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Ventricular functions, aortic elastic properties, and endothelial functions in patients with hypertensive response to treadmill exercise testing

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Aim: Hypertensive response to treadmill exercise testing (TET) is an early marker of future development of hypertension. In this cross-sectional, case-control study we evaluated the relationship of hypertensive response to TET with aortic elastic properties, endothelial functions, and left ventricular functions.

Materials and methods: The study group comprised 33 individuals who underwent TET with suspicion of myocardial ischemia, but no evidence of ischemia and with hypertensive response to TET, and the control group comprised 29 age- and gender-matched subjects. All participants underwent echocardiographic examination, brachial artery ultrasonography, and aortic ultrasonography for the assessment of left ventricular functions, endothelial functions by determining brachial artery flow-mediated dilatation and trinitroglycerine-mediated dilatation, and aortic elastic properties by measuring the aortic diameter 3 cm proximal to the aortic valve.

Results: There was no difference between the groups in terms of echocardiographic left ventricular functions and baseline brachial artery diameters. Flow mediated dilatation showed 46% impairment in the study group compared with control ($P < 0.05$). Endothelium-independent trinitroglycerine dilatation did not differ in the groups ($P > 0.05$). Aortic elastic properties demonstrated impairment in the study group compared to the controls.

Conclusion: Flow mediated dilatation assessed with ultrasonography and echocardiographic variables demonstrated impairment for both endothelial function and aortic elastic properties in the study group in terms of early vascular development of atherosclerosis.

Key words: Aortic elastic properties, endothelial function, treadmill exercise test, flow mediated dilation

Treadmil egzersiz testine hipertansif yanıtı olan hastalarda ventrikül fonksiyonları, aortun elastik özellikleri ve endotel fonksiyonları

Amaç: Treadmill egzersiz testi (TET)'ne hipertansif yanıt gelecekteki hipertansiyon gelişiminin erken belirtisidir. Bu kesitsel vaka kontrol çalışmasında TET'ne hipertansif yanıtla aortun elastik özellikleri, endotel fonksiyonları ve sol ventrikül fonksiyonları arasındaki ilişkiyi değerlendirdik.

Yöntem ve gereç: Çalışma grubunu miyokardiyal iskemi şüphesi ile TET uygulanan ancak herhangi iskemi bulgusu olmayan ve TET'ne hipertansif yanıt gösteren 33 hasta ve kontrol grubunu yaş ve cinsiyetleri uyumlu 29 sağlıklı birey oluşturdu. Tüm katılımcılarda sol ventrikül fonksiyonlarını değerlendirmek için Doppler ve doku Doppler ekokardiyografi, endotel fonksiyonlarını değerlendirmek için brakiyal arter ultrasonografisiyle akım aracılı dilatasyon ve trinitrogliserin aracılı dilatasyon ve aortun elastik özellikleri aort kapağın 3 cm proksimalinden aort çapı ölçülerek belirlendi.

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Bulgular: Her iki grup arasında ekokardiyografik sol ventrikül fonksiyonları ve istirahat brakiyal arter çapında fark yoktu. Çalışma grubunda kontrol grubuna gore brakiyal arter akım aracılı dilatasyonda % 46 bozulma gözlendi (P < 0,05). Endotel bağımsız trinitrogliserin aracılı dilatasyon ise her iki grupta benzerdi (P > 0,05). Aortun elastik özellikleri kontrol grubuyla karşılaştırıldığında çalışma grubunda bozulmuştu.

Sonuç: Ultrasonografiyle belirlenen akım aracılı dilatasyon ve ekokardiyografik değişkenler TET'ne hipertansif yanıt gösteren grupta ateroskleroz gelişiminin erken bulgusu olan hem endotel fonksiyonlarının hem de aortun elastik özelliklerinin bozulduğunu göstermektedir.

Anahtar sözcükler: Aortun elastik özellikleri, endotel fonksiyonları, treadmil egzersiz testi, akım aracılı dilatasyon

Introduction

Treadmill exercise testing (TET) is an important noninvasive diagnostic tool for coronary artery disease. It was also shown that TET exacerbates latent hypertension (1,2) and hypertensive response to TET indicates future development of hypertension (1,2). Also it has been shown that aortic elastic properties were impaired in patients with hypertension and diabetes, and in postmenopausal women (3,4). A recent study revealed a relation between increased aortic stiffness index and hypertensive response to exercise (5). It was also shown that endothelial functions and arterial stiffness and left ventricular diastolic functions were in relation to each other (6,7).

Arterial elasticity represented as aortic elastic properties (AEPs) and endothelial functions can be detected by ultrasonographic imaging techniques. Ultrasonographic techniques utilize endothelium-dependent or flow-mediated dilation (FMD) of the brachial artery, which was validated previously (8,9). It was previously reported that the endothelial dysfunction (ED) is a marker for vascular involvement in any disease affecting the vascular structure, which can be linked with the vascular involvement in atherosclerosis (10). Moreover, left ventricular functions might be attenuated in the early stage of hypertension, which is assessed by hypertensive response to TET and/or impaired endothelial functions.

In this cross-sectional, case-control study we aimed to investigate the relationship of hypertensive response to TET with AEPs and endothelial and left ventricular functions.

Materials and methods

The study group comprised 33 patients (26 male and 7 female) who underwent TET with the suspicion of coronary artery disease with no ischemic ECG changes and showing hypertensive response to TET. Twenty-nine age- and gender-matched healthy subjects (25 male and 4 female) constituted the control group. None of the participants had obstructive vascular disease, which was demonstrated by ultrasonography, angiography, or conventional radiologic examination in the previous 5 years. The study protocol was reviewed and approved by the local ethics committee and written informed consent was obtained from all participants.

A standard form was utilized for the documentation of the presence or absence of known risk factors for atherosclerotic vascular disease, including diabetes mellitus, hypertension (blood pressure > 140/90 mmHg), cigarette smoking (regardless of the amount), and hyperlipidemia (total cholesterol > 200 mg/dL, LDL cholesterol > 130 mg/dL). Hypertensive response to TET was defined as systolic blood pressure > 210 mm Hg in men and > 190 mm Hg in women as described previously (11).

The exclusion criteria were: 1) receiving antihypertensive medication, 2) overt cardiovascular diseases, including coronary heart disease, peripheral artery disease, and congestive heart failure; 3) ECG abnormalities such as abnormal Q waves in 2 or more adjacent leads or heart block; 4) diabetes mellitus, nephrotic syndrome, and hepatic disease; 5) alcohol (ethanol) use >30 mL per day; 6) regular exercise as defined previously (9).

Flow mediated dilatation of the brachial artery diameter following transient ischemia was performed

by utilizing a high-resolution 7 MHz linear array ultrasound transducer, which was attached to a standard echocardiography machine (GE VIVID III, Norway). Measurements were performed in the morning after at least 12 h of fasting state when the patient was in supine position for 20 min in a quiet room by a single observer. All participants were kept in a stable room temperature between 20 and 25 °C and abstained from vitamin C intake, fatty meals, cigarette smoking, and caffeine-containing drinks for at least 12 h before testing. The left arm was positioned by extending the elbow and immobilized with a board. The best visualization of the brachial artery was obtained by scanning in the longitudinal section 4-5 cm above the left antecubital fossa. Gain and depth sector settings were optimized to identify the lumen-vessel wall interface. After optimal transducer positioning, the skin was marked by a permanent marker as a reference for later measurements and the left arm was kept in the same position throughout the study.

Brachial artery internal diameter was measured at the end of the diastole (timed by the QRS complex) as the distance between the intima-media border zones of the brachial artery from the anterior to posterior endothelium. The average of measurements obtained during 3 consecutive cardiac cycles was accepted. In order to create forearm ischemia, the blood pressure sphygmomanometer cuff was placed approximately 3-4 cm proximal to the section of the brachial artery and inflated to 200 mmHg for 5 min. Then, the cuff was deflated and reactive hyperemia was measured 60 s after deflation. Endothelial-dependent peripheral FMD is expressed as a percent change in brachial artery diameter in 1 min after forearm occlusion release, using the baseline resting diameter as a reference; a response < 5% represents endothelial dysfunction.

In addition to endothelium-dependent dilation, endothelium-independent dilation was assessed in all participants by measuring changes in brachial artery diameter following sublingual glyceryl trinitrate (400 µg Nitrolingual Spray) administration.

All participants underwent transthoracic echocardiographic examination. In echocardiographic examination left ventricular systolic and diastolic functions were assessed by Doppler and tissue Doppler imaging. All studies were performed with a standard echocardiography machine equipped with a 2.5 MHz transducer (GE VIVID III, Norway). Left ventricular dimensions were obtained by the parasternal short-axis view at the level of the papillary muscle. Tissue Doppler imaging (TDI) was performed with transducer frequencies of 1.8-3.6 MHz with minimal optimal gain to obtain the best signal to noise ratio. In the apical 4 chamber view, a 5 mm pulsed Doppler sample volume was placed at the level of the lateral mitral annulus, basal septal, and lateral tricuspid annulus (12). The incident angle between the interrogating Doppler beam and longitudinal motion of the ventricle was kept as small as possible and the measurements were performed while all individuals were holding their breath. The myocardial systolic wave (Sm) velocity, the diastolic indices of myocardial early (Em), and atrial contraction (Am) peak velocities were measured.

Aortic elastic properties were derived from the measurements obtained by M-mode recordings of aortic diameter 3 cm proximal to the aortic valve in both groups and were expressed as follows:

- Aortic strain (%) = (aortic diameter in systole – aortic diameter in diastole)/aortic diameter in diastole.
- Aortic distensibility (cm^2/dyn) = 2 × (aortic diameter in systole – aortic diameter in diastole)/(pulse pressure × aortic diameter in diastole).
- Aortic diameter change (mm) = Aortic diameter in systole – aortic diameter in diastole.
- Aortic stiffness index (cm^2/dyn) = 1/log (systolic blood pressure/diastolic blood pressure)/(aortic diameter in systole – aortic diameter in diastole)/aortic diameter in diastole.
- Pressure Modulus = Pulse pressure/((Aortic diameter in systole – aortic diameter in diastole)/aortic diameter in diastole).

All measurements were indexed according to body surface area.

Statistical analysis

All measurements except ED measurements were performed 3 times by 2 investigators, who were blinded to all subjects, and the final average was included in the statistical analysis. Statistical analysis was performed utilizing SPSS version 13.0. Values of selected variables were summarized by standard descriptive statistics and expressed as mean ± SD. Independent-samples t test (Mann-Whitney U test when Levene test is significant) was used to compare continuous and categorical variables between groups. Statistical significance was set as $P < 0.05$.

Echocardiographic reproducibility

The interobserver and intraobserver reproducibility of the echocardiographic measurements were 82% and 89%, respectively. The intraobserver reproducibility of the FMD ultrasonographic measurements was found to be 83%. The intraobserver and interobserver variability were 8% and 9%, respectively, for the echocardiographic assessment and the intraobserver variability of the ultrasonographic brachial artery diameter as well as aortic diameter assessments both in systole and diastole were 3%, 5%, and 6%, respectively.

Results

The demographic and baseline characteristics of both patient and control groups are provided in Table 1. There were no statistically significant difference between patient and control groups in terms of age, body mass index, systolic and diastolic blood pressure, smoking, biochemical parameters, and history of hypertension, and none of the participants was diabetic. Cholesterol levels were found to be mildly increased in the patient group compared to the control group; the difference was not statistically significant (Table 1).

The study group was not receiving any treatment with either statins- or angiotensin-converting enzyme inhibitors. There was no difference between the groups in terms of left ventricular systolic and diastolic functions assessed by Doppler and tissue Doppler parameters (Table 2).

Endothelial function parameters demonstrated 46% impairment in the patient group compared to the controls (Table 3). Endothelium-independent dilatation did not differ between the groups (Table 3). AEPs decreased in the study group compared to the controls (Table 4).

Table 1. Baseline characteristics of the participants.

	Study group (n = 33)	Control group (n = 29)	P value
Gender (male/female)	26/7	24/5	NS
Age (years)	32.6 ± 9.2	29.5 ± 5.8	NS
BMI (kg/m^2)	23.4 ± 2.5	23.1 ± 3.1	NS
Smoker (%)	13	18	NS
Hypertension (%)	2	1	NS
SBP (mmHg)	126 ± 20	128 ± 14	NS
DBP (mmHg)	80 ± 5	78 ± 10	NS
Glycemia (mg/dL)	91 ± 9	90 ± 15	NS
Total cholesterol (mg/dL)	134 ± 41	129 ± 35	NS
HDL cholesterol (mg/dL)	29 ± 4	31 ± 9	NS
LDL cholesterol (mg/dL)	92 ± 33	82 ± 22	NS
Triglyceride(mg/dL)	145 ± 55	139 ± 55	NS

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NS: not significant.

Table 2. Echocardiographic variables.

	Study group (n = 33)	Control group (n = 29)	P value
Ejection fraction (%)	66.7 ± 3.4	66.66 ± 2.93	NS
Fractional shortening (%)	37.5 ± 2.2	37.06 ± 2.64	NS
Mitral lateral S wave (cm/s)	11.54 ± 1.6	11.96 ± 1.87	NS
Mitral lateral E wave (cm/s)	11.70 ± 1.6	12.04 ± 1.97	NS
Mitral lateral A wave (cm/s)	8.8 ± 1.25	8.64 ± 2.02	NS
Septal S wave (cm/s)	12.3 ± 2.01	12.11 ± 2.17	NS
Septal E wave (cm/s)	11.8 ± 5.06	12.25 ± 2.89	NS
Septal A wave (cm/s)	8.4 ± 4.3	9.17 ± 1.88	NS
RV lateral S wave (cm/s)	16.94 ± 5.7	17.75 ± 4.38	NS
RV lateral E wave (cm/s)	15.3 ± 2.55	15.7 ± 2.68	NS
RV lateral A wave (cm/s)	12.7 ± 3.7	13.2 ± 3.72	NS

RV: right ventricle, NS: not significant.

Table 3. Brachial artery endothelial measurements in patients with HrTET and healthy control groups.

	Study group (n = 33)	Control group (n = 29)	P value
Brachial artery Baseline diameter (mm)	4.1 ± 0.2	4.3 ± 0.1	NS
FMD (%)	14.7 ± 2.6	24.2 ± 5.6	0.008
NTG-induced dilation (%)	19.3 ± 2.7	19.8 ± 2.3	NS

FMD: flow mediated dilation, NTG: nitroglycerin, NS: not significant

Table 4. Aortic elastic properties of study and healthy control groups.

	Study group (n = 33)	Control group (n = 29)	P value
Aortic Strain (%)	3.2 ± 0.9	8.9 ± 3.8	<0.001
Aortic distensibility (cm^2/dyn)	1.2 ± 0.2	4.6 ± 2.2	<0.001
Aortic diameter change (mm)	0.9 ± 0.8	3.6 ± 2.6	<0.001
Aortic stiffness index ($cm^2 \times dyn^{-1}$)	29.9 ± 7.2	8.6 ± 5.2	<0.001
Pulse pressure (mmHg)	63 ± 10	42 ± 15	<0.001
Pressure modulus ($cm^2 \times dyn^{-1} \times 10^{-6}$)	149 ± 169	326 ± 118	<0.001

Discussion

Our study demonstrated that AEPs were decreased in the study group compared to healthy controls, and endothelial function was impaired 46% in the study group, which may preclude future vascular atherosclerotic involvement. However, left ventricular diastolic functions were preserved in patients with hypertensive response to TET.

Nitrous oxide (NO) is a potent vasodilator and has well-known short-term effects on muscular tone in large and especially in small arteries. The relationship between brachial FMD and the NO genotype was previously evaluated and modest correlations were found (13). However, long-term effects of NO on AEPs may differ from the short-term effects in the brachial artery during reactive hyperemia. It was speculated that long-term remodeling of aortic structure in response to variability in ambient flow may be impaired in a subset of individuals leading to increased forward wave amplitude and elevated pulse pressure, which is consistent with the decreased AEPs. The clinical significance of an exaggerated blood-pressure rise to exercise has been recognized and debated for over 15 years. Nowadays such a rise represents a risk factor for new-onset hypertension as well as coronary artery disease (14). Moreover, this finding may be due to the very first sign of subclinical atherosclerosis.

The Framingham study showed that an exaggerated diastolic blood-pressure rise was associated with a 2- to 4-fold risk of new-onset hypertension, which may lead to further coronary artery disease (15). A raised recovery systolic blood pressure was also predictive of hypertension in men alone.

Our study demonstrated such a direct effect of hypertensive response to TET with ED, which is consistent with previous reports utilizing an indirect method, for the demonstration of impaired endothelial vasodilating capacity for exercise-induced vasodilatation as well as decreased AEPs (14,15).

Previous studies have shown that hypertensive response to TET in hypertension is related to increased morbidity and mortality from myocardial infarction in terms of adverse left ventricular remodeling (14). Among the possible causes of hypertensive response to TET, ED may play an important role in impairment of FMD, which may contribute to hypertensive response to TET in this particular study (14). Exaggerated diastolic blood pressure can be explained by increased resting peripheral vascular resistance or impaired capacity for FMD. With exercise, reduced FMD would manifest as a greater diastolic blood pressure, yielding impairment in AEPs (increased aortic stiffness, decreased aortic distensibility, diameter change, and elastic modulus). All these findings are consistent with our results, and so we can finally diagnose this aorta as a stiffened aortic structure leading to increased systolic blood pressure, decreased diastolic blood pressure and potentially causing decreased coronary perfusion pressure (15).

It was also reported that genetic determinants that influence the NO production during exercise may have a significant influence on the hypertensive response to TET (14). Endothelial dysfunction may play an important role in the impairment of FMD during exercise, which increased production of NO during exercise, and may be important in modulating the blood pressure response in terms of FMD. Furthermore, excessive sympathetic stimulation and activation of the renin-angiotensin-aldosteron system, endothelial dysfunction, and capillary rarefaction may all contribute to the hypertensive response to TET (16-19).

In our study there was no statistically significant difference in left ventricular diastolic function parameters between the study and control groups. This finding shows preserved ventricular functions in this early stage of hypertension. Although impaired ventricular function was demonstrated in patients with endothelial dysfunction, this coexistence was attributed to altered NO metabolism in endothelial dysfunction (7). However, in the studies mentioned above there were significant numbers of patients with endothelial dysfunction coexisting with clinically overt hypertension or diabetes mellitus, which are independently responsible for causing ventricular dysfunction. However, in our study none of the participants had diabetes mellitus and only 3 participants had clinically overt hypertension. This may explain the preserved ventricular function in our study group.

Conclusion

The decreased AEPs and ED in hypertensive response to TET by utilizing noninvasive techniques may indicate the increased risk of atherosclerosis. Although the pathogenesis of vascular involvement and the tendency to thrombosis has not yet been clearly identified, based on our findings, we recommend following all patients experiencing hypertensive response to TET for the risk of ED with such an easily applicable ultrasonographic method during their routine clinical follow-up. Further studies are needed to elucidate the role of ED in hypertensive response to TET, which may be an early sign of vascular atherosclerotic disease in patients with hypertensive response to TET.

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