Atrial cardiomyopathy in patients with cryptogenic embolic stroke: incidence, instrumental diagnostic features, impact on prognosis

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Latent atrial fibrillation (AF), whose substrate is atrial cardiomyopathy (AC), is considered the main potential pathogenetic mechanism of cryptogenic embolic stroke (CES). Early detection of AC allows to intensify the search for AF in such patients.
Objective: *to compare the characteristics of patients with CES in terms of clinical and anamnestic data, echocardiographic parameters, MRI patterns of infarction foci and disease outcomes depending on the presence of the major markers for AC.*
Material and methods. *We studied 103 patients in the acute phase of CES with a lesion confirmed by MRI data, who were divided into two groups according to the presence (n=17) or absence (n=86) of AC. A comprehensive clinical, laboratory, and instrumental examination was performed and long-term outcomes were assessed. The median follow-up period was 32 months.*
Results. *The incidence of AC in the CES population was 17%; the most common markers were an increase in left atrial volume index and paroxysms of supraventricular tachycardia. Patients with AC-CES were characterised by older age and a two-fold increase in the prevalence of coronary heart disease. Patients with AC-CES were nine times more likely to have a "black artery" symptom on MRI than patients without AC. The predictive accuracy of this clinical pattern was 84%, the sensitivity was 60% and the specificity was 86%. Patients with AC-CES had a significantly higher risk (odds ratio 3.4; 95% confidence interval 1.1–9.9; p=0.023) for a composite outcome that included the development of recurrent ischemic stroke, transient ischemic attack, myocardial infarction or death.*
Conclusion. *AC diagnosed by a combination of echocardiographic and electrocardiographic signs is present in 17% of patients with CES. Patients with AC-CES are characterised by elderly age, the presence of atherosclerosis-associated disease, a specific MRI pattern (the "black artery" symptom) and an unfavourable prognosis during the 2.5-year follow-up period.*

Keywords: *cryptogenic embolic stroke; atrial cardiomyopathy; magnetic resonance imaging*
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According to the ESUS Global Registry, cryptogenic embolic stroke (embolic stroke of indeterminate source P ESUS) occurs in every sixth patient who has undergone a standard diagnostic search for the cause of ischemic stroke (IS) [1]. At the early stage of the concept of ESUS, latent atrial fibrillation (AF) was considered as its leading potential pathogenetic mechanism [2], but in recent years the role of aortoaortic [3] and paradoxical embolism [4] has also been discussed. Latent AF or its substrate, «atrial cardiomyopathy», undoubtedly makes a significant contribution to the development of ESUS in elderly and senile patients [5]. Currently, more than 10 markers of atrial cardiomyopathy (AC) have been described, which can be simplified into 3 groups: electrophysiological (electrocardiographic), structural and functional (echocardiographic) and biochemical. Establishing AC is the most important stage of the diagnostic search for ESUS, as it allows for reasonable intensification of AF monitoring, as well as performing advanced cardiac imaging, including transesophageal echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI) of the heart. In this article, we aimed to characterize a subgroup of patients with ESUS and AC (AC-ESUS).

The purpose of the study is to present a comparative characteristic of patients with ESUS in terms of clinical and anamnestic data, echocardiography parameters, MRI pattern of infarction foci and disease outcomes depending on the presence of the main markers of AC.

Patients and methods. A retrospective analysis of medical data of patients with ESUS who were admitted to the neurological department for patients with acute cerebrovascular accident at the Regional Vascular Center of City Clinical Hospital No. 4 (Perm) for the period from 01/01/2017 to 12/31/2022 was carried out. The standard examination included emergency neuro- and angiovisualization, the scope of which was determined based on the need for reperfusion therapy. A range of studies were also performed aimed at finding the cause of the stroke:

dynamic electrocardiography, 24-hour Holter ECG monitoring, transthoracic echocardiography (EchoCG), duplex scanning of the brachiocephalic arteries, transcranial Dopplerography, CT or MR angiography and other diagnostic tests as indicated.

Determination of the pathogenetic subtype of stroke was carried out using the SSS-TOAST classification [6]. Patients with cardioembolic, atherothrombotic, and lacunar stroke were not included in this study (Fig. 1). Patients with stroke of unknown etiology were assessed for meeting the ESUS criteria:

- Presence of a nonlacunar ischemic lesion on CT or MRI;
- Absence of extra- or intracranial stroke-related cerebral artery stenosis (with lumen narrowing i50%);
- Absence of high-risk cardiac sources of embolism;
- Absence of other causes of stroke: arteritis, dissection, migraine/vasospasm, drug abuse, etc.

The deceased and patients who did not undergo a complete examination were excluded from the analysis. Non-inclusion criteria also included the absence of a cerebral infarction according to MRI and admission later than 72 hours from the onset of symptoms. The final sample included patients with MRI-confirmed hyperacute ESUS, who were further divided into two groups depending on the presence or absence of AC.

The study analyzed data from 7,369 patients with IS, among whom stroke of unknown etiology (I63.9) was diagnosed in 2,574 patients (34.9%). Of this number, ESUS was detected in 415 patients (5.6%). Based on inclusion and non-inclusion criteria, the final study sample size was 103 patients (1.4%) (Fig. 1).

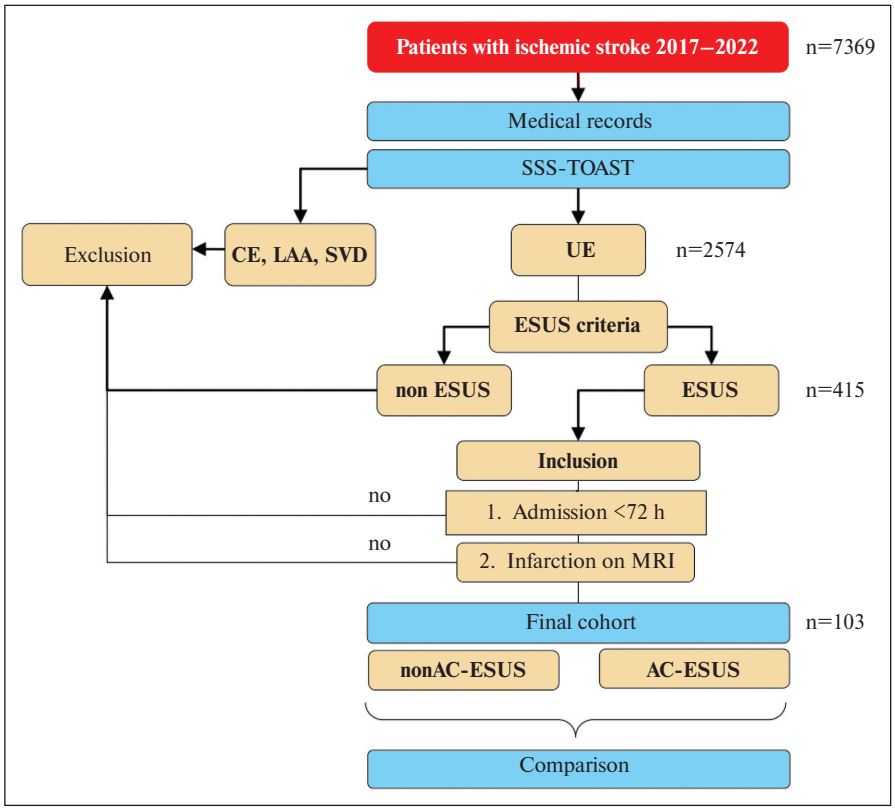

Fig. 1. *Study design*
CE – cardioembolic stroke, LAA P large arteries atherosclerosis, SVD – small vessel disease, UE – undetermined etiology, AC – atrial cardiomyopathy

Analysis of a 12-channel electrocardiogram (ECG) was carried out using the ImageJ software package for image processing (website: *https://imagej.nih.gov/ij*). The indicator of the terminal part of the *P* wave in lead V_1 (P-wave terminal force, $PTFV_1$) was calculated as the product of the amplitude (μV) and duration (ms) of the negative component of the *P* wave (only with a negative or biphasic *P* wave). $PTFV_1$ is a marker of AC with a value of >5000 μV × ms [7].

Ultrasound examination was performed using a GE Vivid S70N scanner. When conducting TT-EchoCG, the diameter of the left atrium, as well as its volume, were assessed as markers of AC using the modified Simpson method, followed by indexing to the patientXs body surface area.

AC was established by combining one electrocardiographic ($PTFV_1$ >5000 μV × ms and/or frequent supraventricular extrasystole (i480 per day) and/or paroxysms of supraventricular tachycardia i20 complexes (duration <30 s) and one echocardiographic criterion (left atrial diameter >40 mm and/or left atrial volume index >34 ml/m^2).

Brain MRI was performed on a GE Healthcare Brivo MR 355 magnetic resonance imaging scanner with a magnetic field strength of 1.5 T. The study protocol included DWI, FLAIR, T2, T1 and SWAN pulse sequences. The following patterns of cerebral infarction were analyzed: cortical infarction, cortical-subcortical infarction, deep non-lacunar infarction, multiple infarctions within one basin, chronic infarction in the same basin, multiple infarctions in different basins, insular lesions, lesions of external border zones, lesions of internal border zones. The presence of hemorrhagic transformation and the «black artery» symptom (Susceptibility Vessel Sign – SVS) were also assessed.

Long-term outcomes of the disease were assessed using a telephone conversation with the patient or his relative, as well as according to data from the Unified State Information System in the field of healthcare (USHIS).

Quantitative parameters were assessed for normality of distribution using the Shapiro–Wilk test. With a normal distribution, mean values and standard deviations (m±σ) were calculated to describe the characteristics. With a different distribution, the median and interquartile range (Me [Q1; Q3]) were calculated to describe quantitative characteristics. Description of qualitative characteristics was carried out by determining absolute and relative frequencies (n, %). Differences between quantitative characteristics were assessed using the Mann–Whitney test. To assess differences between binary characteristics, the Chi-square test and Fisher's exact test were used (depending on the values in

the cells of the contingency tables). The diagnostic value of binary features was assessed by calculating standard classification metrics: accuracy, sensitivity and specificity. Survival analysis was performed using Kaplan–Meier curves and the logistic rank test.

Results. The average age of patients with ESUS was 64.7±6.5 years, the proportion of females was 44.7% (n=46). Among the examined patients, a high prevalence of stroke risk factors was established in the following proportions: arterial hypertension 10/10, dyslipidemia 9/10, obesity, chronic kidney disease, coronary heart disease, smoking 1/4, carotid atherosclerosis and diabetes mellitus 1/5. More than a quarter of patients had a history of a cerebral vascular event (Table 1).

In 9 out of 10 cases, a monophasic course of the disease was observed, every tenth patient had fluctuations/progression of neurological deficit. Among the neurological syndromes, hemiparesis was the most common; acute dizziness occurred in 15% of patients. Notably, no patients with ESUS developed lateral medullary syndrome. On admission, two of the five patients had moderate or severe neurological deficits; the remaining cases had minor strokes. Every fifth patient received reperfusion therapy. In 3 out of 4 cases, cerebral infarction developed as a result of damage to the middle cerebral artery, and a quarter of the patients had a cerebellar stroke. Upon completion of the first stage of treatment and rehabilitation, 3 out of 4 patients had a good functional result, and after 3 months 4 out of 5 patients were functionally independent.

AC markers were analyzed in all patients (Table 2).

The most common marker of AC was an increase in left atrial volume index (2 of 5 patients); electrocardiographic markers were observed less frequently: paroxysms of supraventricular tachycardia (1 of 4 patients), frequent supraventricular extrasystole and $PTFV_1$ >5000 μV × ms (1 of 5 patients). As a result, AC-ESUS was established in 17 (16.5%) and non-AC-ESUS in 86 (83.5%) patients. Comparative characteristics of these subgroups are presented in table 3.

Patients with AC-ESUS were on average 7 years older than patients without AC and were more than twice as likely to have CAD. This subgroup was also characterized by more pronounced left ventricular hypertrophy, in particular, a

Table 1. *General characteristics of the study groups (n=103)*

Marker	General group, abs. (%)	Marker	General group, abs. (%)
Cardiovascular risk factors and diseases		Sensorimotor aphasia, abs (%)	16 (15,5)
History of smoking	25 (24,3)	Ignoring syndrome (neglect), abs (%)	10 (9,7)
Low-density lipoprotein >1.8 mmol/l	95 (92,2)	Hemianopsia, abs (%)	8 (7,8)
Body mass index i30 kg/m^2	30 (29,1)	Acute vestibular syndrome, abs (%)	15 (14,6)
Arterial hypertension	100 (97,1)	Ataxia, abs (%)	17 (16,5)
Chronic kidney disease (glomerular filtration rate <60 ml/min/1.73 m^2)	29 (28,2)	Oculomotor disorders, abs (%)	6 (5,8)
		Severe dysphagia, abs (%)	1 (1)
Atherosclerosis of the carotid arteries (stenosis from 30 to 50%)	22 (21,4)	Lateral medullary syndrome	0 (0)
Diabetes mellitus type 2	18 (17,5)	NIHSS upon admission more than 5 points	45 (43,7)
Coronary artery disease	32 (31,1)	Basin of the middle cerebral artery	76 (73,9)
History of myocardial infarction >1 month old	14 (13,6)	Basin of the posterior cerebral artery	10 (9,7)
History of stroke or transient ischemic attack	27 (26,2)	Basin of the anterior cerebral artery	4 (3,9)
Stroke characteristic		Brainstem (in addition to the perforating branches of the basilar artery)	11 (10,7)
Time from onset of symptoms to admission, hours	9 (4-24)		
Monophasic course with sudden development of deficiency, abs (%)	92 (89,3)	Cerebellum	25 (24,3)
		Several basins	20 (19,4)
Fluctuating or stepwise flow, abs (%)	11 (10,7)	Reperfusion therapy	21 (20,4)
Hemiparesis, abs (%)	64 (62,1)	*Outcome*	
Hemihypesthesia, abs (%)	38 (36,9)	NIHSS at discharge more than 5 points	15 (14,6)
Motor aphasia, abs (%)	15 (14,5)	Rankin scale at discharge more than 2 points	27 (26,2)
Sensory aphasia, abs (%)	1 (1)	Rankin scale after 90 days more than 2 points	20 (19,4)

Note: NIHSS is the US National Institutes of Health Stroke Scale.

higher myocardial mass index. For other parameters, including the value of the left ventricular ejection fraction and the presence of zones of local impairment of myocardial contractility, no statistically significant differences were identified.

The groups of patients with AC-ESUS and non-AC-ESUS were compared according to the MRI pattern of the infarct. No statistically significant differences were found, except that in patients with AC-ESUS of 9.0 [1.4; 59] times more often the «black artery» symptom was observed (Table 3). The predictive accuracy of this clinical pattern was 84%, sensitivity – 60%, specificity – 86%. It is important to note that the values of the metrics require further clarification as the size of the group of patients with AC-ESUS increases. The median follow-up period for patients was 32 [19; 46] months. The frequencies of recorded cardiovascular events are presented in table 4.

Table 2. *Markers of atrial cardiomyopathy in patients with CES (n=103)*

Marker	General group, abs. (%)
ECG	
PTFV1 >5000 μV × ms	19 (18,4)
Supraventricular extrasystole	15 (14,6)
Advanced interatrial block	2 (1,9)
24-hour Holter ECG monitoring	
Frequent supraventricular extrasystole (⩾480 per day)	20 (19,4)
Paroxysms of supraventricular tachycardia	27 (26,2)
Transthoracic echocardiography	
Left atrium diameter >40 mm	28 (27,2)
Left atrial volume index >34 ml/m^2	45 (43,7)

Note: PTFV1 – P-wave terminal force.

Table 3. *Comparison of patients according to the presence of AC-CES based on clinical, echocardiographic and neuroimaging parameters*

Marker	General group (n=103)	AC nonAC-ESUS (n=86)	AC-ESUS (n=17)	p
Age	64 [58; 71]	63 [57; 70]	70 [61; 79]	0,046
Coronary artery disease	32 (31%)	22 (26%)	10 (59%)	0,007
Thickness of the interventricular septum, mm	13 [12; 14]	13 [12; 14]	13 [13; 15]	0,004
Thickness of the posterior wall of the left ventricle, mm	12 [11; 12]	12 [11; 12]	12 [12; 13]	0,005
Myocardial mass index	117 [97; 132]	113 [96; 128]	127 [118; 141]	0,001
Symptom of "black artery"	5 (5%)	2 (2%)	3 (18%)	0,031

Repeated ischemic stroke developed in 12 patients (12%). In patients with AC-ESUS, composite outcome No. 1 was observed statistically significantly more often (3.4 [1.1; 9.9] times, p=0.023), which included the development of recurrent IS, TIA, myocardial infarction or death, as well as composite outcome No. 2 (3.1 [1.1; 8.9] times, p=0.033), in which newly diagnosed AF was added to the specified parameters. Statistically significant differences were established between the survival rates of the two groups of patients (p<0.001). Detailed dynamics of survival are presented in the form of Kaplan–Meier curves in Figure 2.

Discussion. The concept of AC is that under the influence of various etiological factors, the development of electrical and mechanical dysfunction of the atria, fibrosis of the myocardium occurs, which determines the formation of atrial ectopic activity and an increased risk of thrombus formation. The progression of AC with the development of AF closes the vicious circle of structural and functional remodeling and increases the risk of stroke [8].

Currently, clear criteria for AC have not been defined, and the frequency of its detection varies significantly from study to study, which may be due to different approaches to diagnosis, as well as the peculiarities of selecting patients in the ESUS group. So, according to the results of Shirin Jalini et al. (Canada, 2019), AC, in accordance with the criterion «$PTFV_1$ >5000 μV × ms *or* severe dilation of the left atrium», was detected in 26.6% of patients with ESUS [9]. In a study by Ana Rita Silva et al. (Portugal, 2022) AC, diagnosed in the presence of one of the following criteria – marked enlargement of the left atrium, PTFV1 >5000 μV × ms or increased atrial ectopic activity, was found in 42.7% of patients [10], and in the work of George Ntaios et al. (Greece, Switzerland, 2019) – in 45% of patients with ESUS [11]. The highest prevalence of AC in ESUS (63%) was presented in the study by Shadi Yagh et al. (USA, 2016). In this work, AC was established in the presence of one of the following criteria: marked enlargement of the left atrium, PTFV1 >5000 μV × ms *or* NT-proBNP >250 pg/ml [12].

Our study showed that AC occurs in 17% of patients with ESUS. The relatively low prevalence of AC among patients with ESUS is due to the use of more stringent diagnostic criteria in the form of a *combination* of electrocardiographic and echocardiographic markers. In this study, the left atrial volume index was assessed as an echocardiographic criterion, which, according to Tan BYQ et al. (2020), is the optimal structural marker of AC [13]. Other authors have demonstrated an independent relationship between this parameter and the detection of AF after ESUS [14]. In our opinion, the key role of the echocardiographic criterion in the diagnosis of AC is due to the fact that the diagnosis of AC in patients with ESUS implies resolving the issue not only of a more in-depth examination, but also of secondary prevention – the prescription of anticoagulant therapy. Thus, in the NAVIGATE ESUS RCT, the administration of rivaroxaban improved the prog-

nosis only in the subgroup of patients with a left atrium size >46 mm [15], while the presence of electrocardiographic markers had no determining significance.

Thus, it is possible to assume that isolated increased arrhythmogenic activity reflects initial, in some cases reversible, functional disorders within the framework of the AC phenomenon, while pathological remodeling with an increase in the size of the left atrium is persistent changes that are associated with the risk of thrombosis. This hypothesis is consistent with the results of the NOAH-AFNET 6 trial, in which the administration of edoxaban in the presence of only electrocardiographic criteria for AC (atrial high-rate episodes) did not affect the incidence of ischemic events, but increased the risk of bleeding [16].

Table 4. *Subsequent cardiovascular events in patients depending on the presence of AC-CES, n (%)*

Event	Group AC-ESUS (n=17)	Group non-AC-ESUS (n=86)	p-value
IS	4 (24%)	8 (9%)	0,109
TIA	0 (0%)	2 (2%)	1,000
Hemorrhagic stroke	0	0	-
MI	2 (12%)	1 (1%)	0,070
AF	3 (18%)	7 (8%)	0,363
Composite outcome No. 1 (IS+TIA+MI+death)	8 (47%)	18 (21%)	0,023
Composite outcome No. 2 (IS+TIA+MI+death+AF)	9 (53%)	23 (27%)	0,033

Note: TIA – transient ischemic attack, IS – ischemic stroke, MI – myocardial infarction, AF – atrial fibrillation.

Next, we analyzed the frequency of occurrence of individual AC markers. An increase in left atrial volume index >34 ml/m^2 was observed in 43.7% of patients with ESUS. Left atrial diameter greater than 40 mm, which is the optimal threshold for predicting the detection of AF [17], occurred in 27.2% of patients. In the study by Shadi Yagh et al, pronounced LA dilatation occurred in 5% of patients [12], in the work of Shirin Jalini – in 8% of patients [9], however, in these studies a higher threshold for left atrium dilatation was used. In a study by Tan BYQ et al. (2020) left atrial volume index >34 ml/m^2 was observed in 21.1% of patients with ESUS [13], in the work of Marzieh Tajmirriahi (Iran, 2022) this percentage was 46.9% [18], which corresponds to our data.

Paroxysms of supraventricular tachycardia were detected in 26.2% of patients. In a study by Poli S. et al. (2016) episodes of supraventricular tachycardia according to 72-hour monitoring were found in 36% of patients and were, along with an increase in the diameter of the left atrium, a predictor of detection of AF during intracardial monitoring [19]. In a study by Markus Kneihsl et al. (Austria, 2022) paroxysms of SVT lasting more than 20 cardiac cycles were observed in 2.7% of patients with cryptogenic stroke; however, in the group in which AF was subsequently detected, this figure was 17.6% [20]. In our opinion, the frequency of detection of supraventricular tachycardia may depend on the careful selection of patients in the ESUS group, which explains the significant scattering of data in the presented studies. We detected supraventricular extrasystole on a routine ECG in 14.6% of patients. The AF-ESUS study showed that this phenomenon was observed in 26.5% of patients with ESUS, and its presence increased the likelihood of detecting AF by 1.8P3.2 times, depending on the number of extrasystoles [21].

PTFV$_1$ >5000 μV × ms was found in 18.4% of patients, which is consistent with the results of the study by Shadi Yagh et al. (20% of patients with ESUS) [12]. PTFV1 reflects pathophysiological processes of left atrium remodeling, including dilatation, fibrosis, myocyte hypertrophy and increased filling pressure. According to the study by Li TYW et al. (2021), in patients with ESUS, an increased PTFV$_1$ value is associated with detection of AF using an ECG loop recorder [7].

The next stage in our work was to characterize patients with ESUS depending on the presence of AC. Patients with AC-ESUS were on average 7 years older than patients without AC and were more than twice as likely to have CAD. This subgroup was also characterized by the presence of left ventricular hypertrophy, in particular a higher myocardial mass index. For other parameters, including the value of the left ventricular ejection fraction and the presence of zones of local impairment of myocardial contractility, no statistically significant differences were identified. Similar results were obtained in the Shadi Yaghi study: patients with AC-ESUS were also older (76 years vs 62 years), more often suffered from arterial hypertension and coronary artery disease [12]. Similar results were obtained by Ana Rita Silva et al. [10].

We did not find any differences in the infarction pattern depending on the presence of AC, which is consistent with the Vollmuth data. et al. (2020), according to which the MRI pattern in cryptogenic stroke is not associated with the likelihood of detecting AF during intracardial monitoring [22], although

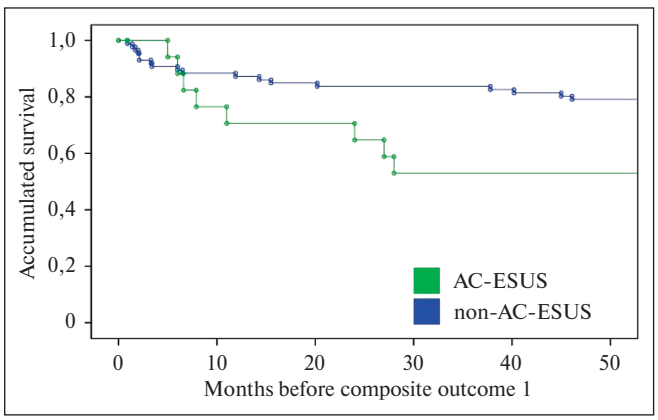

Fig. 2. *Survival curve for composite outcome 1*

this conclusion should be considered premature due to the small number of patients in the AC-ESUS group. Notably, patients with AC-ESUS were 9 times more likely to have the «black artery»/SVS symptom, which is characteristic of «red» thromboemboli with a high red blood cell count [23]. The predictive accuracy of this clinical pattern was 84%, sensitivity – 60%, specificity – 86%. According to Dong–Wan Kang et al. (2017), SVS was detected in 86% of patients with the cardioembolic subtype of stroke, which is significantly more common than with other mechanisms [24]. The association of SVS with the cardioembolic subtype of stroke is also indicated by the results of the THRACE (THRombectomie des Arteres CErebrales) study [25]. In a study by Hanan Alhazmi et al. (2021) showed that patients with cardioembolic stroke and patients with ESUS with large artery occlusion are characterized by similar SVS length [26]. Thus, the presence of the «black artery» symptom in some patients with PC-ESUS additionally indicates their possible affiliation with cardioembolic stroke.

The median follow-up period for patients was 32 (19P46) months. During this time, recurrent IS developed in 12 patients (12%), AF was detected in 10 patients (10%), but no differences in these indicators were found depending on the presence of AC. For comparison, in the RE-SPECT ESUS RCT, the rate of recurrent stroke in patients in ESUS during 19 months of follow-up was 7.1% (or 4.5% per year) [27], in the NAVIGATE ESUS RCT, the rate of recurrent stroke was 4.7 % per year [15]. In a study by Yan Hou et al. (USA, 2022) during an average of 3 years of follow-up, recurrent stroke developed in 11.4% of patients with ESUS aged 50 years or older [28]. Comparing the frequency of detection of AF with other studies is impractical, since in our work a special protocol for additional search for arrhythmia at the outpatient stage was not used.

Analysis of composite outcomes showed that patients with AC-ESUS were 3.4 times more likely to experience one or a combination of the following events: recurrent ischemic stroke, TIA, myocardial infarction or death – 47% versus 21%. Vikrant Jagadeesan et al. (2020) demonstrated that one third of patients with ESUS were readmitted to hospital within a year. The main reasons for hospitalization are stroke or TIA (30%), coronary artery disease (11%) and peripheral arterial disease (6%). Moreover, patients with ESUS and left atrial dilatation are characterized by a 1.5 times higher risk of readmission due to cardiovascular and cerebrovascular events [29].

Conclusion. Almost every fifth patient in ESUS has AC, the most common markers of which are an increase in the left atrium volume index combined with paroxysms of supraventricular tachycardia. The AC phenotype of ESUS is associated with older age of patients, the presence of coronary artery disease, and left ventricular hypertrophy. Every fifth patient with AC-ESUS has a «black artery» symptom on MRI, the predictive accuracy of which is 84%. Patients with AC-ESUS have a poor long-term prognosis, with cardiovascular events or death occurring in every second case over an average of 2.5 years of follow-up. Thus, the study indicates the feasibility of identifying the AC phenotype of ESUS in the acute period of stroke in order to intensify diagnostic and preventive measures for these patients.

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