity, BMI ≥25 kg/m²; high BP, SBP ≥135 mmHg or DBP ≥80 mmHg; hyperglycemia, fasting blood glucose ≥10 mg/dl; proteinuria (±) or over by dipstick; metabolic syndrome, obese subjects with 2 or more components described above.

BP, blood pressure. Other abbreviations see in Table 1.

Table 3 HR Quartile and Frequencies of BP Outcomes or 3-Year BP Change

<table>
<thead>
<tr>
<th>Quartile 1 (n=1,033)</th>
<th>Quartile 2 (n=1,162)</th>
<th>Quartile 3 (n=1,012)</th>
<th>Quartile 4 (n=1,124)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing hypertension (%)</td>
<td>4.5</td>
<td>6.8</td>
<td>6.0</td>
<td>7.2</td>
</tr>
<tr>
<td>BP progression (%)*</td>
<td>19.3</td>
<td>23.3</td>
<td>24.3</td>
<td>26.2</td>
</tr>
<tr>
<td>SBP change (mmHg)</td>
<td>0.3</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>DBP change (mmHg)</td>
<td>-1.0</td>
<td>-0.7</td>
<td>-0.8</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

*Progression by 1 or more BP categories, whereby BP categories are defined as SBP 120 mmHg and DBP 80 mmHg; SBP 120–129 mmHg or DBP 80–84 mmHg; SBP 130–139 mmHg or DBP 85–89 mmHg; and SBP ≥140 mmHg, DBP ≥90 mmHg.

Abbreviations see in Tables 1, 2.
associated with BP level, but only a few studies have considered this association to be hazardous. Compared with their report, our study suggests that an elevated HR is associated with developing hypertension within a few years enables us to plan a targeted and cost-effective hypertension prevention program.

Fujiiura et al indicated that a HR greater than 90 beats/min is considered to be hazardous. Compared with their report, the OR for developing hypertension was not statistically significant when using 90 beats/min as the cut-off level in the present study. One of the reasons why 90 beats/min was not the appropriate cut-off level for developing hypertension was probably owing to the small number of subjects who had a HR >90 beats/min (n=94).

The present study suggests that an elevated HR is associated with developing hypertension in normotensive, screened subjects. The increased risk of hypertension was evident at HR levels not considered to be tachycardia in the clinical setting. Resting HR values in the highest quartile conferred a 1.7-fold risk of developing hypertension, even after adjustments for risk factors, including metabolic syndrome, proteinuria, current smoking, current alcohol, and current exercise habits.

Discussion

HR is a simple bio-measurement that does not require special instruments. Despite its simplicity, HR is an important biomarker in the clinical setting because it is associated not only with cardiovascular morbidity and mortality but also with non-cardiovascular disease and all causes of mortality. Previous reports demonstrated that HR is associated with BP level but only a few studies have demonstrated that HR is a significant predictor of hypertension. The subjects of some studies, however, were very different from the general population. In the present study, there was a relatively short interval between the examinations and adjustments were made for metabolic syndrome and proteinuria. The identification of subjects at risk for developing hypertension within a few years enables us to plan a targeted and cost-effective hypertension prevention program.

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The present study suggests that an elevated HR is associated with developing hypertension in normotensive, screened subjects. The increased risk of hypertension was evident at HR levels not considered to be tachycardia in the clinical setting. Resting HR values in the highest quartile conferred a 1.7-fold risk of developing hypertension, even after adjustments for risk factors, including metabolic syndrome, proteinuria, current smoking, current alcohol, and current exercise habits.

Table 4 Multivariable Adjusted ORs for BP Outcomes

<table>
<thead>
<tr>
<th>HR quartile</th>
<th>Developing hypertension p value</th>
<th>BP progression p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>1.0 (Reference)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.56 (1.07–2.28)</td>
<td>1.28 (1.04–1.58)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.35 (0.91–2.02)</td>
<td>1.32 (1.07–1.65)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.66 (1.13–2.42)</td>
<td>1.50 (1.22–1.86)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Model 1: Adjusting for age, gender, current cigarette smoking, current drinking, and habitual exercise. Model 2: Adjusting for aforementioned covariates, in addition to metabolic syndrome and proteinuria.

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1, 2.

HR, Metabolic Syndrome and Proteinuria

An increased HR is associated with increased BP, serum triglyceride levels, fasting blood sugar, and insulin level, most of which are also components of metabolic syndrome and the clustering of these factors also indicate metabolic syndrome. In the adolescent, hypertension and a high resting HR are closely associated with adiposity. These results suggest a significant association between HR and metabolic syndrome. Our results also indicate that subjects with a higher HR had higher frequencies of high BP, dyslipidemia, obesity, hyperglycemia (Table 2), and the clustering of these factors (Fig 2). In addition, our results demonstrated that HR is associated with developing hypertension and BP progression independent of metabolic syndrome. Consequently, subjects with a higher HR are considered to be at high risk for cardiovascular disease.

In the present study, subjects with a higher HR had higher frequencies of proteinuria, although they were all normotensive. Elevated urinary albumin excretion is associated with abnormalities in endothelial function. Albuminuria is considered a marker of vascular damage both in the kidneys and systemic vasculature. Proteinuria, in other words macroalbuminuria, in our subjects was considered to indicate not only target organ damage but also to be a marker of early phase systemic vascular damage. This means that subjects with a higher HR are likely to have early-stage vascular damage, even if they are normotensive. Consequently, damaged resistance vessels result in the progression of hypertension.

Mechanism

A higher HR itself is not considered to be a cardiovascular risk factor, but to be representative of sympathetic overactivity and associated with BP elevation through the following 3 pathways. First, sympathetic over-activity increases vasoconstriction of resistance vessels through adrenergic stimulation, resulting in BP elevation. Second, chronic HR elevation leads to sustained pulsatile stress to the arterial wall, which causes stiffening of the arterial walls and increased BP. Third, sympathetic over-activity causes insulin resistance by adrenergic stimulation leading to the clustering of cardiovascular risk factors, accelerating atherosclerosis, and resulting in elevated BP. This could also be seen in obese adolescents in whom atherosclerosis does not fully develop. In short, subjects with a higher HR...
are likely to develop multiple cardiovascular risk factors or to have damaged resistance vessels, all of which result in hypertension.

Clinical Implications
Prevention of hypertension, the most hazardous factor for cardiovascular disease, is an important public health issue. The Framingham study reported that the frequency of progression to hypertension is associated with BP levels. JNC VII emphasizes that subjects with a systolic BP of at least 120 mmHg or diastolic BP of at least 80 mmHg are at risk for developing hypertension. Prehypertension is a useful category in which biochemical tests such as C-reactive protein, plasma brain natriuretic peptide, aldosterone, or urine albumin:creatinine ratio levels are examined to identify those subjects who are most likely to develop hypertension. Our results demonstrate that an elevated HR could be another bio-measurement for identifying subjects who are at risk for developing hypertension.

Strengths and Limitations
The strengths of the present study include the large sample size of subjects without hypertension and the adjustment for multiple conventional risk factors, including metabolic syndrome or proteinuria.

The present study has several limitations. First, most of the subjects were employees of companies and public organizations, or residents who were concerned about their health, suggesting that they were not a true representation of the general population. They were self-selected and constituted a generally healthy cohort. Second, we did not collect lifestyle or medical history data in the 2000 screening. Consequently, BP status during the follow-up period was based only on the BP readings, without further medical information. This might result in a lower frequency of developing hypertension. Third, the cut-off level beyond which HR is considered hazardous is still unclear. A prospective follow-up study is needed to determine at which level the HR should be considered the ideal cut-off point. Fourth, HR was calculated from a single ECG recording. It is well known that HR fluctuates; the average of several measurements might enable us to obtain a more reliable HR value.

Conclusion
In conclusion, the findings of the present study indicate that a higher HR is a predictor for developing hypertension. More attention should be paid to normotensive subjects with a higher HR.

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References

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