ORIGINAL RESEARCH

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Increased epicardial adipose tissue volume is associated with PR interval prolongation

Abstract

Purpose: Epicardial fat is visceral adipose tissue that possesses inflammatory properties. Inflammation and obesity are associated with cardiovascular disease and arrhythmogenesis, but little is known about the relationship between epicardial fat and PR-Interval prolongation. The purpose of this study was to investigate the association between epicardial adipose tissue (EAT) volume and PR-interval prolongation as assessed by computed tomography (CT) and Twelve-lead ECGs.

Methods: Patients (n=287) were referred for 64-slice CT for exclusion of coronary artery disease and EAT volumes were determined. Twelve-lead ECGs were obtained from each subject and were evaluated by two independent readers.

Results: Patients with significant PR interval prolongation had higher median EAT volume than patients with normal PR interval. Statistically significant correlations were observed between the EAT volume and the PR interval ($p = 0.183$, $p = 0.003$), and QRS duration ($p = 0.144$, $p = 0.018$). Multivariate and trend analyses confirmed that EAT volume was independently associated with the presence of PR interval prolongation. The receiver operator characteristics curve of EAT volume showed that an EAT volume $>144.4 \text{ cm}^3$ was associated with PR interval prolongation.

Conclusion: This study indicates that EAT volume is highly associated with PR interval prolongation. Whether epicardial fat plays a role in the pathogenesis of PR interval prolongation requires future investigation.

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Prolongation of the PR interval, traditionally defined as a duration of >200 ms on electrocardiogram (ECG) (AHA/ACC guidelines) [1], represents a first-degree atrioventricular block and is a commonly encountered clinical finding [2]. Prolongation of the electrocardiographic PR interval is associated with increased risk of atrial fibrillation, pacemaker implantation and death [3]. PR interval length, even in the conventionally normal range, is independently associated with endothelial dysfunction and increased arterial stiffness in healthy subjects who are free of atherosclerotic disease [4]. Several clinical conditions (e.g., autoimmune diseases [5], electrolyte disturbances [6] and primary cardiac pathologies [7]) may result in PR interval prolongation. In addition, a previous study reported that heart rate, PR interval, QRS duration, QTc interval and voltage (R + S or Q wave in leads I, II and III) increased with increasing obesity [8]. Obesity also results in an increase in the production of pro-inflammatory mediators and in the levels of pro-inflammatory cytokines [9]. Research has suggested that elevated levels of inflammatory mediators may induce the production of reactive oxygen species, which accelerate vascular atherosclerosis and arterial calcification [10]. It has also been demonstrated that C-reactive protein (CRP) and cytokines (such as IL-6 and platelet-activating factor) are associated with arrhythmias through the modulation of ion channel function [11,12] and the aggravation of sympathetic tone [11]. Hence, elevated levels of inflammatory mediators may provoke vasculopathy, myocardial fibrosis, sympathetic hyperactivity and ion channel malfunction [12-15], which can lead to a high risk of cardiac arrhythmias and even death.

Visceral adipose tissue (VAT) and the associated obesity play an important role in the development of metabolic syndrome and are well-established risk factors for cardiovascular disease. Epicardial, mesenteric and omental fat are the most important VATs and share the same origin from the splanchnopleuric mesoderm; however, epicardial adipose tissue (EAT) is a special visceral fat depot that surrounds the major branches of the coronary arteries and myocardium. Two recent studies have pointed out that epicardial fat directly contacts the atria and, thus, may have direct atrial arrhythmogenic effects [16,17]. Because it is an epicardial fat depot that serves as a potential source of inflammatory cytokines, and because it is located in anatomic proximity to the heart, EAT can be reasonably assumed to have a relationship with coronary atherosclerosis and arrhythmogenesis [18]. Given the strong association between PR interval prolongation, obesity and inflammation, and given the inflammatory characteristics of EAT and its relationship to cardiovascular disease, we hypothesize that EAT is independently associated with PR interval prolongation in humans.

There has been no published report demonstrating the impact of EAT on PR interval prolongation. In the present study, which is aimed at investigating this hypothesis, we examined whether EAT volume might be associated with prolonged PR interval in a cohort of 287 patients referred for 64-slice CT.

Methods

Study population

The study included 287 consecutive patients who underwent cardiac multi-slice CT for exclusion of coronary artery disease (CAD) due to typical or atypical chest pain, with intermediate pretest probability of CAD, from January 2009 to January 2010 at the Cardiovascular Clinic of E-Da Hospital. Before cardiac multi-slice CT examination, each patient received a detailed interview about his or her medical and personal history. Patients with previous diagnosis of cerebrovascular diseases, heart failure, cardiomyopathy, coronary heart diseases, congenital heart disease, cardiac arrhythmias or who were taking medication that had PR prolongation effect, with the exception of CCBs and β -blockers, were excluded from this study. CVD risk factors were evaluated as follows. The diagnosis of type 2 diabetes mellitus (T2DM) was based on WHO criteria. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg, or if the patient was under antihypertensive treatment. Hyperlipidemia was defined as triglyceride (TG) levels ≥ 150 mg/dL, and/or high-density lipoprotein cholesterol (HDL-C) < 35 mg/dl for men or < 39 mg/dl for women, and/or total cholesterol ≥ 200 mg/dl, and/or low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dl, or patients undergoing treatment for a lipid disorder according to the criteria of Adult Treatment Panel III. Smoking was classified as never having smoked, former smoker (ceased smoking for at least 1 year) or current smoker. Former and current smokers were analyzed as one group and were compared with those who had never smoked. The anthropometric parameters required the calculation of the body mass index (BMI) and waist-to-hip ratio (WHR). Waist and hip circumferences were measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest and the hips were measured at their widest point. Written informed consent was obtained from all patients before enrollment. The study was approved by the Human Research Ethics Committee of I-Shou University E-Da Hospital.

TABLE 1. Clinical characteristics of study participants

Characteristics	Total (N = 287)
Male, n (%)	232 (80.8)
Age (years)	54.7±10.1
Body mass index (kg/m ²)	26.0±4.9
Waist to hip ratio	0.91±0.07
Medical history, n (%)	
Hypertension	145 (50.5)
Hyperlipidemia	207 (72.1)
Diabetes mellitus	43 (15.0)
Coronary artery disease	
Smoking history	87 (30.3)
Mean epicardial adipose tissue volume (cm ³)	134.7±50.5
Mean systolic blood pressure (mmHg)	132±18
Mean diastolic blood pressure (mmHg)	81±13
Mean total-cholesterol (mg/dl)	199.7±37.7
Mean serum LDL level (mg/dl)	121.2±34.4
Mean serum HDL level (mg/dl)	47.7±12.0
Mean serum triglyceride level (mg/dl)	146.0±91.3
Mean serum fasting glucose (mg/dl)	104.8±24.3
Medications, n (%)	
β-Blocker	117 (40.8)
CCB	56 (19.5)
ACEI	24 (8.4)
Statin	98 (34.2)
Mean heart rate (bpm)	68.5±11.1
Mean PR interval (ms)	165.4±22.0
Mean QRS duration (ms)	93.6±13.9
Mean QT interval (ms)	398.5±33.2
Mean QTc interval (ms)	421.4±24.1

All values are means ± SD except where indicated otherwise. LDL, low-density lipoprotein; HDL, high-density lipoprotein; CCB, calcium channel blocker; ACEI, angiotensin- converting enzyme inhibitor; QTc, corrected QT.

Laboratory measurements

Peripheral blood samples were taken from the patients' antecubital vein after fasting for 8 hours. Complete blood cell counts and serum glucose, uric acid, blood urea nitrogen, creatinine and albumin levels and lipid profiles (including triglycerides, total cholesterol, LDL-C and HDL-C) were determined in all patients by standard commercial methods on a parallel, multi-channel analyzer (Hitachi 7170A, Tokyo, Japan), as described in our previous reports [19]. The concentration of plasma C-reactive protein (CRP) was measured by using a high sensitivity method (IMMAGE; Beckman Coulter, Immunochemistry Systems, Brea, CA, USA), which had a detection limit of 0.2 mg/L. The intra-assay coefficient of variation was 4.2%-8.7% for hs-CRP. Samples were measured in duplicate in a single experiment.

64-slice CT scanning protocol and analyses

The coronary CT angiography data was acquired with a 64-slice CT scanner as per our previous study [20]. Reconstructed image data were transferred to a remote workstation (Advantage Windows 4.2; GE Healthcare) for post-processing. Further, CT data analyses, including calculation of EAT volume, were performed as per our previous study [20].

ECG, PR interval measurement

Twelve-lead ECGs were collected for the investigation at the baseline examination using a standardized protocol when the participants enrolled in the study. Standard interval (heart rate, PR, QRS and QT intervals), amplitudes (R, S and T waves and J and ST segments) were analyzed by standard protocols as described elsewhere [21]. In brief, the PR interval was defined and measured from the beginning at the T-P junction at the start of P wave to the initiation of the QRS segment. Measurement of PR interval was made in lead II using a 7 power magnifying loupe on a grid with 0.1 mm calibration. The PR interval was determined as the average measurement from three consecutive beats.

Statistical analysis

Descriptive data were examined for all variables. For continuous variables, results were presented as means ± SD. All statistical analyses were performed using SAS software version 10.0 (SAS institute, Cary, NC, USA). Spearman rank correlation coefficients and simple linear regression analyses were used to examine the correlations between EAT volume and the values of other parameters, and the correlations between PR interval

FIGURE 1. Correlation between the epicardial adipose tissue (EAT) volume and PR interval interval (A) and Framingham risk score (B). The EAT volume was positively correlated with PR interval and Framingham risk score.

and BMI and WHR. Using multiple logistic regression, these variables were assessed for independent associations with the presence of PR interval prolongation. The prevalence of electrocardiographic parameters categorized within the three EAT volume groups were tested for trends. The optimal cutoff point for EAT volume as a predictor for PR interval prolongation

was calculated by receiving operating characteristics (ROC) analysis. All statistical analyses were two-sided and a p value < 0.05 was considered to be statistically significant.

Results

The clinical characteristics of our subjects are shown in Table 1. The prevalence of hypertension, hyperlipidemia and diabetes mellitus were 50.5%, 72.10% and 15.0%, respectively. The mean EAT volume was 134.7 ± 50.5 cm³. Forty-two subjects had a PR interval beyond the conventional normal range of 200 ms. EAT volumes in patients with PR interval prolongation were significantly higher than volumes in subjects without PR interval prolongation (167.4 ± 43.2 cm³ vs. 132.1 ± 49.0 cm³, $p = 0.009$), and PR interval correlated well with BMI and WHR ($\beta = 0.333$, $p < 0.001$; $\beta = 0.316$, $p = 0.001$).

Spearman rank correlation analysis revealed that EAT volume was positively associated with age, sex, BMI, fasting glucose, triglyceride, uric acid and creatinine levels, white blood cell (WBC) count, hs-CRP, PR interval, QRS duration and smoking status. In addition, levels of HDL-cholesterol were negatively associated with levels of EAT volume (Table 2). Classification of subjects into tertiles according to EAT volumes revealed that longer PR intervals were significantly associated with EAT volume (p for trend < 0.05 , Table 3). Simple linear regression analysis revealed that EAT volume was positively associated with PR interval (Figure 1A) and Framingham risk score (Figure 1B).

Multivariate logistic regression analysis was performed to estimate the effects of EAT volume together with several other cardiovascular risk factors in the presence of PR interval prolongation. The presence of PR interval prolongation was associated with age, male gender, fasting glucose, smoking and EAT volume (Table 4). The ROC curve for detection of PR interval prolongation revealed an area under the curve of 0.718 (95% CI: 1.003-1.022, $p = 0.012$) for EAT volume. A EAT volume of > 144.4 cm³ was associated with PR interval prolongation, with a sensitivity of 78.6%, specificity of 64.9% (Figure 2).

Discussion

In the current study, EAT volume was found to be independently associated with PR interval prolongation. The associations between EAT volume and PR interval prolongation still persisted after controlling for conventional risk factors, including age, sex, BMI, SBP, DBP, heart rate, current smoking, the use of medications such as β -blockers and CCBs and total cholesterol, HDL-C, LDL-C, triglyceride, and fasting glucose levels. Furthermore, the ROC curve of EAT volume showed that

FIGURE 2. Receiver operator characteristics curve of epicardial adipose tissue volume for the detection of PR interval prolongation. A threshold value of $>144.4 \text{ cm}^3$ is associated with PR interval prolongation with a sensitivity of 78.6% and specificity of 64.9%.

an EAT volume of $>144.4 \text{ cm}^3$ was associated with PR interval prolongation. Moreover, EAT volume was also found to correlate well with total WBC counts and hs-CRP levels. These findings are in agreement with current evidence regarding the association of inflammation and ventricular arrhythmias [22,23].

In the previous literature, general adiposity has become recognized as a risk factor for atrial fibrillation (AF). Previous studies found that pericardial fat is associated with atrial conduction [24,25] and EAT is associated with blood pressure levels [26], AF [27] and cardiovascular disease [18,20,28,29]. Van Gaal et al. showed that EAT is a biologically active organ that may play a role in the association between obesity and CAD [30]. Our study results reveal a positive association between PR interval and both BMI and WHR. This is consistent with reports noting PR interval prolongation with increasing obesity [8,31,32]. In particular, increasing obesity marks increasing pro-inflammatory cytokines. Yang et al. suggested that obesity reduces naive cells and produces more the effector-memory phenotype of adipose-resident T cells that contribute to adipose tissue inflammation and insulin resistance [9]. Chronic inflammation in patients with obesity provokes vasculopathy, myocardial fibrosis, sympathetic hyperactivity and ion

TABLE 2. Spearman rank correlation coefficients between epicardial adipose tissue volume and clinical laboratory data and electrocardiographic parameters

Variable	r	p value
Age	0.259	<.0001
Sex	0.249	<.0001
Body mass index	0.450	<.0001
Systolic blood pressure	0.112	0.065
Diastolic blood pressure	0.016	0.788
Fasting glucose	0.274	<.0001
Total-cholesterol	0.051	0.416
Triglyceride	0.210	0.001
HDL-cholesterol	-0.206	0.001
LDL-cholesterol	0.025	0.693
Uric acid	0.184	0.004
Blood urea nitrogen	0.134	0.063
Creatinine	0.151	0.014
Albumin	-0.043	0.599
Hematocrit	0.094	0.181
White blood cell count	0.184	0.009
Hs-CRP	0.326	0.0002
ECG rate	0.007	0.909
PR interval	0.183	0.003
QRS duration	0.144	0.018
QT interval	0.003	0.960
QTc interval	0.004	0.943
Current smoking	0.123	0.044

HDL, high-density lipoprotein; LDL, low-density lipoprotein; QTc, corrected QT; ECG, electrocardiogram.

channel malfunction, which result in a high risk of cardiac arrhythmias and death [12-15]. In addition, a number of studies have shown that proinflammatory cytokines (such as CRP and IL-6) are associated with arrhythmias through the modulation of ion channel function [11,12] and the aggravation of sympathetic tone [11]. Myocardial fibrosis, which has been shown to be associated with the inflammatory process, could affect ventricular conduction, causing a delay in repolarization

TABLE 3. Prevalence of electrocardiographic parameters according to epicardial adipose tissue volume

Parameter	First tertile	Second tertile	Third tertile	<i>p</i> for trend
EAT volume (cm ³)	≤110	110–147	>147	
ECG parameters:				
Heart Rate (bpm)	68.2±10.6	69.4±11.6	67.9±11.1	0.851
PR interval (ms)	160.1±19.0	165.3±21.1	170.4±24.4	0.002
QRS duration (ms)	94.6±14.7	90.8±10.9	95.3±15.3	0.737
QT interval (ms)	400.6±33.3	394.7±33.0	400.1±33.2	0.929
QTc interval (ms)	422.9±23.6	420.0±23.1	421.3±25.8	0.649

Data are shown as mean ± SD. EAT, epicardial adipose tissue; ECG, electrocardiogram; QTc, corrected QT.

TABLE 4. Multiple logistic regression analysis with presence of PR interval prolongation as the dependent variable

	exp(B)	95% Confidence Interval	<i>p</i> value
Age	1.07	1.00-1.18	0.048
Sex	2.53	1.15-10.14	0.044
BMI	1.01	0.61-1.13	0.232
Systolic BP	0.98	0.91-1.05	0.546
Diastolic BP	1.04	0.94-1.16	0.457
Heart rate	1.03	0.96-1.10	0.457
Fasting glucose	1.01	1.00-1.12	0.025
Total cholesterol	0.98	0.94-1.03	0.460
Triglyceride	1.01	0.99-1.02	0.260
HDL-cholesterol	1.05	0.97-1.14	0.225
LDL-cholesterol	1.00	0.95-1.04	0.881
Smoking	4.44	2.33-9.29	0.004
β-blockers	2.46	0.47-12.79	0.284
CCBs	0.22	0.02-2.19	0.197
EAT volume	1.02	1.00-1.04	0.038

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CCB, calcium channel blockers, EAT, epicardial adipose tissue.

that could lead to ventricular arrhythmias [11]. Venteclef et al. demonstrated that the secretome from EAT promotes myocardial fibrosis through the secretion of adipo-fibrokinases such as Activin A [33]. EAT, the fat tissue surrounding the coronary

artery, serves not only as a lipid-storing depot but also as an endocrine organ secretion hormone. As an inflammatory tissue that secretes cytokines and chemokines, EAT may act as a pro-inflammatory cytokine, and may play a role in chronic inflammation, thus contributing to the pathogenesis of PR interval prolongation [12]. This speculation must be substantiated by further experiments.

Our results reveal that an EAT volume of >144.4 cm³ was associated with PR interval prolongation. Furthermore, there was a significant association between EAT volume and Framingham risk score. EAT mass was also found to correlate most strongly with metabolic syndrome parameters (e.g., fasting glucose, triglyceride and HDL-C levels and BMI), in a manner similar to that previously reported for VAT. As EAT seems to be a component of VAT, the association between EAT mass and the components of metabolic syndrome may be related to the nature and composition of VAT, suggesting a common pathway for obesity, adiposity, metabolic syndrome and inflammation. Strong evidence has already been published indicating that EAT-induced chronic inflammation occurs locally [34], as well as systemically [35], contributing to high risk for PR interval prolongation, coronary atherosclerosis and premature cardiovascular disease.

A previous study has demonstrated that the PR interval in adults aged 40 years and older is significantly dependent on heart rate and age [36]. In the present study, EAT volume was found to be independently associated with PR interval prolongation, after controlling for conventional risk factors, including age and heart rate. Some limitations of this study need to be considered. First, our study population was relatively small, so further studies with larger populations are needed. Second, the cross-sectional study design limits the inference of a causal relationship between EAT volume and PR interval prolongation.

Moreover, the analyses in this study were based on single measurements of EAT mass, which may not reflect its associated relationships over time. The strength of the current study lies in the application of CT scanning for measuring EAT volume and the concomitant detection of the electrocardiographic parameters in consecutive patients who underwent cardiac multi-slice CT for exclusion of CAD. To further clarify the role of EAT in the pathogenesis of PR interval prolongation, a subsequent study measuring serial changes in EAT volume in obesity, inflammation, or arrhythmogenesis would be worthwhile.

In conclusion, EAT volume was shown to be associated with inflammatory biomarkers and the development of PR interval prolongation, suggesting that EAT may act through inflammatory reactions to play an important role in the pathogenesis of PR interval prolongation; however, the mechanisms by which epicardial fat and PR interval are linked remain to be investigated.

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