Low Heart Rate Variability and Sympathetic Dominance Modifies the Association Between Insulin Resistance and Metabolic Syndrome — The Toon Health Study —

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Background: Insulin resistance is strongly associated with metabolic syndrome (MetS), but it is not known how this association is influenced by the autonomic nervous system, which controls insulin secretion.

Methods and Results: The subjects were 2,016 individuals aged 30–79 years enrolled between 2009 and 2012. MetS was determined using the harmonized MetS definition, which includes waist circumference, blood pressure, triglycerides, high-density lipoprotein cholesterol, and fasting glucose. The homeostasis model assessment index for insulin resistance (HOMA-IR) and Gutt's insulin sensitivity index (ISI) were calculated based on fasting and 2 h-post-load glucose and insulin concentrations in a 75-g oral glucose tolerance test. The 5-min heart rate variability (HRV) was evaluated using time-domain indices of standard deviations of NN intervals (SDNN) and root mean square of successive differences (RMSSD). Power spectral analysis yielded frequency-domain measures for HRV: high-frequency (HF) power, low-frequency (LF) power and LF/HF. Multivariable adjusted logistic models showed that the highest quartiles for SDNN, RMSSD, LF, and HF vs. the lowest quartiles had a significant association with MetS. RMSSD, HF, and LF/HF remained significantly associated with MetS after adjustment for HOMA-IR (or ISI). Additive interactions between the levels of high LF/HF and high HOMA-IR (or low ISI) were significantly positive.

Conclusions: Sympathovagal imbalance as evidenced by low HF and high LF/HF modified the association of insulin resistance or low insulin sensitivity with MetS.

Key Words: Epidemiology; Heart rate variability; Insulin sensitivity; Metabolic syndrome

Metabolic syndrome (MetS) is a diagnosis involving clustered cardiovascular risk factors.¹ Pathologically, insulin resistance (IR) or impaired insulin sensitivity is considered to be the underlying mechanism of MetS.^{2,3} Despite differing MetS definitions across ethnicities, the accumulation of multiple risk factors has been shown to significantly elevate the risk of cardiovascular disease (CVD) outcomes or sudden cardiac death.^{4–7}

Heart rate variability (HRV) is regulated predominantly by cardiac vagal tone, and lower HRV has been associated with an increased risk of diabetes, hypertension, and CVD in epidemiologic studies.^{8–11} HRV assessment is a useful noninvasive tool that reflects the activity of the sym-

pathetic and parasympathetic nervous systems by means of beat-to-beat regulation of heart rate.¹²

Recently, we reported that HRV was strongly associated with IR and insulin sensitivity in a Japanese population,¹³ and we speculated that this was linked to dysfunction of the hepatic insulin-sensitizing substance (HISS) pathway, which is controlled by vagal tone.^{14,15} Thus, low HRV resulting from parasympathetic dysfunction is likely to precede impaired insulin function¹⁶ and increased inflammatory activity,¹⁷ thus raising CVD risk. Several studies have documented the association between HRV and MetS,¹⁸ but few have considered the influence of IR and insulin sensitivity on this association in the general population.

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Table 1. Subjects' Characteristics and Numbers of Metabolic Risk Factors

	No. of metabolic risk factors					P value
	0	1	2	3	≥4	
n	595	489	390	323	219	
Age, years	49.6	58.5	61.7	63.6	64.0	<0.001
Men, %	20.2	30.7	48.5	47.1	46.1	<0.001
BMI, kg/m ²	20.7	22.8	24.1	24.7	26.2	<0.001
WC, cm	76.8	81.8	86.5	88.0	92.3	<0.001
SBP, mmHg	112.3	127.4	131.3	135.2	138.2	<0.001
DBP, mmHg	67.8	77.3	79.2	80.6	82.8	<0.001
HDL-C, mmol/L	1.74	1.62	1.53	1.40	1.35	<0.001
TG, mmol/L†	0.79	0.99	1.16	1.35	1.59	<0.001
FG, mmol/L†	4.88	5.08	5.27	5.40	5.79	<0.001
Fasting insulin, pmol/L†	24.4	29.8	40.4	44.4	57.9	<0.001
HOMA-IR†	0.76	0.97	1.37	1.54	2.15	<0.001
ISI†	2.24	1.99	1.72	1.56	1.37	<0.001
HRV parameters						
lnSDNN, ms	3.69	3.62	3.61	3.60	3.56	0.011
lnRMSSD, ms	3.46	3.32	3.30	3.27	3.22	<0.001
lnLF, ms ²	5.08	4.97	4.99	4.88	4.81	0.077
lnHF, ms ²	4.91	4.67	4.64	4.59	4.46	<0.001
lnLF/HF	1.06	1.09	1.10	1.08	1.11	0.024
Covariates						
Current smoker, %	6.1	7.9	9.6	12.3	13.2	0.007
Regular alcohol drinker, %	53.3	53.2	49.7	48.4	47.5	0.374
Physical activity, METs · h/day	35.7	36.1	35.6	35.4	34.9	0.037

Means and percentages were adjusted for sex and age using analysis of covariance. †Represented as geometric means. BMI, body mass index; DBP, diastolic blood pressure; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; HF, high frequency; HOMA-IR, homeostasis model assessment index for insulin resistance; HRV, heart rate variability; ISI, insulin sensitivity index; LF, low frequency; MET, metabolic equivalents; RMSSD, root mean square of successive differences; SBP, systolic blood pressure; SDNN, standard deviation of NN intervals; TG, triglycerides; WC, waist circumference.

Therefore, the aim of the present study was to examine how the association between insulin function and MetS is modified by the autonomic nervous system.

Methods

Study Subjects

The Toon Health Study enrolled 2,032 men and women, 30–79 years of age, between 2009 and 2012. Subjects in whom HRV was assessed and who did not have atrial fibrillation on ECG were included. Based on these criteria, 2,016 individuals were included in the analysis.

Written informed consent was given by all participants. The study protocol was approved by the Human Ethics Review Committees of Ehime University Graduate School of Medicine (No. 20-2).

Measurements

Overnight fasting blood samples were drawn from the antecubital vein into vacuum tubes containing a serum separator gel (for glucose and blood chemistry). The serum tube was centrifuged immediately at 3,000 g for 15 min, and the separated serum was sent to the laboratory for analysis.

Blood Analysis Enzymatic methods were used to measure serum levels of total cholesterol and triglycerides (TG). Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured using the direct homogeneous method. Lipid mea-

surements were standardized using the CDC NHLBI Lipid Standardization Program provided by the Centers for Disease Control and Prevention (Atlanta, GA, USA).¹⁹ Serum glucose was measured by the hexokinase method (Sysmex, Kobe, Japan) with an automatic analyzer (7600-D; Hitachi Co., Tokyo, Japan). Insulin was measured by electrochemiluminescence method (ECLusys, Roche Diagnostics, Tokyo, Japan).

Blood pressure (BP) was measured twice using an automatic sphygmomanometer (BP-103iII; OMRON Colin Co., Tokyo, Japan) while patients were seated after a rest of at least 5 min. The mean of the 2 measurements was used for analysis. The harmonized MetS definition for Asians was used, which consists of having ≥3 of the following metabolic risk factors:¹ increased waist circumference (≥85 cm in men and ≥90 cm in women), elevated TG (≥1.7 mmol/L), reduced HDL-C (<1.0 mmol/L in men and <1.3 mmol/L in women), elevated BP (systolic BP (SBP) ≥130 mmHg or diastolic BP (DBP) ≥85 mmHg or the current use of any antihypertensive medication), and elevated fasting glucose (FG >7.0 mmol/L or the current use of any antidiabetic medication). Because we did not ask patients about specific medicines they were taking, participants who took antilipidemic drugs were presumed to have high TG and low HDL-C. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

We carried out an oral glucose tolerance test (OGTT) after at least a 10-h fast. Fasting, and 1-h- and 2-h-postload

Table 2. Sex- and Age-Adjusted Means of Metabolic Risk Factors, Numbers of Risk Factors, and MetS Incidence by HRV Parameter Quartiles

HRV parameters	Metabolic risk factors						No. of risk factors	MetS (%)
	WC (cm)	SBP (mmHg)	DBP (mmHg)	HDL-C (mmol/L)	TG (mmol/L)	FG (mmol/L)		
SDNN								
Q1 (low)	84.6	127.4	77.4	1.56	1.10	5.28	1.71	31.5
Q2	83.6	126.1	76.6	1.56	1.09	5.17	1.54	25.5
Q3	82.4	125.3	75.5	1.57	1.03	5.14	1.44	24.8
Q4 (high)	82.8	125.6	74.5	1.60	1.02	5.13	1.49	25.8
P for difference	<0.001	0.269	<0.001	0.190	0.032	0.001	0.004	0.053
P for trend	<0.001	0.201	<0.001	0.029	0.020	<0.001	0.002	0.057
RMSSD								
Q1 (low)	84.8	128.1	78.3	1.54	1.14	5.22	1.79	32.5
Q2	83.4	126.4	76.3	1.55	1.08	5.23	1.56	27.1
Q3	83.2	124.8	75.0	1.58	1.00	5.14	1.47	25.2
Q4 (high)	82.0	125.2	74.5	1.61	1.02	5.13	1.36	23.0
P for difference	<0.001	0.019	<0.001	0.014	<0.001	0.012	<0.001	0.004
P for trend	<0.001	0.028	<0.001	0.002	0.001	<0.001	<0.001	0.002
LF								
Q1 (low)	84.2	126.7	76.9	1.57	1.07	5.23	1.68	31.8
Q2	83.8	125.5	76.2	1.57	1.08	5.18	1.56	27.0
Q3	82.8	126.4	75.9	1.57	1.04	5.15	1.47	24.4
Q4 (high)	82.6	125.9	75.0	1.58	1.04	5.16	1.47	24.3
P for difference	0.012	0.718	0.068	0.976	0.493	0.205	0.034	0.026
P for trend	0.004	0.705	0.003	0.141	0.165	0.032	0.006	0.016
HF								
Q1 (low)	85.4	127.5	78.1	1.55	1.13	5.26	1.79	34.1
Q2	83.2	126.2	76.2	1.56	1.07	5.19	1.56	24.6
Q3	82.4	125.0	75.0	1.58	1.02	5.11	1.45	25.5
Q4 (high)	82.4	125.8	74.7	1.60	1.01	5.15	1.38	23.3
P for difference	<0.001	0.176	<0.001	0.182	0.001	0.003	<0.001	<0.001
P for trend	<0.001	0.173	<0.001	0.014	0.007	0.009	<0.001	0.004
LF/HF								
Q1 (low)	82.7	125.8	75.5	1.59	1.04	5.17	1.52	28.1
Q2	82.8	125.7	76.0	1.57	1.04	5.17	1.43	23.2
Q3	83.5	125.8	75.5	1.56	1.05	5.17	1.53	25.4
Q4 (high)	84.4	127.1	77.1	1.56	1.10	5.22	1.70	31.1
P for difference	0.011	0.517	0.062	0.401	0.170	0.532	0.003	0.019
P for trend	<0.001	0.125	0.010	0.251	0.046	0.211	0.009	0.310

Means and P for differences were calculated using analysis of covariance adjusted for sex and age. P for trend was also tested in the same model with HRV parameters as continuous variables. MetS, metabolic syndrome. Other abbreviations as in Table 1.

glucose and insulin concentrations were measured. The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated as fasting insulin [$\mu\text{U/mL}$] $\times$ FG [mg/dL]/405). The insulin sensitivity index (ISI) was calculated with Gutt's equation as: $m/[\text{mean glucose}]/\log [\text{mean insulin}]$, where $m=[75,000+(0 \text{ min glucose}-120 \text{ min glucose})\times 0.19\times \text{body weight (kg)}]/120$.²⁰

Lifestyle Analysis A self-administered questionnaire was used to assess medical history (presence of hypertension, dyslipidemia, or diabetes), smoking habit, and alcohol consumption. The amount of alcohol consumed each week was evaluated by measuring the weekly frequency of drinking and the type of alcoholic beverage consumed (beer, sake, whiskey, shochu, or wine). A regular alcohol drinker was defined as an individual with alcohol consumption ≥ 1 g/week. Physical activity levels were assessed using a validated questionnaire, which consisted of 14 questions on occupa-

tion, locomotion, housework, sleep time, and leisure time physical activities.²¹ Responses for each physical activity category were converted to metabolic equivalents (METs), according to the Compendium by Ainsworth et al, and expressed as METs $\cdot$ h/day.

Assessment of Autonomic Function

HRV was measured with a fingertip pulse wave sensor (TAS9, YKC Co. Ltd, Japan). The 5-min pulse rate was recorded, followed by calculation of the standard deviation of the normal-to-normal (RR) intervals (SDNN) and root mean square of successive differences in RR intervals (RMSSD). Power spectral analysis of the pulse recordings was also used to obtain frequency-domain measures of HRV. The power spectrum was decomposed into its frequency components and quantified in terms of the relative intensity (power) of each component. The power

Table 3. Multivariable Adjusted OR and 95% CI by HRV Parameter Quartiles for MetS

HRV parameters	Model 1			Model 2			Model 3		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
SDNN									
Q1 (low)	1.00			1.00			1.00		
Q2	0.76	0.57–1.01	0.055	0.76	0.57–1.01	0.059	0.85	0.63–1.16	0.311
Q3	0.71	0.53–0.96	0.024	0.72	0.54–0.97	0.032	0.84	0.61–1.17	0.304
Q4 (high)	0.74	0.55–0.99	0.042	0.75	0.56–1.01	0.062	0.90	0.65–1.25	0.539
P for trend	0.047			0.065			0.623		
RMSSD									
Q1 (low)	1.00			1.00			1.00		
Q2	0.78	0.59–1.04	0.086	0.78	0.59–1.04	0.088	0.82	0.61–1.12	0.213
Q3	0.69	0.51–0.92	0.012	0.68	0.51–0.92	0.011	0.83	0.60–1.15	0.260
Q4 (high)	0.58	0.43–0.79	<0.001	0.58	0.43–0.79	<0.001	0.70	0.51–0.97	0.034
P for trend	0.001			0.002			0.128		
LF									
Q1 (low)	1.00			1.00			1.00		
Q2	0.81	0.62–1.08	0.149	0.83	0.63–1.10	0.184	0.94	0.69–1.27	0.676
Q3	0.68	0.51–0.92	0.013	0.71	0.52–0.96	0.025	0.80	0.57–1.10	0.170
Q4 (high)	0.67	0.49–0.91	0.009	0.69	0.51–0.93	0.015	0.82	0.59–1.14	0.234
P for trend	0.015			0.023			0.332		
HF									
Q1 (low)	1.00			1.00			1.00		
Q2	0.65	0.49–0.86	0.002	0.66	0.50–0.87	0.004	0.73	0.54–0.99	0.042
Q3	0.66	0.49–0.89	0.006	0.66	0.50–0.89	0.006	0.91	0.66–1.25	0.541
Q4 (high)	0.56	0.41–0.75	<0.001	0.57	0.42–0.76	<0.001	0.69	0.50–0.95	0.023
P for trend	0.002			0.003			0.184		
LF/HF									
Q1 (low)	1.33	0.99–1.80	0.058	1.33	0.99–1.79	0.063	1.37	0.99–1.90	0.057
Q2	1.00			1.00			1.00		
Q3	1.16	0.86–1.58	0.334	1.17	0.86–1.58	0.330	1.14	0.82–1.59	0.450
Q4 (high)	1.61	1.20–2.16	0.002	1.62	1.21–2.18	0.001	1.52	1.10–2.09	0.010

Model 1 is adjusted for sex and age. Model 2 is adjusted for model 1 plus smoking, alcohol consumption, and physical activity. Model 3 is adjusted for model 2 plus HOMA-IR. CI, confidence intervals; OR, odds ratio. Other abbreviations as in Tables 1,2.

spectrum was divided into frequency bands, and we used the following parameters for analysis: high-frequency band (HF) (0.15–0.40 Hz) and low-frequency band (LF) (0.04–0.15 Hz). The HF and LF power and the LF/HF ratio were used for further analysis.

To assess the reliability of the HRV parameters, each was measured twice in each individual using the same method at an interval of 2 months ($n=37$). The Pearson's correlation coefficients of these parameters within subjects between days were 0.67 for SDNN, 0.51 for RMSSD, 0.63 for LF, 0.54 for HF, and 0.21 for LF/HF. The coefficients of variation were 0.15, 0.20, 0.29, 0.27, and 0.20, respectively, which were similar to those measured in a validation study.²²

Statistical Analysis

Because of skewed distributions, SDNN, RMSSD, LF, and HF were log-transformed before analysis. The LF/HF ratio was calculated using the log-transformed LF and HF values. TG, HOMA-IR, and ISI were also log-transformed, and geometric means were calculated as representative values. Sex- and age-adjusted means were calculated using analysis of covariance. Odds ratios (ORs) and 95% confidence intervals (CIs) for MetS presence grouped by quartiles of HRV parameters were calculated using logistic

regression analysis and adjusted for sex, age, BMI, smoking, alcohol consumption, physical activity, and HOMA-IR. The trend test for ORs was performed using log-transformed continuous values for SDNN, RMSSD, LF, HF, and LF/HF in each model. Interaction associations between HRV parameters and insulin sensitivity on MetS were examined using additive and multiplicative scales in the logistic models. For additive interactions, the relative excess risk caused by interaction (RERI) was calculated as follows:²³ $OR_{11}-OR_{10}-OR_{01}+1$. If RERI >0, then the additive interaction was defined as being positive. The 95% CI for RERI was also computed to assume RERI >0 was statistically significant. For multiplicative interactions, we calculated P values using the cross-product terms of 2 factors investigated in the logistic models. Statistical significance was assumed at $P<0.05$. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the sex- and age-adjusted means or percentages of the subjects with the specified number of metabolic risk factors. HRV parameters were significantly associated with the number of risk factors. HOMA-IR and ISI had strong positive associations with the number of risk factors.

Table 4. Interaction Associations of HRV Parameters, HOMA-IR, and ISI With MetS

HRV parameters	With/without MetS, n	HOMA-IR		With/without MetS, n	ISI	
		Low (Q1–Q3)	High (Q4)		High (Q2–Q4)	Low (Q1)
SDNN						
High (Q2–Q4)	356/1,154	1.00	7.31 (5.47–9.8)	321/1,124	1.00	5.03 (3.76–6.74)
Low (Q1)	186/320	1.36 (1.00–1.85)	6.72 (4.62–9.8)	165/305	1.26 (0.90–1.75)	5.00 (3.50–7.16)
P for interaction=0.12, RERI (95% CI)=−1.0 (−3.8, 1.9)				P for interaction=0.37, RERI (95% CI)=−0.3 (−2.3, 1.7)		
RMSSD						
High (Q2–Q4)	367/1,171	1.00	6.42 (4.83–8.53)	327/1,138	1.00	4.80 (3.60–6.40)
Low (Q1)	175/303	1.29 (0.94–1.77)	8.32 (5.67–12.2)	159/291	1.36 (0.97–1.90)	5.76 (4.00–8.30)
P for interaction=0.99, RERI (95% CI)=1.6 (−1.6, 4.9)				P for interaction=0.64, RERI (95% CI)=0.6 (−1.6, 2.8)		
LF						
High (Q2–Q4)	355/1,155	1.00	7.58 (5.66–10.1)	323/1,125	1.00	4.88 (3.66–6.51)
Low (Q1)	187/319	1.39 (1.02–1.89)	6.37 (4.38–9.26)	163/304	1.26 (0.90–1.76)	5.39 (3.70–7.85)
P for interaction=0.053, RERI (95% CI)=−1.6 (−4.4, 1.2)				P for interaction=0.62, RERI (95% CI)=0.3 (−1.9, 2.4)		
HF						
High (Q2–Q4)	347/1,167	1.00	5.87 (4.40–7.83)	312/1,132	1.00	4.14 (3.09–5.55)
Low (Q1)	195/307	1.24 (0.90–1.69)	9.40 (6.46–13.7)	174/297	1.17 (0.83–1.64)	6.65 (4.64–9.55)
P for interaction=0.32, RERI (95% CI)=3.3 (−0.2, 6.8)				P for interaction=0.23, RERI (95% CI)=2.3 (−0.01, 4.7)		
LF/HF						
Low (Q1–Q3)	384/1,124	1.00	5.60 (4.24–7.40)	341/1,091	1.00	3.88 (2.93–5.14)
High (Q4)	158/350	1.14 (0.82–1.57)	11.3 (7.45–17.0)	145/338	1.03 (0.73–1.45)	7.50 (5.09–11.0)
P for interaction=0.039, RERI (95% CI)=5.5 (1.0, 10.0)				P for interaction=0.021, RERI (95% CI)=3.6 (0.8, 6.4)		

ORs were adjusted for sex, age, smoking, alcohol consumption, and physical activity. RERI, relative excess risk due to interaction. Other abbreviations as in Tables 1–3.

Table 2 shows sex- and age-adjusted means of the prevalence of metabolic risk factors, mean number of risk factors, and percentages of individuals with MetS by HRV parameter quartiles. SDNN, RMSSD, LF, and HF were negatively associated with increased waist circumference, BP, lipid profiles, and FG. There was a similar negative association of SDNN, RMSSD, LF, and HF with the mean number of metabolic risk factors and the percentage of subjects having MetS. The lowest number of risk factors and percentage of MetS in LF/HF were found in the second quartile.

Multivariate logistic regression analysis for the presence of MetS was done using 3 statistical models (**Table 3**). In Model 1 (sex- and age-adjusted), the highest quartile of SDNN, RMSSD, LF, and HF vs. the lowest one was significantly associated with MetS. For LF/HF, the highest quartile was compared with the second quartile, which was also significant, because the percentage of individuals with MetS was lowest in the second quartile, showing a U-shaped association. When adjusted for BMI, alcohol consumption, and smoking (Model 2), the significant associations remained. Furthermore, when adding HOMA-IR into Model 2 (Model 3), only RMSSD, HF and LF/HF remained associated with MetS, and the association of SDNN and LF was no longer significant. In addition, we calculated ORs adjusted for ISI in place of HOMA-IR, which did not change the associations (data not shown).

In **Table 4**, multiplicative and additive interactions between each HRV and insulin parameter, including the association with MetS, were tested using the joint effect of

ORs on MetS adjusted for covariates. For HOMA-IR, the ORs of the combined effects of high HOMA-IR with low RMSSD, low HF, and high LF/HF on MetS showed more than an 8-fold increase, and the multiplicative interaction of LF/HF with MetS was significant (P for interaction, 0.039). Furthermore, additive interactions for HF and LF/HF with MetS were found. The RERI for HF was 3.3 (95% CI, −0.2 to 6.8, P=0.062) and for LF/HF was 5.5 (95% CI, 1.0–10.0, P=0.016). For ISI, similar interactions were observed for HF and LF/HF. We also found significantly positive additive interactions of low ISI with low HF (RERI=2.3, 95% CI, −0.01 to 4.7, P=0.051) and high LF/HF (RERI=3.6, 95% CI, 0.8–6.4, P=0.012) on MetS.

Discussion

Low RMSSD, low HF, and high LF/HF were significantly associated with MetS, independent of smoking, alcohol consumption, physical activity, and HOMA-IR. Additive interactions of high LF/HF with high HOMA-IR (or low ISI) on MetS were significantly positive. We found that low HRV and sympathetic dominance modified the association of IR or low insulin sensitivity with MetS.

HRV is a noninvasive tool for evaluating autonomic nervous system function.¹² SDNN and LF are considered to represent overall sympathetic and parasympathetic activity, while RMSSD and HF are indices of parasympathetic activity, and LF/HF is an indicator of sympathovagal balance. When adjusted for HOMA-IR (or ISI), the association of SDNN and LF with MetS was greatly attenuated,

and neither HRV parameter showed a significant additive interaction association. The 2 branches of the autonomic nervous system participate in control of insulin action, and insulin itself is strongly implicated in the development of MetS.^{2,3} Thus, our results suggested that overall autonomic function contributes to MetS dependent on IR or insulin sensitivity.

A literature search was performed on the association between HRV and MetS,¹⁸ and included 14 studies that met the inclusion criteria. Of these, however, only 3 involved general populations, and there were few studies that assessed insulin action using OGTTs and the interaction of lowered HRV with MetS. Our data were similar to these previous findings and supported the idea that autonomic imbalance predicts the development of MetS.²⁴ In addition, we have presented new evidence that low RMSSD and HF, or high LF/HF (i.e., an imbalance of sympathovagal activity) was associated with an increased number of metabolic risk factors and MetS.

The mechanism by which enhanced sympathetic activity and lower parasympathetic activity induces or predicts IR is not fully understood. One reasonable explanation is the HISS pathway, which is controlled by vagal tone.^{14,15} HISS is considered to act on skeletal muscle to stimulate glucose storage as glycogen. Therefore, if the parasympathetic function is impaired, HISS is not released from the liver and as a consequence hyperglycemia, hyperinsulinemia, and obesity will occur.

In general, additive interactions are useful to indicate subgroups in which an intervention will be most effective.²³ Alternatively, an interaction test can be used to detect a causal relationship rather than a simple association. Therefore, our results of the interaction tests supported why we can exclude the alternative possibility that MetS or IR induces high sympathetic activity. In addition, socioeconomic status and lifestyle factors affect CVD risk. Vagal tone may be a link between them;^{25,26} risk factors such as a sedentary lifestyle may result in imbalance of the autonomic nervous system, contributing to poor health outcomes. The presence of an additive interaction implies that the link between autonomic imbalance and IR contributes to a constellation of metabolic risk factors.²⁴

The primary strength of the present study is that it included a large number of lifestyle variables and their relationships to OGTT and 1-h- and 2-h-postload insulin concentrations. Nonetheless, several potential limitations should be noted. First, because this was a cross-sectional study, we could not establish a causal relationship between decreased HRV and MetS, although our hypothesized mechanism is that autonomic imbalance links these factors. A longitudinal study is therefore needed to ascertain the association. Second, we could not exclude the effects of agents that influence autonomic cardiac function, such as antihypertensive drugs. Our data on medication use were based on a self-administered questionnaire that did not identify specific classes of drugs. Nonetheless, sensitivity analysis showed that the associations remained unchanged when patients taking antihypertensive drugs were excluded. Third, because our subjects were volunteers from a single community, our findings may not be representative of the general Japanese population.

Conclusions

Low HRV, leading to sympathovagal imbalance, modifies

the association of IR and low insulin sensitivity with MetS. Assessment of HRV is practical as a noninvasive tool to detect MetS risk. Individuals with lower HRV levels and sympathetic dominance are at increased risk of developing MetS as a consequence of accumulation of its components. HRV assessment will provide new insight into preventing the occurrence of MetS and CVD in the clinical setting. The objective of future studies should be to determine whether or not the intervention of increasing vagal tone prevents the development of MetS.

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Conflict of Interest

None.

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