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The role of cardiac adipose tissue depots in assessing the risk of paroxysmal atrial fibrillation in patients with coronary heart disease and arterial hypertension

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The aim of the study was to investigate the influence of the severity of local cardiac depots of adipose tissue on the development of paroxysmal atrial fibrillation (AF) in patients with coronary heart disease (CHD) and arterial hypertension (AH).

Materials and Methods. The study included 82 patients (49 men and 33 women) with CHD aged 37–88 years (mean age — 62 [60; 75] years). Paroxysmal form of AF was diagnosed in 27 patients who constituted the main group.

All patients had anthropometric parameters measured: body mass index, waist circumference, hip circumference. Structural and functional state of myocardium was assessed by echocardiography (EchoCG).

Statistical data processing was performed using MedCalc® Statistical Software version 20.104 (MedCalc Software Ltd, Ostend, Belgium). The nature of the data distribution was assessed using the Kolmogorov-Smirnov criterion. In case of normal distribution, data were presented as mean (M) and standard deviation

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(SD). Nonparametric indicators were represented as median and interquartile range (Me [Q25; Q75]). The correlation between the two quantitative characteristics was assessed using Spearman correlation analysis (r). ROC analysis was performed to determine the threshold value of the studied attribute. Binary logistic regression method was used to assess the possibility to predict the risk of AF development. Differences were considered statistically significant at p<0.05.

Results. There was a correlation between interatrial septal thickness (IST) and waist circumference (WC) (r = 0.5; p = 0.0003), hip circumference (HC) (r = 0.6; p < 0.0001), and epicardial fat thickness (EF) (r = 0.7; p < 0.0001).

ROC analysis showed that IST > 0.7 cm (p<0.001) and EF thickness > 0.6 cm (p < 0.001) were indicative of paroxysmal AF.

Determination of threshold values of IST and EF thickness separately among men and women with the regard to the presence/absence of abdominal obesity (AO) showed that in men without AO, IST thickness > 0.5 cm and EF thickness > 0.7 cm, as well as IST > 0.7 cm in men with AO had a high diagnostic value for determining the probability of AF development.

Conclusion. Epicardial adipose tissue thickness > 0.6 cm (p < 0.001) and IST > 0.6 cm (p < 0.001) may serve as markers of AF in patients with CHD, and determination of EF thickness and IST together with WC measurement may serve as prognostic criteria of AF risk in men with CHD (model significance p = 0.0062).

Thus, the assessment of IST and EF thickness in patients with CHD can be recommended for determination during EchoCG.

Keywords: obesity, atrial fibrillation, epicardial adipose tissue, interatrial septal lipomatosis, predictors.

Conflict of interest: none declared.

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Data from modern epidemiological studies indicate a high prevalence of atrial fibrillation (AF) in the population (approximately 33 million people worldwide). Furthermore, a significant proportion (35%) of cardiovascular disease (CVD) mortality is caused by this arrhythmia [1–3].

Age, arterial hypertension (AH), diabetes mellitus (DM), coronary heart disease (CHD), chronic kidney disease (CKD) and obesity are the main risk factors (RFs) for the development of AF, with obesity being one of the most important RFs (incidence of 25%) [4–6].

Currently, obesity should be understood as a complex multifactorial condition with excessive deposition of adipose tissue leading to the formation of different metabolic phenotypes of obesity [7–9]. In addition, there is evidence in the literature that there is an inverse relationship between body mass index and risk of death — the "obesity paradox" [10].

A number of studies evaluating adipose tissue distribution as a measurable cardiovascular risk factor in a group of patients with AH have found that epicardial fat thickness (EF) > 0.4 cm is associated with the risk of developing AH [11–13]. In addition to the already known mechanisms leading to cardiac remodeling in patients with CHD and AH, the negative effect of EF leading to the formation of local fibrosis in the atrial myocardium and its pathogenetic association with the formation of "re-entry" foci has also been described [11, 14]. In the work of Mitrofanova L.B. et al, devoted to the search for the morphological substrate of AF, the role of fatty infiltration of the interatrial septum (IAS) was demonstrated [15, 16].

The aim of the study was to investigate the influence of the local cardiac adipose tissue depots on the development of paroxysmal form of AF in patients with CHD.

Methods

The study has been carried out by the Cardiologic Department of the "City Clinical Emergency Hospital", Ryazan. The study included 82 patients. The proportion of men was 60% (n = 49), the proportion of women was 40% (n = 33). The mean age of the patients was 62 [60; 75] years.

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The study included patients with CHD represented by unstable angina pectoris, myocardial infarction localised in the anterior wall of the left ventricle (31 %), posterior basal wall (13 %), inferior wall of the left ventricle (19 %), anterolateral wall of the left ventricle (37 %). All patients had a history of AH and chronic heart failure (HF). 21 % of patients had type 2 DM, one patient had a history of diffuse toxic goiter.

The main group (group 1) included 37 patients with paroxysmal form of AF documented by electrocardiography (ECG) or by the daily Holter monitoring. The duration of AF in group 1 patients was 4.3±1.2 years. A first-ever paroxysm of AF was recorded in 30 % (n=11). In patients with MI, paroxysms occurred within the first 24 hours in 75 % of patients and on the second day in 15 % of patients. The duration of the paroxysms did not exceed 48 hours. Emergency sinus rhythm restoration was achieved by a pharmacological cardioversion. 45 patients without AF formed the comparison group (group 2). Comparative characteristics of the patient groups are shown in Table 1.

Table 1. **Clinical characteristics of patients in comparison groups**

Parameter	1 group	2 group
Number of patients, n	37	45
Mean age, years	67.7 [61; 70]	64.2 [58; 72]
Gender: Male, n (%) Female, n (%)	 25 (67 %) 12 (33 %)	 25 (56 %) 20 (44 %)
CHD, n (%) Unstable angina, n (%) Postinfarction cardiosclerosis, n (%) MI, n (%)	37 (100 %) 27* (74 %) 6 (16 %) 4 (10 %)	45 (100 %) 11 (26 %) 22** (48 %) 12 (26 %)
AH, n (%)	37 (100 %)	45 (100 %)

Note. * p < 0.001; ** p = 0.0008.

All patients were treated according to current clinical guidelines [17–20]. Patients with AF received anticoagulant therapy and oral antiarrhythmic drugs were prescribed to maintain sinus rhythm after the cardioversion. Patients hospitalised with non ST-elevation acute coronary syndrome received anticoagulant therapy with unfractionated heparin in the acute phase, acetylsalicylic acid, P2Y12 inhibitors and new oral anticoagulants after the acute phase. 15 % of patients underwent percutaneous transluminal coronary angioplasty with stent implantation. All patients also received drug treatment for secondary prevention: hypolipidaemic therapy, antihypertensive therapy, β-blockers, and diuretics.

The study was conducted in accordance with good clinical practice and the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee of Ryazan State Medical University (extract from protocol #3 dated 11.11.2020). Written informed consent was obtained from all patients prior to enrolment.

Study exclusion criteria:

— heart defects with significant haemodynamic abnormalities;

— cardiomyopathies;

— acute renal failure;

— liver failure;

— severe respiratory failure;

— present malignancy;

— pregnancy;

— severe mental illness.

Anthropometric study was performed: measurement of height and body weight with subsequent calculation of body mass index (BMI), waist circumference (WC) and hip circumference (WC).

EchoCG was performed in all patients after control of AF episode using ultrasound diagnostic medical system HS60-RUS, Korea, Samsung Medison CO., LTD. All examinations were performed by a single specialist. Interatrial septum (IAS) thickness was measured in atrial diastole at the periphery of the fossa ovalis through a subcostal approach. EF thickness was measured in diastole from the parasternal position along the long and short axes of the left ventricle. EchoCG results are shown in Table 2.

Table 2. **Echocardiography data**

Parameter	1 group	2 group
Number of patients, n	37	45
Left ventricular end-diastolic dimension, cm	5.5 [5.1; 5.7]	5.4 [5.1; 5.6]
left ventricular end-systolic dimension, cm	4.03 [3.7; 4.3]	3.8 [3.4; 3.8]
Interatrial septum, cm	1.1 [1.05; 1.25]	1.2 [1.0; 1.3]
Left ventricle posterior wall, cm	1.1 [1.05; 1.2]	1.1 [1.02; 1.2]
Right ventricle anterior-posterior dimension, cm	2.7 [2.5; 2.8]	2.7 [2.4; 2.8]
IST, cm	0.8±0.1 (CI от 0.7 до 0.9)	0.6*±0.2 (CI от 0.5 до 0.6)
EF, cm	0.9±0.1 (CI от 0.8 до 1.0)	0.6**±0.1 (CI от 0.5 до 0.7)

Note. *p = 0.0001; **p < 0.0001

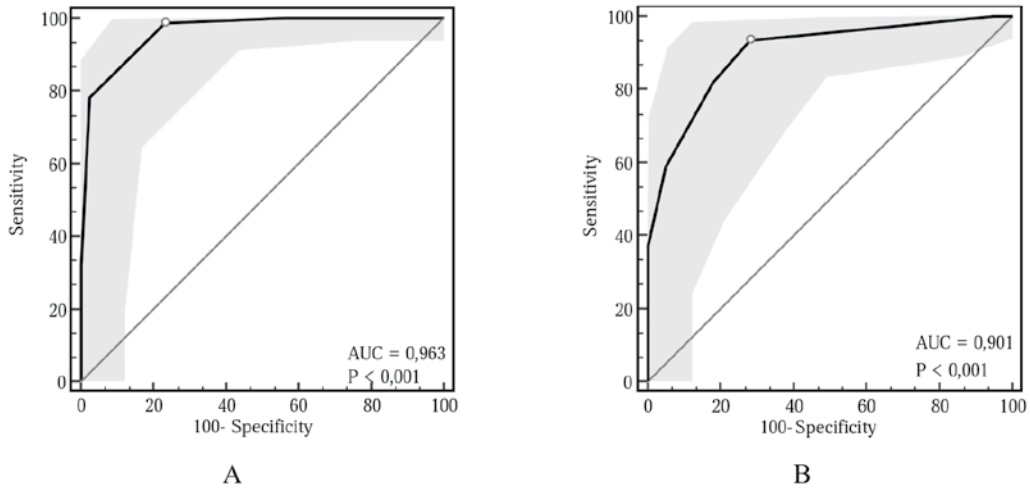

Fig. 1. ROC curves of IAS thickness (A) and EF thickness (B) in patients with CHD

Statistical data processing was performed using MedCalc® Statistical Software version 20.104 (MedCalc Software Ltd, Ostend, Belgium). The nature of the data distribution was assessed using the Kolmogorov-Smirnov criterion. In case of normal distribution, data were presented as mean (M) and standard deviation (SD). Nonparametric indicators were represented as median and interquartile range (Me [Q25; Q75]). The correlation between the two quantitative characteristics was assessed using Spearman correlation analysis (r). ROC analysis was performed to determine the threshold value of the studied attribute. Binary logistic regression method was used to assess the possibility to predict the risk of AF development. Differences were considered statistically significant at $p < 0.05$.

Results

The anthropometric study in the groups showed the following results: BMI was 30.5 [25; 34] kg/m^2 in group 1 and 29.8 [26; 33] kg/m^2 in group 2. HC was 106.8 [98.5; 111.5] cm in group 1 and 102.5 [97.2; 112] cm in group 2. The WC in group 1 was 114±5.5 cm and was significantly greater (p=0.02) than the WC in group 2 (107.5±2.6 cm). No significant differences in BMI and HC were found between the groups compared.

In all subjects, IAS thickness correlated with WC (r = 0.5; p = 0.0003), with HC (r = 0.6; p < 0.0001), and with EF thickness (r = 0.7; p < 0.0001).

In patients with CHD and paroxysmal AF, a positive correlation was found between IAS thickness and EF (r=0.7; p<0.0001).

Multivariate analysis was performed to demonstrate a statistically significant influence of EF thickness and IAS thickness on the probability of detecting AF in patients with CHD and AH. Odds ratio (OR) and confidence interval (CI) were calculated for each parameter: for EF thickness — OR = 5.8; 95 % CI: 0.8–5.6; for IAS thickness — OR = 3.9; 95 % CI: 1.2–6.3.

ROC analysis was performed to determine thresholds for local cardiac adipose depot thickness (Fig. 1). It was found that IAS thickness > 0.7 cm (AUC=0.963; p<0.001, sensitivity — 98.7 %, specificity — 76.9 %) and EF thickness > 0.6 cm (AUC = 0.901; p < 0.001, sensitivity — 93.6 %, specificity — 71.8 %) indicated the presence of the paroxysmal form of AF. Thus, the increase in IAS and EF thickness above the specified thresholds can serve as markers for the presence of AF in patients with CHD and AH.

In addition, ROC analysis of the curves was performed separately in the men's group and in the women's group with and without AF within the gender group (Table 3).

In the group of men without AF (Fig. 2), the threshold for IAS thickness was > 0.5 cm and for EF thickness was > 0.7 cm. In the group of men with AF (Fig. 3), the threshold for MPP thickness was > 0.7 cm. The data obtained were statistically significant and therefore have a high diagnostic value for determining the likelihood of AF development.

Similar analysis of ROC-curves in the group of women did not show statistically significant results.

The binary logistic regression method was used to assess the possibility of predicting the risk of AF development (Nagelkerke R-square was 0.524 (R2 = 0.5750); model significance p = 0.0062).

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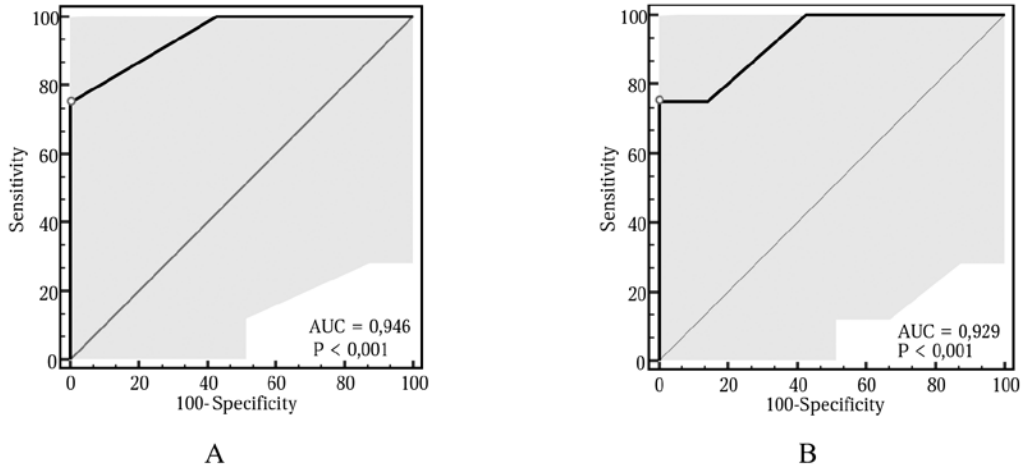

Fig. 2. ROC curves of IAS thickness (A) and EF thickness (B) in men without AO

Table 3. **ROC analysis of IAS and EF thickness thresholds in patients with CHD and arterial hypertension**

Gender	Measured parameter	No AO					AO				
		Parameter value, cm	Area under the curve	p	Sensitivity%	Specificity, %	Parameter value, cm	Area under the curve	p	Sensitivity, %	Specificity, %
Male	IAS	>0.5	0.946	<0.0001	75	100	>0.7	0.838	0.0237	75	100
	EF	>0.7	0.929	<0.0001	75	100	>0.8	0.688	0.3694	75	95
Female	IAS	>0.6	0.623	0.5	62	52	>0.7	0.595	0.4996	66	64
	EF	>0.7	0.541	0.456	58	41	>0.6	0.524	0.8971	33	43

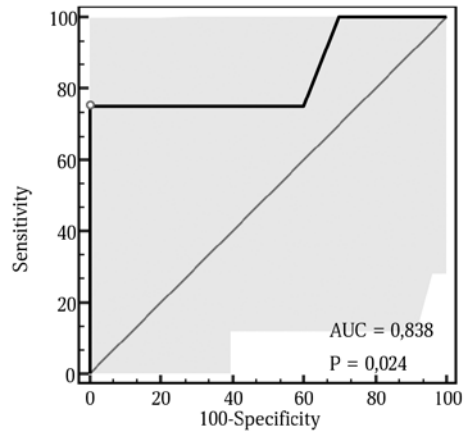

Fig. 3. ROC curves of IAS thickness in men with AO

The obtained model can be used to predict the risk of AF in men using as diagnostic criteria the thickness of EF and IAS thickness measured in diastole, as well as the presence or absence of AO.

Discussion

The conducted study showed that EF thickness in CHD patients with paroxysmal form of AF has significantly higher values compared to patients with CHD without arrhythmias (p = 0.0026). IAS thickness > 0.8 cm indicates the presence of paroxysmal form of AF, which is consistent with the already available data in the work of Czerny A. et al. devoted to the study of the role of EF in the development of AF in patients with AH [11].

In our study, we found that in patients with CHD, IAS thickness > 0.65 cm indicated the presence of a paroxysmal form of AF, which is also confirmed in a number of works [15, 21].

The ROC analysis, based on the comparison of patients within group 1 by sex and by the presence or absence of AO, showed that IAS thickness > 0.5 cm and EF thickness > 0.7 cm in CHD men without AO, and IAS thickness > 0.7 cm in men with AO can be used to assess the likelihood of developing AF. No such correlation applied to women.

According to the literature, the role of EF in the aetiopathogenesis of AF is not only due to a systemic influence, but also due to local effects associated with an increase in the amount of proinflammatory and profibrotic biologically active substances. The disruption of the structure and function of adipose tissue, regardless of its amount or total body weight,

may contribute to an increase in cardiovascular risk [22]. However, more detailed studies (also regarding the activity of fibrosis markers) are needed to address the role of lipomatous hypertrophy of IAS in AF.

Conclusion

The data obtained suggest the existence of a direct correlation between the expression of cardiac adipose tissue depots and the risk of developing the paroxysmal form of AF in patients with CHD.

EF thickness > 0.6 cm ($p<0.001$) and IAS thickness > 0.6 cm ($p < 0.001$) can serve as markers for the presence of AF in patients with CHD, and determination of EF thickness and IAS thickness together with WC measurement can serve as prognostic criteria for the risk of AF in men with CHD (model significance $p = 0.0062$).

Therefore, assessment of IAS and EF thickness during echocardiography can be recommended in CHD patients.

Conflict of interest: none declared.

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