



FEATURES OF VASCULAR AUTOREGULATION IN PATIENTS WITH INITIAL MANIFESTATIONS OF THE CHRONIC CEREBRAL ISCHEMIA

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Summary: - Studied were the cerebral hemodynamics and various brain blood flow autoregulation circuits in patients with initial manifestations of the chronic cerebral ischemia (IMCCI) using Doppler sonography. Forty-eight patients (29 women and 19 men) in the age of 28 to 55 years with IMCCI caused by arterial hypertension (AH) in 30 patients, and by cerebral atherosclerosis (CA) in 18 patients were investigated. The controls were 25 healthy adults matching as to gender and age.

The cerebral hemodynamics was studied by measuring the linear blood flow velocity (BFV) in extra- and intracranial vessels on a Doppler sonography. The state of various autoregulation circuits was carried out by functionally loading the patients with: hypercapnia, calculating the reactivity coefficient CrCO₂, nitroglycerine, calculating the reactivity coefficient CrFNT, and orthostatic loading, determining the orthostatic instability. The investigation of cerebral hemodynamics has revealed isolated hemodynamically insignificant lesions of the carotids (63.7 %) or vertebral (36.3 %) arteries in 28.4 % patients with IMCCI accompanied by the BFV interhemispheric asymmetries (20-30 %) in the Willis' arteries in 68 % of the patients. The investigation of CVR has shown that the patients with IMCCI have disorders of the autoregulative response as to metabolic and myogenic circuits with the tendency to hyperreactivity in the patients with AH and hyporeactivity in those with CA.

The patients also have the inverted reactions to nitroglycerine and orthostatic loads, this inversion being more pronounced in the patients with CA with the tendency to increase in the groups of older patients. The analysis of obtained data makes it possible to suppose that the CVR changes at various levels of autoregulation characterising the dysfunctioning of homeostatic range support mechanisms are the triggering mechanism of cerebral hemodynamic disorders in the patients with IMCCI. Unifying various values of the CVR as to the Doppler sonography data makes it possible to optimise diagnosing and treatment tactics for the patients with IMCCI.

Keywords: Initial manifestations of the chronic cerebral ischemia, cerebrovascular reactivity, transcranial Doppler sonography, hypercapnic load, orthostatic load, functional nitroglycerin test.

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Introduction

Evaluating the mechanisms leading to initial manifestations of the chronic cerebral ischemia (IMCCI) is a major challenge in the modern clinical angioneurology. Cerebrovascular pathology (CVP) remains one of the leading causes of mortality, the main cause of disability, and a decrease in the quality of life [1]. Over the past 10-15 years, Ukraine has seen a steady trend towards an increase in the prevalence and incidence of CVP, especially chronic progressive forms, which is associated with the growth of various extreme influences. Many manifestations of CVP form clinical syndromes quite early, which lead to social and everyday maladaptation, disability, etc. [2].

It is known that cognitive deficit accompanies CCI, is a leading syndrome, especially with its long-term development, and has a significant negative impact on the rehabilitation process of patients with CVP [3].

These circumstances dictate the need for: rapid response to the development of the disease, timely diagnosis of vascular pathology of the central nervous system (CNS) with the development and use of modern adequate, including surgical, treatment strategies [4-5]. The initial manifestations of the CCI play the most important role in the structure of cerebrovascular diseases [6]. They are responsible for 60 to 75 % of all cases of vascular pathology of the brain. The IMCCI incidence reaches 4,8 % to 8,1 % in men aged from 20 to 54. At present the following significant IMCCI factors are recognised: morphological changes in extra- and intracranial arteries; disorders of cerebral and cardiac hemodynamics; disorders of physical and chemical and biochemical properties of the blood; changes in the brain metabolism [7,8].

The method of transcranial dopplerography (TCD) of the major vessels of the head has been successfully used to diagnose lesions of extracranial and intracranial sections of the major arteries [9]. Cerebrovascular reactivity (CVR) is considered as an integral indicator of the adaptive capabilities of the cerebral circulatory system, the ability of the brain vessels to respond to changing functioning conditions and to optimize blood flow in accordance with these conditions. The use of functional loads in order to assess the reactivity of cerebral vessels makes it possible to objectify the activities of regulatory mechanisms that control cerebral circulation and ensure its functional stability [10]. The most interesting is the possibility to evaluate the cerebrovascular reactivity by means of Doppler sonography, because the values obtained from unified diversely directed tests are independent objective criteria for evaluating the brain blood flow dysfunction that characterise the reserves and adaptation abilities of the brain blood flow under varying circumstances. The analysis of published works

makes it possible to consider the CVR as a measure of compensatory abilities of the system that is objectively estimated by means of reactivity coefficients characterising the degree to which the hemodynamical parameters match the conditions of functioning. The functional loading implemented by various autoregulation circuits (hyper- and hypocapnic loading, implemented mainly by the metabolic circuit, nitro-glycerine and compression ones implemented by myogenic circuit, ortho- and antiorthostatic ones implemented by neurogenic circuit) makes it possible to obtain the most comprehensive information on the state of homeostatic range of the brain blood flow system [10].

All mentioned above considered, the search for the hemodynamic characteristics of the basic factors of initial brain ischemia is of prior importance.

The aim. Was to Doppler sonography study of cerebrovascular reactivity in young with IMCCI.

Materials and Methods

We have investigated 48 patients (29 women and 19 men) aged from 28 to 55 with the signs of IMCCI revealed after neurological and instrumental investigation. In 30 thirty patients with the IMCCI the etiologic factor was arterial hypertension (AH) in stage I or II, in 18 patients it was the cerebral atherosclerosis (CA). The control group (CG) were 25 healthy adults matching in gender and age.

The state of blood flow in cerebral arteries and indicators of cerebrovascular reactivity (CVR) were studied using Ultima PA ultrasound device (RADMIR, Ukraine). The study was performed indicators of linear blood flow velocity (BFV) in middle cerebral (MCA), anterior cerebral (ACA), posterior cerebral (PCA) arteries, siphons of internal carotid arteries, intracranial segments of vertebral arteries (VA), basilar arteries (BA), and the reactivity coefficients to hypercapnic (CrCO₂) and orthostatic (CrOL) loads, functional nitroglycerin (CrFNT) test.

Results and Discussion

The investigation of carotids and vertebral arteries has shown that 28,4 % of the patients have isolated lesions of carotids (63,7 %) or vertebral (36,3 %) arteries. Stenosing lesions in all cases did not exceed 60 % of the vessel aperture (hemodynamically insignificant).

The TCD data of 58,1 % of the patients with IMCCI have revealed a moderate interhemispheric asymmetry of the BFV (20 % to 30 %) in the Willis' arteries without the signs of stenosis (controls -16,7 %).

The collateral blood flow investigation by means of compression trials has not revealed a significant difference between the main group and controls (disintegration of the circle of Willis has been found in 11 % of the patients with IMCCI and in 8 % of the controls).

The metabolic circuit was investigated by means of hypercapnic loading implemented by the patient arbitrary keeping the breath during 40 to 60 seconds. Then the hypercapnic loading coefficient of reactivity (CrCO₂) was calculated as the ratio of BFV in the middle brain artery at CO₂ loading to BVF at rest. To study the myogenic circuit we used the sublingual administration of 0.05 mg of nitroglycerine. As the available literature lacks the data on the nitro-glycerine test, we have proposed to determine the coefficient of reactivity to nitro-glycerine loading (CrFNT).

The neurogenic mechanism of autoregulation was studied by orthostatic test. We compared the BFV values at rest and at orthostatic loading. We considered the reduction of BFV in the MCA by more than 10 % as an 'orthostatic insufficiency'.

Table 1 presents the results of CVR testing in controls and patients with IMCCI. The values of CrCO₂ were different in junior and senior controls (1.36±0.05 and 1.32±0.06, respectively). It should be noted that the obtained values of CrCO₂ in the CG (1.43±0.04 and 1.37±0.06, respectively).

We have found the differences in the CrCO₂ values in various etiologic groups of patients with IMCCI (1.41±0.06 and 1.38±0.04 in patients with AH and 1.24±0.08 in patients with CA). Thus, the hyperreactive response to hypercapnia is more specific for the patients with AH, while the hyporeactive one is characteristic for those with CA.

Table 1. Values of CrCO₂ index in healthy persons and patients with IMCCI as to the hypercapnic loading data

Age groups	CG	Patients with IMCCI	
		AH	CA
< 40	1.36±0.05	1.43±0.06	1.28±0.05
> 40	1.32±0.06	1.38±0.04	1.24±0.08

When studying the myogenic component of CVR by means of nitroglycerine test, we investigated both the quantitative values (CrFNT) and the direction of autoregulative reactions. In the patients with IMCCI these values differed from those of the controls (0.15±0.03 in juniors and 0.13±0.04 in seniors). The tendencies of autoregulative response determined during CO₂ loading were also detected during nitro-glycerine testing. The tendency to hyperreactive response has been detected in the patients with AH (0.18±0.06 and 0.15±0.04), that to the hyporeactive one - in those with CA (0.14±0.03 and 0.12±0.04) (Table 2).

Table 2. Values of CrFNT index in healthy persons and patients with IMCCI as to the nitroglycerine loading data

Age groups	CG	Patients with IMCCI	
		AH	CA
< 40	0.15±0.03	0.18±0.06	0.14±0.03
> 40	0.13±0.04	0.15±0.04	0.12±0.04

Of interest is the investigation of the direction of autoregulation reactions during the nitro-glycerine test. Three types of the reactions have been discovered: direct one (BFV slowing down in the MCA), negative one (no BFV changes) and paradoxical one (BFV increasing). The results are given in Table 3. The group of patients with AH manifest lower percentage of those with inadequate vascular reactions (no such reactions in the juniors, negative reaction in 15.2 % of the senior patients) compared to the patients with CA (16.7 % and 24.0 %, respectively) and the presence of paradoxical reactions in 8.3 % of the seniors).

Table 3. Percentage of the types of reactions to nitroglycerine loading in healthy persons and patients with IMCCI

Type of reactions	CG		Patients with IMCCI			
			AH		CA	
	< 40	> 40	< 40	> 40	< 40	> 40
Direct	100	100	100	84.8	83.3	66.8
Negative	-	-	-	15.2	16.7	24.9
Paradoxical	-	-	-	-	-	8.3

The results of neurogenic circuit of autoregulation investigation using orthostatic loading are given in Table 4. The percentage of the patients with orthostatic instability was substantially higher for the patients with CA (33.4 % and 41.5 %) compared to the patients with AH (20.5 % and 22.8 %). The majority of the patients combined the orthostatic instability with hyperreactive version of CrCO₂ and CrFNT values, as well as with inadequate reactions to nitroglycerine.

Table 4. Percentage of the types of reactions to orthostatic loading in healthy persons and patients with IMCCI

Type of reactions	CG		Patients with IMCCI			
			AH		CA	
	< 40	> 40	< 40	> 40	< 40	> 40
Normal	92.3	85.6	70.5	67.2	66.6	59.5
Orthostatic instability	7.7	14.4	29.5	22.8	33.4	41.5

Conclusions

1. The patients with IMCCI manifest changes in the CVR over all circuits of autoregulation, that are more pronounced in the patients with AH in respect to those with CA.
2. The basis of the IMCCI are the disturbances of the brain vessel tonus and reactivity caused by dysfunction of the vasomotor centres, as well as closely related changes in neuro- and vasoactive substance concentrations.
3. The further efforts in this direction are expedient for unifying qualitative and quantitative estimates of vascular autoregulation in patients with IMCCI of various geneses.

Conflict of interest

The authors of the manuscript consciously declare that there is no actual or potential conflict of interest regarding the results of this work with pharmaceutical companies, biomedical device manufacturers, other organizations whose products, services, financial support may be related to the subject of the materials provided, or who sponsored the research conducted.

Compliance with ethical standards

The authors of the manuscript consciously certify that the study was conducted using data from primary medical records and included clinical observations of patients. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki of the World Medical Association on the ethical principles of conducting scientific medical research involving human subjects, the European Society Directive 86/609 on the participation of humans in biomedical research, as well as the Order of the Ministry of Health of Ukraine No 690 of September 23, 2009. Informed consent to participate in the study was obtained from all participants after providing them with clear, complete and accessible information about the purpose, design and methodology of the study, its potential risks, expected benefits and possible alternatives. All participants confirmed their voluntary participation by signing an informed consent document. Participants had the right to refuse participation at any time without giving reasons. In accordance with confidentiality regulations, all data was collected anonymously and processed in compliance with applicable data protection legislation. All information was used exclusively for this study and was summarized for further analysis of the results.

Primary data and materials

The authors of the manuscript consciously declare that the work uses the results of their own clinical studies, which were systematized and analyzed by the authors. Primary data include generalized patient indicators, laboratory results, protocols and obtained quantitative characteristics. All materials are stored in the archive of the research group

and can be provided upon reasonable request to the corresponding author, taking into account the requirements of confidentiality and ethical norms.

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