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Blockage of Angiotensin 2 Receptor-1 Effects Not Only on Stress-induced Myocardial Dynamics but on Circulating Cathecolamins in Hypertensive Patients

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Abstract

We aimed to investigate alterations at plasma norepinephrine (NE) levels during rest and exercise and to evaluate tissue Doppler imaging (TDI) parameters in patients with essential hypertension after 6 months from treatment with olmesartan 20 mg. Fourty patients were included in the study. Rest and exercise plasma NE levels were evaluated before and after olmesartan 20 mg treatment. Plasma NE levels were studied by HPLC (high performance liquid chromatography) device. Nevertheless, we examined whether there was a relationship between TDI parameters and plasma NE levels. After 6 months from treatment with olmesartan, rest plasma NE levels ($p<0.05$) and exercise plasma NE levels ($p<0.001$) were significantly decreased. Left ventricular mass index (LVMI) and septal myocardial performance index (MPI) were significantly decreased. Systolic septal myocardial velocity (Sm) and early diastolic septal myocardial velocity (Em) were significantly increased. In addition, E/Em ratio, and isovolumetric relaxation time (IVRT) were significantly decreased. Plasma NE levels were seen increased as synchronous with increasing of LVMI. In addition, we observed that plasma NE levels are in relation with LVMI, Sm, Em and E/Em ratio. Consequently, olmesartan treatment, reduces the levels of plasma NE. It also effects on stress-induced systolic and diastolic myocardial functions. These findings support the argument that improvement in myocardial dynamics in patients with HT is related to circulating cathecolamins under stress after angiotensin II receptor subtype 1 blocker therapy.

Keywords: Hypertension • Olmesartan treatment • Plasma levels of norepinephrine • Left ventricular mass index • Rest and exercise tissue doppler echocardiography

Introduction

Hypertension is the major risk factor for cardiovascular disease and the leading cause for heart failure development. [1] Myocardial tissue remodeling and left ventricular hypertrophy (LVH) are some of the 'end-organ damage' manifestations of hypertension on the cardiac tissue specifically [2,3]. In patients with LVH, real-time three dimensional echocardiography has provided the documentation of regional details of hypertension-mediated LV remodeling [4,5]. In patients with hypertensive LVH, blockade of angiotensin 2 (AT-II) receptor-1 (AT1) positively contributes to myocardial diastolic function [6]. Angiotensin-II via the AT1 receptor play an important role for the development of LVH and regulation of sympathetic system [7]. The experimental studies have shown the catecholamines that the negative effects of cardiac tissue independently blood pressure [8,9]. Angiotensin-II via the AT1 receptor blockade, the effects of exercise tissue Doppler imaging (TDI) and catecholamine levels previously not considered clearly. In our study, we aimed to investigate alterations at plasma norepinephrine (NE) levels during rest and exercise, and to evaluate TDI parameters in patients with essential hypertension after treatment with olmesartan for 6 months.

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Methods

Patient population

Fourty consecutive patients with essential hypertension were included into the study. The written consent of the study was given to all subjects and the study protocol was consistent with the declaration of Helsinki. Personal history of the disease and cardiovascular risk factors were evaluated, and those who had previous myocardial infarction or acute coronary syndrome or procedures of coronary revascularization, stroke or transient cerebral ischemic attack, diastolic and systolic heart failure, adrenal gland and kidney disease, peripheral vascular disease, irregulary hypertension, atrial fibrillation, hypertrophic cardiomyopathy, valvular heart disease, thyroid function disease, glycogen storage disease, collogen tissue disease, pheochromocytoma, muscular dystrophy, patients using drugs that affect catecholamine levels, patients with orthopedic problem, endocrinal disease including diabetes mellitus were excluded from the present study. All patients had sinus rhythm and normal cardiothoracic ratio. Rest and exercise (bicycle ergometry) was performed plasma NE levels and TDI parameters were determined before and after 6 months of treatment with olmesartan.

Echocardiographic protocol

Patients were studied in the left lateral decubitus position (Vingmed System 5, 1.5–2.5 MHz transducer; GE Vingmed, Horten, Norway). The ECG was recorded simultaneously. Digital data were acquired during passively held end-expiration and transferred to a Macintosh computer for off-line measurement. Standard resting echocardiographic studies consisted of M-mode, cross-sectional, and Doppler blood flow measurements (mean of three consecutive beats). M-mode tracings from the parasternal long-axis view were used to measure diameter of the left atrium, septal wall thickness, LV diameter and posterior wall thickness in diastole. LV volumes and ejection fraction were calculated by the modified biplane Simpson's method. The LV end-diastolic and end-systolic volumes were derived from LV internal dimensions using the

Teichholz et al.'s Formula [10]. LV mass (LVM) was estimated by the method of Devereux, with the application of the American Society of Echocardiography (ASE) recommendations [11]. According to standart criteria, men with an LV mass index (LVMI) >134 g/m2 and women >110 g/m2 were regarded as having LVH [11].

Tissue Doppler ımaging

TDI permits a quantitative assessment of both global and regional function and timing of myocardial velocities. TDI was performed at transducer frequencies of 3.5-4.0 MHz by adjusting spectral Doppler filters until a Nyquist limit of 15-20 cm/s was reached and using minimal adequate gain. TDI was performed using LV apical 4-chamber, and sample volume was subsequently placed on the basal segments of septal and lateral walls using apical four-chamber view. It is documented that basal region has the greatest tissue velocity, and the most reliable tissue velocity compared with other regions during stress TDI [12]. The imaging angle was adjusted to ensure a parallel alignment of the sampling window with the myocardial segment of interest. Color noise reduction was adjusted, and a color Doppler scanning frame rate of 100 to 140 Hz was used. Systolic septal basal myocardial velocity (Sm), early diastolic septal basal myocardial velocity (Em), late diastolic septal basal myocardial velocity (Am), systolic lateral basal miyocardial velocity (Sa), isovolumetric contraction time (IVCT), contraction time (CT) and isovolumetric relaxation time (IVRT) were measured from TDI. Tei index was used for the calculation of the myocardial performance indeks (MPI).10 The supine position bicycle ergometry was used for exercise echocardiography. During submaximal exercise (heart rate>100 pulse/min) [13], TDI parameters were recorded in all patients.

Measurement of plasma NE levels

Blood samples were taken at 5 cc heparinized tubes during rest and exercise in the patients, and approximately 10 minutes centrifuged at 2500 rpm. Plasma NE levels were measured by HPLC (high performance liquid chromatography) device. The kit reference range of plasma NE levels were 120-680 pg/ml in adult. The same procedure was re-evaluated 6 months after treatment with olmesartan 20 mg.

Statistical analysis

We used the SPSS 17 software program for statistical analysis. Measurement results are presented as mean and standard deviation. Data comparison of both groups was made with unpaired t-test. The level of $p<0.05$ was considered statistically meaningful. Correlation between variables was determined using Pearson correlation test.

Results

22 female patients (55%) and 18 males patients with hypertension (55%) were included into the study. The mean body mass index (BMI) was 31 ± 5 kg/m^2, and 48% of patients were obese. The LVMI was increased in 58% of the patients. Increased LVMI ratio was detected higher in women than men. Demographic and clinical characteristics of patients are shown in Table 1. Basic echocardiographic characteristics of patients are also shown in Table 1. After 6 months treatment with olmesartan, mean plasma NE levels decreased from 871 ± 115 pg/ml to 766 ± 104 pg/ml ($p<0.05$) during rest, and mean plasma NE level decreased from 1110 ± 143 pg/ml to 951 ± 113 pg/ml ($p<0.001$) during exercise.

In addition, plasma NE levels at rest and exercise in women was significantly higher than men. Heart rate, BMI (Figure 1), LVMI (Figure 2), exercise Sm (Figure 3), exercise E/Em ratio and septal IVRT were related to plasma NE levels. The relationship between plasma NE levels and other parameters are shown in Table 1. Mitral E velocity, mitral A velocity, E/A ratio, Sm and Em were increased in both rest and exercise after the olmesartan treatment. Additionally, E-wave deceleration time, E/Em ratio and septal MPI were decreased after the treatment. The changes in echocardiographic parameters after olmesartan treatment are also shown in Table 1. Rest and exercise plasma NE levels were significantly decreased after the treatment.

Discusion

Essential HT increases LVM, leads to LVH and impairs the systolic and diastolic functions [14]. LVH is the most common cardiac complication of essential HT in clinical practice [15]. In our study, we demonstrated approximately half of patients with increased LVM according to Devereux formula. Angiotensin-II via the AT1 receptor leads to the increase in LVM [6]. In our study, after treatment of olmesartan, LVM was significantly reduced. We demonstrated those with increased LVM, and Sm was decreased. In particular, the lateral and septal basal myocardial tissue velocities are known to be reliable in evaluation of regional LV function [16]. In our study, Sa was not significantly changed in contrasr Sm, which is similar obsrevation to previous studies that indicate the first affected area is the septal wall in hypertensives [17]. The LIFE study, the relationship beetween decrease in LVM and improvement in diastolic myocardial functions was observed [18]. In our study, systolic and diastolic myocardial tissue velocities in rest and exercise were improved after treatment with olmesartan. In particular, increased Sm and Em and decreased E/Em ratio are some of the indicators of beneficial effect of Angiotensin-II antagonist therapy. The previous studies were reported that the Sm is directly related to myocardial contractility and it is best reflects the contractility [19]. In our study, Sm both rest and exercise and Em in exercise were increased after the olmesartan treatment. Furthermore, E-wave deceleration time, E/Em ratio and septal MPI were decreased after the treatment. In addition, we identified that

Table 1. The changes in echocardiographic parameters after treatment with olmesartan.

Variables	Rest			Exercise		
	Pre- treatment	Post-Treatment	p value	Pre-treatment	Post- Treatment	p value
Mitral E Velocity (m/s)	0.7 ± 0.2	0.9 ± 0.2	<0.001**	0.8 ± 0.2	1.0 ± 0.3	<0.001**
Mitral A Velocity (m/s)	0.8 ± 0.2	1.0 ± 0.1	<0.001**	0.9 ± 0.2	1.1 ± 0.2	<0.05*
EDEC (ms)	211 ± 33	189 ± 32	<0.05*	197 ± 32	183 ± 33	<0.05*
E/A ratio	0.9 ± 0.3	1.0 ± 0.3	>0.05	1.0 ± 0.3	1.1 ± 0.3	>0.05
E/Em ratio	0.08 ± 0.02	0.06 ± 0.01	<0.05*	0.09 ± 0.03	0.06 ± 0.02	<0.05*
Sm (cm/s)	7.9 ± 1.7	8.4 ± 1.5	<0.05*	9.2 ± 2.1	9.7 ± 1.9	<0.05*
Em (cm/s)	7.6 ± 1.7	8.0 ± 1.4	<0.05*	10.1 ± 3.0	10.4 ± 2.7	<0.05*
Am (cm/s)	8.8 ± 1.8	8.3 ± 1.4	<0.05*	10.0 ± 2.7	9.8 ± 2.4	>0.05
Septal IVCT (ms)	64 ± 14	58 ± 13	<0.05*	61 ± 10	49 ± 10	<0.05*
Septal CT (ms)	282 ± 24	297 ± 19	<0.05*	259 ± 25	277 ± 24	<0.05*
Septal IVRT (ms)	77 ± 17	68 ± 14	<0.05*	53 ± 12	54 ± 13	>0.05
Septal MPI	0.45 ± 0.09	0.43 ± 0.08	<0.05*	0.47 ± 0.08	0.42 ± 0.07	<0.001**

*statistically significant
**statistically clear significant
(Abbreviation: EDEC; E Wave Declaration Time, Sm; Septal Basal Myocardial Systolic Velocity, Em; Septal basal myocardial early diastolic velocity, Am; Septal basal myocardia late diastolic velocity, IVCT; Isovolumetric Contraction Time, CT; Contraction Time, IVRT; Isovolumetric Relaxation Time, MPI; Myocardial Performance Index).

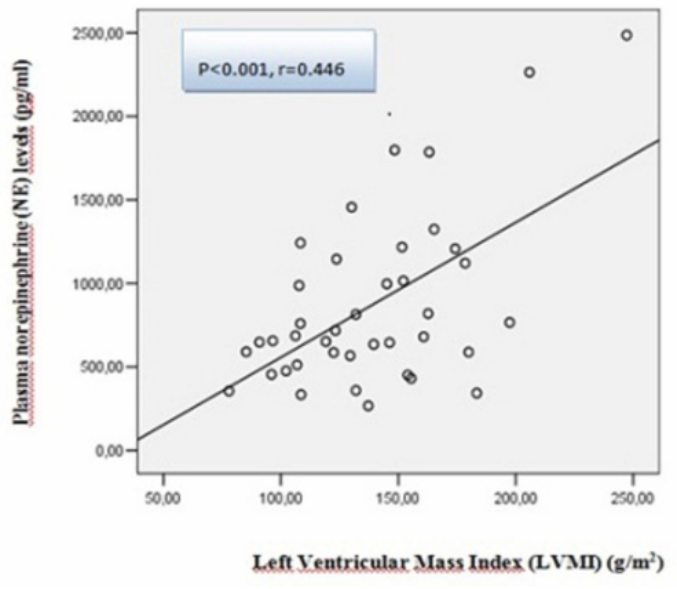

Figure 1. The relationship between plasma evelsNE l and LVMI.

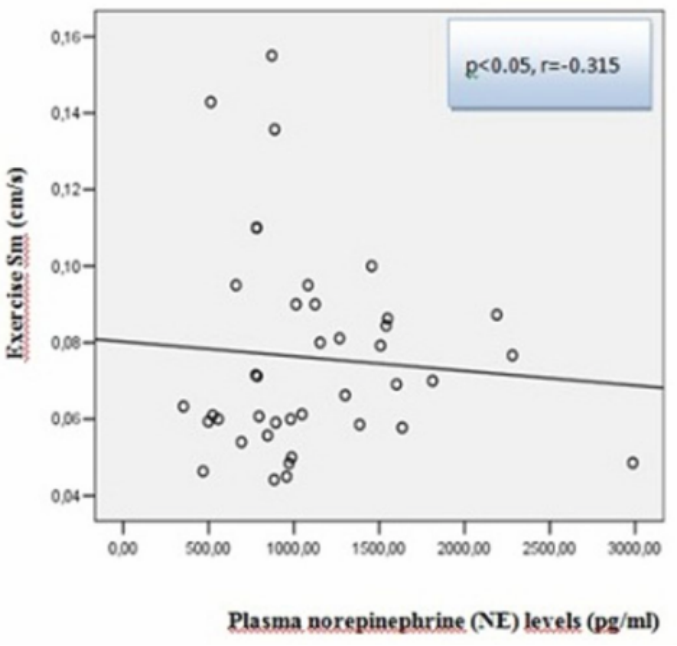

Figure 2. The relationship between exercise plasma NE levels and exercise Sm.

Sm, E/Em ratio and LVMI are related to plasma NE levels.

Von Euler, et al. found levels of plasma NE in 30-40% of patients with hypertension increased [20]. Hsueh, et al. have showed that plasma NE levels were associated with LVM [21]. One study demonstrates that LV hypercontractility exists in patients with borderline blood pressure elevations suggests that patients with elevated blood pressures have a greater velocity of fiber shortening in relation to end-systolic wall stress [23]. Microneurography and isotope dilution studies of sympathetic activity in hypertensives have shown that increased sympathetic activity and its trophic effects on cardiac muscle are directly related to the development of LVH [24]. Increased sympathetic activity is correlated with the LV mass index suggesting an association between sympathetic hyperactivity and myocardial mass [25]. In pressure overload model, early marked increase in AT1 receptor density in the LV myocardium increases both plasma NE concentration and LV myocardial epinephrine content. Plasma NE levels are associated with RAAS [20,21]. AT-II via the AT1 receptor leads to the development of LVH and the regulation of sympathetic activity [7]. The ARBs contribute to the regression LVH and healing of the diastolic myocardial functions by AT1 receptor blokade.6 Olmesartan is one of

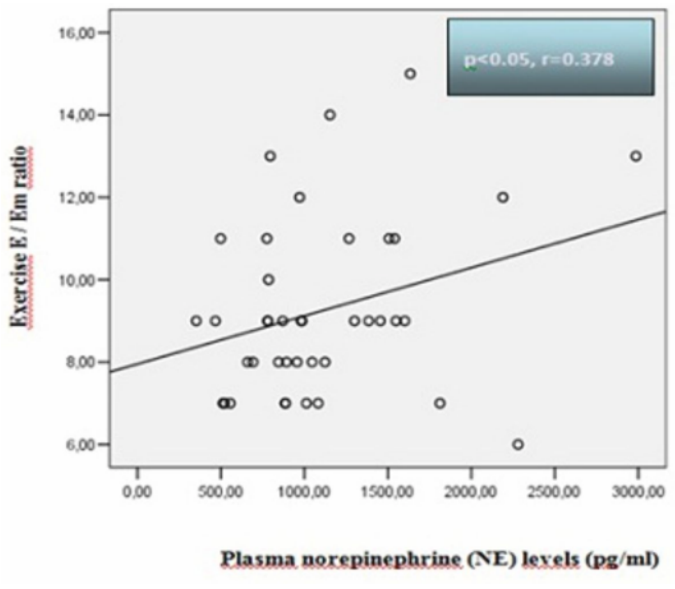

Figure 3. The relationship between exercise plasma NE levels and exercise E/Em ratio.

the powerful ARBs and binded to AT1 receptors with high affinity. In a study in rats has been shown rats injected with low concentrations olmesartan directly by affecting the adrenal nikotinerjik and muscarinic cholinergic receptors and inhibit the release of catecholamines. 22 However, olmesartan directly reduces the calcium release from adrenomedullar chromaffin cells [22]. In our study, after 6 months of treatment with olmesartan significantly decreased levels of plasma NE. Especially, a negative impact of increased exercise plasma NE levels was seen on systolic and diastolic myocardial functions. In our study, a positive correlation was found between plasma NE levels and LVMI. In addition, we observed Sm and E/Em ratio were associated with plasma NE levels. The LIFE study has demostrated that the losartan treatment reduces LVM, improves abnormal relaxation and increases E/A ratio [18]. Olmesartan treatment, to provide a positive contribution to systolic and diastolic myocardial tissue velocities and significantly reduced the levels of plasma NE. Especially, the parameters during exercise were significantly more healing may be associated with reduction plasma NE levels. Protection of exercise-induced myocardial contractility should be one of the main goals of antihypertensive therapy. Treatment with the reduction of plasma catecholamine levels a positive contribution of myocardial dynamics in the course of exercise can reduce heart failure by providing.

Conclusion

In our study, high plasma NE levels have been identified in rest and exercise. Especially, after the olmesartan treatment, exercise plasma NE levels were significantly decreased. After the olmesartan treatment, we observed that systolic and diastolic miyocardial tissue functions were improved. Especially, the relationship between plasma NE levels and exercise Sm (figure 3), exercise Em and exercise E/Em ratio (figure 4) were found to be. In addition, after the treatment, significantly LVM decreased and association of LVM with plasma NE levels were observed. Consequently, blockade of AT-II AT1 receptor reduces the high plasma NE levels and LVMI. In addition, exercise myocardial tissue paremeters contributes to these positively (increases Sm and Em, decreases E/Em ratio).

Limitations

Supine bicycle exercise was not easy method to apply in terms of the operator and the patient. One of the limitations of Tissue Doppler imaging is to be dependent on the angle and the possible presence of artifacts. In addition, the holistic movement at the heart of regional tissue Doppler velocities in space affect the assessment of myocardial function can be said that restricts.

Conflict of Interest

None.

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