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Higher Heart Rate May Predispose to Obesity and Diabetes Mellitus: 20-Year Prospective Study in a General Population

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BACKGROUND

Emerging evidence indicates an association between sympathetic activation and metabolic syndrome. However, sympathetic activation in metabolic syndrome may be a cause, consequence, or just epiphenomenon. To elucidate this issue, the predictive power of resting heart rate for the development of abnormal glucose and lipid metabolisms after 20 years was evaluated in a general population.

METHODS

A total of 637 participants (>20 years old) underwent a health examination in 1979 including measurements of blood chemistries. Resting heart rate (bpm) was measured by an electrocardiogram. In 1999, all of the study participants again underwent a health examination, including electrocardiogram and blood chemistries. Because four of them had atrial fibrillation, and 19 subjects were taking antihypertensive medication in 1979, they were excluded from analysis. Therefore, a complete dataset of 614 subjects was available.

RESULTS

As was reported in our previous article, in 1999 we found a linear and significant ($P < 0.05$) cross-sectional relationship between resting heart rate and a cluster of cardiometabolic risk factors (blood pressure (BP), free fatty acid (FFA), plasma glucose, and homeostasis model assessment (HOMA) index). Baseline higher heart rate (heart rate ≥80 bpm in 1979) predicted the development of obesity, diabetes mellitus (DM), and insulin resistance in 1999 after adjustments for age, sex, and other confounders.

CONCLUSION

This is one of the first prospective reports demonstrating that higher heart rate may predispose to the development of obesity and DM, suggesting that the sympathetic nerve system may play a role in the development of obesity and DM.

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Several studies[1–7] have shown that elevated heart rate is an important predictor for death, especially from cardiovascular diseases. The association between tachycardia and cardiovascular disease may be explained by the fact that tachycardia is associated with obesity, sympathetic activation, and hypertension.[5,8] The cluster of cardiometabolic abnormalities associated with obesity and hypertension is called the metabolic syndrome.[9] Although the underlying mechanisms have not been elucidated, higher heart rate may be a key component of metabolic syndrome. Several cross-sectional studies[10–13] have reported a relationship between tachycardia and metabolic syndrome; however, no longitudinal studies have been available to confirm this association; thus, it is still controversial whether higher heart rate in metabolic syndrome is a cause, consequence, or just epiphenomenon.

Accordingly, we measured resting heart rate in a general population and then re-examined cardiometabolic factors in this same population 20 years later.

METHODS

Study population. Periodic epidemiological surveys were performed in 1979 and 1999 in a rural farming community located in southwestern Japan (Tanushimaru, a cohort of the Seven Countries Study). Invitations to participate in the examination were mailed to all of the residents in the area. In 1999, we performed a health examination which 637 participants underwent. Because there was a health examination done in 1979 by others in the same cohort, we picked up their data in 1979. Because 19 subjects were taking antihypertensive medication and four had atrial fibrillation in 1979, they were excluded from the analysis. Consequently, a complete dataset of 614 subjects (224 men and 390 women) was available for analysis.

Data collection. In 1979, we measured height, weight, and body mass index (BMI). Blood pressure (BP) was measured in the supine position twice at 3-min interval using an upright

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standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. The second BP with the fifth phase diastolic pressure was used for analysis. Because the reliability of our findings depends on the accuracy of heart rate measurements, we used electrocardiograms. Resting heart rate (bpm) was taken as the average of rates measured in leads I and V_6 of a one-channel recorder. Blood was drawn from the antecubital vein in the morning after a 12-h fast for determinations of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), creatinine, and uric acid levels. Estimated glomerular filtration rate was calculated by the Cockcroft–Gault formula. Fasting blood samples were centrifuged within 1 h after collection. These chemistries were measured at a commercially available laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan). In 1999, we repeated those measurements with the same methods. In addition, we measured waist circumference at the level of the umbilicus in the standing position. We also measured plasma insulin (IRI), free fatty acid (FFA), and glycosylated hemoglobin A_{1c} (HbA_{1c}), and checked whether or not participants were taking medications for hypertension, hypercholesterolemia, or diabetes mellitus (DM). The subjects' use of alcohol and cigarettes was ascertained by questionnaire in 1979 and in 1999.

Elevated FFA was defined as ≥0.85 mEq/l (mean ± 1 s.d. of FFA). Homeostasis model assessment (HOMA) index[14] was calculated by FPG × IRI/22.4, and insulin resistance was defined as HOMA index >1.73 according to the diagnostic criteria used in Japan for insulin resistance.[15] Japanese are much smaller than people of Western countries, and therefore it is not appropriate to use the criteria of abdominal obesity of the Adult Treatment Panel III.[16] Accordingly, we adopted the criteria for abdominal obesity proposed by the Japan Society for the Study of Obesity, i.e., waist circumference of over 85 cm for men, and over 90 cm for women.[9] Subjects with obesity were defined as those with BMI ≥25 kg/m^2. Hypertensives were defined as those with systolic BP ≥140 and/or diastolic BP ≥90 mm Hg and/or those receiving antihypertensive medications. Subjects with hypercholesterolemia and hypertriglyceridemia were defined as those with TC ≥220 mg/dl and TG ≥150 mg/dl, respectively, and/or those taking lipid-lowering drugs. Subjects with low HDL-c were defined as those with HDL-c <40 mg/dl in men and with HDL-c <50 mg/dl in women. Subjects with diabetes were defined as those with FPG ≥126 mg/dl or HbA_{1c} ≥6.5%, or those taking oral hypoglycemic agents and receiving insulin injection.

This study was approved by the Tanushimaru branch of the Japan Medical Association, and by the mayor and the welfare section of the Tanushimaru town office, as well as by the Ethics Committee of Kurume University School of Medicine. All participants gave informed consent.

Statistical analysis. For statistical analysis, because of skewed distributions, natural logarithmic (ln) transformations were performed for TG, FPG, and IRI. Log-transformed values were reconverted to antilogarithm forms in the tables. Results are presented as means and ranges. Medication, smoking and alcohol intake were used as dummy variables. They were classified into current habitual use or not. Differences between two groups were determined by paired *t*-test. Participants were stratified into four heart rate groups (<60, 60–69, 70–79, and ≥80 bpm), and all parameters were compared using analysis of covariance adjusted for age and sex. To obtain odds ratios for the effects of resting heart rate on the development of cardiometabolic risk factors, multiple logistic regression analysis adjusted for age, sex, BMI, and FPG at baseline in 1979 was used for categorical parameters to test differences between the lowest vs. other heart rate groups. Statistical significance was defined as $P < 0.05$. All analyses were performed with the use of the SAS system (Release 6.12, SAS Institute, Cary, NC).

RESULTS

Demographic data for the 614 participants in 1979 and 1999 are shown in **Table 1**. The data indicate that most people were normotensive. Twenty years later, BMI was larger. Systolic and diastolic BPs were significantly higher in 1999 than in 1979. TC and HDL-c increased. However, TG decreased. The use of medications for DM and hypercholesterolemia was still low in 1999, 1.3 and 4.4%, respectively. The percentage of subjects of hypertensives increased to 18.9% in 1999.

The cross-sectional association in 1979 between four heart rate groups (<60, 60–69, 70–79, and ≥80 bpm) and parameters was analyzed by analysis of covariance after adjustments for age and sex. Significant relationships were found between heart rate and systolic BP ($P < 0.001$), diastolic BP ($P < 0.01$), or FPG ($P < 0.01$). The cross-sectional association in 1999 between heart rate and parameters was analyzed by multiple linear regression analysis and by analysis of covariance after adjustments for age and sex, and the results are shown in **Table 2**. Systolic and diastolic BP, FFA, FPG, IRI, and HOMA index revealed significant trends across the heart rate groups. These data indicate a positive association between heart rate and a cluster of cardiometabolic risk factors but do not clarify any causative relationship. Accordingly, we investigated whether higher heart rate at baseline in 1979 predicted the development of cardiometabolic risk factors in 1999. The odds ratios and 95% confidence intervals of cardiometabolic risk factors after adjusting for confounding factors stratified into four heart rate groups are shown in **Table 3**. Significant and high odds ratios were obtained for obesity, insulin resistance, and DM when heart rate <60 bpm was considered the reference after adjustments for BMI and FPG in addition to age and sex. These results may indicate that higher heart rate at baseline predicts the development of obesity, insulin resistance, and DM 20 years later.

DISCUSSION

We hypothesized that higher heart rate may predispose to the development of metabolic syndrome and/or DM. This study confirmed our previous results demonstrating a cross-sectional relationship between higher heart rate and a cluster of cardiometabolic factors. In addition and more importantly, we have

Table 1 | Demographic data at baseline (1979) and at follow-up (1999)

Parameters	1979 (Mean (range))	1999 (Mean (range))	*P* value
Number	614	614	
Age (years)	43.2 (21–71)	62.7 (41–90)	<0.01
Body weight (kg)	55.9 (37–90)	56.2 (31–104)	0.32
BMI (kg/m^2)	22.7 (16.0–40.9)	23.2 (15.5–37.1)	<0.01
Heart rate (beats/min)	67 (40–108)	63 (40–106)	<0.01
SBP (mm Hg)	126 (88–204)	139 (90–222)	<0.01
DBP (mm Hg)	74 (48–140)	82 (52–124)	<0.01
TC (mg/dl)	182.9 (72–325)	201.5 (107–317)	<0.01
HDL-c (mg/dl)	48.1 (22–91)	56.5 (22–171)	<0.01
TG (mg/dl)	103.6 (20.9–555.6)	96.0 (27.9–473.4)	<0.01
FPG (mg/dl)	95.7 (54.1–270.4)	95.0 (68.0–208.5)	0.54
Estimated GFR (ml/min)	71.4 (27.8–146.9)	67.2 (16.6–151.7)	<0.01
Uric acid (mg/dl)	4.3 (0.5–9.2)	4.9 (0.2–11.2)	<0.01
Waist (cm)	NA	77 (55–105)	
FFA (mEq/l)	NA	0.6 (0.1–1.7)	
Hemoglobin A1c (%)	NA	5.2 (3.8–10.8)	
Insulin (μU/ml)	NA	4.7 (1.2–15.6)	
Frequency			
Sex: men (%)	224 (36)	224 (36)	—
Smoking: yes (%)	192 (31.3)	83 (13.5)	<0.01
Alcohol intake: (%)	128 (20.8)	111 (18.1)	0.08
Medication: yes (%)			
Hypertension	0 (0.0)	116 (18.9)	
Diabetes mellitus	NA	8 (1.3)	
Hyperlipidemia	NA	27 (4.4)	

Estimated GFR was calculated by the Cockcroft–Gault formula. Data are means (range) or %, unless indicated otherwise.
BMI, body mass index; DBP, diastolic blood pressure; FFA, free fatty acid; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2 | Cross-sectional analysis of heart rate and parameters in 1999 by analysis of covariance adjusted for age and sex

Heart rate	<60	60–69	70–79	≥80	*P* value
Number	216	262	100	36	
Waist (cm)	76.9 (0.6)	76.7 (0.5)	77.2 (0.8)	77.7 (1.4)	0.89
BMI (kg/m^2)	23.4 (0.2)	23.1 (0.2)	23.2 (0.3)	23.2 (0.5)	0.83
SBP (mm Hg)	135 (1.4)	138 (1.3)	146 (2.1)	150 (3.4)	<0.01
DBP (mm Hg)	79 (0.8)	81 (0.7)	86 (1.2)	89 (2.0)	<0.01
TC (mg/dl)	200.6 (2.2)	200.4 (2.0)	202.4 (3.3)	212.6 (5.5)	0.20
HDL-c (mg/dl)	56.4 (1.0)	56.5 (0.9)	55.9 (1.4)	58.5 (2.3)	0.82
TG (mg/dl)	89.9 (1.0)	98.2 (1.0)	99.6 (1.1)	106.3 (1.1)	0.12
FFA (mEq/l)	0.56 (0.02)	0.60 (0.02)	0.69 (0.02)	0.77 (0.04)	<0.01
FPG (mg/dl)	93.2 (1.0)	94.4 (1.0)	100.9 (1.0)	97.6 (1.0)	0.01
HbA_{1c} (%)	5.1 (0.1)	5.2 (0.1)	5.4 (0.1)	5.1 (0.1)	0.20
HOMA index	1.0 (1.0)	1.1 (1.0)	1.3 (1.1)	1.3 (1.1)	0.01
Estimated GFR (ml/min)	69.2 (1.6)	67.1 (1.1)	65.7 (1.4)	67.4 (2.5)	0.43
Uric acid (mg/dl)	4.9 (0.1)	4.8 (0.1)	4.8 (0.1)	5.2 (0.2)	0.21
Smoking (%)	11.8	13.7	14.5	13.7	0.92
Alcohol intake (%)	24.4	16.3	16.2	17.6	0.22
HT medication (%)	14.4	16.8	27.0	46.1	<0.01
DM medication (%)	0.4	1.5	3.0	2.2	0.10
HL medication	3.7	4.6	6.0	2.9	0.84

The parameters are age and sex-adjusted means (s.e.) or %, unless otherwise indicated.
BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FFA, free fatty acid; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; HL, Hyperlipidemia; HOMA, homeostasis model assessment; HT, hypertension; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

now demonstrated that higher heart rate ≥80 bpm at baseline predicted the development of obesity, insulin resistance, and DM 20 years later. Our results may suggest a causative role of sympathetic activation in the development of obesity and DM.

Several investigators reported the interrelationship of heart rate with some cardiometabolic risk factors.[6,7,17–20] We also found significant cross-sectional relationships in this study between heart rate and BP, FFA, FPG, IRI, or HOMA index (**Table 2**). However, we did not find such relationships for BMI, TC, HDL-c, and TG. It is not clear why heart rate was not associated with BMI and lipid profiles in the cross-sectional analysis in 1999 (**Table 2**). Because it is well known that obese people tend to have faster heart rates,[21,22] we think that this result may be due to the fact that the incidence of obesity was so low in our population (25.4% for BMI ≥25 kg/m^2 and 2.1% for BMI ≥30 kg/m^2). Despite the relatively high prevalence of the use of antihypertensive medications, a significant cross-sectional association was found between heart rate and BP (**Table 2**). Some antihypertensive medications affect heart rate. We don't know what types of antihypertensive medications were started after 1979 and being administered in 1999. It is possible that the cross-sectional analysis shown in **Table 2** may be confounded by antihypertensive medication.

To our knowledge, this study is one of the first prospective studies for the impact of higher heart rate on the development of cardiometabolic factors 20 years later. As shown in **Table 3**, the odds ratios for the development of cardiometabolic factors in the heart rate ranges >80 bpm were significantly larger than 2.0, indicating a significant predictive value of higher heart rate ≥80 bpm for the developments of obesity, insulin resistance and DM. Carnethon *et al.*[23] reported that no relationship was found between baseline heart rate and future diabetes after adjustment for BMI in the long-term follow-up study. We think that the difference may be due to the fact that the incidence of obesity at baseline was so low (mean BMI = 22.7 kg/m^2) in our population compared with their population (mean BMI = 26.1 kg/m^2). Notably, they reported that heart rate was positively associated with future diabetes in nonobese participants, consistent with our results.

Table 3 | Odds ratios and 95% confidence intervals of parameters for the development of cardiometabolic risk factors by multiple logistic regression analysis adjusted for age, sex, BMI, and FPG at baseline in 1979

Heart rate (bpm)	<60	60–69	70–79	≥80
Number	127	270	166	51
Obesity	ref	0.65 (0.35–1.23)	0.66 (0.32–1.35)	2.34 (1.09–5.90)*
Abdominal obesity	ref	1.47 (0.73–3.01)	1.18 (0.51–2.75)	1.91 (0.93–6.05)
Hypertension	ref	1.38 (0.33–5.73)	1.61 (0.35–7.36)	1.95 (0.35–8.36)
Hypercholesterolemia	ref	0.69 (0.42–1.15)	0.87 (0.51–1.49)	1.11 (0.53–2.32)
Low HDL-cholesterol	ref	0.84 (0.39–1.78)	0.93 (0.41–2.14)	0.36 (0.08–1.69)
Hypertriglyceridemia	ref	0.95 (0.55–1.66)	1.02 (0.55–1.88)	1.03 (0.44–2.43)
High FFA	ref	1.03 (0.61–1.74)	1.03 (0.57–1.84)	1.83 (0.84–3.97)
Insulin resistance	ref	1.35 (0.78–2.32)	1.15 (0.63–2.11)	2.20 (1.04–5.07)*
Diabetes mellitus	ref	2.15 (0.68–6.76)	2.91 (0.89–9.53)	5.39 (1.34–21.8)**

BMI, body mass index, FFA, free fatty acid; FPG, fasting plasma glucose; HDL, high-density lipoprotein.
*$P < 0.05$, **$P < 0.01$.

Higher heart rate did not predict the development of hypertension (Table 3). The reason for this is unclear and may be due to the use and the type of antihypertensive medications. Unfortunately, we have no data for the type of antihypertensive medications. One possibility may be age at the entry. Tecumseh Study reported the positive relationship between heart rate and development of hypertension in adolescents.[24] Thus, some confounders for the relation among sympathetic nervous system and BP may exist during 20 years between 20s and 40s.

Heart rate is influenced by both sympathetic and parasympathetic nerve activities. If higher heart rate is considered mainly hyper-sympathetic activity, our findings may appear paradoxical because sympathetic activation increases energy expenditure. However, several lines of evidence from longitudinal studies in Tecumseh[24] and Osaka[25] do suggest that sympathetic nerve activation may play a role in the development of obesity. It has also been reported that dietary weight loss decreased sympathetic activity in subjects with metabolic syndrome.[26] Moreover, chronic sympathetic overactivity may facilitate the development of obesity via downregulation of β-adrenoceptor-mediated thermogenic responses.[24,27]

There are at least three mechanisms by which sympathetic activation may predispose to DM.[10] It was demonstrated by Deibert and DeFronzo that stimulation of β-adrenergic receptors causes acute insulin resistance.[28] They infused epinephrine in humans, which causes an acute reduction in the insulin-stimulated uptake of glucose.[28] Second, chronic β-adrenergic stimulation increases the proportion of insulin-resistant fast-twitch muscle fibers in rats.[29] The third mechanism may be the most important: sympathetic activation causes vasoconstriction and decreases skeletal muscle blood flow, resulting in the impairment of glucose uptake into the skeletal muscle.[20]

The cohort where we studied is a typical farming community located in southwestern Japan (Japanese cohort of the Seven Countries Studies). This cohort is fairly representative in Japan as shown by the fact that the demographical backgrounds provided in Table 1 were very similar to those of the National Survey of Cardiovascular Diseases.[30] As was the case in other areas in Japan, this cohort underwent rapid westernization from 1979 to 1999. Although the mean values of BMI, BP, lipid profiles, and glucose profiles were still in the normal ranges in 1999 (Table 1), they gained weight, BP was higher despite 19% use of hypertensive medications, and TC was higher compared to 1979. As shown in Table 1, diastolic BP increased from 74 to 82 mm Hg 20 years later at 63-years old. The increase in diastolic BP at 63 may be somewhat odd to Caucasian people. However, Japan is now the most aged nation in the world. In Japan diastolic BP increases gradually to age of around 60s and then begins to decline thereafter.[31] Because Japanese people are skinner than Caucasians, criteria for obesity may deserve discussion. In Western countries, obesity is defined as BMI ≥30 kg/m^2, whereas in Japan it is defined as BMI ≥25 kg/m^2. Likewise, the definition of abdominal obesity in Japan is different from that in Western countries. According to the Japanese Diabetic Society, waist circumference of >85 cm for men and 90 cm for women are criteria for obesity in Japan.[9]

The limitations of this study are, first, that we were not able to obtain baseline data for waist circumference, FFA, hemoglobin A_{1c}, insulin, inflammatory markers, and medication of diabetes or dyslipidemia 20 years ago and therefore, the data in Table 3 were not adjusted for them. Second, this study was conducted in Japan where the incidence of obesity is low compared to Caucasians.

Although our data suggest a role for sympathetic nerve activation in developments of obesity and DM, we are not suggesting the use of β-blockers because it has been shown in hypertensive patients that the use of β-blockers may lead to a high incidence of new-onset of DM, especially with diuretics.[32,33]

In conclusion, this study is one of the first prospective studies demonstrating that higher heart rate (≥80 bpm) may predispose to obesity and DM 20 years later in a general population.

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