Peculiarities of Vasomotor Reaction of Cerebral Vessels in Arterial Hypertension

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We studied vasomotor activity of rat cerebral vessels. Peculiarities of endothelium-dependent reactions of cerebral arteries in induced arterial hypertension were revealed. Quantitative and qualitative relationships between the parameters of the vasomotor apparatus of cerebral arteries and parameters of circulatory homeostasis were determined.

Key Words: *rat; cerebral circulation; vasodilation; vasoconstriction; magnetic resonance imaging*

Cerebrovascular complications, being the main cause of disability and lethal outcome in arterial hypertension (AH), often determine the fate of these patients [3].

A concept of endothelial injury as a predictor of damage to the target organs in AH is now of particular importance. An early manifestation of endothelial dysfunction is decreased production of endothelium-relaxing factors mediating dilatory reactions of arteries and ensuring adequate blood supply [6]. Imbalance of endothelium vasomotor function also manifest in alteration of constrictor capacities of arteries [4,7]. Despite great practical and theoretical importance of this problem, the data characterizing the state of cerebral circulation in AH are scanty and contradictory.

In the present study we undertook complex evaluation of the state of the vasomotor apparatus of rat cerebral arteries in AH according to the data of magnetic resonance imaging.

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MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 200-300 g (n=100). The animals were kept under standard vivarium conditions at natural illumination with free access to food and water. The animals were randomly divided into experimental (n=80) and control (n=20) groups. In group 1, experimental cardiorenal model of AH was reproduced by replacing drinking water and standard fodder with 1% NaCl and special semisynthetic cardiovasopathogenic diet with increased electrolyte content. Blood pressure was measured using a MedLab U/4c501 system (MedLab) for noninvasive blood pressure monitoring in rats by the tail-cuff method. Systolic and diastolic pressure in the control group was 110.5±8.3 and 75.3±3.6 mm Hg, respectively, and in the experimental group 156.2± 9.6 and 94.6±5.2 mm Hg, respectively (p<0.0001).

Before magnetic resonance scanning the animals were narcotized with rometar (Xylazinum, Spofa) in a concentration of 1 mg/ml and immobilized with relanium in a concentration of 2 mg/ml, intraperitoneally. Magnetic resonance imaging was performed on a PharmaScan US 70/16 tomograph (Bruker) for experimental studied operated at 7.0 T magnetic field strength and 300 MHz frequency and equipped with a BGA 09P coil. Anatomic and

topographic structure of the cerebral vascular bed was evaluated by the standard method [1]. Layer-by-layer sections in the frontal, sagittal, and horizontal planes for obtaining T2 images and proton density-weighted images were made using pulse sequences RARE 8, MSME, GEFI. Occipital 3D reconstruction of the vascular network was performed using Para Vision 3.0 software (Bruker).

Vasomotor reactions of cerebral arteries were studied in pharmacological tests with the following agents: acetylcholine for evaluation of endothelium-dependent vasodilation (VD_{ED}), nitroglycerin for evaluation of endothelium-independent vasodilation (VD_{EI}), N-monomethyl-L-arginine (L-NMMA) for evaluation of endothelium-dependent vasoconstriction (VC_{ED}), and norepinephrine for evaluation of endothelium-independent vasoconstriction (VC_{EI}) according to the standard protocol [2]. For interpretation of the results of these tests, the diameter of arteries was measured before and after the test by using 2 points set by a cursor of the tomography at the adventitia/media boundary of the lateral arterial wall and at the media/adventitia boundary of the medial arterial wall. Vasomotor reaction was evaluated as the percent ratio of the change in artery diameter and signal intensity integral during the test to the corresponding values at rest.

The data were processed by methods of variation statistics using Excel 2003 software. Significance of differences between the groups was evaluated using Student's *t* test. The differences were significant at $p<0.05$.

RESULTS

In all animals, satisfactory images of the cerebral basin were obtained, which allowed evaluation of the diameters of arteries and calculation of the percent of dilation and constriction as well as the dynamics of integral signal intensity.

Analysis of magnetic resonance scans of cerebral vessels in animals with AH showed clear-cut tendency to a decrease in the diameter of arteries and increase in integral intensity of the signal from major arteries of the left and right hemispheres compared to the corresponding parameters in intact animals ($p=0.05$; Table 1).

In control rats, administration of acetylcholine induced more pronounced increase in the diameter of cerebral arteries and decrease in signal intensity integral compared to the experimental group ($p<0.001$). Hence, equivalent endothelium-dependent stimulus did not induce adequate VD_{ED} in the cerebral basin of hypertensive rats (it was 2-fold below the control).

Nitroglycerin-induced vasodilation was similar in both groups, integral signal intensity differed insignificantly (Table 1).

Hence, the dilation component of the vasomotor apparatus in AH was inhibited primarily due to impairment of endothelium-dependent mechanism, while myogenic dilation of cerebral arteries was preserved.

Analysis of the constrictor component of the vasomotor function in cerebral arteries revealed significant differences between the groups. In animals with AH, the decrease in vessel diameter during VC_{ED} was more pronounced ($p<0.001$), while the signal intensity integral increased to a greater extent than in controls ($p<0.001$).

The decrease in the diameter of cerebral vessels and the increase in signal intensity integral in response to injection of norepinephrine were similar in AH and normotensive animals (Table 1).

Our measurements showed that endothelium-dependent constrictor response of cerebral arteries

TABLE 1. Parameters of Vasomotor Function of Rat Cerebral Arteries

Parameter	Control	Animals with AH
Initial diameter of artery, mm	0.87±0.03	0.77±0.03*
Diameter of artery during acetylcholine test, mm	1.05±0.05	0.90±0.05**
VD_{ED}, %	22.83±1.66	11.31±0.91***
Diameter of artery during nitroglycerin test, mm	1.21±0.07	0.93±0.04**
VD_{EI}, %	31.92±2.43	29.42±1.71
Diameter of artery during L-NMMA test, mm	0.71±0.04	0.55±0.04**
VC_{ED}, %	-11.16±0.94	-26.31±0.97***
Diameter of artery during norepinephrine test, mm	0.61±0.01	0.58±0.01*
VC_{EI}, %	-28.71±1.04	-29.83±1.95

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to the control.

in AH animals increased by 2.4 times compared to than in normotensive animals. The observed excessive constrictor reaction attests to a decrease in adaptation potential of autoregulation of cerebral vessels.

The relationships between the parameters of vasomotor apparatus of cerebral arteries and parameters of circulatory homeostasis were evaluated using correlation analysis. In both animal groups, a positive correlation was found between VD_{ED} and VD_{EI} (r=0.77; p<0.05). In AH animals, a negative correlation was found between VD_{ED} and VC_{ED} (r=0.51; p<0.05). In none cases, correlations between VD_{ED} of cerebral vessels and systolic and diastolic blood pressure were observed.

It is well known that cerebral catastrophes in AH often result from angiospastic and angiosclerotic changes in vessels, which are the markers of the damage to the target organs in these patients [3]. Hypertonic angioencephalopathy is characterized by acute and chronic changes in cerebral vessels associated with AH [5]. The decrease in vessel diameter observed in our study agrees with published data and is a visual substrate of changes in the architectonics of cerebral vascular bed against the background of chronic hypertension. The lumen of cerebral vessels in AH is always narrowed first at the expense of adaptive and tonic mechanisms and later due to structural remodeling of the vascular wall [8]. We found that VD_{ED} of cerebral vessels in hypertensive rats was reduced compared to that in controls. These findings together with the negative correlation between VD_{ED} and VC_{ED} can attest to endothelial dysfunction in this pathology. The absence of correlations between systemic blood pressure and vasomotor function of cerebral vessels can be determined by pronounced autoregulation of cerebral circulation.

Thus, physiological resistance of the vasomotor function of the endothelium in cerebral vessels is impaired during AH. Various factors, including AH, reduce the efficiency of ionic channel work and impair deformability and mechanical sensitivity of endothelial cells [2]. Another possible mechanism of the development of endothelial dysfunction in cerebral vessels is a decrease in basal NO level. This is confirmed by measurement of VC_{ED} induced by NO synthase inhibitor L-NMMA: equivalent doses of L-NMMA produced more pronounced vasoconstriction in rats with AH compared to that in normotensive animals. Our findings agree with the data on sharply increased capacity of cerebral arteries to spastic reactions under conditions of functional insufficiency of the endothelium [6]. The physiological reaction of cerebral arteries to nitroglycerin and norepinephrine in animals with AH suggests that the myogenic component of regulation is preserved. We cannot made definite conclusion whether the observed disturbances in the endothelium-dependent mechanism of regulation of vessel diameter in hypertensive rats are a result of reduced NO synthesis or its impaired expression. The problem of correction of vasomotor disturbances in cerebral vessels during AH also requires further investigation.

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