Opposite relations of epicardial adipose tissue to left atrial size in paroxysmal and permanent atrial fibrillation

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Abstract

Objectives: Atrial fibrillation has been associated with obesity in epidemiological studies. Epicardial adipose tissue is an ectopic fat depot in the proximity of atria, with endocrine and inflammatory properties that is implicated in the pathophysiology of atrial fibrillation. Inflammation also has a role in atrial arrhythmogenesis. The aim of this study was to investigate the potential relations of epicardial adipose tissue to left atrial size and to adiponectin and the pro-inflammatory mediators, high-sensitivity C-reactive protein, and interleukin-6 in paroxysmal and permanent atrial fibrillation.

Methods: This was a cross-sectional study of 103 atrial fibrillation patients, divided into two subgroups of paroxysmal and permanent atrial fibrillation, and 81 controls, in sinus rhythm. Echocardiography was used for estimation of epicardial adipose tissue and left atrial size and high-sensitivity C-reactive protein, interleukin-6 and adiponectin were measured in all subjects.

Results: Atrial fibrillation patients had significantly larger epicardial adipose tissue compared with controls (0.43 ± 0.17 vs 0.34 ± 0.17 cm, $p = 0.002$). Atrial fibrillation presence was independently related to epicardial adipose tissue thickness ($b = 0.09$, $p = 0.002$). Opposite associations of epicardial adipose tissue with left atrial volume existed in atrial fibrillation subgroups; in the paroxysmal subgroup, epicardial adipose tissue was directly related to left atrial volume ($R = 0.3$, $p = 0.03$), but in the permanent one the relation was inverse ($R = -0.7$, $p < 0.0001$). Adiponectin, high-sensitivity C-reactive protein and interleukin-6 were elevated in both atrial fibrillation groups. Only interleukin-6 was related to epicardial adipose tissue size.

Conclusion: Opposite associations of epicardial adipose tissue with left atrial size in paroxysmal and permanent Atrial fibrillation and elevated inflammatory markers, suggest a role of epicardial adipose tissue and inflammation in the fibrotic and remodeling process.

Introduction

A number of epidemiological studies have linked obesity to atrial fibrillation (AF). There is an increased incidence, severity, and progression of AF in overweight populations, while stable weight loss decreases the AF burden and recurrence.[1,2] Among the novel mechanisms involved in the pathophysiology of AF substrate, increasing evidence exists for the arrhythmogenic impact of local epicardial fat depots on the human atria.[3] Epicardial adipose tissue (EAT) serves as a store for myocardial needs. Featuring specific brown fat characteristics, it contributes to thermoregulation, while it also modulates coronary vasomotion and forms a protective framework for cardiac autonomic nerves and ganglia.[4,5] The most interesting hypothesis is that EAT is an endocrine organ

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that contributes to the inflammatory burden through a paracrine manner.[6] Epidemiological studies have linked EAT thickness with AF severity.[7–9] Adiponectin is an adipokine secreted from EAT that has anti-inflammatory, antiatherogenic, and antihypertrophic via multiple cell-signaling mechanisms.[10] Adiponectin levels are reduced in different pathologic conditions, including metabolic syndrome, nonalcoholic fatty liver disease, diabetes, obesity, and ischemic heart disease[11,12] and have been also suggested as an independent prognostic biomarker in AF.[13]

The aim of this study was to investigate the association of EAT with left atrial (LA) size and with plasma levels of adiponectin and pro-inflammatory mediators, in paroxysmal and permanent AF.

Methods

Study participants

This was a cross-sectional study of 103 patients with AF and 81 normal controls, with no history of AF. The AF patients were consecutively identified from the outpatient clinic, in an 11-month period and were referred for clinical evaluation and echocardiography; they were divided into two subgroups of paroxysmal and permanent AF, according to the patterns described in the recent guidelines:[14] the subgroup of paroxysmal AF consisted of 55 patients who had AF episodes that were self-terminating within 48 h, or up to 7 days, or were medically or electrically cardioverted within 7 days. The subgroup of permanent AF consisted of 48 patients in whom AF was accepted by the patient or physician and no rhythm control was pursued. Patients with persistent AF were purposely not included. The control group consisted of 81 patients who were on sinus rhythm in the electrocardiogram performed and had no history of AF. These patients were referred for outpatient echocardiography and were matched for diabetes, body surface area, body mass index, and waist circumference. Patients with moderate and severe valvular disease and severe heart failure New York Heart Association class III–IV were excluded, in order to minimize their effect on atrial structure. We also excluded subjects with malignancy and any collagen or autoimmune disease; recent infection, or any febrile illness; recent surgery; acute coronary syndromes diagnosed by clinical symptoms and cardiac biomarkers; obstructive sleep apnea; chronic kidney or hepatic failure. The study protocol adhered to the declaration of the Helsinki principles and was approved by the Hospitals' Ethics Committee. Written informed consent was obtained from all subjects.

Clinical and laboratory evaluations

Medical history and data about age, gender, diabetes, coronary artery disease, dyslipidemia, and hypertension were obtained from all the study participants. Anthropometric evaluation included measurement of height, weight, waist circumference, body surface area, and body mass index. Levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, high-sensitivity C-reactive protein (hs-CRP), interleukin-6, and adiponectin were obtained by venous samples after an overnight fast. Levels of hs-CRP were measured by an immunonephelometry assay (BN Prospec System, Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany), with an assay range of 0.175–100 mg/L. Interleukin-6 levels were measured by a quantitative sandwich enzyme immunoassay technique (R&D Systems Inc.), with an assay range of 0.156–10 pg/mL and a sensitivity of 0.039 pg/mL. Serum adiponectin levels were determined by a quantitative sandwich enzyme immunoassay technique (R&D Systems Inc., Minneapolis, MN, USA), in duplicate, using a specific monoclonal antibody with a sensitivity of 0.246 ng/mL and an assay range of 2.46–2500 ng/mL.

Echocardiography

A transthoracic echocardiogram was performed, using a PHILIPS iE33 XMATRIX Ultrasound System (Philips Medical Systems, Bothell, WA, USA). LA diameter, LA volume, left ventricular diameter, and ejection fraction measurements were performed according to the current guidelines.[15] The thickness of EAT was measured on the right ventricular free wall of the two-dimensional parasternal long-axis view at end systole as previously described.[16,17] We preferred the area above the right ventricle as this has the thickest EAT layer. In addition, the parasternal long-axis view allows optimal beam orientation and more accurate measurement. The anterior echo-lucent space between the linear echo-dense visceral pericardium and the right ventricular epicardium was considered to be EAT. Pericardial fat was identified as the hypoechoic space anterior to the EAT and the parietal pericardium. Pericardial fat does not deform substantially and does not change size during the cardiac cycle (Figure 1). Echocardiographic recordings were reviewed by two independent expert operators. In a sample of 20 randomly selected patients, the intraobserver and interobserver variability correlation values for the echocardiographic parameters were 0.95.

Statistical analyses

Statistical analyses were performed using the "Statistica" software program (version 10 StatSoft Inc., Tulsa, Oklahoma). Continuous variables were expressed as mean ± standard deviation. Data were tested for normal distribution by the Kolmogorov test. Relations between categorical variables were assessed by standard two-way tables (chi-square). One-way analysis of variance was used to compare continuous variables between groups. Univariate analysis was used to identify potent relationships between clinical

and biochemical variables and EAT thickness. Variables found to be associated with EAT were entered in a multivariate linear regression analysis. A two-tailed p value < 0.05 was considered significant.

Results

Clinical and echocardiographic characteristics are summarized in Table 1. Patients without AF were younger than patients with paroxysmal and permanent AF ($p < 0.001$). The two groups were matched for body mass index, waist circumference, and for comorbidities such as dyslipidemia

Figure 1. Echocardiographic measurement of epicardial adipose tissue (EAT) in the parasternal long axis view. The anterior echo-lucent space between the linear echo-dense visceral pericardium and the right ventricular epicardium was considered to be EAT. Pericardial fat (PERI FAT), was identified as the hypoechoic space anterior to the EAT and the parietal pericardium.

and diabetes. Medications with a potential effect on AF development, such as statins, angiotensin- converting-enzyme inhibitors, angiotensin-receptor blockers, and b-blockers did not differ between groups. Coronary artery disease and hypertension were more common in AF patients, however, there were no differences between the paroxysmal and permanent AF subgroups. Total cholesterol and low-density lipoprotein cholesterol were more elevated in controls. There were no associations of epicardial and pericardial fat thickness with the presence of diabetes, hypertension, coronary artery disease, or dyslipidemia. Epicardial and pericardial fat thickness were also not related to lipid levels. Pericardial fat thickness was positively related to body mass index and waist circumference ($p = 0.01$, $p = 0.02$ and $p = 0.03$, respectively), but no such relation existed for epicardial fat.

As Figure 2 demonstrates, patients with paroxysmal AF had significantly greater EAT compared with controls and with permanent AF patients. Variables univariately associated with EAT thickness were age, female gender, interleukin-6 levels, and the presence of AF. When these variables were entered in a multivariate linear regression analysis, we showed that only the AF presence remained strongly associated with EAT thickness (Table 2).

As expected, LA size was found to be significantly larger in patients with AF compared with patients in sinus rhythm, and in permanent compared with paroxysmal AF patients (Table 1). Interestingly, we found opposite associations of EAT thickness with LA volume in the paroxysmal and the permanent AF subgroups. In the paroxysmal AF, EAT thickness was directly related to LA volume ($R = 0.3$, $p = 0.03$); on the contrary, in the permanent AF subgroup there was an inverse relation of EAT to LA volume ($R = -0.7$, $p < 0.0001$; Figure 3).

Table 1. Clinical and echocardiographic characteristics of patients with atrial fibrillation and controls. Values are expressed as mean $\pm$ SD or number (percent).

Variable	Paroxysmal AF ($n = 55$)	Permanent AF ($n = 48$)	p value	F or x^2	All AF ($n = 103$)	Controls ($n = 81$)	p value	F or x^2
Age (years)	66.6 ± 12.5	73.7 ± 9	0.01	11	69 ± 8	50 ± 13	<0.001	112
Men, n, (%)	29 (51.8)	22 (45.8)	0.05	6.1	55 (48.6)	54 (66.6)	0.01	6.2
Hypertension, n, (%)	39 (49.4)	40 (50.5)	0.1	2.6	79 (71)	31 (28.2)	<0.001	26
Diabetes mellitus, n, (%)	17 (30)	10 (21)	0.3	1.2	27 (24)	26 (30)	0.23	1.4
CAD, n, (%)	15 (26.8)	14 (29)	0.8	0.07	29 (26)	6 (7.4)	<0.001	11
Dyslipidemia, n, (%)	25 (49)	30 (68)	0.06	3.6	55 (57)	46 (57)	0.9	0.02
Waist circumference (cm)	104 ± 14	105 ± 13	0.8	0.06	104 ± 14	106 ± 14	0.3	0.9
BSA (m²)	1.97 ± 0.7	1.94 ± 0.2	0.6	0.2	2 ± 0.2	2 ± 0.2	0.2	1.5
BMI (kg/m²)	29.2 ± 5.5	29.5 ± 6.9	0.8	0.04	29 ± 6	30.2 ± 5.4	0.5	0.6
LA diameter (mm)	42.8 ± 6.6	49.3 ± 5.7	0.001	12	45.5 ± 7	37.6 ± 5	<0.0001	31
LA volume (mL)	74 ± 32	100 ± 27	0.06	3.5	81 ± 31	42 ± 17	<0.0001	30
LA volume index (mL/m²)	37 ± 17	47 ± 14	0.04	4.2	41 ± 16	20 ± 7	<0.0001	36
LVEF (%)	56 ± 9	45 ± 9	0.0001	17	52 ± 10	57 ± 9	<0.0001	17
Pericardial fat (cm)	0.43 ± 0.2	0.38 ± 0.1	0.3	0.9	0.4 ± 0.1	0.46 ± 0.2	0.32	1.1

AF: atrial fibrillation; BMI: body mass index; BSA: body surface area; CAD: coronary artery disease; LA: left atrial; LVEF: left ventricular ejection fraction.

The levels of inflammatory markers hs-CRP, interleukin-6, and adiponectin were significantly elevated in AF compared with controls, with no differences between the two AF subgroups (Table 3). All inflammatory markers were positively related to LA volume ($R = 0.5$, $p < 0.0001$ for interleukin, $R = 0.2$, $p = 0.02$ for hs-CRP, and $R = 0.2$, $p = 0.003$ for adiponectin).

Discussion

The major finding of this study was the confirmation that epicardial fat is increased in AF patients, mainly in paroxysmal AF. In addition, it seems to be differently associated with LA size, depending on the AF type: EAT is directly related to LA size in paroxysmal and inversely related in permanent AF. We further demonstrated that AF patients have increased
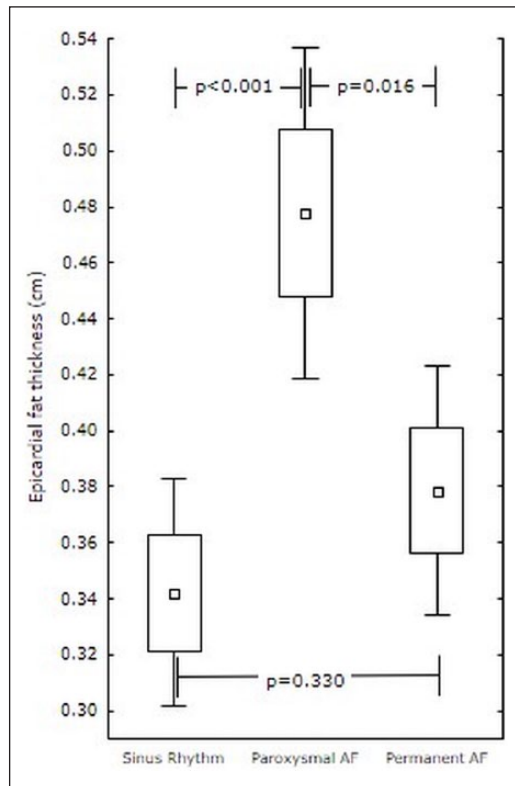
Figure 2. Differences in epicardial fat thickness among patients with paroxysmal AF, permanent AF, and sinus rhythm controls

plasma levels of inflammatory markers and adiponectin, highlighting the role of inflammation in the pathogenesis of this complex arrhythmia.

A number of epidemiological studies[1,2] have demonstrated the role of obesity in AF, which continues to be under exploration.[18] There is compelling evidence for the local effect of epicardial and pericardial fat in the pathogenesis of AF, possibly through fatty atrial infiltration, fibrosis, and inflammation.[7–9] In the existing literature, both epicardial and pericardial fat have been related to the presence and burden of AF. Pericardial fat, estimated by cardiac computed tomography[7] or magnetic resonance,[19] has been highly associated with paroxysmal and persistent AF, independently of LA enlargement. Yorgun et al.,[20] using multidetector computed tomography, also demonstrated that both peri-atrial and total EAT thickness were associated with AF and they were also positively related to the LA diameter. Interestingly, in another study, only the posterior epicardial fat pad, between the left atrium and the esophagus, was related to AF burden.[8] The mixed reported results among the various studies are probably explained by differences in the quantification of epicardial and pericardial fat due to methodologic issues. In our study, we calculated the epicardial and pericardial fat thickness using echocardiography, an acceptable and safe imaging modality, as reviewed by experts in the field.[3] We found that epicardial fat thickness was independently related mainly to paroxysmal AF, whereas this did not apply for pericardial fat. This finding supports the assumption that these two types of fat deposits around the heart have distinctive properties apart from their location. Moreover, we demonstrated opposite associations of epicardial fat and LA size in different types of AF. Epicardial fat size increased in parallel to LA size in paroxysmal AF, albeit it decreased as LA volume enlarged in permanent AF (where EAT thickness was similar to controls). This interesting finding highlights the role of structural atrial remodeling in permanent AF, which seems to be associated with less epicardial fat. We could hypothesize that epicardial fat may shrink in permanent AF, due to a transition from fatty to fibrotic, with enlarging left atrium, while in paroxysmal AF, atrial remodeling alterations and epicardial fat fibrosis might be not as prominent yet. Although this assumption needs further exploration, it is supported by an elegant study of human and sheep atria, in which Haemers et al.[21] provided clear evidence of a greater fibrosis of adipose tissue in the atrial subepicardium

Table 2. Univariate and multivariate linear regression for the associations of epicardial adipose tissue and baseline variables.

	Univariate linear regression		Multivariate linear regression	
	B	P	b	p
Age (years)	0.25	0.002	0.0	0.7
Sex (female)	5.7	0.01	0.03	0.3
Interleukin-6 (pg/mL)	0.2	0.02	0.0	0.6
Atrial fibrillation	10.4	0.001	0.09	0.02

and, thus, less adipose tissue in permanent AF compared with paroxysmal AF.

In our study, we further sought to investigate the possible association of adiponectin and pro-inflammatory markers with EAT in the two different types of AF. We found increased plasma levels of hs-CRP, interleukin-6, and adiponectin, both in paroxysmal and permanent AF. All inflammatory markers were directly associated with LA size, which is in keeping with previous reports,[22] and interleukin-6 was related to EAT, albeit there were no differences between paroxysmal and permanent AF. This finding highlights the role of inflammation in the atrial structure; however, no firm conclusions can be drawn regarding causality. The elevated levels of adiponectin found in all AF patients of our study deserve special mention. Various adipo-fibrokines, secreted by EAT and diffused into the adjacent atrial myocardium, contribute to fibrosis in a paracrine manner.[23] Adiponectin is a cytokine exhibiting important effects, as it stimulates endothelium-dependent and -independent vasorelaxation, has anti-inflammatory properties, and inhibits growth

factors. Hypoadiponectinemia is prevalent in conditions related to obesity and the metabolic syndrome, situations linked to AF risk. Our finding of significantly increased adiponectin levels in AF could be possibly explained by the disconnection of the hormone from its receptors in AF and, therefore, an ineffective counter-regulatory response. Our results are in line with the study of Shimano et al.,[24] who demonstrated elevated adiponectin in persistent AF, attributing it to collagen degradation and fibrosis, and with Macheret et al.,[25] who also found a positive relation of adiponectin and incident AF. In addition, other studies have also reported high adiponectin levels in persistent AF[24] or in older adults with AF risk.[25] However, there are studies with conflicting results, which have demonstrated that lower adiponectin levels have being associated with postoperative AF.[26] The large Framingham Offspring Study also did not confirm a relationship between adiponectin concentrations and incident AF.[27] Furthermore, Kourliouros et al.[28] investigated the role of both, the circulating plasma levels and the locally, epicardial tissue-produced adiponectin, in the development of
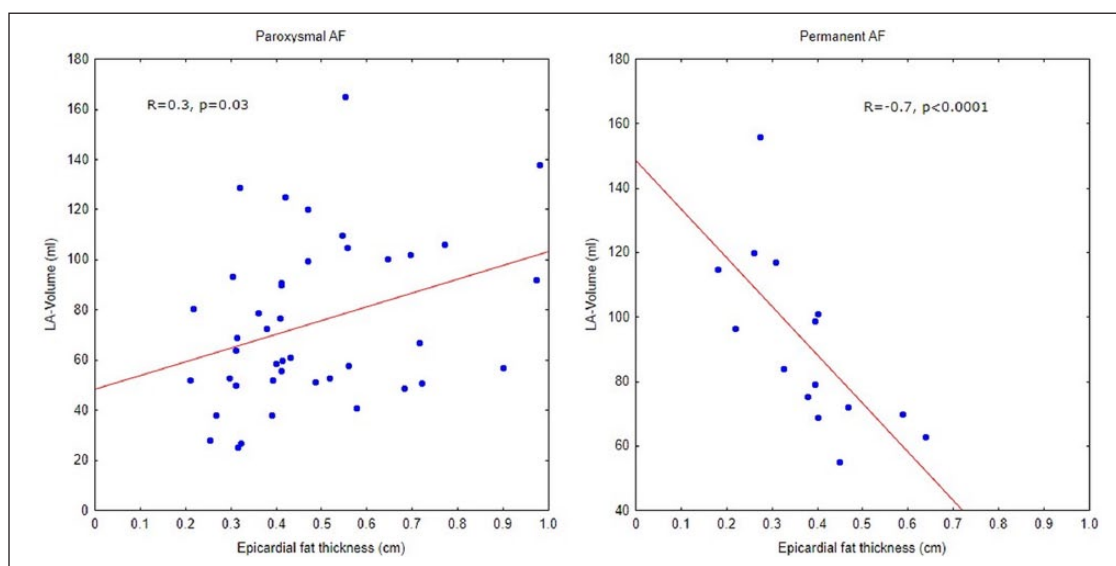
Figure 3. Relations of epicardial fat thickness to left atrial (LA) volume in the paroxysmal and the permanent atrial fibrillation (AF) subgroups.

Table 3. Laboratory measurements in the study groups. Values are expressed as mean ± standard deviation.

Variable	Paroxysmal AF (n = 55)	Permanent AF (n = 48)	p value	F	All AF (n = 103)	Controls (n = 81)	p value	F
Cholesterol (mg/dL)	186 ± 41	158 ± 40	0.006	8	173 ± 45	198 ± 45	0.0004	8
HDL (mg/dL)	51 ± 18	48 ± 17	0.5	0.3	50 ± 18	49 ± 15	0.8	0.2
LDL (mg/dL)	108 ± 32	89 ± 27	0.01	7	99 ± 31	120 ± 42	0.001	7
Triglycerides (mg/dL)	130 ± 75	108 ± 48	0.2	1.7	120 ± 64	142 ± 92	0.2	1.6
hs-CRP (mg/L)	7.8 ± 10.4	4.4 ± 3.7	0.1	2.2	6.2 ± 8.2	3.6 ± 4.8	0.004	5.6
Interleukin-6 (pg/mL)	10.6 ± 18	9 ± 11	0.7	0.1	10 ± 15	2 ± 1	0.0002	9
Adiponectin (ng/mL)	8728 ± 5713	10913 ± 5613	0.1	2.4	9713 ± 5717	6310 ± 3820	0.0001	9

AF: atrial fibrillation; hs-CPR: high-sensitivity C-reactive protein; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

AF following cardiac surgery; it was only the epicardially produced adiponectin that was associated with sinus rhythm maintenance. Putting it all together, the exact role of adiponectin in the pathophysiology of AF remains unclear and further research with experimental and clinical studies is needed to investigate the detailed mechanisms, by which both circulating and locally produced adiponectin are implicated in paroxysmal and permanent AF.

The important strengths of our study include the use of standardized measures of total and visceral adiposity, like body mass index and waist circumference, which, to our knowledge, have not been provided or controlled for in other studies, as well as the additional estimation of inflammatory markers and adiponectin. Patients of both the study groups did not differ in obesity characteristics (body mass index, body surface area, and waist circumference), which have been associated with cardiac adiposity, and they were also matched for diabetes and dyslipidemia, which have been linked both to systemic and cardiac adiposity, and to increased inflammatory burden. However, some study limitations need to be mentioned. Patients in the control group were younger than AF patients. There were some differences in comorbidities between the groups, as coronary artery disease and hypertension were more prevalent in AF compared with controls, and cholesterol levels were more elevated in the controls. Finally, we used echocardiography for the assessment of epicardial and pericardial fat, and certainly, estimations of EAT volume by magnetic resonance imaging or computed tomography offer more accurate and precise measurements of total fat mass.

In conclusion, epicardial fat seems to be increased only in paroxysmal AF. The opposite associations of epicardial fat with LA size in paroxysmal and permanent AF may suggest a role of EAT in the remodeling process. Further research is needed to elucidate the mechanisms by which epicardial fat is related to AF and the role of adiponectin.

Author's Note

The authors S.N.P. and D.T. contributed equally to this work.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of National and Kapodistrian University of Athens, Medical School, Department of Clinical Therapeutics, Athens, Greece. The Ethics approval number is: 198/03-03-2017 (3rd/21-02-2017 Session).

Informed consent

Written informed consent was obtained from all subjects before the study.

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