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ORIGINAL ARTICLE OPEN ACCESS

The Relationship between the Amount of Epicardial Adipose Tissue Measured on Echocardiography and Decreased Heart Rate Recovery in Exercise Stress Test in Patients with Metabolic Syndrome

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Introduction: In this study, the impact of the epicardial adipose tissue (EAT) thickness on the heart rate recovery (HRV) was investigated by comparing the HRV values in the second minute of the recovery phase of the exercise test applied to metabolic syndrome (MS) patients and the healthy control group.

Materials and Methods: A total of 78 people, 30 of them healthy control group, and 48 of them diagnosed with MS for the first time were included in the study which was carried out in a Uludağ University's Medical Faculty Hospital in Turkey. The study was designed prospectively. The EAT thickness measurement was performed and recorded for all individuals. All patients underwent a symptom-limited exercise test following the Bruce protocol. The relationship between known risk factors of coronary artery disease of the EAT thickness measured by echocardiography and decreased HRV index in the recovery phase in the exercise stress test was investigated.

Results: Metabolic syndrome group was found out to have a significantly thicker EAT thickness ($p<0.01$). Recovery 2^{nd}-minute heart rate change was determined to be statistically different between the two groups ($p<0.05$). The triglyceride levels went up, so did the EAT thickness. Within the MS group, ones having an LDL>160 mg/dl level had a significantly thicker EAT than the ones with an LDL<160 level. The group with an HDL level<40 mg/dl had a significantly thicker EAT thickness. In the cases included in the study, the most important variable affecting the recovery 2^{nd}-minute heart rate variation (HRV_2) was determined to be the EAT ($p<0.01$).

Conclusion: The routine measurement of the EAT might be a good indicator of the coronary artery diseases before the apparent ischemic findings emerge, which is supported by the findings of the present study.

Keywords: Epicardial fat, heart rate recovery, metabolic syndrome, echocardiography, exercise stress test

Introduction

Metabolic Syndrome (MS) is a modern life disease in which multiple fatal systemic disorders such as glucose intolerance starting with insulin resistance or diabetes mellitus, obesity, hypertension, and coronary artery disease blend with each other. NHANES III study, carried out in the USA, reported MS incidence in the population of over 20 years of age was 34% and it was three-fold in the 40-59 age group compared to the 20-39 age (1).

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According to TEKHARF study data, general MS prevalence is 49.6% in males and 54.5% in females in the over 40 years age group in Turkey (2). It has been demonstrated that there is excess epicardial adipose tissue in MS patients and that it is associated with coronary artery disease (CAD)(3).

Heart Rate Recovery (HRR) is defined as the post-exercise decrease in heart rate (4). HRR is observed as a rapid decline in the first 30 seconds following exercise. Many researchers have evaluated abnormal HRR at various times of exercise tests. Cole et al. reported that the risk of death for any reason during the six years was approximately 4 times higher in individuals with first-minute HRR≤12 beats than those with >12 beats (4). In the Lipid Research Clinics Prevalence study, after 12 years of follow-up, mortality was reported to be 2.58 times higher in patients with HRR<43 beats in the second minute after exercise test than those with HRR>43 beats (5). As corroborated by many studies, HRR is a significant predictor of all-cause mortality, independent of the severity of atherosclerosis in coronary arteries, left ventricular function, and exercise capacity.

This study aims to investigate the impact of the epicardial adipose tissue (EAT) thickness on the HRR by comparing the heart rate recovery in the second minute (HRR 2^{nd}-min) of the recovery phase of the exercise test in MS patients and the healthy control group.

Materials and Methods

A total of 78 people were included in the study. 48 were patients diagnosed with MS for the first time in Uludağ University's Medical Faculty Hospital in Turkey and 30 were the healthy control group. The study group was initially planned as 100 participants, however, 22 participants were excluded due to such reasons as not achieving the exercise test, having a history of drug use due to DM, HT, HL, having ischemic heart disease, rheumatic valve disease, congenital heart disease, the pericardial disease in anamnesis or echocardiographic findings. The study was designed prospectively. Special attention was given to form the patient and control groups similar in terms of age, gender, and risk factors. Demographic, blood biochemistry, exercise stress test and echo cardiography data of the participants were recorded. ATP III criteria were used in metabolic syndrome diagnosis. Patients who met at least 3 MS criteria and whose waist circumference was over 88 cm in females and over 102 cm in males were admitted to the study. The relation ship between known risk factors of CAD of EAT measured by echocardiography and decreased heart rate recovery index in the recovery phase in the exercise stress test was investigated.

In epicardial fat thickness measurement; para sternal long-axis and parasternal short-axis images at the end of 3 cardiac cycles, using 2-D and M-Mode techniques areas adjacent to the right ventricular free wall, near the ventricular basal 1/3 section of the echo-free area between myocardium and visceral peri cardium perpendicular to the aortic annulus at end-diastole and average of all measurements were recorded.

All patients underwent a symptom-limited exercise test following the Bruce protocol. During the exercise stress test, the systolic and diastolic blood pressures of the patients were measured manually at the beginning of the test and the second minute of each stage. The exercise stress test was ceased in case the patients had fatigue and maximal heart rate was reached. After the test was over, 3 minutes of recording was taken during the recovery phase.

Systolic, diastolic, and heart rate values were recorded every minute during the recovery phase. Second-minute heart rate recovery (HRV_2) was found by subtracting the recovery second-minute heart rate from the peak heart rate. An $HRV_2 \leq 43$ was considered to be a decreased heart rate recovery.

We used Statistical Package for Social sciences (SPSS) 15 (Inc., Chicago, Illinois, USA) software for statistical analysis. The one-sample Kolmo gorov-Smirnov test was used in assessing the normal distribution of the samples. The One-Way ANOVA test, Student t-test, Man Whitney and Ki-Square was used in the analysis. Pearson correlation test and Linear Regression was also used for data. The findings were stated as percentages and frequencies for categorical variables and as mean±standard deviation (SD). P<0.05 was accepted as statistically significant in all the analyses.

Results

Seventy-eight cases were included in the study. They were 48 patients diagnosed with metabolic syndrome and 30 cases consisting of the control group. The metabolic syndrome group consisted of 27 females and 21 males (48.2% 44,8% respectively) and the control group consisted of 15 females and 15 males (50% and 50% respectively). The respective average ages of the MS and the control groups were 45.31±5.48 and 37.9±5.56. Respective BMIs of the metabolic syndrome and the control groups were calculated as follows: 33.2±5.36 (52.2-26) ve 25.56±2.78 (32.3-2) kg/m^2. Of the cases admitted to the study, heart disease history in the family was 35.4% in the MS group and, 36.7% in the control group, which didn't constitute a statistically significant difference (p>0.05). The percentage of smokers was 56.2 in the MS and 30 in the control, which was a significant difference (p<0.01). Besides, statistically significant results for hypertension and hyperlipidemia parameters were also determined between MS and control (Table 1).

Table 1. Basic characteristics of the patients and control

Variables	Metabolic syndrome (n:48)	Control (n:30)	P value
Gender (Male/Female)	21/27	15/15	0.59
Age (years)	45.3±5.4 (31-50)	37.5±5.56 (27-50)	0.698
BMI (kg/m^2)	33.2 (26-52.2)	25.56 (20-32.3)	0.45
Hypertension (n,%)	22 (45.8%)	1 (3.3%)	<0.001
Hyperlipidemia (n,%)	38 (79.2%)	6 (20%)	<0.001
Family history	17 (35.4%)	11 (36.7%)	0.91
Smoking (n,%)	27 (56.2%)	9 (30%)	0.005
Obesity (n,%)	47 (97.9%)	13 (43.3%)	<0.001
Waist circumference	104.4±9.4	89.5±8.73	0.455

BMI: Body mass index

While TSH, hemoglobin, HDL cholesterol, and creatinine values weren't significantly (p>0.05) different in both groups, fasting blood sugar, total cholesterol (p<0.01), LDL cholesterol, and triglyceride (p<0.05) of the MS group were found out to be statistically higher (Table 2).

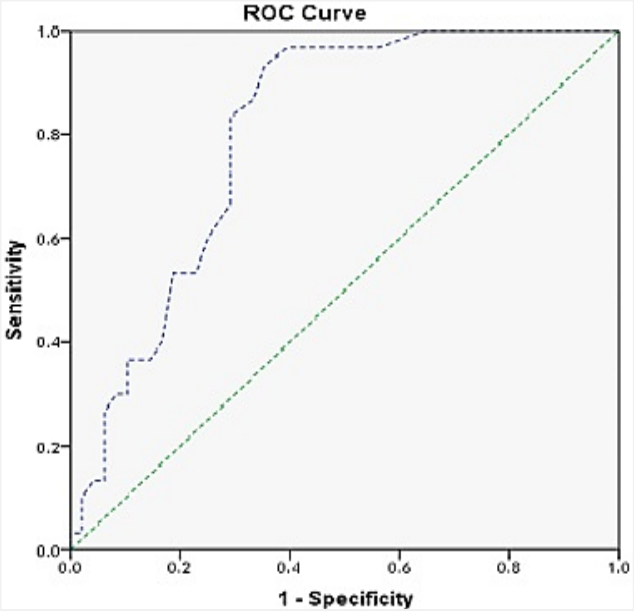


Figure 1. Recovery cut-off evaluation for 2nd-minute heart rate change

MS group was found out to have a significantly thicker EAT (p<0.01) (Table 2). MS and control group recovery HRV_2 was found by subtracting recovery 2nd-minute heart rate from peak heart rate. The cut-off value for the MS and control groups was determined as ≤43 by using a ROC Curve (Area under the curve=0.802; p<0.001) (Figure 1).

Table 2. Laboratory characteristics of patient and control

Variables	Metabolic syndrome (n:48)	Control (n:30)	P value
Fasting Blood Sugar (mg/dl)	122.08±67.3	85.8±10.05	<0.001
Creatinine (mg/dl)	0.81±0.17	0.79±0.12	0.2
T. Cholesterol (mg/dl)	218.1±49.8	191.1±35.7	0.007
HDL (mg/dl)	39.7±8.99	44.67±10.2	0.37
LDL (mg/dl)	141.6±49.3	120.8±28.8	0.02
Triglyceride (mg/dl)	231±280.4	134.3±90.4	0.03
Hemoglobin (g/dl)	13.98±1.4	14.29±1.62	0.3
TSH	1.56±0.89	1.48±0.71	0.62
Epicardial Adipose Tissue Thickness (mm)	6.11±1.69	3.7±0.67	0.001

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein, TSH: Thyroid-Stimulating Hormone

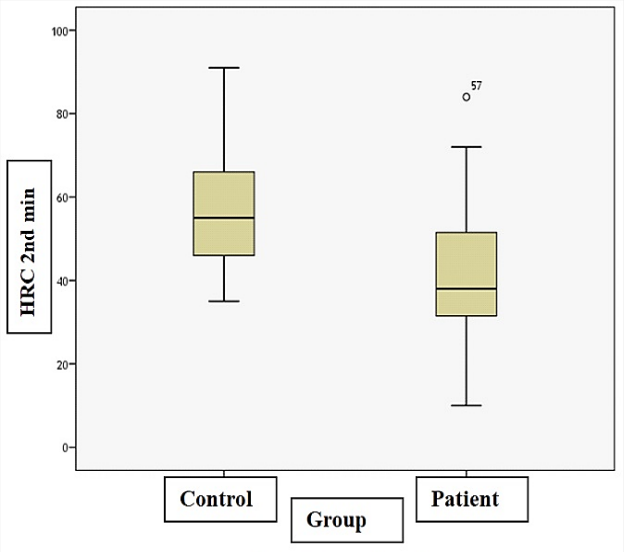


Figure 2. Recovery 2nd-minute heart rate change

Recovery 2nd-minute heart rate change was determined to be statistically different between the two groups (p<0.05) (Figure 2). MS group triglyceride, total cholesterol, LDL, and fasting sugar levels were determined as significantly higher. It was observed that as the triglyceride levels went up, so did EAT thickness. No correlation was observed between the HRV and the triglyceride level.

Within the MS, ones having an LDL>160 mg/dl level had a significantly thicker EAT than the ones with an LDL<160 level, however, no difference was determined in its effect on the HRV. The group with HDL<40 mg/dl had a significantly thicker EAT, however, the group with HDL>40 mg/dl didn't have a difference in terms of HRV. Considering all the results, triglyceride, total cholesterol, LDL, HDL levels and BMI didn't have an impact on the heart rate recovery independent of the EAT. In the cases, epicardial adipose tissue was determined to be important variable affecting the recovery 2nd-minute HRV_2 at the level of p<0.01 (Table 3).

Table 3. Relationship between heart rate variability and epicardial adipose tissue

Variables	HRR 2	n	Epicardial Adipose Tissue Thickness (mm)	P value
In All Cases	≤43	39	6.17±1.6	0.001
	>43	39	4.2±1.42	
Patient	≤43	34	6.52±1.4	0.007
	>43	14	5.11±1.9	
Control	≤43	5	3.76±0.7	0.83
	>43	25	3.68±0.68	

Discussion

Fatalities due to coronary artery disease are still high despite developing treatment options. Appropriate risk categorization should be performed to ascertain the appropriate treatment options for each patient (7). The main research areas of cardiology are preventing the

catastrophic consequences of coronary artery disease and finding out the trigger factors, biomarkers, and therapeutic molecules.

EAT is a component of visceral adipose tissue located between the heart and pericardium, especially in the atrioventricular sulcus, lateral to the right ventricle, and around the coronary arteries (8). Many researchers have shown that the increased EAT is associated with insulin resistance, metabolic syndrome, adiponectin, LDL, and increased blood pressure. Iacobellis et al. reported in their research that EAT could be measured via echocardiography, computerized tomography, and magnetic resonance. Among such modalities, echocardiography seems to be the most practical approach in that it is practical, cost-effective, and does not contain radiation (9).

Researches on EAT determined that some paracrine and autocrine cytokines secreted by EAT were important factors of inflammation and atherogenesis responsible for main physio pathological mechanisms of the CAD. EAT was found out to be associated with plasminogen activator inhibitor-1, proatherogenic and pro inflammatory adipokines, visfatin, monocyte chemoattractant protein-1, and increased CRP. All these findings support the idea that EAT has important effects on CAD (10).

Metabolic syndrome is a collection of many risk factors associated with CAD. Many studies are showing that EAT is increased significantly in a person with MS (11-13). The present study has determined that EAT in the MS group is significantly increased compared to the control group. Post-exercise decreased HRV is an important symptom of autonomic dysfunction and is associated with all-cause mortality (14). We have focused especially on the post-exercise 2nd-minute heart rate recovery and epicardial adipose tissue relationship. Results of the Lipid Research Clinics Prevalence study demonstrated that patients with decreased post-exercise 2nd-minute heart rate recovery had a four-fold mortality risk (5). In this study, we have examined the relationship of the epicardial adipose tissue, an early marker of the CAD, which is an important cause of mortality in patients with MS, and also a good non-invasive indicator of exercise capacity in obesity treatment, with the decreased heart rate recovery (15).

In our study, we have determined that EAT is associated with decreased heart rate recovery regardless of the other risk factors important for the CAD, which indicates that EAT is not only a patch of fat but also has important physiological effects (16). An increasing number of studies on EAT demonstrate that this parameter, which would be examined during the routine echocardiographic examination would be very beneficial in the prognosis determination. Sengul et al, similar to our study, found out EAT to be associated with decreased heart rate recovery (17). This study aimed to find simple approaches that would be useful in early diagnosis of the CAD, in patients with MS. When CAD progresses, its cost as well as its mortality rate increase. Studies focus on non-invasive and simple prognostic identifiers. We believe that routine measurement of the EAT might be a good indicator of the CAD before the apparent ischemic findings emerge, which is supported by the findings of the study.

Ethical Statement

The study was approved by the University Ethics Committee for Clinical Research Studies and all the patients were informed about the study.

Conflicts of Interest

The authors declared no conflict of interest.

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