

## HEART RATE VARIABILITY IN PATIENTS WITH METABOLIC SYNDROME

\*Özcan Özdemir M.D., \*\*Fehmi Kaçmaz M.D., \*\*\*Ömer Alyan M.D., \*\*\*\*Bilal Geyik M.D., \*\*\*\*\*Tahir Durmaz, M.D.,

\*Çağ Hospital, Cardiology Clinics, ANKARA, \*\*Government Hospital, Cardiology Clinics, BINGOL, \*\*\*Dicle University, Cardiology Department, DIYARBAKIR, \*\*\*\*Kocatepe Heart Center, ANKARA, \*\*\*\*\*Ataturk Education and Research Hospital, Cardiology Clinics, ANKARA

**S**Metabolik sendrom (MetS) çeşitli metabolik bozuklukların bir arada bulunması ile karakterize artmış diabetes mellitus ve kardiyovasküler hastalık gelişimi ile birliktelik gösteren bir klinik sendromdur. Kalp hız değişikliği (KHD) artmış kardiyak mortalite riskini belirlemede yaygın olarak kullanılmaktadır. Bu çalışmada, MetS'lu hastalarda KHD ve KHD'yi etkileyen faktörleri araştırmak amaçlanmıştır.

Çalışmaya 56 hasta (20 erkek, 36 kadın) alınmıştır. C-reaktif peptid (CRP) ve açlık kan şekeri (AKŞ) MetS'lu hastalarda yüksek bulunmuştur. MetS'lu hastalarda, KHD parametrelerinden ortalama kalp hızı (OKH), LF ve LF/HF oranı yüksek; SDNN, RMSSD, PNN50 ve HF değerleri düşük bulunmuştur. Korelasyon analizinde SDNN'nin bel çevresi (BÇ) ( $r=-0.4$ ,  $p=0.001$ ) ve AKŞ ( $r=-0.3$ ,  $p=0.03$ ) ile; LF'nin BÇ ( $r=0.6$ ,  $p=0.001$ ) ve AKŞ ( $r=0.5$ ,  $p=0.001$ ) ile; HF'nin BÇ ( $r=-0.4$ ,  $p=0.003$ ), CRP ( $r=-0.3$ ,  $p=0.02$ ) ve AKŞ ( $r=-0.4$ ,  $p=0.04$ ); LF/HF'nin ise BÇ ( $r=0.6$ ,  $p=0.001$ ), CRP ( $r=0.3$ ,

$p=0.01$ ) ve AKŞ ( $r=0.6$ ,  $p=0.001$ ) ile ilişkili olduğu görülmüştür. Regresyon analizinde ide SDNN'yi etkileyen bağımsız değişkenin BÇ ( $\beta=-0.4$ ,  $p=0.02$ ); LF/HF oranını etkileyen bağımsız değişkenlerin ise BÇ ( $\beta=0.4$ ,  $p=0.01$ ) ve AKŞ ( $\beta=0.3$ ,  $p=0.02$ ) olduğu bulunmuştur.

Sonuç olarak, MetS'lu hastalarda KHD azalmış, sempatetik aktivite artmış ve sempatovagal denge bozulmuştur. MetS kriterlerinden bir çoğunun KHD parametreleri ile ilişkili olduğu görülmüşse de KHD'ni etkileyen bağımsız değişkenlerin bel çevresi ve açlık kan şekeri olduğu saptanmıştır. Azalmış KHD ve bozulmuş sempatovagal dengenin MetS'lu hastalarda artmış ani ölüm riskiyle ilişkili olabileceği düşünülmüştür.

**Anahtar kelimeler:** Metabolik sendrom, Kalp hız değişikliği

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### INTRODUCTON

Metabolic syndrome (MetS) is characterized by the clustering of glucose intolerance, insulin resistance, central obesity, dyslipidemia, and hypertension, each of which is a risk factor for cardiovascular disease<sup>1</sup>. This syndrome is increasing in importance due to its becoming more common in several countries<sup>2,3</sup> and because it is known to play an important role in cardiovascular morbidity and mortality and the development of diabetes<sup>4,5</sup>. Subjects with metabolic syndrome have autonomic nervous system dysfunction characterized by predominance of the sympathetic nervous system in many organs. The mechanisms linking metabolic

syndrome with sympathetic activation are complex and not clearly understood. Whether sympathetic overactivity is involved in the development of the metabolic syndrome or is a consequence of it remains to be elucidated since data from prospective studies are missing<sup>6</sup>.

Heart rate variability (HRV), another predictor of cardiovascular disease, has been widely used to assess cardiac autonomic balance due to its noninvasive measurement and high repeatability<sup>7</sup>. Decreased HRV is considered to be an accurate indicator of poor outcome in the general population and in patients with cardiovascular disease, diabetes mellitus, and other conditions<sup>8,9</sup>. A recent study reported an association between HRV and MetS, suggesting that MetS disorders adversely affect cardiac autonomic control and reduced cardiac autonomic control contributes to an increased risk of cardiovascular events in individuals

Corresponding Author: Dr. Özcan ÖZDEMİR  
Kardelen Mah. Batıpark Konutları A blok  
No:15 Batıkent/ANKARA  
e-mail: drozdemir75@yahoo.com  
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with these diseases<sup>10</sup>. In this study, we aimed to show the heart rate variability in the patients with MetS and the factors affecting HRV parameters.

## MATERIAL and METHODS

**Study Population:** The patients underwent coronary angiography in our clinics were enrolled in this study. The inclusion criteria were the following: agreement and cooperation of the subject to participate in the study, performance of HRV measurement, several tests for examining MetS components, and response to the interview. All subjects completed HRV tests conducted by trained technicians, and after fasting for 12 hours, a blood sample was drawn for triglyceride, C-reactive protein (CRP), highdensity lipoprotein (HDL) cholesterol, lowdensity lipoprotein (LDL) and fasting blood glucose (FBG). The subjects also responded to a questionnaire that included general characteristics. The average blood pressure (BP) was taken by a physician using mercury manometers after subjects tested for 5 minutes in a sitting position. The waist circumference (WC) was measured at the midpoint between the lower rib and the iliac crest while participants were in a standing position at the end of a normal expiration. Anthropometric measurements including height, weight, and the sagittal abdominal diameter were taken under standardized conditions by the same three trained technicians and the methods have been previously reported<sup>11</sup>. Patients with acute or chronic inflammatory disease, myeloproliferative disorders, malignancies, renal, hepatic or thyroid disease or those treated with immunosuppressive or cytotoxic drugs, acute coronary syndromes within 3 months, atrial fibrillation were excluded. Written informed consent was obtained from all subjects. Local ethics committee approved the study.

Definition of the metabolic syndrome; National Cholesterol Education Program III (NCEP III) criteria: According to the NCEP III criteria, three or more alterations among the following are required to define the MetS: large waist circumference (88 cm in women and 102 cm in men), elevated triglycerides (150 mg/dL), low HDL cholesterol (men ,40 mg/dL and women, 50 mg/dL), elevated fasting glucose (110 mg/dL) and elevated systolic (130 mmHg) or diastolic blood pressure (85 mmHg), or use of anti-hypertensive medications<sup>12</sup>.

**Heart rate variability analysis:** All subjects underwent 3 channel 24-hr Holter ambulatory ECG monitoring (Biomedical System Century 2000/3000 Holter

System, Version 1.32). Recordings were analyzed by 'Biomedical Systems Century 2000/3000 HRV Package System', following manual adjustment of RR intervals. Analog data was digitized at 200 Hz and edited by a cardiologist. The validation procedure consisted of beat labeling and tagging of noisy regions. The continuous series of RR (NN) intervals (tachogram) was obtained and all 5-min segments with at most 5 isolated ectopic beats were retained for spectral analysis. Recordings with <18 h of data or <85% of qualified sinus beats were excluded. The time and frequency-domain analysis of HRV were performed according to the recommendation of the task force<sup>7</sup>. The mean heart rate, standard deviation of all NN intervals (SDNN), the standard deviation of the 5-minute mean RR intervals (SDANN), root mean square of successive differences (RMSSD) were measured in the time domain analysis of HRV. A reduced SDNN has been considered reflecting diminished vagal and increased sympathetic modulation of sinus node. The power spectrum of HRV was measured using fast-Fourier transform analysis in 4 frequency bands: <0.0033 Hz (ultra low frequency, ULF), 0.0033 to 0.04 (very low frequency, VLF), 0.04 to 0.15 (low frequency, LF) and 0.15 to 0.40 (high frequency, HF). HF was used a marker of parasympathetic nervous system and LF was used a marker of parasympathetic nervous system and sympathetic activity<sup>7</sup>. We also measured the ratio of low to high frequency power (LF/HF) reflecting the sympathovagal balance. High values indicated dominant sympathetic activity<sup>13</sup>.

## DATA ANALYSIS

The results are given as means  $\pm$  SD or the number. The values were log-transformed and a normal distribution was confirmed by the Komolgorov-Smirnov goodness-of-fit test ( $P>0.15$ ). Based on the NCEP-ATP III, the two groups (with vs. without MetS) were compared with each other using the t-test and chi-square test. Pearson's correlation coefficients between HRV indices and all MetS components were calculated. The relationship between MetS and HRV variables was investigated by linear regression.

## RESULTS

Fifty-six<sup>56</sup> patients (20 male, 36 female) were enrolled in this study. There were no differences between both groups regarding age, sex, hypertension, diabetes mellitus, coronary artery disease, smoking and drugs such as ACE inhibitors. Statin

**Table 1:** Basal Clinical Variables of Patients with and without Metabolic Syndrome

Variables	Metabolic Syndrome (n=32)	Control (n=24)	P
Age	60.7±10.4	63.2±7.4	0.4
Male/Female	9/23	11/13	0.2
DM	2	1	0.7
HT	28	19	0.4
Smoking	19	17	0.4
CAD	25	20	0.06
Statin	17	2	0.001
ACE-I	22	14	0.3
BMI	27.9±7.5	22.7±1.6	0.001
WC	105.2±7.9	79.4±5.5	0.001

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary artery disease, BMI: Body mass index, WC: Waist Circumference

**Table 2:** Laboratory Parameters of Patients with and without Metabolic Syndrome

Variables	Metabolic Syndrome (n=32)	Control (n=24)	P
Total Cholesterol	190.7±48.2	211.5±28.4	0.04
Triglyceride	184.7±77.4	152.8±26.6	0.04
HDL	40.0±8.4	44.1±8.8	0.08
LDL	112.7±37.3	135.7±30.3	0.001
CRP	8.0±7.1	4.7±1.2	0.02
Uric acid	6.2±1.4	4.5±0.9	0.001
Fibrinogen	4.0±1.4	4.2±0.8	0.6
FBG	104.7±12.0	90.7±4.6	0.001

HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C-reactive peptide, FBG: Fasting blood glucose.

**Table 3:** Heart Rate Variability Analysis of Patients

Variables	Metabolic Syndrome (n=32)	Control (n=24)	P
Mean HR	76.6±8.9	70.9±4.5	0.006
SDNN	84.1±14.5	108.4±34.1	0.001
RMSSD	26.3±7.0	38.8±7.6	0.001
PNN50	9.5±2.5	14.4±3.2	0.001
LF (nu)	62.0±7.7	50.3±4.2	0.001
HF (nu)	34.6±7.0	40.8±4.3	0.001
LF/HF	1.9±0.4	1.2±0.1	0.001

HR: Heart rate

use, body mass index (BMI) and waist circumference (WC) were higher in patients with MetS. Total and LDL-cholesterol levels were higher, HDL levels were lower in the control group. C-reactive peptide (CRP), uric acid and fasting blood glucose (FBG) levels were higher in the patients with MetS (Table 1). As to HRV parameters, mean heart rate (HR), LF and LF/HF ratio were higher; SDNN, RMSSD, PNN50 and HF were lower in the patients with MetS (Table 2). Correlation analysis showed that mean HR was correlated with TG (r=0.4, p=0.006); SDNN was correlated

with WC (r=-0.4, p=0.001) and FBG (r=-0.3, p=0.03); RMSSD was correlated with WC (r=-0.5, p=0.001); PNN50 was correlated with WC (r=-0.6, p=0.001), CRP (r=-0.3, p=0.02) and FBG (r=-0.4, p=0.002); LF was correlated with WC (r=0.6, p=0.001) and FBG (r=0.5, p=0.001); HF was correlated with WC (r=-0.4, p=0.003), CRP (r=-0.3, p=0.02) and FBG (r=-0.4, p=0.04); LF/HF was correlated with WC (r=0.6, p=0.001), CRP (r=0.3, p=0.01) and FBG (r=0.6, p=0.001) (Table 3). Regression analysis demonstrated that the only independent factor affecting SDNN

**Table 4:** Correlation analysis

	Age	TG	HDL	WC	CRP	FBG
Mean HR	r=0.02 p=0.9	r= 0.4 p=0.006	r=-0.1 p=0.7	r=0.2 p=0.09	r=-0.1 p=0.3	r=0.2 p=0.1
SDNN	r=-0.1 p=0.7	r= 0.1 p= 0.6	r=0.1 p=0.6	r=-0.4 p=0.001	r=-0.2 p=0.2	r=-0.3 p=0.03
RMSSD	r=-0.1 p=0.3	r=- 0.1 p= 0.4	r=0.3 p=0.06	r=-0.5 p=0.001	r=-0.1 p=0.4	r=-0.2 p=0.07
PNN50	r=-0.2 p=0.3	r=- 0.1 p= 0.6	r=0.2 p=0.2	r=-0.6 p=0.001	r=-0.3 p=0.02	r=-0.4 p=0.002
LF	r=-0.2 p=0.4	r= 0.1 p= 0.5	r=-0.2 p=0.2	r=0.6 p=0.001	r=0.6 p=0.2	r=0.5 p=0.001
HF	r=-0.2 p=0.3	r=- 0.1 p=0.5	r=- 0.1 p=0.4	r=-0.4 p=0.003	r=-0.3 p=0.02	r=-0.4 p=0.04
LF/HF	r=0.1 p=0.8	r= 0.1 p=0.5	r=-0.2 p=0.2	r=0.6 p=0.001	r=0.3 p=0.01	r=0.6 p=0.001

WC: Waist circumference

**Table 5:** Factors affecting SDNN in patients with metabolic syndrome

Variables	$\beta$	S.E.	t	p
Age	-0.2	0.4	-0.8	0.4
CAD	0.4	0.9	0.1	0.7
Mean BP	-0.1	11.5	-0.3	0.7
FBG	-0.1	0.4	-0.5	0.6
TG	0.01	0.06	0.09	0.9
HDL	-0.02	0.4	-0.2	0.8
WC	-0.4	0.3	-2.5	0.02
CRP	-0.09	0.01	0.5	0.6

BP: Blood pressure, CAD: Coronary artery disease

**Table 6:** Factors affecting LF/HF ratio in patients with metabolic syndrome

Variables	$\beta$	S.E.	t	p
Age	0.1	0.01	-1.1	0.3
CAD	0.3	0.2	0.5	0.5
Mean BP	0.1	0.2	0.2	0.9
FBG	0.3	0.05	2.4	0.02
TG	-0.1	0.001	-0.5	0.7
HDL	-0.04	0.004	1.0	0.3
WC	0.4	0.004	2.7	0.01
CRP	0.3	0.02	2.1	0.05

was WC ( $\beta=-0.4$ ,  $p=0.02$ ) (Table 4); independent factors affecting LF/HF were FBG ( $\beta=0.3$ ,  $p=0.02$ ) and WC ( $\beta=0.4$ ,  $p=0.01$ ) (Table 5). Factors affecting LF/HF ratio in patients with metabolic syndrome were shown in Table 6.

## DISCUSSION

The main results of the present study are as follows: (i) MetS is associated with lower HRV and

impaired sympathovagal balance; (ii) MetS components are differently associated with HRV components; and (iii) Waist circumference and fasting blood glucose are independent determinants of SDNN and LF/HF ratio in the patients with MetS.

Metabolic syndrome is independently associated with a corrected QT interval duration. This result calls for careful ECG monitoring among persons with MetS for early detection of a long corrected QT inter-

val in order to prevent severe and often fatal arrhythmias<sup>14,15</sup>. Previous studies have shown that hypertension, dyslipidaemia, obesity, diabetes and impaired glucose metabolism are associated with lower HRV<sup>16-18</sup> stated that MetS is associated with lower HRV young adults. Lower vagal activity and increase in sympathetic activity are more prominent in women with MetS. In our study, gender is not a determinant for HRV in patients with MetS. Min et al<sup>19</sup> showed that the overall means of the HRV indices in the group with MetS were significantly lower than those in the group without MetS in Korean adults, and there was a proportional relationship between the components of MetS and HRV.

These associations have not been elucidated, though several explanations have been given. The reduction in HRV seen in the MetS subjects may be explained by the underlying pathophysiology of MetS<sup>20</sup>. Central obesity is considered important in the aetiology of MetS<sup>12</sup>. To be precise, obesity is responsible for decreasing adiponectin, which is produced by adipose tissue, resulting in insulin resistance<sup>21,22</sup>. Insulin resistance, in turn, leads to increased serum insulin levels, which can activate the sympathetic nervous system via glucose metabolism in the ventral medial hypothalamus<sup>22</sup>. Therefore, an increase in sympathetic activity could reflect an increased risk of cardiovascular disease and may be associated with reduced activity of the cardiac autonomic nervous system, which is reflected by the HRV. Alternatively, as suggested by Moller and Kaufman, individuals with MetS have high levels of adipose tissue, atherogenic dyslipidemia, hypertension, and proinflammatory or prothrombotic events, each of which is associated with cardiac autonomic imbalance<sup>23</sup>. Haensel et al. showed<sup>24</sup> that HRV is inversely correlated with inflammatory markers such as CRP and interleukin-6 in healthy individuals as well as in those with cardiovascular diseases. Especially, low frequency heart rate variability, a complex measure reflecting both parasympathetic and sympathetic activity, is the more commonly associated measure linked to inflammatory markers. In our study, CRP was found to be correlated with PNN50, HF and LF/HF ratio but CRP was not an independent determinant. MetS, or a number of MetS components, can have adverse effects on cardiac autonomic control. As in our study, HRV is significantly correlated with most components of MetS, and each MetS component is associated with imbalance in the cardiac autonomic system<sup>25-27</sup>. Cardiac sympathovagal imbalance may affect blood pressure, and obesity may alter the functioning of the

autonomic nervous system<sup>25,26</sup>. Triglyceride, HDL, cholesterol, and fasting blood glucose levels are also related to the regulation of autonomic cardiac function in the general population<sup>27</sup>. Bjorntorp and Rosmond<sup>28</sup> have suggested that the development of MetS is associated with abnormal regulation of the hypothalamic-pituitary-adrenal axis, following elevated cortisol secretion, low sex steroid and growth hormone secretions, and activation of the central sympathetic nervous system. The mechanisms linking MetS with sympathetic activation are complex and not clearly understood. Whether sympathetic overactivity is involved in the development of the metabolic syndrome or is a consequence of it remains to be elucidated since data from prospective studies are missing<sup>6</sup>. But previous studies<sup>18,19</sup> and our results clearly showed that HRV decreases and sympathetic activity increases in the patients with MetS. MetS is associated with a 68% increase in the risk of sudden death, independently of coronary heart disease risk factors, in the middle-aged men initially free of diabetes and ischaemic cardiac disease<sup>29</sup>. Therefore, the increased sympathetic activity and decreased heart rate variability may be responsible for this increased sudden death in patients with MetS.

As a result, HRV decreased, sympathetic activity increased and sympathovagal balance impaired in the patients with MetS. Although most of the components of the MetS are correlated with HRV parameters, waist circumference and fasting blood glucose are two independent parameters affecting HRV. The decreased HRV and impaired sympathovagal balance may partly responsible for the increased sudden death risk in the patients with MetS.

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