Assessing Metabolic Syndrome Through Increased Heart Rate During Exercise

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Abstract- The present study aimed to assess changes in resting and maximum heart rates as primary indicators of cardiac autonomic function in metabolic syndrome (MetS) patients and to determine their value for discriminating MetS from non-MetS. 468 participants were enrolled in this cross-sectional study and assessed according to the updated adult treatment panel III (ATP-III) definition of MetS. Resting and maximum heart rates were recorded following the Bruce protocol during an exercise. A receiver operating characteristic (ROC) curve was used to identify the best cutoff point for discriminating MetS from the non-MetS state. 194 participants (41.5%) were diagnosed as MetS. The mean resting heart rate (RHR) was not statistically different between the two groups (P=0.078). However, the mean maximum heart (MHR) rate was considerably higher in participants with MetS (142.37±14.84 beats per min) compared to the non-MetS group (134.62±21.63 beats per min) (P<0.001). In the MetS group, the MHR was positively correlated with the serum triglyceride level (β=0.185, P=0.033) and was inversely associated with age (β=-0.469, P<0.001). The MHR had a moderate value for discriminating MetS from the non-MetS state (c=0.580, P=0.004) with the optimal cutoff point of 140 beats per min. In MetS patients, the MHR was significantly greater compared to non-MetS subjects and was directly correlated with serum triglyceride levels and inversely with advanced age. Moreover, MHR can be used as a suspicious indicator for identifying MetS.

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Keywords: Metabolic syndrome; Maximum heart rate; Resting heart rate; Exercise test; Serum triglyceride

Introduction

Metabolic syndrome (MetS) has been clearly identified as the main factor in morbidity associated with cardiovascular disease, and in mortality from all causes (1-5). MetS confer a 5-fold increase in the risk of type 2 diabetes mellitus (6) and increase the risk of cardiovascular disease (CVD) 2.33 fold among the Iranian population (7). In this regard, several predictive and associated factors with MetS are reported in order to lower the incidence of MetS (8,9). The mechanisms associating MetS with cardiovascular disease have been examined in many studies, and the incidents of insulin resistance, endothelial dysfunction, and cardiac hypertrophy in MetS patients that are mediated by cardiometabolic clustering phenomenon are believed to lead to an alteration in the pathways of the autonomic nervous system (10-14). However, the underlying pathogenesis is incompletely understood (15). Pulse wave velocity, an acknowledged marker of arterial stiffness, was found to be associated with MetS, even in the absence of hypertension (16).

An increase in sympathetic discharge and, thus, an enhancement in the release of the adrenergic cardiovascular drive, almost invariably characterizes hemodynamic components such as the heart rate (HR) in metabolic syndrome (12-14,17). Heart rate recovery (HRR) as a function of vagal reactivation, which is an independent risk predictor of cardiovascular disease and mortality, is strongly associated with metabolic syndrome. There is also evidence of autonomic dysfunction such as sympathetic and parasympathetic dysregulation in those who suffer from MetS, hence a slow HRR after exercise, which may be a major marker for the relative sympathetic overactivity (11).

Therefore, changes in heart rate following

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sympathetic pathway defect in MetS patients can be a common finding leading increased risk of cardiovascular diseases. A previous study has assessed the association between the RHR and HRR with MetS (18). The present study aimed to assess changes in both the resting and maximum HR during an exercise test in MetS patients determine its possible value for discriminating MetS from non-MetS conditions and assess the correlation of maximum HR with other cardiovascular variables.

Materials and Methods

This cross-sectional study was part of the Isfahan Cohort Study (ICS), which was population-based and previously reported (19,20). ICS was conducted in 2001 in three central provinces in Iran, including Isfahan, Arak, and Najafabad with 6323 participants aged 35 years and older. The primary outcomes of the cohort were the detection of the incidence of cardiovascular disease (CVD), and resulting mortality and morbidity, as well as the incidence of major risk factors for CVD (21).

The 468 consecutive subjects who were enrolled in this sub-study attended our medical center for assessment of the appearance of MetS and gave their written informed consent for participation according to the instructions of the ethics committee at the Isfahan Cardiovascular Research Center.

The patients with current or past malignancy or immunosuppressive therapy, known inflammatory disease, pregnancy, steroidal or non-steroidal anti-inflammatory treatment, acute infection, invasive cardiac procedures, or cardiac arrhythmias such as atrial fibrillation, or atherothrombotic events such as myocardial infarction, cerebrovascular event or peripheral arterial disease during the prior six months, were excluded. Also, those who were taking thyroid replacement medication, or cardiovascular drugs such as alpha blockers, beta blockers, calcium channel blockers, antiarrhythmic drugs or digoxin, were also excluded.

Baseline characteristics including demographics, anthropometric parameters, medical history of cardiovascular risk factors, as well as laboratory indices, were measured by trained nurses. For biochemical analysis, 5 ml blood samples were drawn after 12 hour overnight fasting for measuring lipid profiles and fasting blood sugar levels. Plasma glucose was measured using a glucose oxidase-peroxidase method. The serum lipid profile was also determined by standard enzymatic procedures.

Risk factors for coronary artery disease were assessed as per the following definitions; Current smoking history: if patients regularly smoked a tobacco product(s) one or more times per day or had smoked during the 30 days prior to admission (22); Hypercholesterolemia: total cholesterol>190 mg/dl (5.0 mmol/L), HDL-cholesterol<40 mg/dl (1.03 mmol/L) in men, and <50 mg/dl (1.3 mmol/L) in women, Triglycerides>180 mg/dl (2.0 mmol/L) (23); Hypertension: SBP≥140 mmHg and/or DBP≥90 mmHg and/or use of antihypertensive treatment (24); Diabetes mellitus: symptoms of diabetes plus at least one of the following lab results: plasma glucose concentration≥200 mg/dl (11.1 mmol/L), fasting plasma glucose≥126 mg/dl (7.0 mmol/L), and 2h post-prandial≥200 mg/dl (11.1 mmol/L) (25).

Blood pressure was measured using a standard mercury sphygmomanometer on the right arm with subjects seated and having rested for at least 10 minutes. Waist circumference (WC) was measured by tape around the horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest. Body weight and height were measured by a digital scale accurate to the nearest 0.1 kg and a wall stadiometer, respectively. To measure body mass index (BMI), the Quetelet formula was used (weight in kilograms divided by the square of the height in meters). Total cholesterol, high density lipoprotein cholesterol (HDL-C), triglycerides, and blood glucose were assessed using a spectrophotometer. The variation coefficient was<5% for all laboratory measurements.

The updated Adult Treatment Panel (ATP-III) definition of metabolic syndrome was met when three or more of the following criteria were present; Waist circumference≥102 cm (40 inches) in men and 88 cm (35 inches) in women; HDL<40 mg/dl (1.03 mmol/l) in men, or less than 50 mg/dl (1.30 mmol/l) in women, or specific treatment for this lipid abnormality; Triglycerides≥150 mg/dl (1.7 mmol/l) in men and women, or specific treatment for this lipid abnormality; Blood pressure≥130 mm Hg systolic or≥85 mm Hg diastolic in men and women, or treatment of previously diagnosed hypertension; Fasting glucose≥100 mg/dl (5.6 mmol/l) in men and women (26).

The stress test followed the Bruce or modified Bruce treadmill protocols (27), which are non-invasive measures of functional capacity and exercise tolerance in individuals with known or suspected cardiovascular disorders. Functional capacity is represented by the maximal workload attained and expressed in metabolic equivalents (MET). Height, weight, BMI, and WC were obtained on the day of the stress test. Blood pressure and the resting heart rate were taken before and at the end of the stress test. MHR during the stress test and the test

duration were measured.

Results were presented as mean±standard deviation (SD) for quantitative variables and were summarized for categorical variables by absolute frequencies and percentages. Categorical variables were compared using chi-square test, or Fisher's exact test when more than 20% of cells with an expected count of less than 5 were observed. Quantitative variables were also compared using a t test or Mann-Whitney U test. Multivariate linear regression analysis was used to compare between-group differences in heart rates with the presence of study confounders including demographic parameters and hemodynamic indices. A receiver operating characteristic (ROC) curve was used to identify the best cutoff point by which to maximize the sensitivity and specificity of discriminating MetS from non-MetS state. For the statistical analysis, the statistical software SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL) was used. *P*.values of 0.05 or less were considered statistically significant.

Results

According to the ATP-III classification, among 468 subjects enrolled into this study, 194 participants (41.5%) were diagnosed as MetS. As shown in Table 1, the male to female ratio was significantly lower in the MetS group than the non-MetS group (42.3% vs. 56.2%, respectively, *P*=0.003), but with a comparable mean age between them (*P*=0.398).

Table 1. Baseline characteristics in MetS and non-MetS groups

Characteristics	MetS group	No-MetS group	*P*.value
Male gender(%)	82 (42.3)	154 (56.2)	0.003
Age (year)	56.86 ± 9.33	56.11 ± 9.63	0.398
Body mass index (kg/m^2)	30.94 ± 4.38	26.84 ± 4.17	< 0.001
Waist circumference (cm)	99.38 ± 9.08	88.14 ± 9.32	< 0.001
Waist to hip ratio	0.96 ± 0.07	0.89 ± 0.07	< 0.001
Hypercholesterolemia (%)	178 (91.8)	179 (65.3)	< 0.001
Diabetes mellitus (%)	68 (35.1)	7 (2.6)	< 0.001
Hypertension(%)	123 (63.4)	56 (20.4)	< 0.001
Current smoking(%)	20 (10.3)	46 (16.8)	< 0.001
Fasting blood sugar(mg/dl)	109.07 ± 46.35	83.02 ± 16.99	< 0.001
Total cholesterol(mg/dl)	215.26 ± 46.24	206.26 ± 37.40	0.025
Total triglyceride(mg/dl)	248.40 ± 159.02	138.77 ± 62.45	< 0.001
High density lipoprotein(mg/dl)	42.08 ± 8.96	48.99 ± 12.03	< 0.001
Low density lipoprotein(mg/dl)	119.84 ± 27.91	118.77 ± 24.79	0.671
Left Ventricular ejection fraction	60.72 ± 5.82	61.43 ± 4.73	0.148
Resting Heart rate	85.11 ± 17.34	82.17 ± 13.39	0.078
Maximum heart rate	142.37 ± 14.84	134.62 ± 21.63	< 0.001

Also, BMI was significantly greater in the MetS group (30.94±4.38) in comparison with the non-MetS group (26.84±4.17) (*P*<0.05). All components of MetS were significantly higher in the former group of participants (*P*>0.05), while the level of serum low-density lipoprotein was almost similar between the groups.

The two study groups were also alike in terms of the mean left ventricular ejection fraction as measured by two-dimensional echocardiography, at 60.72±5.82 for the MetS group and 61.43±4.73 for the non-MetS group (*P*=0.148).

The mean resting heart rate was not statistically different between the groups, at 85.11±17.34 beats per minute for the MetS participants and 82.17±13.39 beats per minute for the non-MetS participants (*P*=0.078). However, the mean maximum heart rate was considerably higher in participants with MetS (142.37±14.84 beats per minute) compared with the non-MetS group (134.62±21.63 beats per minute) (*P*<0.001).

In a multivariable logistic regression model and with the presence of the different components of MetS as confounders (Table 2), maximum heart rate was identified as a strong determinant for MetS (OR=1.028, 95% CI: 1.009-1.048, *P*=0.004). In the MetS group, maximum heart rate was positively correlated with serum triglyceride level (β=0.185, *P*=0.033) and also

was adversely associated with patients' age (β=-0.469, P<0.001), but not with other variables (Table 3).

Table 2. Multivariate regression analysis to determine value of maximum heart rate as a predictor of metabolic syndrome

Item	Multivariate *P*.value	Odds Ratio	95% Confidence Interval
Maximum heart rate	0.004	1.028	1.009-1.048
Male gender	0.922	1.034	0.530-2.016
Age (year)	0.143	0.968	0.927-1.011
Body mass index (kg/m^2)	< 0.001	1.258	1.154-1.322
Hypercholesterolemia	< 0.001	12.188	4.886-30.402
Diabetes mellitus	< 0.001	52.961	15.416-181.947
Hypertension	< 0.001	10.700	5.342-21.432
Current smoking	0.569	1.310	0.517-3.324

Hosmer-Lemeshow goodness of fit: χ^2 = 11.654, P = 0.167

Table 3. Correlation of maximum heart rates with other study variables

Variables	Beta coefficient	*P*.value
Age	-0.469	< 0.001
Waist circumference	0.001	0.993
Body mass index	-0.026	0.768
Fasting blood sugar	0.156	0.071
Total cholesterol	0.007	0.939
Total triglyceride	0.185	0.033
High density lipoprotein	-0.136	0.118
Low density lipoprotein	-0.087	0.320
Mean systolic blood pressure	-0.121	0.165
Mean diastolic blood pressure	0.102	0.241
Left ventricular ejection fraction	--	0.115

According to the ROC curve analysis (Figure 1), the maximum heart rate measurement had a moderate value for discriminating MetS from non-MetS (c=0.580, 95% CI: 0.534-0.637, P=0.004). The optimal cut-off point of maximum heart rate for discriminating MetS from non-MetS was 140 beats per min yielding a sensitivity of 55.2% and a specificity of 51.1%.

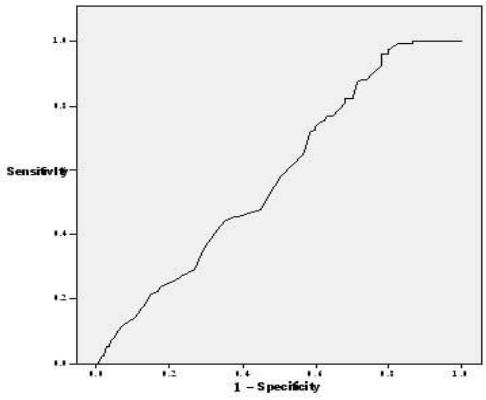

Figure 1. Receiver operator characteristic (ROC) curves were constructed to investigate the diagnostic power of the maximum heart rate for discriminating MetS from non-MetS state

Discussion

As previously noted, an increase in heart rate recovery in MetS patients has been demonstrated. However, changes in maximum heart rate associated with MetS can represent cardiovascular defects, especially within the high cardiac workload. The present study revealed a significant increase in the maximum heart rate during exercise in the MetS patients in comparison with the non-MetS controls, even after adjusting for demographic parameters, unlike the resting heart rate, which was similar in both groups. This maximum heart rate was associated with serum triglycerides level and inversely with advanced age. Also, the optimal cut-off point for discriminating MetS to non-MetS patients was determined as 140 beats per minute, with a sensitivity and specificity of 55.2% and 51.1%, respectively. Based on these levels of sensitivity and specificity, this cut-off point can be considered as a suspicious indicator for MetS.

According to the findings of Rossi *et al*., MetS has a potential effect on heart rate reactivity in patients in supine positions, reflecting defects in the sympathetic and parasympathetic systems (26). Our findings also show that MetS affects the maximum heart rate reactivity. One possible reason is that maximum heart rate is not simply an indicator of a high sympathetic drive but rather a coordinated interaction between parasympathetic reactivation and sympathetic withdrawal during exercise recovery (28).

However, the present study did not support the findings of Rana *et al*., (29), which identified an association between a higher resting heart rate and MetS. Our results included a similar resting heart rate between the groups.

Although we did not find an association between hypertension and maximum heart rate in MetS, in another study, pulse wave velocity was associated with arterial wall stiffness and elevated heart rate in MetS, even in the absence of hypertension (16). In this context, however, the index of maximum heart rate in our study was observed to be associated with hypertriglyceridemia in MetS patients, indicating that increased maximum heart rate in MetS patients may be mediated by defects in the structural and regulating pathways of triglyceride metabolism in these patients. Previously, it was shown that MetS in animal models could evolve with progressive autonomic dysfunction, with specific derangements occurring very early (30). Due to the inverse association of maximum heart rate with patient age, these defects may be more apparent in younger age groups. Our study shows that an increased maximum heart rate during the exercise test is a potential predictor for increased serum triglycerides in MetS patients, which could also predict the presence or progression of cardiovascular disorders. In summary, our observations show autonomic dysfunction in MetS patients, especially in those with high serum triglycerides, regardless of age.

We also showed that heart rate has a moderate value for discriminating MetS from non-MetS, with moderate sensitivity and specificity. It can only be considered as a suspicious indicator for MetS. Determination of new criteria for MetS requires comprehensive Meta-analysis.

MetS adversely affect autonomic cardiac control, and reduced autonomic cardiac control could contribute to an increased risk of cardiovascular events in individuals who exhibit MetS (18,31). The sympathetic nervous system may also elevate heart rate with a subsequent decrease in stroke volume and left ventricular ejection time (32). However, impaired left ventricular systolic and diastolic function has previously been found in subjects with MetS (33). Thus, diminished stroke index in these subjects may also be related to structural and functional alterations in the heart (34).

Maximum heart rate with a cut-off point of 140 beats per min has a moderate sensitivity and specificity for discriminating MetS from non-MetS. Although an elevated maximum heart rate in these patients may be mediated by defects in the structural or regulating pathways of triglyceride metabolism, which may also be present at younger ages, measurement of maximum heart rate can be used as a suspicious indicator for identifying MetS.

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