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Role of epicardial adipose tissue in the development of atrial fibrillation in hypertensive patients

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Obesity is a progressing epidemic, the prevalence of which has doubled over the past 30 years. The distribution of adipose tissue is an important factor in predicting the risk of cardiovascular events. The most significant inflammatory activity is characteristic of epicardial adipose tissue (EAT), the role of which in the development of atrial fibrillation (AF) remains a subject of discussion.

Aim. To study the effect of EAT size on the development of AF in hypertensive (HTN) patients.

Material and methods. The study included 95 patients with HTN aged 38-72 years (mean age, 61,5±1,8 years), including 45 patients with paroxysmal AF (group I) and 50 patients in the comparison group (group II). In order to assess the severity of visceral obesity, all patients underwent a general examination and echocardiography. To determine the EAT volume, cardiac multislice computed tomography was performed.

Results. Echocardiography revealed that the EAT thickness was significantly greater in hypertensive patients with paroxysmal AF than in the comparison group: 11,6±0,8 and 8,6±0,4 mm, respectively (p<0,001). According to cardiac multislice computed tomography, a significant increase in EAT volume was revealed in patients of group I (4,6±0,4 ml) compared with group II (3,5±0,25 ml) (p=0,019). In hypertensive patients with paroxysmal AF, a positive moderate relationship between the EAT volume and left atrial volume was revealed (r=0,7, p=0,022). Multivariate analysis showed that in hypertensive patients, EAT thickness >10 mm and volume >6 ml can serve as integral markers of the onset of paroxysmal AF.

Conclusion. Integral markers of AF in hypertensive patients are an increase in the EAT thickness >10 mm (odds ratio, 4,1; 95% confidence interval, 1,1-5,6) and volume >6 ml (odds ratio 3,7; 95%, confidence interval 1,0-4,2).

Key words: obesity, atrial fibrillation, epicardial adipose tissue, predictors.

Relationships and Activities: none.

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Obesity is a growing epidemic, the overall prevalence of which has doubled over the past 30 years. In Russia, more than 24% of the population is overweight [1]. The modern lifestyle provokes changes in the work and rest schedule, nutrition, and physical activity, therefore obesity and overweight can be considered problems of modern times [2].

It has been proven that obesity is an independent risk factor for the development of hypertension (HTN), diabetes, coronary artery disease (CAD), and heart failure (HF). The role of obesity in the development of atrial fibrillation (AF) is discussed [3]. Several influence mechanisms of excess body weight on the development of arrhythmias are described in modern studies: activation of sympathoadrenal system, renin-angiotensin-aldosterone system hyperactivity, development of HTN, insulin resistance, lipid metabolism disorders, and systemic inflammation [4, 5].

Concomitant cardiovascular disease in obese patients increases the likelihood of the development and progression of cardiac arrhythmias. The first place among the causes of AF is held by hypertension, which is diagnosed in 30% of patients with various arrhythmias. The mechanisms leading to the AF associated with HTN include the occurrence of atrial triggered activity, structural and electrical atrial remodeling, and systemic inflammation.

The distribution of adipose tissue is an important factor in predicting the risk of cardiovascular events. In contrast to subcutaneous fat, which accounts for up to 75% of the total-body adipose tissue, visceral fat is considered as a hormone-producing tissue [6]. The most significant inflammatory activity is observed in epicardial adipose tissue (EAT), which surrounds the myocardium, is located between the epicardium and the visceral pericardial layer, and is close to the myocardium. The functions of EAT include lipid accumulation, thermoregulation, and protection of the autonomic cardiac ganglia.

One of the largest studies that examined the effect of visceral adipose tissue on the development of

arrhythmias was the meta-analysis by Shamloo AS, et al. [7]. The authors have shown that the prevalence of visceral obesity is higher in patients with AF compared to patients without arrhythmias [7]. Similar results were obtained in the study by Zhu YM, et al. [8]. EAT secretes some biologically active substances that contribute to an increase in fatty infiltration of atrial myocardium and an increase in fibrotic activity.

At the same time, there are data not only on the damaging, but also on the cardioprotective function of EAT, which was demonstrated in the study [9]. The authors showed that in EAT and visceral fat, as compared to subcutaneous fat, the expression of three genes encoding enzymes of arachidonic acid metabolism is increased: the *PTDS* gene encoding prostaglandin D2, which has vasodilator and anticoagulant effects and is involved in the plaque stabilization, as well as *NMB* and *ACL1* genes, responsible for the incorporation of arachidonic acid within membrane phospholipids and its turnover [9].

Thus, the role of EAT in AF development remains a matter in dispute. In the modern medical literature, there are practically no works devoted to the EAT role in AF development in patients with HTN.

The aim was to study the effect of EAT size on the development of AF in hypertensive patients.

Material and methods

The study included 95 patients with HTN aged 38-72 years (mean age, 61,5±1,8 years), including 45 patients with paroxysmal AF (group I) and 50 patients of the comparison group (group II). The clinical characteristics of the patients are presented in Table 1.

The inclusion criterion in group I (n=45) was the documented paroxysmal AF in HTN patients, confirmed by electrocardiography (ECG) or 24-hpur Holter monitoring. The comparison group consisted of 50 hypertensive patients without cardiac arrhythmias.

Table 1

Clinical characteristics of patients in groups I and II

	Group I	Group II	p
Number of patients, n	45	50	ns
Mean age, years	60,0±1,8	54,91±2,5	ns
Females, n (%)	22 (49%)	24 (48%)	ns
Males, n (%)	23 (51%)	26 (52%)	ns
HTN, n (%)	45 (100%)	50 (100%)	ns
Grade I, n (%)	8 (17,8%)	13 (26%)	ns
Grade II, n (%)	7 (15,6%)	10 (20%)	ns
Grade III, n (%)	30 (66,6%)	27 (54%)	ns
Duration of hypertension, years	16,5±1,4	12,6±1,4	ns
Obesity, n (%)	45 (100%)	50 (100%)	ns
Class I, n (%)	21 (46,7%)	25 (50%)	ns
Class II, n (%)	15 (33,3%)	15 (30%)	ns
Class III, n (%)	9 (20%)	10 (20%)	ns

Note: ns — not significant.

There were following exclusion criteria: secondary HTN; class I-IV angina of effort; prior myocardial infarction or cerebral stroke; acute coronary syndrome; class III-IV HF; inflammatory heart disease; heart defects; severe disease of kidneys, liver, lungs; anemia; cancer; pregnancy; mental illness.

All patients signed informed consent. The study was approved by the local ethics committee (protocol № 10-19 dated July 17, 2019).

The studied groups were comparable in sex, age, prevalence of obesity, and HTN duration. The duration of AF in patients of group I was 5,9±1,1 years. The incidence of AF episodes was 2,4±0,9 episodes per month.

One of the most important prognosis indicators in patients with AF is the risk assessment of stroke and thromboembolic events using the CHA_2DS_2VASc score (Congestive Heart failure, Hypertension, Age (2 ball), Diabetes mellitus, Stroke (2 ball), Vascular disease, Age, Sex category) and bleeding using the HAS-BLED score (Hypertension, Abnormal renal-liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (65 years), Drugs or alcohol concomitantly). In patients with paroxysmal AF and HTN, the mean CHA_2DS_2VASc and HAS-BLED scores were 2,2±0,4 and 1,6±0,3, respectively.

In order to assess the severity of visceral obesity, all patients underwent a general clinical examination with an anthropometric assessment: body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), sagittal abdominal diameter (SAD).

The structural and functional myocardial state was assessed by echocardiography using a Siemens ultrasound system (Germany). EAT thickness was assessed in the parasternal long axis view.

To determine the volume of EAT, cardiac multislice computed tomography (MSCT) was performed using a Toshiba Aquillion 640 scanner (Japan). We received 5 slices with a thickness of 0,5 cm and radio signal range from -150 to -70 Hounsfield units (HU), starting from the base of the heart at tracheal bifurcation level and ending with the apex of the heart above the diaphragm. After calculating the volume of each of the five slices, the values were summed up. The obtained images were processed on a Toshiba Aquillion 640 workstation.

Statistical processing was carried out using the SPSS 23.0 program. The results were described using the arithmetic mean (M) and standard deviation (σ). Statistical analysis was performed using the nonparametric Mann-Whitney test. Correlation analysis was carried out using Pearson's correlation test. The influence of quantitative traits on AF development was assessed by the Cox linear regression. The differences were considered significant at $p<0,05$.

Results

There were no significant differences in BMI and SAD between hypertensive patients with paroxysmal AF and those without cardiac arrhythmias. The mean BMI was 31,97±1,67 and 34,43±1,2 kg/m^2, respectively. Significant differences were found in WC and WHtR: in the group of obese patients with AF, the WC was 118,9±3,3 cm, while in patients without arrhythmias —

Table 2

Anthropometric parameters in patients of groups I and II

Parameters	Group I	Group II	p
BMI, kg/m^2	34,43±1,2	31,97±1,67	ns
WC, cm	118,9±3,3	110,2±1,4	0,038
WHR	1,05±0,04	1,09±0,09	ns
WHtR	0,7±0,02	0,6±0,02	0,001
SAD, cm	29,5±0,82	27,4±1,09	ns

Note: ns — not significant.

Table 3

Echocardiographic parameters of groups I and II

Parameters	Group I	Group II	p
LVEF, %	55,0±2,18	59,1±1,1	ns
LV posterior wall thickness, mm	9,9±0,3	9,5±0,2	ns
Interventricular septal thickness, mm	10,05±0,9	11,1±0,5	ns
LV EDV, ml	111,4±12,9	108,5±3,2	ns
LV ESV, ml	54,9±12,5	42,4±1,9	ns
LV mass, g	182,4±15,9	188,0±9,5	ns
LA volume, ml	72,4±1,5	63,2±2,6	0,007
E/A	0,7±0,02	0,8±0,05	ns
EAT thickness, mm	11,6±0,8	8,6±0,4	<0,001

Note: LVEF — LV ejection fraction, EDV — end-diastolic volume, ESV — end-systolic volume, E/A — ratio of peak velocity blood flow in early diastole to peak velocity flow in late diastole.

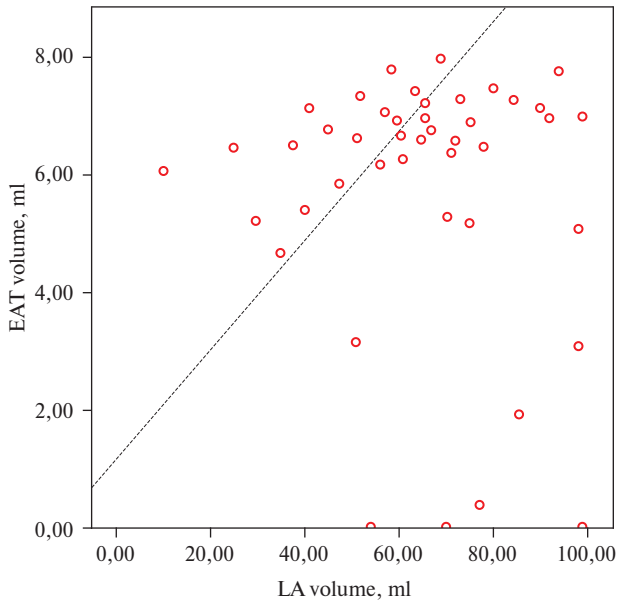

Figure 1. Correlation between EAT volume and LA volume in patients of group I.

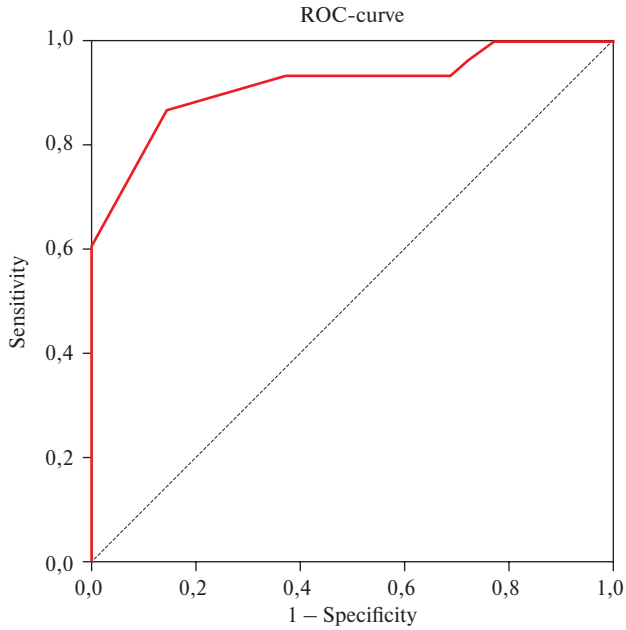

Figure 2. ROC-curve of the EAT thickness.

110,2±1,4 cm (p=0,038); the WHtR in patients with obesity and AF was 0,7±0,02, while in patients without arrhythmias — 0,6±0,02 (p=0,001) (Table 2).

According to echocardiography, there were no significant differences between the study groups in either LV systolic or diastolic function (Table 3). The EAT thickness was significantly higher in patients with HTN and paroxysmal AF than in the comparison group: 11,6±0,8 and 8,6±0,4 mm, respectively (p<0,001).

Significantly higher EAT volume was revealed in patients of group I (4,6±0,4 ml) compared with patients in group II (3,5±0,25 ml) (p=0,019).

In patients with hypertension and paroxysmal AF, a positive moderate relationship was found between the volumes of EAT and left atrial (LA) (r=0,7, p=0,022) (Figure 1).

In the group of hypertensive patients with paroxysmal AF, the contribution of anthropometric parameters, echocardiography, and EAT sizes in AF was assessed. The selected parameters were included in the Cox regression model for predictive value analysis.

Multivariate analysis revealed a significant effect of EAT thickness (odds ratio, 4,1; 95% confidence interval (CI), 1,1-5,6) assessed by echocardiography and EAT volume (OR, 3,7; 95% CI, 1,0-4,2) assessed by cardiac MSCT on AF likelihood in HTN patients.

To determine the threshold values for EAT thickness and volume, a ROC analysis was performed (Figure 2). In hypertensive patients, an EAT thickness >10 mm with a sensitivity of 81,6% and a specificity of 79,8% indicates the paroxysmal AF (area under the curve (AUC), 0,915).

EAT volume ⩾6 ml also had a high diagnostic value with a sensitivity of 83,2% and specificity of 80,7% (Figure 3) for paroxysmal AF in HTN patients (AUC, 0,891).

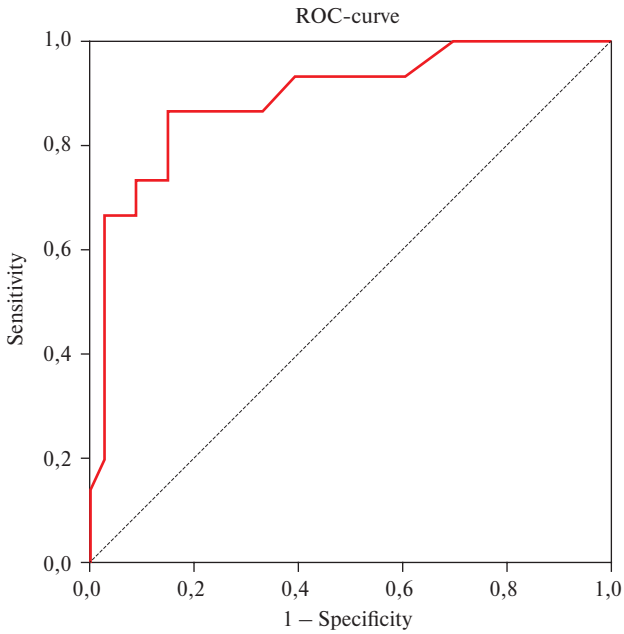

Figure 3. ROC-curve of the EAT volume.

Thus, increased thickness and volume of EAT can serve as markers of AF in hypertensive patients.

Discussion

The overwhelming majority of patients had a "secondary" AF, which develops due to cardiac or noncardiac diseases, which lead to electrophysiological and structural atrial remodeling. Along with the already studied reasons, such as HTN, HF, CAD, obesity can also be considered. It is visceral obesity, according to most authors, is one of the most significant predictors of adverse cardiovascular events.

In the present study, it was found that in patients with HTN and paroxysmal AF, the detection rate of visceral obesity was significantly higher than in patients without cardiac arrhythmias. At the same time, the BMI in the studied groups were comparable, and significant differences were observed only in the mean WC and WHtR values. Similar results were obtained in the Framingham study, which included 3217 participants [10].

Echocardiography reveled a significantly higher EAT thickness in group I compared with group II. In hypertensive patients with paroxysmal AF, a relationship was established between the EAT thickness and the LA size. This relationship characterizes the negative effect of EAT increase on the LA structural remodeling, which increases the risk of AF. The most accurate method for EAT assessment is to determine its volume using cardiac MSCT. In our study, the volume of EAT was significantly greater in hypertensive patients with AF than in patients without cardiac arrhythmias. Multivariate analysis revealed that an increase in the EAT thickness >10 mm and volume >6 ml are reliable markers of AF in HTN patients.

The role of visceral obesity in AF development is probably mediated by its effect on the structural and electrical atrial remodeling. Haemers P, et al. proved that subepicardial fatty infiltration significantly increases the risk of AF [11]. The study by Venteclef N, et al. [12] showed that humoral factors produced by EAT lead to active atrial fibrosis in rats. EAT can have following effects: release of adipokines that can initiate the development of fibrosis; expression of pro-inflammatory cytokines involved in the atrial remodeling; promotion of fatty infiltration of atrial cardiomyocytes. It also contains ganglionated plexuses that play an important role in the development of a proarrhythmogenic substrate in the myocardium [13-16].

Thus, an increase in the thickness and volume of EAT are integral markers of arrhythmias in hypertensive patients. Multivariate analysis, for the first time, revealed the threshold values of thickness and volume of EAT, which can help in diagnosis of AF in hypertensive patients.

Conclusion

1. In hypertensive patients with paroxysmal AF, when compared with those without cardiac arrhythmias, significantly higher thickness and volume of EAT were revealed.

2. In hypertensive patients with paroxysmal AF, the EAT thickness is positively associated with an increase in the LA volume (r=0,77).

3. The integral markers of AF in hypertensive patients are EAT thickness >10 mm and volume >6 ml.

Relationships and Activities: none.

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