Psychiatria Danubina, 2022; Vol. 34, Suppl. 8, pp 256-261 *Conference paper*

CRYPTOGENIC STROKE IN THE CONTEXT OF PANDEMIC-RELATED STRESS: THE ROLE OF ARTERIAL HEMODYNAMICS

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SUMMARY

Background: *Up to 45% of ischemic strokes are cryptogenic, which is an impediment to proposing preventative measures. In this investigation we aimed to study underlying heart arrhythmias in patients with cryptogenic stroke, taking into consideration the context of the COVID-19 pandemic and stressful lockdown conditions.*

Subjects and methods: *In this cross-sectional study we observed 52 patients with cryptogenic stroke >1 month after acute presentation, and a control group consisting of 88 patients without stroke. All patients undewent the laboratory and instrumental investigation consisting of the following: lipid spectrum; hemostasiograms; hemoglobin A1c; transthoracic or/and transesophageal echocardiography; 24-hours monitoring of ECG; computer tomography or magnetic resonance imaging of the brain. We studied the hemodynamics of the common carotid arteries using Doppler ultrasound imaging and digital sphygmography (SG).*

Results: *The groups were indentical with respect to the preponderance of study parameters (sex, age, comorbidities, instrumental and laboratory data). The ischemic stroke group had a statistically significant difference in the prevalence of the first type of extrasystolic arrhythmia according to our gradation of extrasystoles, which are ventricular systoles of extrasystolic contraction appearing before the transmitral blood flow peak (peak E in echocardiography). We observed that earlier ventricular systoles of extrasystole in the cardiac cycle predicted for greater growth of hemodynamic and kinetic parameters. Calculating the indices of a four-field table established the significant relationship between the moment of appearance of extrasystolic ventricular contraction in the cardiac cycle and the risk for cryptogenic stroke (normalized value of the Pearson coefficient (C`) of the two paramaters was 0.318).*

Conclusions: *Extrasystolic arrhythmia appeared as an additional risk factor of earlier stroke. The most dangerous type of arrhythmia was when the ventricular contraction of the extrasystole appeared before the transmitral blood flow peak in the cardiac cycle. This observation could present a risk-marker for brain-related cardiovascular complications such as stroke, which might be patients suffering from different internal diseases, especially in the context of environmental stress conditions of the current pandemic and its related lockdown measures.*

Key words: *cardiovascular - COVID-19 pandemic - cryptogenic stroke - extrasystoles - psychocardiology - psychosomatic - risk of stroke - stress*

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INTRODUCTION

Stroke is one of the most widespread and common cardiovascular events around the world, which brings an enormous burden of disability (Kunst et al. 2011, Murray et al. 2010, Zahra et al. 2015, Béjot et al. 2016). Despite preventive measures such as antismoking campaigns, the expected number of strokes in the European Union is expected to rise to oiver 1.5 million cases by 2025 (James et al. 2018, Virani et al. 2020, Bennett et al. 2014, Mathers et al. 2006). This prognostication preceded the COVID-19 pandemic, which is likely to have exacerbated various cardiovascular risk factors. High level of distress related to the COVID-19 pandemic and its associated social isolation measures along with unfavorable changes in life habits and the penetration of the infodemic into society, all contributed to rising incidences of affective and mood disorders, which are well-known to be associated with cardiovascular complications and stress-related nature of ischemic strokes (including large-vessel disease, small-vessel disease and cryptogenic stroke) (Fountoualkis et al. 2022a,b, Jood et al. 2009, Iftene et al. 2022, Senior 2009, Smirnova et al. 2021). Unfortunately, during the last two years we have all born witness to the lack of hospital beds and health care professionals in the face of added burdens to the health-care system. Many specialized hospitals have in effect been transformed into infectious disease departments, which has impaired their ability to provide general medical care to all those in need, including the stroke patients. On the other hand, we have noted a significantly increased incidence of thromboembolic events, including stroke, in patients with COVID-19, which we attribute to due to prothrombotic and microvascular effect of the virus itself (Wang et al. 2022). Thus, we can only expect a continuing increase in stroke cases and associated complications (Gardener et al. 2020, Messas et al. 2020).

Acute stroke patients should undergo a thorough investigation of risk factors and pre-existing conditions upon their admission to the neurology department. Nonetheless, many strokes arise for unknown reasons. Indeed, data from the American Heart Association and the American Association of Stroke indicate a cryptogenic origin of up to 45% of ischemic stroke cases (Kleindorfer at al. 2021).

Among the heart arrhythmias, atrial fibrillation is at the top of the list of risk factors of stroke. However, several studies have reported that the occurrence of extrasystoles is elevated in stroke patients, but the causality of this association has not been examined in detail (Benjamin et al. 2019, Kleindorfer at al. 2021). Here we aimed to study the incidence of heart arrhythmias in patients who had survived an earlier cryptogenic stroke, as compared with a non-neurological patient control group. We tailored this investigation for the context of COVID-19 pandemic, which represents a relevant psychological stressor, while bringing an elevated risk of stroke due to prothrombotic effects of the culpable virus.

SUBJECTS AND METHODS

We observed 52 patients (29 females, 55.8%) at one month after admission to the clinic following a cryptogenic stroke. Including criteria: cryptogenic stroke in anamnesis dating back one month or more, and provision of signed, informed consent to participate in the investigation, which had been approved by institutional experimental ethics authorities. Exclusion criteria were atrial fibrillation of any type, intra-cardiac thrombi, heart tumors, aortic or heart aneurisms, dilated cardiomyopathy, prosthetic valves, hemodynamically significant atherosclerotic carotid stenosis (70% and more), hematological diseases with hypercoagulation syndrome, and COVID-19 in the anamnesis. In the control group, we included 88 patients without cryptogenic stroke, those visiting general practitioners.

All patients underwent laboratory and instrumental investigation, including the following assessments; lipid spectrum, hemostasiograms; hemoglobin A1c; transthoracic or/and transesophageal echocardiography; 24-hours monitoring of ECG; computer tomography or magnetic resonance imaging of the brain. In the 24-hours ECG monitoring, we analyzed the main following parameters: pacemaker (sinus rhythm or not); heart rate, including circadian variability; existence of supraventricular or ventricular ectopic activity; blockades of any types; ST segment dynamics; PQ interval variability; QT interval dynamics.

We studied the hemodynamics of common carotid arteries using the methods of Doppler ultrasound imaging and digital sphygmography (SG). These two methods enabled us to characterize different aspect of the intra-arterial hemodynamics. In Doppler ultrasound, we calculated the linear blood flow velocity and volume flow in the common carotid artery during the spread of the regular pulse wave, and the extrasystolic and first post-extrasystolic waves, when present. On the other hand, the method of digital SG furnished an analysis of kinetic parameters of the arterial wall (speed, acceleration, power, work), likewise during the spread of the regular pulse wave, and extrasystole and the first post-extrasystolic wave, when present. Based on a synthesis of these results, we allocated the extrasystolic arrhythmia up to the first appearance ventricular contraction during an extrasystole in the cardiac cycle, irrespective of the electrical ectopic center localization. Thus, we divided the diagnosed extrasystole events into two main types: 1) extrasystoles, which are ventricular systoles of extrasystolic contractions appearing before the transmitral blood flow peak (peak E in echocardiography); 2) extrasystoles, the ventricular systoles of extrasystolic contraction appearing after the transmitral blood flow peak (peak E in echocardiography).

In our statistical analyses, we calculated Doppler ultrasound imaging data parameters (linear blood flow velocity, volume flow), and the SG-based common carotid arteries kinetic parameters (speed, acceleration, power, work) in all the patients for the regular pulse wave, extrasystolic wave, and the first post-extrasystolic wave. We performed one-way analysis of variance (ANOVA) to compare the mean values for the different types of extrasystoles and in means during regular heart rhythm for each analyzing parameter, using the threshold of $p \leq 0.05$ for statistical significance. We then evaluated the indices of a four-field table to establish the relationships between the moment of appearance of ventricular contraction of extrasystole in cardiac cycle and the onset of the stroke.

RESULTS

Key socio-demographic and clinical characteristics were generally similar for patients of the main stroke group and the control group, indicating good matching (Table 1). Both groups were also identical with respect to plasma lipid level (Table 2). The data from instrumental investigations also demonstrated that heart function was similar in the patients of the stroke group and the control group, except for the 24-hours ECG monitoring indicators. Here, the stroke group showed statistically significant differences in the prevalence of the first

Table 1. Socio-demographic and clinical characteristics of patients in the stroke versus the control groups

Socio-demographic and clinical variables, including the history and present internal diseases N (%)	Stroke group N=52	Control group N=88	Chi^2 p-value
Males	29 (56%)	45 (51%)	0.829
Females	23 (44%)	43 (49%)	
Mean age (SD) (y.o.)	63.1±5.3	61.9±5.9	0.866
History of smoking less than 7 years	12 (23%)	18 (20%)	0.715
Family history in cardiovascular diseases	24 (46%)	40 (45%)	0.937
History of myocardial infarction	11 (21%)	17 (19%)	0.794
History of arterial embolism of lower extremities	1 (2%)	1 (1%)	0.705
History of carotid endarterectomy	0 (0%)	0 (0%)	1.000
Arterial hypertension 1 grade	22 (42%)	37 (42%)	0.656
Arterial hypertension 2 grade	28 (54%)	45 (51%)	0.757
Heart failure NYHA I	35 (67%)	59 (67%)	0.975
Heart failure NYHA II	14 (27%)	25 (28%)	0.850
Chronic obstructive pulmonary disease, mild degree	8 (15%)	17 (19%)	0.558
Chronic kidney disease 1	5 (10%)	11 (13%)	0.605
Chronic kidney disease 2	2 (4%)	5 (6%)	0.631
Obesity	10 (19%)	18 (20%)	0.862

Table 2. Lipid spectrum levels in patients of the stroke vs the control groups

Lipids indicators - N (%) participants		Stroke group N=52	Control group N=88
Cholesterol*,	<5	41 (79)	64 (73)
mmol/l	≥5	11 (21)	24 (27)
HDL- Cholesterol*,	<1	3 (6)	3 (3)
mmol/l	≥1	49 (94)	85 (97)
LDL- Cholesterol*,	<4	49 (94)	84 (95)
mmol/l	≥4	3 (6)	4 (5)

Note: * $p>0.05$

type of extrasystolic arrhythmia, according to our gradation/scoring criteria (namely, extrasystoles, which are the ventricular systoles of extrasystolic contraction appearing before the transmitral blood flow peak, i.e., peak E in echocardiography) (Table 3).

We next analyzed the main hemodynamic parameters of common carotid arteries during regular heart rhythm and in both types of extrasystoles, divided up to the moment of appearance of the ventricular contraction. During the spread of the first post-extrasystolic wave, we observed the statistically significant growth of the main hemodynamic parameters in both types of extrasystoles, especially in the first type (Table 4).

The digital sphygmography findings for the common carotid artery showed a comparable pattern, and also demonstrated statistically significant increase of the main kinetic parameters of the common carotid artery wall (speed, acceleration, power, work) during the spread of the first post-extrasystolic wave, which was more prominent during the first type of extrasystoles. The parameter of work calculated by the digital sphygmography is presented in Figure 1.

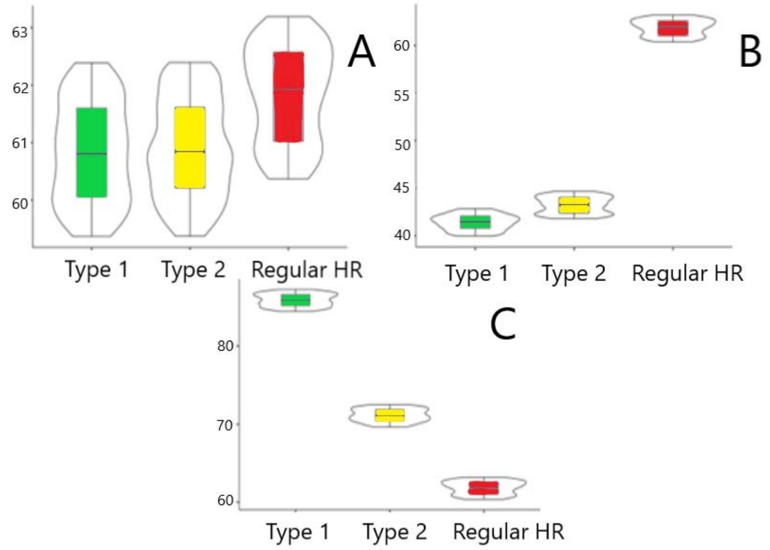
Table 3. Between-group comparison on the findings in relation to the cardiovascular dysfunction, as assessed using the instrumental diagnostic methods, in the stroke vs the control groups

Diagnostic variables - N (%)		Stroke group N=52	Control group N=88	Chi^2, p-value
Ejection fraction by Sympson, %	<40	2 (4%)	0 (0%)	0.064
	40-49	12 (23%)	6 (7%)	0.006
	≥50	38 (73%)	82 (93%)	0.002
Hypokinetic walls in left ventricle		11 (21%)	15 (17%)	0.546
Ascendance aorta, mm	<40	52 (100%)	88 (100%)	1.000
Pulmonary artery pressure	<30	52 (100%)	88 (100%)	1.000
Intra-heart thrombi		0 (0%)	0 (0%)	1.000
Coronary arteries stenoses		39 (75%)	68 (77%)	0.760
Hemodynamically insignificant carotid bifurcation stenoses		18 (35%)	5 (6%)	<0.001
Atherosclerotic plaque type III		6 (12%)	1 (1%)	0.007
Extrasystoles, the ventricular systoles of extrasystolic contraction of which appear before the transmitral blood flow peak (peak E, echocardiography)		37 (71%)	7 (8%)	<0.001
Extrasystoles, the ventricular systoles of extrasystolic contraction of which appear after the transmitral blood flow peak (peak E, echocardiography)		15 (29%)	81 (92%)	<0.001

Table 4. Doppler ultrasound investigation indicators on the common carotid artery

Diagnostic variables - Mean (SD)	Extrasystoles, the ventricular systoles of extrasystolic contraction of which appear before the transmitral blood flow peak (peak E, echocardiography)*	Extrasystoles, the ventricular systoles of extrasystolic contraction of which appear after the transmitral blood flow peak (peak E, echocardiography)*	Regular pulse wave*
Linear blood flow velocity in common carotid artery, m/sec	1.21±0.36**	0.94±0.22**	0.72±0.26
Volume flow in common carotid artery, ml/min	576±54**	432±39**	360±48
Systolic blood pressure, mm Hg	162±28**	146±24**	118±17

Note: * $p<0.05$; ** the data in 1st post-extrasystolic contraction wave



Note: A - regular contraction, B - extrasystole, C - first post-extrasystolic contraction. Type 1- extrasystoles, the ventricular systoles of extrasystolic contraction of which appear before the transmitral blood flow peak (peak E in echocardiography); Type 2 - extrasystoles, the ventricular systoles of extrasystolic contraction of which appear after the transmitral blood flow peak (peak E in echocardiography); regular HR - regular heart rhythm pulse wave

Figure 1. Kinetic parameter – work – calculated by the digital sphygmography on common carotid artery

Our main results were as follows: if an earlier ventricular systole of the extrasystole appeared in the cardiac cycle, there was a greater increase of the hemodynamic and kinetic parameters. Results of our four-field table calculation established a relationship between the moment of onset of ventricular contraction in an extrasystole in cardiac cycle and the history of ischemic stroke. The normalized value of the Pearson coefficient of the correlation (C`; was 0.318, indicating that cardiac features accounted for 10% of the risk for stroke history (R^2)).

DISCUSSION

Cryptogenic stroke remains a vexing problem around the world, despite the availability of a wide range of preventive, diagnostic and treatment measures. Despite these innovations, some 45% of all ischemic strokes are cryptogenic (Asplund 2005). Atrial fibrillation is the main arrhythmia that is known to increase the risk of stroke, because of its association with thrombus formation. However, was have in our clinical routine observed many cases of stroke in patients without any hemodynamically significant atherosclerotic lesions of the brachiocephalic arteries, and who never experienced any kind of atrial fibrillation. In this investigation, we gave particular attention to presence of heart arrhythmias in this category of patients. Extrasystolic arrhythmia is one of the most widely spread heart arrhythmias in humans. The predominant classifications of extrasystolic arrhythmia are based on electrophysiological principles, namely the localization of the ectopic center. In our present work, we used another gradation of extrasystoles in consideration of cardiac cycle biomechanics, with division of cycles according to the moment of ventricular contractions of the extrasystoles first appearance in cardiac cycle, before or after the transmitral blood flow peak. Remarkably, the category of patients with cryptogenic stroke had a significantly elevated prevalence of the first type of extrasystoles according to our classification. Could this be a key moment in the cardiac cycle for risk of ischemic stroke, and can extrasystoles at this phase of the cycle represent an additional risk factor for this kind of complication? We predicted an analysis of intra-arterial hemodynamics in both types of extrasystoles might help to elucidate this issue. Our investigation revealed the following pattern: the earlier an extrasystole appears in the cardiac cycle, the greater the associated increase of hemodynamic and kinetic parameters. The relevant parameters were linear blood flow velocity and volume blood flow in Doppler ultrasound imaging, as well as velocity, acceleration, power, and work in digital SG. We contend that these increased parameters for the spreading of the wave of the first post-extrasystolic contraction could lead to cumulative mechanical trauma, which would exacerbate the instability of existing intra-cranial atherosclerotic plaques, thus promoting a source of further embolism and stroke. In this sense, the first post-extrasystolic contraction is more dangerous than extrasystole itself, because it can become a destructive mechanical force in the arterial wall (Germanova et al. 2020, 2021). The repeated mechanical trauma can injure an otherwise stable atherosclerotic plaque. If such a vulnerable plaque tears, this will give rise to parietal thrombosis with further embolism, leading to a transient ischemic attack or stroke.

CONCLUSIONS

Extrasystolic arrhythmia might represent a hitherto unappreciated risk factor for the strokes of seemingly cryptogenic origin. The most dangerous type of extrasystolic arrhythmia emerging from this study is when ventricular contraction of the extrasystole precedes the transmitral blood flow peak in the cardiac cycle. We propose that this phenomenon presents a useful risk-marker of brain-related cardiovascular complications such as stroke, which should be routinely monitored in patients suffering from internal diseases, especially perhaps in the present context of additional environmental stress due to the COVID-19 pandemic and its related strict social isolation measures.

Limitations of the study

The major limitations of the study are the small simple size, and the lack of analysis of the confounding and contributing factors that might have affected the incidence of the stroke and its association with cardiovascular parameters. In addition, the context of stressful circumstances due to the ongoing pandemic and associated lockdown measures could have influenced stroke incidence in a vulnerable population. As such, we see a need for greater consideration of mental health and neuropsychological assessments to clarify the factors that contribute to the risk of stroke in patients suffering from the variety of different internal diseases. Cardiovascular and endothelial complications of SARS-Cov-2 infection might also be relevant factors in an expanded predictive model for cryptogenic strokes.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Olga Germanova, Daria Smirnova & Asel Usenova collected the data with advice from Giuseppe Tavormina, Paul Cumming & Giuseppe Galati.

Olga Germanova, Daria Smirnova, Asel Usenova & Giuseppe Tavormina analyzed the data.

Olga Germanova wrote the first draft of the manuscript, which has been revised by Daria Smirnova & Paul Cumming, and upon input from other coauthors.

Giuseppe Galati designed the project.

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