Review

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Atrial Cardiomyopathy and Cryptogenic Stroke

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BACKGROUND The frequency of cryptogenic stroke (CS) is about 30% of all cases of ischemic stroke (IS). Patients with CS represent a heterogeneous group of patients and require an individualized approach to antithrombotic therapy for secondary prevention. The frequency of development of repeated acute cerebrovascular events in patients with CS is 4.5% per year, which exceeds this indicator in patients with an established pathogenetic variant of IS. Until recently, the dominant point of view, suggesting that the main cause of CS is paroxysmal atrial fibrillation (AF) and for the secondary prevention of IS in this cohort of patients, oral anticoagulants may be more effective than antiplatelet agents, has not been confirmed. The causal relationship between IS and AF is currently not fully understood. Apparently, AF serves as a marker of atrial cardiomyopathy, which is the direct cause of IS.

AIM OF STUDY Raising the awareness of neurologists about the causes, pathogenetic mechanisms of development and methods for diagnosing IS in patients with atrial cardiomyopathy.

MATERIAL AND METHODS To achieve this aim, the results of scientific studies on atrial cardiomyopathy as a risk factor for CS were analyzed. The literature search was carried out in electronic search systems Scopus, eLibrary, PubMed using the keywords: ischemic stroke, cryptogenic stroke, atrial cardiomyopathy, pathogenesis of ischemic stroke. Scientific articles published between 1957 and 2021 were selected to be analyzed. And 36% of the analyzed papers on the topic of CS were published no more than 5 years ago.

CONCLUSION The cumulative evidence suggests that atrial fibrillation is not the only cause of embolic events in patients with evidence of atrial dysfunction. Atrial cardiomyopathy can be the cause of thromboembolic syndrome and cryptogenic stroke, even in the absence of atrial fibrillation, therefore, the latter should be considered as a common manifestation of the underlying atrial cardiomyopathy. Since the majority of cardiac thrombi in patients with atrial fibrillation originate in the left atrium, it is likely that patients with atrial cardiomyopathy and cryptogenic stroke represent a group of patients who may be indicated for anticoagulant therapy as a secondary prevention of ischemic stroke and systemic embolism. However, this hypothesis needs to be confirmed.

Keywords: ischemic stroke, cryptogenic stroke, atrial cardiomyopathy, pathogenesis of ischemic stroke

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AF - atrial fibrillation
ASA - acetylsalicylic acid
CI - confidence interval
CS - cryptogenic stroke
ECG - electrocardiogram
IS - ischemic stroke
LA - left atrium
MPAC - multiple premature atrial contractions
MRI - magnetic resonance imaging
OD - odds ratio
OFO - open foramen ovale
PSVT - paroxysmal supraventricular tachycardia

The frequency of cryptogenic stroke (CS) is about 30% of all cases of ischemic stroke (IS). Patients with CS represent a heterogeneous group of patients and require an individualized approach to antithrombotic therapy for secondary prevention of CS. The frequency of development of repeated acute disorders of cerebral circulation in patients with CS is 4.5% per year, which exceeds this indicator in patients with an established pathogenetic variant of IS [1]. Until recently, the dominant point of view, suggesting that the main cause of CS is paroxysmal atrial fibrillation (AF) and for the secondary prevention of IS in this cohort of patients, oral anticoagulants may be more effective than antiplatelets, has not been confirmed. Thus, the results of the NAVIGATE ESUS and RE-SPECT ESUS studies, which purpose was to study the safety and efficacy of oral anticoagulants (rivaroxaban and dabigatran) compared with acetylsalicylic acid (ASA) in patients meeting the ESUS criteria, showed that the frequency of bleeding in groups of patients treated with rivaroxaban and dabigatran is higher compared to the results of using ASA, and the effectiveness in preventing recurrent IS and (or) systemic embolism does not exceed that of ASA [2, 3]. Moreover, in 70% of patients with CS, continued electrocardiographic (ECG-) monitoring, even after 36 months, did not reveal AF paroxysms, which was another evidence of the heterogeneity of the group of patients with CS [4].

The causal relationship between IS and AF is currently not fully understood. In the ASSERT and TRENDS studies, AF paroxysms were registered only in 25% of patients 30 days before a cerebrovascular event using an implantable device [5, 6]. This temporal uncertainty suggested that AF is not the main cause of IS. Apparently, AF serves as a marker of atrial cardiomyopathy, which is the direct cause of IS [7]. Also in favor of the concept of atrial cardiomyopathy as the main cause of thrombosis are the results of the study by *Warraich H.G. et al*. (2014), who recorded blood flow in the left atrial appendage (LA), characteristic of AF, in 25% of patients with paroxysmal AF and IS during transesophageal echocardiography against the background of sinus rhythm [8]. Moreover, histological analysis of blood clots extracted from large cerebral arteries in patients with CS and cardioembolic pathogenetic variant of IS showed a similar composition of the ratio of fibrin/platelets, RBC and WBC. However, the composition of thrombi in patients with CS was significantly different from that in patients with noncardioembolic IS in terms of the fibrin/platelet ratio [9].

Thus, the concept of atrial cardiomyopathy was formed, which, even in the absence of AF, can be a source of acute cerebral embolism. The term "cardiomyopathy " was first introduced by *Bridgen W.* in 1957 to refer to isolated non-coronary myocardial disease [10]. The concept of atrial cardiomyopathy was proposed in 1972 by *Nagle R.E. et al.* who described a familial syndrome, which is expressed exclusively by damage to the atria and the atrioventricular conduction system and is accompanied by an ectopic supraventricular rhythm and atrioventricular block [11]. Working group consensus of the European Heart Rhythm Association (EHR*A*), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Society for Pacing and Electrophysiology (SOLAECE), in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA) defined atrial cardiomyopathy as a complex of structural, contractile, or electrophysiological changes that affect the atria and contribute to the development of clinically significant manifestations [12].

Atrial cardiomyopathy results from many pathophysiological processes, including systemic and subclinical pro-inflammatory conditions such as arterial hypertension, diabetes mellitus, obesity, chronic coronary heart disease, sleep apnea, and elder age [13]. These factors, interacting with each other, lead to the activation of the renin-angiotensin-aldosterone system and the production of angiotensin II, thereby inducing cardiomyocyte hypertrophy, endothelial dysfunction and myocardial fibrosis. Among other things, angiotensin II activates the

production of reactive oxygen species, which leads to an overload of calcium ions and, as a result, electrical myocardial remodeling. Also, angiotensin II inhibits the production of transforming growth factor β by cardiomyocytes and fibroblasts, which leads to atrial fibrosis. The result of all of the above is the electrical and structural remodeling of the myocardium. Moreover, these pro-inflammatory conditions lead to infiltration of inflammatory cells into the myocardium. Inflammatory cytokines promote the production of tissue factor, thereby inducing thrombus formation [13].

Atrial cardiomyopathy, even in the absence of AF, predisposes to intracardiac thrombus formation, which may be the cause of CS [13]. From a practical point of view, the use of anticoagulants in patients with atrial cardiomyopathy may be more effective in the secondary prevention of IS than antiplatelet therapy. The validity of this hypothesis will be established after the results of the ARCADIA study are published [14].

According to the SPOTRIAS analysis, approximately 65% of patients with CS have at least one marker of atrial cardiomyopathy. Since only 30% of patients with CS will have AF verified, therefore, in 35% of patients, atrial cardiomyopathy is not combined with AF [7]. Recent studies confirm the fact that atrial cardiomyopathy is a risk factor for IS, regardless of the presence of AF [15, 16]. Atrial cardiomyopathy, according to Ahmad M.I. et al. (2020), increases the risk of a fatal outcome of IS by 76% (hazard ratio 1.76; 95% CI (confidence interval) from 1.02 to 3.04) [17]. The results of the CHS study showed that such markers of cardiomyopathy as the voltage of the terminal part of the P wave in lead VI and the concentration of natriuretic peptide in the blood plasma are independently associated with the risk of IS [18]. According to *Sebasigari D. et al*. (2015), such markers of atrial cardiopathy as LA expansion, prolongation of the *PR* interval, and voltage of the terminal part of the *P wave* in lead VI were weakly associated with the detection of AF in patients with CS, which once again confirms the hypothesis of embologenicity mechanisms independent of the presence of AF. atria [19].

Currently, a number of markers of atrial cardiomyopathy have been established, which can be divided into three groups: radiological, electrocardiographic and laboratory.

RADIOLOGICAL MARKERS OF ATRIAL CARDIOMYOPATHY

Echocardiographic ones include the expansion of the LA, a decrease in the blood flow velocity in it, as well as the phenomenon of spontaneous echo contrast, etc. [7, 20, 21].

It has been established that LA expansion is associated with an increased risk of thromboembolic events even in the absence of AF. So, in the study of *Arauz A. et al*. (2019) found that the LA size index (cutoff point 3 cm/m2 ; odds ratio (OR) 7.5, 95% CI 1.24–45.2; $p = 0.02$), as well as the spherical index LA levels (cut-off point 42 cm^3/m^2, OR: 6.5; 95% CI, 1.32–32.07, $p = 0.02$) are predictors of thromboembolic events [22]. *Di Tullio MR et al*. (1999) found that the LA index is associated with the risk of developing IS (adjusted OR 1.47 per 10 mm/1.7 m^2, 95% CI 1.03–2.11) [23]. According to *Jing Chen et al*. (2021), the frequency of verification of pronounced LA expansion (more than 47 mm) in patients with CS was significantly higher than in patients with atherothrombotic and lacunar pathogenetic variants of IS (5.3% vs. 1.6%, $p = 0.014$ and 5.3 % versus 1.2%, $p = 0.008$, respectively) [24]. However, in a previous study by *Jalini S. et al* . (2019) found no such differences [25]. It was also found that moderate and pronounced expansion of the LA are independent risk factors for recurrent IS [20].

A decrease in blood flow velocity in the LA auricle can contribute to blood stasis and, as a result, thrombus formation. For example, in a study by *Lee JM et al*. (2014) indicators of blood flow velocity in the LA appendage in patients with IS were statistically significantly lower than in patients without IS (36±19 cm/s versus 55±20 cm/s, $p < 0.001$) [26].

Morphological features of the LA appendage may predispose to thrombus formation even in the absence of AF [27, 28]. In a study by *Di Biase L. et al*. (2012) revealed the following prevalence of anatomical forms of the LA abalone: "chicken wing" — 48%, "cactus" — 30%, "windsock" — 19%, "cauliflower" — 3% [27]. The results of the study showed that the “chicken wing” shape of the LA is the least likely to predispose to the development of thrombotic complications, while the “cauliflower” shape, on the contrary, has the highest ability to predispose to thrombotic events [27]. The hemodynamic feature of patients with the “chicken wing” form of the LA was a statistically significantly higher blood flow rate compared to that in patients with other anatomical forms of the LA (55±19 versus 41±20 cm/s, $p < 0.001$), as well as a smaller area of the LA auricle opening (4.4±1.6 vs. 4.9±2.2 cm^2, p = 0.013), which apparently determined the low predisposition to thrombus formation [28, 29].

Another morphological prerequisite that increases the risk of thrombus formation in the LA appendage is the number of anatomical lobules of the LA. In a study by *Yamamoto M. et al.* (2014), the number of anatomical lobules of the LA in patients with AF turned out to be an independent risk factor for thrombosis [30]. The absolute majority of patients (94.4%) with verified thrombosis of the LA appendage had at least 3 anatomical lobules of the LA appendage [30].

Magnetic resonance imaging (MRI), in addition to assessing the shape of the LA, allows assessing the severity of its fibrous changes. In a study *by Akoum N. et al.* (2013), using high-field contrast enhanced MRI, it was found that signs of fibrosis of the LA auricle are associated with a decrease in blood flow velocity in it, which can lead to blood stasis, thrombosis, and, as a result, IS [31]. *Marrouche N.F. et al*. (2014) found that LA fibrosis in patients with AF who underwent radiofrequency catheter ablation was independently associated with the likelihood of AF recurrence [32]. Also, using contrast-enhanced MRI of the heart, a relationship was established between the severity of LA fibrosis and IS in history. Thus, in patients with a history of AF and IS, the severity of LA fibrosis was significantly higher than in patients with AF alone [33]. In the study by *Fonseca A.* (2018), the severity of LA fibrosis was statistically significantly higher in patients with CS than in patients with an established cause of IS (18% vs. 10.5%, $p = 0.03$), while being comparable to the group of patients with AF [34]. However, the prevalence of cardiomyopathy according to cardiac MRI in patients with IS did not exceed 5.3% (5% in cardioembolic, 8.6% in CS, and 0% in patients with other pathogenetic variants) [35]. Thus, cardiac MRI may be a useful diagnostic tool in patients with CS to assess the structure and anatomy of the LA, as well as to assess the risk of recurrent IS. However, the relationship between LA fibrosis and stroke risk in the absence of AF is currently unclear, requiring further research.

ELECTROCARDIOGRAPHIC MARKERS OF ATRIAL CARDIOMYOPATHY

Electrocardiographic markers of atrial cardiomyopathy are paroxysmal supraventricular tachycardia, prolongation of the PR interval, terminal P wave voltage in lead VI of more than 5000 μV ms, and *P* wave widening [36–39].

In a study by *Kamel H. et al*. (2013) found that paroxysmal supraventricular tachycardia (PSVT) is an independent risk factor for IS. Thus, the cumulative incidence of IS in patients with PSVT significantly exceeded that in patients without PSVT (0.94%; 95% CI, 0.76-1.16% vs. 0.21%; 95% CI, 0.21-0, 22% respectively) [39]. It was also found that paroxysms of AF were recorded in 12% of patients with PSVT during the year [40].

In a study *by Jalini S. et al*. (2019), such a marker of atrial cardiomyopathy as the voltage of the terminal part of the P wave in lead VI of more than 5000 μV ms was statistically significantly more often detected in patients with CS compared with patients with atherothrombotic and lacunar pathogenetic variants of IS (26.6% versus 9.4 % and 15.6%, $p < 0.001$, respectively) [25].

According to *Thijs V.N. et al*. (2016), prolongation of the *PR interval* on the electrocardiogram is associated with an increased likelihood of detecting AF paroxysm in patients with CS [41]. In a study by *Montalvo M. et al*. (2017), prolongation of the PR interval up to 200 ms or more was statistically significantly more often detected in patients with CS than in patients with noncardioembolic stroke of established etiology (23.2% vs. 13.8%, $p = 0.009$) [36].

P wave expansion or atrial block occurs when conduction from the right to the left atrium is impaired, usually at a point close to the atrial septum [42]. In turn, interatrial block is associated with AF and atrial cardiomyopathy [43, 44]. Conduction of an impulse from the right atrium to the left occurs through discrete communications, the most significant of which is the Bachmann bundle, which runs along the upper part of the interatrial septum. *Ariyarajah V. et al*. (2006) suggested that stretching or increasing pressure in the upper part of the interatrial septum can lead to dysfunction of the Bachmann's bundle and, as a result, the formation of interatrial block of impulse conduction [45]. For example, in a study by *Cotter P.E. et al*. (2011), the frequency of detection of interatrial block in patients with CS and open foramen ovale (OFO) was higher than in patients with CS without OFO, as well as in a group of healthy respondents (46.3%, 21.4% and 15%, respectively) [46]. Meta-analysis by *He J. et al.* (2017) showed that the expansion of the P wave to 110–120 ms or more is an independent risk factor for IS [38]. Thus, the expansion of the P wave on the ECG may reflect a violation of intra-atrial conduction and be a biomarker of atrial cardiomyopathy.

Bayes syndrome, characterized by the simultaneous presence of supraventricular arrhythmia and severe interatrial blockade, is another marker of atrial cardiomyopathy. It has been established that this syndrome increases the risk of developing IS, as well as vascular cognitive impairment [47, 48].

Multiple premature atrial contractions (MPAC) in a study by *Jung-Joon Cha et al.* (2020) were associated with the risk of recurrent IS in patients with CS. The incidence of AF in patients with C and MPAS was statistically significantly higher than in patients without MPAS (4.4% vs. 1.2%, $p = 0.019$). However, multivariate analysis showed that MPAS is an AF-independent risk factor for recurrent IS in patients with CI (RR 2.49, 95% CI, 1.05–5.88, $p = 0.038$) [49].

LABORATORY MARKERS OF ATRIAL CARDIOMYOPATHY

Laboratory markers of atrial cardiomyopathy include brain natriuretic peptide and cardiac troponin [50-53].

Brain natriuretic peptide is a serum marker that is released by the myocardium in response to stretch, and its level increases in heart failure and other structural damage to the heart. It has been established that brain natriuretic peptide is an independent predictor of cardiovascular and cerebrovascular events. In a study by *Rodriguez-Yanez M. et al.* (2013), a natriuretic peptide concentration of more than 360 pg/ml increased the probability of detecting AF 5-fold in patients with CS [51]. However, in a study by *Jing Chen et al.* (2021), the frequency of detecting elevated concentrations of this marker (more than 250 pg/ml) in patients with CS did not statistically significantly differ from that in patients with atherothrombotic and lacunar pathogenetic variants of IS (32.7%, 37.3% and 12.6% respectively) [24].

It has been established that in 5–34% of patients with IS, the blood level of cardiac troponin is elevated in the absence of clinical and electrophysiological signs of acute myocardial injury [52, 53]. *Merkler AE et al.* (2017) found that in patients with CS this is observed statistically significantly more often than in patients with non-cardioembolic IS (17% versus 8.9%, $p = 0.003$) [54]. The clinical significance of this marker is currently unclear. Further studies are needed to determine whether an increase in troponin levels is the cause of CS or its consequence. In turn, the TRELAS study showed that coronary artery lesions were verified only in 24% of patients with IS and an increase in the concentration of cardiac troponin, which indicates various reasons for the elevation of the level of this marker in patients with IS [55].

CONCLUSION

The totality of evidence suggests that atrial fibrillation is not the only cause of embolic events in patients with evidence of atrial dysfunction. Atrial cardiomyopathy can cause thromboembolic syndrome and cryptogenic stroke, even in the absence of atrial fibrillation. Therefore, the latter should be considered as a common manifestation of the underlying atrial cardiomyopathy. Since the majority of cardiac thrombi in patients with atrial fibrillation originate in the left atrium, it is likely that patients with atrial cardiomyopathy and cryptogenic stroke represent a group of patients who may be indicated for anticoagulant therapy as a secondary prevention of ischemic stroke and systemic embolism. However, this hypothesis needs to be confirmed. Despite the fact that markers of atrial cardiomyopathy are currently established, their threshold values remain unestablished. Enrollment of patients in the ARCADIA trial is ongoing to investigate the benefit of apixaban over acetylsalicylic acid in patients with cryptogenic stroke and markers of atrial cardiomyopathy.

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