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Blood pressure recovery ratio after exercise test predicts increased carotid intima media thickness in patients with metabolic syndrome

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Abstract

Aim: We aimed to evaluate the relation of BP recovery ratio (BPRR) and carotid intima media thickness (CIMT) in patients with metabolic syndrome. Abnormal blood pressure (BP) recovery after physical exercise is related with coronary artery disease, impaired left ventricular diastolic function and pulse wave velocity.

Materials and Methods: Among patients who had negative elective exercise test, 109 patients with metabolic syndrome (MetS) were included (65 males, 44 females; mean age 54.8±8.3 years) in our study. Study population were divided into two groups as low carotid IMT (CIMT≤0.9) and high carotid IMT (>0.9). The BPRR was computed by dividing the third minute systolic BP (SBP) by the peak exercise systolic BP.

Results: The BPRR was 0.88 and 0.91 in the low and high carotid IMT group, respectively (p=0.008). Patients in increased carotid IMT group had lower values of septal e´, higher creatinine values and higher rates of statin use (p<0.05 for all). BPRR was positively correlated with carotid IMT (r=0.251, p=0.009). Statin use (OR = 5.754, p<0.001) and BPRR (OR=3.036, p=0.008) were found as independent predictors of increased carotid IMT. Every 0.1 unit increment in BPRR was found to correspond to 203.6% higher risk for increased carotid IMT. The cut-off value of BPRR was 0,921 for predicting increased carotid IMT. The area under the curve (AUC) was 0.634 (p=0.018).

Conclusion: We found a strong correlation between BPRR and carotid IMT. BPRR and carotid IMT, when performed together, may improve their predictive ability for detecting the patients with high CV risk.

Introduction

Carotid intima media thickness (CIMT) is a simple and approved measurement which reliably predicts current subclinical atherosclerosis and cardiovascular (CV) risk [1, 2.] Although routine CIMT measurement has not been recommended, it is suggested in patients with carotid bruit, previous cerebrovascular disease, or in patients with evidence of vascular disease [2, 3].

After exercise, SBP decreases rapidly from peak exercise level to pre-exercise levels in healthy individuals [4]. Blood pressure recovery ratio (BPRR) is defined with this formula: (the systolic BP in the third minute of the recovery / the peak systolic BP during exercise). Rapidity of systolic BP decrease after exercise may indicate physical fitness and higher aerobic capacity of a person [5]. Low BP recovery after graded exercise have previously been associated with coronary artery disease (CAD), abnormal endothelial function, impaired left ventricular (LV) diastolic function and pulse wave velocity [6-8]. Since CIMT is an early sign of CV events and subclinical atherosclerosis, aim of our study was to evaluate the relation of BPRR and CIMT in individuals with metabolic syndrome.

Materials and Methods

Study cohort

After getting approval from the local ethics committee (MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee, Decision no: 08), 109 patients with negative elective exercise test result and metabolic syndrome (MetS) were included (65 males, 44 females; mean age 54.8±8.3 years) in this study. In accordance with NCEP ATP III criteria, patients with three or more of these criteria was accepted to have MetS: (1) abdominal

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obesity (waist circumference ≥90 cm and ≥85 cm for men and women, respectively); (2) triglycerides ≥150 mg/dL, and/or medication for triglycerides; (3) HDL cholesterol <40 mg/dL and <50 mg/dL for men and women, respectively; (4) systolic BP ≥130/85 mmHg or previous hypertension treatment, and/or a previous hypertension history; and (5) FPG ≥100 mg/dL, and/or drug treatment for type 2 diabetes (DM) [9]. Patients with ACS or a history of coronary intervention, known or detected carotid plaques, severe renal failure, heart failure, severe valvular heart disease, atrial fibrillation, hypo- or hyperthyroidism, neoplastic diseases were excluded from our study. Study population were divided into two groups as low CIMT (CIMT≤0.9) and high CIMT (>0.9) as recommended in latest ESC hypertension guidelines [2].

Waist circumference measurement was performed from the midpoint of the distance between the lowest costa and the top of the crista iliaca after gentle expiration. Electrocardiogram, routine laboratory tests such as CBC, lipid profile, fasting blood glucose, creatinine were measured in all patients.

Echocardiography

Philips Affiniti 50 echocardiography device with a 2.5 MHz transducer was employed to perform 2-dimensional and Doppler echocardiography. The biplane Simpson's method was performed to evaluate LV ejection fraction (EF) [10]. The peak early (E) and late (A) transmitral filling velocities and E/A ratio was measured. The isovolumetric relaxation time (IVRT), the isovolumetric contraction time (ICT) and the ejection time (ET) was measured. MPI = (ICT+IVRT)/ET equation was used to determine MPI [11].

Exercise stress test

Exercise test was performed to all patients in accordance with Bruce protocol. The test was accompanied by a cardiologist. 12-lead ECG was recorded throughout the stress test. BP and HR were recorded at baseline, peak and 3rd minute of the recovery. Heart recovery rate was computed by the difference between maximum HR achieved during exercise and HR at 1 minute of the recovery period. The BP recovery ratio was computed by dividing the third minute systolic BP by the peak exercise systolic BP [8]. Functional capacity was evaluated as metabolic equivalents of the task (MET).

Carotid intima thickness measurement

We performed neck ultrasound in supine position as patient's head turned 45° away from scanned side. High resolution B-mode ultrasonography (LOGIQ E9 XDclear 2.0 - GE Healthcare, Illinois, USA) with a 2-9 MHz broadband transducer was employed for evaluation of the carotid arteries. Carotid IMT measurements were performed on common carotid artery posterior wall, 10 mm proximal part below the tip of the flow-divider at longitudinal axis. CIMT was defined as the distance from the interface of the lumen and intima to the interface between the media and adventitia. In each measurement, automatic intima media thickness measurement software (GE Healthcare, Illinois, USA) which performs approximately 200-250 points measurement on the posterior wall of the CCA and gives the average of these measurements. The mean of the maximal IMT of the posterior wall of the right and left carotid arteries was accepted as CIMT.

Statistical analysis

Statistical analyzes were conducted with SPSS program, version 21.0, (SPSS Inc. Chicago, Illinois). Continuous variables are expressed as mean±SD and categorical variables are expressed as percentages. We performed Shapiro-Wilk test for testing normality. The Student t test and Mann-Whitney U test were performed for normally and non-normally distributed continuous variables, respectively. The chi-square test was performed for comparing categorical data and frequencies. Statistical significance was accepted as a p value <0.05 for all comparisons. Pearson's correlation were performed to test the correlation between two continuous variables. The determinants related with high CIMT were evaluated in the logistic regression analyses. The p value and odds ratio (OR) were used to express findings with a confidence interval of 95%. ROC analysis was performed to evaluate the cut-off value of BPRR for predicting high CIMT.

Results

Baseline characteristics

Table 1 demonstrates the comparison of the baseline clinical and demographic parameters. Creatinine were significantly higher, septal e´ were significantly lower in the carotid IMT group. Higher percentage of statin use was detected in patients with increased carotid IMT (P<0.05). Echocardiographic parameters in the two groups is shown in Table 2.

Exercise stress test parameters

Comparison of variables regarding exercise stress test is shown in Table 3. The BPRR was 0.88 and 0.91 in the low and high carotid IMT group, respectively (p=0.008).

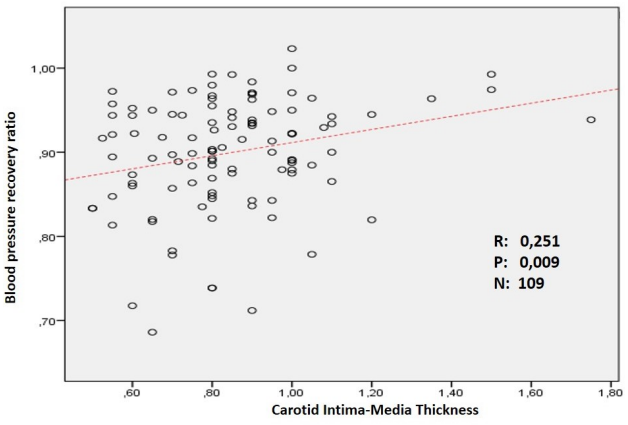

Figure 1. Scatter plot diagram of the relationship between blood pressure recovery ratio and carotid intima media thickness.

Table 1. Comparison of the baseline clinical and demographic features.

	Low IMT n=66	High IMT n=43	p
Age (years)	53.9 ± 8.3	56.1 ± 8.2	0.175
Gender (Male,%)	36 (54)	29 (67)	0.180
DM (n,%)	30 (45)	16 (38)	0.394
HT (n,%)	42 (63)	29 (67)	0.684
Smoking status (n,%)	24 (36)	15 (35)	0.875
Body mass index (kg/m^2)	30.7 ± 3.4	30.5 ± 3.4	0.734
Waist circumference (cm)	102.0 ± 7.8	103.5 ± 7.1	0.308
Hemoglobin (g/dl)	13.8 ± 1.4	13.9 ± 1.5	0.779
Creatinine (mg/dl)	0.77 ± 0.14	0.84 ± 0.22	**0.049**
Total cholesterol (mg/dl)	198.1 ± 30.4	207.0 ± 36.7	0.240
LDL cholesterol (mg/dl)	118.1 ± 30.6	128.8 ± 42.3	0.173
HDL cholesterol (mg/dl)	43.5 ± 11.2	46.6 ± 16.7	0.305
Triglycerides (mg/dl)	175.5 ± 81.0	183.5 ± 111.4	0.958
Fasting blood glucose (mg/dl)	111.5 ± 31.6	120.6 ± 50.5	0.250
Blood urea nitrogen (mg/L)	12.0 ± 4.5	10.1 ± 5.2	0.062
ARB (n,%)	9 (14)	6 (14)	0.963
ACEi (n,%)	14 (21)	9 (21)	0.972
Beta-blockers (n,%)	23 (35)	9 (21)	0.119
Asetil salisilik asit (n,%)	32 (48)	27 (63)	0.143
Statin (n,%)	13 (20)	24 (56)	**<0.001**
Calcium channel blocker (n,%)	21 (32) 0	10 (23)	0.333
HeartScore (%)	4.2 ± 3.6	6.6 ± 6.8	0.062
Carotid intima-media thickness (cm)	0.71 ± 0.1	1.04 ± 0.18	**<0.001**

Abbreviations: LDL - low density lipoprotein; HDL - high density lipoprotein; LA - left atrium; LVEDD: Left ventricular end diastolic diameter, IVS - Interventricular septum; MV – mitral valve.

Table 2. Comparison of echocardiographic parameters.

	Low IMT n=66	High IMT n=43	p
Ejection Fraction (%)	60.1 ± 2.9	59.6 ± 2.4	0.378
LVEDD (mm)	48.2 ± 1.6	48.4 ± 1.8	0.521
E wave deceleration time (s)	174.5 ± 14.1	171.8 ± 16.0	0.359
MV E/A ratio	1.09 ± 0.16	1.03 ± 0.14	0.062
Lateral annular e´ velocity (cm/s)	12.1 ± 2.3	11.4 ± 1.9	0.137
Septal annular e´ velocity (cm/s)	10.1 ± 1.7	9.4 ± 1.3	**0.035**
Mitral E/e´ratio	7.7 ± 1.7	7.9 ± 1.7	0.517
Posterior wall thickness (mm)	9.5 ± 1.0	9.5 ± 1.4	0.740
IVS thickness (mm)	9.8 ± 1.2	9.7 ± 1.2	0.885
LA diameter (mm)	31.1 ± 2.1	31.4 ± 2.7	0.457
LA volume (mL)	32.9 ± 4.1	31.9 ± 4.4	0.232
LA volume index (mL / m²)	21.9 ± 3.0	22.6 ± 3.4	0.237
Myocardial performance index	0.40 ± 0.03	0.41 ± 0.03	0.277

Abbreviations: IMT: Intima media thickness, LA - left atrium; LVEDD – Left ventricular end diastolic diameter, IVS - Interventricular septum; MV – mitral valve.

In bivariate analysis, BPRR was positively correlated with carotid IMT (r=0.251, p=0.009. Figure 1 demonstrates scatter plot chart for the correlation of BPRR and CIMT.

Multivariate analysis

In multivariate binary logistic regression analysis, statin use (OR = 5.754, p<0.001) and blood pressure recovery ratio (OR = 3.036, p=0.008) were independent predictors of increased carotid intima media thickness. Every 0.1 unit increment in BPRR was found to correspond to 203.6% higher risk for increased CIMT. Table 4 demonstrates results of binary logistic regression analysis to evaluate the independent predictors of increased CIMT.

Table 3. Comparison of exercise stress testing parameters.

	Low IMT n=66	High IMT n=43	p
Resting SBP (mmHg)	136.9 ± 16.4	142.5 ± 18.5	0.103
Resting DBP (mmHg)	81.5 ± 11.3	85.8 ± 12.1	0.065
Peak SBP (mmHg)	168.7 ± 21.8	170.7 ± 25.5	0.663
SBP at 3 minutes (mmHg)	149.1 ± 19.9	156.4 ± 20.3	0.068
BPRR	0.88± 0.07	0.91 ± 0.05	**0.018**
HRR (beat/min)	30.1 ± 15.2	28.4 ± 15.1	0.569
Metabolic equivalent	10.5 ± 8.0	9.6 ± 2.6	0.468

Abbreviations: IMT: Intima media thickness, SBP; systolic blood pressure; BPRR; blood pressure recovery ratio; HR: heart rate; HRR: heart rate recovery pressure; BPRR; blood pressure recovery ratio; HR: heart rate; HRR: heart rate recovery.

Table 4. Multivariate logistic regression analyses to determine the independent predictors of high carotid intima media thickness.

Variable	p	Odds Ratio	95% CI	
			Lower	Upper
Statin use	**<0.001**	**5.754**	**2.237**	**14.803**
BPRR	**0.008**	**3.036**	**1.336**	**6.897**
Creatinine	0.146			
MV Septal annular e´ velocity	0.078			

Abbreviations: IMT: Intima media thickness, BPRR: Blood pressure recovery ratio; MV: mitral valve.

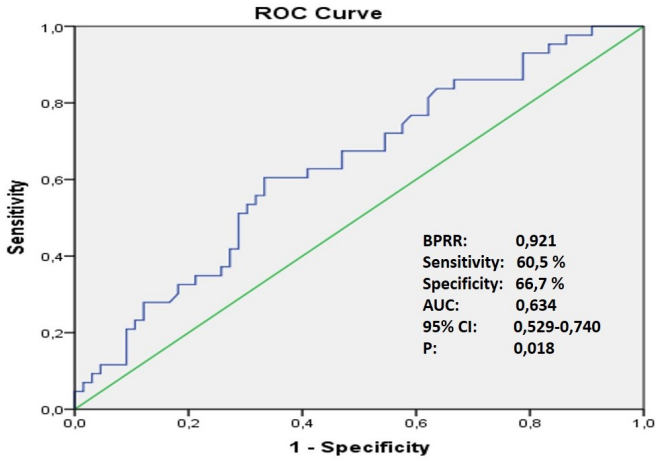

Figure 2. ROC curve analysis to determine predictive value of blood pressure recovery ratio for predicting carotid intima media thickness.

ROC curve analysis

The cut-off value of BPRR obtained by ROC curve analysis is 0,921 to predict increased carotid intima media thickness (sensitivity: 60.5%, specificity: 66.7%). The area un-

der the curve (AUC) was 0.634 (p=0.018). ROC curve analysis is shown in Figure 2.

Discussion

This is the first study which investigates the association between CIMT and systolic BP recovery ratio. The main findings of this study are that; 1) BPRR is positively correlated with CIMT. 2) Blood pressure recovery ratio (OR=3.036, p=0.008) and statin use (OR=5.754, p<0.001) were found as independent determinants of increased carotid intima media thickness. It is found that each 0.1 unit increase in the blood pressure recovery rate increased the likelihood of a high carotid intima media thickness by 203.6%.

Although more effective diagnostic methods have been developed in the field of cardiology, exercise stress test continues to be widely used, and is the primarily used non-invasive diagnostic method in all over the world. The reasons for the frequent use of exercise stress test are the facts that provocation with exercise is the most physiological method and exercise electrocardiography is an inexpensive and easy to apply diagnostic method that is widely accessible in almost all cardiology clinics. Although the focus has been ST-segment depression, exercise test gives other important prognostic and diagnostic data such as exercise capacity, chronotropic competence, HR response, BP recovery.

The rapidity of SBP decrease after exercise may indicate physical fitness and higher aerobic capacity of a person [5]. Abnormal response is known as delay of the return of SBP to normal [12]. In the previous studies, the delay in SBP decline in the recovery period was demonstrated to be useful for predicting CAD diagnosis and severity. First, Amon et al. [13] demonstrated the relationship of the presence of CAD with abnormal SBP recovery. In the study of Amon et al., sensitivity of BPRR was higher than angina and ST depression for diagnosis of CAD [13]. Yamaguchi et al. found that when combined with BPRR, the positive predictive value of significant ST segment depression for detecting CAD improved from 60% to 81% [14]. Similarly, Tsuda et al. [15] found abnormal systolic BPRR measurements in 70% of patients in single vessel disease, 80% in two vessel disease, 82% in three vessel disease, and 100% of those with LMCA disease. In a previous study, abnormal systolic BP recovery after stress test was found as a non-independent predictor of mortality in low-risk population [16]. In a recent study, BPRR at 3 minute was found to be correlated with endothelial dysfunction and left ventricular diastolic dysfunction (E/e´). [6]. Kontsas et al. [8] showed a reverse association between PWV and aerobic exercise capacity and BPRR in hypertensive patients. Steptoe et al. [17] reported a significant relation between CIMT and delayed BP recovery. In the study of Steptoe et al. [17], different from our study, they used stressful behavioral tasks instead of exercise test. Besides, they performed BP measuring after 40 to 45 minutes of these tasks. Unlike the study of Steptoe et al., we used validated version of BPRR as used in the previous studies [6, 8, 13-16]. In our study, we found a strong positive correlation between BP recovery ratio and carotid IMT. In addition, BPRR was found as an independent predictor of high CIMT. The relationship between CIMT and BPRR can be explained by a combination of many factors. BP increase during exercise and BP decrease after exercise are controlled by several autonomic and neurohormonal mechanisms. A delay in the BP decline after exercise may be the result of increased sympathetic response to exercise which emerges as excessive levels of circulating catecholamines, excessive sympathetic nerve stimulation or both. Another autonomic mechanism may be blunting of parasympathetic activity, reduce of sympathetic withdrawal after exercise or both. The delay in the BP decline may also be the result of impairment of exercise induced vasodilatation due to diminished arterial compliance. Chronic vascular smooth muscle hypertrophy, subclinical atherosclerosis or attenuated release of NO or other vasodilator agents with chronic endothelial dysfunction may be thought as the reasons of this low arterial compliance. Therefore, the association of CIMT and BPRR can be thought as a correlational relationship instead of a causal relationship. Both can be seen as the consequences of chronic diseases such as HT, DM or metabolic syndrome.

CIMT measurement is a comfortable and non-invasive investigation which gives important information regarding current subclinical atherosclerosis and future cardiovascular events. It has also well-known associations with other risk factors and outcomes of therapeutic interventions [18]. In our study population, we found statin use and BPRR as independent parameters for predicting high CIMT. However, the association of CIMT and statin use cannot be thought as a cause effect relationship. When we performed a subgroup analysis, we found higher rates of HT (81% vs 57%) and higher values of SCORE (6.0 vs 4.7%), diastolic BP (86.7 vs 81.4 mmHg) and systolic BP (143.7 vs 136.7 mmHg) in patients who use statins. Although not statistically significant, patients using statin therapy had even higher plasma levels of LDL (123.5 vs 122.0 mg/dl) and triglycerides (199.3 vs 168.2 mg/dl) despite the use of statin therapy. Therefore, statin use, similar to CIMT, is also a consequence of scenarios causing high cardiovascular risk.

Our study has several limitations. As we performed our study in a single-center, our study population may have differences from general population. Our sample size is relatively small. This may be the reason for some variables (e.g., creatinine and septal annular e´ velocity) did not reach statistical significance to be independent predictors of increased CIMT. Therefore, larger studies are needed to clarify our findings. The study does not include follow-up data on cardiovascular events or long-term outcomes, limiting the clinical utility of the findings. The relationship between BPRR and CIMT may be correlational rather than causal. However, we did not explore potential confounding factors extensively. We did not compare utility of BPRR against other established cardiovascular risk models. Even though the p value of ROC curve analysis is 0.018, the area under the curve (AUC) of 0.634 for predicting high CIMT is relatively low, limiting the clinical utility of this finding.

Conclusion

Consequently, we found a strong correlation between BPRR and carotid IMT in patients with metabolic syndrome. BPRR and carotid IMT, when performed together, may improve their predictive ability for detecting the patients with increased CV risk.

Ethical approval

Ethical approval was obtained for this study from Mustafa Kemal University Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (Date: 23.11.2017, Decision no: 08).

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