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The relationship between total epicardial fat volume and atrial fibrillation

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Abstract

Background

Obesity is an important risk factor for atrial fibrillation (AF). Local epicardial fat enclosed by the visceral pericardial sac has been hypothesized to exert local pathogenic effects on cardiac structures. We aimed to characterize the relationship between total epicardial fat volume assessed by non contrast cardiac CT and AF.

Methods

This case control study conducted from May 2013 to December 2014 in cardiology and radiology departments of Benha University Hospitals. Fifty patients with a history of AF were taken up plus control group of 50 reference patients without history of AF. All patients underwent cardiac CT imaging to measure total epicardial fat volume (EFV), together with systemic obesity indices as body mass index (BMI), waist circumference and body weight plus echocardiographic parameters as left atrium (LA) volume index, left ventricular ejection fraction. All these were examined in relation to the presence and chronicity of AF.

Results

EFV was significantly associated with the presence of AF (p values<0.05).Significant positive correlation between EFV and AF chronicity was denoted. Patients with persistent AF had significantly larger EFV versus patients with paroxysmal AF (p value = 0.002). EFV was positively correlated with LA volume index (r = +0.45, p<0.001) Multivariate logistic regression model for AF risk factors revealed that EFV was the strongest independent risk factor for AF with highest odds ratio (2.13,95%CI: 1.01 to 3.06) followed by odds ratio (1.81,1.55 and 0.8) for LA volume index ,waist circumference and BMI respectively.

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Conclusion

Epicardial fat is associated with the presence of AF and predicts chronicity. These associations are independent to systemic measures of adiposity and sensitive echocardigraphic parameters as LA volume index. These findings are consistent with the hypothesis of a local pathogenic effect of epicardial fat on the arrhythmogenic substrate supporting AF

Key words

Atrial fibrillation, cardiac CT imaging, obesity, epicardial fat.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia found in clinical practice (1). It also accounts for 1/3 of hospital admissions for cardiac rhythm disturbances (2). Systemic obesity is a common modifiable risk factor for different cardiovascular disorders including AF. Above and beyond hazardous effect of obesity, Epicardial fat defined as the local visceral fat depot enclosed by the visceral pericardial sac shares the same blood supply as adjacent myocardium and also show paracrine functions. This is the risky fat that is metabolically active and has been hypothesized to exert a local pathogenic inflammatory effect on nearby cardiac structures (3). In recent years, several studies have shown that an increased epicardial fat volume noninvasively measured by CT or MRI images was strongly associated with the presence of coronary artery disease and atrial fibrillation, and adverse cardiovascular events (4). Because multiple factors are related to epicardial fat, we hypothesized whether epicardial fat could be independently associated with AF after adjusting multiple factors potentially related to epicardial fat. Therefore, this study was conducted to assess the relationship between epicardil fat volume and the presence and progression of AF when considering co variables related to epicaerdial fat.

Materials and Methods

Study population

This study was a case control study conducted from May 2013 to December 2014 in cardiology and radiology departments in Benha University Hospitals and local private centers. One hundred patients selected from cardiology department in Benha University Hospital. Their age ranged from 45 to 65 years and their body mass index (BMI) ranged from 25 to 32. They were divided into two groups as follows: AF group included 50 patients with a documented history of AF. Control group included 50 patients with intermediate risk and had no history of AF. They had age and sex matching to AF group.

All patients in both groups were referred for non-contrast CT for the evaluation of the volume of the total epicardial fat (EFV). This study was approved by the ethical committee in the faculty of medicine, Benha University.

Methods

All patients were subjected to the following:

History taking: Age, Sex, Smoking, hypertension, diabetes mellitus, thyrotoxicosis and documented history of AF.

Anthropometric measurements: Weight in kilograms, height in meters, waist circumference and body mass index (BMI) ranged from 25 to 32.

Clinical examination: Full general and local cardiac examination.

Echocardiography: Transthoracic echocardiography was performed with a commercially available system (Vivid Seven, General Electric, Milwaukee, WI). Left atrial volume was calculated using the modified biplane Simpson's method from the apical 2-chamber and 4-chamber views. (Figure 1) LA volume index was calculated (LA volume (ml)/BSA (m^2). Left atrial enlargement was defined as LA volume index > 22±6 (ml/m^2) for both men and women. Left ventricular ejection fraction (LVEF) was measured using the Simpson method. An LVEF <50% was considered abnormal. Structural heart disease was defined as moderate or greater amount of valvular regurgitation or left ventricular hypertrophy (5).

Non contrast CT. Imaging Technique: All CT scans were performed on a different local radiation centers including CT unit in Benha University Hospital with The Aquilion ONE ViSION CT scanner , Toshiba America Medical Systems , USA. All images were interpreted by a single radiologist who had more than 15 years of experience in the interpretation of CT scanning field and he was blinded to the history of AF. Tomogram was taken from tracheal bifurcation to the diaphragm in a single breath-hold in the cranio-caudal direction. The superior heart limit slice is typically chosen at the split of the pulmonary artery. The

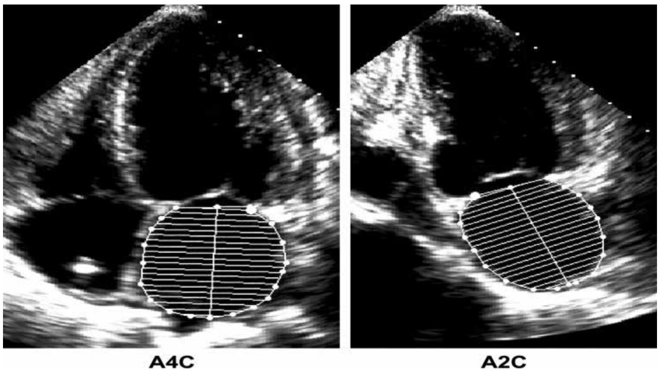

Figure 1. Left atrial volume was calculated using the modified biplane Simpson's method.

anatomic landmark for the inferior limit of the heart is typically the most inferior slice of the myocardium or the most inferior slice with the posterior descending artery (6). Image reconstruction was performed using retrospective ECG-gated acquisition spiral mode. Since epicardial fat is a compressible structure, End systolic frames are used to avoid suspected attenuation of fat during diastole by myocardial mass. A 3-D workstation was used to reconstruct axial images retrospectively at an optimal window. The image data sets were analyzed by means of Multiplanar reformatted images (vertical, long-axis, and short-axis views), curved Multiplanar reformatted images, thin-slab maximum-intensity projection images, and volume-rendered images (6).

Measurement of epicardial fat volume (EFV): Using the 5.0-mm-thick axial slices the parietal pericardium was manually traced in every fourth slice starting from the bifurcation of pulmonary artery to the diaphragm. The computer software (Toshiba - Aquilion ONE 640) then automatically interpolated and traced the parietal pericardium in all slices interposed between the manually traced slices to measure the EFV in cm^3. The total number of slices was 30 to 40 per heart. All automatically traced slices were examined and verified for accuracy. To ensure adequate gating and minimal motion artifact, patients in AF received beta-blockers and have CT scanning only if the ventricular response was <80 beats/min. The typical processing time for this method is 7–10 minutes. Standard fat attenuation values are used to define fat attenuation by CT; for non-contrast CT typically an attenuation range of (–30, –190) Hounsfield Units is used. Fat voxels within this attenuation range within the visceral pericardium are classified as epicardial fat, and within the inner thoracic cavity classified as thoracic fat (7) (Figure 2).

Statistical analysis of the collected data

Results were collected, tabulated, statistically analyzed using statistical Package of Social Science (SPSS) version 11 by Department of University Academic Computing Technologies (UACT) (American University in Cairo).

Two main statistical methods were used to present data:

Descriptive statistics: in which quantitative data were presented in the form of mean (x), standard de-

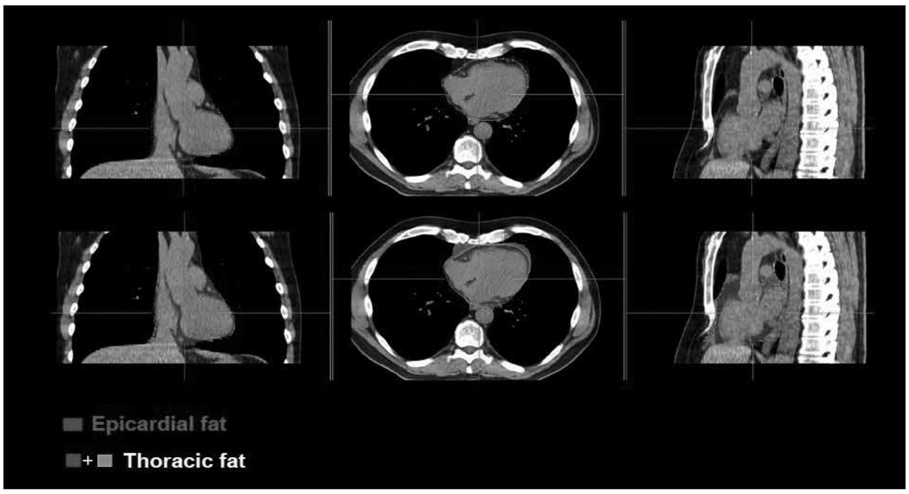

Figure 2. Measurement of EFV and thoracic fat From Noncontract CT

viation and range, and qualitative data were presented in the form of number and percentage (%).

Analytical (inferential) statistics: used to find out the possible association between many factors and the targeted disease. The following statistical tests were applied.

Chi-Squared test (χ^2), Fischer exact test, t-test, Mann-Whitney test.

Correlation: Correlation is a statistical technique that can show whether and how strongly pairs of variables are related.

Binary logistic regression: A statistical measure that attempts to determine the strength of the relationship between one dependent variable (usually denoted by Y) and a series of other changing variables (known as independent variables).

P-value of <0.05 was considered statistically significant.

Results

Patient characteristics

There was age and sex matching between AF and control groups (P value = 0.15). Mean age equal 58.56 ±8.79 and 55.80±7.13 for AF and control group respectively.

As regards clinical history, rate of DM and thyrotoxicosis was significantly higher (P value = 0.03 & 0.01) among the AF group. Hypertension and smoking showed no significant differences in both groups (p value > 0.05). As regard systemic obesity indices, AF group were of significantly larger weight, BMI and waist circumference (P value = 0.038, 0.01 and 0.001) respectively.

As regards different echocardiographic parameters, AF group showed significantly larger LA volume indices & LA diameters (P value <0.001). The results showed insignificant difference in both studied groups as regards LVEF% and Lt. ventricular thickness (P value = 0.2 & 0.59).

Relation between EFV and different parameters

The AF group had a significantly larger EFV than the control group (170.34±44.58 cm^3 versus 107.28±40.08 cm^3, p < 0.001) (Table 1). EFV was positively correlated with body weight (r = 0.25, p = 0.08), BMI (r = 0.38, p = 0.007), and LA volume index (r = 0.39, P = 0.005). There were no correlations between EFV and weight (r = 0.25, P = 0.08), waist (r = 0.01, P = 0.95), age, left ventricular ejection fraction, and left ventricular wall thickness (P > 0.05 for all) (Table2).

Table 1. **Comparison of demographic, echocardiographic and CT data in the two groups**

Variable	AF group	Control group	P value
Age	58.56 ±8.79	55.80±7.13	0.15
Men	35(70%)	33(68%)	0.15
Weight (kg)	89.48±10.94	89.48±10.94	0.038
BMI	29.21±4.76	27.02±3.60	0.01
Waist circumference (cm)	103.20±7.94	98.10± 6.94	0.001
HTN	25%	20%	>0.05
DM	20%	6%	0.03
Thyrotoxicosis	12%	0%	0.01
smoking	30%	25%	>0.05
Lt atrial diameter (mm) X ± SD Range	43.36±7.11 31 – 59	31.26±6.66 20 – 42	<0.001
LA volume index (ml/m^2) X ± SD Range	33.5±6.11 29-36	22.56±6.8 20-24	<0.001
LV EF % X ± SD Range	50.36±8.19 32 – 62	63.32±6.33 54 – 75	0.20
Lt. ventricular thickness /cm X ± SD Range	1.08±0.31 0.60 – 1.90	1.03 ± 0.37 0.60 – 1.6	0.59
Epicardial fat volume (EFV) X ± SD Range	170.34±44.58 cm^3 90 – 259	107.28±40.08 cm^3 45 – 211	<0.001

BMI=body mass index, HTN=hypertension,DM=diabetes mellitus, LA=left atrium , LV=left ventricle , EF = ejection fraction.
SD = slandered deviation.

Table 2. **Correlation between pericardial fat volume and other parameters among AF group**

	pericardial fat volume (AF group)	
	Correlation coefficient - r-	P value
Age	- 0.32	0.02
Weight /year	+ 0.25	0.08
BMI	+ 0.38	0.007
Waist circumference	+ 0.01	0.95
Left atrial volume index	+ 0.39	0.005
LVEF %	+ 0.16	0.27
Left ventricular wall thickness	+ 0.21	0.14

BMI=body mass index, LVEF=left ventricle ejection fraction.

Multivariate regression model for risk factors of AF

Using Wald test for multiple parameters , this model revealed that EFV and LA volume index were independent risk factors for occurrence of AF with highest odds ratio (2.13 & 1.81) & highest Wald x2 values (10.34 & 11.94) respectively. While obesity indices as

Table 3. **Multivariate logistic regression model for risk factors of AF**

Risk factors	Wald x^2	P value	Odds Ratio (Exp. Beta)	95% CI	
				Lower	Upper
DM	0.03	0.85	0.88	0.07	9.13
Thyrotoxicosis	0.06	0.81	0.91	0.13	8.70
Weight	0.18	0.67	1.02	0.93	1.12
BMI	1.11	0.29	0.87	0.66	1.13
Waist circumference	5.65	0.02	1.55	1.02	1.99
Lt. atrial volume index	11.94	0.001	1.81	1.11	2.45
Epicardial fat volume	10.34	0.001	2.13	1.01	3.06

Wald x^2 = Wald Test on multiple parameters, CI = Confidence interval, DM=diabetes mellitus, BMI=body mass index.

BMI, waist circumference and weight showed lower odds ratio (0.87, 1.55 & 1.02) and lower Wald x^2 values (1.11, 5.6, 0.18 respectively) (Table 3). This data concluded that EFV by CT and LA volume index by echocardiography were the strongest independent risk factors for AF occurrence.

Impact of EFV on the progression of AF

66% of the AF group had paroxysmal AF and 34% had persistent AF. There was no significant difference between persistent and paroxysmal AF as regards age (P value = 0.34). There was significant association between persistent AF and male sex as 88.2% of persistent AF subjects were males versus only 60% among paroxysmal AF cases. Hypertension, DM, smoking and thyrotoxicosis showed no significant differences among paroxysmal AF and persistent AF cases (P value > 0.05). Persistent AF group were of significantly larger weight and BMI than paroxysmal AF group (P value <0.05).

Persistent AF group showed significantly larger LA volume indices than paroxysmal AF group (P value = 0.005). No significant difference between two groups as regards LVEF (%) and Left ventricular thickness (P value >0.05). The group with persistent AF had significantly larger EFV than those with paroxysmal AF group (196.29±49.48 cm^3 versus 156.97±35.88 cm^3 and P value = 0.002) (Table 4).

Table 4. **Comparison between paroxysmal AF subgroup and persistant AF subgroup as regard different risk factors.**

variable	Paroxysmal AF N=33	Persistant AF N=17	T test	P value
Age /year X ± SD Range	59.42 ±8.22 38 – 78	56.88±9.85 40 – 74	0.97	0.34
Male	20(60%)	15(88%)	4.02	0.04
HTN	17(51.5%)	8(47.1%)	0.09	0.76
DM	4(12.1%)	6(35.5%)	3.77	0.07
Thyrotoxicosis	5(15.2%)	1(5.9%)	0.91	0.65
smoking	14(32.4%)	10(58.9%)	1.46	0.48
Weight /kg X ± SD	85.51±10.40	97.18 ±7.38	4.58	<0.001
BMI X ± SD	26.68 ±2.99	34.13±3.55	7.82	<0.001
Waist circumference X ± SD	101.97±6.94	105.59±9.37	1.41	0.17
Lt atrial volume index (ml/m^2) X ± SD	31.39±6.25	37.18±7.28	2.93	0.005
LVEF (%) X ± SD	50.51±8.72	50.06±7.29	0.18	0.85
Lt. ventricular thickness /cm X ± SD	1.10±0.32	1.04±0.29	0.70	0.49
Epicardial fat volume X ± SD	156.97±35.88 cm^3	196.29±49.48 cm^3	Mann Whitney U 3.23	0.002

SD=standerd deviation , DM=diabetes mellitus, BMI=body mass index.

Discussion

Major findings

In the current study, detailed echocardiography and non contrast CT examination were used to present new information regarding the interrelationships between localized epicardial fat depots and AF. The results revealed that, patients with AF had significantly larger EFV compared with control group (P <0.001). (Table 1) There was a strong association between EFV and AF chronicity. Persistent AF patients had a significantly larger EFV compared with paroxysmal AF patients (P = 0.002). (Table 4) These results were in aggrement with Chekakie et al. 2010 who examined the association between epicardial fat and AF chronicity using non contrast CT and demonstrated a significant association of EFV with both paroxysmal and persistent AF. EFV was associated with both paroxysmal AF (odds ratio 1.11, 95% CI: 1.01 to 1.23; p=0.04) and persistent AF (odds ratio 1.18, 95% CI: 1.05 to 1.33; P=0.004) (8). In current study, epicardial fat was strongely associated with the presence of AF (odds ratio: 2.13; 95% confidence interval: 1.01 to 3.06, P = 0.04) and this association was completely independent to DM, thyrotoxicosis, weight, waist circumference, BMI.(Table 2) Finally, strong positive correlations between EFV and LA volume indices were documented (r = +0.39, p value = 0.005). While more systemic measures of adiposity as waist, weight had a lack of same close positive correlations to EFV (r = +0.01 and +0.25, P value = 0.95 and 0.08).(Table 2) Our data suggest that epicardial fat may have a pathogenic effect on the anatomically contiguous atria, above and beyond systemic effects of generalized adiposity. Such effect could promote an arrhythmogenic substrate initiating AF.

The difference and novelty of the study

In spite our results were in agreement with many previous studies, to our knowledge the present study is unique in using both CT to assess epicardial fat volume plus echocardiographic measures of LA volume in AF patients. This study provides the first report of a clear association between epicardial fat, LA volume index and AF occurrence. Previous studies as Thanassoulis et al. 2010 who reviewed the Framingham Heart Study and revealed association between epicardial fat and AF occurrence (P=0.02) not used the atrial dimension as a covariate in the multivariable model, while in the present study we aimed to use LA volume parameters side by side to different obesity indices in the multivariable model and showed that EFV and LA volume index were independent risk factors for occurrence of AF (9). Iacobellis et al. 2007, who tested the relation between epicardial adipose tissue and atrial dimensions by echocardiography in morbidly obese subjects, found that epicardial fat has been strongly associated with LA dimensions in AF patients. They had two limitations; first they analyzed epicardial fat thickness using echocardiography instead of epicardial fat volume assessed by cardiac CT which is known to be more accurate measure. Second they used LA volume instead of LA volume index which could limit the strength of the results and the conclusion obtained from their study (10).

Hypothesis of a local pathogenic effect of epicardial fat

At a local level, pericardial fat has been associated with increased expression of numerous inflammatory markers (11-12). Intracardiac inflammatory markers have also been observed to be greater than peripheral inflammatory markers, and greatest in the left atrium, which plays a critical role in AF genesis (13). Cytokines have also been shown to activate fibroblasts, with the extracellular matrix deposition and fibrosis causing electro anatomical remodeling (14). Therefore, the present finding supports the notion that epicardial fat may exert deleterious effects on the anatomically contiguous atria and promote arrhythmogenesis.

Clinical Implications

With the increasing use and availability of CT scan, EFV assessed by CT scan may be used to identify the patients with undetected AF or asymptomatic AF.

Study limitations

The relatively limited number of the patients could limit the strength of results and conclusion obtained from this study.

Conclusion

Epicardial fat is associated with the presence of AF and predicts chronicity of AF. These associations are both independent of systemic measures of adiposity. EFV and LA volume index were independent risk factors for occurrence of AF. Associations between EFV and LA volume changes could explain the mechanism of AF initiation. These findings are consistent with the hypothesis of a local pathogenic effect of epicardial fat on the arrhythmogenic substrate supporting AF.

Conflict of interest:
The authors declare no conflict of interests.

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