doi.org/10.36721/PJPS.2020.33.5.SP.2455-2460.1

Contribution of mechanical and electrical cardiovascular factors in patients with ischemic stroke

Lavinia Duica[1,3], Elisabeta Antonescu[1,2], Maria Totan[1,4], Mihail Pirlog[5] and Sinziana Calina Silisteanu[6]

[1]Lucian Blaga University of Sibiu, Faculty of Medicine, Sibiu, Romania
[2]County Clinical Emergency Hospital, Sibiu, Romania
[3]Hospital of Psychiatry „Doctor Gheorghe Preda" Sibiu, Romania
[4]Children's Hospital, Sibiu, Romania
[5]University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Craiova, Romania
[6]Stefan cel Mare University of Suceava, Department of Health and Human Development, Suceava, Romania

Abstract: Stroke represents the third - leading cause of death after heart and neoplastic isease and is one of the biggest cause of disability worldwide. Cardioembolism, through its principal mechanism - atrial fibrillation - constitute an important cause of ischemic stroke. Otherwise, left ventricular hypertrophy (LVH) has been associated with a twofold increase in stroke risk. The study aims at highlighting significant associations between several risk factors of stroke - LVH and atrial fibrillation (AF), respectively LVH and cardiac stenosis contributeng to ischemic stroke. The study comprised of 256 patients with stroke, hospitalized in the County Clinical Emergency Hospital, Sibiu, Romania; they were examined by ultrasound by echocardiography and carotid Duplex echography. The patients were divided in subgroups that were later compared to one another: 167 patients had atrial fibrillation (group A), 89 patients did not have atrial fibrillation (group B). Then both groups were divided in 2 subgroups (with or without LVH). It has been identified another two groups (66 patients with carotid stenosis <50%) and 116 patients with carotid stenosis >50% and each group was divided in 2 subgroups (with or without LVH). LVH is an important contributing factor in ischemic stroke in patients also presenting carotid stenosis > 50%.

Keywords: Stroke, LVH, hypertensive cardiopathy, carotid stenosis, carotid duplex echography.

INTRODUCTION

Stroke is the second leading cause of mortality in the developed countries with 4.5 million deaths per year. Incidence and mortality by stroke increase with age and, as population age increases rapidly in most developed countries, stroke is a common burden to society through the important economic costs it implies (Simats *et al.,* 2016). Although stroke is a very serious neurological condition due to the multiple disabilities of the individual, its complications like neurodegenerative conditions (Schneider, 2016), depression (Robinson and Jorge, 2016), pain (Harrison and Filed, 2015) implies high costs for the patients themselves, for the family, the healthcare staff and for society in general.

Hypertension and mechanical stress in the myocardium induce reactive oxygen species (ROS) growth in cardiomyocytes, activating the Mitogen-activated protein kinase (MAPK). Some cytokines produced by T helper cells are neurotoxic (Totan *et al.,* 2019). Activation of T lymphocytes results in the production of interferon G which increases the synthesis of inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukina 1 (IL-1) (Duica *et al.,* 2018) and consecutively, IL-6 that stimulate the production of inflammatory proteins and cardiac hypertrophy (Kurniavan *et al.,* 2018).

Approximately 45% of strokes are due to vascular thrombosis of large and small arteries, 20% have an embolic cause (Kanyal, 2015), and others have an unknown cause (Mutica *et al.,* 2016). Cerebral embolism can be of cardiac or arterial origin. In about 1/3 of patients with ischemic stroke, the emboli come from the heart, especially in atrial fibrillation (Zandieh *et al.,* 2015). The second most important source of emboli is represented by atherothrombotic lesions, thus resulting an arterio-arterial embolism.

Carotid stenosis is a major risk factor for stroke and cerebrovascular disease. Doppler examination in patients at high risk is considered as a primary and secondary prevention measure for ischemic stroke (Kumar *et al.,* 2019). It is believed that 20-30% of all ischemic strokes result from carotid artery stenosis, a medical condition that may or may not be symptomatic (Mohanty *et al.,* 2018). Symptomatic carotid artery stenosis is represented by stroke, ischemic stroke or various neurological deficits (Baradaran *et al.,* 2016).

On the other hand, The EUROSTROKE project investigated the association between left ventricular hypertrophy (LVH) (Minnesota criteria) and fatal or non-fatal, ischemic or haemorrhagic stroke. LVH has been

**Corresponding author:* e-mail: bety_antonescu@yahoo.com

associated with a twofold increase in stroke risk, association which is higher for fatal stroke, as well as in the case of smokers (Bots *et al.,* 2016).

The study aims at highlighting significant associations between several risk factors of stroke - LVH and atrial fibrillation, respectively LVH and cardiac stenosis contributing to ischemic stroke. Numerous clinical trials have studied the significant association of LVH, atrial fibrillation, carotid stenosis with ischemic stroke. This study discusses the significant association of two of these risk factors and the ischemic stroke.

MATERIALS AND METHODS

In this retrospective study, 256 patients with stroke were admitted to County Clinical Emergency Hospital Sibiu and were examined by ultrasound by echocardiography and carotid Duplex echography.

The most important pathophysiological mechanism of ischemic stroke is the thromboembolic mechanism of cardiac origin. The group of 256 patients were divided into 2 subgroups: 167 patients had atrial fibrillation (group A), 89 patients did not have atrial fibrillation (group B).

These patients divided into 2 subgroups were re-divided according to the presence or absence of LVH, resulting in 2 subgroups, as follows:
Group A (with atrial fibrillation) with or without LVH
Group B (without atrial fibrillation) with or without LV

The degree of carotid stenosis was assessed, identifying two subgroups as follows:
Group 1 (without stenosis or with carotid stenosis <50%) -116 patients with or without LVH
Group 2 (with carotid stenosis >50%) -66 patients with or without LVH

Ethical approval
This study protocol was approved by the Research Ethics Committee of the university hospital. The study, being a retrospective one, did not required a written consent of the involved patients.

STATISTICAL ANALYSIS

Graph Pd Prism software (version 5.0) was used to process the data. Chi square test was performed to establish if there were significance associations between these variables.

RESULTS

The socio-demographic analysis of the group showed 43.75% women and 56.25% men. As for the age of the patients, they were mostly between 50 and 80 years old. We had no cases under the age of 40, a very small number of patients were in the age group of 40-50 years. Also, few patients were over 80 years old, probably due to the fact that stroke in these patients is often fatal (fig.1).

Left ventricular hypertrophy was present in the two groups in a similar proportion. Almost three quarters of the total number of patients presented LVH.

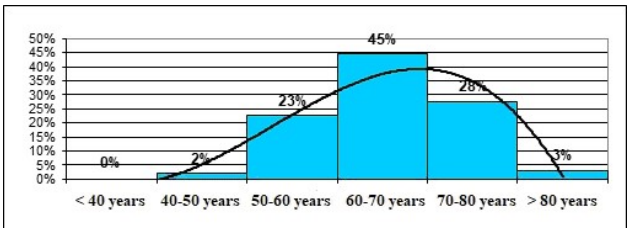

Fig. 1: The age distribution of the patients

Of the total of 256 persons investigated with stroke, 167 persons with atrial fibrillation were identified, 119 of whom also presented LVH and 89 persons without atrial fibrillation of whom 67 also presented LVH (table 1).

In our study, an association between stroke and atrial fibrillation (group A) was identified at a $p<0.001$ but in the same group, there was an association between stroke and absence of LVH, which indicates that the presence of LVH does not exert an influence on the occurrence of stroke, in addition of atrial fibrillation (table 2).

Regarding the presence of carotid stenosis, the following were noticed: no stenosis; insignificant stenosis <50%, stenosis at significance limit (50-70%], significant stenosis (70-90%), limited stenosis> 90%.

Of the total of 256 stroke patients, 116 (66 patients with LVH and 50 patients without LVH) were without carotid stenosis or had insignificant carotid stenosis, while the remaining 140 (116 patients with LVH and 24 patients without LVH) had carotid stenosis> 50% (table 3).

There was no association between stroke and insignificant carotid stenosis with or without LVH (<50%) at $p>0.05$ (table 4) but studying the association in patients with ischemic stroke with carotid stenosis >50% with LVH indicates there is a significant association at $p<0.001$ (table 5).

DISCUSSIONS

The presence of LVH (on ECG or echocardiography) is important clinically because it is associated with increases in the incidence of heart failure, ventricular arrhythmias, death following myocardial infarction, decreased LV ejection fraction, sudden cardiac death, aortic root dilation, and a cerebrovascular event (Eskerud, 2019).

Table 1: Patients with stroke and atrial fibrillation (group A) and with stroke without atrial fibrillation (group B).

	Group A		Group B	
	With LVH	Without LVH	With LVH	Without LVH
No. of patients	119	48	67	22
% patients	71%	29%	75%	25%
Total patients	n = 167		n = 89	
% total patients	65.2%		34.8%	

Table 2: Patients with stroke and arterial fibrillation (group A) - without and with LVH

Patients with stroke and atrial fibrillation (group A)	N	%	p-value
Without LVH	48	29	p<0.001
With LVH	119	71	p<0.001
Total	167	100.0	

Table 3: Patients with different grades of carotid stenosis - with and without LVH (Group 1 and Group 2)

Degree of carotid stenosis	Group 1 Without stenosis or carotid stenosis < 50%		Total	Group 2 Carotid stenosis >50%			Total
	Without stenosis	< 50%		50-70%	70-90%	>90%	
With LVH	29	37	66	69	36	11	116
Without LVH	31	19	50	14	7	3	24

A prospective study analysed 922 patients with acute ischemic stroke in terms of prediction of increased stroke severity by LVH detected by electrocardiographic criteria. This study revealed a significant association between LVH diagnosed according to the Cornell index (the sum of R wave in AVL and the S wave in V3 is greater than 28 millimetres in males or greater than 20 mm in females) and not according to Sokolow-Lyon index (the sum S wave in V1 plus the R wave in V5 or V6 is greater than 35 mm) and stroke severity and intra-hospital mortality (Tziomalos *et al.,* 2018).

The prediction of stroke according to the presence of LVH was analysed on a group of 1048 patients aged over 65 years with LVH according to electrocardiographic and echocardiographic criteria. The study has shown that both types of criteria (electrocardiographic and echo-cardiographic) can predict the risk of stroke (O'Neal *et al.,* 2015). Other study shows that LVH diagnosed by ECG is associated with an excess risk for stroke in Chinese hypertensive population, especially in the age group of younger than 65 years (Zhao, 2019).

In our study, we didn't find a significant relation between stroke and LVH maybe because the age distribution of our subjects fell into 40-80 years category, the mentioned studies take into consideration the interval of age over 65 years of age.

Instead, we find a significant association between stroke and LVH with atrial fibrillation. Indeed, other study reveals that LVH diagnosed by ECG was also confirmed to be a predictor in patients with AF for risk of stroke and death (Cuspidi *et al.,* 2019).

Many studies have found a biological gradient between AF burden and stroke (Vanassche *et al.,* 2015). A single brief episode of subclinical AF is associated with a 2-fold higher risk of stroke in older patients with vascular risk factors (Van Gelder *et al.,* 2017) whereas young and otherwise healthy patients with clinically apparent AF do not face a significantly increased stroke risk (Chao *et al.,* 2016).

Significant multicentric trials - North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Symptomatic Trial (EST) - showed the significance of carotid lesions in stroke patients (Anadani *et al.,* 2019). Population studies using carotid ultrasound estimated the prevalence of carotid stenosis as 0.5-0.8% of the general population, and significant carotid stenosis (over 60%) was estimated to be 1% in those over 65 years of age. The rate of stroke in asymptomatic patients with carotid stenosis of at least 80% is between 3.5 and 5% per year (Baradaran *et al.,* 2016).

In our study we found a strong association between stroke with LVH and carotid stenosis >50%. In other studies,

Table 4: The association between stroke and carotid stenosis

Total patients with stroke (N=256)	N	%	p value
Without carotid stenosis or with insignificant carotid stenosis	116	45.31%	p>0.05, not significant
With carotid stenosis >50%	140	54.68%	
Total	256	100	

Table 5: The association between ischemic stroke with carotid stenosis > 50% and LVH

Patients with stroke	Without stenosis or with insignificant stenosis	With stenosis >50%	p value
Without LVH With LVH Total	50 (73,5%)	18 (26,5%)	p>0.05

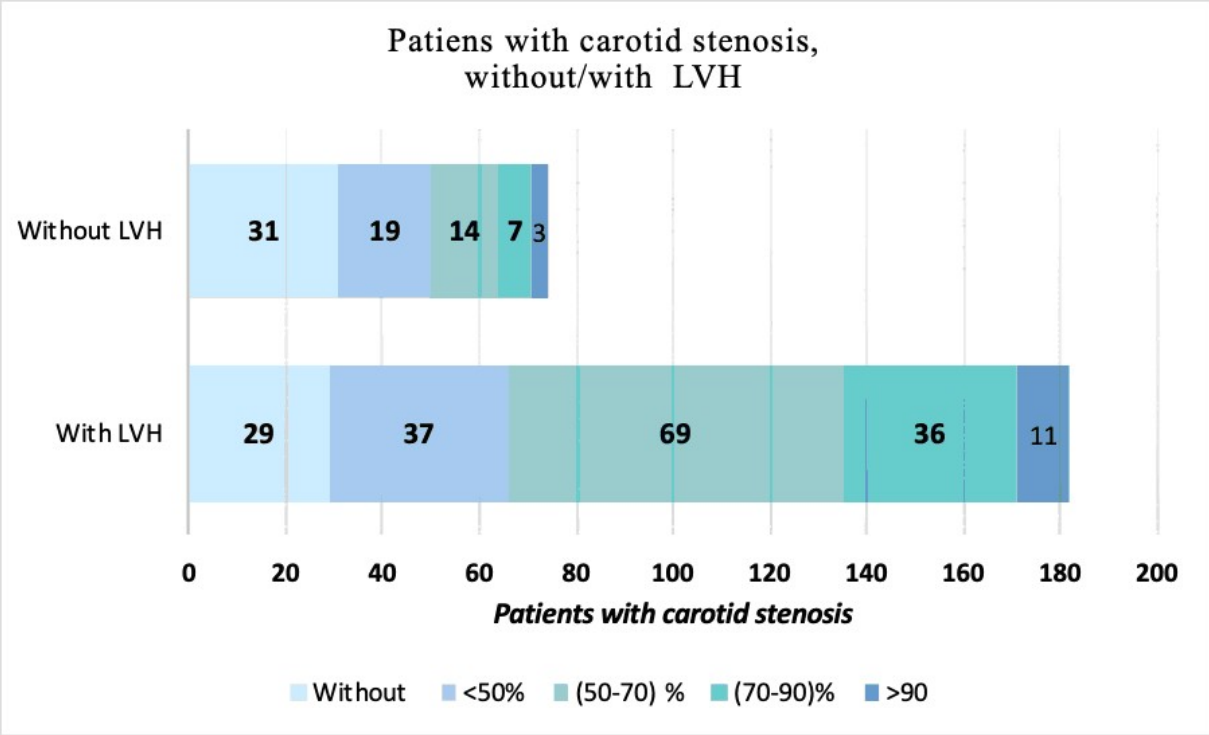

Fig. 2: Patients with carotid stenosis without or with LVH

too, the risk of stroke increases with the degree of carotid stenosis (Xu Y *et al.,* 2017). A study conducted by Khan *et al* revealed carotid stenosis in only 18.18% of stroke patients, the study including only patients with stenosis greater than 70% (Saengsuwan *et al.,* 2017), and also the study conducted by Alexandrova *et al*. reported higher stenosis or equal to 70% in 17% of 348 patients (Naylor *et al*., 2018)

CONCLUSIONS

Ischemic stroke is a neurological condition that occurs due to a thromboembolic mechanism. Regarding the embolic cause of cerebral ischemic lesions, either atrial fibrillation or other atherothrombotic lesions are incriminated.

In this study we analysed the relationship between atrial fibrillation and LVH, respectively carotid stenosis and LVH in the patients with ischemic stroke to highlight significant associations between these risk factors in the production of ischemic stroke.

There was an association between stroke and arterial fibrillation in the group without LVH at p value<0.001. In patients with ischemic stroke with carotid stenosis >50% and LVH, it was shown that there was a significant association at a p< 0.001.

Apart from the mechanical and electrical cardiovascular factors, as risk factors for stroke, in the future the biochemical analyses could permit rapid identification of stroke in the emergency department. The evaluation of

traces elements – serum magnesium, iron, copper, zinc - that may be useful for the prediction and diagnosis of stroke status. For example, measuring iron ions through spectrophotometry (Totan *et al.,* 2018) or genetic analysis (Gill *et al.,* 2018).

ACKNOWLEDGEMENT

Authors are grateful for financial support of Medical and Health Science and Technology Development Plan of Shandong Province 2017WS030, China.

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