This journal is the official publication of Bangladesh Society of Physiologists (BSP)
Web URL: www.banglajol.info/index.php/JBSP

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pISSN-1983-1213; e-ISSN-2219-7508

Article

Article information:
Received: 15th June 2019
Accepted: 28th February 2020
DOI: https://doi.org/10.3329/jbsp.v15i1.48115

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Cite this article:
Munni HA, Begum S. Relationship of heart rate variability with iron status in metabolic syndrome
Bangladesh Soc Physiol 2020;15(1): 46-51

Relationship of heart rate variability with iron status in metabolic syndrome

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Abstract

Background: Clustering of some most dreadful cardiovascular risk factors gives rise to metabolic syndrome (MetS). Higher iron status and impaired cardiac autonomic status may important play role in increased risk of cardiovascular morbidity in this group of patients. **Objective:** To observe the relationship of HRV with iron status in patients with MetS. **Methods:** This cross-sectional study was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from March, 2019 to February, 2020. For this study, 35 MetS female patients aged 25 to 45 years were enrolled in MetS group and equal number of age and sex matched apparently healthy subjects constituted control group. For evaluation of iron status, serum iron, serum ferritin, total iron binding capacity (TIBC) and transferrin saturation (Tsat) were measured by autoanalyzer. HRV was assessed by Powerlab 8/35, AD instruments, Australia. Data were expressed as mean±SD. Statistical analysis was done by Independent sample 't' test and Pearson's correlation coefficient test as applicable. **Results:** In this study, resting pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) were significantly ($p<0.001$) higher and mean heart rate, standard deviation of the RR intervals (SDRR),mean R-R interval, standard deviation of the difference betweensuccessive RR intervals (SDSD), square root of mean squared differences of successive RR intervals (RMSSD), proportion of difference of successive RR interval greater than 50 ms (pRR50) were significantly ($p<0.001$) lower in MetS patients compared to control. Among the parameters of iron status, serum ferritin was significantly ($p\leq<0.05$) higher and TIBCwas significantly($p<0.05$) lower in MetS patients in comparison to control. On correlation analysis, only the TIBC showed significant positive correlation with mean RR interval, SDRR, CVRR, SDSD, RMSSD, pRR50 ($p<0.05$) in MetS patients. **Conclusion:** This study reveals that poor parasympathetic activity is related to higher iron status in metabolic syndrome patients.

Keywords: Metabolic syndrome, iron status, heart rate variability

Introduction

Metabolic syndrome (MetS) is a cluster of major risk factors associated with cardiovascular disease (CVD) and type 2 Diabetes Mellitus. For its associated with higher risk of CVD (twofold), it is also known as cardiometabolic syndrome. According to International Diabetes Federation (IDF), MetS constitutes of central obesity plus any 2 or more of – hypertriglyceridemia, low HDL cholesterol, hypertension, fasting hyperglycemia.[1-2] Cardiovascular dynamic alteration associated with MetS is manifested by autonomic dysfunction.[3-4] Heart rate variability (HRV) is a valuable, widely used method to quantify autonomic function and its individual components.[5] It can be useful for detecting any physiological or pathological modification in heart rate.[6] HRV can be analyzed by several methods. Among them, time domain measures are simplest to perform. They can detect either the instantaneous heart rate at any specific point of time or RR interval between successive normal QRS complex of ECG.[5] Time domain variables can be derived directly from RR intervals (eg. SDRR) or by statistical calculation of difference between them (eg. SDSD, RMSSD, pRR50).[4] Several studies have reported lower HRV characterized by overactive sympathetic nervous system and hypoactive parasympathetic nervous system in MetS.[3,7-9]

Iron, an essential trace element, plays a key role in many biological processes, including oxygen transport, DNA biosynthesis, and electron transport. Ferritin is the major iron storage protein and a small fraction of body ferritin circulates in the plasma. It is used as a clinical biomarker to assess iron status. In addition, serum iron, serum ferritin, total iron binding capacity (TIBC) and transferrin saturation (Tsat) can be measured to observe iron status.[10-11] Several previous studies found considerably higher iron and ferritin in MetS.[11-12] Datz and his colleagues[13]observed hyperferritinemia with normal or mildly elevated transferrin saturation in this syndrome. On In contrast, some studies found no association between serum iron and MetS.[15-16]

Due to the ability of iron to transfer electron between ferrous and ferric forms, excess iron is detrimental- mostly via production of reactive oxygen species (ROS) (hydroxyl radical) by Fenton and Haber-Weiss reaction and therefore is a potent risk factor for cardiovascular system related morbidity and mortality.[11-12,16]

Despite adequate reports regarding iron overload and low HRV in MetS, little is known about the relationship between them in MetS. Exploring this relationship may be helpful in prevention, early diagnosis and effective management of CVD related morbidity in this group of patients.

Methods

This cross-sectional study was conducted in Department of Physiology, BSMMU, Shahbag, Dhaka during 2019. For this purpose, 35 female subjects with Mets diagnosed according to IDF[1] criteriaand aged 25-45 years were selected by purposive sampling from Department of Endocrinology, BSMMU and to compare with them, 35 apparently healthy subjects of similar age and sex were collected through personal contact and were enrolled in comparison group. All data were taken during proliferative phase of menstrual cycle to avoid hormonal influence. After proper review of the ethical aspects, Institutional Review Board of BSMMU approved this study procedure. Informed written consent was taken from all subjects. Subjects suffering from cardiac, respiratory, renal, thyroid disorders, any acute or chronic inflammation, menstrual abnormality were excluded from this study. Known case of hemochromatosis, thalassemia, women having history of blood transfusion within last 3 months, having history of recent major surgery or illness, taking hormonal contraceptives or iron fortified vitamin, pregnant, lactating mother, women after menopause were also excluded from this study. Detail family, menstrual, medical and dietary

history was taken and thorough physical examination was done. Resting pulse rate, blood pressure, anthropometric parameters- waist circumference (WC), weight, height were measured. Then 9 ml of venous blood was collected for estimation of fasting plasma glucose, lipid profile, serum SGPT, and serum creatinine in the laboratory of Department of Biochemistry and Molecular Biology and complete blood count (CBC) in Department of Laboratory Medicine by automated analyzer confirm diagnosis. Then few instructions were given for preparing the subjects for HRV. At previous night of the HRV recording day, they were requested to finish their meal by 9:00 pm and to have a sound sleep avoiding any type of stress. They were forbidden to take any sedative hypnotic medication. On the test day morning, they were advised to have a light breakfast without tea or coffee and to attend the autonomic nerve function laboratory in the Department of Physiology, BSMMU between 8:00am to 9:00 am. To adjust to the controlled laboratory environment, the subjects were advised to take rest for 15-20 minutes and during this period they were forbidden to talk, eat or drink, to perform physical or mental activity or sleep. ECG was recorded in lead II for 5 minutes by data acquisition device Power Lab 8/35 (AD Instrument, Australia). Analysis of RR interval of HRV was done by Lab chart software.

Data were expressed as Mean ± SD. Statistical analysis was done using SPSS version 16. Independent sample 't' test and Pearson's correlation coefficient test were done, p value of £0.05 was considered as statistically significant.

Results

Baseline general characteristics of all subjects are shown in Table I. Age was comparable in subjects of both groups, but according to MetS definition, WC, FPG, serum TG were significantly ($p<0.001$) higher and serum HDL-C was significantly ($p<0.05$) lower in group MetS in comparison to healthy subjects (Table I). MetS subjects had significantly higher resting pulse rate, SBP and DBP ($p<0.001$) compared to healthy subjects (Table II). In this study, the mean value of heart rate was significantly ($p<0.001$) higher and mean RR interval, SDRR, CVRR, SDSD, RM SSD, pRR50 were significantly ($p<0.001$) lower in group MetS than that of healthy subjects (Table III).

Table I General characteristics in two groups (N=70)

Variables	**MetS** (n=35)	**Control** (n=35)	**p value**
Age	37.89±6.07	35.34±5.94	0.081^{ns}
(years)	(25-45)	(25-45)	
WC	95.51±5.97	75.60±3.09	0.000^{***}
(cm)	(83 -113)	(64-79)	
FPG(mmol/L)	8.70±3.45(5.0-16.9)	5.01±0.35(4.40-5.60)	0.000^{***}
HDL-C	39.26±7.04	44.34±10.14	0.017^{*}
(mg/dL)	(23-56)	(31-68)	
TG	232.89±108.47	95.74±25.95	0.000^{***}
(mg/dL)	(98-466)	(30-145)	

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analyses were done by Independent sample 't' test; Group A- Subjects with metabolic syndrome; Group B- Comparison group; WC- Waist circumference; FPG- Fasting plasma glucose; HDL-C- High density lipoprotein cholesterol; TG- Triglyceride; ns- Non significant ($p>0.05$); ***$p<0.001$; *$p<0.05$; N-Total number of subjects; n- Number of subjects in each group.

Table II: Resting pulse rate and blood pressure in two groups (N=70)

Variables	MetS(n=35)	Control(n=35)	p value
Pulse	87.40±8.69	73.97±7.14	0.000***
(beats/min)	(65.00-104.00)	(60.00-88.00)	
SBP	132.00±13.02	116.43±6.92	0.000***
(mm of Hg)	(110.00-160.00)	(100.00-125.00)	
DBP	85.00±9.39	73.14±6.07	0.000***
(mm of Hg)	(70.00-100.00)	(60.00-80.00)	

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analyses were done by Independent sample 't' test; MetS- Metabolic syndrome; SBP- Systolic blood pressure; DBP- Diastolic blood pressure; *** p<0.001; N- Total number of subjects; n- Number of subjects in each group.

Table III: Time domain measures of HRV in two groups (N=70)

Variables	MetS(n=35)	Control(n=35)	p value
Mean heart rate	87.55±9.96	75.77±7.22	0.000***
(beats/min)	(64.90-104.20)	(60.11-89.23)	
Mean RR interval	695.66±85.86	802.33±80.58	0.000***
(ms)	(575.80-925.30)	(673.60-1004.00)	
SDRR	22.66±10.95	46.86±16.53	0.000***
(ms)	(6.01-49.61)	(12.56-78.12)	
CVRR	0.03±0.01	0.06±0.02	0.000***
	(0.01-0.06)	(0.02-0.09)	
SDSD	18.47±18.27	43.44±21.01	0.000***
(ms)	(2.75-72.18)	(7.94-90.36)	
RMSSD	18.49±18.34	43.33±20.95	0.000***
(ms)	(2.75-72.14)	(7.93-90.23)	
pRR50	2.62±7.38	21.74±19.35	0.000***
(%)	(0.00-35.07)	(0.00-62.91)	

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analyses were done by Independent sample 't' test; MetS- Metabolic syndrome; SDRR- Standard deviation of all RR interval; CVRR- Coefficient of variance of RR interval; SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50- Proportion of differences of successive RR interval >50 ms; *** p<0.001; n- Number of subjects in each group ; N- Total number of subjects.

In MetS group, serum ferritin was significantly ($p<0.05$) higher and TIBC was significantly ($p<0.05$) lower than those of control group. (Table IV).

The correlation between all time domain parameters and serum iron, serum ferritin and Tsat were statistically non-significant ($p>0.05$) in MetS group (Table V,VI). In correlation analysis, in MetS group, significant positive correlation was found between mean RR interval, SDRR, CVRR, pRR50 ($p<0.01$), SDSD, RMSSD ($p<0.05$) and TIBC (Table VI).

Table IV: Parameters of iron status in two groups (N=70)

Variables	MetS(n=35)	Control (n=35)	p value
Iron	61.83±28.40	68.49±20.59	0.266^{ns}
(µg/dL)	(25-144)	(29-110)	
Ferritin	122.57±143.47	60.55±40.82	0.017^{*}
(ng/mL)	(7.60-526.90)	(5.53-172.33)	
TIBC	286.63±99.75	325.77±49.65	0.041^{*}
(µg/dL)	(102-494)	(215-407)	
Tsat	24.43±15.41	21.65±7.22	0.337^{ns}
(%)	(5.47-69.23)	(7.80-40.74)	

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analyses were done by Independent sample 't' test;MetS- Metabolic syndrome; TIBC- Total iron binding capacity; Tsat- transferrin saturation; $^{*}p<0.05$; ns- N

Table V: Correlations of time domain HRV measures with serum iron and serum ferritin inMetS group (n=35)

VariablesMetS	Serum iron		Serum ferritin	
	r value	p value	r value	p value
Mean heart rate	0.098	0.575^{ns}	0.103	0.554^{ns}
Mean RR interval	0.267	0.121^{ns}	-0.140	0.422^{ns}
SDRR	0.119	0.497^{ns}	-0.039	0.822^{ns}
CVRR	0.009	0.961^{ns}	-0.128	0.465^{ns}
SDSD	-0.022	0.902^{ns}	0.044	0.801^{ns}
RMSSD	0.030	0.863^{ns}	0.043	0.808^{ns}
pRR50	0.023	0.895^{ns}	-0.122	0.484^{ns}

Statistical analyses were done by Pearson's correlation coefficient (r) test. MetS- Metabolic syndrome; SDRR- Standard deviation of all RR intervals; CVRR- Coefficient of variance of RR interval; SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50- Proportion of differences of successive RR interval >50 ms; ns- Non significant ($p>0.05$); n- Number of subjects.

Table VI: Correlations of time domain HRV measures with TIBC and Tsat inMetS group (n=35)

VariablesMetS	TIBC		Tsat	
	r value	p value	r value	p value
Mean heart rate	-0.154	0.377^{ns}	-0.038	0.827^{ns}
Mean RR interval	0.501	0.002**	-0.202	0.243^{ns}
SDRR	0.452	0.006**	-0.297	0.084^{ns}
CVRR	0.476	0.004**	-0.289	0.093^{ns}
SDSD	0.402	0.017*	-0.272	0.114^{ns}
RMSSD	0.405	0.016*	-0.246	0.155^{ns}
pRR50	0.499	0.002**	-0.198	0.255^{ns}

Statistical analyses were done by Pearson's correlation coefficient (r) test. MetS- Metabolic syndrome; TIBC- Total iron binding capacity; Tsat- Transferrin saturation; SDRR- Standard deviation of all RR interval; CVRR- Coefficient of variance of RR interval; SDSD-Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50- Proportion of differences of successive RR interval >50ms; ns- Non significant ($p>0.05$); $^{*}p<0.05$; $^{**}p<0.01$; n- number of subjects.

Discussion

In this study, significantly higher resting pulse rate, SBP and DBP in MetS patients compared to their healthy counterpart were consistent with other studies.[3-4,7-8]

Here, significant higher mean HR and lower mean RR interval, SDRR, SDSD, RMSSD, pRR50 in MetS patients compared to healthy subjects suggestive of lower HRV and lower parasympathetic activity in current series of MeS and this agreed with observations with other researches.[3-4,7,17]

The current study revealed significantly higher serum ferritin but significantly lower TIBC suggesting higher iron status/store in MetS patients.. Findings of serum ferritin were similar to other previous studies.[11-12,18-20] But contrast to findings regarding TIBC in MetS.[11, 21] In the present study, a significant positive correlation of time domain parameters with TIBC in MetS indicates a positive relationship of cardiac parasympathetic tonic activity with iron binding capacity in MeS patients.

Obesity is assumed as the core pathogenesis of metabolic abnormalities associated with the Mets. In obesity, iron export from enterocyte, hepatocyte, the macrophage is impaired via several mechanisms.[22] Sequestration of iron leads to higher cellular and serum ferritin. As cellular store is high, this may cause decreased TIBC in MetS.

TIBC is an indirect measure of serum transferrin, which keeps the iron in a bound inactive state. In MetS, glycation may cause impaired iron binding capacity of transferrin[23]and also glycation of RBC membrane protein may cause excessive lysis and release of free iron.[24] As there is not enough transferrin to bind with this free iron, increased free iron concentration may cause excessive reactive oxygen species (ROS) production via Fenton and Haber- Weiss reactions.[16,23] ROS may lead to reduced nitric oxide (NO) bioavailability via decreased production and increased inactivation of NO.[25] Centrally acting NO modulates preganglionic parasympathetic neurons within the nucleus ambiguous and the dorsal vagal motor nucleus. NO facilitates cardio-vagal activity presynaptically via increasing release of Ach from nerve terminal.[25-26] It is involved in

cholinergic inhibition of L-type Ca^{2+} current ($I_{Ca,L}$) in cardiac pacemaker cell and thus in Ach induced bradycardia.[26]

Conclusion

From the results of this study, it may be concluded that cardiac parasympathetic impairment is related to iron status in metabolic syndrome.

Conflict of interest-None

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