ОРИГИНАЛЬНАЯ СТАТЬЯ

CARDIAC CT-BASED ASSESSMENT OF EPICARDIAL ADIPOSE TISSUE DISTRIBUTION AND VOLUME IN PATIENTS WITH ATRIAL FIBRILLATION IN COMPARISON WITH HEALTHY INDIVIDUALS

Nikitin N., Minin S., Losik D., Mikheenko I., Romanov A.

Meshalkin National Medical Research Center. Novosibirsk, Russia.

The association between the presence of atrial fibrillation (AF) and an increased epicardial adipose tissue (EAT) volume has been established, linking a certain amount of probable and possible pathophysiologic mechanisms that could contribute to promoting arrhythmogenesis. In the present study, we aimed to assess the reliability of EAT volume measurements on cardiac CT with adjusted thresholds for fat detection and analyze the association of EAT distribution and volume with the clinical presentation in AF patients in comparison with healthy individuals.
Materials and methods. 45 consecutive AF patients (mean age 55.2 ± 10.3 years, mean AF duration 49.0 ± 38.4 months) with different AF patterns scheduled for an initial ablation for AF and 15 healthy individuals (mean age 36.2 ± 12.6 years) without a history or symptoms of cardiovascular diseases were included. The total, as well as periatrial EAT volumes, were obtained on cardiac CT datasets with adjusted thresholds for fat detection.

Results. The mean difference (95% CI) of total EAT between healthy individuals and AF patients were 103 ml (74, 132 ml; p<0.01) and 33.6 ml (24.8, 42.4 ml; p<0.01) for periatrial EAT. Patients with persistent AF had slightly more total EAT volume but did not significantly differ from patients with paroxysmal AF or long-standing persistent AF.

Conclusion. Cardiac CT allows to reliably quantify the volume of EAT. Patients with AF have significantly large EAT volumes compared to individuals without a history of cardiovascular diseases. There is no significant difference in EAT volumes and distribution between patients with different patterns of AF.

Keywords: epicardial adipose tissue, epicardial fat, atrial fibrillation, healthy individuals, computed tomography.

Corresponding author: Nikita Nikitin, e-mail; n_nikitin@outlook.com

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ОЦЕНКА РАСПРЕДЕЛЕНИЯ И ОБЪЕМА ЭПИКАРДИАЛЬНОЙ ЖИРОВОЙ ТКАНИ У БОЛЬНЫХ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ ПО СРАВНЕНИЮ СО ЗДОРОВЫМИ ЛИЦАМИ НА ОСНОВЕ ДАННЫХ КТ СЕРДЦА

Никитин Н., Минин С., Лосик Д., Михеенко И., Романов А.

ФГБУ Национальный медицинский исследовательский центр им. Мешалкина. г. Новосибирск, Россия.

Цель исследования. Была установлена связь между наличием фибрилляции предсердий (AF) и увеличением объема эпикардиальной жировой ткани (EAT), учитывая определенное количество вероятных и возможных патофизиологических механизмов, которые могут способствовать развитию аритмий. Целью настоящего исследования являлась оценка достоверности измерений объема EAT при КТ сердца с откорректированными порогами обнаружения жировой ткани и анализ связи распределения и объема EAT с клиническими проявлениями у пациентов с фибрилляцией предсердий по сравнению со здоровыми людьми.

Материалы и методы. В исследование были включены 45 пациентов с фибрилляцией предсердий (средний возраст 55,2 ± 10,3 лет, средняя продолжительность фибрилляции предсердий 49,0 ± 38,4 месяцев) с различными её типами, запланированными для первоначальной аблации, и 15 здоровых добровольцев (средний возраст 36,2 ± 12,6 лет) без симптомов сердечно-сосудистых заболеваний на момент исследования или в анамнезе. Общий объем эпикардиальной жировой ткани, а также объем жировой ткани в области предсердий был получен при обработке данных КТ сердца с откорректированными пороговыми значениями для обнаружения жировой ткани.

Результаты. Средняя разница (95% CI) общего объема эпикардиальной жировой ткани между здоровыми людьми и пациентами с фибрилляцией предсердий составляла 103 мл (74, 132 мл; р <0,01) и 33,6 мл (24,8, 42,4 мл; р <0,01) для жировой ткани в области предсердий. Пациенты с персистирующей фибрилляцией предсердий имели немного больший общий объем эпикардиальной жировой ткани, но существенно не отличались от пациентов с пароксизмальной фибрилляцией предсердий или длительно стойкой фибрилляцией предсердий.

Вывод. КТ сердца позволяет достоверно количественно оценить объем эпикардиальной жировой ткани. Пациенты с фибрилляцией предсердий имеют значительно больший объем эпикардиальной жировой ткани по сравнению с людьми без сердечно-сосудистых заболеваний в анамнезе. Нет существенной разницы в объемах и распределении эпикардиальной жировой ткани между пациентами с разными типами фибрилляцией предсердий.

Ключевые слова: эпикардиальная жировая ткань, эпикардиальный жир, фибрилляция предсердий, здоровые люди, компьютерная томография.

Контактный автор: Никитин Н., e-mail: n_nikitin@outlook.com

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Atrial fibrillation (AF) is the most common, sustained arrhythmia diagnosed in clinical practice. It has been proved that AF is associated with a 1.5-2-fold increased risk of mortality and development of major cardiovascular events, which makes it necessary to carry out a whole range of therapeutic and cost-effective measures in each case of the disease [1].

It seems very important to timely correct modifiable risk factors associated with AF. Excessive body weight and obesity are increasingly recognized as a major modifiable determinant of AF [2]. Although body mass index and other clinical measures are useful indications of general adiposity, much recent interest has focused on epicardial adipose tissue (EAT), a distinct adipose tissue depot that can be readily assessed using non-invasive imaging techniques. The association between the presence of AF and an increased EAT volume has been established, linking a certain amount of probable and possible pathophysiologic mechanisms that could contribute to promoting arrhythmogenesis [3]. EAT has been also associated with AF recurrence in patients undergoing AF ablation [4]. Therefore, it seems reasonable to assume that EAT may subsequently become a new target and prognostic factor AF therapy, which will require an accurate and robust assessment of.

According to recent meta-analysis which analyzed the relationship between AF and EAT it has been shown that there is a relevant heterogeneity among studies in EAT volume measurements, which could be affected by acquisition and quantification parameters [5, 6]. For instance, it was demonstrated that there is an overestimation of EAT volume on non-contrast CT as well as using identical thresholds for EAT volume quantification on contrast-enhanced CT that led to an underestimation of EAT volume.

In the present study, we aimed to assess EAT volumes on cardiac CT datasets, which is the most commonly used in routine clinical practice before ablation procedure of AF patients, with adjusted thresholds for fat detection. Additionally, we analyzed the association of EAT distribution and volume with the clinical presentation in AF patients in comparison with healthy individuals.

Materials and Methods.

This was a single-center, observational study. The study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki and was approved by the Local Ethics Committee of Meshalkin National Medical Research Center. All patients and healthy individuals signed informed consent.

Patient Selection.

The study included 2 groups of subjects.

First group – 45 consecutive AF patients scheduled for an initial ablation for AF at our hospital.

The main inclusion criteria for AF patients were documented, symptomatic, drug resistant AF and indications for CA according consensus statement [8]. In the AF group, 15 patients had paroxysmal AF (PAF), 15 had persistent AF (PersAF) and 15 had long-standing persistent AF (LSPers AF). The burden of pre-existing AF was classified at the time of the index ablation procedure [3 categories: paroxysmal (at least 1 day of AF but <7 consecutive days of AF), persistent (at least 7 consecutive days with >23 h of AF, but less than 12 months) or long-standing persistent (>12 months of AF)]. The duration of AF was calculated in months since symptoms onset till operation.

In the healthy individuals group were enrolled 15 men and women, who were subjected to coronary angiography CT due to suspected coronary artery regression. Inclusion criteria were healthy men or women aged 18-75 years without history of heart disease. Exclusion criteria included any history of heart disease, hypertension, diabetes, chronic kidney disease, neuropathy and any contraindication to iodinated contrast media.

Body mass index (BMI) was calculated for each patient using their documented height and weight at the time of the imaging using the Mosteller formula. 20 subjects were randomly selected for use in the intraobserver analysis.

Cardiac CT acquisition.

CT data acquisition was performed using a 320-row detector CT system. Images were acquired in volume acquisition mode with 120 kV tube voltage, 0.35-second gantry rotation time and tube current from 40 to 580 mAs based on automatic tube current modulation. Iodinated contrast medium with a 350 mgI/ml iodine concentration was injected in an antecubital vein using the biphasic protocol (70-85 ml contrast agent followed by a 30-35 ml mixture consisting of 30% contrast agent and 70% normal saline respectively) at 5-6 ml/s rate. A prospectively ECG-triggered scan mode was applied when the heart rate was <65 bpm. All cardiac CT data sets were reconstructed in the mid-diastolic phase (70-80% R-R interval) with a section thickness of 1.0 mm (reconstruction increment, 1.0 mm) using an iterative reconstruction algorithm.

Quantification of epicardial adipose tissue volume.

Epicardial adipose tissue (EAT) volume measurements were performed on a dedicated workstation (GE Advantage 4.7) by a single observer with 5 years of experience in cardiac CT blinded to clinical data. EAT was defined as the fat between the visceral layer of the pericardium and the surface of the heart [7]. EAT was separated from pericardial fat by manually tracing pericardial contour every 5-10 slices below the start point and software automatically tracing out the segments in between selected slices (Fig. 1A). The start point for pericardial tracing was set at the bifurcation of the pulmonary trunk and the inferior point at the end of the pericardial sac. Adipose tissue voxels within the traced areas were identified using a threshold attenuation range from –190 to 0 Hounsfield units (HU) according to a previously published study [6]. The voxels in each slice were summed to determine the total EAT volume. Thereafter, the periatrial EAT volume was manually segmented from the total EAT, that was obtained by deleting EAT volume off the left ventricular side anterior to the mitral annulus and the right atrial side anterior to the right superior PV, and then from the lower side of the coronary sinus from the total EAT, leaving the EAT surrounding the LA (Fig. 1B) [8]. The periatrial to total EAT volume ratio (P/T) as well as total and periatrial EAT volumes indexed to body mass index (BMI) were obtained. As for the reproducibility of the total and periatrial EAT volumes measurements the intraobserver correlations were calculated.

Statistics.

Descriptive statistics are presented as median [interquartile range] for continuous variables and frequencies and percentages for categorical variables. Continuous variables between groups were assessed and compared using the Kruskal–Wallis test (in case of more than two groups) and by the T-test in the case of two groups. Intraobserver measurements were calculated with intra-

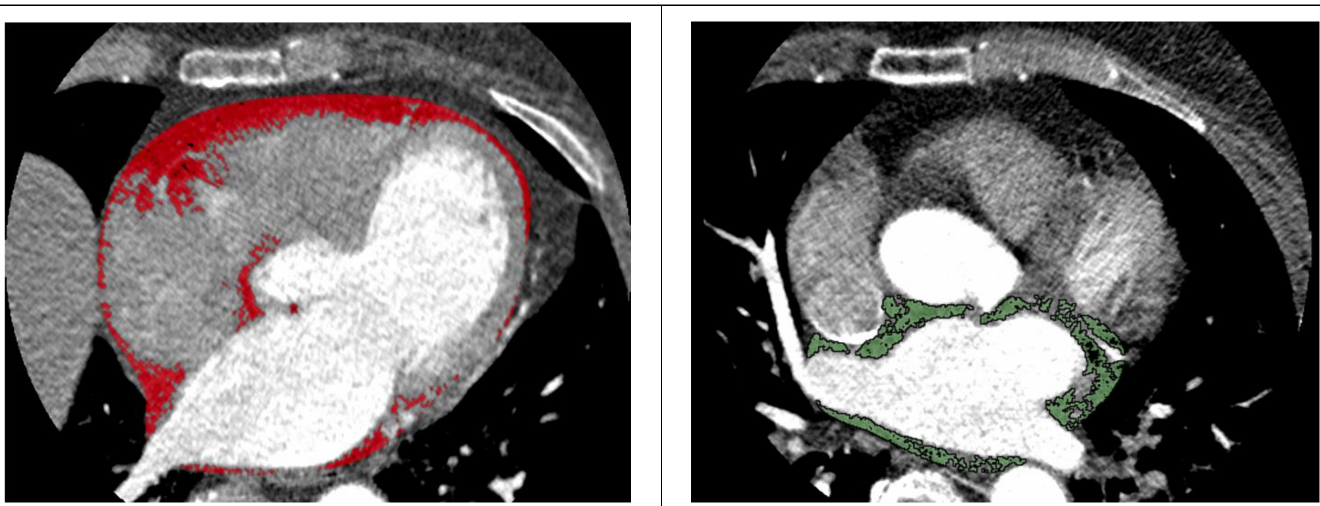

Fig. 1 a (Рис. 1 а) | Fig. 1 b (Рис. 1 б)

Fig. 1. CT.

Example of computed tomography slices depicting tracing areas of epicardial adipose tissue (EAT) depositions. Total EAT (A, shaded in red) and periatrial EAT (B, shaded in green).

Рис. 1. КТ.

Примеры компьютерных томограмм, демонстрирующих области отложения эпикардиальной жировой ткани (EAT). Общий объём эпикардиальной жировой ткани (A, заштрихован красным) и эпикардиальной жировой ткани в области предсердия (B, заштрихован зеленым).

class correlation coefficients (ICC) with a confidence interval of 95 %. All analyses were done using R (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). All p-values were based on a two-sided test and a p-value <0.05 was considered statistically significant.

Results.

The main characteristics of the study participants are presented in Table 1. Patients with AF were older, had higher BMI and higher values for most other cardiovascular risk factors in comparison with healthy individuals.

In comparison between groups of patients with different AF patterns, there were no significant differences in clinical variables (Table 2). Notably, there is no significant difference in duration of AF between patients' groups. Herewith, patients with PersAF had slightly more total EAT volume but did not significantly differ from patients with PAF or LSPers AF (Fig. 2).

Healthy individuals had significantly lower total and periatrial EAT volumes compared with AF patients. The mean difference (95% CI) of total EAT between healthy individuals and AF patients were 103 ml (74, 132 ml; p<0.01) and 33.6 ml (24.8, 42.4 ml; p<0.01) for periatrial EAT.

The intraobserver measurements for total EAT volume and periatrial EAT volume were highly reliable (ICC = 0.96, p<0.01 and 0.89, p<0.01, respectively).

The calculation of P/T EAT ratio, as well as indexation of total and periatrial, EAT volumes to BMI did not add any extra information in our research tasks.

Discussion.

The present study has found that there are not any significant differences in EAT volume and distribution between patients with different patterns of AF and comparable AF duration. In addition, we confirmed a known fact that patients with AF have significantly large EAT volume compared to individuals without a history of cardiovascular diseases. Further, we showed that the estimation of the total, as well as periatrial, EAT volumes using cardiac CT images and adjusted thresholds for fat detection is highly reliable.

For many years, AF is still the main heart rhythm disorder with an increasing number of patients due to population ageing. In the past 10 years, there has been an increased interest in EAT and its supposed role in the development of cardiovascular diseases. It was hypothesized that EAT plays an important role in the pathophysiology and natural history of AF. Previous studies have shown strong relationships between EAT volume and AF, in particular, the association of EAT volume with increased risk of AF as well as with AF recurrence after ablation [4, 9]. Consequently, that relationship between EAT and AF development should be inferred from a number of proposed pathophysiological mechanisms.

EAT may lead to AF via structural and elec-

Table №1. Characteristics of study participants.

Variable	Healthy Individuals (n = 15)	AF Patients (n = 45)	p-value
Age (years)	36.2 ± 12.6	55.2 ± 10.3	<0.001
Gender (% male)	8 (53.3)	25 (55.5)	0.881
BMI (kg/m^2)	24.1 ± 2.9	31.3 ± 4.7	<0.001
Smokers, n (%)	4 (26.7)	0 (0)	<0.001
Hypertension, n (%)	0 (0)	32 (71.1)	<0.001
Diabetes, n (%)	0 (0)	5 (11.1)	0.178
Cardiac CT			
Total EAT, ml	68.7 ± 22.7	171.8 ± 54.2	<0.001
Periatrial EAT, ml	17.3 ± 5.3	50.9 ± 16.6	<0.001
P/T EAT ratio, %	25.6 ± 4.4	30.0 ± 6.0	0.012
BMI indexed total EAT	2.81 ± 0.68	5.56 ± 1.68	<0.001
BMI indexed periatrial EAT	0.71 ± 0.16	1.65 ± 0.53	<0.001

AF – atrial fibrillation, BMI – body mass index, EAT – epicardial adipose tissue, P/T – periatrial-to-total EAT volumes ratio.

trical remodeling of the atria by both direct (e.g. by the infiltration of adipose tissue leading to altered atrial electrophysiological properties) and indirect mechanisms (e.g. by acting as a source for paracrine modulators of myocardial inflammation and oxidative stress) [3]. Also, it was demonstrated that EAT has a close relationship with cardiac autonomic nervous system functioning, directly modulating cardiac electrophysiological properties and is the target of exposure for the treatment of AF [10, 11].

The results of our study are in line with findings of Greif et al. who also demonstrated in their large cohort (943 patients with sinus rhythm and 354 patients with AF) that patients without a history of AF had significantly lower mean EAT volumes compared to patients with AF [12]. However, according to comparison with their data, it seems that there is a substantial underestimation of total EAT volume in our study. One reason for this observation could be the discrepancy in EAT quantification methods. This fact is confirmed by a recent meta-analysis which showed a relevant heterogeneity in EAT volume among studies [5, 6]. The study results of Marwan et al. apparently demonstrated the influence of acquisition parameters and contrast enhancement on EAT volume quantification. It has been shown that there is a systematic overestimation of EAT volume in non-contrast data sets if a low-voltage acquisition protocol was performed and the upper threshold for fat detection was not adjusted. Moreover, it was found that quantification of EAT volume in contrast-enhanced data sets underestimates EAT volume compared to non-contrast scans. As a result, for a good accuracy for CT based assessment of EAT volume, Marwan et al. recommended using an upper threshold of -40 HU for 100 kV non-contrast images and 0 HU for contrast-enhanced data sets. It should be noted that the mean total

Table №2. Characteristics of study subjects stratified by the atrial fibrillation pattern.
Characteristics of study subjects stratified by the atrial fibrillation pattern.

Variable	All AF patients (n = 45)	PAF (n = 15)	PersAF (n = 15)	LSPersAF (n = 15)	p-value
N	45	15	15	15	NA
Age (years)	55.2 ± 10.3	57.5 ± 11.6	55.7 ± 8.8	52.5 ± 10.3	0.45
Gender, n (% male)	25 (55.6)	6 (40)	10 (66.7)	9 (60)	0.34
BMI (kg/m^2)	31.3 ± 4.7	31.6 ± 4.1	31.8 ± 4.9	30.5 ± 5.2	0.74
Smokers, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Hypertension, n (%)	32 (71)	11 (73.3)	12 (80)	9 (60)	0.51
Diabetes, n (%)	5 (11)	2 (13.3)	1 (6.7)	2 (13.3)	0.78
AF duration, month	49.0 ± 38.4	63.9 ± 45.4	36.2 ± 18.4	46.7 ± 42.7	0.10
EAT					
Total EAT, ml	172 ± 54.2	159.6 ± 42.2	187.6 ± 62.1	168.2 ± 56.3	0.37
Periatrial EAT, ml	50.9 ± 16.6	45.5 ± 11.8	54.3 ± 17.7	52.8 ± 19.3	0.23
P/T EAT ratio, %	30.0 ± 6.1	29.2 ± 6.7	29.3 ± 4.9	31.5 ± 6.5	0.54
BMI indexed total EAT	5.56 ± 1.68	5.07 ± 1.24	5.98 ± 1.78	5.63 ± 1.94	0.27
BMI indexed periatrial EAT	1.65 ± 0.54	1.45 ± 0.37	1.75 ± 0.59	1.76 ± 0.59	0.13

AF – atrial fibrillation, PAF – paroxysmal atrial fibrillation, PersAF – persistent atrial fibrillation, LSPersAF – longstanding persistent atrial fibrillation, BMI – body mass index, EAT – epicardial adipose tissue, P/T – periatrial-to-total EAT volumes ratio.

EAT volume in our study subjects was comparable to data of Marwan's study, which was calculated with the same acquisition parameters and thresholds settings. This observation again confirms the need to use a standardized methodology of EAT volume calculation in order to increase the reproducibility of results and application in clinical trials.

The present study did not demonstrate the significant difference in total EAT volume as well as in periatrial EAT volume between patients with different patterns of AF. One reason for this is a small sample size of study participants. Another explanation has to be found into the intrinsic limitation of AF classification. Despite the difference in AF burden, there was no significant difference in AF duration between patients with different patterns of AF.

Besides that, all groups of patients with different patterns of AF were overweight mostly and did not differ significantly in BMI. This fact also supports the absence of significant differences in BMI-indexed fat volumes.

We found a slight increase in the volume of EAT in patients with PersAF compared to patients with both PAF and LSPersAF. Herewith in a recent

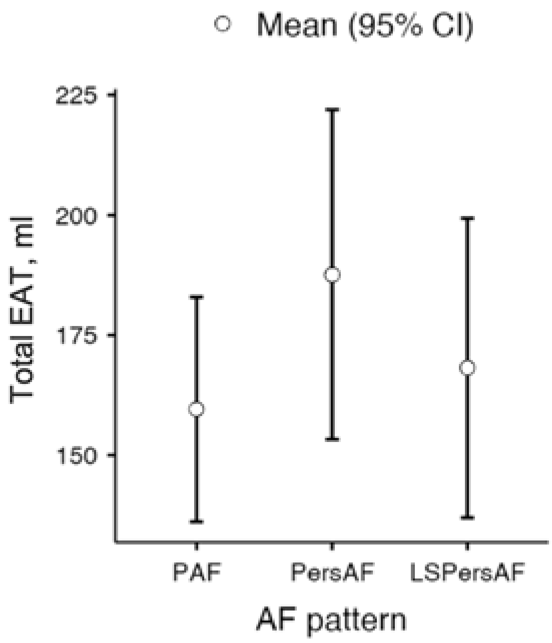

Fig. 2 a (Рис. 2 а)

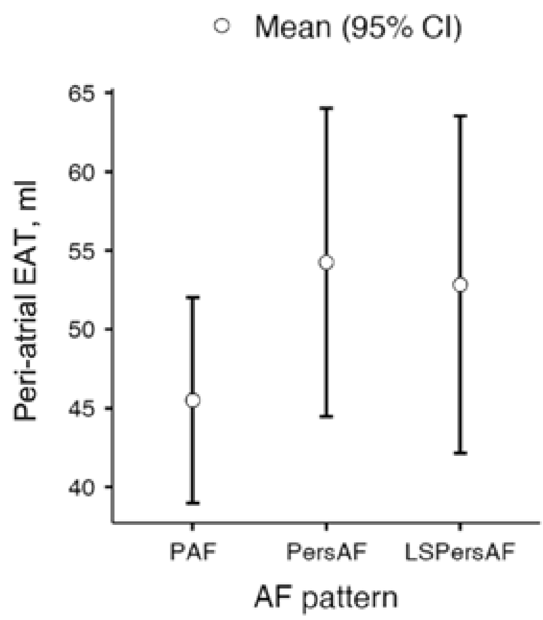

Fig. 2 b (Рис. 2 б)

Fig. 2. Diagrams.

a – Comparison of the mean total EAT volume between groups of patients with different patterns of AF.

b – Comparison of the mean periatrial EAT volume between groups of patients with different patterns of AF. AF – atrial fibrillation, PAF – paroxysmal atrial fibrillation, PersAF – persistent atrial fibrillation, LSPersAF – longstanding persistent atrial fibrillation, EAT – epicardial adipose tissue.

Рис. 2. Диаграммы.

а – Сравнение среднего общего объема эпикардиальной жировой ткани между группами пациентов с различными типами фибрилляции предсердий.

б – Сравнение среднего объема эпикардиальной жировой ткани в области предсердий между группами пациентов с различными типами фибрилляции предсердий. AF - фибрилляция предсердий, PAF - пароксизмальная фибрилляция предсердий, PersAF - стойкая фибрилляция предсердий, LSPersAF – длительная стойкая фибрилляция предсердий, EAT – эпикардиальная жировая ткань.

meta-analysis [5, 9] it has been found that there is the strongest EAT-AF relationship in patients with PersAF who showed an increased amount of EAT with respect to patients with PAF. The pathophysiological hypothesis reflects the reduced role of EAT in those patients with auto-limiting AF where triggers (gastro-oesophagal reflux and vagal hyper tone) plays a major role compared with modulators. Other explanations of that observation could be linked with cardiac autonomic nervous system (CANS) properties. In particular, ganglionated plexi are embedded within EAT, causing both parasympathetic and sympathetic stimulation and resulting in modulation of cardiac electrophysiological processes. It has been demonstrated that there are differences between patients with PAF and PersAF in sympathetic branch activity of CANS [13]. Thus, it becomes appropriate to assess the relationship between EAT and CANS in patients with AF.

Conclusion.

Cardiac CT allows to reliably quantify the volume as well as assess the distribution of EAT. Patients with AF have significantly large EAT volumes compared to individuals without a history of cardiovascular diseases. There is no significant difference in EAT volumes and distribution between patients with different patterns of AF.

Declarations.

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Conflicts of interest/Competing interests. The authors declare that they have no conflict of interest.

Availability of data and material. The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics approval. The study protocol was approved by the Local Medical Ethics Committee. Written informed consent, according to the declaration of Helsinki, was obtained from all participants.

Study Limitation.

The primary limitation of the present study is the relatively small number of subjects included, which might have influenced the statistical analysis. Another limitation that should be noted the difference in BMI between patients and patients with AF which could have influenced the difference in EAT volumes.

Consent for publication. Consent for publication of results was obtained through the informed consent form which was signed by each subject before any trial-related procedures were performed.

Authors' contributions.

The study design was set up by SM, DL and AR. Data collection and interpretation study was carried out by NN, SM and IM. AR was the principal investigator of this study. All authors read and approved the final manuscript.

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