Biomarkers of atrial cardiopathy in patients with different pathogenetic subtypes of ischemic stroke

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Studies of the biomarkers of atrial cardiopathy seem to be promising for identifying patients with cryptogenic stroke (CS), in which an intensive search for atrial fibrillation is indicated. Nevertheless, the diagnostic value of these markers and their threshold values require clarification.

***Objective:** to present the characteristics of echocardiographic markers for atrial cardiopathy and the serum concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in embolic CS versus cardioembolic stroke (CES) and non-cardioembolic stroke (non-CES) to determine the threshold values of parameters with the highest sensitivity and specificity in differentiating CES and non-CES.*

Patients and methods. A total of 259 patients with ischemic stroke were examined. The standard examination additionally involved calculation of the parameters that reflected left atrial LA) function (LAF): LA emptying fraction (LAEF), and LA functional index (LAFI). The serum NT-proBNP concentration was also determined in 75 patients.

***Results and discussion.** The patients with CES versus those with CS and non-CES were characterized by a considerable increase in LA diameter (4.3 [3.5; 4.5] cm vs 3.7 [3.4; 4.0] cm vs 3.7 [3.4; 3.9] cm; p=0.005 and p=0.009, respectively), LAVI (35.7 [30.5; 39.9] ml/m² vs 28.5 [25.6; 34.6] ml/m2 vs 27.1 [24.5; 31.2] ml/m2; p < 0.001) and NT-proBNP level (559 [409; 1144] pg/ml vs 164 [65; 308] pg/ml vs 191 [63; 446] pg/ml; p=0.002 and p=0.019, respectively), as well as by a lower LAEF value [50.3 [48.5; 51.1]% vs 54.7 [51.6; 56.6]% vs 54.9 [52.5; 56.8]%; p<0.001). The only parameter that showed significant differences between all the three groups (CES, CS, and non-CES) was LAFI (0.24 [0.2; 0.32] units vs 0.37 [0.3; 0.47] units vs 0.40 [0.34; 0.47] units; p<0.001), while maintaining the differences in the values for the two groups (CS and non-CES) (p=0.004). The following threshold values of biomarkers were obtained for CES and non-CES; these were a LA diameter of 41.5 mm (p<0.001), a LAVI of 36.3 ml/m² (p<0.001), a LAEF of 51.8% (p<0.001), a LAFI of 0.28 units (p<0.001), and an NT-proBNP of 316 pg/ml (p<0.001). Analysis of the ROC curves and the area under the curve (AUC) revealed that the most informative criteria for sensitivity and specificity were LAEF (79 and 88%, AUC 0.89), NT-proBNP (67 and 91%, AUC 0.89) and LAFI (93 and 72%, AUC 0.81).*

***Conclusion.** The CS group and non-CES one are comparable in the echocardiographic manifestations of atrial cardiopathy and in serum NT-proBNP values. LAEF and NT-proBNP concentrations are promising biomarkers to classify CS patients into potential arterio- and cardioembolic types.*

***Keywords:** atrial cardiopathy, cryptogenic stroke, biomarkers, echocardiography, left atrial emptying fraction, NT-proBNP.*

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***For reference:** Mekhryakov SA, Kulesh AA, Syromyatnikova LI, Sobyanin KV. Biomarkers of atrial cardiopathy in patients with different pathogenetic subtypes of ischemic stroke. Nevrologiya, Neiropsikhiatriya, Psikhosomatika. 2020;13(1). **DOI**: 10.14412/2074-2711-2021-1*

Introduction. The etiology of every third ischemic stroke remains unknown, which limits the effectiveness of secondary prevention [1, 2]. While at a young age the main cause of cryptogenic stroke (CS) is an patent foramen ovale and dissection of the artery wall [3, 4, 5, 6], in the elderly, as a rule, latent atrial fibrillation (AF) acts as such [7, 8]. Despite the fact that AF has long been considered as a direct cause of thrombosis and cardioembolism, it is known that only in a small proportion of patients, AF paroxysm coincides in time with stroke or TIA [9]. Based on this, it has been suggested that AF may be a consequence of atrial dysfunction (cardiopathy), which, in turn, is a direct cause of embolic events [10]. The main biomarkers of atrial cardiopathy include: paroxysmal supraventricular tachycardia, atrial ectopia, ECG P wave variability, an increase in the size of the left atrium (LA), features of the LA appendage morphology according to cardiac MRI, as well as the level of pro-natriuretic N-terminal peptide B-type (N-terminal pro-brain natriuretic peptide (NT-proBNP) >250 pg/ml [11, 12, 13].

From a practical point of view, the most convenient, affordable, not requiring significant additional costs, is a comprehensive assessment of echocardiographic parameters and serum NT-proBNP concentration. Determination of these markers of atrial cardiopathy in routine clinical practice will make it possible to outline the target subgroup of patients with CS who, in addition to the standard examination, may require prolonged ECG monitoring. To implement this promising task, it is first necessary to establish the threshold values of these markers, which make it possible to differentiate between cardioembolic stroke (CES) and non-cardioembolic stroke (non-CES). A number of recent studies have been devoted to determining the role of markers of atrial cardiopathy in embolic CS, which have shown the diagnostic value of LA diameter [14], left atrial volume index (LAVI) [15, 16], left atrial emptying fraction, LAEF), left atrial function index (LAFI), and NT-proBNP concentration [17, 18, 19]. The introduction of these biomarkers into routine clinical practice requires confirmation of their diagnostic value in the domestic patient population, determination of the most informative indicators and, due to the inconsistency of research results, specification of threshold values.

Purpose: to present the characteristics of echocardiographic markers of atrial cardiopathy and NT-proBNP concentration in blood serum in embolic CS in comparison with CES and non-CES and to determine the threshold values of indicators that have the highest sensitivity and specificity in differentiating CES and non-CES.

Patients and methods. We examined 259 patients with ischemic stroke who were urgently admitted to the neurological department of the Regional Vascular Center of Hospital No. 4 in Perm. Selective inclusion of patients was carried out. The inclusion criteria for the study were: age from 18 to 75 years, the presence of ischemic stroke (CES against the background of a permanent form of AF, atherothrombotic, lacunar or cryptogenic), verified according to neuroimaging data. The study did not include patients over 75 years of age; with a prehospital result of the modified Rankin scale (mRS) more than 3 points; with other neurological, psychiatric (including dementia) and somatic diseases that determine the severity of the general condition; complicated course of stroke. The exclusion criterion was also the presence of a patent foramen ovale.

Patients underwent examination aimed at finding the causes of ACVA, including MRI of the brain, MR angiography, duplex scanning of the carotid and vertebral arteries, CT angiography from the aortic arch, digital subtraction angiography (if indicated), transthoracic (TTE) and transesophageal (according to indications) echocardiography, transcranial dopplerography with a bubble-test, electrocardiography and Holter heart rate monitoring (from 24 to 72 hours).

Depending on the etiology of stroke, patients were divided into three groups: CS (n=128), CES with AF (n=32), and non-CES (n=99 patients, 46 of them with atherothrombotic and 53 with lacunar stroke). CI was understood as embolic CI in accordance with the ESUS criteria (embolic strokes of undetermined source) [2]. The number of patients in each subgroup was predetermined based on the statistical power of the sample and the possibility of subgroup analysis.

Table 1. General characteristics of the study groups.

Indicator	General group, n=259	CS*, n=128	CES**, n=32	Non-CES***, n=99	p-value
Age, years	66 (57-71)	62,5 (54-70)	70,5 (67-76)	67 (58-72)	*-** <0,001 *-*** 0,020 **-*** 0,005
Female, abs. (%)	105 (40,5)	57 (44,5)	22 (69)	26 (26)	*-*** 0,001
BMI, kg/m2	27 (24-30)	26,9 (23,7-30)	27,5 (25-30)	26,9 (24-29)	NS
Arterial hypertension, abs. (%)	247 (95,3)	119 (92,9)	32 (100)	96 (96,9)	NS
IHD, abs. (%)	92 (35,5)	26 (20,3)	21 (65,6)	45 (45,4)	*-** <0,001
Stroke-associated artery stenosis >50% or occlusioin, abs. (%)	42 (16,2)	0	0	42 (42,4)	-
Stroke-associated artery stenosis 30-50%, abs. (%)	64 (24,7)	38 (29,6)	12 (37,5)	14 (14,1)	-
Stroke-associated artery stenosis <30%, abs. (%)	28 (10,8)	15 (11,7)	2 (6,2)	11 (11,1)	-
Stroke-associated artery intracranial stenosis, abs. (%)	4 (1,5)	0	0	4 (4,0)	-
Diabetes melitus, abs (%)	57 (22)	28 (21,8)	10 (31,3)	19 (19,2)	NS
History of stroke, abs. (%)	77 (29,7)	44 (34,3)	9 (28,1)	24 (24,2)	NS
NIHSS upon admission, points	6 (3-9)	6 (3,5-9)	6 (3,5-11)	6 (3-8)	NS
NIHSS at discharge, points	2 (1-5)	3 (0-6,5)	2 (1-6)	2 (1-5)	NS
Rankin scale upon admission, points	4 (4-5)	4 (4-5)	4 (4-4)	4 (4-5)	NS
Rankin scale at discharge, points	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	NS

Note: NS - differences are statistically insignificant, NIHSS - stroke scale of the US National Institutes of Health, BMI - body mass index, ICH - ischemic heart disease.

Ultrasound examination was performed on a PHILIPS CX5. When performing TTE, the standard protocol is supplemented with echocardiographic indicators that allow assessing the anatomy and function of the LA. In all patients, LA volume was measured using the biplane disc method (modified Simpson's method) using a four-chamber and two-chamber apical positions at the end of systole and at the end of ventricular diastole. These indicators were indexed according to the patient's body surface area. The functional characteristic of the LA was determined using two parameters - LAEF and LAFI, which were calculated using the formulas [20]:

LAEF = ([LAESVi - LAEDVi]/LAESVi) · 100.

LAFI = (LAEF · LVOT-VTI)/LAESVi*

*LAEF- left atrial emptying fraction, LAESVi-left atrial end-systolic volume index, LAEDVi-left atrial end-diastolic volume index, LAFI- left atrial function index, LVOT-VTI-left ventricle outflow tract velocity time integral.

In some patients (n = 75), NT-proBNP concentration was determined using standard test systems for enzyme-linked immunosorbent assay on days 4-7 of illness. Statistical processing was carried out using the STATISTICA 10.0 application package, the Python programming language, the Scipy and Statsmodels libraries. Comparative analysis of two independent groups in terms of quantitative criteria was performed using the Mann-

Whitney test, for a qualitative attribute - using the Chi-square test. The correlation analysis was performed using Spearman's test. The tables show the median and interquartile range. The threshold values for each of the echocardiographic markers of atrial cardiopathy and the Nt-proBNP concentration were selected according to the Gini criterion, while a minimum decision tree was built dividing the sample by belonging to CES and non-CES. The statistical significance of the cut-off values was assessed by the Welch test. Average values in the tables are presented as median, 25% and 75% quartile.

Results. In a comparative assessment of the three groups, all patients belonged to the elderly category with a predominance of the elderly in the CES group, and the younger in the CS group. The proportion of females was higher among patients with CS, compared with the non-CES group. Ischemic heart disease was more often observed in the CES group than in the CS group. The groups did not differ in other clinical and functional parameters (Table 1). No cardiac pathology that could cause a stroke (mitral stenosis, mechanical prostheses, myocardial infarction in the next 4 weeks, left ventricular aneurysm and the presence of parietal thrombi in the left chambers of the heart, ejection fraction less than 35%) was also not identified.

The first stage in the general group of patients established the relationship of echocardiographic parameters, NT-proBNP values (Fig. 1, E), after which the differences in these indicators between the studied groups were determined (Table 2).

With the development of stroke of the cardiembolic subtype, signs of atriomegaly were revealed in terms of LA diameter, LAVI with a natural increase in NT-proBNP levels and a decrease in LAEF and LAFI values in comparison with the CS, non-CES groups. It is important to note that the only parameter for which significant differences were found between all three groups was LAFI (Figure 1, D). In terms of both the mean LAFI value and other echocardiographic parameters, the NT-proBNP level, the group of patients with CS occupied an intermediate position (Fig. 1, A-E).

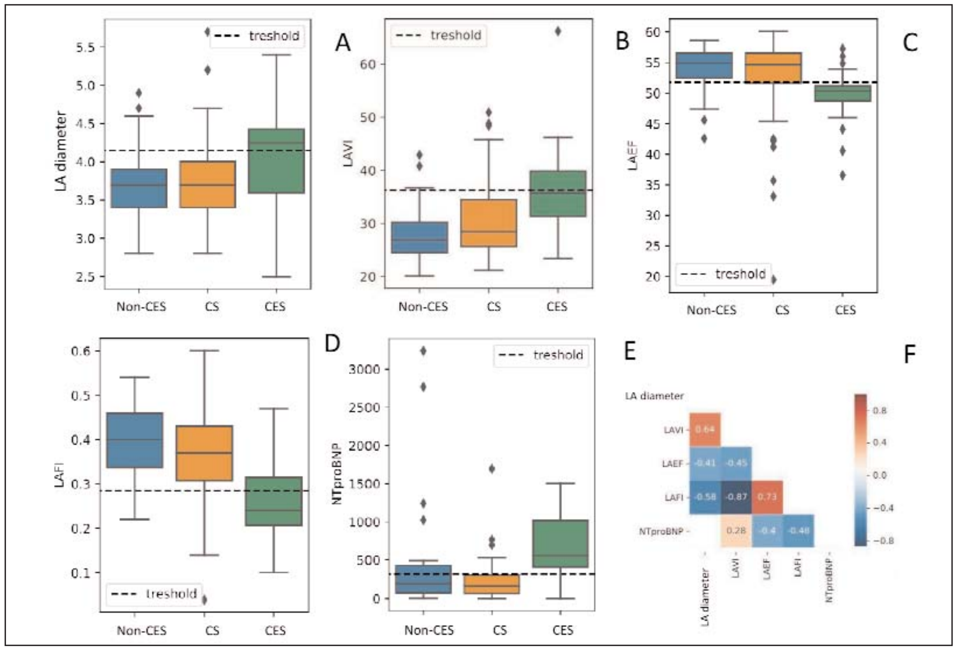

Fig. 1. *Comparative characteristics and relationship of the parameters of atrial cardiopathy in patients of three groups.*
a — LA diameter; b — LAVI; c — LAEF; d — LAFI; e — NT-proBNP; e — the correlation matrix of echocardiographic markers and NT-proBNP concentration, the color scale corresponds to Spearman's coefficient at p<0.05

At the next stage of the analysis, the threshold values of echocardiographic markers of atrial cardiopathy and NT-proBNP concentration were selected, which most effectively separated the groups of patients with CES and non-CES according to the Gini criterion. The construction of ROC curves (Fig. 2)

Table 2. Comparative characteristics of biomarkers of atrial cardiopathy in patients depending on the subtype of stroke.

Indicator	CS* (n=128)	CES** (n=32)	non-CES*** (n=99)	p-value
LA diameter, cm	3,7 (3,4-4,0)	4,3 (3,5-4,5)	3,7 (3,4-3,9)	*-** 0,005 **-*** 0,009
LAVI, ml/m^2	28,5 (25,6-34,6)	35,7 (30,5-39,9)	27,1 (24,5-31,2)	*-** <0,001 **-*** <0,001 *-*** 0,060
LAEF, %	54,7 (51,6-56,6)	50,3 (48,5-51,1)	54,9 (52,5-56,8)	*-** <0,001 **-*** <0,001
LAFI, ед.	0,37 (0,3-0,47)	0,24 (0,2-0,32)	0,40 (0,34-0,47)	*-** <0,001 *-*** 0,004 **-*** <0,001
NT-proBNP, pg/ml	164 (65-308)	559 (409-1144)	191 (63-446)	*-** 0,002 **-*** 0,019

Note: LA - left atrium, LAVI - left atrial volume index, LAEF - left atrial emptying fraction, LAFI - left atrial functional index, NT-proBNP - pro-natriuretic N-terminal peptide B-type, CS - cryptogenic stroke, CES- cardioembolic stroke, non-CES - non-cardioembolic stroke.

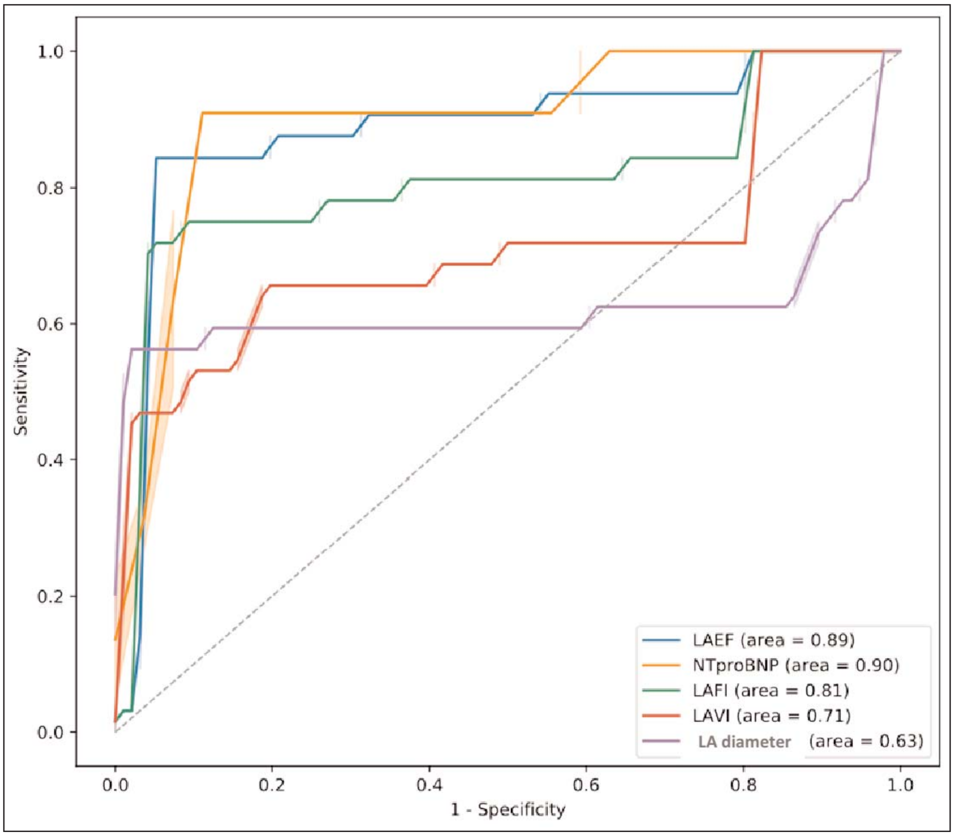

Fig. 2. *ROC curves of echocardiographic markers for atrial cardiopathy and NT-proBNP. ROC – receiver operating characteristic*

was carried out, the values of sensitivity and specificity for the classifiers corresponding to the selected threshold values of biomarkers were calculated, the results are shown in Table. 3.

Analysis of ROC curves and area under the curve revealed that, according to the sensitivity and specificity criteria, the studied parameters are arranged in the following descending sequence LAEF, NT-proBNP, LAFI, LAVI and LA diameter. It should be noted that the Nt-proBNP concentration has the highest specificity at low sensitivity; among the echocardiographic parameters, the LAEF value was the most balanced in terms of sensitivity and specificity.

Table 3. Sensitivity and specificity of echocardiographic markers of atrial cardiopathy and NT- proBNP in differentiating cardioembolic and non-cardioembolic strokes.

	Threshold	Area under the curve	P-value	Sensitivity	Specificity
LAEF, %	51,8	0,89	<0,001	0,79	0,88
NT-proBNP, pg/ml	316	0,90	<0,001	0,67	0,91
LAFI, units	0,28	0,81	<0,001	0,93	0,72
LAVI, ml/m^2	36,3	0,71	<0,001	0,97	0,47
LA diameter, cm	4,15	0,63	<0,001	0,89	0,56

LA - left atrium, LAVI - left atrial volume index, LAEF - left atrial emptying fraction, LAFI - left atrial functional index, NT-proBNP - pro-natriuretic B-type N-terminal peptide

Discussion. In this study, we studied the features of echocardiographic markers of atrial cardiopathy and NT-proBNP in patients with three types of ischemic stroke - CS, CES and non-CES, who were treated in a regional vascular center.

The concept of atrial cardiopathy (cardiomyopathy, atriopathy) is that under the influence of various etiological factors, mechanical dysfunction and procoagulatory changes develop, which leads to stroke, and through electrical dysfunction and fibrosis, to the onset and progression of AF [21, 22].

The development of atrial cardiopathy, like AF, is based on the activation of the profibrotic, proinflammatory potential and neurohumoral systems due to a negative combination of genetic predisposition, cardiovascular risk factors, which determines the electrical and morphological remodeling of the LA myocardium, the tendency to hypercoagulation and thrombosis [23, 24]. Atrial cardiopathy can independently provoke an embolic event due to the occurrence of other atrial arrhythmias, atriomegaly, fibrosis, inflammation, and coagulation disorders [25]. Signs of atrial cardiopathy are observed in approximately 65% of patients with CS, and 35–45% of patients with embolic CS have cardiopathy without AF [26]. However, there are currently no data from randomized clinical trials that would make it possible to make a decision to initiate anticoagulant prophylaxis only on the basis of the presence of one or another marker of atrial cardiopathy in the absence of AF. Until the publication of the results of the ongoing ARCADIA study [27], a pragmatic approach remains in force, which implies the need to verify AF for the administration of oral anticoagulants. The search for thrombosis of the LA appendage, which occurs in some patients with signs of atrial cardiopathy, seems promising, but so far it is hardly feasible in routine practice due to the low availability of transesophageal echocardiography and cardiac MRI.

In our study, it was found that echocardiographic (LA diameter, LAVI, LAEF and LAFI) and neurohumoral (NT-proBNP) indicators of atrial cardiopathy have the maximum deviations in CEI in comparison with non-CES. According to the study, LAFI is the most promising for further research in terms of differential diagnosis of the stroke subtype, which was the only parameter by which all three study groups were significantly different. The intermediate position of the discussed parameters in relation to the CS group reflects the progression of atrial cardiopathy, in which the thrombogenic contribution of LA is minimal in persons with atherostrombotic and lacunar strokes, becomes significant in CS, and is expected to be maximal in the cardioembolic subtype.

The threshold value of the LA diameter, which allows differentiating CES and non-CES with 89% sensitivity and 56% specificity, was 41.5 mm, which is close to 40 mm, which in the work of Perlepe K. et al. (2020) [14] made it possible to predict the detection of AF in patients with embolic CS within 10 years of follow-up. The mean LA diameter obtained in this international study, in the CS and non-CES groups equal to 37 mm vs 38.5 mm, also turned out to be similar to the data we presented. The volumetric indicators of the drug Perlepe K. et al. were not analyzed due to the small number of observations, however, the authors report that the LAVI values are more accurate in comparison with direct linear measurement, and its study may give more accurate results [14], which is consistent with our results.

According to our data, the LAVI value turned out to be significantly higher in the CES group (35.7 ml / m^2), while between the CS groups (27.1 ml / m^2) and non-CES (28.5 ml / m^2) there were differences that did not reach level of statistical significance ($p = 0.06$). In a similarly designed study by Jordan K. et al. (2019) [15] LAVI indices in the CES group also significantly exceeded those among patients with non-CES (41.4 ± 18.0 vs. 28.6 ± 12.2 ml / m^2), although significant differences between the ESUS and non-CES groups were obtained was not ($p = 0.61$). In 18.2% of patients with ESUS who underwent ECG monitoring at the outpatient stage, AF was recorded, and an increased LAVI was an independent predictor of its occurrence. In another study, Kamel H. et al. (2019) [16] demonstrated that LAVI in the ESUS group exceeds that among patients with non-CES (33.3 ± 13.6 vs. 30.9 ± 10.7 ml / m^2, $p = 0.01$), which is more degree is consistent with our data.

The features of functional markers of LA in patients with CS have been studied to a much lesser extent. In the present study, it was revealed that the values of LAFI and LAEF are reduced in patients with CES in comparison with CS and non-CES, while the latter marker in these groups also had significant differences (Table 2). The obtained differences in functional markers of LA when comparing the CES group with other subtypes of stroke correspond to the results of the study by Ferkh A. et al. (2019) [28], in which LAFI and LAEF were lower in patients with CES ($n = 38$) in comparison with non-CES (this subtype included mainly stroke of unspecified etiology ($n = 42$), as well as against the background of pathology of large ($n = 9$) and small arteries ($n = 2$)). At the same time, the authors showed that LAFI⩽0.3 is an independent predictor of CES In our study, the LAFI threshold for differentiating CES and non-CES corresponded to 0.28.

It is interesting that, according to Ferkh A. et al., The volumetric indices of LA (LAVI) and its functional characteristics (LAFI) significantly differed in patients with ESUS and those in the control group. However, this study did not compare echocardiographic markers between patients with CS and non-CES due to the small size of the latter subgroup.

Our study also revealed differences in serum NT-proBNP concentration between patients with CES and CS/non-CES. The threshold value of the peptide, which allows differentiating CES and non-CES, was 316 pg/ml, which is slightly lower than the value obtained by Zhao J. et al. (2020) at 341 pg/ml [17], but higher than that determined in the work of Fonseca A.C. et al. (2014) [18], which may be due to the peculiarities of the test systems used. According to the results of the subanalysis of the Find-AFRANDOMISED study, measuring the BNP concentration in the first week after CT allows to identify the subgroup of patients in whom prolonged Holter ECG monitoring is most effective (the number needed to screen indicator decreases from 18 to 3) [29]. At the same time, Kneihsl M. and colleagues (2019) also showed that measuring the NT-proBNP concentration on the first day of CT is useful in selecting patients for extended heart rate monitoring, while its level <505 pg /ml is characterized by a high negative predictive value [19]. This approach seems to us promising for use in clinical practice, but requires verification and prospective observation in the considered cohort of patients.

Analysis of ROC curves and area under the curve revealed that LAEF, LAFI, and NT-proBNP are the most informative in terms of sensitivity and specificity. At the same time, multidirectional values of high specificity and low sensitivity are inherent for the NT-proBNP biomarker, while LAEF is characterized by a balance according to these criteria. However, this result must be interpreted with caution, as the sample size of patients in whom echocardiographic parameters were measured was larger than the number of patients with an estimated NT-proBNP concentration. Nevertheless, at present, LAEF with a cut-off value of 51.8% seems to be the most promising marker that can be used to differentiate CES from non-CES, with a corresponding determination of the cardio and noncardiophenotype among patients with CS.

It is interesting in relation to LAEF to understand its physiological meaning. It is known that the functioning of LA can be divided into 3 phases (functions) [30]: the function of the reservoir, the conduit and the booster-pump. The first phase lasts during left ventricular systole, when the LA accumulates blood from the pulmonary veins. According to some authors [31], the LAEF indicator is represented only by two subsequent components: a passive phase of fast and slow filling (early diastole), when the LA functions as a pipeline, directing the blood flow from the pulmonary veins to the left ventricle and active (late diastole - atrial systole). In late diastole, the LA functions as a pump by contraction of muscle fibers. Thus, in patients with impaired relaxation of the left ventricle, an increase in diastolic pressure leads not only to a decrease in the passive function of the LA, but also provokes pathological remodeling in the form of dilatation of the LA, expansion of the pulmonary veins with an increased risk of AF. In response to this, the proportion of the active component to maintain LAEF increases [30]. Thus, normal LAEF values reflect the functional consistency of the atrial myocardium, in which adaptive compensation is possible due to a decrease in the proportion of the passive component, and the remodeling processes associated with AF, despite LA dilatation, are reversible [31]. At the same time, other authors [28, 32] consider LAEF as an indicator reflecting the reservoir function of LA. In our opinion, LAEF characterizes a single process associated not only with the mechanism of blood transfer from the LA to the left ventricle, but also with the initial volume of deposited blood. The limitations of this study include the unequal number of patients depending on the pathogenetic subtype of stroke;

small number of patients for subgroup analysis with measured serum NT-proBNP concentration; data are obtained from examining patients at one center, which limits the extrapolation of study results to the general population.

Conclusion. Thus, the study showed that patients with CS in terms of echocardiographic characteristics of atrial cardiopathy and NT-proBNP concentration in blood serum are more similar to the non-CES group (atherothrombotic and lacunar) than to patients with CES, which requires further study of the groups under consideration. In this case, the LAEF value and the NT-proBNP concentration are the optimal markers for categorizing patients with CS into possible arterio- and cardioembolic variants. Thus, for patients with CS and LAEF less than 51.8% and/or serum NT-proBNP levels of more than 316 pg/ml, it is optimal to recommend prolonged heart rate monitoring to search for AF followed by the appointment of adequate secondary prophylaxis, while patients with the opposite result should search for a source arterio-arterial embolism.

REFERENCES

1. Nouh A, Hussain M, Mehta T, Yaghi S. Embolic Strokes of Unknown Source and Cryptogenic Stroke: Implications in Clinical Practice. *Front Neurol.* 2016 Mar 21;7:37. doi: 10.3389/fneur.2016.00037. eCollection 2016.
2. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* 2014 Apr;13(4):429-38. doi: 10.1016/S1474-4422(13)70310-7
3. Калашникова ЛА, Добрынина ЛА. Ишемический инсульт в молодом возрасте. Журнал неврологии и психиатрии им. С.С. Корсакова. Спецвыпуски. 2017;117(8):3-12. doi: 10.17116/jnevro2017117823-12 [Kalashnikova LA, Dobrynina LA. Ischemic stroke in young adults. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova = S.S. Korsakov Journal of Neurology and Psychiatry.* 2017;117(8): 3-12. doi: 10.17116/jnevro2017117823-12 (In Russ.)].
4. Кулеш АА, Огнерубов ДВ, Мехряков СА и др. Инсульт, ассоциированный с открытым овальным окном: подходы к диагностике и возможности эндоваскулярной профилактики (клинические наблюдения и обзор литературы). Неврология, нейропсихиатрия, психосоматика. 2020;12(2):72-8. doi: 10.14412/2074-2711-2020-2-72-78 [Kulesh AA, Ognerubov DV, Mekhryakov SA, et al. Patent foramen ovale-related stroke: diagnostic approaches and the possibility of endovascular prophylaxis (clinical cases and literature review). *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2020;12(2):72-8. doi: 10.14412/2074-2711-2020-2-72-78 (In Russ.)].
5. Мехряков СА, Кулеш АА, Покаленко ЕА и др. Феномен парадоксальной эмболии у пациентов с эмболическим криптогенным инсультом. Неврология, нейропсихиатрия, психосоматика. 2020;12(1):13-21. doi: 10.14412/2074-2711-2020-1-13-21 [Mekhryakov SA, Kulesh AA, Pokalenko EA, et al. The paradoxical embolism phenomenon in patients with embolic cryptogenic stroke. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2020;12(1):13-21. doi: 10.14412/2074-2711-2020-1-13-21 (In Russ.)].
6. Кулеш АА, Шестаков ВВ. Открытое овальное окно и эмболический криптогенный инсульт. Неврология, нейропсихиатрия, психосоматика. 2019;11(2):4-11. doi: 10.14412/2074-2711-2019-2-4-11 [Kulesh AA, Shestakov VV. Patent foramen ovale and embolic cryptogenic stroke. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2019;11(2):4-11. doi: 10.14412/2074-2711-2019-2-4-11 (In Russ.)].
7. Кулеш АА, Дробаха ВЕ, Шестаков ВВ. Криптогенный инсульт. Неврология, нейропсихиатрия, психосоматика. 2019;11(4): 14-21. doi: 10.14412/2074-2711-2019-4-14-21 [Kulesh AA, Drobakha VE, Shestakov VV. Cryptogenic stroke. *Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics.* 2019;11(4): 14-21. doi: 10.14412/2074-2711-2019-4-14-21 (In Russ.)].
8. Кулеш АА, Сыромятникова ЛИ, Дробаха ВЕ и др. Криптогенный инсульт: Руководство. Москва: ГЭОТАР-Медиа; 2020. 128 с. doi: 10.33029/9704-5597-5-CS-2020-1-128 [Kulesh AA, Syromyatnikova LI, Drobakha VE, et al. *Kriptogennyy insul't: Rukovodstvo* [Cryptogenic stroke: A guide]. Moscow: GEOTAR-Media; 2020. 128 p. doi: 10.33029/9704-5597-5-CS-2020-1-128 (In Russ.)].
9. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation.* 2014 May 27;129(21):2094-9. doi: 10.1161/CIRCULATIONAHA.113.007825. Epub 2014 Mar 14.
10. Kamel H, Okin PM, Longstreth WT Jr, et al. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol.* 2015;11(3):323-31.
11. Tandon K, Tirschwell D, Longstreth WT, et al. Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation. *Neurology.* 2019 Jul 23;93(4):e381-7. doi: 10.1212/WNL.0000000000007827. Epub 2019 Jun 25.
12. Kamel H, Bartz TM, Elkind MSV, et al. Atrial Cardiopathy and the Risk of Ischemic Stroke in the CHS (Cardiovascular Health Study). *Stroke.* 2018 Apr;49(4):980-6. doi: 10.1161/STROKEAHA.117.020059. Epub 2018 Mar 13.
13. Meisel K, Yuan K, Fang Q, et al. Embolic Stroke of Undetermined Source: A Population with Left Atrial Dysfunction. *J Stroke Cerebrovasc Dis.* 2019 Jul;28(7):1891-6. doi: 10.1016/j.jstrokecerebrovasdis.2019.04.004. Epub 2019 Apr 26.
14. Perlepe K, Sirimarco G, Strambo D, et al. Left atrial diameter thresholds and new incident atrial fibrillation in embolic stroke of undetermined source. *Eur J Intern Med.* 2020;75:30-4. doi: 10.1016/j.ejim.2020.01.002
15. Jordan K, Yaghi S, Poppas A, et al. Left Atrial Volume Index Is Associated With Cardioembolic Stroke and Atrial Fibrillation Detection After Embolic Stroke of Undetermined Source. *Stroke.* 2019;50(8):1997-2001. doi:10.1161/STROKEAHA.119.025384
16. Kamel H, Okin PM, Merkler AE, et al. Relationship between left atrial volume and ischemic stroke subtype. *Ann Clin Transl Neurol.* 2019;6(8):1480-6. doi: 10.1002/acn3.50841
17. Zhao J, Zhang Y, Yuan F, et al. Diagnostic value of N-terminal pro B-type natriuretic peptide for nonvalvular atrial fibrillation in acute ischemic stroke patients: A retrospective multicenter case-control study [published online ahead of print, 2020 Apr 6]. *J Neurol Sci.* 2020; 414:116822. doi: 10.1016/j.jns.2020.116822
18. Fonseca AC, Brito D, Pinho e Melo T, et al. N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients. *Int J Stroke.* 2014;9(4):419-25. doi: 10.1111/ijs.12126
19. Kneihsl M, Gattringer T, Bisping E, et al. Blood Biomarkers of Heart Failure and Hypercoagulation to Identify Atrial Fibrillation-Related Stroke. *Stroke.* 2019;50(8): 2223-6. doi: 10.1161/STROKEAHA.119.025339
20. Sargento L, Vicente Simoes A, Longo S, et al. Left atrial function index predicts long-term survival in stable outpatients with systolic heart failure. *Eur Heart J Cardiovasc Imaging.* 2017 Feb;18(2):119-27. doi: 10.1093/ehjci/jew196. Epub 2016 Sep 27.
21. Guichard JB, Nattel S. Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? *J Am Coll Cardiol.* 2017 Aug 8;70(6):756-765. doi: 10.1016/j.jacc.2017.06.033
22. Schnabel RB, Haeusler KG, Healey JS, et al. Searching for Atrial Fibrillation Poststroke: A White Paper of the AF-SCREEN International Collaboration [published correction appears in Circulation. 2020 Feb 25;141(8): e99]. *Circulation.* 2019;140(22):1834-50. doi: 10.1161/CIRCULATIONAHA.119.040267
23. Василец ЛМ, Григориади НЕ, Карпунина НС и др. Иммунный статус у больных ишемической болезнью сердца с персистирующей фибрилляцией предсердий. Клиническая медицина. 2013;(5):32-4. [Vasilets LM, Grigoriadi NE, Karpunina NS,

et al. Immune status in patients with ischemic heart disease with persistent atrial fibrillation. *Klinicheskaya meditsina*. 2013;(5):32-4 (In Russ.)].
24. Григориади НЕ, Василец ЛМ, Ратанова ЕА и др. Роль воспаления и кардиального фиброза в возникновении и становлении фибрилляции предсердий различной этиологии. Клиническая медицина. 2013;(10):34-7.
[Grigoriadi NE, Vasilets LM, Ratanova EA, et al. The role of inflammation and cardiac fibrosis in the onset and development of atrial fibrillation of various etiologies. *Klinicheskaya meditsina*. 2013;(10):34-7 (In Russ.)].
25. Elkind MSV. Atrial cardiopathy and stroke prevention. Review. Curr Cardiol Rep. 2018 Sep 12;20(11):103. doi: 10.1007/s11886-018-1053-0
26. Yaghi S, Bernstein RA, Passman R, Okin PM. Furie Cryptogenic Stroke: Research and Practice. *Circ Res*. 2017 Feb 3;120(3):527-540. doi: 10.1161/CIRCRESAHA.116.308447
27. Kamel H, Longstreth WT Jr, Tirschwell DL, et al. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods. *Int J Stroke*. 2019 Feb;14(2):207-14. doi: 10.1177/1747493018799981
28. Ferkh A, Brown P, O'Keefe E, et al. Clinical and echocardiographic characteristics of cardioembolic stroke. *Eur J Neurol*. 2019 Oct; 26(10):1310-1317. doi: 10.1111/ene.13981. Epub 2019 May 31.
29. Wasser K, Weber-Krü ger M, Grö schel S, et al. Brain Natriuretic Peptide and Discovery of Atrial Fibrillation After Stroke: A Subanalysis of the Find-AFRANDOMISED Trial. *Stroke*. 2020 Feb;51(2):395-401. doi: 10.1161/STROKEAHA.119.026496. Epub 2019 Dec 9.
30. Mehrzad R, Rajab M, Spodick DH. The three integrated phases of left atrial macrophysiology and their interactions. *Int J Mol Sci*. 2014 Aug 27;15(9):15146-60. doi: 10.3390/ijms150915146
31. Chung-Chuan Chou, Hui-Ling Lee, Po-Cheng Chang, et al. Left atrial emptying fraction predicts recurrence of atrial fibrillation after radiofrequency catheter ablation. *PLoS One*. 2018;13(1):e0191196. doi: 10.1371/journal.pone.0191196
32. Russo C, Jin Z, Liu R, et al. Left Atrial Volumes and Reservoir Function Are Associated With Subclinical Cerebrovascular Disease: The Cardiovascular Abnormalities and Brain Lesions (CABL) Study. *JACC Cardiovasc Imaging*. 2013 Mar;6(3):313-23. doi: 10.1016/j.jcmg.2012.10.019

Received/Reviewed/Accepted
27.07.2020/3.10.2020/6.10.2020

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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