# Role of insular cortex lesions in determining the pathogenetic subtype of ischemic stroke

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*Timely evaluation of cardioembolic stroke (CES) caused by atrial fibrillation is critical from the point of view of the possibility of prescribing effective secondary prevention with oral anticoagulants. Insular lesion is considered as a promising neuroimaging marker of CES.*

***Objective:*** *to analyze the role of insular cortex lesions using magnetic resonance imaging (MRI) of the brain as a potential neuroimaging marker of the pathogenetic subtype of ischemic stroke (IS).*

***Patients and methods.*** *225 patients in the acute period of IS were examined. Depending on the stroke etiology, patients were divided into three groups: cryptogenic stroke (CS; n=99), CES (n=45), and non-CES (n=81). All patients underwent an MRI of the brain to analyze the insular cortex lesions. In 57 patients, foci of cerebral infarction were additionally marked manually on axial slices of diffusion-weighted MRI using the Anatomist software. The calculated MRI characteristics of foci for CES and non-CES groups were used to construct a decision tree in the WEKA 3.6 package. Echocardiographic markers of atrial cardiopathy were assessed in all patients - the left atrium (LA) emptying fraction and LA function index; in 68 patients, the concentration of serum NT-proBNP was also assessed.*

***Results and discussion.*** *The insula was affected in 12% of patients: most often in CES (33%), significantly less often in CS and non-CES (6 and 7.4%, respectively), without significant differences between the latter groups. The presence of insula lesion in relation to CES has a sensitivity of 33% and a specificity of 93% (p=0.002); odds ratio 6.25; 95% confidence interval 2.22–17.63. In most patients, the posterior insular cortex was involved in the pathological process. Isolated insular infarction occurred in only one patient with CES, while the involvement of the insula and adjacent zone, and the combination of insular infarction with territorial infarction, were observed more often. The group of patients with insular lesions was distinguished by the predominance of women, greater severity of stroke at admission, less deficit at discharge, larger LA diameter, lower LA emptying fraction, and functional index. CES was four times more common in the insular lesion group, while CS was two times more common in those without insular lesions. Insula involvement identifies three out of five CES patients according to the decision tree. Further analysis of the total lesion volume can locate almost all remaining patients with CES: they are characterized by the indicator >12 sm$^3$.*

***Conclusion.*** *Insular lesions allow reliable differentiation of patients with CES and non-CES and can be considered a potential marker of the cardioembolic subtype of IS, which requires further investigation.*

***Keywords:*** *cardioembolic stroke; cryptogenic stroke; magnetic resonance imaging; insula.*

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The modern concept of the development of angioneurology dictates the need not only for early reperfusion therapy in order to improve functional outcomes, but also for the appointment of personalized prophylaxis to prevent recurrent cerebral events, which is possible only if the pathogenetic subtype of ischemic stroke (IS) is established. Of particular importance is the early diagnosis of cardioembolic stroke (CES), since the appointment of oral anticoagulants in this situation can reduce the risk of recurrent cerebral catastrophe by 66% [1]. Nevertheless, in every third or fourth patient, the cause of IS remains unclear during standard examination, which makes it possible to diagnose cryptogenic stroke (CS) [2]. The etiology of CS may be due to cardioembolism against the background of an undetected embologenic source in the heart (for example, paroxysmal atrial fibrillation – AF); aorto-arterial embolism (atheromatosis of the aortic arch, non-stenosing vulnerable plaques of extra- and intracranial arteries); paradoxical, as well as cancer-associated embolism [3]. Of these reasons, latent AF is of particular importance in relation to patient management, which justifies the need to search for markers applicable in the work of vascular departments. We have previously shown that the left atrial emptying fraction (LAEF) and NT-proBNP concentration are promising biomarkers for categorizing patients with CS into possible arterio- and cardioembolic variants [4]. In the work of J. Kang et al. [5] showed that damage to the insular cortex is associated with CES. Since neuroimaging is performed for all patients with IS at admission, taking into account the factor of insular involvement seems to be useful in determining the direction of the diagnostic search.

**Purpose** is to analyze the role of damage to the insular cortex according to magnetic resonance imaging (MRI) of the brain as a potential neuroimaging marker of the pathogenetic subtype of IS.

**Patients and methods.** We examined 225 patients with IS who were urgently admitted to the neurological department of the Regional Vascular Center of Perm City Clinical Hospital No. 4. Selective inclusion of patients was carried out. The inclusion criteria for the study were age from 18 to 90 years, the presence of IS

(CES against the background of a permanent form of AF, atherothrombotic, lacunar or cryptogenic), verified by MRI of the brain. The study did not include patients with a pre-hospital study result on the Modified Rankin scale > 3 points; with other neurological, psychiatric diseases (including dementia); with somatic diseases that determine the severity of the general condition; complicated course of a stroke; patients who did not undergo MRI of the brain.

Patients underwent an examination aimed at finding the cause of IS, including MRI with angiography, duplex scanning of the carotid and vertebral arteries, computed tomography (CT) with angiography from the aortic arch, digital subtraction angiography (if indicated), transthoracic and, if indicated, transesophageal echocardiography, transcranial dopplerography with a bubble test, electrocardiography and Holter monitoring of the heart rate (from 24 to 72 hours).

Depending on the etiology of stroke, patients were divided into three groups: CS (etiology not established; n=99), CES (AF was the cause of stroke; n=45) and non-CES (another cause of stroke is atherosclerosis or cerebral microangiopathy; n=81). CS was defined as embolic CS according to the criteria for embolic stroke of undetermined source (ESUS) [3]. The number of patients in each subgroup was predetermined based on the statistical power of the sample and the possibility of subgroup analysis.

*Determination of markers of atrial cardiopathy*. During transthoracic echocardiography, LA volume was measured in all patients by the biplane disc method (modified Simpson method) using four- and two-chamber apical positions at the end of ventricular systole and at the end of ventricular diastole. These indicators were indexed according to the surface area of the patient's body. The functional characteristic of the LA was determined using two parameters – left atrial emptying fraction (LAEF) and left atrial function index (LAFI) [6]. In 68 patients on the 4th–7th day of illness, the concentration of pro-natriuretic N-terminal peptide B-type (NT-proBNP) was determined using standard test systems for enzyme immunoassay.

*MRI of the brain*. On days 5–10, all patients underwent MRI of the brain using a Brivo MR355 high-field magnetic resonance tomograph (GE Helthcare, USA) with a magnetic field strength of 1.5 T. The study protocol included a number of pulse sequences: T2, T1, FLAIR (Fluid Attenuation Inversion Recovery); T2 Star Weighted ANgiography (SWAN) gradient sequence and Diffusion-Weighted Imaging (DWI). The following parameters characterizing acute insular infarction were analyzed: the affected part (anterior, middle, posterior), isolated involvement, damage to adjacent parts of the brain, the presence of a large territorial infarction in the basin of the middle cerebral artery (MCA) and distant foci of infarction.

In 57 patients, foci of cerebral infarction were additionally marked manually on axial slices of diffusion-weighted MRI images using the Anatomist software [7]. Diffusion-weighted images and their corresponding binary masks of foci were combined with individual structural T1-images using an affine transformation implemented in the DIPY package [8]. Individual T1 images and foci masks combined with them were reduced to the general template MNI 152 ICBM 2009c [9] using the registerLesionToTemplate function of the specialized LESYMAP software [10]. To assess the degree of damage to the basins of the anterior, middle, and posterior cerebral arteries, as well as the involvement of the cerebellum and brainstem, masks of the corresponding territories marked on the general MNI template were used [11]. Additional masks for the left and right hemispheres were manually created using the Anatomist software to assess insular involvement on the general MNI template. Both the facts of the presence of a lesion in the indicated areas and the given volumes of lesions in the corresponding areas were analyzed. The calculated MRI characteristics of lesions for CES and non-CES groups were used to construct a decision tree in the WEKA 3.6 package [12]. The resulting decision tree was used to evaluate the most likely IS subtype in the CS group.

Table 1. *General characteristics of the study participants*

| Indicator | General group (n=225) | CS* (n=99) | CES** (n=45) | non-CES*** (n=81) | p-value |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | |
| Age, years* | 66 [57; 71] | 62,5 [54; 70] | 70,5 [67; 76] | 67 [58; 72] | $p_{1-2}$<0,001 $p_{1-3}$=0,020 $p_{2-3}$=0,005 |
| Female, n (%) | 105 (40,5) | 57 (44,5) | 22 (69) | 26 (26) | $p_{1-3}$=0,001 |
| BMI, kg/m$^2$* | 27 [24; 30] | 26,9 [23,7; 30] | 27,5 [25; 30] | 26,9 [24; 29] | NS |
| Артериальная гипертензия, n (%) | 247 (95,3) | 119 (92,9) | 32 (71) | 96 (96,9) | NS |
| AF, n (%) | 45 (20) | 0 | 45 (100) | 0 | – |
| IHD (angina, PICS), n (%) | 75 (33,3) | 19 (19,2) | 27 (60) | 29 (35,8) | $p_{1-2}$<0,001 $p_{1-3}$=0,012 $p_{2-3}$=0,009 |
| Stroke-associated artery stenosis >50% or occlusion, n (%) | 25 (11,1) | 0 | 0 | 25 (30,9) | – |
| Diabetes melitus, n (%) | 55 (24,4) | 25 (25,3) | 11 (24,4) | 19 (23,5) | NS |
| History of stroke, n (%) | 59 (26,2) | 29 (29,3) | 11 (24,4) | 19 (23,5) | NS |
| NIHSS upon admisson, points* | 6 [3; 8] | 6 [3,5; 8,5] | 7,5 [4; 10] | 6 [3; 8] | NS |
| NIHSS at discharge, points* | 2 [1; 5] | 4 [1; 6] | 2 [1; 4] | 2 [1; 5] | NS |
| Rankin scale at discharge, points* | 2 [1; 3] | 2 [1; 3] | 2 [1; 3] | 2 [1; 3] | NS |

***Note.*** * – values are presented as: Me [25th; 75th percentile]. BMI – body mass index; AF – atrial fibrillation; IHD – ischemic heart disease; PICS – postinfarction cardiosclerosis; NIHSS – stroke scale of the US National Institutes of Health. NS – differences are statistically insignificant.

*Statistical* processing was carried out using the Statistica 10.0 software package (StatSoft Inc., USA), the Python programming language, and the Scipy and Statsmodels libraries. Comparative analysis of two independent groups by quantitative trait was performed using the Mann–Whitney test, by qualitative trait – using the ?2 test, analysis for evaluating the threshold – using the Welch test. When conducting the correlation analysis, the Spearman test was used. The average values in the tables are presented as a median (Me) [25th; 75th percentile].

Table 2. *Characteristics of insular lesions*

| Indicator | General group (n=225) | CS (n=99) | CES (n=45) | non-CES (n=81) | p-value |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | |
| Insular infarction, n (%) | 26 (12) | 6 (6) | 15 (33,3) | 5 (7,4) | $p_{1-2}$<0,001 $p_{2-3}$<0,001 |
| Right/left, n (%) | 10 (39) / 16 (61) | 2 (33) / 4 (67) | 6 (40) / 9 (60) | 2 (40) / 3 (60) | – |
| Part of the insula: | | | | | |
| anterior | 8 | 4 | 3 | 1 | – |
| middle | 13 | 3 | 8 | 2 | – |
| posterior | 19 | 5 | 12 | 2 | – |
| Isolated infarction, n (%) | 1 (0,4) | 0 | 1 (2,2) | 0 | – |
| Insula + adjacent zone, n (%) | 24 (10,6) | 5 (5) | 14 (31,1) | 5 (6,2) | – |
| Insula + remote zone, n (%) | 4 (1,7) | 1 (1) | 2 (4,4) | 1 (1,2) | – |
| Insula + territorial infarction, n (%) | 11 (4,9) | 5 (5) | 3 (6,6) | 3 (3,7) | – |

Table 3. *Comparative characteristics of patients with and without insular infarctions*

| Indicator | Patients with insular infarction (n=26) | Patients without insular infarction (n=199) | p-value |
|---|---|---|---|
| Age, years* | 69 [58; 71] | 66 [58; 72] | NS |
| Sex, male/female, n (%) | 10 (39) / 16 (61) | 120 (60) / 79 (40) | 0,027 |
| IHD, n (%) | 13 (50) | 62 (31) | 0,058 |
| Diabetes melitus, n (%) | 8 (31) | 47 (24) | NS |
| CES, n (%) | 15 (58) | 30 (15) | <0,001 |
| non-CES, n (%) | 5 (19) | 75 (38) | 0,062 |
| КИ, n (%) | 6 (23) | 93 (47) | 0,021 |
| LA diameter, cm* | 4,2 [3,5; 4,6] | 3,7 [3,4; 4,1] | 0,034 |
| LAVI, ml/m$^2$* | 34,7 [25,6; 42,3] | 28,3 [25,1; 34,9] | NS |
| LAEF, %* | 50,8 [48,0; 53,9] | 53,7 [50,4; 56,2] | 0,004 |
| LAFI, units* | 0,31 [0,20; 0,43] | 0,37 [0,28; 0,45] | 0,027 |
| EF, %* | 58 [56; 62] | 58 [50; 60] | NS |
| NT-proBNP, pg/ml* | 422,3 [155,5; 690,9] | 198 [46; 531,5] | NS |
| NIHSS upon admission* | 9,5 [7; 14] | 6 [3; 8] | <0,001 |
| NIHSS at discharge* | 2 [1; 5] | 3,5 [1; 11] | 0,009 |
| mRS at discharge* | 2 [1; 4] | 2 [1; 3] | NS |

***Note.*** * – values are presented as: Me [25th; 75th percentile]. IHD – ischemic heart disease; LAVI – left atrial volume index; EF – left ventricle ejection fraction; mRS – modified Rankin Scale.

**Results.** The formed groups of patients differed in age (the largest – in CES, the smallest – in CS), gender (there were more women in the CES group than in the non-CES group) and the incidence of coronary heart disease (CHD; most often observed in CES, the least CS); no differences in other parameters were found (Table 1).

The insula was affected in 12% of patients: most often (33%) in CES, much less frequently in CS and non-CES (6 and 7.4%, respectively), without significant differences between the last two groups. Thus, the islet lesion in relation to CES has a sensitivity of 33% and a specificity of 93% (p=0.002). The odds ratio for CES in patients with insular lesion is 6.25 (95% CI, 2.22–17.63). The left insula was more commonly affected. In most patients, the posterior insular cortex was involved in the pathological process, in half of the patients the middle part was involved, the anterior insula suffered least of all. Isolated insula infarction occurred only in one patient with CES, lesions of the insula and adjacent zone were more often observed, as well as a combination of insula infarction with territorial infarction (Table 2).

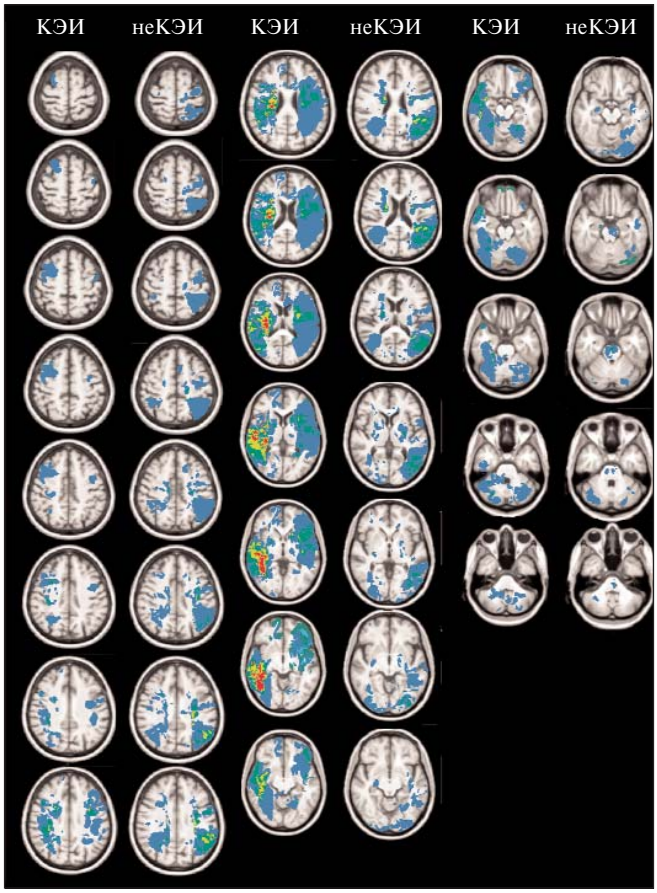


**Fig. 1.** *Spatial distribution of stroke foci in CES and non-CES groups. Heat maps superimposed on axial sections of MR-images show how often the selected voxels belonged to the area of the stroke focus in the corresponding group of patients: red – voxels assigned to the focus area in four or more patients in the group; yellow – in three patients of the group; green – in two patients; blue – voxels that were assigned to the focus area only in one patient from the group*

The group of patients with insular lesions was distinguished by the predominance of women, greater severity of stroke at admission and less deficit at discharge, larger LA diameter, lower LAEF and LAFI values, and the pathogenetic structure of stroke: CES was 4 times more common in the insular lesion group, while CS – 2 times more often in the group without insular lesions (Table 3).

Due to the small number of patients with insular lesion in the CS group (n=6), it is not possible to assess the differences between CS subgroups with and without insular involvement. The

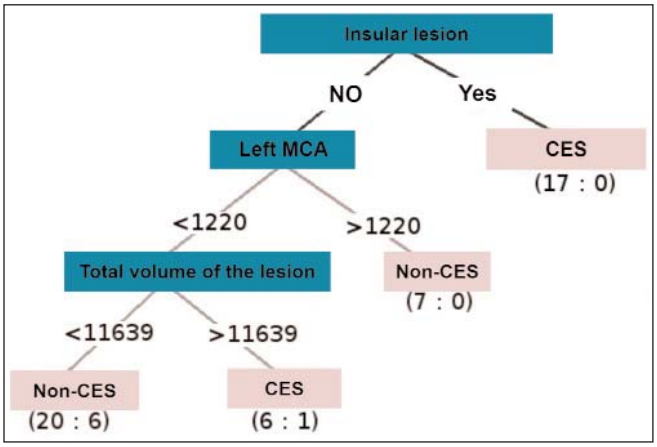


**Fig. 2.** *Decision tree for classifying CES and non-CES groups based on MRI characteristics of the lesion. The numbers in brackets in the leaves of the tree reflect the number of correctly and incorrectly classified cases, respectively*

spatial distribution of foci of cerebral infarction in the CES and non-CES groups is shown in Fig. 1.

A decision tree for the classification of groups (CES and non-CES), built on the basis of MRI characteristics of the lesion, showed that the presence of an insular lesion makes it possible to distinguish a subgroup of 17 people from 57 patients who had marked foci (or 59% of all patients in the group CES, which included 29 people), containing only patients with CES. Further, from the remaining 40 patients, a subgroup of 7 patients in the non-CES group (25% of all patients in the non-CES group) can be distinguished, characterized by a relatively extensive lesion of the MCA basin (>1220 $mm^3$). For the classification of the remaining 33 patients, the most informative was the total volume of the lesion: the group with a large lesion volume contained mainly patients from the CES group (6 people out of 7), and the group with a lesion volume <11,639 $mm^3$ – patients from the non-CES group (20 people from 26; Fig. 2).

**Discussion.** The study showed that insular involvement occurs in 12% of patients with IS and is 5 times more common in CES compared to other stroke subtypes. CES was diagnosed in 58% of patients with insula infarction and only in 15% of patients without this lesion, while CS was observed in almost half of patients with an intact insula and only in a quarter of patients with this localization of infarction. Thus, the islet lesion in relation to CES has 33% sensitivity and 93% specificity. The data obtained generally correlate with the results of the study by J. Kang et al. [5], in which insular infarction was observed in 8.5% of patients with IS, the incidence of CES with islet involvement was 53%, while in patients without insula involvement it was 30%. Analysis of data from the Athens Registry (1212 patients with insular infarction) revealed that CES occurred in 47% of patients, while stroke of unknown etiology occurred in 34% of those examined [13].

The analysis of insular involvement demonstrated that in the study population, patients with CS are similar in this factor to patients with non-CES. Our previous study also showed that patients with CS in terms of echocardiographic characteristics of atrial cardiopathy and serum NT-proBNP concentrations are more similar to non-CES than to patients with CES [4], which confirms the need for an in-depth assessment of potential sources of aortic – arterial embolism (CT with angiography function, MRI of atherosclerotic plaques, transesophageal echocardiography, transcranial Doppler monitoring) in this group [14].

In terms of the prevalence of insular infarcts, most patients had involvement of the insula and the adjacent zone, as well as a combination of insular infarction with territorial infarction, which is typical for MCA embolic occlusion. It is known that the insula is directly supplied with blood by the proximal sections of the two main branches of the MCA (M2), where they depart from the main trunk at a right angle. This anatomical feature predisposes to embolism, especially in AF, when the embolus occludes the M1 to M2 junction. The insula is sensitive to ischemia, as it lacks pial collateral blood flow from the anterior and posterior cerebral arteries [15]. This fact, combined with the fact that CES is characterized by distal migration of the embolus [16], probably explains the damage to the islet and adjacent zones with a twofold less frequent development of territorial infarction. Thus, the insular lesion is a pathogenetically substantiated marker of CES. It is noteworthy that, with initially greater severity of IS, patients with insular lesions were characterized by better clinical dynamics than patients with an intact insula, which also correlates with the results of the study by J. Kang et al. [5] and may be associated with the already mentioned migration of the cardioembolus, which determines, in particular, the "dramatic improvement" that occurs in 5–12% of patients [16].

The study also showed that patients with insular lesion are characterized by the presence of echocardiographic signs of atrial cardiopathy, which correlates with a fourfold higher incidence of CES in this subgroup. An analysis of the relationship between insular lesions and markers of atrial cardiopathy in patients with CS, which is impossible in the framework of this work due to the small sample size, seems promising in relation to the development of algorithms for diagnosing the causes of this type of stroke.

The semi-automated analysis of the localization and size of infarct foci (lesion load analysis) used in the study demonstrated that the very fact of insular lesion makes it possible to identify three out of five patients with CES. Further analysis of the total volume of the lesion makes it possible to identify almost all remaining patients with CES: they are characterized by the value of this indicator >12 $cm^3$. The applicability of this algorithm in patients with CS should be evaluated in future studies.

**Conclusion.** Thus, the insular lesion makes it possible to reliably differentiate patients with CES and non-CES and can be considered as a potential marker of the cardioembolic subtype of CS, which requires further research.

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**Conflict of Interest Statement**

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