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Abnormal Systolic Blood Pressure during Treadmill Test and Brachial Artery Flow – Mediated Vasodilatation Impairment

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A B S T R A C T

The aim of the study was to assess the relationship between systolic blood pressure during maximal treadmill test (SBP_{mtt}) and flow-mediated vasodilation (FMD). Abnormal rise of SBP_{mtt} is the phenomenon more frequent in hypertensive persons but it could be found in normotensive subjects too. 199 subjects referred to treadmill test were enrolled in the study. Four groups were formed: hypertensives with abnormal SBP_{mtt} (group A), hypertensives with normal SBP_{mtt} (group B), normotensives with abnormal SBP_{mtt} (group C) and normotensives with normal SBP_{mtt} (group D). Rise of SBP_{mtt} above 200 mmHg was considered abnormal reaction. Simple linear regression analysis showed significant inverse relationship between SBP_{mtt} and FMD ($F=20.2036$, $p<0.001$, $R^2=0.0956$). Mean FMD index was worst in hypertensive subjects with abnormal SBP_{mtt} (group A), followed by normotensives with abnormal SBP_{mtt} (group C), hypertensives with normal SBP_{mtt} (group B) and the best was in normotensives with normal SBP_{mtt} (3.56±5.17, 4.19±5.14, 6.81±8.43 and 10.92±7.48%, respectively). In multivariate regression analysis FMD showed significant association with abnormal SBP_{mtt} ($p<0.001$) along with brachial artery diameter ($p<0.001$), male gender ($p<0.001$), but not with hypertension ($p=0.073$), BMI ($p=0.137$) and total cholesterol ($p=0.23$) (coefficients: –0.26, –0.40, –0.27, –0.13, –0.11 and –0.07, respectively). There was a significant inverse relationship between SBP_{mtt} and FMD. An impairment of FMD exists in normotensive subjects with abnormal SBP_{mtt}. In hypertensives with abnormal SBP_{mtt} an additional impairment of FMD exists when compared to hypertensives with normal SBP_{mtt}. Abnormal SBP_{mtt} should be taken into account in global cardiovascular risk assessment.

Key words: *exercise systolic blood pressure, hypertension, flow-mediated vasodilatation, endothelial dysfunction*

Introduction

A physiologic reaction during exercise comprises of progressive increase in systolic blood pressure (SBP), mean blood pressure and pulse pressure. Diastolic blood pressure during exercise shows little variation; it either slowly elevates, maintains the same level or slowly decreases, especially in younger subjects[1]. The systolic blood pressure during maximal treadmill test (SBP_{mtt}) is higher among men[2], and African Americans show higher rise in SBP_{mtt} than Caucasians[3]. Trained subjects with higher maximal work capacities react to exercise with smaller increase of systolic blood pressure[4] and with lower heart rate[5].

Some subjects experience abnormal rise in SBP during exercise. This phenomenon expresses variability of blood pressure reaction to exercise, as an example of bio-

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logical diversity and is probably related to genetic factors[6]. Abnormal rise in SBP during exercise test is not a rare phenomenon. It is more frequent in hypertensive subjects but could be also found in normotensive subjects[7]. Some authors consider SBP above 200 mmHg as abnormal reaction to exercise, while others take the cut-off at 220 mmHg[8]. Unfortunately, there is no consensus on the cut-off value of SBP_{mtt}[8]. Relationship between cardiovascular morbidity and mortality and SBP_{mtt}, as an additional risk factor, was found in several studies[9–11]. On the other hand, FMD as a marker of endothelial dysfunction is decreased in the presence of all traditional major risk factors for cardiovascular diseases[12–15].

The aim of this study was to determine the relationship between SBP_{mtt} achieved during maximal treadmill test and brachial artery flow-mediated vasodilatation (FMD) as an index of endothelial function. The second aim was to assess whether normotensive subjects with abnormal SBP_{mtt} differ from normotensive subjects with normal rise in SBP_{mtt} regarding to FMD as well as hypertensive subjects with abnormal SBP_{mtt} to hypertensive subjects with normal rise in SBP_{mtt}.

Subjects and Methods

Subjects who were referred to treadmill test in Cardiovascular department Clinical Hospital Dubrava during period February 2002 and April 2003 were enrolled in this study. All subjects were Caucasians. Exclusion criteria included history of myocardial infarction, valvular heart disease, secondary hypertension, any endocrine, respiratory or kidney disease, and any acute disease. All subjects had given informed consent to participate in the study, which was approved by the local ethical committee.

All subjects were asked for details in their medical history and had a brief cardiovascular examination to exclude symptomatic cardiovascular disease and to assess their cardiovascular risk factors. All subjects had blood pressure and pulse measured after at least 10 minutes of rest in the supine position. Hypertension was defined as resting diastolic blood pressure (DBP) over 90 mmHg or systolic blood pressure over 140 mmHg. In all subjects total serum cholesterol was also measured. Only mild hypertensive subjects with SBP between 140–159 mmHg and DBP between 90–99 mmHg were included in the study. Subjects with moderate and severe hypertension having a risk related to possible drug therapy interruption were not included. Subjects on antihypertensive medication were asked to withhold it for at least 48 hours before brachial artery vascular reactivity measurements was performed.

Exercise test

Exercise test was performed on a treadmill Marquette Hellige Medical system according to Bruce protocol. During exercise the subjects were under continuous ECG monitoring. Blood pressure was measured with mercury sphygmomanometer every 3 minutes at the end of every step. If SBP higher than 200 mmHg was reached, test was stopped and the subject was considered to have an abnormal SBP_{mtt} reaction.

Brachial artery vascular reactivity measurements

Endothelial function was assessed non-invasively by measuring endothelium-dependent dilation. High-resolution external ultrasound (7 MHz compact linear ultrasound transducer ATL HDI 3000) was used to measure changes in brachial artery diameter in response to reactive hyperemia and in response to glyceryltrinitrate. The subject's right arm was comfortably immobilized in the extended position to allow consistent imaging of the brachial artery. After an initial 10 minutes rest in the supine position, baseline recordings of brachial artery diameter and flow velocity were performed. The right brachial artery was scanned in longitudinal sections of 2–15 cm above the elbow (control scan). Depth and gain settings were optimized to identify the vessel wall to lumen interface, and a resting scan recorder. The distance from the antecubital crease was noted and the following examinations were all performed in the same position. Diameter measurements were taken at end-diastole, coincident with R-wave on the continuously recorded electrocardiography trace. The brachial artery diameter was measured using the leading edge of the near wall to the leading edge of the far wall of the artery along a line perpendicular to the artery's long axis using an electronic caliper. Diameter changes were expressed as the percentage change relative to the mean baseline scan (100%). Reactive hyperemia was induced by inflation and then deflation of standard sphygmomanometer cuff placed around the forearm (below the scanned part of the artery), inflated to approximately 200 mmHg for 5 min. The artery was scanned prior to cuff inflation and for 90 seconds after cuff deflation. Hyperemia was calculated as the ratio of the post deflation flow to the resting flow value. Arterial flow velocity measurements were obtained using a pulsed Doppler at 60° to the vessel with range gate (1.5 mm) in the center of the artery. Volume flow was measured during rest as well as during the peak response of the maximum flow in a single cardiac cycle during the 10–20 second periods after cuff release. After at least 10 minutes rest, a further control scan was recorded and finally 400 μg of glyceryltrinitrate spray was administered sublingually. The final scan was performed 3 min after glyceryltrinitrate. Images were recorded on videotape for subsequent off-line analysis on the same instrument[16].

Statistical analysis

According to the maximal systolic blood pressure recorded during treadmill test, 4 groups were formed: hypertensive subjects with abnormal SBP_{mtt} (group A), hypertensive subjects with normal SBP_{mtt} (group B), normotensive subjects with abnormal SBP_{mtt} (group C) and normotensive subjects with normal SBP_{mtt} (group D). Group's characteristics were analyzed with ANOVA test. Relationship between SBP_{mtt} and FMD was analyzed by

TABLE 1
DEMOGRAPHIC CHARACTERISTICS AND ATHEROSCLEROSIS RISK FACTORS IN THE FOUR GROUPS

	Group A	Group B	Group C	Group D	F	p
Number of subjects	57	46	43	53		
Age (years), X±SD	53.84±8.60	53.89±8.47	51.88±11.53	49.32±11.12	1.83	0.142
Male/female, N:N (%)	31:26 (54.39%)	31:15 (67.39%)	25:18 (58.14%)	29:24 (54.72%)	1.25	0.291
Weight (kg), X±SD	86.07±14.60	80.54±14.30	83.74±13.02	77.64±17.60	5.21	0.002
Hight (cm), X±SD	169.23±8.63	170.84±8.31	173.58±8.85	172.49±11.12	3.66	0.013
BMI (kg/m^2), X±SD	29.93±3.77	27.54±3,73	27.74±3.31	25.82±3.83	12.99	0.000
Diameter of brachial artery (mm), X±SD	43.57±8.09	40.69±6.03	43.46±6.72	38.53±7.52	8.33	0.000
Colesterol (mg/dL), X±SD	5.99±1.10	5.96±1.14	6.08±1.07	5.96±1.07	1.73	0.160
Current smokers, N (%)	12 (21.05%)	7 (15.22%)	15 (34.88%)	12 (22.64%)	1.86	0.136
SBPr (mmHg)	155±13 (130–190)	142±17 (105–170)	143±12 (120–170)	126±14 (100–180)	37.99	0.000
DBPr (mmHg)	98±9 (80–120)	91±12 (60–115)	90±7 (75–105)	82±10 (65110)	24.02	0.000
Antihypertensive therapy	57	46	0	0		
GTN dilatation (%)	8.76±8.99	17.83±10.24	12.50±7.70	23.60±12.57		

BMI – body mass index, SBPr – systolic blood pressure at rest, DBPr – diastolic blood pressure at rest, SD – standard deviation, GTN – glyceryltrinitrate

linear regression analysis. Forward stepwise multiple regression analysis was used to investigate the contribution of available predictor variables to the FMD. Only p values <0.05 were considered statistically significant.

Results

A consecutive sample of 199 subjects (116 men, 83 women, median age 52.5, range 23–71 years) was enrolled in this study. Baseline characteristics of all groups of subjects are shown in Table 1.

Linear regression analysis showed a significant inverse relationship between SBP_{mtt} and FMD in all subjects ($F=20.20$, $p<0.001$, $R^2=0.0956$) (Figure1). Moreover, in the group of normotensive subjects (group C and D combined) a significant relationship was found between SBP_{mtt} and FMD by linear regression analysis ($F=8.57$, $p=0.004$, $R^2=0.086$), but not in the subgroup of hypertensive subjects (group A and B combined) ($F=1.01$, $p=0.316$, $R^2=0.01$). In normotensive subjects (group C and D combined) FMD was higher than in hypertensive subjects (group A and B combined) (7.45±6.25 vs. 4.51±4.84**;** $p<0.01$). In hypertensive subjects with abnormal SBP_{mtt} (group A), FMD was worst followed by normotensive subjects with abnormal SBP_{mtt} (group C), hypertensive subjects with normal SBP_{mtt} (group B) and, at last, normotensive subjects with normal SBP_{mtt} (3.56±5.17, 4.19±5.14, 6.81±8.43 and 10.92±7.48%, respectively; $p<0.001$) (Figure 2).

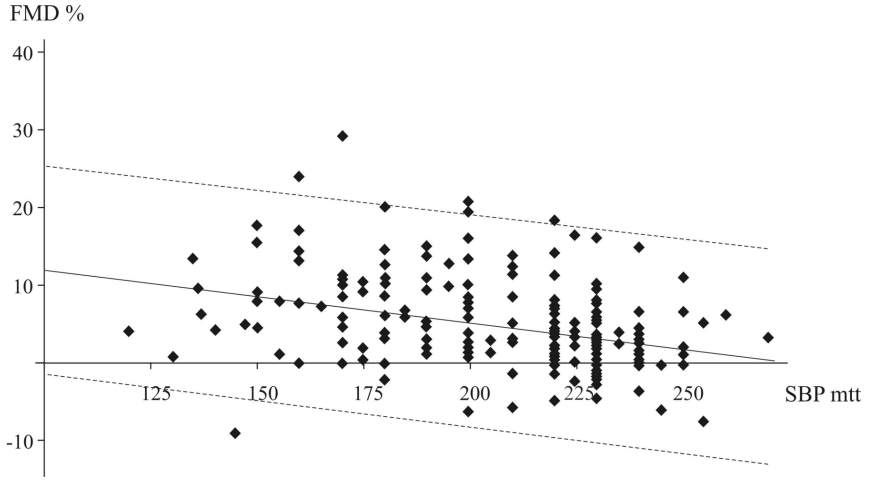

Fig 1. Relationship between FMD and SBP_{mtt} in all subjects. The solid central line is the standard linear regression line. The dashed lines represent 2 standard deviations from the mean (95% confidence interval), $R^2=0.0956$, $p<0.001$.

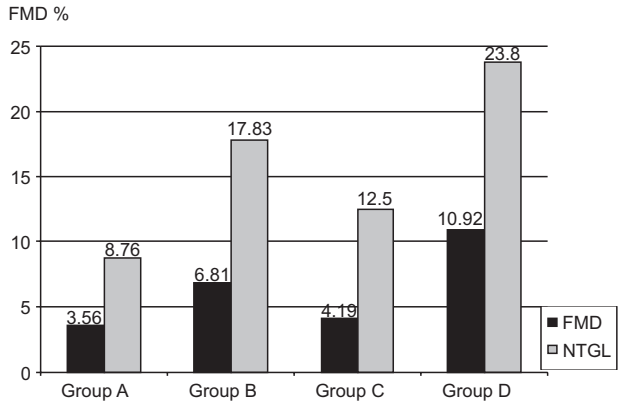

Fig 2. Flow-mediated dilatation (FMD) and glyceryltrinitrate dilatation (GTN) in hypertensive subjects with abnormal SBP_{mtt} (group A), hypertensive subjects with normal SBP_{mtt} (group B), normotensive subjects with abnormal SBP_{mtt} (group C), normotensive subjects with normal SBP_{mtt} (group D).

TABLE 2
MULTIVARIATE REGRESSION ANALYSIS WITH FMD AS DEPENDENT VARIABLE

Predictor variable	Standardized regression coefficient	p value
Abnormal SBP_{mtt}	–0.26	<0.001
Brachial artery diameter	–0.40	<0.001
Male gender	0.27	<0.001
Hypertension	–0.13	0.073
BMI	0.11	0.137
Total cholesterol	–0.07	0.23

SBP_{mtt} – systolic blood pressure during maximal treadmill test, BMI – body mass index

Multivariate regression analysis showed a significant association between FMD and abnormal SBP_{mtt} ($p<0.001$), along with brachial artery diameter ($p<0.001$), male gender ($p<0.001$), but not with hypertension ($p=0.073$), BMI ($p=0.137$) and total serum cholesterol ($p=0.23$) (Table 2).

Discussion

Arterial blood pressure during exercise differs from the resting values. SBP increases in relation to exercise. There is a linear relationship between SBP, increased workload and heart rate during exercise. Arterial hypertension as a cardiovascular risk factor refers to the blood pressure values in resting. Some investigators have suggested that exercise blood pressure measurement gives additional information in cardiovascular risk assessment due to higher mortality among subjects with abnormal systolic blood pressure at exercise (SBP_{mtt})[9–11].

Investigation of FMD offeres new, noninvasive and reproducible method for assessment of endothelial function. Reduced FMD was found in the presence of all major risk factors for cardiovascular diseases[12–15]. Systolic blood pressure hyper-reactivity during exercise decreases the ability of vessel wall diameter to increase in relation to increased flow. We found a statistically significant relationship between SBP_{mtt} and FMD. In subjects with lower $SBP_{mtt,}$ the FMD was higher, and in patients with higher SBP_{mtt} FMD showed minimal changes, indicating that subjects with abnormal SBP_{mtt} are likely to have endothelial dysfunction.

Hypertensive subjects have increased blood pressure at rest, but during exercise some had normal $SBP_{mtt.}$ Lower FMD was found in this subject group, and our results show consistency with reported findings of other autors[17]. Relationship between FMD and SBP_{mtt} in hypertensive subjects was not statistically significant in this study, in contrast to findings among normotensive subjects. Increased change in diameter of brachial artery in relation to increased flow was higher in normotensive group in comparison with hypertensives. Hypertensive subjects have poorer ability to increase vessel wall diameter in response to flow. Thus, hypertensive subjects have decreased endothelial function regardless of whether they do have abnormal SBP_{mtt} or not.

Hypertensive subjects with abnormal SBP_{mtt} were not studied concerning endothelial dysfunction as a subgroup. This study showed that they had the worst FMD value and thus they are at the highest risk of developing atherosclerosis and consequent cardiovascular diseases. Their ability to change diameter to the flow is minimal in comparison with other groups.

Hypertensive subjects with normal SBP_{mtt} were included in hypertensive group in previous studies and were not studied as a subgroup considering endothelial dysfunction. In this study their FMD ($6.81\pm8.43\%$) was better when compared with all hypertensive subjects (group A and B combined; $4.19\pm5.14\%$, $p<0.05$) and particularly with hypertensive subjects with abnormal SBP_{mtt} (group A $3.56\pm5.17\%$, $p<0.01$). Thus, hypertensive subjects with normal SBP_{mtt} have better endothelial function than hypertensive subjects with abnormal SBP_{mtt}. Surprisingly, their FMD is even better then FMD in normotensive subjects with abnormal SBP_{mtt} ($4.19\pm5.14\%$, $p<0.05$). The greater percentage of women in group B and smokers in group C is not statistically significant to explain the difference of FMD found between these two groups.

In normotensive subjects with normal SBP_{mtt} the expected normal value of FMD was found, but it was better than FMD in all normotensive subjects. Hence, this group of normotensives has a higher vascular reactivity to stress than any other group as well as the best endothelial function.

Normotensives with abnormal SBP_{mtt} (group C), in previous studies were included among normotensive subjects (C and D groups combined) and were not studied as a subgroup concerning their endothelial function. We

found low values of FMD (4.19±5.14%) in this group. This was an unexpected result for normotensive subjects. Even more, they showed lower FMD mean value than hypertensive subjects with normal SBP_{mtt}. Our data show that the normotensive subjects with abnormal SBP_{mtt} have worst impairment of endothelial function than hypertensive subjects with normal SBP_{mtt}. Normotensive subjects with abnormal SBP_{mtt} have also impaired endothelial function, and according to our data they should be at higher risk for atherosclerosis development than hypertensive subjects with normal SBP_{mtt}.

The subjects with abnormal SBP_{mtt} are more often hypertensive but they could be normotensive too[6]. In general population the prevalence of hypertensive persons is smaller than normotensive persons. Thus, in absolute numbers in general population normotensive persons with abnormal SBP_{mtt} may prevail over hypertensive persons with abnormal SBP_{mtt}. Therefore, we should pay more attention to these subjects concerning the risk stratification for atherosclerosis. It can be speculated if they are future hypertensives and if they should be treated, although they have normal blood pressure values at rest.

The present study has several limitations. Firstly, only persons with mild hypertension were included in the study. Those with moderate and severe hypertension were excluded because of potential risk of treatment interruption. This may limit the application of the results to a general population of hypertensive persons. Secondly, except for hypertension, other risk factors were not taken into the consideration. This could have introduced confounding effect. Given these limitations, the study requires further validation in a different population. Anyhow, the study demonstrates a significant relationship between SBP_{mtt} and FMD and stresses potential importance of SBP_{mtt} in cardiovascular risk assessment.

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ABNORMALNI SISTOLIČKI KRVNI TLAK U TESTU OPTEREĆENJA I POREMEĆAJ O PROTOKU OVISNE DILATACIJE BRAHIJALNE ARTERIJE

SAŽETAK

Cilj ovog istraživanja bio je utvrditi odnos između sistoličkog krvnog tlaka za vrijeme maksimalnog testa opterećenja i o protoku ovisne dilatacije. Pretjerani porast SKT_{mtt} je fenomen čest u hipertoničara ali se može pojaviti i kod normotoničara također. U ispitivanje smo uključili 199 ispitanika. Formirane su četiri grupe: hipertoničari s abnormalnim porastom SKT_{mtt} (Grupa A), hipertoničari s normalnim porastom SKT_{mtt} (grupa B), normotoničari s abnormalnim porastom SKT_{mtt} (Grupa C) i normotoničari s normalnim porastom SKT_{mtt} (Grupa D). Porast SKT_{mtt} preko 200 mm Hg smatrao se abnormalan. Jednostavnom linearnom regresijskom analizom nađena je statistički značajna negativna ovisnost između SKT_{mtt} i FMD ($F=20.2036$, $p<0.001$, $R^2=0.0956$). Srednja vrijednost indeksa FMD u pojediniom grupama bila je najniža u hipertoničara s abnormalnim porasto SKT_{mtt} (3.56±5.17) (Grupa A), izad njih su bili normotoničari s abnormalnim vrijednostima SKT_{mtt} (4.19±5.14) (Grupa B), zatim hipertoničari s normalnim vrijednostima SKT_{mtt}

(6.81±8.43) (Grupa C) i najviše vrijednosti su postignute u normotoničara s normalnim porastom SKT_{mtt} 10.92±7.48 (Grupa D). Multivarijatnom regresijskom analizom FMD je pokazao značajnu povezanost s abnormalnim SKT_{mtt} ($p<0.001$) koju su slijedili dijametar brahijalne arterije ($p<0.001$), spol ($p<0.001$) ali ne i hipertenzija ($p=0.073$), BMI ($p=0.137$) i ukupni kolesterol ($p=0.23$). Oštećenje FMD postoji u normotoničara s abnormalnim SKT_{mtt}. U hipertoničara s abnormalnim SKT_{mtt} postoji dodatno oštećenje FMD u odnosu na hipertoničare s normalnim SKT_{mtt}. Abnormalan SKT_{mtt} bi se trebao uzeti u obzir u globalnoj procijeni kardiovaskularnog rizika.