Original Article

Heart Rate Elevation Precedes the Development of Metabolic Syndrome in Japanese Men: A Prospective Study

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This observational study of Japanese men without metabolic syndrome (MetS) (age: 41±8 years) was conducted to clarify whether or not heart rate elevation precedes the development of full-blown MetS. MetS was defined based on two modifications of the criteria of the Japanese Expert Committee on the Diagnosis and Classification of Metabolic Syndrome. Premetabolic syndrome subjects were defined as those having one component of MetS with increased body mass index (BMI). Among the subjects without MetS (*n*=1,859 when the BMI criterion was ≥25 and *n*=2,020 when the BMI criterion was ≥27.5), the incidence of progression to full-blown MetS by the time of the second examination at the end of the 3-year study period was higher in the subjects with premetabolic syndrome than in those without it. The receiver-operator characteristic curve analysis and binary logistic regression analysis revealed that the odds ratio (OR) of a heart rate ≥69 beats/min at the first examination for progression to full-blown MetS by the time of the second examination was significant in subjects with premetabolic syndrome (BMI≥25: OR=3.64 [1.22–10.88]; BMI≥27.5: OR=3.67 [1.28–10.55]; *p*<0.05). Thus, heart rate elevation appears to precede the development of full-blown MetS in subjects with premetabolic syndrome. Heart rate seems to be a simple and useful marker for predicting the progression to full-blown MetS of middle-aged Japanese men with premetabolic syndrome. (*Hypertens Res* 2007; 30: 417–426)

***Key Words*: heart rate, metabolic syndrome, sympathetic nervous system**

Introduction

Recently, attention has been paid to metabolic syndrome (MetS), which refers to the clustering of several cardiovascular risk factors (obesity, dyslipidemia, raised blood pressure and raised plasma glucose) as a potent atherogenic state and which has been reported to be associated with poor cardiovascular outcomes (*1*, *2*). Estimates of the prevalence of MetS indicate that this condition is now common in the general population. Some studies have demonstrated that subjects having one or two components of MetS frequently show progression to full-blown MetS (*3*, *4*). Therefore, it would be desirable to have an appropriate method to stratify the risk of progression to full-blown MetS in these subjects. It has been suggested that genetic and environmental factors act in concert in the pathogenesis of MetS (*5*). Some studies have also suggested that sympathetic nervous activity may play a role in the pathogenesis of MetS (*6*–*8*). Heart rate is a marker of sympathetic activity, and several factors, such as emotions, tobacco use, alcohol consumption and atherosclerotic risk factors (hypertension, obesity, high cholesterol) are well

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known to affect heart rate (*7*, *9*, *10*). Cross-sectional studies demonstrated heart rate elevation in subjects with MetS (*11*, *12*). However, no study until now has evaluated whether or not elevated heart rate precedes the development of full-blown MetS. If precedence is confirmed, heart rate monitoring may be a useful approach to stratifying the risk of progression to full-blown MetS.

Our recent 3-year observational cohort studies have demonstrated that arterial stiffness, as assessed by measurement of the brachial-ankle pulse wave velocity (PWV), increased with increases in the number of MetS components (*13*), and that increased arterial stiffness precedes the progression to hypertension in subjects with high-normal blood pressure, a MetS component (*14*). The instrument used for measuring brachial-ankle PWV also simultaneously measures heart rate. The present observational study was conducted in the same cohort to clarify whether heart rate elevation and/or increased brachial-ankle PWV may precede the development of full-blown MetS.

Methods

Design and Subjects

The subjects of this observational study were Japanese male employees of a single large construction company. Their routine annual health checkups included evaluation of atherosclerotic risk factors (body mass index [BMI], serum levels of triglycerides [TG], high-density lipoprotein cholesterol [HDL] and total cholesterol [TC], fasting plasma glucose [FPG] and blood pressure). Smoking status (current smokers *vs*. non-smokers) and habitual alcohol intake status (zero intake, non-drinker group; 1–14 g/day, light alcohol intake group; 15–29 g/day, moderate alcohol intake group; over 30 g/day, heavy alcohol intake group) were assessed using a self-administered questionnaire. For this study, in addition to the routine tests, brachial-ankle PWV measurements were also conducted on two occasions: at the beginning and at the end of the 3-year study period. The details of this observational study protocol are described elsewhere (*15–17*). The study was initiated in the year 2000. Subjects with positive atherosclerotic risk factors (TC≥6.22 mmol/L, FPG≥6.93 mmol/L and blood pressure≥140/90 mmHg) were managed in accordance with the guidelines of the Japan Atherosclerosis Society (*18*), Japan Diabetes Society (*19*), and Japanese Society of Hypertension (*20*). Subjects with these abnormalities were advised to visit their company's health care center as a first step, and a management plan, including therapeutic lifestyle modifications, was drawn for each subject by by a team consisting of a doctor, a nurse and a nutritionist. In this protocol, while subjects with BMI≥25 kg/m^2, HDL<1.03 mmol/L, TG≥1.70 mmol/L, raised blood pressure (≥130/85 mmHg and <140/90 mmHg) or raised plasma glucose (≥6.11 mmol/L and <6.93 mmol/L) were not provided with the aggressive approach for therapeutic lifestyle modifications. Instead, these subjects received a written recommendation for lifestyle modifications (weight reduction; a diet rich in fruits, vegetables and low-fat dairy products along with reduced intake of saturated and total fat; dietary sodium reduction; regular physical activity; moderation of alcohol consumption) and a recommendation for an annual follow-up (*15–17*).

Subjects meeting any of the following criteria were considered ineligible for the present study: FPG≥6.93 mmol/L, age at the first examination in this observational study >64 years, intake of medication for hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, renal disease, arrhythmia or atherosclerosis obliterans. Verbal informed consent was obtained from all of the participants prior to their participation in this study. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University.

Blood Pressure and Heart Rate Measurements

Blood pressure and heart rate were measured in an air-conditioned room (24–26°C) earmarked exclusively for this purpose. Blood pressure was determined as the mean of two measurements obtained in an office setting by the conventional cuff method, using a mercury sphygmomanometer, in the sitting position. The brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan) in accordance with a previously described methodology (*15–17*). In this measurement, electrocardiographic electrodes were placed on both wrists and then heart rate was measured in the supine position. Both measurements were conducted after the subjects had rested for at least 5 min.

Pulse Wave Velocity

Brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd.), in accordance with a previously described methodology (*15–17*). Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached to the left chest. Electrocardiograms and phonocardiograms were used to provide timing markers for the device. Occlusion cuffs, which were connected to both the plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles while the subjects lay in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. The brachial and post-tibial arterial pressure waveforms, determined by the plethysmographic sensor and recorded for 10 s, were stored. The measurements were conducted after the subjects had rested for at least 5 min in the supine position, in an air-conditioned room (24–26°C) earmarked exclusively for this purpose. The subjects were instructed to abstain from smoking for at least 2 h prior to the measurements. The interobserver and intraobserver coefficients of variation for the measurement have

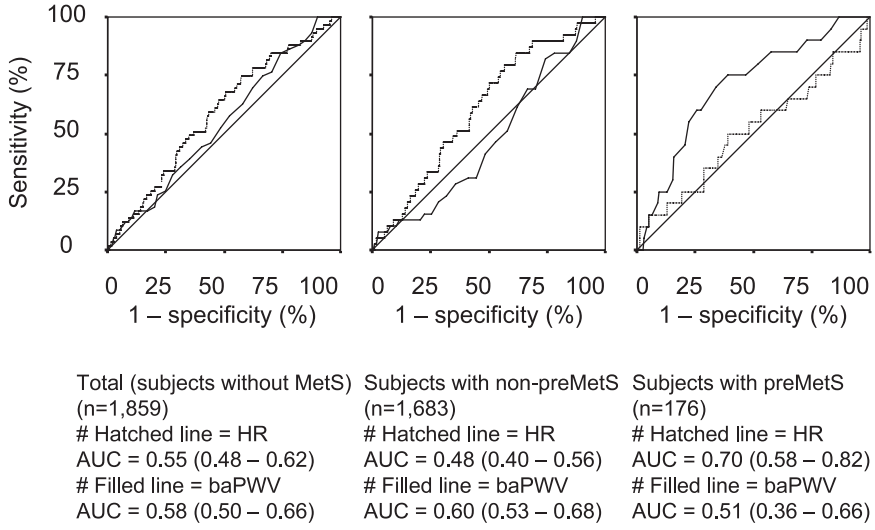

Fig. 1. *Receiver-operator characteristics curve for heart rate and brachial-ankle pulse wave velocity to predict the progression to full-blown metabolic syndrome (metabolic syndrome was defined using a body mass index ≥25 criterion). MetS, metabolic syndrome; AUC, area under curve with 95% confidential interval; HR, heart rate; baPWV, brachial-ankle pulse wave velocity; non-preMetS, non-premetabolic syndrome; preMetS, premetabolic syndrome.*

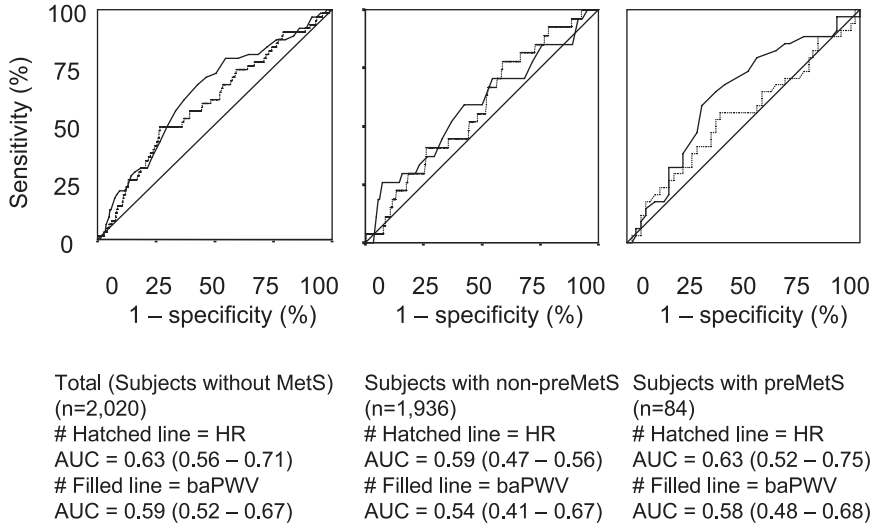

Fig. 2. *Receiver-operator characteristics curve for heart rate and brachial-ankle pulse wave velocity to predict the progression to full-blown metabolic syndrome (metabolic syndrome was defined using a body mass index ≥27.5 criterion). MetS, metabolic syndrome; AUC, area under curve with 95% confidential interval; HR, heart rate; baPWV, brachial-ankle pulse wave velocity; non-preMetS, non-premetabolic syndrome; preMetS, premetabolic syndrome.*

been reported to be 8.4% and 10.0%, respectively (*15*). The blood pressure determined by the oscillometric sensor and heart rate were simultaneously obtained during the measurement of brachial-ankle PWV.

Definition of Metabolic Syndrome and Premetabolic Syndrome Subjects

Because waist circumference measurements were not available in this study, we adopted two modified versions of the criteria of the Japanese Expert Committee on the Diagnosis and Classification of Metabolic Syndrome (*21*) for the clini-

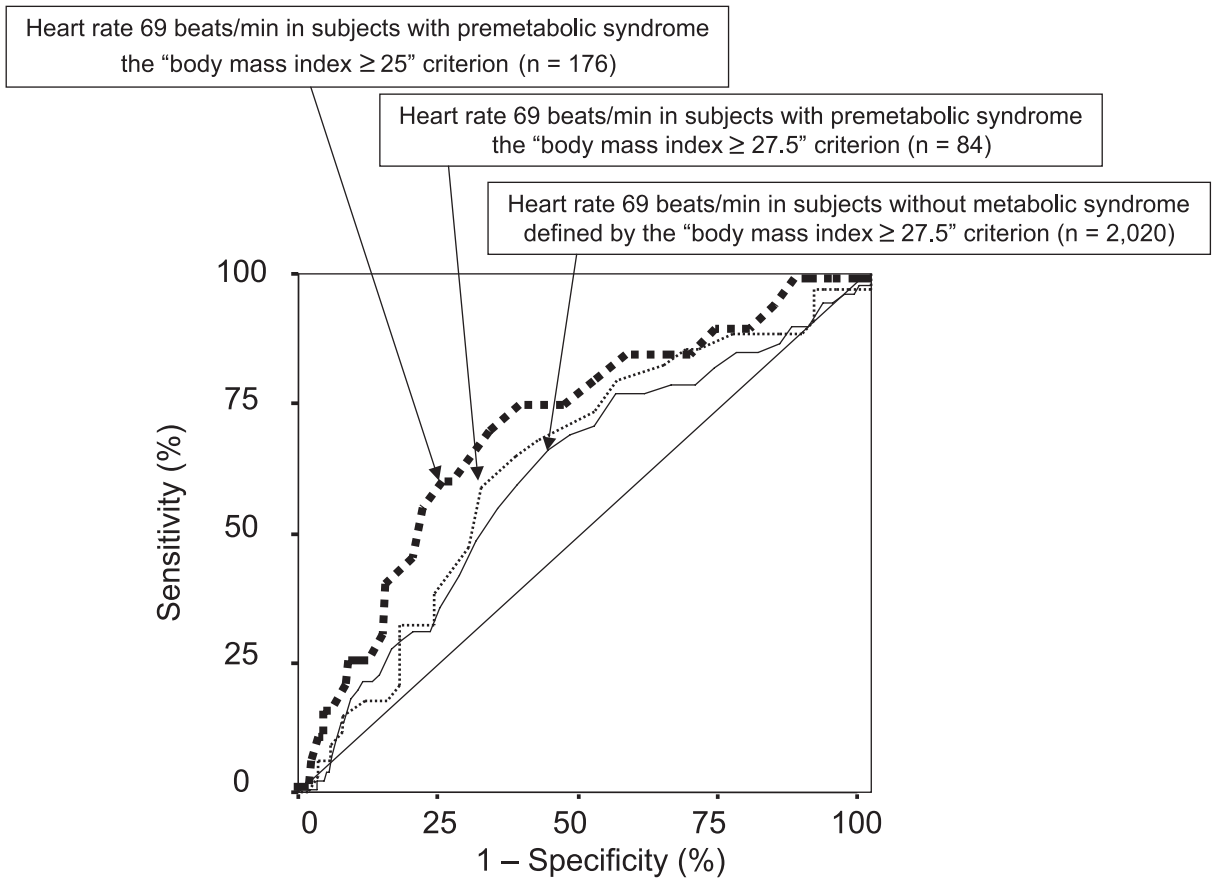

Fig. 3. *Receiver-operator characteristics curves to estimate the best cutoff value of heart rate for predicting progression to full-blown metabolic syndrome.*

cal recognition of MetS in this study; namely, BMI≥25 and BMI≥27.5 (based on the WHO Expert Consultation Committee) (*22*, *23*), plus at least two of three risk factors: dyslipidemia (TG>1.70 mmol/L and/or HDL<1.03 mmol/L), raised blood pressure (blood pressure≥130/85 mmHg) and raised plasma glucose (fasting plasma glucose ≥6.11 mmol/L). In addition, subjects with a BMI≥25 (or ≥27.5, depending on the modified version used) plus only one of the above additional components were categorized as having premetabolic syndrome. All of the remaining subjects—that is, those with one or none of the above-described MetS components, were categorized as subjects without premetabolic syndrome.

Laboratory Measurements

The TG, HDL, TC, FPG and plasma creatinine levels were measured using enzymatic methods (Falco Biosystems, Tokyo, Japan). All of the blood samples were obtained in the morning after the patients had fasted overnight.

Statistical Analysis

Data were expressed as means±SD. To assess the usefulness of measuring the brachial-ankle PWV and heart rate to identify individuals at high risk of developing full-blown MetS, the areas under the curve (AUC) of the receiver-operating characteristic (ROC) curve were compared. Then, binary logistic regression analysis was performed to assess the association between heart rate at the first examination (analyzed as a categorical variable) and the risk of progression to full-blown MetS by the time of the second examination. These analyses were performed with adjustments for covariates (values at the first examination of age, BMI, systolic and diastolic arterial pressures, TG, HDL and FPG, smoking status, and alcohol intake status). The difference in each variable between the two study groups was evaluated using Welch's *t*-test for continuous variables and the χ^2 test for categorical variables.

Binary logistic regression analysis was also performed to assess the association between heart rate at the first examination (analyzed as a categorical variable) and the risk of progression to MetS; that is, progression from TG and/or HDL,

blood pressure and/or FPG values in the normal range at the first examination to values satisfying the criteria for the diagnosis of MetS by the time of the second examination (*i.e.*, dyslipidemia: TG>1.70 mmol/L and/or HDL<1.03 mmol/L, raised blood pressure: blood pressure≥130/85 mmHg and/or raised plasma glucose, fasting plasma glucose ≥6.11 mmol/L; no progression=0 and progression=1).

All the analyses were conducted using SPSS software for Windows, version 11.0J (SPSS, Chicago, USA). A p value <0.05 was considered to denote statistical significance.

Results

The results of this observational study are described in detail elsewhere (*16*, *17*). Briefly, demographic and laboratory examinations were successfully conducted on two occasions for a total of 2,389 Japanese male subjects. The subjects ranged in age from 29 to 76 years. At the first examination, 207 subjects were under medication for hypertension, dyslipidemia, diabetes mellitus, heart disease, stroke, renal disease, arrhythmia and/or atherosclerosis obliterans and were therefore excluded from the analysis. During the study period (spanning the first and second examinations), 102 subjects were started on medication for one or more of these diseases. When the definition of premetabolic syndrome was based on BMI≥25, 221 subjects were defined as having MetS at the first examination, and the data on 1,859 subjects were successfully included in the present analysis. When the definition of premetabolic syndrome was based on BMI≥27.5, 60 subjects were defined as having MetS at the first examination, and the data on 2,020 subjects were successfully included in the present analysis.

The results of the ROC curve analyses suggested that heart rate, rather than brachial-ankle PWV, more accurately predicted the progression to full-blown MetS in subjects with premetabolic syndrome (defined as either BMI≥25 or ≥27.5) and in those without MetS (BMI≥27.5) (Figs. 1 and 2). Figure 3 shows the ROC curve of the association between heart rate and progression to full-blown MetS in these three groups. The optimal cutoff value of heart rate for predicting the progression to full-blown MetS was found to be 69 beats/min in subjects with premetabolic syndrome defined by BMI≥25 (sensitivity=61% and specificity=75%) and those with premetabolic syndrome defined by BMI≥27.5 (sensitivity=60% and specificity=68%). In subjects without MetS (defined by BMI≥27.5), the optimal cutoff value of heart rate for predicting the progression to full-blown MetS was 66 beats/min (sensitivity=68% and specificity=58%).

Table 1 shows the clinical characteristics of the premetabolic syndrome subjects and of subjects without the syndrome defined according to both criteria (BMI≥25 and ≥27.5). Heart rate and brachial-ankle PWV were higher in the premetabolic syndrome subjects than in subjects without the syndrome when the BMI criterion was ≥27.5. The percentages of subjects with a history of smoking and alcohol consumption were higher in the premetabolic syndrome subjects than in the subjects without the syndrome. Table 2 shows the clinical characteristics of the two groups divided by heart rate, *i.e.*, ≥69 beats/min and <69 beats/min, in subjects with premetabolic syndrome defined according to both BMI criteria. The frequency of smoking and the brachial-ankle PWV were higher in subjects with a heart rate ≥69 beats/min than that in those with a heart rate <69 beats/min.

The results of the analysis revealed that 20 (11.3%) premetabolic syndrome subjects (n=176) and 39 (2.3%) subjects without the syndrome (n=1,683) as defined according to the BMI≥25 criterion showed progression to full-blown MetS by the time of the second examination. On the other hand, 34 (40.4%) premetabolic syndrome subjects (n=84) and 27 (1.4%) subjects without the syndrome (n=1,936) as defined according to the BMI≥27.5 criterion showed progression to full-blown MetS by the time of the second examination. Binary logistic regression analysis also revealed that the odds ratio of a heart rate ≥69 beats/min at the first examination for progression to full-blown MetS by the time of the second examination was significant in subjects with premetabolic syndrome (defined by BMI≥25 and BMI≥27.5) even after adjustment for confounding variables (Table 3). However, in the subjects without MetS (defined by BMI≥27.5), the odds ratio of heart rates ≥66 beats/min at the first examination for progression to full-blown MetS by the time of the second examination was not significant (Table 3). Binary logistic regression analysis also revealed that in the premetabolic syndrome subjects defined by the BMI≥25 criterion but by the BMI≥27.5 criterion, the odds ratio of a heart rate ≥69 beats/min at the first examination was significant for progression to raised blood pressure by the time of the second examination (Table 4).

Discussion

Cardiovascular drugs (especially antihypertensive drugs) are known to modify sympathetic nervous activity and arterial stiffness (*24*, *25*). Therefore, the present study was conducted in subjects not on any medication. Considering our previous results, which suggested that arterial stiffness increased as the number of MetS components increased and that increased arterial stiffness preceded the progression to hypertension (*13*, *14*), it is possible that increased arterial stiffness is a predictor of the progression to full-blown MetS. However, the results of the ROC curve analysis demonstrated that heart rate was more accurate than brachial-ankle PWV for predicting the progression to full-blown MetS.

Activation of the sympathetic tone has been reported to be associated with worsening of each pathophysiological component of MetS (*26*, *27*). Masuo *et al*. demonstrated that elevation of the plasma norepinephrine levels preceded the development of insulin resistance and the elevation of blood pressure in their subjects (*28*). Heart rate elevation, which is thought to be related to sympathetic overactivity, has been

Table 2. Clinical Characteristics of the Subjects with HR≥69 Beats/min and Those with HR<69 Beats/min in Premetabolic Syndrome Subjects

	Group category			
	≥69 beats/min		<69 beats/min	
	1st	2nd	1st	2nd
Defined by the BMI≥25.0 criterion				
Number of subjects	46		130	
Age (years)	42±7		42±9	
BMI (kg/m^2)	26.4±1.4	26.3±1.5	26.8±2.0	26.9±2.1
Smoking (*n* (%))	30 (65.2)	26 (56.5)*	54 (41.5)†	47 (36.2)*,†
Alc (N/L/M/H)	8/21/12/5	6/24/13/3	20/69/32/9	16/71/32/11
SBP (mmHg)	125±11	126±10	127±11	126±11
DBP (mmHg)	79±7	78±9	78±8	77±9
HR (beats/min)	75±6	71±7	60±5†	62±8†
TC (mmol/L)	5.3±0.9	5.5±0.9	5.3±0.8	5.5±0.9*
HDL (mmol/L)	1.2±0.3	1.3±0.3	1.3±0.3	1.5±0.3
TG (mmol/L)	2.1±1.8	1.9±1.3	1.8±1.5	1.8±1.4
FPG (mmol/L)	5.2±0.4	5.0±0.4	5.1±0.4	5.0±0.4
baPWV (cm/s)	1,303±156	1,314±161*	1,243±162†	1,289±148*
Number of Dyslip	28	26	56	45
Number of RBP	18	20	74	48
Number of RPG	0	0	0	0
Defined by the BMI≥27.5 criterion				
Number of subjects	36		48	
Age (years)	44±8		40±8†	
BMI (kg/m^2)	29.3±1.8	29.5±2.1	29.3±2.0	29.3±2.0
Smoking (*n* (%))	18 (66.7)	16 (61.1)*	24 (37.5)†	22 (33.3)†,*
Alc (N/L/M/H)	7/17/10/2	6/16/10/4	10/25/10/3	7/26/10/5
SBP (mmHg)	134±13	138±14*	129±14	130±13†
DBP (mmHg)	83±9	86±10*	80±10	81±9†
HR (beats/min)	76±8	76±12	62±6†	64±8†
TC (mmol/L)	5.5±0.8	5.6±0.8	5.4±0.9	5.5±0.9
HDL (mmol/L)	1.2±0.2	1.3±0.2	1.2±0.2	1.2±0.3
TG (mmol/L)	1.5±0.6	1.8±0.9*	1.7±0.9	1.9±1.0*
FPG (mmol/L)	5.3±0.5	5.3±0.6	5.2±0.5	5.3±0.7
baPWV (cm/s)	1,305±180	1,357±188*	1,286±185†	1,317±200*
Number of Dyslip	8	20	19	23
Number of RBP	27	32	28	27
Number of RPG	1	5	1	5

preMetS, premetabolic syndrome subjects; non-preMetS, non-premetabolic syndrome subjects; 1st, 1st examination; 2nd, 2nd examination; BMI, body mass index; Alc, alcohol intake (number of subjects; N, non-drinker; L, light intake, M, moderate intake, H, heavy intake); SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, serum total cholesterol; HDL, serum high density lipoprotein cholesterol; TG, serum triglycerides; FPG, fasting plasma glucose; baPWV, brachial-ankle pulse wave velocity; Dyslip, subjects with dyslipidemia; RBP, subjects with raised blood pressure; RPG, subjects with raised plasma glucose. *$p<0.05$ *vs*. that at the 1st examination; $^{\dagger}p<0.05$ *vs*. that in the premetabolic syndrome subjects

activity may have a role in the pathogenesis of MetS (*21–23*). On the other hand, obesity causes sympathetic activation *via* several mechanisms, such as hyperinsulinemia, hyperleptinemia and activation of the renin-angiotensin system (*30*). Obesity may be a cause of the sympathetic activation related to MetS. A significant correlation ($r=0.08$, $p<0.01$) between BMI and heart rate was noted in all the participants ($n=2,080$) ($r=0.08$, $p<0.01$). Heart rate, BMI and the prevalence rate of progression to full-blown MetS were higher in subjects with premetabolic syndrome than in those without it as defined by the BMI≥27.5 criterion. Thus, while the cause-effect relationship between MetS and sympathetic activation remains to be clarified, the severity of obesity might be related, at least in part, to progression to full-blown MetS, *via*

Table 1. Clinical Characteristics of the Premetabolic Syndrome Subjects and Non-Premetabolic Syndrome Subjects

	Group category			
	PreMetS		Non-preMetS	
	1st	2nd	1st	2nd
Defined by the BMI≥25.0 criterion				
Number of subjects	176		1,683	
Age (years)	42±8		41±9	
BMI (kg/m^2)	26.7±1.9	26.8±2.0	22.7±2.2†	23.0±2.3*,†
Smoking (*n* (%))	84 (47.7)	73 (40.4)*	676 (41.5)†	580 (34.5)*,†
Alc (N/L/M/H)	28/90/44/14	22/95/45/14	250/1,008/324/101†	188/1,046/346/103†
SBP (mmHg)	127±11	126±10	121±13†	123±13*,†
DBP (mmHg)	78±8	78±9	75±10†	74±10†
HR (beats/min)	64±9	65±8	64±10	65±10
TC (mmol/L)	5.3±0.8	5.5±0.9*	5.0±0.8†	5.2±0.8*,†
HDL (mmol/L)	1.3±0.3	1.3±0.3	1.5±0.3†	1.5±0.3†
TG (mmol/L)	1.9±1.5	1.8±1.3	1.2±0.8†	1.3±0.8*,†
FPG (mmol/L)	5.1±0.4	5.0±0.4	5.1±0.7	5.1±0.7
baPWV (cm/s)	1,260±182	1,296±151*	1,237±182	1,276±181*
Number of Dyslip	84	71	274	385
Number of RBP	92	68	501	550
Number of RPG	0	0	63	58
Defined by the BMI≥27.5 criterion				
Number of subjects	84		1,936	
Age (years)	42±8		42±9	
BMI (kg/m^2)	29.3±1.8	29.4±2.1	23.1±2.3†	23.4±2.5*,†
Smoking (*n* (%))	42 (50.0)	38 (45.2)*	790 (40.8)	683 (35.2)*
Alc (N/L/M/H)	17/42/20/5	13/42/20/9	285/1,137/378/136†	220/1,172/414/130†
SBP (mmHg)	131±13	133±13	123±14†	124±13*,†
DBP (mmHg)	81±9	83±10	76±10†	75±10†
HR (beats/min)	68±10	69±12	65±10†	65±9†
TC (mmol/L)	5.4±0.8	5.6±0.9*	5.0±0.8†	5.2±0.9*,†
HDL (mmol/L)	1.2±0.2	1.3±0.3	1.4±0.3†	1.5±0.3*,†
TG (mmol/L)	1.6±0.9	1.8±1.0*	1.3±0.9†	1.4±1.0*,†
FPG (mmol/L)	5.2±0.5	5.3±0.7	5.2±0.7	5.1±0.7†
baPWV (cm/s)	1,294±182	1,334±195*	1,247±182†	1,287±182*,†
Number of Dyslip	27	43	413	517
Number of RBP	55	59	697	703
Number of RPG	2	10	87	81

preMetS, premetabolic syndrome subjects; non-preMetS, non-premetabolic syndrome subjects; 1st, 1st examination; 2nd, 2nd examination; BMI, body mass index; Alc, alcohol intake (number of subjects; N, non-drinker; L, light intake, M, moderate intake; H, heavy intake); SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, serum total cholesterol; HDL, serum high density lipoprotein cholesterol; TG, serum triglycerides; FPG, fasting plasma glucose; baPWV, brachial-ankle pulse wave velocity; Dyslip, subjects with dyslipidemia; RBP, subjects with raised blood pressure; RPG, subjects with raised plasma glucose. *$p<0.05$ *vs*. that at the 1st examination; $^{\dagger}p<0.05$ *vs*. that in the premetabolic syndrome subjects.

demonstrated to be a predictor of future hypertension (*29*). While recent studies have demonstrated heart rate elevation in subjects with MetS (*11*, *12*), no study until now has examined whether or not heart rate elevation might be a predictor of future MetS. Since each MetS component has been shown to be related to heart rate elevation (*9*, *10*), it is possible to propose that this elevation is a mere epiphenomenon of clustering of the individual components (*9*, *10*). In the present study, however, heart rate elevation was found to be significantly related to the risk of progression to full-blown MetS in premetabolic syndrome subjects defined using either criterion (BMI≥25 or ≥27.5) (*18*, *19*), even after adjusting for the value of each component. Thus, heart rate elevation might be an independent predictor of the progression to full-blown MetS.

Previous reports have proposed that sympathetic nervous

Table 3. Results of a Binary Logistic Regression Analysis to Assess the Usefulness of Heart Rate Elevation (≥69 Beats/min or ≥66 Beats/min) to Predict the Progression to Full-Blown Metabolic Syndrome

	Crude OR (95% CI)	Adjusted OR (95% CI)
Heart rate elevation≥69 beats/min		
PreMetS (defined by the BMI≥25 criterion: $n=176$)	4.23 (1.62–11.01)†	3.64 (1.22–10.88)*
PreMetS (defined by the BMI≥27.5 criterion: $n=84$)	3.04 (1.23–7.51)*	3.67 (1.28–10.55)*
Heart rate elevation≥66 beats/min		
Total subjects without MetS (defined by the BMI≥27.5 criterion: $n=2,020$)	2.76 (1.61–4.74)†	2.10 (0.98–4.12)

OR, odds ratio; CI, confidential interval; MetS, metabolic syndrome; preMetS, premetabolic syndrome subjects; BMI, body mass index. *$p<0.05$; †$p<0.01$.

Table 4. Results of Binary Regression Analysis to Assess of Heart Rate Elevation (≥69 Beats/min) to Predict the Progression of the Metabolic Syndrome Parameters

Parameters	OR (95% CI)
Defined by the BMI≥25 criterion	
Dyslipidemia	1.86 (0.72–4.82)
Raised blood pressure	4.79 (2.02–11.32)†
Raised plasma glucose	non
Defined by the BMI≥27.5 criterion	
Dyslipidemia	2.43 (0.92–6.41)
Raised blood pressure	1.76 (0.49–6.35)
Raised plasma glucose	2.16 (0.51–9.10)

OR, odds ratio; CI, confidential interval; BMI, body mass index; non, none of the subjects showed progression to raised plasma glucose during the follow-up period. †$p<0.01$.

sympathetic activation.

Among the components of MetS, some studies have demonstrated that the presence of hypertension intensified sympathetic overactivity in cases of MetS (*31–33*). It is still not clear whether sympathetic overactivity is more specifically associated with some components rather than others. In this study, heart rate elevation preceded the progression to raised blood pressure in subjects with premetabolic syndrome as defined according to the BMI≥25 criterion but according to the ≥27.5 criterion. Therefore, among the MetS components, sympathetic overactivity may contribute, at least in part, to progression to raised blood pressure. However, MetS components other than hypertension are also associated with heart rate elevation (*9*, *10*). It is possible that the duration of follow-up and the number of subjects in this study were not sufficient to clarify whether or not sympathetic overactivity is specifically associated with the progression of MetS components other than raised blood pressure.

Clinical Implications

The results of this 3-year observational study revealed that premetabolic syndrome subjects frequently progress to full-blown MetS. However, no strategy has been established to stratify the risk of progression to MetS or to manage premetabolic syndrome subjects. While lifestyle modifications can prevent the development of each MetS component, the modification of lifestyles may not be successful for some premetabolic syndrome subjects, because of the large number of such subjects in the general population (*34–36*). Selective reinforcement of lifestyle modifications in individuals at high risk of progressing to full-blown MetS among premetabolic syndrome subjects may be useful for successfully implementing lifestyle modifications. In this context, while the Framingham study suggested that a heart rate of ≥85 beats/min is a risk factor for cardiovascular disease (*37*), the odds ratio of this heart rate for progression to full-blown MetS in our subjects was not significant (data not shown). On the other hand, the Ohasama study suggested that a heart rate ≥70 beats/min is a useful marker for predicting survival in the general population (*38*), and the present results suggest that ≥69 beats/min is also a marker of a high risk of progression to full-blown MetS in premetabolic syndrome subjects.

Limitations

The present study had the following limitations: 1) The results must be confirmed by conducting the measurements in other conditions or situations, *e.g.*, using heart rate measurements obtained in an office setting (*9*); using well-established methods to assess the sympathetic tone, such as plasma norepinephrine spill-over measurements, heart rate variability or direct recording of the sympathetic nerve traffic (*31–33*); using waist circumference as a criterion of MetS; studying elderly subjects, female subjects and subjects of other ethnicities. 2) While sleep apnea, white coat phenomenon and lifestyle modifications have been reported to affect the sympathetic tone (*36*, *39*, *40*), the influences of these factors on heart rate elevation could not be evaluated in the present subjects. 3) The reason why elevated heart rate was useful as a predictor of progression to full-blown MetS in patients with premetabolic syndrome, but not in those without any components of the syndrome, could not be clarified in this study. Further studies (*e.g.*, with a longer follow-up period) are proposed to clarify this issue.

Conclusion

The present results revealed that premetabolic syndrome subjects frequently show progression to full-blown MetS and that heart rate elevation precedes the manifestation of full-blown MetS in these subjects, independent of each MetS component's influence. The monitoring of heart rate elevation (over 69 beats/min) may become a simple and useful marker for predicting the progression to full-blown MetS in middle-aged Japanese men with premetabolic syndrome.

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