Mekhryakov S.A.[1], Kulesh A.A.[1, 2], Pokalenko E.A.[1, 2], Syromyatnikova L.I.[1, 2], Kulikova S.P.[3], Drobakha V.E.[1, 2], Shestakov V.V.[2], Karakulova Yu.V.[2]

[1]City Clinical Hospital Four, Perm, Russia; [2]Acad. E.A. Vagner Perm State Medical University, Ministry of Health of Russia, Perm, Russia; [3]Higher School of Economics, Moscow, Russia

[1]26, Petropavlovskaya St., Perm 614990; [2]2, Kim St., Perm 614107; [3]20, Myasnitskaya St., Moscow 101000

The paradoxical embolism phenomenon in patients with embolic cryptogenic stroke

Patent foramen ovale (PFO) is an important cause of embolic cryptogenic stroke (ECS) in young patients. The main mechanism in this case is paradoxical embolism (PE), the basis for which is a right-to-left (R-L) shunt.

***Objective:** to comparatively characterize patients who have undergone ECS, with and without an R-L shunt, as evidenced by transcranial Doppler with the bubble test (TCD-BT).*

***Patients and methods.** In 40 patients with acute ECS, an R-L shunt was sought using TCD-BT, followed by transesophageal echocardiography (TEE). The left atrial volume index (LAVI) was additionally calculated. Brain damage was analyzed by probabilistic mapping of foci according to magnetic resonance imaging.*

***Results and discussion.** The mean age of the examined patients was 51.5 (39.5–60.0) years; of them there were 22 women and 18 men. An R-L shunt was detected in 24 (60.0%) of patients with cryptogenic embolism that was mainly grades 2 and 3 (41.0 and 35.0%). TEE could visualize PFO (1.0 to 5.5 mm in size) in 16 (40%) patients and atrial septal aneurysm in 3 (7.5%). PFO was not found in 5 patients with positive results of TCD-BT, which may suggest that there is either a pulmonary shunt or a false-negative TEE. The patients with an R-L shunt versus those without an R-L-shunt showed lower LAVIs (23.9 and 26.5 mL/m2) (p=0.016). This fact may additionally confirm the causative role of PFO in the development of stroke, whereas higher LAVIs in the non R-L shunt subgroup should alert to the presence of atrial cardiopathy and initiate an appropriate diagnostic search for latent atrial fibrillation. According to the presence or absence of an R-L shunt, the groups did not significantly differ in gender, age, and clinical characteristics of the stroke. In patients with PFO, a lesion focus was most commonly localized in the middle cerebral artery bed (35.3%), cerebellum (23.5%), and posterior cerebral artery (17.6%). Five (29.0%) patients were ascertained to have several foci of acute stroke. There was a trend towards the larger size of cerebral infarction foci and their specific localization in the vertebrobasilar bed in PE, which determined the high (35.3%) incidence of ataxia with the onset of the disease.*

***Conclusion.** PE causes ECS in 60.0% of cases. The distinctive feature of patients with an R-L shunt is lower LAVIs and a trend towards the larger size of cerebral infarction foci and their specific localization in the vertebrobasilar bed.*

***Keywords:** paradoxical embolism; patent foramen ovale; cryptogenic stroke.*

Contact:** Aleksey Aleksandrovich Kulesh; **aleksey.kulesh@gmail.com

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Cryptogenic stroke (CS) occurs in one third of patients with ischemic stroke [1, 2]. After excluding the routine examination of cardioembolism from large sources, diseases of the large and small arteries, an expanded diagnostic protocol allows you to identify causes such as brain accidents such as non-stenotic atherosclerosis, dissection, atheroma of the arch and aorta, cardioembolism from sources of medium risk, a patent foramen ovale (PFO) and hypercoagulable status [2, 3].

The determination of the CS mechanism is necessary for the effective secondary prophylaxis, the possibilities of which with an individualized approach are significantly expanded due to the introduction of direct oral anticoagulants, new antiplatelet agents, and endovascular treatment methods into routine practice. In clinical studies and routine practice, the concept of embolic stroke with an undefined source of embolism (ESUS) is used [4], which is currently undergoing active rethinking due to the neutral results obtained based on this research concepts of NAVIGATE-ESUS [5] and RESPECT-ESUS [6]. PFO is a significant cause of ESUS in young patients [7]. So, PFO is observed in 50-60% of patients with CS of young and middle age, and the probability of detecting this anomaly in them is 3 times higher than in patients with an established cause of stroke [8]. Moreover, the exact share of PFO-associated CS remains unknown, which is associated with the features of the applied methods and algorithms for diagnosing CS [9]. The main mechanism of PFO-associated ischemic stroke (IS) is paradoxical embolism (PE), which is based on the right-sided shunt (RLS) - blood flow from right to left due to PFO [10, 11].

PFO can be detected by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and transcranial dopplerography (TCD). TCD allows you to determine up to 10% of PFO missed during the TEE, and is characterized by 97% sensitivity and 93% specificity [12-14]. With TCD, it is possible to evaluate the functional value of the RLS by using bubble test - TCD-bubble study (TCD-BS). According to the provision for the management of patients with the European Cardiology Association PFO in 2019, TCD-BS is more sensitive than contrast CT-echocardiography as a diagnostic method of choice in determining the RLS [15].

Despite the relevance of the problem, in the domestic literature we have encountered only a few studies devoted to PFO in

CS. In 2008, Z.A. Suslin et al. [16], having examined 84 patients with IS, they concluded that with the specified stroke subtypes in most cases (64%) there are conditions for PE in the form of PFO and pulmonary shunt (51 and 13% of patients, respectively), while PFO is characterized by anatomical and functional features. The authors also found that readiness for PE is determined in 94% of patients with CS, is mainly due to PFO (in 88%) and is often the only cause of stroke.

In the study of M.V. Glebova [17] showed that the combination of PFO> 3 mm with a more pronounced shunt, revealed by the contrast TCD method, has an independent pathogenetic value in the development of IS. In connection with the emergence of new opportunities for secondary prevention in patients with IS against the background of PFO (endovascular occlusion), it seems relevant to optimize approaches to the diagnosis of this pathology in the conditions of the vascular departments.

Purpose is provide comparative description of patients with ECS with presence and absence of RLS according to transcranial dopplerography with bubble study (TCD-BS).

Materials and methods. In addition to the standard examinations 40 patients with ECS or transient ischemic attack were searched for RLS using TCD-BS and transesophageal echocardiography (TEE). Additionally, the measurement of the left atrial volume index (LAVI) was performed. A brain lesion was visualized using probabilistic mapping of foci.

The criteria for inclusion in the study were: age from 18 to 75 years; the presence of ECS or transient ischemic attack (TIA) [4] and the conduct of patients during hospitalization with TEE and/or TCD-BS. The study did not include patients older than 75 years; patients with a modified Rankin Scale (mRS) score before admission >3 points; patients with other neurological, psychiatric (including dementia), somatic diseases that determine the general condition; patients with complications of a stroke; patients with an established cause of stroke.

All patients underwent an examination aimed at searching for the causes of stroke, including magnetic resonance imaging (MRI) of the brain, MR angiography, duplex scanning of the carotid and vertebral arteries, TTE, electrocardiography (ECG) and holter monitoring ECG (HM-ECG).

As a result of the examination, 32 (80.0%) patients were diagnosed with IS, and 8 (20.0%) had TIA. The average NIHSS (National Institutes of Health Stroke Scale) result for admission was 2.0 points. At the same time, minor stroke was observed in 60.0% of cases, moderate stroke in 37.5% and severe stroke in 2.5%. In every 4th patient, ECS developed on awakening; in every 10th patient, an analogue of the Valsalva maneuver (physical activity) took place in the debut of the disease. According to clinical and/or neuroimaging data, in 27.5% of cases, stroke occurred in the carotid pool, in 27.5% in the vertebrobasilar and in 25.0% combined lesions of the arterial pools were noted.

Ultrasound was performed on a PHILIPS CX50. At the first stage of the search for the RLS, TCD-BS was performed. For contrasting, 9 ml of 0.9% saline was used with 1 ml of 3% hydrogen peroxide added [18]. TCD used transtemporal access with the location of blood flow in the middle cerebral artery (MCA). With the impermeability of the temporal window, suboccipital access was used [19]. The introduction of a contrast medium was accompanied by a Valsalva test. The shunt volume was graded based on the TCD data for five degrees [20]: 0th degree – the

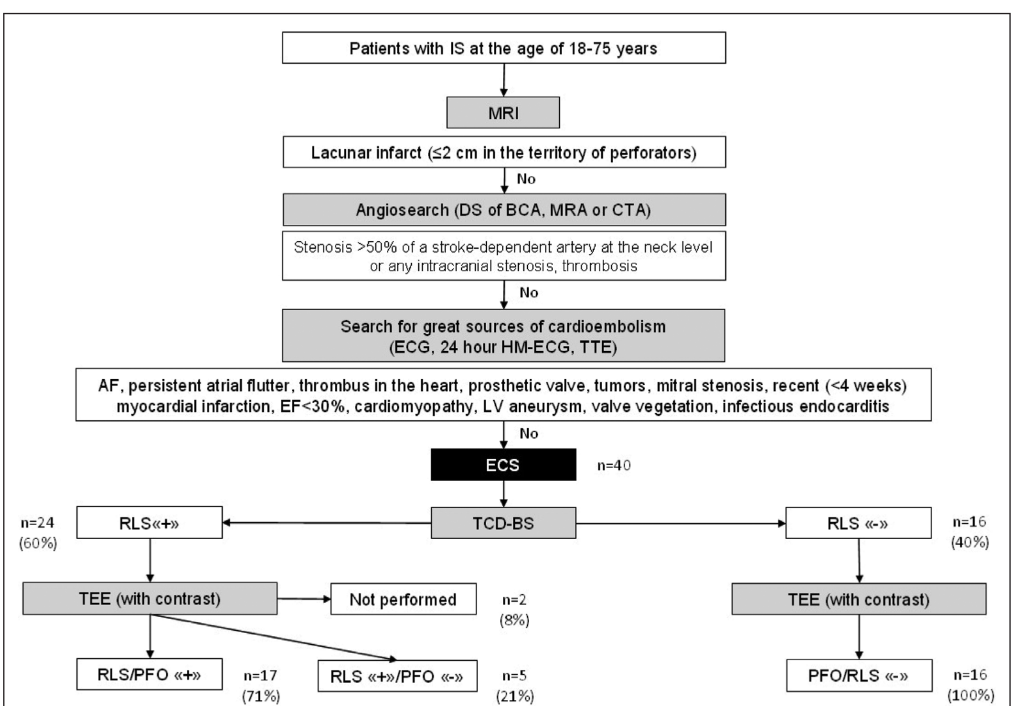

Fig. 1. *Research design. DS BCA – duplex scanning of brachiocephalic arteries; MRA – magnetic resonance angiography; CTA – computed tomographic angiography; AF – atrial fibrillation; EF – ejection fraction; LV – left ventricle; RLS – right-left shunt.*

absence of high intensity transient signals (HITS); 1st degree – 1–10 HITS; 2nd degree – 11–25 HITS; 3rd degree – > 25 («shower» effect) and 4th degree – «curtain».

The TTE was not included in the search algorithm for the RLS, since it has a low sensitivity compared to TCD-BS (45.1 versus 96.1%) [13].

At the second stage of the diagnosis of RLS, patients with a positive TCD-BS result were performed with TEE, and contrast was also used to increase the diagnostic significance. Performing a Valsalva test with TEE is difficult, therefore, as an alternative method, a short (from 10 to 20 sec.) pressure on the abdominal wall was used. The sample was regarded as positive if at least one microbubble was recorded in the cavity of the left atrium during the first 3 cardiocycles.

Additionally, the left atrial volume index (LAVI) was calculated in all patients. For this, the volume of the left atrium was first measured by the biplane method of discs (modified Simpson method) using the four-chamber and two-chamber apical positions at the end of ventricular systole. Then the volume was indexed in accordance with the surface area of the patient's body. LAVI values not exceeding 34 ml/m^2 were taken as the norm [21, 22].

The construction of probability maps of the localization of foci was performed manually and cut using the Anatomist program on T2-FLAIR images and diffusion-weighted images. The markup was carried out for each patient by three researchers. After marking, individual T2-FLAIR images were recorded using an affinity transform maximizing mutual information between images with a standard MNI152 T1 template in BrainVISA. The calculated transformation was applied to labeled foci. After conversion to the MNI space, the marked areas were combined into one image and superimposed on the MNI152 T1 template, while the color intensity encoded the number of patients in whom this voxel was assigned to the affected area.

For statistical data processing, the Statistica 10.0 application package was used. A comparative analysis of two independent groups by quantitative criteria was performed using the Mann – Whitney criterion, and by qualitative criteria, using the ?2 criterion. When conducting a correlation analysis, the Spearman criterion was used. The tables show the median and interquartile range.

Results. The general characteristics of the patients are given in table 1.

RLS in TCD-BS was detected in 24 patients: in 17 of them, TEE confirmed the presence of PFO, while in 5PFO it was not identified. Another 2 patients were not able to study due to the presence of contraindications (diverticulum and varicose veins of the esophagus). A negative result of TCD-BS in 16 patients in 100% of cases was confirmed by the data of TEE (Fig. 1).

The following is a comparative assessment of patients depending on the presence of a RLS (Table 2).

We did not reveal statistically significant differences in clinical characteristics between groups depending on the presence or absence of RLS. Among the patients with RLS, women predominated, the vast majority of the examined did not have functional limitations before the development of this stroke, cardiovascular risk factors and diseases were observed in a small part of patients. Moreover, in a quarter of cases there was a history of stroke. Upon admission to the hospital, most patients had a small neurological deficit. Based on the analysis, it was found that patients with RLS had a tendency to a rarer prehospital intake of antiplatelet agents, and large sizes of the focus of brain infarction. At the same time, the group of patients with RLS had a statistically significant higher blood red blood cell

Table 1. *General characteristics of patients with ECS (n=40)*

Criterion	Value
Medical history	
Age, years	51,5 (39,5–60,0) [21–72]
Female/male, n (%)	22 (55)/18 (45)
MRS before hospitalization >1 point, n (%)	3 (7,5)
BMI, kg/m^2	25,9 (23,1–29,4)
Smoking, n (%)	8 (20,0)
Stroke in close relatives, n (%)	7 (17,5)
History of stroke, n (%)	10 (25,0)
Coronary artery disease, n (%)	2 (5,0)
Hypertonic disease, n (%)	28 (70,0)
Diabetes melitus, n (%)	3 (7,5)
Taking antiplatelet agents before hospitalization, n (%)	9 (23,7)
Migraine, n (%)	2 (5,0)
Clinical characteristic of stroke	
Acute ischemic stroke, n (%)	32 (80,0)
TIA, n (%)	8 (20,0)
NIHSS on admission, n (%):	
0–4 points	24 (60,0)
5–14points	15 (37,5)
>15 points	1 (2,5)
Stroke, n (%):	
After awakening	10 (25,0)
After the Valsalva maneuver	4 (10,0)
Characteristic of foci of infarction	
LMCA, n (%)	7 (17,5)
RMCA, n (%)	4 (10,0)
VBB (except PCA), n (%)	6 (15,0)
PCA, n (%)	5 (12,5)
Several number of basins, n (%)	10 (25,0)
The lack of focus on MRI/CT, n (%)	8 (20,0)

Note. BMI – body mass index; LMCA – left middle cerebral artery; LMCA – right middle cerebral artery; VBB – vertebrobasilar basin: PCA – posterior cerebral artery; CT – computed tomogram.

content (p=0.031), lower LAVI parameters compared with patients without RLS (p=0.016; Fig. 2).

Probabilistic maps of localization of foci of acute cerebral infarction in patients of both groups are presented in Fig. 3.

Visual assessment of fig. 3 allows us to conclude that for patients with RLS, localization of foci of acute infarction in the vertebrobasilar basin is characteristic, while for patients without shunts, frequent involvement of deep hemispheric zones, although these differences are not statistically significant. The age of 17 patients with a RLS on the background of PFO or atrial septal defect (ASD) ranged from 22 to 70 years, women (10 out of 17) prevailed, 12 (70.6%) patients had IS, in 5 (29.4 %) - TIA. In 6 (35.3%) patients, the neurological deficit was> 5 points according to NIHSS. The most common clinical manifestations of stroke were ataxia (35.3%), aphasia (29.4%), hemiparesis (23.5%), and impaired sensitivity (23.5%). In 8 (47.1%) patients, a history of ECS triggers was not identified, and in 7 (41.2%) symptoms occurred upon awakening. The MCA basin (35.2%), as well as the cerebellum (23.5%) and the PCA region (17.6%) were most often involved in the lesion site. In 5 patients, several foci of acute infarction were visualized (29.4%). The size of the focus varied from 5 to 68 mm. RLS was found in 16 (94.1%) patients and in 1 (5.9%) - ASD; concomitant atrial septal aneurysm was detected in 3 (17.6%) cases. PFO size - from 1 to 5.5 mm. The 2nd and 3rd degrees of the RLS were most often observed (41.2 and 35.3%, respectively). The result of the Risk of Paradoxical Embolism Score (RoPE)> 5 points was observed in 10 (58.8%) patients, while in the subgroup of people over 60 years of age it was 4.3 points. In 15 (88.2%) patients at discharge, mRS ranged from 0 to 2 points.

The most illustrative examples of RLS and PFO in our patients are shown in Fig. 4.

Discussion. The present study examined a sample of middle-aged patients (51.5 years) with CS, most of whom did not have significant cardiovascular risk factors and diseases. A quarter of patients underwent stroke earlier, but without the formation of persistent functional disorders. In 4/5 patients after neuroimaging, CS was established, which in most cases showed a small neurological deficit, although more than a third of patients had a moderate stroke. It is noteworthy that in our patients the carotid and basilar basins were equally affected (27.5% each), in addition, every 4th patient had multiple infarction.

A RLS was found in TCD-BS in 24 patients, and in 17 of them, with TEE, PFO was detected. Patients with a RLS differed from patients with a negative TCD-BS by a higher content of red blood cells, a tendency to a larger heart attack and a statistically lower LAVI.

Of greatest interest, in our opinion, is the last difference. An increase in left atrium is associated with IS and mute cerebral infarction [23–25]. The determination of LAVI, which takes into account not only the volume of the left atrium, but also the surface area of the body, is currently considered the best metric for predicting a cardiovascular outcome

Table 2. *Clinical characteristics of patient groups depending on the presence of RLS*

Criterion	RLS+ (n=24)	RLS- (n=16)	p-level
Age, years	49,0 (38,5–60,5)	53,0 (45,5–59,5)	0,59 MW
Female/male, n (%)	14 (58,3)/10 (41,7)	8 (50,0)/8 (50,0)	0,87 Chi
Premorbid status			
MRS before hospitalization >0 points, n (%)	2 (8,3)	1 (6,3)	0,053 Chi
Body mass index, kg/м^2	26,5 (23,1–29,3)	24,5 (22,7–27,7)	0,36 MW
Smoking, n (%)	3 (12,5)	5 (31,3)	0,14 Chi
Coronary artery disease, n (%)	1 (4,2)	1 (6,3)	0,76 Chi
History of myocardial infarction, n (%)	0 (0)	1 (6,3)	0,21 Chi
Diabetes melitus, n (%)	1 (4,2)	2 (12,5)	0,33 Chi
Taking antiplatelet agents before hospitalization, n (%)	4 (16,6)	5 (31,3)	0,054 Chi
Stroke characteristic			
History of stroke, n (%)	6 (25,0)	5 (31,3)	0,46 Chi
NIHSS on admission, points	2 (0–6)	3 (1,5–6,5)	0,33 MW
SBP on admission, mmHg	130,2 (120,4–145,2)	132,5 (130,5–140,1)	0,32 MW
The maximum size of the lesion on MRI, mm	38,6 (13,0–53,8)	15,4 (8,5–22,5)	0,07 MW
The number of acute foci, n	1,0 (0–1)	1,0 (0–1)	0,47 MW
Total number of foci, n	1,0 (0–3)	1,5 (1–4,5)	0,42 MW
Carotid basin, n (%)	14 (58,3)	9 (56,3)	0,59 Chi
Vertebrobasilar basin , n (%)	5 (20,8)	5 (31,3)	0,54 Chi
Defeat several basins, n (%)	8 (33,3)	4 (25,0)	0,44 Chi
White matter hyperintensities (Fazekas), points	0 (0–1)	0 (0–1)	0,30 MW
Red blood cells, $\cdot 10^{12}$ g/l	4,7 (4,5–4,9)	4,5 (4,1–4,8)	0,031 MW
LAVI, ml/m^2	23,9 (22,2–27,4)	26,5 (25,4–29,6)	0,016 MW

Note. MI – myocardial infarction; SBP – systolic blood pressure; St – Student's criterion; Chi – χ^2; MW – Mann–Whitney's criterion.

[26–28]. LAVI reflects an increase in the atrial chamber, which theoretically predisposes to blood stasis, endothelial damage and thrombosis and is considered as one of the biomarkers of atrial cardiopathy [24]. The latter, even in the absence of AF, can cause ECS [29, 30].

We found that in patients with RLS, LAVI is lower than in a group of patients comparable in age, but without a RLS. Formerly K. Jordan et al. [31] showed that LAVI is associated with a cardioembolic subtype of stroke, as well as with the likelihood of detecting AF during 30-day monitoring after ECS A direct comparison of our LAVI values with those of K. Jordan et al. impossible due to significant age differences between the studied groups (average age 52.5 versus 71.3 years). Nevertheless, it can be assumed that with comparable age and burden of cardiovascular risk factors and diseases, patients with ECS without RLS are more likely to have atrial cardiopathy compared with patients with RLS, which indicates the advisability of prolonged cardiac monitoring.

It is noteworthy that atrial cardiopathy and the possibility of regression after endovascular occlusion are also described in patients with PFO. In a study of 719 patients with PFO, G. Rigatelli et al. [32] showed that in the surgical treatment group (endovascular occlusion PFO, n = 495), a larger diameter of the left atrium was preoperatively observed compared to that in the conservative therapy group, and within a year after occlusion it decreased. The increased diameter of the left atrium is associated with a permanent RLS, the presence of the "curtain" phenomenon, atrial septal aneurysm and multiple foci of brain damage. A left atrial diameter of ⩾43 mm was a predictor of a high RoPE score. In our study, the relationship between LAVI and PFO/shunt parameters was not fixed, which, in addition to the small sample size, may be associated with a smaller proportion of patients with hemodynamically significant RLS. So, in the cohort examined by G. Rigatelli et al. in 38.2% of cases there was a RLS without the Valsalva maneuver, in 63.6% - the phenomenon of "curtain" and in 36.3% - the phenomenon of "shower". Also, more than half of the patients (63.6%) had atrial septal aneurysm, which is significantly lower than the corresponding indicators in this study. Thus, a lower LAVI in the RLS group may additionally confirm the causative role of PFO in the occurrence of stroke, whereas in the subgroup without a RLS, a higher value of LAVI should alert to the presence of atrial cardiopathy and initiate an appropriate diagnostic search for latent AF.

When discussing patients with PFO and the RLS, it should be noted that the age of 4 patients exceeded 60 years, and the solution of the issue of endovascular occlusion of PFO in this subgroup is associated with the greatest difficulties. According to the European regulation for the management of patients with PFO, in a group of people over 65 years old, the decision to conduct endovascular treatment is made on an individual basis [15]. The result of the RoPE scale in patients over 60 did not reach 6 points, which corresponds to less than 50% of the probability of a causal relationship between PFO and the development of stroke [33], therefore endovascular treatment is not recommended for these patients.

Noteworthy is the high incidence (35.3%) of ataxia in the debut of stroke, associated with the involvement of the vertebrobasilar basin, especially the cerebellum. This clinical feature, taking into account the relatively young age of patients and the low severity of vascular risk factors, increases the likelihood of untimely diagnosis of stroke. The problem is aggravated by the fact that other symptoms indicating focal brain damage were absent in the patients, and in 2 patients, the heart attack focus did not form according to MRI data. In 41.2% of cases, symptoms occurred upon awakening, which confirms the importance of this clinical clue for the diagnosis of PFO-associated IS.

At the same time, we did not reveal a high frequency of immobilization and maneuver of Valsalva, known triggers of

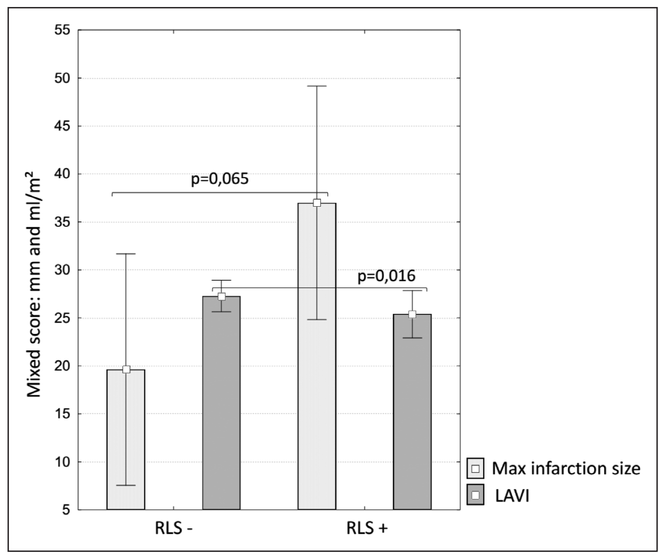

Fig. 2. *Differences in the size of the focus of infarction and LAVI between groups. Combined scale, mm; ml/m²*

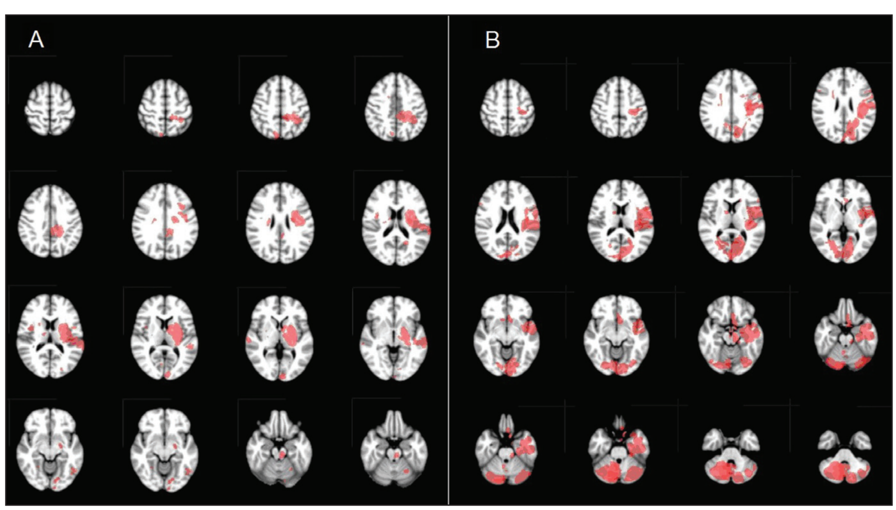

Fig. 3. *Probabilistic maps of localization of foci of acute cerebral infarction in patients with the absence of (A) and the presence of (B) RLS.*

PFO-associated stroke [34]. In 29.4% of cases there were several foci (up to 10), which is consistent with the idea of the multi-focal nature of brain damage in this category of patients. However, in the presence of a lesion, its size in most patients exceeded 20 mm, which does not allow one to consider such lesions as «small scattered» [35, 36]. In 64.7% of cases, a large PFO (⩾2 mm) was visualized [37]. The smaller size of the PFO, combined with the lower severity of the RLS, complicates the choice of treatment tactics [15]. In 6 patients the «shower» effect was revealed, and in 1 – the «curtain» effect. Moreover, the size of the RLS corresponding to ⩾20 microbubbles is one of the high-risk factors of PFO [37]. Atrial septal aneurysm, significantly increasing the etiological value of PFO was associated with PFO/ ASD in 3 of 17 patients.

The diagnostic value of various ultrasound modalities is especially clearly shown in 5 patients with positive TCD-BS results, but without revealed PFO. The result can indicate either the presence of pulmonary shunt in patients or a false-negative result of TEE. Regarding the first version, it will be fair to note that a significant drawback of TCD-BS is the impossibility of differentiating the morphological substrate of the shunt: PFO, ASD or pulmonary shunt.

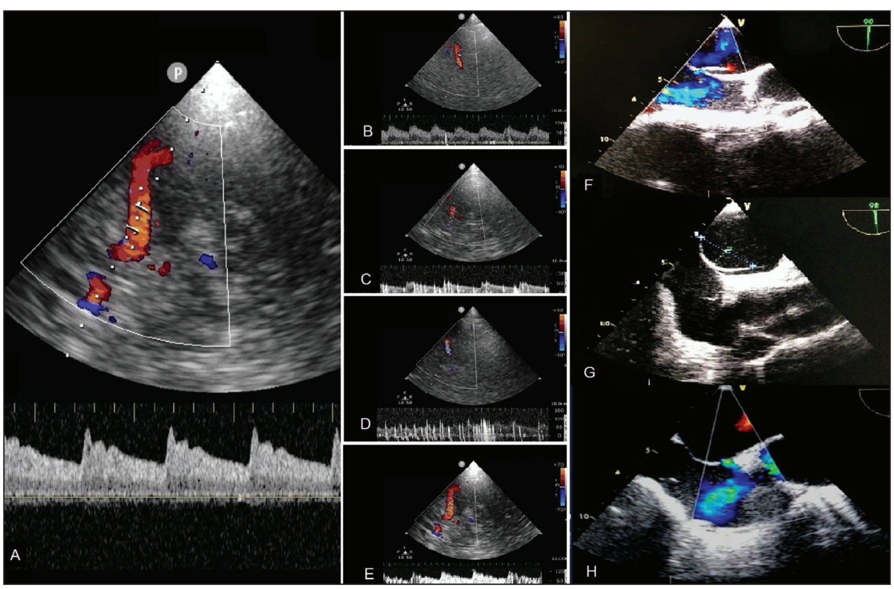

Fig. 4. *Gradation of the shunt by the number of HITS according to the TCD-BS (A–D): A – 0 degree; B – 1st degree; C – 2nd degree; D – 3rd degree; E – 4th degree. Variants of anatomical changes of interatrial septum in patients with RLS according to the data of TEE (F–H): F – PFO with left-right shunt; G – PFO with interatrial septal aneurysm; H – ASD.*

Contrast TEE is considered the «gold standard» for the diagnosis of RLS, and in some cases allows to differentiate the cardiac and pulmonary shunt. So, according to the recommendations of the American Echocardiographic Society, the presence of a cardiac shunt can be assumed if at least one microbubble of a contrast medium appeared in the left atrium after a tight filling of the right atrium during the first 3 cardiocycles. If this happened after the 5th cardiocycle, the presence of pulmonary shunt (pulmonary arteriovenous malformations) should be suspected [38, 39].

However, the use of microbubbles in the left atrium as a time criterion is an unreliable reference point and cannot be unambiguously interpreted in favor of a specific localization of the shunt. In patients with low pressure in the right atrium, a delayed Valsalva maneuver, there may be a delay in the appearance of microbubbles in the left chamber, while in patients with significant pulmonary arteriovenous malformations, an early appearance of contrast medium in the left atrium is sometimes noted. It must be pointed out that only their direct visualization can reliably differentiate cardiac and pulmonary shunts [40].

TEE, although it is a standard for diagnosing PFO and ASD, does not always make it possible to exclude the existence of a RLS. In addition to the above described, the presence of the Eustachian valve, which prevents the entry of microbubbles from the superior vena cava to the interatrial septum, can lead to false negative results of bubble study [41–43]. The fact that TEE, being the "gold standard", is also able to demonstrate a false negative result, is evidenced by the meta-analysis of M.K. Mojadidi et al. [44]. The authors showed that compared with autopsy, cardiac surgery and cardiac catheterization, TEE has only 89% sensitivity and 91% specificity. Thus, the cause of the detected RLS in 5 patients remains unknown.

Conclusion. In general, our study confirmed that PFO is a significant cause of ECS. A characteristic feature of patients with the presence of a RLS according to TCD-BS is a lower LAVI, in addition, there is a tendency to a larger size of foci of cerebral infarction with their predominant localization in the vertebrobasilar basin, as indicated by the results of probabilistic mapping of MRI data.

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