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Relationship between Myogenic Reaction and Autoregulation of Cerebral Circulation

V. V. Alexandrin

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Dilatation of rat pial arterioles at constant arteriolar wall strain during autoregulation of cerebral circulation was shown by the method of biomicroscopy. Wavelet-analysis of cerebral blood flow oscillations during this period revealed increased oscillation amplitude in the endothelial and neurogenic frequency ranges and unchanged amplitude at myogenic frequency range. These findings probably attest to the leading role of myogenic reaction in the autoregulation.

Key Words: *autoregulation of cerebral circulation; pial arterioles; myogenic reaction*

Autoregulation of cerebral blood flow consists in the maintenance of constant volume blood flow in a wide range of perfusion pressure at the expense of variations of the diameter of cerebral arterioles [4]. The mechanisms of blood flow autoregulation employ all factors affecting the vascular tone: metabolic, neurogenic, endothelial, and myogenic. It is currently accepted that myogenic reaction of arterioles plays the leading role [6], but this hypothesis was not verified on intact vascular bed of the brain. At the same time, experiments with artificial perfusion of fragments of brain arterioles showed that myogenic reaction is aimed at regulation of vessel wall tension [9], in particular, at the maintenance of its constant value [8]. This allows quantitative evaluation of myogenic reaction by calculating changes in vessel wall tension in a certain site of cerebral vascular bed (according to the Laplace law). To this end, two parameters should be determined: inner vessel diameter and intravascular pressure. Unfortunately, the second parameter cannot be measured in absolute units *in situ* because of high vulnerability of the autoregulation mechanism to external influences, but its relative changes can be evaluated from systemic blood pressure (SBP) values.

Here we studied changes in myogenic reaction of pial arterioles *in situ* during autoregulation of cerebral blood flow.

MATERIALS AND METHODS

Experiments were performed on narcotized (300 mg/kg chloral hydrate, intraperitoneally) albino mature outbred male rats weighing 260-300 g in strict adherence to Order of Ministry of Health of the Russian Federation No. 267, June 19, 2003. For measuring SBP and blood loss, both femoral arteries were isolated and catheterized (heparin was administered intraarterially in a dose of 500 U/kg). Animal's head was rigidly fixed in stereotaxis (2 cm above the body) and the temporal bone was trephined (5×3 mm window) without damaging the dura matter for blood flow recording and monitoring of pial vessels in the middle cerebral artery basin. After preparation and 30-min

Laboratory of Molecular Mechanisms of Thrombogenesis and Thrombolysis, Research Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow, Russia. ***Address for correspondence:*** aleksandrina-81@mail.ru. V. V. Alexandrin

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stabilization, the initial parameters were recorded. In series I (n=26), myogenic reaction of rat pial arterioles during autoregulation of cerebral blood flow in response to graduated blood loss was studied. To this end, biomicroscopy of pial arterioles through the dura matter was performed under a ML-2 microscope (×6 eyepiece, ×10 contact objective) in polarized light [2]. The observation area unit was 0.35 mm^2. Arteriolar bifurcations, branching of the maternal arterioles into two daughter vessels, were the object of the observation. The inner diameter of arterioles was measured by negative images. These measurements yielded a relationship between the diameter of pial arteries and SBP at the initial state and after blood loss. From these data, tension of the vessel wall was calculated by the Laplace formula: T=C×P×D, where T is tension of the vessel wall, P is SBP, D is the diameter of the arteriole, and C is a coefficient of proportionality between the systemic and intravascular pressure.

Then, changes in vessel wall tension were calculated by the formula: relative tension of vessel wall= $(T_{initial}/T_{after\ blood\ loss})\times 100\%$.

An assumption was made that blood loss does not affect C (this agrees with previous experimental data [5]). Due to this simplification, coefficient C in numerator and denominator is reduced and only SBP values are required for calculation. Local blood flow in this series was recorded with a LAKK-01 device (Lazma, 1-mm probe).

In series II (n=11), the changes in cerebral blood flow oscillation spectra were studies for evaluation of factors affecting the vascular tone under conditions of graduated blood loss. To this end, we used a new method based on the existence of oscillations of different frequencies and amplitudes in microcirculatory blood flow which can be analyzed by spectral wavelet analysis [3].

It was experimentally proven (with the use of various pharmacological blockers), that particular frequency ranges are related to certain regulators of the vascular tone. According to published reports, the following frequency ranges were identified for rats: 0.01-0.04 Hz for endothelial NO, 0.04-0.15 Hz for neuronal sympathetic influences, and 0.15-0.4 Hz for myogenic tone [7]. A LAKK-01 device (Lazma) was used in the experiments. Laser Doppler flowmetry in red channel of laser radiation (λ=0.63 μ) with spectral wavelet analysis of blood flow oscillations was performed in the temporal area of the neocortex before (initial) and after blood loss. For wavelet-analysis, 600-sec records were used. The oscillatory component of the total perfusion was evaluated by mean square deviation of blood flow oscillations and their standardized amplitudes in the specified ranges [3] were determined by wavelet-analysis (2.2.0.507 software, Lazma)

The results were processed using Student t test. The differences were significant at p<0.05.

RESULTS

In experimental series I, myogenic reaction of 48 arteriolar bifurcations was studied. The arterioles of three branching orders by the initial diameter were divided into 3 groups: 22-25 μ (group 1), 32 μ (group 2), and 43-45 μ (group 3). After step-wise blood pressure decrease from 84 to 70 mm Hg (by 15%), to 59 mm Hg (by 31%), and to 49 mm Hg (by 43%), the local blood flow decreased by 3, 7, and 16%, respectively, which attested to its effective autoregulation. The diameter of all groups of arterioles increased proportionally to the blood pressure drop: by 12-17, 45-51, and 71-84%, respectively. However, this increase was not accompanied by changes the relative tension of the vessel walls (Table 1). Significant changes of this parameter were observed only after SBP drop to 38 mm Hg, which was accompanied by failure of autoregulation of cerebral blood flow. We realize conditional character of evaluation of vessel wall tension, but similar reactions of arterioles of different groups confirm our assumption that the proportionality coefficient did not change after blood loss. Moreover, the data obtained in other laboratories during studies of the reaction of cerebral arterioles to SBP drop (without calculation of vessel wall tension) suggest that the relationships between the diameter of pial arteries and SBP are always described by hyperbolas [10] conforming the Laplace law (on the assumption of constant T value). These findings probably attest to an important role of myogenic reaction in autoregulation.

However, the contribution of other factors affecting the vascular tone into this process remains unclear. Therefore, in experimental series II we studied changes in cerebral blood flow oscillation spectra. In the initial state, oscillations of the endothelial, neurogenic, and myogenic ranges were present in all records of wavelet-spectra (Table 2, Fig. 1).

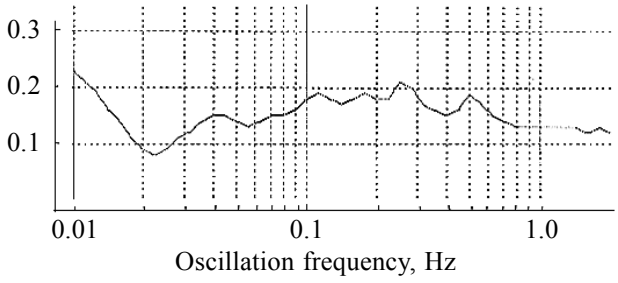

Fig. 1. Wavelet spectrum of blood flow oscillations in rat parietal neocortex at the initial state. Here and on Figs. 2, 3: Ordinate: amplitude of blood flow oscillations (perfusion units).

TABLE 1. Changes in Cerebral Circulation, Diameter of Pial Arterioles, and Relative Tension of Arteriolar Vessel Walls in Response to Gradual Decrease in SBP Caused by Blood Loss (*M*±*m*)

Parameter	BP drop by 15% (1st blood loss)		BP drop by 31% (2nd blood loss)		BP drop by 43 and 56%		
	initial	after blood loss	initial	after blood loss	initial	after blood loss	
						3rd blood loss	4th blood loss
SBP, mm Hg	84.1±0.9	71.2±0.7*	86.1±0.9	59.3±0.6*	87.2±1.2	49.6±0.5*	38.3±1.2*
Cerebral blood flow, %	100	97.3±1.2	100	93.1±2.2*	100	84.3±1.3*	63.2±2.4*
Group 1+							
Diameter of arterioles, μ	24.5±1.5 (*n*=6)	28.7±1.2	22.2±0.6 (*n*=17)	32.5±0.8*	23.1±0.8 (*n*=12)	42.3±1.3*	44.3±2.0*
Relative tension of vessel wall, %	100	101.4±3.2	100	99.3±1.2	100	103.2±2.4	85.4±3.2*
Group 2+							
Diameter of arterioles, μ	31.5±0.6 (*n*=16)	36.2±0.6*	31.8±0.5 (*n*=18)	47.2±1.4*	31.4±0.6 (*n*=13)	57.3±1.7*	61.3±5.4*
Relative tension of vessel wall, %	100	98.5±1.3	100	101.3±1.4	100	103.5±2	83.2±6.2*
Group 3+							
Diameter of arterioles, μ	43.3±0.9 (*n*=10)	49.5±0.9*	42.9±1.1 (*n*=7)	65.2±2.7*	45.1±1.6 (*n*=5)	77.2±2.2*	77.4±5.3
Relative tension of vessel wall, %	100	97.4±1.3	100	102.7±1.6	100	102.3±2.2	81.2±5.3*

Note. +Groups of blood vessels by the initial diameter; *n*: number of vessels. Here and in Table 2: *$p<0.05$ compared to initial state.

TABLE 2. Standardized Amplitudes and Frequencies of Oscillations for Different Frequency Ranges in the Initial State and after Gradual Blood Loss (*M*±*m*)

Parameter	Initial	After blood loss		
		BP drop by 15%	BP drop by 31%	BP drop by 43-56%
SBP, mm Hg	86.3±0.6	69.5±1.1*	53.3±1.1*	45.6±0.7*
Cerebral blood flow, %	100	93.1±3.4	89.1±4.7*	74.3±3.6*
Endothelial range (0.01-0.15 Hz)				
frequency, Hz	0.022±0.003	0.0136±0.0013	0.0164±0.0021	0.0140±0.0012
standardized amplitude	10.76±0.97	9.9±1.5	14.4±1.4*	10.78±1.40
Endothelial range (0.04-0.04 Hz)				
frequency, Hz	0.080±0.008	0.081±0.009	0.076±0.009	0.0610±0.0045
standardized amplitude	10.64±1.00	10.45±1.37	12.14±2.00	16.2±1.9*
Myogenic range (0.15-0.4 Hz)				
frequency, Hz	0.250±0.016	0.240±0.013	0.260±0.019	0.250±0.022
standardized amplitude	11.3±1.4	8.60±0.82	8.22±0.75	10.30±0.97

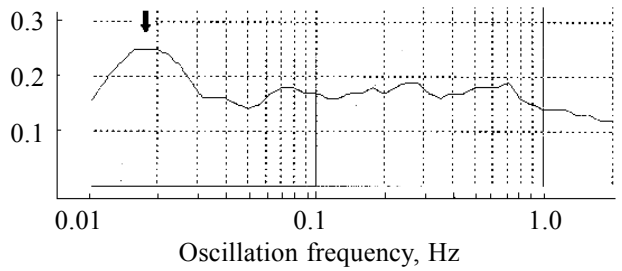

Fig. 2. Wavelet spectrum of blood flow oscillation in rat parietal neocortex against the background of the second blood loss. Arrow shows the increase in oscillation amplitude in the endothelial range.

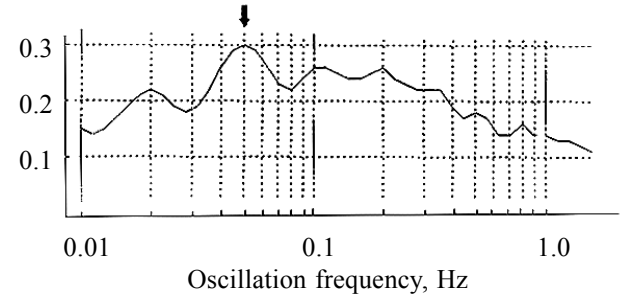

Fig. 3. Wavelet spectrum of blood flow oscillation in rat parietal neocortex against the background of the third blood loss. Arrow shows the increase in oscillation amplitude in the neurogenic range.

After the first blood loss, SBP decreased from 86 to 69 mm Hg and cerebral blood flow decreased by 7%, but in none of the three spectra appreciable changes in oscillation amplitudes were detected. After the second blood loss, SBP decreased to 53 mm Hg, cerebral blood flow decreased by 11%, and an increase in oscillation amplitude was detected in the middle of the frequency range corresponding to endothelial component (Table 2, Fig. 2). After the third blood loss, SBP decreased to 45 mm Hg, cerebral blood flow decreased by 26%, and an increase in oscillation amplitude was detected in the middle of the frequency range corresponding to neurogenic component (Table 2, Fig. 3). Thus, under conditions of autoregulation of cerebral blood flow we observed an increase in the oscillation amplitude corresponding to endothelial and neurogenic influences, whereas the myogenic component remained unchanged. The increment in oscillation amplitude is now interpreted as an increase in the contribution of endothelial and neurogenic factors into arteriolar distension [3]. The fact that oscillation amplitude in the frequency range corresponding to the myogenic component remained unchanged under these conditions agrees with the data obtained in experimental series I, *i.e.* suggests that the tension of the vessel wall is a peculiar vessel distention limit under conditions of reduced perfusion pressure. Using a mathematical model we previously showed that regulation of vessel wall tension is sufficient for the maintenance of blood flow through a particular arteriole [1]. Thus, our findings suggest that myogenic reaction play a leading role in autoregulation of cerebral blood flow.

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