Prehipertansiyonda epikardiyal yağ dokusu kalınlığı ile kan basıncı düzeyleri arasındakı ilişki

Relation between epicardial adipose tissue thickness and blood pressure levels in prehypertension

Dr. Osman Turak, Dr. Fırat Özcan, Dr. Uğur Canpolat, Dr. Mehmet A Mendi, Dr. Fatih Öksüz, Dr. Özcan Özeke, Dr. Derya Tok, Kumral Çağlı, Dr. Dursun Aras, Dr. Sinan Aydoğdu

Clinics of Cardiology, Higher Specialization, and Training Hospital, Ankara, Turkey

ÖZET

Amaç: Epikardiyal yağ dokusunun (EYD) kalınlığının artışı kardiyovasküler hastalıklar için bir risk faktörüdür. Önceki çalışmalar normotansif bireylere göre hipertansif hastalarda EYD kalınlığının arttığını göstermiştir. Biz bu çalışmada normotansif, prehipertansif ve hipertansif bireyler arasında ekokardiyograf ile ölçülen EYD kalınlığı arasında fark olup olmadığını ve ayrıca prehipertansiferde EYD kalınlığının kan basıncı düzeyi ile ilişkisini araştırmayı amaçladık.

Çalışma planı: Çalışmaya Amerikan Hipertansiyon Kılavuzu'na (Ulusal Komite'nin 7. Raporu) göre prehipertansif (n=50), hipertansif (n=50) ve normotansif sağlıklı (n=50) bireyler alındı. Tüm katılımcılara transtorasik ekokardiyograf incelemesi yapıldı. EYD kalınlığı parasternal uzun aks penceresinden sistol fazının sonunda ölçüldü.

Bulgular: Normotansif sağlıklı bireylerle karşılaştırıldığında prehipertansif ve hipertansif bireylerde EYD kalınlığı anlamlı olarak artmıştır (sırasıyla, 4,1±1,1 mm, 5,4±1,3 mm ve 6,6±1,5 mm, p<0.001). Yaş, cinsiyet, yüksek yoğunluklu lipoprotein, bel çevresi ve beden kütle indeksi gibi faktörlere göre düzeltme yapıldığında EYD kalınlığı normansif, prehipertansif ve hipertansif gruplarda sırasıyla 4.3±1.2 mm, 5,3±1,2 mm ve 6,4±1,4 mm olarak ölçüldü (p=0,001). Prehipertansif grupta, çok değişkenli doğrusal regresyon analizine göre EYD kalınlığı hem sistolik (r=0,305, p=0,001) hem de diyastolik (r=0,297, p=0,001) kan basınçları ile diğer risk faktörlerinden bağımsız olarak pozitif yönde anlamlı ilişkili bulundu.

Sonuç: Ekokardiyograf ile ölçülen EYD kalınlığı hipertansif hastalara ek olarak prehipertansiferde de normal kan basıncına sahip bireyler ile kıyaslandığında diğer faktörlerden bağımsız şekilde artmıştır. Ayrıca prehipertansif hastalarda sistolik ve diastolik kan basıncı düzeyleri EYD kalınlığı ile anlamlı olarak ilişkilidir.

ABSTRACT

Objectives: Increased epicardial adipose tissue (EAT) thickness is a risk factor for cardiovascular diseases. Previous studies have demonstrated that EAT thickness increases in patients with hypertension compared with normotensive individuals. In the current study, we aimed to evaluate vvhether echocardiographically measured EAT thickness differs among normotensive, prehypertensive, and hypertensive patients, and the relation between EAT thickness and blood pressure levels in prehypertensives.

Study design: Prehypertensive (n=50) and hypertensive (n=50) and normotensive patients, and healthy subjects (n=50) as assessed by the American Hypertension Guidelines (Joint National Committee 7) were enrolled in the study. Ali participants undervvent transthoracic echocardiographic examination. EAT thickness was measured from the parasternal long-axis view at end-systole.

Results: Compared with normotensives, EAT thickness was signifcantly increased in prehypertensive, and hypertensive patients (4.1±1.1 mm, 5.4±1.3 mm and 6.6±1.5 mm, respectively, p<0.001). After adjustment for confounding factors like age, gender, high-density lipoprotein, waist circumference, and body mass index, EAT thickness in the normotensive, prehypertensive and hypertensive groups was measured as 4.3±1.2 mm, 5.3±1.2 mm and 6.4±1.4 mm, respectively (p=0.001). In the prehypertensive group, multivariate linear regression analysis showed that EAT thickness was positively correlated with both systolic (r=0.305, p=0.001) and diastolic (r=0.297, p=0.001) blood pressures, independent of other risk factors. Conclusion: In addition to hypertensive subjects, echocardiographically measured EAT thickness is increased in prehypertensive patients when compared with normotensive subjects, independent of other factors. Additionally, increased EAT thickness is signifcantly correlated with systolic and diastolic blood pressure levels in patients with prehypertension.

Submitted on: 08.29. 2013 Accepted for publication on: 01.03. 2014 Address of correspondence:: Dr. Osman Turak. Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi,Kardiyoloji Kliniği, Ankara. Phone: +90 312 - 306 11 34 e-mail: <u>osmanturak@yahoo.com</u> © 2014 Türk Kardiyoloji Derneği



Blood pressure values between normal, and hypertension limits are called prehypertensive values. In clinical practice diagnosis of prehypertension is made based on the measurements of systolic blood pressure of 120-139 mm Hg and/or diastolic blood pressure of 80-90 mm Hg. ^[1] Prehypertension is not an apparent indicator of the future development of hypertension.. However it is an absolute indicator that these individuals should start to implement life style changes.^[2] Studies have shown that cardiovascular mortality rates markedly increase in prehypertensive individuals relative to normotensives.^[3,4]

According to various investigations, visceral adipose tissue is metabolically more active, so it is more harmful for the cardiovascular system when compared with the subcutaneous fat tissue.^[5] Epicardial adipose tissue (EAT) is visceral fat tissue around the heart [6] and in healthy individuals its thickness is nearly 5 mm.^[7] Previous studies have demonstrated that EAT thickness is significantly greater in hypertensives when compared with normotensives which has been positively correlated with blood pressure levels.^[7,8] However the same correlation between EAT thickness, and blood pressure measurements in prehypertensive individuals has not been investigated yet. In the present study, we aimed to investigate if any difference exists between prehypertensive, and hypertensive patients regarding echocardiographically measured EAT thickness, and also inquire presence of any correlation between EAT thickness, and blood pressure levels.

PATIENTS AND METHOD

Patient group

We enrolled 50 prehypertensive, 50 newly-diagnosed hypertensive patients, and 50 normotensive healthy individuals in the study. Ambulatory blood pressure measurements were performed using sphyngomanometer in the outpatient clinics. Blood pressure measurements were done after patients' resting period of at least 5 minutes. The patients were asked if they had drunk coffee or tea within the last 30 minutes or smoked within the last 30 minutes, and if they didn't then blood pressure measurements were made. While measuring blood pressures (BP), the arm of the seated patient was supported at the level of the heart. BP measurements were made from both arms, and the higher BP value was included in the evaluation.

Abbreviations:

BMI: Body mass index **EAT:** Epica**r**dial adipose tissue **MRI** Magnetic resonance imaging

Diagnosis of the hypertension was based on systolic blood pressure of \geq 140 mm Hg, and /or diastolic blood pressure of \geq 90 mm Hg, while diagnosis of prehypertension on systolic BP 120-139 mm Hg and/or diastolic blood pressure of 80-89 mm Hg as measured at two separate clinical visits..^[1] Patients receiving antihypertensive treatment, and those with diagnosis of hypertension due to secondary causes, and renal dysfunction (GFR < 90 mL/min/1.73 m²), history of coronary artery disease, hepatic failure, hypothyroidism, hyperthyroidism, systemic inflammatory disease were excluded from the study. The study was performed in compliance with the principles of Declaration of Helsinki, and after approval of the Ethics Committee, and informed consent of the patients were obtained.

Transthoracic echocardiographic examination

Transthoracic echocardiographic examination of all participants was performed using 2.5-3.5 MHz ultrasound probe (Vivid 7, GE-Vingmed Ultrasound AS, Horten, while the patient was laid in the lateral Norway) decubitus position. All examinations were recorded on digital media, and digital records were used for echocardiographic examinations realized by a cardiologist experienced in echocardiography but blinded to patients'data. Standard echocardiographic measurements including the size of the left atrium, left ventricular diameters, left ventricular wall thickness, and left ventricular ejection fraction were made in compliance with guidelines American Society the of of Echocardiography.^[910] Left ventricular mass index was calculated according to Devereux formula.[11]

Determination of the epicardial adipose tissue, and measurement of its thickness

Epicardial adipose tissue is detected as a relatively hypoechoic area interposed between the right ventricle, and the internal leaflet of the pericardium. From this area the maximum end-systolic EAT thickness was measured from a plane parallel to the aortic valve.^[6] To detect intraobservational variation, EAT thickness of randomly selected 30 individuals was measured again. Accordingly intraclass correlation coefficient analysis was used to estimate reproducibility of EAT thickness. Reproducibility of measurements of EAT thickness was quiet good (intraclass correlation coefficient = 0.932; p<0.001).

Statistical Evaluation

Statistical calculations were performed using "SPSS for Windows 17.0" package program. For the determination of the distribution characteristics of continuous data Kolmogorov-Smirnov test was employed. Accordingly, for statistical analysis of numerical data demonstrating normal distribution pattern in each three groups ANOVA (one-way analysis of variance) test, and for those with nonnormal distribution Kruskal-Wallis test were used. For the analysis of categorical variables, chi-square or Fisher's exact test were used. When cofactors were taken into consideration, statistical analysis of EAT thickness among 3 groups was realized using ANCOVA (one-way analysis of covariance) test. Multivariate linear regression analysis was used to demonstrate the presence of a correlation between EAT thickness, systolic, and diastolic blood pressure levels independent from other factors. For all statistical calculations p< 0.05 was accepted as statistically significant.

RESULTS

Clinical characteristics, and laboratory test results of the groups included in the study are presented in Table 1. Any significant intergroup difference was not detected as for age, gender, smoking, and diabetes mellitus.

Table 1. Demographic characteristics of the study groups

Body mass index (BMI), and waist circumference were greater, and HDL-cholesterol level increased in prehypertensive, and hypertensive group when compared with the control group (p<0.05).

Left ventricular diameters, ejection fraction, and left atrial diameterd were not different between groups, left ventricular wsall thickness, and left ventricular mass index were significantly higher in the hypertensive, and prehypertensive groups relative to thye control group (Table 2). EAT was measured as 4.1±1.1 mm, 5.4±1.3 mm, and 6.6±1.5 mm in the normotensive, prehypertensive, and hypertensive groups respectively (p<0.001, ANOVA) (Figure 1). When adjustments were made for cofactors as age, gender, HDL-cholesterol, waist circumference, and BMI EAT thickness was measured as 4.3 ± 1.2 mm. 5.3 ± 1.2 mm, and 6.4 ± 1.4 mm in the normotensive, prehypertensive. hypertensive and groups. respectively (p=0.001, ANCOVA). As shown in Tables 3, and 4, in multivariate linear regression analysis, a positive, and significant correlation was detected between EAT thickness, and both systolic (r=0.305, p=0.001), and diastolic (r=0.297, p=0.001) blood pressure levels independent from other factors

Variables	Control	Prehypertensive	Hypertensive	р
	(n=50)	(n=50)	(n=50)	
Age (year)	51.9±10.4	50.6±9.8	52.7±10.2	0.511
Men, n (%)	27 (54)	30 (60)	29 (58)	0.826
Body mass index (kg/m²)	26.7±3.2	27.3±3.5	28.9±4.1	0.001
Waist circumference (cm)	84.4±7.5	94.7±9.3	102.4±10.5	<0.001
Smoking, n (%)	10 (20)	16 (32)	20 (40)	0.092
Diabetes mellitus, n (%)	6 (12)	8 (16)	13 (26)	0.172
Systolic blood pressure (mmHg)	119.7±5.8	135.3±8.5	154.9±10.2	<0.001
Diastolic blood pressure (mmHg)	74.2±5.3	84.2±6.6	94.1±8.2	<0.001
Heart rate (beat/min)	72.5±9.1	75.3±9.4	76.5±9.9	0.398
Fasting glucose (mg/dl)	91 (84-100)	95 (87-103)	99 (87-108)	0.542
Serum creatinine (mg/dl)	0.80 (0.60-1.00)	0.90 (0.70-1.00)	1.0 (0.70-1.1)	0.149
Fasting blood glucose				
Total cholesterol (mg/dl)	205.1±34.9	209.8±37.6	203.5±36.2	0.457
HDL Cholesterol (mg/dl)	47.1±5.3	45.0±5.4	42.9±4.7	0.001
LDL Cholesterol (mg/dl)	121.7±33.5	127.2±32.5	128.7±28.8	0.364
Triglyceride (mg/dl)	144 (113-184)	148 (107-184)	143 (110-177)	0.433
Hemoglobin (g/L)	14.5±1.2	14.3±1.4	14.2±1.6	0.331

Variables	Control	Prehypertensive	Hypertensive	р
	(n=50)	(n=50)	(n=50)	
Left ventricular ejection fraction (%)	62.3±2.9	62.1±3.1	61.7±3.4	0.344 ^a
Left ventricular end-diastolic diameter (cm)	4.4±0.3	4.7±0.3	4.9±0.4	0.231ª
Left ventricular end-systolic diameter (cm)	2.6±0.2	2.9±0.3	3.3±0.4	0.193a
Interventricular septum thickness (mm)	9.0±1.3	9.8±1.4	10.9±1.5	< 0.001 ^{bcd}
Posterior wall thickness (mm)	9.0±0.9	10.4±1.3	11.3±1.5	< 0.001 ^{bcd}
Left ventricular mass index (gr/m ²)	83.4±12.5	92.2±16.3	111.0+24.3	< 0.001 ^{bcd}
Left atrial diameter (cm)	3.8±0.3	3.9±0.4	4.1±0.4	0.347 ^a
Epicardial adipose tissue (mm)	4.1± 1.1	5.4±1.3	6.6±1.5	0.001 ^{bcd}

Table 2. 2-dimensional, and M-mode transthoracic echocardiographic data of the study participants

a: ANOVA; b: between the control, and prehypertensive groups; c: between control, and the hypertensive groups; d: between prehypertensive, and hypertensive groups.

DISCUSSION

Presently, hypertension is considered to be the most important treatable cardiovascular risk factor in the whole world.^[12] According to the data of the World Health Organization every year nearly 7.5 million individuals are dying of hypertension.^[13] Though prehypertension which courses with relatively lower blood pressure levels is considered as the apparent precursor of hypertension, it is not an innocent clinical entity. When compared with the individual with normal blood pressure values, major cardiovascular events as atherosclerosis, and stroke are experienced prominently more often by prehypertensive individuals.^[3,14]

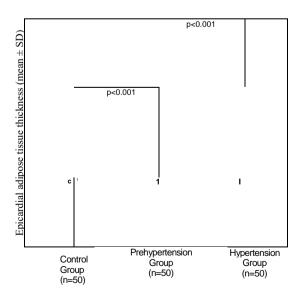


Figure 1 Comparisons between echocardiographically evaluated epicardial adipose tissue thickness of study groups

In a meta-analysis encompassing nearly one million subjects, and 61 observational studies, prehypertension has been shown to increase cardiovascular, and allcause mortality rates.^[3] When compared with individuals with normal blood pressure values, obesity, insulin resistance, and worse blood lipid are more frequently encountered profile in prehypertensive individual.^[14,15] As has been indicated in epidemiological studies, one of the most important risk factors in the development of hypertension, and prehypertension is increased fat tissue in the body. ^[16, 17] Besides, a positive linear correlation exists between the degree of lipoidosis, and blood pressure levels..^[16] BMI which indicates whole body lipoidosis, and as an indicator of visceral lipoidosis waist circumference have been demonstrated to be related to the development of prehypertension..[16,17] Data from our country also tend to support the above information. Erem et al.^[18] conducted a study on 4809 prehypertensive individuals in the Trabzon region, and demonstrated the presence of a significant correlation independent form other factors between increased blood pressure levels, waist circumference, and BMI in prehypertensive individuals.

Epicardial adipose tissue (EAT), is a visceral adipose tissue which envelopes heart, and it is interposed between the myocardial tissue, and internal layer of the pericardium. Protective effects of this tissue on mechanical, and metabolic functions of the cardiovascular (CV) system have been demonstrated, however it has been evidenced that increased amounts of EAT starts to exert adverse effects on CV system..^[19-21] In addition to its systemic effects, the most important characteristic of EAT which discriminates it from other visceral adipose tissue is its ability to exert paracrine effects on myocardium, and coronary arteries via secretion of many proinflammatory, proatherogenic molecules ^[19]

Variables	Systolic blood pressure	•
	Beta regression coefficient	р
Age (year)	0.201	0.047
LDL- cholesterol (md/dl)	0.084	0.547
HDL-cholesterol (mg/dl)	-0.204	0.031
Triglyceride (mg/dl)	0.106	0.307
Waist circumference (cm)	0.395	<0.001
Body mass index (kg/m ²)	0.234	0.021
Left ventricular ejection fraction (%)	0.042	0.644
Left ventricular mass index (gr/m ²)	0.227	0.012
Epicardial adipose tissue thickness (mm)	0.305	0.001

Table 3.In a multivariate linear regression analysis, the independent correlation between systolic blood pressure, clinical, echocardiographic, and laboratory data in prehypertensive individuals (R^2 = 0.475, p<0.001)

Table 4. In a multivariate linear regression analysis, the independent correlation between diastolic blood pressure, clinical, echocardiographic, and laboratory data in prehypertensive individuals (R²=0.459, p<0.001)

Variables	Diastolic blood pressure		
	Beta regression coefficient	р	
Age, year	0.165	0.082	
LDL cholesterol (mg/dl)	0.097	0.504	
HDL cholesterol (mg/dl)	-0.215	0.024	
Triglyceride (mg/dl)	0.132	0.285	
Waist circumference (cm)	0.376	<0.001	
Body mass index (kg/m ²)	0.129	0.185	
Left ventricular ejection fraction (%)	0.066	0.748	
Left ventricular mass index (gr/m ²)	0.206	0.030	
Epicardial adipose tissue thickness (mm)	0.297	0.001	

EAT cells secrete many metabolically active molecules including tumour necrosis factor- α , monocyte chemoattractant protein-1, resistin, interleukin-6, interleukin-8, and interleukin-1 β .^[19] As indicated above, these molecules lead to systemic inflammation, and also with their direct paracrine effects create an inflammatory environment involving myocardium, and coronary arteries. Because of these factors, EAT has been considered as a new cardiovascular risk factor..^[19] Though the impact of EAT on the development of hypertension is not clearly known, in studies performed both with healthy individuals, and those with cardiovascular risk factors has been demonstrated..^[22,23] In addition, adverse cardiovascular effects of EAT in hypertensive patients have been analyzed from different perspectives

Sengul et al.^[8] investigated the impact of increased EAT thickness on nocturnal blood pressure, and demonstrated a correlation between increased EAT thickness, and higher blood pressure levels during night hours in hypertensive patients (non-dipper hypertension)..In another study by Şengül et al.^[24], the authors revealed that healthy individuals with increased EAT thickness gave exaggerated responses to exercise stress test. Pierdomenico et al.^[25] disclosed that increased EAT thickness in hypertensive patients with normal body weights, and waist circumference was related with the development of metabolic syndrome

In another study performed on 135 cases with newly diagnosed essential hypertension, the investigators demonstrated significant increases in EAT thickness in hypertensive patients with diastolic dysfunction relative to hypertensives with normal left ventricular diastolic function.^[26] In this study, correlation between increased EAT thickness, and systemic inflammation independent was demonstrated from other anthropometric parametres. Very few studies have investigated EAT thickness, and its clinical significance in prehypertensive patients. Sironi et al. used cardiac magnetic resonance imaging (MRI) method to demonstrate significant increase in EAT thickness in prehypertensives relative to normo tensives. In their study, even though globally ventricular systolic function appeared to be normal in prehypertensives, the authors emphasized the presence of regional systolic dysfunction, and contribution of insulin resistance, dyslipidemia, and also increased EAT thickness to the development of regional systolic dysfunction in prehypertensive individuals.

Cardiac MRI or computed tomographic methods estimate epicardial adipose tissue more accurately than transthoracic echocardiographic modalities, however the latter method are available in few centers in addition to their higher cost.^[6] Besides close correlations between measurements of EAT thickness performed using MRI, and echocardiography have been demonstrated (r=0.864).^[28] In the present study we have displayed significant increases in EAT thickness, in prehypertensives relative to normotensives, and in hypertensives when compared with prehypertensives using transthoracic echocardiography. Besides, in our study, we have also demonstrated a positive, and a significant correlation between both systolic, and diastolic blood pressure levels with EAT thickness, independent from age, waist circumference, BMI, and blood lipid levels. Current studies have shown that body weight control, and exercise can decrease both blood pressure levels^[29], and amount of EAT. ^[30] In consideration of unfavourable effects of high blood pressure levels, and increased EAT thickness on cardiovascular system, all prehypertensive patients should be recommended to make favourable modifications in their life styles as soon as possible.

Limitations of the Study

Our study is a cross-sectional investigation reflecting data of a single center.

Besides, relatively small number of patients were included in the study. Prehypertensive individuals were not followed up as for development of hypertension or adverse cardiovascular events. Therefore the impact of increased EAT thickness on future adverse effects was not investigated. Although we have demonstrated the presence of a positive, and significant correlation between EAT thickness, systolic, and diastolic blood pressures, we couldn't explain the fundamental underlying mechanism of this correlation. Blood pressure measurements of the patients were made in the outpatient clinics on an ambulatory basis, and probability of white coat hypertension could not be ruled out using sophisticated methods. A few patients were using statins (control group. n=2: prehypertension group, n=2, and hypertension group, n=3). Since these small number of statin users in the groups were close to each other, the effect of statin use was not included in the multilinear regression analysis.

Conflict of interest: None declared

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Anahtar sözcükler: Ekokardiyograf; epikart; hipertansiyon; kan basıncı; vücut ağırlığı; yağ dokusu/patoloji.

Key vvords: Echocardiography; epicardium; hypertension; blood pressure; body vveight; adipose tissue/pathology.