The relationship between epicardial adipose tissue and P wave and QT dispersions

Epikardiyal adipoz dokunun P dalga ve QT dispersiyonu ile ilişkisi

Yüksel Çiçek, M.D., Sıtkı Doğan, M.D.,# Murtaza Emre Durakoğlugil, M.D., Akif Serhat Balcıoğlu, M.D.,* Turan Erdoğan, M.D., Ömer Şatıroğlu, M.D., Zakir Karadağ, M.D., Hakan Duman, M.D., Mehmet Bostan, M.D.

Department of Cardiology, Recep Tayyip Erdoğan University Faculty of Medicine, Rize
#Department of Cardiology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize
*Department of Cardiology, Başkent University, Alanya Medical and Research Center, Antalya

ABSTRACT

Objective: Epicardial adipose tissue (EAT) secretes various pro-inflammatory and atherogenic mediators that have several endocrine and paracrine effects on heart. This study investigated the influence of EAT on QT and P wave dispersions (QTd, PWd), as simple, non-invasive tools of proarrhythmia on surface ECG.

Methods: This was a cross-sectional study and included 70 patients with normal coronary arteries who underwent 12-derivation electrocardiography, echocardiography and biochemical examinations in order for QTd, PWd, and EAT thickness to be measured.

Results: Median EAT thickness was 4.1 mm. Correlation analyses revealed that EAT was significantly associated with age (r=0.412, p<0.001), weight (r=0.262, p=0.028), body mass index (r=0.396, p<0.001), left atrium diameter (r=0.518, p<0.001), fasting plasma glucose (r=0.245, p=0.041), maximum P wave duration (r=0.343, p=0.004), minimum P wave duration (r=0.275, p=0.021) and PWd (r=0.265, p=0.026). No relation was found between study parameters and QTd. However, P wave dispersion was significantly related to EAT thickness (r=0.265, p=0.026), left atrium diameter (r=0.483, p<0.001), and the triglyceride levels (r=0.267, p=0.028). Multiple linear regression analyses revealed left atrial diameter as the only independent predictor of PWd.

Conclusion: A significant association between EAT and PWd was demonstrated in the study. While EAT is related to both increased PWd and left atrial size, left atrial diameter seems to be more important than EAT for prediction of atrial fibrillation (AF) in patients with normal coronary arteries.

ÖZET

Amaç: Epikardiyal adipoz doku (EAD) kalpte pek çok endokrin ve parakrin etkiye sahip olan çeşitli enflamatuvar ve aterojenik ajanları salgılar. Bu çalışmada, EAD'nin elektrokardiyografinin (EKG) basit, non-invaziv aritmi belirteçleri olan QT ve P dalga dispersiyonu (QTd, PDd) üzerine etkisini araştırmayı planladık.

Yöntemler: Kesitsel yapıda çalışmamıza koroner arterleri normal 70 hasta alındı. Bu hastalara 12 derivasyon EKG, ekokardiyografi, biyokimyasal çalışmalar yapılarak, QTd, PDd ve EAD kalınlığı hesaplandı.

Bulgular: Ortanca EAD 4.1 mm olarak bulundu. EAD yaş (r=0.412, p<0.001), vücut ağırlığı (r=0.262, p=0.028), beden kitle indeksi (r=0.396, p<0.001), sol atriyum boyutu (r=0.518, p<0.001), açlık plazma glukozu (r=0.245, p=0.041), maksimum P dalga süresi (r=0.343, p=0.004), minimum P dalga süresi (r=0.275, p=0.021) ve PDd (r=0.265, p=0.026) ile koreleydi. QTd ile çalışılan parametreler arasında ilişki saptanmadı. Ancak PDd; EAD kalınlığı (r=0.265, p=0.026), sol atriyum boyutu (r=0.483, p<0.001) ve trigliserit düzeyi (r=0.267, p=0.028) ile ilişkiliydi. Çok değişkenli analiz sol atriyum boyutunun PDd'nin tek bağımsız belirleyicisi olduğunu ortaya koydu.

Sonuç: Çalışmamızda EAD ile PDd arasında anlamlı bir ilişki saptadık. Her ne kadar EAD hem PDd ve hem de sol atriyum boyutu ile ilişkili ise de, sol atriyum boyutu, koroner arterleri normal hastalarda atriyum fibrilasyonu riski için EAD'den daha önemli gibi görülmektedir.

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Correspondence: Dr. Murtaza Emre Durakoğlugil. Recep Tayyip Erdoğan Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 53100 İslampaşa, Rize, Turkey.
Tel: +90 464 - 212 30 09 e-mail: emredur@hotmail.com

Visceral adipose tissue, an organ with endocrine and paracrine effects, secretes both pro-inflammatory and pro-atherogenic cytokines.[1] Epicardial adipose tissue (EAT), a specific type of visceral adipose tissue, is localized between the pericardium and myocardium. Even though the pathophysiologic association of EAT with several cardiovascular disorders has been identified,[2] the role of EAT in normal physiology has not yet been completely understood. However, several functions including protection of coronary arteries against powerful cardiac contraction, regulation of fatty acid homeostasis in the coronary microcirculation, and thermogenesis have been proposed.[3] EAT, like other visceral adipose tissues, secretes various pro-inflammatory (tumor necrosis factor [TNF]-α, interleukin [IL] 6, macrophage chemoattractant protein [MCP], IL 16, plasminogen activator inhibitor-1, soluble intercellular adhesion molecules), and atherogenic (leptin, resistin, adiponectin, visfatin) mediators[4,5] There is considerable evidence that EAT is associated with several cardiac pathologies including coronary artery disease (CAD),[6] coronary artery ectasia,[7] metabolic syndrome,[8] ascending aortic dilation,[9] increased left ventricular mass,[10] and left atrial dilation.[11]

QT (QTd) dispersion is the difference between the maximum and minimum body surface QT interval.[12] Increased QT dispersion reflects inhomogeneity of myocardial repolarization, which may be related to malign arrhythmias.[13] P wave dispersion (PWd), the difference between the longest and shortest P wave duration in surface electrocardiogram (ECG), is independently related to recurrent and paroxysmal atrial fibrillation.[13,14] Since EAT mainly covers coronary vessels and, to a lesser extent, surrounds the atria, the free wall of the right ventricle, and the left ventricular apex,[15] EAT may influence cardiac conduction as well. Therefore, the study investigated the influence of EAT on QT and P wave dispersions, as simple, non-invasive tools of proarrhythmia on surface ECG.

METHODS

Patient selection and study protocol

Enrolled in the study were 70 consecutive patients who underwent coronary angiography in our clinic on suspicion of CAD, and who were found to have normal coronary arteries. All patients had routine 12-derivation electrocardiography, echocardiography, and biochemical measurements prior to coronary angiography. This study was performed in accordance with Helsinki principles and approved by the local Ethics Committee. Medical history and demographic characteristics of the patients were noted.

Abbreviations:

BMI	*Body mass index*
CAD	*Coronary artery disease*
EAT	*Epicardial adipose tissue*
ECG	*Electrocardiogram*
IL	*Interleukin*
PWd	*P wave dispersion*
QTc	*Corrected QT*
QTd	*QT interval dispersion*
TNF	*Tumor necrosis factor*

Exclusion criteria were history of diabetes mellitus, CAD, atrial fibrillation (paroxysmal, persistent, permanent), chronic renal and hepatic disorders, electrolyte imbalance, and drug usage that might influence QT interval, including β-blockers, amiodarone, propafenone, verapamil and diltiazem. Patients with cardiomyopathy, moderate to severe valvular dysfunction, and pericardial disorders were also excluded according to echocardiographic findings.

Baseline characteristics of the patients were recorded. Hypertension (HT) was defined as the documentation of blood pressure exceeding 140/90 mmHg. Diabetes mellitus was defined as fasting plasma glucose levels over 126 mg/dL or glucose levels over 200 mg/dL at any measurement, or active use of antidiabetic treatment. Patients who were using tobacco products on admission to our hospital and those who had quit smoking within the previous year were considered smokers. Body mass index (BMI) was calculated by the following formula: BMI = weight (kg)/height^2 (m).

Routine measurements

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 hours before coronary angiography. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Serum CRP levels were evaluated by nephelometry.

Calculation of QTd and PWd

All patients underwent 12-lead ECG (Cardiofax S, Nihon Kohden, Tokyo, Japan), prior to coronary angiography, at a paper speed of 25 mm/s and a calibration of

1mV = 10 mm. One cardiologist, blinded to the study results, conducted all ECG analyses using a magnifying glass. An appropriate ECG was determined by its ability to measure QT and P wave duration in at least 9 of the 12 ECG leads recorded simultaneously. QT interval was measured from the beginning of the QRS complex to the end of the T wave, which was defined as return to the baseline in each ECG lead. In the event of a U wave, QT interval was measured to the nadir of the curve between the T and U waves. [12] The corrected QT (QTc) duration was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). Three consecutive cycles were measured in each lead and using three values, mean QT and QTc of each lead were calculated. Dispersion of QT interval was calculated as the difference between the longest and shortest QT interval measured in each individual ECG lead (QTd = maximum QT duration - minimum QT duration).

Onset of the P wave was defined as the junction between the isoelectric line and the beginning of the P wave deflection, and offset of the P wave was defined as the junction between the end of the P wave deflection and the isoelectric line. P wave dispersion was calculated as the difference between the maximum

Table 1. Patient baseline characteristics, echocardiographic and laboratory findings

Variables	n=70
Age, years	50.9±11.3
Gender, male/female n (%)	34/36 (48.6/51.4)
Hypertension, n (%)	28 (40.0)
Smoking, n (%)	34 (48.6)
Height (cm)	172.0±6.7
Weight (kg)	77.0±11.3
Body mass index (kg/m^2)	26.0±3.0
Heart rate, beats per minute	75.1±14.6
Left atrium diameter (mm)	3.6 (2.8–4.5)
Fasting plasma glucose (mg/dL)	98.5 (73.0–183.0)
High-density lipoprotein cholesterol (mg/dL)	39.5 (23.0–132.0)
Low-density lipoprotein cholesterol (mg/dL)	122.0 (53.0–301.0)
Triglycerides (mg/dL)	115.5 (44.0–404.0)
Alanine amino transferase (U/L)	17.0 (10.0–62.0)
Aspartate transaminase (U/L)	17.5 (10.0–43.0)
Plasma creatinine (mg/dL)	0.78 (0.59–1.28)
Thyroid stimulating hormone (mIU/mL)	1.0 (0.0-8.3)
Plasma C-reactive protein level (mg/L)	0.33 (0.0–5.4)
Hemoglobin (g/dL)	13.3±1.6
Leukocytes (10^3/uL)	6450.0 (621.0–13900.0)
Platelets (10^3/uL)	247.6±60.5
Epicardial adipose tissue (mm)	4.1 (2.7–6.6)
Maximum QT interval (msec)	410 (340–475)
Minimum QT interval (msec)	375 (317–440)
Corrected QT interval (msec)	426 (386–483)
QT dispersion (msec)	30 (20–80)
Maximum p-wave duration (msec)	100 (75–150)
Minimum p-wave duration (msec)	80 (50–110)
P-wave dispersion (msec)	25 (15–50)

and minimum P wave durations (PWd = maximum P wave duration - minimum P wave duration).

Evaluation of epicardial adipose tissue

Patients were imaged in the left lateral decubitus position by an experienced cardiologist with a GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway). EAT was evaluated on the free wall of the right ventricle from the parasternal long-axis view, using the aortic annulus as anatomic reference. We elected to evaluate EAT thickness using this area because it is known to have the thickest EAT layer. EAT, identified as an echo-free space under the pericardial layer on 2-dimensional echocardiography, was measured perpendicularly in front of the right ventricular free wall at end-diastole.[16,17] We magnified each still image for better visualization and accurate measurement of EAT thickness and measured the thickest point of EAT in each cycle. To standardize the measuring axis, we used the aortic annulus as anatomical reference. The measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. The average value comprising three cardiac cycles of each echocardiographical view was used for statistical analyses.

Statistical analyses

Statistical analyses were performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). The distributions of continuous variables were tested using the Kolmogorov Smirnov

Table 2. Correlation coefficients and significance levels between EAT thickness and baseline characteristics, echocardiography and laboratory measurements

Variables	Coefficient of correlation	*p*
Age	0.412	<0.001
Height	-0.067	0.579
Weight	0.262	0.028
Body mass index	0.396	<0.001
Heart rate	0.119	0.328
Left atrium diameter	0.518	<0.001
Fasting plasma glucose	0.245	0.041
High-density lipoprotein cholesterol	-0.159	0.195
Low-density lipoprotein cholesterol	0.250	0.040
Triglycerides	0.105	0.393
Alanine amino transferase	0.103	0.396
Aspartate transaminase	0.135	0.266
Plasma creatinine	0.020	0.870
Thyroid stimulating hormone	0.043	0.729
Plasma C-reactive protein level	0.177	0.187
Hemoglobin	0.146	0.229
Leukocytes	0.083	0.494
Platelets	0.135	0.264
Maximum QT interval	0.085	0.485
Minimum QT interval	0.091	0.454
Corrected QT interval	0.140	0.247
QT dispersion	0.160	0.186
Maximum p-wave duration	0.343	0.004
Minimum p-wave duration	0.275	0.021
P-wave dispersion	0.265	0.026

Table 3. Correlation coefficients and significance levels between both P-wave dispersion and QT dispersion, and baseline characteristics, echocardiography and laboratory measurements

	P-wave dispersion		QT dispersion	
	r	p	r	p
Age	0.194	0.108	0.099	0.413
Height	-0.148	0.220	-0.104	0.391
Weight	0.056	0.644	0.050	0.683
Body mass index	0.207	0.085	0.157	0.194
Heart rate	0.041	0.736	-0.047	0.701
Left atrium diameter	0.483	<0.001	0.083	0.495
Fasting plasma glucose	0.107	0.376	-0.030	0.804
High-density lipoprotein cholesterol	-0.172	0.160	-0.150	0.222
Low-density lipoprotein cholesterol	0.116	0.347	0.059	0.633
Triglycerides	0.267	0.028	0.083	0.500
Alanine amino transferase	0.024	0.844	-0.034	0.778
Aspartate transaminase	-0.008	0.947	0.148	0.221
Plasma creatinine	0.100	0.412	0.025	0.839
Thyroid stimulating hormone	-0.007	0.954	-0.057	0.650
Plasma C-reactive protein level	0.029	0.831	-0.119	0.377
Hemoglobin	-0.135	0.265	0.105	0.386
Leukocytes	-0.218	0.070	-0.063	0.604
Platelets	-0.144	0.234	0.170	0.159
Epicardial adipose tissue	0.265	0.026	0.160	0.186

test. Data were shown as mean±SD or median (min-max), where applicable. The differences in medians between groups were compared using the Mann Whitney U test. Degrees of association between continuous variables were evaluated using Spearman's Rank Correlation analyses.

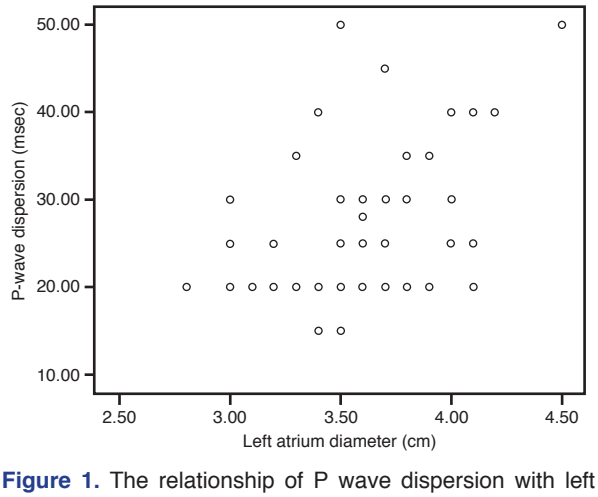

Figure 1. The relationship of P wave dispersion with left atrial diameter.

Determining the best predictor(s) affecting P-wave dispersion was done by Multiple Linear Regression Analysis after adjustment for all possible confounding factors. Any variable with a p value <0.10 in a univariable test was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Coefficient of regression and 95% confidence intervals for each independent variable were also calculated. Logarithmic transformation was used for P-wave dispersion in regression analysis because of non-normal distribution. A p value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The study included 70 patients (36 female, 51.4%)

of mean age 50.9±11.3. All had normal coronary arteries. Of the participants, 40% were hypertensive and 48.6% were current smokers. Mean BMI was 26.0±3.0 kg/m^2, and median EAT thickness was 4.1 mm (Table 1).

Epicardial adipose tissue and study parameters

Correlation analyses revealed EAT to be significantly associated with age (r=0.412, p<0.001), weight (r=0.262, p=0.028), BMI (r=0.396, p<0.001), left atrium diameter (r=0.518, p<0.001), fasting plasma glucose (r=0.245, p=0.041), maximum P wave duration (r=0.343, p=0.004), minimum P wave duration (r=0.275, p=0.021) and P wave dispersion (r=0.265, p=0.026) (Table 2).

QTd, PWd and study parameters

We could not find any relation between investigated parameters and QT dispersion. However, P wave dispersion was significantly related to left atrium diameter (r=0.483, p<0.001), and the triglyceride levels (r=0.267, p=0.028) (Table 3, Figure 1).

Gender, hypertension and smoking status

While there were no differences in EAT, PWd, and QTd between groups formed by gender, and smoking status, there was a significant increase in EAT and PWd in hypertensive patients (Table 4).

Multivariate analyses

Determining the best predictor(s) which affect P-wave dispersion was done by Multiple Linear Regression Analysis after adjustment for all possible confounding factors. Regression analyses including hypertension, body mass index, left atrial diameter triglycerides, leukocytes, and EAT revealed left atrial

Table 4. Epicardial adipose tissue, P-wave dispersion and QT dispersion levels according to gender, hypertension and smoking status

Variables	EAT	P-wave dispersion	QT dispersion
Gender			
Female	4.1 (2.7–6.2)	25.0 (20.0–45.0)	30.0 (20.0–80.0)
Male	4.3 (3.0–6.6)	25.0 (15.0–50.0)	35.0 (20.0–60.0)
p-value	0.271	0.713	0.385
Hypertension			
No	4.1 (2.7–6.4)	25.0 (15.0–50.0)	30.0 (20.0–80.0)
Yes	4.6 (3.5–6.6)	30.0 (20.0–50.0)	32.5 (20.0–60.0)
p-value	0.004	0.036	0.556
Smoking			
No	4.1 (2.7–6.4)	25.0 (15.0–45.0)	30.0 (20.0–80.0)
Yes	4.3 (2.9–6.6)	25.0 (15.0–50.0)	30.0 (20.0–65.0)
p-value	0.814	0.823	0.600

Table 5. Results of multiple linear regression analysis for determining the best predictor(s) of P-wave dispersion

Variables	Coefficient of regression	95% Confidence Interval		*p*
		Lower limit	Upper limit	
Hypertension	0.01789	-0.12151	0.15728	0.798
Body mass index	0.00194	-0.01996	0.02383	0.860
Left atrium diameter	0.39421	0.17465	0.61377	<0.001
Triglycerides	0.00046	-0.00042	0.00135	0.300
Leukocytes	-0.00001	-0.00004	0.00001	0.269
Epicardial adipose tissue	-0.00503	-0.08143	0.07136	0.896

diameter as the only independent predictor of P wave dispersion (Coefficient of regression= 0.39, p<0.001) (Table 5).

DISCUSSION

The study demonstrated a significant association between EAT and PWd, while no such relation was found between QT interval dispersion (QTd) and EAT. However, the association between EAT and PWd was weak and left atrial diameter was the only independent predictor of PWd. Additionally, the study showed that EAT is related to age, body mass index, left atrial diameter as well as PWd in patients with normal coronary arteries. To the best of the authors' knowledge, this study is the first displaying such associations in this selected patient population.

Recently, visceral adipose tissue has attracted considerable interest since it is the source of many adipokines that affect the cardiovascular system either locally or systemically.[18] EAT is a special fat depot which is related to visceral fat rather than total adiposity and shares the same microcirculation with myocardial tissue.[15] Echocardiographic measurement of EAT is an objective, noninvasive, readily available, and greatly less expensive method of visceral fat evaluation than the current gold standard, magnetic resonance imaging. EAT offers a more sensitive and specific index of true visceral fat content by avoiding the possible confounding effect of subcutaneous abdominal fat.[16]

EAT relates to various forms of atherosclerosis, including presence and severity of CAD,[19] coronary artery ectasia,[7] and slow coronary flow.[20] Previous studies have suggested increased QTd in patients with ischemic CAD.[21,22] We could not document any relationship between QTd and EAT in the present study. There may be two explanations for this finding. Since ischemia is the main determinant of QTd, the impact of EAT on QTd may not be strong enough to make a noticeable change in patients with normal coronary arteries. Secondly, the distribution of EAT is mainly around the coronary vessels, which may limit the effect on ventricular conduction. However, previous studies have demonstrated EAT as related to several entities, including increased left ventricular mass,[10] left atrial diameter,[11] and ascending aortic dilation,[9] which may be related to direct perfusion rather than coronary circulation. Therefore, the authors think that the notion on the distribution of EAT may be irrelevant due to abundant paracrine effects.

Several studies have reported an association between EAT thickness and left atrial size, either by echocardiography or cardiac computerized tomography.[11,23] The present study also detected a positive correlation between EAT and left atrial diameter. Since left atrium size is one of the most important predictors of AF, and AF is closely related with inflammation,[24] EAT, being related with both increased left atrium size and inflammation, has been blamed in AF pathogenesis as well. Recent studies have documented increased epicardial adipose tissue in patients with paroxysmal AF compared with controls, and even higher epicardial fat in patients with permanent/persistent AF than in those with paroxysmal AF.[25,26] Girerd et al. demonstrated that periatrial epicardial fat volume rather than total EAT thickness correlated with inflammatory markers in patients with permanent AF.[27] Therefore, the local influence of EAT seems to be very important in AF pathogenesis.

P wave dispersion, reflecting inhomogeneous propagation of sinus impulse in atria, is independently related to recurrent and paroxysmal AF.[14] While epicardial fat may affect electrical propagation locally, additional effects may ensue, including diastolic dysfunction, left ventricular hypertrophy, and eventually left atrial dilation,[10,11] all of which would increase PWd. Even though PWd was associated with EAT in the present study, this weak association was not independent of left atrial diameter. This might be because of the exclusion of patients with any form of AF, and because EAT is increased in AF patients. Recently, the Heinz Nixdorf Recall study, which included 3467 participants who underwent non-contrast computerized tomography demonstrated that EAT was associated with AF. However, this relation lost its significance when adjusted for risk factors including left atrial size.[23] Thus, left atrial diameter appears to be a better predictor of AF than epicardial fat.

Our study has several limitations, the most important being its small sample size. Moreover, our study was cross-sectional and did not implicate causality. Currently, magnetic resonance imaging is the gold standard diagnostic method for measuring epicardial fat thickness. Non-use of MRI in our research is a study limitation. Although epicardial fat is readily

visualized with the high-speed computed tomography and MRI, widespread use of these methods for assessment of EAT is not practical. Echocardiography provides an objective, noninvasive, readily available method and is a great deal less expensive than MRI or computed tomography for measuring epicardial fat.

In conclusion, we demonstrated that EAT is associated with PWd in this study. However, left atrial diameter, rather than EAT, was the only independent predictor of P wave dispersion. Left atrial diameter would appear to be a better predictor of AF in patients with normal coronary arteries.

Conflict-of-interest issues regarding the authorship or article: None declared

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