https://doi.org/10.35336/VA-1461

RELATIONSHIP BETWEEN EPICARDIAL ADIPOSE TISSUE CHARACTERISTICS MEASURED BY MULTIDETECTOR COMPUTED TOMOGRAPHY AND BLOOD BIOMARKERS IN PATIENTS WITH ATRIAL FIBRILLATION

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Aim. To evaluate the association of computed tomography measurements (volume and density) of epicardial adipose tissue (EAT) with the blood concentration of adipokines, proinflammatory cytokines and catecholamines in patients with atrial fibrillation (AF).

Methods. We included 32 patients (median age 58.5 (52.5; 64.0); 18 men) with AF scheduled for radiofrequency ablation. All patients underwent multispiral computed tomographic coronary angiography and segmentation of the EAT. In addition, the concentration of adiponectin, leptin, resistin, interleukins 1b, 6, 8 and methanephrine in the blood was determined by enzyme immunoassay.

Results. A negative correlation was established between the volume and the density of EAT ($r = -0.5$, $p<0.05$). The X-ray density of EAT negatively correlated with the concentration of methanephrine ($r = -0.4$) and leptin ($r = -0.4$), and positively correlated with the concentration of interleukin-8 ($r=0.36$). In addition, the duration of AF was negatively correlated with the density of EAT ($r=-0.42$, $p<0.05$) and positively correlated with the concentration of blood methanephrine ($r=0.34$, $p<0.05$). No associations were found between the volume of EAT and the studied blood biomarkers.

Conclusion. The results of the study showed an association between EAT X-ray density and the concentration of leptin, interleukin-8 and metanephrine in AF patients.

Key words: atrial fibrillation; epicardial adipose tissue; computed tomography; X-ray density; metanephrine; blood biomarkers

Conflict of Interest: none.
Funding: none.
Received: 28.01.2025 **Revision Received:** 14.04.2025 **Accepted:** 21.04.2025
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For citation: Sazonova SI, Popov EV, Moskovskih TV, Ilyushenkova YuN, Varlamova YuV, Batalov RE, Gusakova AM, Kravchenko ES, Popov SV. Relationship between epicardial adipose tissue characteristics measured by multidetector computed tomography and blood biomarkers in patients with atrial fibrillation. *Journal of Arrhythmology*. 2025;32(2): 5-11. https://doi.org/10.35336/VA-1461.

In recent years, increasing attention has been paid to the potential use of morphometric parameters of epicardial adipose tissue (EAT), as assessed by various imaging modalities (echocardiography, computed tomography), as markers of coronary artery (CA) atherosclerosis progression and predictors of adverse cardiovascular events [1-3]. In addition, several studies have demonstrated an association between the volume or density of EAT and the risk of developing and maintaining atrial fibrillation (AF) [4, 5]. This association is thought to stem, on the one hand, from the capacity of EAT to produce a range of biologically active substances that contribute to "metabolic inflammation" and exert deleterious effects on myocardial tissue, and, on the other hand, from the ability of EAT to infiltrate and electrically uncouple myocardial fibres [4-6].

It has also been suggested that EAT exerts proarrhythmic effects through modulation of autonomic regulation of the heart. In particular, reduced heart rate variability and turbulence have been observed in patients with a higher EAT volume [7, 8]. At the same time, A.B. Romanov et al., using a novel scintigraphic technique, demonstrated a positive correlation between the volume of peri-atrial adipose tissue and sympathetic ganglionic activity in the atria [9]. A possible explanation for these findings lies in endogenous adipokine stimulation and increased catecholamine concentrations in both EAT and the peripheral blood of patients with AF. However, the exact mechanisms through which EAT influences myocardial function and contributes to AF pathogenesis remain unclear, warranting further investigation.

The aim of the present study was to evaluate the association between computed tomography (CT)-derived characteristics of epicardial adipose tissue (volume and density) and the concentrations of adipokines, proinflammatory cytokines, and catecholamines in the blood of patients with atrial fibrillation.

METHODS

A total of 32 patients (median age 58.5 [52.5; 64.0]; 18 men) with atrial fibrillation (AF) were prospectively enrolled in the study. These patients were undergoing evaluation at the Department of Surgical Treatment of Complex Cardiac Rhythm Disorders and Cardiac Pacing, and had been scheduled for radiofrequency catheter ablation (RFCA) for AF. The indications for RFCA were determined in accordance with current guidelines for the diagnosis and management of arrhythmias [10]. Prior to the intervention, all patients underwent a full standard clinical and instrumental evaluation, as well as multislice CT-CA tomography coronary angiography (MSCT-CA) to exclude obstructive atherosclerotic lesions of the coronary arteries.

Before performing MSCT-CA, blood samples were collected to determine the concentrations of adipose tissue-related hormones (adiponectin, leptin, resistin), proinflammatory cytokines (interleukins 1β, 6, and 8), and metanephrine.

Inclusion criteria for the study group were as follows:

- Age over 18 years, regardless of sex;
- AF refractory to antiarrhythmic drug therapy;
- Written informed consent to participate in the study.

Exclusion criteria included:

- History of myocardial revascularisation;
- Myocarditis or cardiomyopathies;
- Coronary artery stenosis >50%;
- Congenital or acquired heart defects;
- Chronic heart failure (NYHA class > II);
- Presence of thrombus in the left atrium or other heart chambers;
- Inability to undergo contrast-enhanced cardiac CT;
- Diabetes mellitus;
- Hyperthyroidism or hypothyroidism;
- Grade III or IV obesity;
- Grade III arterial hypertension;
- Presence of other arrhythmias (e.g., sick sinus syndrome, tachyarrhythmias, WPW syndrome).

The clinical characteristics of the study group are presented in Table 1.

In addition to the main study group, a control group was formed, consisting of 20 individuals without rhythm disturbances who underwent MSCT-CA to exclude coronary atherosclerosis.

Inclusion criteria for the control group:

- Age between 18 and 50 years;
- No signs of atherosclerotic coronary artery disease on MSCT-CA;
- Informed consent to participate in the study.

Exclusion criteria:

- History of cardiac rhythm or conduction disturbances, or other confirmed cardiovascular diseases;
- Body Mass Index (BMI) >28;
- Endocrine disorders.

All control group participants were invited for blood sampling three days after MSCT-CA. The clinical characteristics of the control group are provided in Table 2.

It is important to note that statistically significant differences in age and BMI were observed between the study and control groups ($p<0.05$). This precluded a meaningful statistical comparison of radiological parameters between the groups. However, due to the absence of established reference values for EAT volume and density, the control group data were used as approximate reference values.

MSCT-CA

At the time of the scan, all patients were in sinus rhythm with a heart rate of 50-65 beats per minute. MSCT-CA was performed using a 64-slice CT scanner (GE Discovery NM/CT 570c, GE Healthcare, Milwaukee, WI, USA) in accordance with the standard protocol outlined in the Recommendations for Coronary CT Angiography [11]. The study consisted of two scanning phases: a non-contrast phase (calcium scoring) and a contrast-enhanced phase. The acquired data was reconstructed and analyzed using the Advantage Workstation 4.6 (GE Healthcare).

EAT segmentation

EAT segmentation was conducted on the non-contrast ECG-synchronized 3D DICOM image series (calcium scoring phase), which were exported into the 3D Slicer software application (Boston, MA, USA) [12]. Segmentation of EAT (see Figure 1) was performed manually using a variable-sized tool across slices, within the adipose tissue density range from -190 to -30 Hounsfield Units (HU), from the bifurcation of the pulmonary trunk to the apex of the heart [13]. Using the SlicerRadiomics module (version 4.10.2), the total EAT

Table 1.
Clinical characteristics of patients with atrial fibrillation (n=32)

Indicator	Value
Age, years*	58.5 (52.5; 64.0)
Sex, male, n (%)	18 (56.3)
Body mass index*	29.0 (24.9; 33.1)
Disease duration, months*	24.0 (9.0; 60.0)
Hypertension, n (%)	28 (87.5)
Coronary atherosclerosis[#], n (%)	14 (43.8)
Ischaemic heart disease, n (%)	14 (43.8)
Diabetes mellitus, n (%)	6 (18.8)
Smoking, n (%)	8 (25.0)
Paroxysmal AF, n (%)	21 (65.6)
Non-paroxysmal[$] AF, n (%)	11 (34.4)
Chronic heart failure, n (%)	12 (37.5)
LV EF, %*	66.5 (64.0; 68.0)
LV end-diastolic volume, mL*	97.0 (88.5; 107.0)
LV end-systolic volume, mL*	33.5 (28.0; 38.0)
Left atrial volume, cm^3*	116 (94.7;138.0)

Note: here and below, * - data are presented as Me (Q1; Q3); n - number of patients; [#] - without significant luminal stenosis; AF - atrial fibrillatijn; LV - left ventricular; EF - ejection fraction; .

volume and mean EAT density within the segmented volume were calculated.

Laboratory methods

To assess biomarker concentrations, whole blood samples were collected from patients included in the study. Samples were centrifuged at 3,000 rpm to separate blood components and plasma. The plasma was then frozen and stored at -25 °C. After thawing, concentrations of omentin (RayBiotech, China), leptin (DBC, Canada), resistin (BioVendor, USA), adiponectin (BioVendor, USA), interleukins IL-1β, IL-6, IL-8 (Vector-BEST, Russia), and metanephrine (Labor Diagnostika Nord, Germany) were measured in the plasma using enzyme-linked immunosorbent assay (ELISA). Optical density measurements, calibration curve construction, quantitative analysis, and data processing were performed using the Infinite F50 microplate reader and Magellan Tracker software (Austria).

Statistical analysis

Statistical analysis was conducted using STATISTICA 12.0 (StatSoft Inc., Tulsa, OK, USA). The Shapiro-Wilk test was used to assess the normality of data distribution. For variables that did not follow a normal distribution, the results were expressed as median (Me) and interquartile ranges (25th and 75th percentiles). The Mann-Whitney U test was applied to assess the statistical significance of intergroup differences for independent samples. Correlation between quantitative and categorical variables was analysed using Spearman's rank correlation coefficient.

RESULTS

According to radiological assessment, patients with AF had a median EAT of 141.0 cm³ (IQR: 113.3-187.5) and a median EAT density of -81 HU (IQR: -88.5 to -75.5). In the control group, the EAT volume was significantly lower at 107.5 cm³ (IQR: 86.9-126.1; $p < 0.05$), while the EAT density was significantly higher at -74 HU (IQR: -78 to -73; $p < 0.05$) compared to the study group. However, these differences are likely attributable to substantial clinical and instrumental disparities between the groups, particularly in terms of age and BMI. Nevertheless, a negative correlation between EAT volume and density was identified in both groups ($r = -0.5$, $p < 0.05$).

Table 2.

Clinical characteristics of patients in the control group (n=20)

Indicator	Value
Sex male, n	15
Age, years*	33 (35; 40)
BMI*	24,1 (26,2; 27,5)
Pre-test probability of CAD, %*	8 (5; 12)

As shown in Table 3, patients with AF exhibited elevated levels of proinflammatory interleukins and plasma metanephrine. Leptin levels in the study group exceeded the reference range by 30%, while adiponectin concentrations were significantly lower than in the control group. In the AF group, EAT density showed a negative correlation with plasma metanephrine ($r = -0.4$) and leptin ($r = -0.4$), and a positive correlation with interleukin-8 concentration ($r = 0.36$) (see Table 4). No statistically significant correlations between EAT density and biomarkers were observed in the control group. Moreover, EAT volume was not associated with any of the studied biomarkers in either group.

When stratifying patients by AF subtype (persistent vs. paroxysmal), those with persistent AF exhibited significantly greater left atrial volumes (112.0 cm³ [IQR: 83.0-143.1] vs. 107.0 cm³ [IQR: 80.0-127.0]) and EAT volumes (147.4 cm³ [IQR: 110.4-214.8] vs. 144.8 cm³ [IQR: 110.4-196.0]). No significant differences were observed between subgroups in terms of EAT density or biomarker concentrations. Correlation analysis further revealed that AF duration was negatively associated with EAT density ($r = -0.42$, $p < 0.05$) and positively associated with plasma metanephrine levels ($r = 0.34$, $p < 0.05$).

DISCUSSION

To date, numerous studies, including meta-analyses, have demonstrated a direct association between EAT volume and the risk of AF, independent of BMI [6]. Several studies have shown that the volume of EAT and periatrial fat is associated with an increased risk of AF recurrence following RFCA [6]. Moreover, it has been demonstrated that patients with persistent AF have a larger volume of pericardial fat than those with paroxysmal AF [14, 15]. Our findings were consistent with these reports: EAT volume was significantly higher in the AF group compared to the control group, and among AF patients, those with persistent AF had greater EAT volume than those with paroxysmal AF.

In recent years, increasing attention has been paid to the radiological density of EAT [16, 17], which is believed

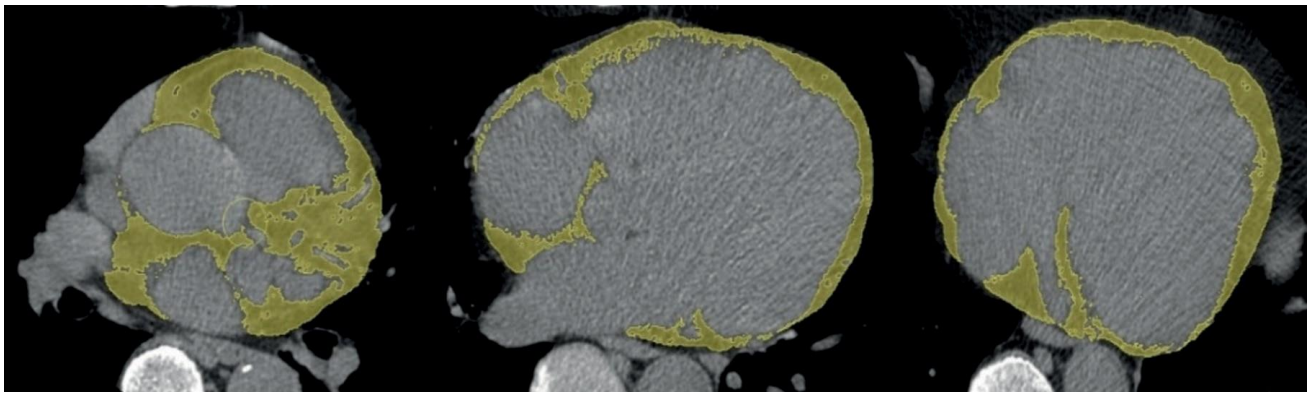

Figure 1. Segmentation of epicardial adipose tissue on non-contrast heart CT images (epicardial adipose tissue highlighted in yellow).

to reflect the structural and functional state of adipose tissue. A study by J.E. Lake et al. (2019) demonstrated that CT images of adipose tissue composed of larger adipocytes exhibit lower radiodensity compared to fat tissue composed of smaller, poorly differentiated adipocytes [18]. Other factors that influence this parameter include inflammation and subsequent fibrosis of the adipose tissue, which may lead to increased radiodensity [19].

Findings on EAT radiodensity in AF patients have varied across studies [14, 16, 17]. For instance, A.T. Huber et al. (2024) reported significantly lower EAT radiodensity in patients with persistent AF compared to those with paroxysmal AF [16]. Conversely, M. Nodera et al. (2024) found higher EAT radiodensity in AF patients compared to controls, which differs from our results [17]. Nevertheless, the latter study also identified a negative correlation between EAT volume and radiodensity, consistent with our data [17]. These discrepancies may be explained by differences in clinical and instrumental characteristics of the study populations, variations in the methodology for EAT measurement, and potential differences between total EAT density and periatrial fat density [17].

It is important to note that periatrial adipose tissue is in close anatomical proximity to the atrial myocardium and pulmonary vein ostia, making it particularly relevant for investigating both the mechanisms of arrhythmogenesis and predictors of post-ablation AF recurrence. It has been shown that the thickness and radiodensity of periatrial fat are more strongly associated with arrhythmia recurrence after catheter ablation than the same parameters measured in total EAT. However, given that the primary aim of our study was to assess the effects of circulating blood biomarkers, which act systemically, total EAT was chosen as the object of investigation.

Recent studies have demonstrated that local tissue-level proinflammatory and profibrotic cytokines and chemokines in EAT are associated with both EAT fibrosis and atrial myocardial fibrosis in AF patients [20]. In addition, certain circulating proinflammatory cytokines, such as interleukin-6, have been linked to myocardial inflammation and AF recurrence after RFA [21].

A number of other circulating biomarkers - including leptin, adiponectin, and resistin - have also been implicated in the development and maintenance of AF [22]. In this context, our findings of elevated circulating levels of proinflammatory cytokines and leptin, along with decreased adiponectin levels in AF patients compared to controls, are in full agreement with the existing literature.

To our knowledge, there are currently no published studies directly comparing EAT radiodensity with circulating biomarkers in patients with AF. However, the positive correlation identified in our study between EAT radiodensity and serum interleukin-8 levels aligns with previous findings demonstrating a positive association between inflammation and fibrosis within EAT and increased tissue radiodensity [20].

The observed inverse correlation between circulating leptin levels and EAT radiodensity in AF patients may be attributed to adipocyte hypertrophy and increased intracellular lipid droplet accumulation under conditions of hyperleptinaemia. However, a study by O.A. Koshelskaia et al. (2023) did not establish a link between serum leptin concentrations and adipocyte hypertrophy in histological EAT samples. This may be due to the fact that samples were collected from patients with advanced coronary atherosclerosis and markedly elevated baseline leptin levels [23].

It is well known that one of the central mechanisms in the pathogenesis and progression of AF is autonomic imbalance and sympathetic overactivity [7]. Several studies using myocardial scintigraphy with ^123I-metaiodobenzylguanidine have demonstrated that increased sympathetic nervous system activity is associated with a higher risk of AF recurrence after RFA [24-26]. In the study by F. Polat and A.L. Ko (2023), urinary metanephrine levels were significantly higher in patients with AF compared to controls [27]. Similarly, our study showed higher circulating metanephrine concentrations in AF patients than in those without arrhythmia. Moreover, we observed a positive correlation between metanephrine levels and arrhythmia duration, and a negative correlation between metanephrine levels and EAT

Table 3.

Blood biomarkers in patients with atrial fibrillation and in the control group

Indicator	AF group (n=32)	Control (n=20)	p-value
Leptin (ng/mL)	14.18 (4.69; 24.31)	Норма менее 11.1	<0.05
Resistin (ng/mL)	3.75 (3.15; 4.55)	3.62 (3.12; 4.25)	ns
Adiponectin (μg/mL)	5.29 (3.79; 8.76)	11.59 (10.63; 13.21)	<0.05
Interleukin-6 (pg/mL)	1.99 (1.64; 2.49)	1.50 (0.45; 1.91)	<0.05
Interleukin-1β (pg/mL)	2.20(1.57; 2.96)	1.80 (0.95; 2.19)	<0.05
Interleukin-8 (pg/mL)	3.94 (3.5; 6.91)	3.38 (2.45; 4.10)	<0.05
Metanephrine (pg/mL)	28.8 (21.44; 49.3)	18.75 (9.9; 20.74)	<0.05

Note: Here and below: ns - no statistically significant differences.

Table 4.

Correlations between radiological characteristics of epicardial adipose tissue and blood biomarkers in patients with atrial fibrillation

Biomarker	EAT Volume	p-value	EAT Density	p-value
Leptin (ng/mL)	0.33	ns	-0.4	<0.05
Resistin (ng/mL)	-0.01	ns	0.2	ns
Adiponectin (μg/mL)	0.13	ns	0.06	ns
Interleukin-6 (pg/mL)	-0.01	ns	0.25	ns
Interleukin-1β (pg/mL)	-0.16	ns	-0.06	ns
Interleukin-8 (pg/mL)	-0.3	ns	0.36	<0.05
Metanephrine (pg/mL)	-0.01	ns	-0.4	<0.05

Note: EAT - epicardial adipose tissue.

radiodensity. A plausible pathophysiological explanation may involve increased adrenergic activation of ganglionated plexi embedded in EAT, potentially due to elevated catecholamine content in hypertrophied fat tissue or alterations in calcium ion flux [28, 29]. An additional mechanism of systemic sympathetic activation in our AF cohort may be hyperleptinaemia [30], which also demonstrated a negative association with EAT radiodensity.

Study limitations

This study has several limitations. First, the relatively small sample size may affect the generalisability of our findings. Second, the inclusion of a few patients with diabetes mellitus may have influenced results. However, we were unable to identify any reports in the available literature specifically addressing the impact of diabetes on EAT radiodensity.

CONCLUSION

The results of this study demonstrated an association between the radiodensity of epicardial adipose tissue and serum concentrations of leptin, interleukin-8, and metanephrine in patients with AF. These findings are consistent with previous hypotheses suggesting that EAT may exert an activating effect on the sympathetic ganglia located within it and may also contribute to the systemic inflammatory response characteristic of this arrhythmia. Given that cardiac CT is a widely available and accurate imaging modality routinely performed in patients with cardiovascular disease, radiological parameters of EAT - such as its volume and density - appear to be promising tools for risk stratification in AF patients prior to catheter ablation.

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