The influence of α-adducin gene polymorphism on response of blood pressure to exercise in patients with hypertension

Hipertansiyonu olan hastalarda egzersize kan basıncı cevabı üzerine α-addusin gen polimorfizminin etkisi

Emin Alioğlu, Ertuğrul Ercan[1], İstemihan Tengiz, Uğur Önsel Türk, Metin Ergün[3], Semra Akgöz[2], Çetin İşlegen[3], Afig Berdeli[4]

Department of Cardiology, Central Hospital, İzmir
[1]Department of Cardiology and [2]Department of Biostatistics, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale
[3]Department of Sport Medicine and [4]Department of Pediatrics, Faculty of Medicine, Ege University, İzmir, Turkey

ABSTRACT

Objective: Clinical studies have indicated that an excessive response of blood pressure (BP) to exercise predicts risk of cardiovascular mortality. Although the mechanism responsible for the excessive BP response to exercise has not been revealed, there are some plausible mechanisms linking with underlying structural abnormalities in the cardiovascular system. Carriers of the Trp460 allele of the α-adducin Gly460Trp polymorphism have an increased risk of hypertension. The aim of the present study was to examine the influence of α-adducin gene polymorphism on response of BP to exercise in patients with hypertension.

Methods: The cross-sectional observational study consisted of 49 hypertensive patients (29 women and 20 men; mean age, 53.1±8.8 years). All participants underwent a multistage exercise treadmill test according to the Bruce protocol. Arterial BPs were compared at rest, peak exercise and end of the recovery phase. Patients were classified according to their α-adducin gene polymorphisms; Gly460Gly homozygotes - Group 1 (n=28) and Trp460Trp homozygotes and Gly460Trp heterozygotes - Group 2 (n=21). Statistical analysis was performed using Chi-square, unpaired t, Mann-Whitney U and ANCOVA tests.

Results: Mean exercise duration and mean exercise capacity in metabolic equivalents were not different between Group 1 and 2. The major finding of the study was that systolic BP responses at peak exercise and recovery period (3. min) were significantly higher (p=0.036) in hypertensive patients carrying at least one Trp460 allele of the α-adducin gene.

Conclusion: Our results suggest that genetic variants that alter renal function and/or vasoreactivity are logical candidates to explain some of the individual variability in the BP response to exercise. *(Anadolu Kardiyol Derg 2010; 10: 400-4)*

Key words: Gene polymorphism, α-adducin, essential hypertension, exercise

ÖZET

Amaç: Egzersize cevap olarak aşırı kan basıncı yükselmesinin kardiyovasküler mortalitenin öngördürücüsü olduğu gösterilmiştir. Buna ilişkin mekanizmalar net olarak ortaya konmamış olsa da, altta yatan mekanizmaların kardiyovasküler sistemin yapısal anormallikleri ile ilgili olması muhtemeldir. Alfa addusin geni Gly460Trp polimorfizmi gösteren ve Trp460 alleli taşıyıcılarında artmış hipertansiyon riski söz konusudur. Bu çalışmada, hipertansif hastalarda α-addusin gen polimorfizminin egzersize olan kan basıncı cevabına etkisi araştırıldı.

Yöntemler: Vaka-kontrollü, enine-kesitsel çalışmaya 49 hipertansif hasta (29 kadın ve 20 erkek; ortalama yaş 53.1±8.8 yıl) alındı. Tüm hastalara Bruce protokolüne göre egzersiz stres testi uygulandı. İstirahat, pik ve toparlanma sonu fazlarında elde edilen arteryel kan basıncı değerleri karşılaştırıldı. Hastalar α-addusin gen polimorfizmlerine göre sınıflandırıldı; Grup 1 Gly460Gly homozigot (n=28), Grup 2 ise Trp460Trp homozigot ve Gly460Trp heterozigottu (n=21). İstatistiksel analizde Ki-kare, eşleştirilmemiş t, Mann-Whitney U ve ANCOVA testleri kullanıldı.

Bulgular: Ortalama egzersiz süre ve kapasiteleri her iki grupta benzer düzeylerdeydi. Alfa addusin geni için en az bir Trp460 alleli taşıyan hipertansif hastalarda, pik ve toparlanma sonu (3. dk) sistolik kan basınçlarında artmış bir cevap saptandı (p=0.036).

Sonuç: Bulgularımız egzersize olan kan basıncı cevaplarındaki bireysel değişkenlikleri açıklamada, renal fonksiyonları ve/veya vazoreaktiviteyi değiştiren genetik varyasyonların etkili olabileceğini desteklemektedir. *(Anadolu Kardiyol Derg 2010; 10: 400-4)*

Anahtar kelimeler: Gen polimorfizmi, α-addusin, esansiyel hipertansiyon, egzersiz

Address for Correspondence/Yazışma Adresi: Dr. Emin Alioğlu, Department of Cardiology, Central Hospital, İzmir, Turkey
Phone: +90 232 341 67 67 Fax: +90 232 341 68 68 E-mail: dreminalioglu@yahoo.com

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Introduction

Hypertension is an increasingly important medical and public health issue and a major risk factor for myocardial infarction, stroke and renal disease. The causes of hypertension are heterogeneous. Studies of the Milan hypertensive (MHS) rat and of humans with essential hypertension suggest that genetic alterations in adducin may contribute to hypertension (1).

Adducin is a heterodimeric cytoskeleton protein that consists of α-, β- and γ- similar subunits. Three human genes that map to different chromosomes encode these subunits (2). The α-subunit plays an important role in the determination of cellular morphology and motility in the regulation of membrane ion transport (3, 4). Carriers of the Trp460 allele of the α-adducin Gly460Trp polymorphism have an increased risk of hypertension (5, 6). However, the knowledge on the association between the alpha-adducin gene polymorphism and blood pressure (BP) response to exercise in hypertension is limited.

Clinical studies have indicated that an excessive response of BP to exercise predicts future hypertension and risk of cardiovascular mortality (7-10). This suggest that maladaptation of the cardiovascular system to exercise stress is related to the pathogenesis of hypertension. However, the mechanism of this association has not been confirmed, although an augmented sympathetic response to exercise (11-13) and baroreflex abnormality (14, 15) have been discussed.

The aim of the present study was to examine the influence of α-adducin gene polymorphism on response of BP to exercise in patients with hypertension.

Methods

Study population

The cross-sectional, observational study consisted of 49 hypertensive patients (29 women and 20 men; mean age, 53.1±8.8 years) who were admitted to cardiology clinic in the Aegean region, West of Turkey. All patients were Caucasian and were receiving some type of antihypertensive treatment at the time. Informed consent was obtained from all patients. The patients completed a standard questionnaire on demographic characteristics, cigarette smoking and presence of diabetes mellitus or dyslipidemia.

Body mass index (BMI, kg/m^2) was calculated from height and weight measurements. All patients underwent transthoracic echocardiography and treadmill exercise testing. Subjects were eligible for the study if exercise was only limited by symptoms of fatigue or dyspnea but not by angina, syncope, or claudication. The exclusion criteria were presence of coronary artery disease, left ventricular systolic dysfunction (left ventricular ejection fraction <50%), stage 2 or 3 hypertension, secondary hypertension, severe valvular heart disease, autoimmune disease, chronic or acute infectious disease, use of oral contraceptives, steroids or anti-inflammatory drugs within the last three months, renal failure or cancer. Other exclusion criteria were the inability to reach stage II in the standard Bruce protocol and the use of beta-blockers or non-dihydropyridine calcium-channel blockers.

Echocardiographic examination

Patients were studied using two-dimensionally guided M-mode echocardiography (Hewlett-Packward Sonos 2500 and 4500, Hewlett-Packard Co., Andover, MA, USA) in standard views. Left ventricular internal dimension, interventricular septal thickness and left ventricular posterior wall thickness were measured at end-diastole. Recordings analyzed by single investigator who was unaware of patients' clinic and laboratory findings. The measurements were averaged from five consecutive cardiac cycles. Left ventricular mass (LVM) was calculated using the formula validated by Devereux (16):

$$LVM\ (gr) = 0.80\ [1.04\ X\ [(EDD+VS+PW)^3-EDD^3]]+0.6.$$

LVM index (gr/m^2) was obtained by dividing LVM to body surface area.

Exercise treadmill test

All participants were studied with a multistage exercise treadmill test according to the Bruce protocol (Kardiosis ARS Treadmill, Kardiosis Ltd, İstanbul, Turkey) (17). Subjects remained on the treadmill for up to two 3-minute stages. Systolic and diastolic BPs were recorded by a manually inflated cuff attached to a mercury column sphygmomanometer when the subject was standing immediately before testing and during the last minute of each 3-minute exercise stage. Subjects exercised until reaching an age-specific target heart rate or the development of symptoms necessitating termination of the test. The recovery phase was 3 minutes, with BP and heart rate recorded in the upright (sitting) position at the end of each minute. Subjects who had abnormal exercise stress test were excluded from the study. Exercise capacity in metabolic equivalents (METs) was estimated using the formula described by the American College of Sports Medicine (18). Arterial BPs were compared at rest, peak exercise and end of the recovery phase.

Genomic DNA preparation and quantitation

Two ml of whole blood samples was collected into EDTA-anticoagulated tubes by standard venipuncture method. Genomic DNA was extracted from EDTA -anticoagulated whole blood samples employing the QIAmp Blood DNA mini-kit (Qiagen, Hilden, Germany) following manufacturer's instructions. DNA concentration was determined by the PicoGreen dsDNA quantitation kit (Molecular Probes Inc., Eugene, OR, USA) according to the manufacturer's instructions and diluted as 100ng/µl.

Polymerase chain reaction: ADD gene polymorphism was genotyped be method of Kato et al. (19). Briefly, two allele-specific primers and their nonselective complementary strand

primer were mixed and used for the PCR amplification in a single reaction. The following primer sets were used:

FP-614G, 5'-GGGGCGACGAAGCTTCCGAGGTAG-3';
FP-614T,5'-GCTGAACTCTGGCCCAGGCGACGAAGCTTCCGAGGATT-3';
RP-614, 5-CCTCCGAAGCCCCAGCTACCCA-3'

PCR conditions: Amplification was carried out on a GeneAmp PCR System 9700 (PE Applied Biosystems, Foster City, CA, USA) in a 25 µl reaction mixture in 0.2 ml thin-wall PCR strip tubes (Axygen Scientific, Inc., CA, USA) containing 1µl genomic DNA solution, GeneAmp Gold Buffer (15 mmol/l Tris-HCl,pH 8.0, 50 mmol/l KCl) (PE Applied Biosystems, Foster City, USA) , 3.0 mmol MgCl2, 50 µmol/l each of the dGTP,dATp,dTTP and dCTP (Promega, Madison, WI, USA), 5 pmol each allele specific forward and 10 pmol reverse primers and 1.0 U AmpliTaq Gold polymerase (PE Applied Biosystems, Foster City, CA, USA). The cycling conditions comprised a hot start at 950C for 10 min, followed by 35 amplification cycles at 95 0 C for 30 s, 600 C for 30 s, and 720C for 25 s, followed by one elongation step at 72°C for 5 min.

The size of PCR products was 220 bp and 234 bp for the 460Gly and 460Trp alleles, respectively, which were clearly resolved on 3% agarose gel (NuSieve, FMC Bioproducts, Rockland, Maine, USA).

Statistical analysis

Statistical analysis was performed using SPSS 15 version for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean±standard deviation or median and interquartile range. Categorical variables are presented as frequencies (n, %). Pearson Chi-square test and Fisher's Exact test were used for the comparison of categorical variables between groups. Student's t-test, and when necessary Mann-Whitney U test were used for the comparison of the continuous variables between the groups. Normality of numeric data was tested with Kolmogorov-Smirnov test. After the assessment of normality assumption, repeated measures ANCOVAs test with between-subjects factors (with independent measures on the α-adducin gene polymorphisms and diuretics groups and repeated measures in the time periods) was performed with Greenhouse-Geisser adjustment. The covariates separately examined in these analyses were age, BMI, LVM index, hypertension's duration and exercise duration. A *p* value of less than 0.05 was regarded as a statistically significant difference.

Results

Genotype distributions of patients were as follows; 57% of the sample were Gly460Gly homozygotes (Group 1, n=28), 4% were Trp460Trp homozygotes and 39% were Gly460Trp heterozygotes. Because of the low frequency of the α-adducin Trp460Trp homozygote, patients with Gly460Trp and Trp460Trp genotypes were enrolled together to Group 2 (n=21) for further analysis.

Clinical and metabolic parameters of the groups are shown in Table 1. Mean exercise duration and median exercise capacity in metabolic equivalents (METs) were not different between Group 1 and 2 (p=0.967 and p=0.527, respectively). Mean rest, peak exercise heart rate and reached target heart rate were not different between the groups. Systolic and diastolic BPs were recorded when the subject was standing immediately before testing and during the last minute of each 3-minute exercise stage (Stage I to IV respectively). The BP alterations between the stages II to IV were not statistically significant (p=0.275). All of the other BP alterations between the stages were significant (p<0.0001) Diastolic BPs did not show significant difference at any stage of the test between the groups. Exercise characteristics of the study groups are shown in Table 2. Systolic BPs at peak exercise and the recovery period (at 3 min.) were significantly different between the groups (p=0.015 and p=0.047 respectively). Mean rest, peak exercise heart rate and reached target heart rate were not different between the groups (p=0.39; F=0.8). When the covariate was BMI, systolic BPs at rest, stage 2 and the recovery period (at 3 min.) were significantly different between the groups (p=0.03; F=3.7). Diastolic BPs did not show significant difference at any stage of the test between the groups (p=0.21; F=1.6).

Table 1. Demographic characteristics of the groups

Variables	Group 1 (n=28)	Group 2 (n=21)	*p
Male, n (%)	11 (39)	9 (43)	0.801
Mean age, years	51.9±8.5	54.8±9.3	0.268
Diabetes mellitus, n(%)	7 (25)	2 (10)	0.267
Dyslipidemia, n(%)	9 (32)	9 (43)	0.441
Current smoker, n (%)	12 (43)	7 (33)	0.498
BMI, kg/m^2	29.4±3.7	29.0±4.8	0.689
LVM index, gr/m^2	109.9±30.7	107.2±27.7	0.754
Hypertension duration, years	5 (1.2-10)	5 (3-10)	0.433
Medication, %			
Diuretics	39	57	0.215
ACEI	50	43	0.620
ARB	25	38	0.325
CCB	21	19	0.998

Data are expressed as mean±SD, median (25th-75th percentiles) and proportions/percentages
*Chi-square, unpaired Student's t, and Mann-Whitney U tests
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, BMI - body mass index, CCB - calcium channel blocker, LVM - left ventricular mass

In addition the possible impact of diuretic treatment on BP response was excluded by the multivariate analyses and systolic BPs responses at peak and recovery period were statistically different after exclusion of diuretic intake (p=0.03; F=3.7) (Table 3). When the age, BMI, LVM index, hypertension's duration and exercise duration were selected as the covariates the difference between the groups was still significant (p<0.05).

Discussion

In the present study, we examined the effects of the α-adducin Gly460Trp polymorphism on BP response to exercise

Table 2. Exercise characteristics of the study groups

Variables	Group 1 (n=28)	Group 2 (n=21)	p
Exercise duration, min	7.9±2.8	7.9±1.9	[a]0.967
Workload, METs	9.9 (9.9-12.7)	9.9 (9.9-12.9)	[b]0.527
Heart rate, beat/min			
at rest	85.4±13.7	88.3±17.3	
at peak exercise	146.6±21.1	149.7±13.4	[x]<0.001
Target HR reached, %	86.9±11.1	90.3±8.9	[y]0.392
*Systolic blood pressure, mmHg			
at rest	122.0±11.4	127.7±9.3	
at stage 2	140.5±12.6	143.2±9.0	[x]<0.001
at peak exercise	161.5±14.9	171.4±11.5	[y]0.036
at recovery, 3 min	137.9±10.0	142.7±4.9	
**Diastolic blood pressure, mmHg			
at rest	80.1±6.8	83.1±5.9	
at stage 2	88.1±6.2	90.3±4.0	[x]<0.001
at peak exercise	102.4±8.6	105.5±6.3	[y]0.212
at recovery, 3 min	85.4±6.2	85.0±5.6	

Data are expressed as mean±SD, median (25^{th}-75^{th} percentiles) and proportions/percentages
[a]p-Student's t-test with equal variances assumed
[b]p-Mann-Whitney U test
*When the covariate was BMI at two-way mixed design ANCOVA; [x]p - p value for time [y]p - p value for group
**Two - way mixed design ANOVA; [x]p - p value for time [y]p - p value for group
METs - metabolic equivalents

Table 3. Blood pressure response to exercise according to diuretic use in studied groups

Systolic blood pressure, mmHg		Group 1 (n=28)	Group 2 (n=21)	*p
Diuretic taking patients	at rest	126±14	127±9	[x]<0.001
	at peak exercise	163±16	171±12	[y]0.036
	at recovery, 3 min	140±11	144±4	[z]0.282
Other patients	at rest	119±8	128±9	
	at peak exercise	160±14	171±11	
	at recovery, 3 min	136±9	140±5	

Data are expressed as mean±SD
Three - way mixed design ANOVA; [x]p - p value for time, [y]p - p value for alfa-adducin group, [z]p - p value for diuretic group

in hypertensive patients. The major finding of the study was that the α-adducin Gly460Trp polymorphism interacted with exercise intensity to alter the systolic BP response to dynamic exercise. Systolic BP responses at peak exercise and recovery period (3. min) were significantly higher in hypertensive patients carrying at least one Trp460 allele of the α-adducin gene.

It has been indicated that an excessive response of BP to exercise predicts risk of cardiovascular mortality (7, 10). Although the mechanism responsible for the excessive BP response to exercise has not been revealed, there are some plausible mechanisms linking with underlying structural abnormalities in the cardiovascular system. Some authors (21) found that the total peripheral resistance in those with excessive BP response to exercise did not fall adequately to compensate for the rise in cardiac output during exercise. Accordingly, the excessive BP response to exercise can partially be explained by increased peripheral vascular resistance and impaired capacity for exercise-induced vasodilatation. These responses of peripheral vascular function can be explained by a hyper-reactivity of sympathetic nerves and an increased vascular response to adrenergic stimulation or by a thickening of the arteriolar wall that alters its ability to respond to vasoconstrictor stimuli (22). Possible confounding effect of antihypertensive treatment on adrenergic response is prevented as patients under beta- blocker treatment excluded. The inherited tendency toward hypertension predominately resides in the kidney (23). The renin-angiotensin-aldosterone system is a major BP regulatory system; therefore, genetic variants that alter renal function are logical candidates to explain some of the individual variability in the BP response to exercise. Our present results suggest that the α-adducin Gly460Trp polymorphism may be useful in identifying patients who have an excessive response of BP to exercise. Diuretic treatment is cornerstone of the hypertensive treatment. The possible impact of diuretic treatment on BP response was excluded by multivariate analyses and systolic BPs responses at peak and recovery period were still statistically different.

Polymorphisms in several genes have been associated with BP levels (20). One of these is the gene encoding for α-adducin (ADD1). Carriers of the Trp460 allele of the α-adducin Gly460Trp polymorphism have an increased risk of hypertension (5, 6) notably volume-expanded low renin hypertension (24). People with the Trp460 allele has a lowered BP to greater levels in response to diuretic therapy and are more responsive to sodium challenges (25) compared with α-adducin Gly460Gly homozygotes. These observations are attributed to associations of the Trp460 allele with increased Na+/K+-ATPase activity and renal tubular sodium reabsorption as well as elevated levels of plasma ouabain, a natriuretic hormone that has vasoconstrictive properties (5, 6, 26). An excessive systolic BP response at peak exercise and recovery period (3. min) in hypertensive patients carrying at least one Trp460 allele of the α-adducin gene is probably due to vasoconstrictive properties of the Trp460 allele. Pescatello et al. (27) have been showed that the α-adducin Gly460Trp polymorphism may be useful in identifying subsets of patients likely to benefit from the antihypertensive effects of aerobic exercise.

Genotype distributions of our patients were as follows; Gly460Gly homozygotes were 57%, Trp460Trp homozygotes were 4% and Gly460Trp heterozygotes were 39%. These distributions were similar with the study reported by Lanzani et al. (28) from Italy. They have confirmed the involvement of the ADD1 gene variants in BP regulation in 512 hypertensive patients. The genotypic frequencies of ADD1 polymorphism were 69.5% for Gly460Gly homozygotes, 2.5% for Trp460Trp homozygotes and 27.9% for Gly460Trp heterozygotes in their study.

Study limitations

There are several limitations in our study. First, we had a small study group and we recommend that these results be replicated in a larger group. Second, we disregarded the effect of drug administration time, dosage and combination therapy between the groups. Another limitation of the study was absence of data on plasma renin, salt intake or salt sensitivity to explain the physiological role of the α-adducin polymorphism. The absence of healthy controls can also be regarded as one of the limitations of our study.

Conclusion

In summary, the major finding of the present study was that the α-adducin Gly460Trp polymorphism is associated with systolic BP response to dynamic exercise. Our results suggest that genetic variants that alter renal function and/or vasoreactivity are logical candidates to explain some of the individual variability in the BP response to exercise.

Conflict of interest: None declared.

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