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ORIGINAL ARTICLE

The effect of metabolic syndrome on heart rate turbulence in non-diabetic patients

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Abstract

Background: *Metabolic syndrome (MetS), which includes a cluster of risk factors, is being increasingly recognized as a new risk factor for cardiovascular disease. Heart rate turbulence (HRT) is a Holter-based non-invasive method for detecting cardiac autonomic imbalance and is an independent, powerful predictor of cardiac arrhythmias and sudden cardiac death in different patient groups. This study evaluated the effect of MetS on HRT in non-diabetic patients.*

Methods: *This study included 80 non-diabetic MetS subjects and 50 healthy subjects. All 130 subjects underwent a 24-h ambulatory Holter electrocardiogram recording. Two indices of HRT were analyzed: turbulence onset (TO) and turbulence slope (TS). HRT values were classified into 3 categories for risk stratification: 1) Category 0, TO and TS were normal; 2) Category 1, either TO or TS was abnormal; 3) Category 2, both TO and TS were abnormal.*

Results: *When we compared MetS rates in the HRT risk stratification groups, there were significant differences for all groups as compared with the controls (Category 0 = MetS 28.8%, n = 15, Control 71.2%, n = 37, p < 0.001; Category 1 = MetS 80.8%, n = 42, Control 19.2%, n = 10, p < 0.001; Category 2 = MetS 88.5%, n = 23, Control 11.5%, n = 3, p < 0.001). In addition, TO and TS abnormalities were correlated with the number of MetS components (r = 0.608, p < 0.001; r = –0.388, p < 0.001, respectively).*

Conclusions: *To our knowledge, this is the first study to establish a relationship between HRT and MetS. These findings suggest that MetS adversely affects HRT scores. In addition, the number of MetS components is related to impaired HRT scores.* (Cardiol J 2012; 19, 5: 507–512)

Key words: metabolic syndrome, heart rate turbulence, cardiovascular risk

Introduction

Heart rate turbulence (HRT) is a Holter-based non-invasive method for detecting cardiac autonomic imbalance. This evaluation method is based on the physiological sinus node response to a premature ventricular beat [1]. Cardiac autonomic im-balance, manifested by impaired HRT, is a powerful risk factor for sudden cardiac death and malignant ventricular arrhythmia in patients with myocardial infarction or congestive heart failure [2, 3].

Metabolic syndrome (MetS) consists of a group of cardiovascular (CV) risk factors that includes abdominal obesity, dyslipidemia, hypertension, and

impaired glucose metabolism. Despite the ties to dyslipidemia, insulin resistance, elevated blood pressure, and abdominal obesity, the main pathophysiological mechanism underlying the increased CV risk is unclear. Autonomic dysfunction has also been implicated in the pathophysiology of MetS [4]. MetS is associated with a 2-fold increase in CV outcomes and a 1.5-fold increase in all-cause mortality [5]. Cardiac autonomic dysfunction may contribute to the pathophysiological process of MetS with respect to CV outcomes. We hypothesized that the increased CV risk of MetS was related to cardiac autonomic dysfunction.

This study evaluated the relationship between MetS and cardiac autonomic dysfunction as detected by HRT. Since diabetic neuropathy and autonomic dysfunction in diabetic patients may affect HRT analysis, the study evaluated non-diabetic patients.

Methods

Patients

Eighty non-diabetic patients with MetS and 50 healthy age and sex matched subjects from Saitama Medical University Hospital Cardiology Department outpatient clinics were enrolled in this study. The control group consisted of 50 healthy persons, whose Holter recordings demonstrated ventricular premature beats (VPB) suitable (> 6/day) for HRT analysis. Subjects were excluded if they had rhythms other than sinus as atrial fibrillation or flutter, diabetes mellitus, coronary artery disease, an implanted permanent pacemaker, drug use that may influence HRT such as; beta blockers, Ca++ channel blockers, Group I and IV antiarrhythmics, ACE inhibitors, etc., inadequate VPB to measure HRT, and refusal to provide informed consent for the study. The study was approved by the local ethic committee and all subjects gave written informed consent.

Anthropometric analysis

Body weight and height was measured with the patient in light clothes without shoes to the nearest 0.5 kg and 0.5 cm. Waist circumference was measured horizontally in quiet expiration, halfway between the lower rib and the iliac crest. Body mass index was calculated as weight [kg] divided by height squared [m].

Metabolic syndrome definition

The presence of MetS was established according to National cholesterol education program-adult treatment panel III criteria, using the Asian Pacific World Health Organization modification [1]. MetS was diagnosed if more than 3 of the following components are present; a) abdominal obesity: waist circumference > 90 cm in men and > 80 cm in women; b) triglyceride level 1.7 mmol/L or greater; c) HDL-cholesterol less than or equal to 1.0 mmol/L in men and less than or equal to 1.3 mmol/L in women; d) blood pressure: ≥ 130/85 mm Hg; e) fasting glucose level of 6.1 mmol/L or greater.

Holter monitoring and HRT analysis

The 24-h Holter recordings of all patients were analyzed to obtain the HRT parameters of turbulence onset (TO) and turbulence slope (TS). Recordings were performed with a GE Marquette SEER system digitizing at 125 samples per second (GE Marquette, Milwaukee, WI). QRS detection, morphology classification (normal, aberrant, premature aberrant) and measurement of the RR interval were automatically performed by the system. All Holter files were reviewed and manually corrected. HRT analysis was performed on sequences of sinus RR intervals after VPB. The evaluated sinus rhythm immediately before and after the VPB was free from any arrhythmia or other artifacts. The HRT after a VPB comprises two parameters: TO, which represents the initial acceleration (shortening of R-R intervals); and TS, which represents the subsequent deceleration (prolongation of R-R intervals) [2]. In mathematical terms, TO (%) (normal < 0) is the difference between the sum of the first two R-R intervals after the compensatory pause following a VPB and the sum of the last two R-R intervals preceding the VPB, divided by the sum of the last two R-R intervals preceding the VPB. The TS (normal > 2.5 ms/R-R interval number) were accepted as the steepest slope of a regression line over any sequence of five consecutive R-R intervals. The average of HRT values measured for all convenient VPBs was accepted as the final HRT value to characterize the patient [3, 4]. For the risk stratification HRT values [5] are classified into 3 categories: 1) Category 0: TO and TS are normal; 2) Category 1: one of TO or TS is abnormal; 3) Category 2: both TO and TS are abnormal.

Statistical analysis

All statistical analyses were performed using the SPSS software package 15.0 (SPSS Inc, Chicago, IL, USA). Data are presented as frequencies and percentages for categorical variables and mean ± SD for continuous variables. Differences between 2 groups were assessed using the χ^2 and unpaired t-tests. Because total onset, total slope and MetS

Table 1. Baseline characteristics of the two study groups.

	MetS group (n = 80)	Control group (n = 50)	P
Age [years]	42.1 ± 5.0	41.0 ± 5.1	0.351
Gender (male/female)	38/42	24/26	0.647
Body mass index [kg/m^2]	28.7 ± 4.6	28.3 ± 4.9	0.693
Waist circumference [cm]:			
Men	103.1 ± 16.8	94.8 ± 11.7	0.041
Women	107.2 ± 12.7	95.5 ± 12.4	0.032
Fasting plasma glucose [mg/dL]	101.7 ± 21.2	94.3 ± 11.4	0.306
Triglyceride [mg/dL]	161.6 ± 65.4	105.0 ± 44.2	*0.028*
HDL-cholesterol [mg/dL]	41 ± 8	46 ± 12	*0.038*
Current smoking	42 (52.5%)	13 (26.0%)	*0.012*
Systolic blood pressure [mm Hg]	132.5 ± 8.5	123.3 ± 6.4	0.009
Diastolic blood pressure [mm Hg]	89.2 ± 8.7	72.4 ± 6.2	0.011

values were not normally distributed, between--group differences were assessed by the one-way ANOVA. Pearson's and Spearman's correlation coefficients were used to test the relationship between the TO, TS and MetS factors. Linear logistic regression analysis was performed to identify the independent determinants of MetS (including systolic blood pressure, diastolic blood pressure, waist circumference, triglyceride levels, HDL-cholesterol levels, fasting glucose, TO and TS). A value of $p < 0.05$ was considered statistically significant.

Results

Eighty MetS patients (38 [47.5%] male, 42 [52.5%] female) and 50 healthy control (24 [48.0%] male, 26 [52.0%] female) were included in this study. MetS group clinical characteristics were shown in Table 1. When we compare the MetS rates with respect to the HRT risk stratification groups, there were significant differences for all category (Category 0 = MetS 28.8%, n: 15, Control 71.2%, n: 37, $p < 0.001$; Category 1 = MetS 80.8%, n: 42, Control 19.2%, n: 10, $p < 0.001$; Category 2 = MetS 88.5%, n: 23, Control 11.5%, n: 3, $p < 0.001$, respectively) (Fig. 1). TO and TS values of MetS group were significantly different compared with
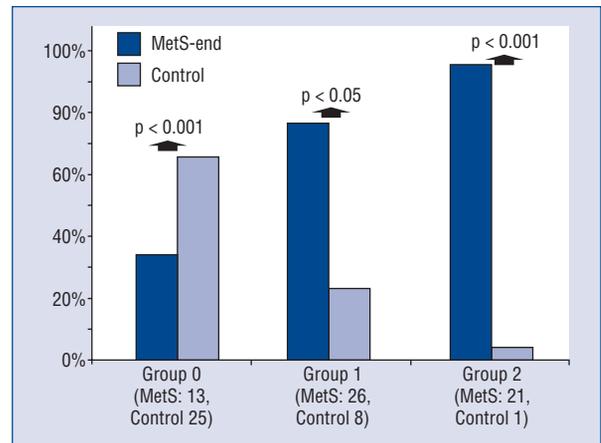
Figure 1. Metabolic syndrome (MetS) rates with respect to the heart rate turbulence risk stratification group.

the control group (0.36 ± 1.40 vs. –0.49 ± 1.03, $p < 0.001$; 2.44 ± 1.37 vs. 1.92 ± 0.70, $p = 0.012$, respectively).

In the subgroup analysis of MetS group, patients were compared in number of MetS components, there were statistically significant difference in TO and TS values (Table 2). Also a strong positive correlation between the number of MetS com-

Table 2. Subgroup analysis of metabolic syndrome (MetS) group in total onset and total slope.

	MetS (mc: 3)	MetS (mc: 4)	MetS (mc: 5)	P
Total onset	–0.5 ± 1.2	0.7 ± 0.9	1.6 ± 1.1	< 0.001
Total slope	3.2 ± 0.5	2.0 ± 1.3	1.4 ± 1.2	< 0.001

mc — number of the metabolic syndrome components
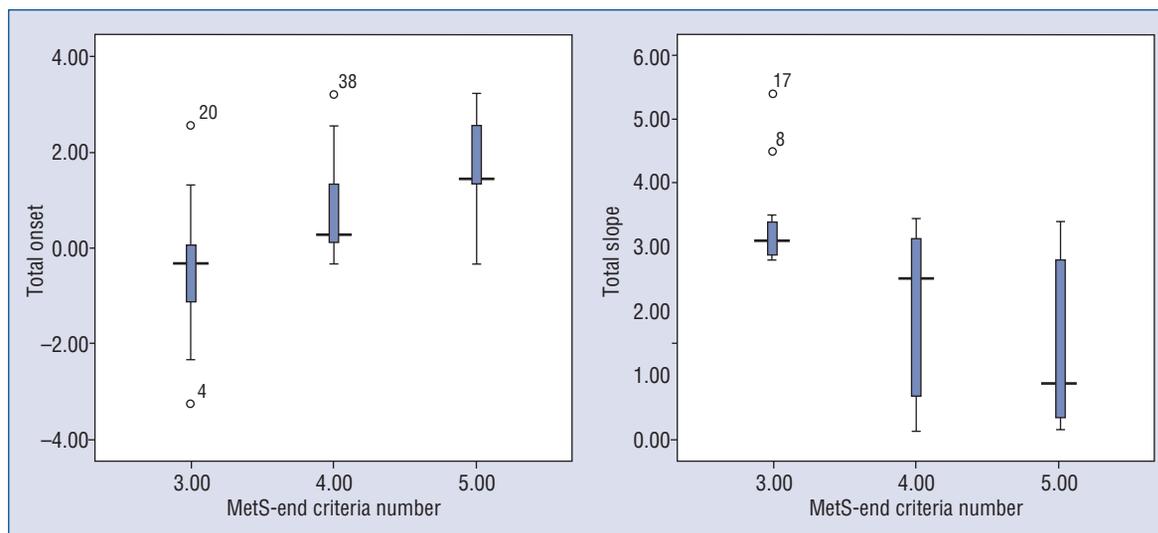
Figure 2. Correlation between metabolic syndrome (MetS) criteria number and heart rate turbulence parameters.

ponents and TO, a moderate negative correlation between the number of MetS components and TS were detected (r = 0.608, p < 0.001, r = –0.388, p < 0.001) (Fig. 2). In linear logistic regression analysis (including systolic blood pressure, diastolic blood pressure, waist circumference, triglyceride levels, HDL-cholesterol, fasting glucose, TO and TS) waist circumference, systolic blood pressure, triglyceride levels and TO was found to be significant and independent predictors of MetS (Table 3).

Patients who have 5 components of MetS were more likely than the 3 components MetS patients to have Category 2 (adjusted odds ratio [OR] = 1.4; 95% confidence interval [CI] = 1.03–2.03; p = 0.04). Patients who have 4 criteria of MetS were not more likely than 3 criteria MetS group to have Category 1 turbulence (adjusted OR = 1.2; 95% CI = 0.8––1.9; p = 0.29) but were more likely to have Category 2 turbulence (adjusted OR = 1.8; 95% CI = 1.1––3.0; p = 0.03). All group of MetS were more likely than the Control group to have Category 1 or Category 2 turbulence (respectively, 2.3; 95% CI = 1.1––4.9; p = 0.03; 1.4; 95% CI = 1.03–2.03; p = 0.04; 1.3; 95% CI = 1.1–1.9; p = 0.038).

A statistically significant difference between the two groups was found in terms of VPB number detected by 24-h Holter (MetS: 36.73 ± 28.81; Control: 10.58 ± 10.31; p < 0.001). A statistically strong significant positive correlation was found between the number of VPB and number of MetS components (r = 0.695, p < 0.001). When 3 groups according to the number of MetS components were formed, a statistically significant difference was

Table 3. Linear logistic regression analysis of variables associated with metabolic syndrome.

	Beta	95% CI	P
Fasting glucose	0.285	0.001–0.002	0.250
Waist circumference	0.372	0.006–0.014	< 0.001
Triglyceride	0.290	0.001–0.002	0.005
HDL-cholesterol	0.033	–0.010–0.007	0.394
Systolic BP	0.321	0.004–0.018	0.002
Diastolic BP	0.127	–0.003–0.014	0.184
Total onset	0.201	0.002–0.012	0.009
Total slope	0.031	–0.002–0.001	0.588

CI — confidence interval; BP — blood pressure

found in terms of the VPB number among the groups (12.85 ± 4.59; 40.60 ± 34.93; 80.34 ± 67.80; p < 0.001, respectively).

Discussion

The principal findings of our study were that 1) MetS patients were more likely to have abnormal HRT than the control group, 2) the TO and TS were significantly different between the MetS and Control groups, 3) there were significant differences in TO and TS in the MetS subgroup analysis when comparing the number of MetS components, 4) TO was a significant, independent predictor of MetS presence, and 5) there was a significant positive correlation between the numbers of VPBs and MetS components.

The heart is highly innervated by vagal and sympathetic fibers and is very sensitive to autonomic influences [6]. The autonomic nervous system responds to all changes sensed by baroreceptors and chemoreceptors to maintain CV homeostasis [2]. Studies have shown that cardiac autonomic dysfunction plays an essential role in the development of CV disease in MetS patients [7, 8]. HRT is an important parameter for evaluating cardiac autonomic functions. A blunted HRT reflects cardiac autonomic dysfunction, especially reduced baroreflex sensitivity [5]. HRT is reduced not only following myocardial infarction, but also in patients with a variety of diseases affecting the heart, congestive heart failure, and possibly diabetes. Further, HRT may provide clinically useful risk stratification information [9–11].

Many studies have suggested that MetS is a powerful predictor of the risk of developing CV disease [12]. In a meta-analysis of 21 studies, CV disease, coronary heart disease, stroke, and mortality were more prevalent in patients with MetS than in patients without it [13]. We found a similar result in that MetS patients demonstrated abnormal HRT more often than the control group. In addition, the MetS group showed abnormal TO and TS values as compared with the control group. We believe that the relationship between MetS and CV disease development is related to cardiac autonomic dysfunction.

The number of MetS components is associated with CV mortality and morbidity [7, 8]. Protorov and Glukhovsky [14] showed a significant correlation between arrhythmias and the number of MetS components. Similarly, we found that the number of MetS components was positively correlated with TO and negatively correlated with TS. Therefore, the number of MetS components, including abdominal obesity, low HDL-cholesterol levels, hypertriglyceridemia, high blood pressure, and high fasting glucose, is an important factor for increased CV risk.

Cardiac autonomic dysfunction in patients with MetS can be evaluated using different parameters, such as heart rate variability (and heart rate recovery. However, HRT has not been used in this situation. Studies have established a relationship between cardiac autonomic dysfunction and MetS. One study revealed that heart rate recovery is significantly impaired in young adult males with MetS [7]. Stein et al. [15] found that reduced heart rate variability was a valuable marker of cardiac autonomic dysfunction, and was associated with MetS, independent of fasting glucose levels. We also determined that HRT was impaired in MetS patients without diabetes mellitus as compared with healthy subjects. To our knowledge, this is the first study establishing a relationship between HRT and MetS.

Another important risk factor for CV mortality is VPBs [16]. Premature ventricular contractions leading to ventricular tachycardia, which can in turn degenerate into ventricular fibrillation, is a common mechanism underlying sudden cardiac death. Clinically, a decrease in premature ventricular contractions would improve ventricular function and sudden cardiac death [17]. Provotorov and Glukhovsky [18] found that patients with MetS more frequently had polymorphic VPBs associated with an elevated mean heart rate. Similarly, we found a significant difference between the MetS and Control groups in terms of VPBs and a significant positive correlation between the numbers of VPBs and MetS components.

Limitations of the study

The main limitation of our study was the small sample size. Since a small sample size results in low statistical power for equivalency testing, negative results may be simply due to chance. In addition, we did not examine the impact of circadian variation. Diurnal fluctuations in autonomic tone suggest one value for HRT in 24 h. This may also influence the results.

Conclusions

In conclusion, our results revealed that HRT is significantly impaired in MetS patients without diabetes mellitus. HRT is a significant predictor of cardiac autonomic dysfunction and it is useful to identify MetS patients without diabetes mellitus who have potentially increased CV risk.

Conflict of interest: none declared

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