ORIGINAL ARTICLE

The relationship between echocardiographic epicardial adipose tissue, P-wave dispersion, and corrected QT interval

Ekokardiyografik epikardiyal yağ dokusu ile P dalga dispersiyonu ve düzeltilmiş QT aralığı arasındaki ilişki

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ABSTRACT

Objective: Epicardial adipose tissue (EAT) secretes various pro-inflammatory and atherogenic substances that have several effects on the heart. The goal of this study was to evaluate the association between EAT thickness and both P-wave dispersion (Pd) and corrected QT interval (QTc), as simple, non-invasive indicators of arrhythmia on a surface electrocardiogram.

Methods: This retrospective observational study included 216 patients who had normal coronary arteries observed on coronary angiography. Each patient underwent 12-derivation electrocardiography to measure Pd and QTc, and transthoracic echocardiography to measure EAT thickness. The patients were divided into 2 groups according to the median EAT value (EAT low group: <5.35 mm; EAT high group: ≥5.35 mm).

Results: P-wave dispersion (p=0.001) was significantly greater in the EAT high group compared with the EAT low group. However, the QTc (p=0.004) was significantly greater in the latter group. The median left ventricular end-diastolic diameter (p=0.033), mean left ventricular end-systolic diameter (p=0.039), and mean left atrial diameter (p=0.012) were significantly greater in the EAT high group. Multiple logistic regression analysis using the backward elimination method revealed that the leukocyte count (Odds ratio [OR]: 1.000; 95% confidence interval [CI]: 1.000–1.000; p=0.001), Pd (OR: 1.1026; 95% CI: 1.010–1.043; p=0.002), QTc interval (OR: 0.988; 95% CI: 0.979–0.997; p=0.009), and left ventricular ejection fraction (OR: 0.922; 95% CI: 0.859–0.989; p=0.023) were independently associated with greater EAT thickness.

Conclusion: Echocardiographic end-diastolic EAT thickness on the free wall of the right ventricle was associated with Pd and QTc in patients with normal coronary arteries.

ÖZET

Amaç: Epikardiyal yağ dokusu (EYD), kalp üzerinde çeşitli etkilere sahip çeşitli pro-enflamatuvar ve aterojenik maddeleri salgılar. Bu çalışmada, pro-aritminin basit, invaziv olmayan, elektrokardiyografik parametreleri olan P dalga dispersiyonu (Pd) ve düzeltilmiş QT (QTd) aralığı ile EYD kalınlığı arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Bu geriye dönük gözlemsel çalışmaya, koroner anjiyografide koroner arterleri normal bulunan 216 hasta dahil edildi. Her hastaya Pd ve QTd aralığını ölçmek için 12 derivasyonlu elektrokardiyografi ve EYD kalınlığını ölçmek için transtorasik ekokardiyografi uygulandı. Hastalar ortanca EYD değerine göre iki gruba ayrıldı (EYD kalınlığı düşük (<5.35 mm) olan grup ve EYD kalınlığı yüksek (≥5.35 mm) olan grup).

Bulgular: Epikardiyal yağ dokusu kalınlığı yüksek grupta Pd EYD kalınlığı düşük gruba göre anlamlı olarak artmıştır (p=0.001). Bununla birlikte, QTd aralığı EYD kalınlığı düşük grupta anlamlı olarak artmıştır (p=0.004). EYD kalınlığı yüksek grupta ortanca sol ventrikül diyastol sonu çapı (p =0.033), ortalama sol ventrikül sistol sonu çapı (p=0.039) ve ortalama sol atriyum çapı (p=0.012) EYD kalınlığı düşük gruba göre anlamlı olarak artmıştı. Geriye dönük yöntemle yapılan çoklu lojistik regresyon analizi sonucunda lökosit sayısı (Odds oranı - OO=1.000, %95 Güven aralığı - GA: 1.000–1.000, p=0.001), Pd (OO=1.1026, %95 GA: 1.010–1.043, p=0.002), QTd aralığı (OO=0.988, %95 GA: 0.979–0.997, p=0.009) ve sol ventrikül ejeksiyon fraksiyonu (OO=0.922, %95 GA: 0.859–0.989, p=0.023) bağımsız olarak yüksek EYD kalınlığı ile ilişkiliydi.

Sonuç: Sağ ventrikülün serbest duvarında ekokardiyografik diyastol sonu EYD kalınlığı normal koroner arterleri olan hastalarda Pd ve QTd aralığı ile ilişkilidir.

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Epicardial adipose tissue (EAT) is a specific accumulation of visceral adipose tissue in the pericardial sac. It is considered metabolically active tissue and secretes various hormones, vasoactive substances, pro-inflammatory cytokines, and pro-atherogenic mediators, including tumor necrosis factor-α, interleukin-1β, interleukin-6, interleukin-6 soluble receptor, interleukin-16, macrophage chemoattractant protein, plasminogen activator inhibitor-1, leptin, resistin, adiponectin, and visfatin, which may have substantial and different effects on cardiac functions.[1–3]

P-wave dispersion (Pd) is a noninvasively determined electrocardiographic marker of atrial remodeling and a predictor of recurrent and paroxysmal atrial fibrillation (AF).[4,5] It is defined as the difference between the widest and the narrowest P-wave duration recorded on a 12-derivation electrocardiogram (ECG). The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is associated with inhomogeneity of myocardial repolarization and consequent malignant ventricular arrhythmias in the setting of prolongation or shortening.[6,7]

Previous studies have reported an association between EAT and several cardiac pathologies, including coronary artery disease (CAD),[8] coronary artery ectasia,[9] ascending aortic dilation,[10] increased left ventricular mass,[11] left atrial enlargement[12] and atrial arrhythmia, such as AF.[13] These relationships may be a result of the paracrine effect of reactive oxygen species and adipocytokines. However, there are not enough available data regarding the association between EAT and ventricular arrhythmias. The aim of this study was to evaluate the association between EAT thickness and both Pd and corrected QT interval (QTc) as simple indicators of atrial and ventricular arrhythmia observed on ECG.

METHODS

Patient population and study design

This single-center, retrospective, observational study included a total of 216 Turkish patients (90 male and 126 female; mean age 56.1±10.4 years) who were admitted to cardiology clinic and underwent coronary angiography due to suspected ischemic heart disease on the basis of clinical indications, including typical chest discomfort and/or abnormal stress test results between January 2016 and June 2016. Patients who had a sinus rhythm and normal coronary arteries as assessed with coronary angiography were included.

Patients with previously documented CAD, symptoms of congestive heart failure and/or a left ventricular ejection fraction (LVEF) <45%, moderate to severe valvular dysfunction, pericardial disease, cardiac pacemaker, history of cardiac arrhythmia, atrioventricular conduction abnormality, presence of U-wave and/or immeasurable Pd and QT interval on ECG, acute and/or chronic infective and/or inflammatory disease, malignancy, chronic kidney disease (estimated glomerular filtration rate <90 mL/minute/1.73 m^2), chronic hepatic disease, chronic pulmonary disease, cerebrovascular disease, abnormal thyroid function test, electrolyte imbalance, or a history of drug intake that could affect Pd and QT interval, including class IA, class III, and class IV antiarrhythmic drugs, antipsychotics, antidepressants, antibiotics, antivirals, and antineoplastic agents, were excluded. This study was conducted in accordance with the Declaration of Helsinki. The Institutional ethics committee approved the study protocol and waived the need to obtain written informed consent due to the retrospective nature of the study.

Abbreviations:

AF	*Atrial fibrillation*
BMI	*Body mass index*
BSA	*Body surface area*
CAD	*Coronary artery disease*
CI	*Confidence interval*
DM	*Diabetes mellitus*
EAT	*Epicardial adipose tissue*
ECG	*Electrocardiogram*
HPL	*Hyperlipidemia*
hs-CRP	*High-sensitivity C-reactive protein*
LAD	*Left atrial diameter*
LVEDD	*Left ventricular end-diastolic diameter*
LVEF	*Left ventricular ejection fraction*
LVESD	*Left ventricular end-systolic diameter*
OR	*Odds ratio*
Pd	*P-wave dispersion*
QTc	*Corrected QT interval*
TTE	*Transthoracic echocardiography*

Data concerning cardiovascular risk factors, including age; gender; presence of hypertension, diabetes mellitus (DM), or hyperlipidemia (HPL); and smoking were recorded. All of the patients underwent a routine 12-derivation ECG, transthoracic echocardiography (TTE), and had biochemical measurements performed prior to coronary angiography. The body mass index (BMI) and body surface area (BSA) of each patient was calculated using the following formulas: BMI=weight (kg)/height^2 (m^2) and BSA=$\sqrt{}$weight (kg)*height (cm)/3600.

Blood measurements

Venous blood samples were obtained from all of the

patients on admission. Complete blood counts were measured with a Sysmex K-1000 auto-analyzer (Block Scientific, Bohemia, NY, USA). Routine blood chemistry panels were measured with a standard auto-analyzer. High-sensitivity C-reactive protein (hs-CRP) concentrations were measured with an Aeroset auto-analyzer (Abbott Laboratories, Lake Bluff, IL, USA) using a spectrophotometric analysis kit (Scil Diagnostics GmbH, Viernheim, Germany).

Electrocardiography and measurements of corrected QT interval and P-wave dispersion

Each patient underwent a 12-lead ECG (CardioFax S; Nihon Kohden, Tokyo, Japan) at a paper speed of 50 mm/second and calibration of 1mV=10 mm at rest in the supine position. An appropriate ECG was defined as displaying QT intervals and P-wave durations in all 12 derivations. One cardiologist, blinded to the echocardiographic measurements of the patients, analyzed each ECG result manually using calipers and magnifying glasses. The QT interval was the mean value derived from 3 cardiac cycles and was measured from lead II and lead V5 or V6,[14] using the threshold method from the beginning of the QRS complex until the end of the T-wave. Then, the longest value was determined and corrected to the heart rate using Bazett's formula ($QTc=QT/\sqrt{RR}$). The onset of the P-wave was defined as the initial deflection from the isoelectric baseline defined by the T-P segment, and offset of the P-wave was defined as the junction of the end of the P-wave and its return to baseline.[15] Although measurement of Pd has not yet been standardized, it has been defined as the difference between the widest and the narrowest P-wave duration recorded from multiple ECG leads (Pd=maximum P-wave duration - minimum P-wave duration).[16] The same cardiologist analyzed predischarge ECG results of 20 randomly selected patients to assess the reproducibility of QTc and Pd measurements. Using the Bland–Altman method, the mean difference for intra-observation for QTc and Pd was 1.2% (5.3±16.3%) and 8% (4.0±12.3%), respectively, indicating good reproducibility.

Transthoracic echocardiography and measurement of epicardial adipose tissue thickness

Each patient underwent TTE using a 3.5-MHz transducer (EPIQ 7; Philips Healthcare, Andover, MA, USA) at rest, in the left lateral decubitus position. A cardiologist, blinded to the Pd and QTc measurements of the patients, analyzed digitally stored echocardiograms performed by an experienced cardiologist. All of the measurements were performed according to the criteria proposed by the American Society of Echocardiography guidelines.[17] A 2-dimensional anteroposterior linear measurement of the left atrium was created using the parasternal long-axis view at ventricular end-systole, from the leading edge of the posterior aortic wall to the leading edge of the posterior wall of the left atrium. The left atrial volume was measured using the apical 4-chamber and apical 2-chamber views at ventricular end-systole, according to the modified Simpson's method. Left atrial volume index was measured by dividing the left atrial volume by the BSA. The Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method. Echocardiographic EAT is identified as the relatively hypoechoic space between the right ventricle free wall and the visceral layer of the pericardium. EAT thickness was vertically measured at the thickest level using the parasternal long-axis view, using the aortic root as the reference point for the measurement, at ventricular end-diastole (Fig. 1).[18,19] EAT thickness was determined as a mean value derived from 3 cardiac cycles. The same cardiologist evaluated predischarge TTE results of 20 randomly selected patients to assess the reproducibility of EAT thickness measurements. Using the Bland–Altman method, the mean difference in terms of intra-observation was 3.8% (0.23±0.54%), indicating good reproducibility.

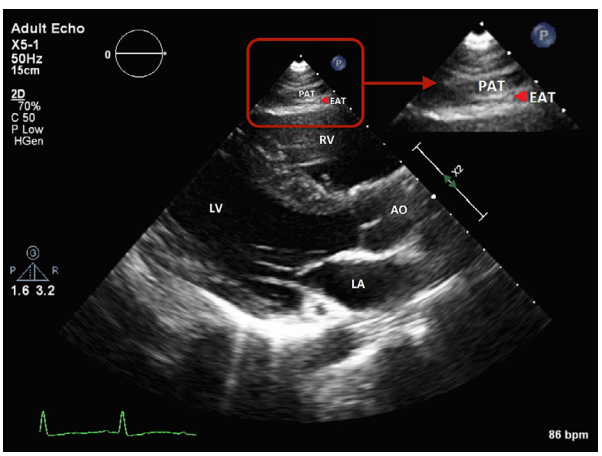

Figure 1. Echocardiography measurement of end-diastolic epicardial adipose tissue thickness from the parasternal long-axis. Ao: Aorta; EAT: Epicardial adipose tissue (arrowhead); LA: Left atrium; LV: Left ventricle; PAT: Pericardial adipose tissue; RV: Right ventricle.

Statistical analysis

Data analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA). Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±SD and/or median (minimum-maximum), as appropriate. Categorical variables were expressed as number (n) and percentage. Comparison of continuous variables between study groups was performed using the independent samples t-test and the Mann–Whitney U test, as appropriate. Comparison of categorical variables between study groups was performed using a chi-square test with Yates's continuity correction for DM and HPL. All of the possible factors ($p<0.25$) of the univariate analysis: gender, BSA, DM, hemoglobin level, leukocyte count, platelet count, neutrophil

Table 1. Baseline, laboratory, electrocardiographic, and echocardiographic characteristics of the study groups

Variable	EAT low group (n=108)	EAT high group (n=108)	*p**
Baseline characteristics			
Age (years)	56.2±10.1	56.0±10.7	0.865
Gender (male), n (%)	39 (36.1)	51 (47.2)	0.098
Body mass index (kg/m^2)	28.3 (21.5–48.1)	28.7 (21.3–47.6)	0.380
Body surface area (m^2)	1.90±0.17	1.95±0.18	0.049
Diabetes mellitus, n (%)	27 (25.0)	17 (15.7)	0.128
Hyperlipidemia, n (%)	24 (22.2)	17 (15.7)	0.298
Hypertension, n (%)	46 (42.6)	40 (37.0)	0.404
Smoking, n (%)	27 (25)	32 (29.6)	0.445
Laboratory findings			
Hemoglobin (g/dL)	13.3 (8.2–16.4)	13.5 (9.3–17.8)	0.140
Leukocyte count, x10^3/uL	6.8 (1.9–14.5)	7.7 (4.2–14.5)	<0.001
Platelet count, x10^3/uL	236 (113–520)	224 (123–471)	0.140
Neutrophil count, x10^3/uL	4.1 (1.8–10.7)	4.8 (2.2–11.5)	0.033
High-sensitivity C-reactive protein (mg/dL)	0.4 (0.0–3.0)	0.2 (0.0–11.9)	0.130
Electrocardiographic findings			
Heart rate (bpm)	77±14	79±11	0.299
Minimum p-wave duration (ms)	60 (40–120)	60 (40–120)	0.575
Maximum p-wave duration (ms)	120 (80–160)	120 (60–160)	0.634
P-wave dispersion (ms)	40 (10–80)	40 (10–80)	0.001
PR interval (ms)	160 (100–200)	160 (100–240)	0.795
QRS duration (ms)	80 (60–160)	80 (60–160)	0.631
Corrected QT interval (ms)	429 (360–530)	417 (354–539)	0.004
Echocardiographic findings			
Left ventricular end-diastolic diameter (mm)	46 (23–61)	47 (28–57)	0.033
Left ventricular end-systolic diameter (mm)	28.7±5.2	30.2±5.4	0.039
Left ventricular ejection fraction (%)	62 (48–75)	62 (45–68)	0.073
Left atrial diameter (mm)	33.5±3.5	34.7±3.4	0.011
Left atrial volume (mL)	39 (23–71)	39 (25–78)	0.737
Left atrial volume index (mL/m^2)	20 (10–35)	20 (13–43)	0.744

Data are presented as number (percentage), mean value±SD, and median (minimum-maximum).
*p value was calculated using an independent samples t-test and the Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. The independent samples t-test was performed for age, body surface area, heart rate, left ventricular end-systolic diameter, and left atrial diameter.
EAT: Epicardial adipose tissue.

count, hs-CRP, Pd, QTc, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), LVEF, and left atrial diameter (LAD) were selected for the multivariate analysis and multiple logistic regression analysis using the backward method was performed to determine the variables independently associated with high EAT thickness. The odds ratio (OR) and 95% confidence interval (CI) of each independent variable were calculated. The patients were divided into 2 groups according to the median EAT value (EAT low group <5.35 mm and EAT high group ≥5.35 mm). A 2-tailed p-value of less than 0.05 was considered significant.

RESULTS

The baseline, laboratory, electrocardiographic, and echocardiographic characteristics of the study groups are presented in Table 1. The BSA (p=0.049), leucocyte count (p<0.001), and neutrophil count (p=0.033) were significantly greater in the EAT high group compared with the EAT low group.

P-wave dispersion (p=0.001) was significantly greater in the EAT high group compared with the EAT low group; however, the QTc was significantly greater in the latter group (p=0.004). The median LVEDD (p=0.033), mean LVESD (p=0.039), and mean LAD (p=0.012) were each significantly greater in the EAT high group compared with the EAT low group.

Independent predictors of high EAT thickness are shown in Table 2. All of the possible factors (p<0.25) in the univariate analysis: gender, BSA, DM, hemoglobin level, leukocyte count, platelet count, neutrophil count, hs-CRP, Pd, QTc, LVEDD, LVESD, LVEF, and LAD, were selected for the multivariate analysis and multiple logistic regression analysis was performed using the backward method to determine the variables independently associated with high EAT thickness. This analysis revealed that leukocyte count (OR: 1.000; 95% CI: 1.000–1.000; p=0.001), Pd (OR: 1.1026; 95% CI: 1.010–1.043; p=0.002), QTc interval (OR: 0.988; 95% CI: 0.979–0.997; p=0.009), and LVEF (OR: 0.922; 95% CI: 0.859–0.989; p=0.023) were independently associated with greater EAT thickness.

DISCUSSION

The major finding of our study is that Pd and QTc are independently associated with echocardiographic end-diastolic EAT thickness on the free wall of the right ventricle in patients with normal coronary arteries. To the best of our knowledge, this is the first report demonstrating such correlations.

There are some unresolved issues regarding echocardiographic measurement of EAT. Different cut-off values for increased EAT have been reported,[20–22] and the cut-off value at which the risk increases is still not well known. In addition, there is no standard echocardiographic method to measure EAT thickness, which in turn complicates interpretation of the results of studies related to this topic.[2,18–20,23] In our research, we used the median EAT (5.35 mm) as a cut-off value for increased EAT in men and women, and EAT thickness was measured using the 2-dimensional parasternal long-axis view at end-diastole.

Epicardial adipose tissue, which shares microcirculation with the myocardium,[24] secretes various adipocytokines and exhibits autocrine, paracrine, and endocrine effects,[25] contributing to different cardiovascular pathologies, including diastolic dysfunction,[26] left ventricular hypertrophy,[11] left atrial dilation,[12] and AF.[27] It has been hypothesized that interactions between EAT and the adjacent myocardial tissue might cause structural remodeling and lead to cardiac arrhythmias.

Table 2. Independent predictors of high epicardial adipose tissue thickness

Variable	OR (95% CI)	*p*
Leukocyte count	1.000 (1.000–1.000)	0.001
P-wave dispersion (ms)	1.026 (1.010–1.043)	0.002
Corrected QT interval (ms)	0.988 (0.979–0.997)	0.009
Left ventricular ejection fraction (%)	0.922 (0.859–0.989)	0.023
Left atrial diameter (mm)	1.091 (1.000– 1.191)	0.051

OR: Odds ratio; CI: Confidence interval.

P-wave dispersion reflects the inhomogeneous propagation of sinus impulse in the atria, which could be affected by paracrine and endocrine effects of several adipocytokines abundantly secreted by increased EAT, such as transforming growth factors, interleukins and tumor necrosis factor-α, which have previously been reported to be related to recurrent and paroxysmal AF.[5] A recent study reported a significant association between EAT and Pd.[23] However, this relationship lost its significance when adjusted for risk factors such as LAD, which appeared to be a better predictor of AF than EAT thickness. Our study revealed that EAT was independently associated with Pd and LAD, although the latter association did not reach a significant level. The distinction between these results could be related to the sample size of each study. In comparison with the population evaluated by Çiçek et al.,[23] our relatively large sample size assured an adequate power to detect statistical significance. In fact, our study results are consistent with a previous study that reported an association between EAT thickness and LAD.[12] Thus, a possible mechanism for an association between EAT and Pd could be due to the contribution of these adipocytokines to structural remodeling of the atrial myocardium.[28,29]

There is increasing evidence suggesting that overexpression of cytokines, especially interleukin-1β, interleukin-6, and tumor necrosis factor-α, could play a role in the pathogenesis of long QT and that the likely mechanisms of action involve reactive oxygen species and ceramide pathways.[30] Our study revealed a negative correlation between EAT and QTc. Impaired cardiac sympathetic activity in patients with increased EAT thickness could contribute to this association, as well as the abundant secretion of adipocytokines. Cardiac sympathetic activity has been reported to have a relationship to EAT, Pd, and the QT interval.[31–33]

This study population consisted of patients who had normal coronary arteries as observed on a coronary angiography performed due to suspected ischemic heart disease on the basis of clinical indications, including typical chest discomfort and/or abnormal stress test results. The clinical symptoms of these patients may be related to non-atherosclerotic CAD etiologies, including coronary vasospasm, endothelial dysfunction, and intramural CAD. Data regarding the relationship between Pd, QTc, and non-atherosclerotic CAD etiologies are limited. Suzuki et al.,[34] reported that patients with vasospastic angina exhibited an increased baseline QTc dispersion compared with patients with atypical chest pain. Similarly, Parchure et al.,[35] demonstrated that QT dispersion is greater in patients with vasospastic angina complicated by cardiac arrest and syncope when compared with patients without such events. In addition, prolonged QTc has been reported to have an association with endothelial dysfunction, arterial stiffness, impaired coronary perfusion, and accelerated arterial aging.[36]

Study limitations

Our study should be evaluated with some limitations. First, the retrospective observational design did not allow us to either deduce causation between EAT thickness and the ECG parameters or follow up with the patients to detect any atrial or ventricular arrhythmias. Second, a correlation between echocardiographic and computed tomographic and/or magnetic resonance imaging measurements of EAT was not available. Echocardiographic EAT is a linear measurement at a specific, single location, and therefore may not reflect the total epicardial adipose volume. Although magnetic resonance imaging is still the current gold standard used to evaluate visceral adipose tissue, echocardiographic measurement of EAT is an objective, readily available, noninvasive, and much less expensive method. Third, the lack of a standard cut-off values of EAT thickness could affect the interpretation of the results. We used a cut-off value comparable with the value previously reported by Eroglu et al.[37] Last, our study was conducted with a specific population with chest discomfort and/or abnormal stress test results and normal coronary arteries as evaluated by coronary angiography.

Conclusion

Echocardiographic end-diastolic EAT thickness on the free wall of the right ventricle is associated with ECG markers of cardiac arrhythmias, such as Pd and QTc, in patients with clinically suspected CAD who had normal coronary angiogram results.

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Keywords: Corrected QT interval; epicardial adipose tissue; P-wave dispersion.

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