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The State of Cerebral Blood Flow during Hypertensive Crises and the Possibility of its Correction

E. N. Tashkenbaeva, G. T. Madjidova, G. I Sunnatova
Samarkand State Medical University, 2nd Professor of the Department of Internal Medicine and Cardiology, Samarkand Uzbekistan.

O. S. Nekbaeva, N. T. Umarova
Doctor's office, Samarkand branch of the Republican Scientific Center for Urgent Ambulance, Samarkand Uzbekistan

Abstract: It is known that hypertension remains one of the most pressing problems of modern cardiology due to its high prevalence, severity of complications and subsequent adverse outcomes as a result of target organ damage. In terms of the frequency of cerebral circulatory disorders associated with hypertension, Uzbekistan and the CIS countries occupy one of the leading places in the world, and strokes in our country occur 4 times more often than in developed countries [1]. One of the causes of cerebrovascular accidents is the uncontrollability of arterial hypertension (AH) and the development of hypertensive crises (HCs). The number of calls from emergency medical services teams regarding HA increased by an average of 1.5 times.

Among the mechanisms responsible for the regulation of blood pressure (BP), the leading role is assigned to vascular endothelial cells due to their unique ability to release a number of vasoactive substances and participate in the transmission of signals to smooth muscle cells (SMCs) [2].

One of the factors that causes relaxation of vascular smooth muscles is the universal angioprotector - nitric oxide (NO), which regulates peripheral resistance, the distribution of blood flow in the vascular network, regulates basal vascular tone by inhibiting the synthesis of endothelin -1 and limiting the release of norepinephrine from sympathetic nerve endings [2].

Currently, many antiatherogenic effects of NO have been discovered, in particular due to the inhibition of leukocyte adhesion, suppression of the expression of proinflammatory genes, inhibition of activation, secretion, adhesion, platelet aggregation and proliferation of SMCs in the vessel wall [5].

In recent years, it has been proven that the development of atherosclerosis involves not only NO, but also systemic inflammation as a result of the interaction of intercellular association: macrophage–T–lymphocyte–GM K [9].

In the pathogenesis of inflammatory changes in the vascular system, among many cytokines, IL-1, 6, 10 and tumor necrosis factor (TNF) become of primary importance, while only IL-10 has an anti-inflammatory effect [6].

The purpose of our study was to study the state of cerebral blood flow, the content of NO and a number of cytokines (TNF, IL-6, IL-10) in the blood serum of patients with hypertension during the development of a hypertensive crisis and their dynamics during treatment with the slow calcium channel blocker (SCBC) amlodipine and cerebroprotector .

Material and methods of the study

The criteria for inclusion in the study were the presence of hypertension with a low, medium and high risk of developing cardiovascular complications (CVC) for 10 years (50 people comparable in age and gender). Among patients with hypertension, the following groups were randomly identified:

1. Patients receiving antihypertensive therapy without BMMC and Cavinton -Forte (15 people).

2. Patients with antihypertensive therapy , including Normodipine (15 people).

3. Patients with antihypertensive therapy, including Normodipine and Cavinton -forte (20 people).

In order to exclude the possible contribution of other pathological processes to the study results, patients with hypertension did not have associated conditions in the form of cerebrovascular diseases (ischemic or hemorrhagic stroke, transient ischemic attack), heart disease (MI, coronary revascularization , congestive heart failure), kidney disease (diabetic nephropathy, renal failure), peripheral arterial disease, severe retinopathy (hemorrhages or exudates, papilledema), diabetes mellitus. Accordingly, the exclusion criterion was the presence of hypertension with a very high risk of developing cardiovascular complications within 10 years. The average age of those examined with hypertension was 48.1±2.2 years.

Blood pressure values corresponded to moderate hypertension. The average level of systolic blood pressure (SBP) was 169.6±3.7 mmHg , diastolic blood pressure (DBP) was 101.2±2.9 mmHg . 65% of patients (n=39) were overweight. The average value of venous blood glucose was within 5.6±0.8 mmol /l. The initial level of total cholesterol was 5.9±0.7 mmol /l. Thirty-one patients had a family history of early development of CVD.

56.6% (n=34) of patients had a high risk of developing CVS, 38.3% (n=23) had a moderate risk of developing CVS, and 5% (n=3) were in the group with a low risk of developing CVS. The control group included 30 normotensive people, matched for gender and age, without coronary risk factors.

Study design

Before inclusion in the study, all patients received recommendations on self-monitoring of blood pressure, diet, and physical activity.

After performing all the studies provided for by the protocol (generally accepted methods - clinical and biochemical blood tests, general urine analysis, ECG, ECHO-KG, ultrasound of the kidneys, examination by an ophthalmologist, “special” methods - determination of NO metabolites in blood serum, enzyme-linked immunosorbent assay IL-6, IL-10 and TNF, transcranial Dopplerography of cerebral vessels (TCDG GM)) all patients received antihypertensive therapy. The 1st group of patients took various antihypertensive drugs - ACE inhibitors, adrenoblockers , diuretics - and blockers . Group 2 received Normo dipin , the initial dose was 5 mg/ day , if necessary the dose was increased to 10 mg/ day . to achieve a therapeutic effect. Group 3 received treatment with Normodipine and Cavinton -forte at a dose of 1 tablet 3 times a day. The duration of therapy was 12 weeks. Twice, at control visits (once a month), a comprehensive clinical examination of patients was carried out, any side effects and drug tolerability were recorded.

The antihypertensive effect of therapy was assessed based on data from the “BP Observation Diary” kept by patients.

In all patients, the effect of therapy on the state of cerebral blood flow was assessed using the GM TCD method using an ultrasound device "ANGIODIN" from BIOSS, operating in real time with a transcranial sensor with a frequency of 2 MHz. In clinical practice, vasospasm in the cerebral arteries is most often assessed by the linear blood flow velocity (LBV) in the middle cerebral artery (MCA), since it is the final artery and is more accessible for location. Accordingly, the following BFV parameters were assessed: Vmaxs (maximum systolic blood flow velocity), Vendd (minimum diastolic blood flow velocity), Vmean (average blood flow velocity), PI (pulsatility index) and IR (resistance index) in the MCA ..

Markers of systemic inflammation (pro-inflammatory – IL-6, TNF and anti-inflammatory – IL-10) were determined by ELISA.

To test the statistical significance of changes in quantitative parameters relative to the initial level, a paired Student's t test was used .

Results and discussion

The study of cerebral blood flow indicators is presented in Table 1. According to the results obtained, no disturbances in the main blood flow of the brain were found in the control group. At the same time, in hypertensive patients, an increase in LSC parameters was noted during GC, which indicates the presence of a vasospastic reaction in the vessels of the brain. The degree of vasospasm is judged by the systolic blood flow velocity. Thus, Vmaxs during GC in group 1 was 124.4±6.1 cm/ s , in group 2 – 135.6±2.9 cm/s, which corresponds to a mild degree of vasospasm , and in group 3 group – 148.8±1.1 cm/s, corresponding to the average degree of vasospasm . Moreover, the Vmaxs indicators did not differ significantly between the groups (the patients were randomly divided into groups). By the time of re-examination after 12 weeks, against the background of antihypertensive therapy, a decrease in blood flow velocity parameters was observed in all groups. Vmaxs after treatment in the group treated without BMCC was 116.5±2.2 cm/s, in the group taking Normodipine - 96.2±1.4 cm/s and in patients treated with Normodipine and Cavinton - forte - 97.3 ±1.5 cm/s. However, a significant decrease in indicators was noted only in patients taking Normodipine as monotherapy or in combination with Cavinton -forte, and in the latter the decrease in LSC was more significant. This may be due to the ability of Cavinton to inhibit Ca2+/ calmodulin-dependent cGMP -PDE, thereby increasing the level of cAMP and cGMP , which cause a positive vascular effect and, as a result, improve cerebral blood flow [11]. The results of some PET studies also show that taking Cavinton increases regional cerebral blood flow [11].

The parameters of maximum systolic or end-diastolic velocities reflect blood flow during a specific period of the cardiac cycle, without providing information about the true velocity of blood flow in the vessel over the entire period of the cardiac cycle. More indicative is the calculation of values such as IR and PI, which also allow one to judge the value of peripheral resistance [12]. Moreover, the PI value more accurately reflects the state of blood flow, since it depends on all flow rates, which gives it an advantage in terms of information content [13]. Figure 1 shows the dynamics of PI indicators. In hypertensive patients during the period of GC there is a significant increase in PI compared to the control group. Thus, in patients treated without BMCC, PI was at the level of 0.90±0.02, in those taking only Normodipine - 0.92±0.04 and in those receiving Normodipine and Cavinton -forte simultaneously - 0.99±0.11. At the same time, PI in normotensive people was 0.75±0.05. After antihypertensive therapy, PI parameters decreased, amounting to 0.88±0.01 in group 1, 0.81±0.01 in group 2, and 0.71±0.16 in group 3. At the same time, a significant decrease in PI, as well as in the maximum systolic blood flow velocity, occurred only in those patients who took Normodipine as monotherapy or in combination with Cavinton -Forte. Moreover, in the latter, PI indicators after treatment were comparable to PI in the control group, which may indicate a significant contribution of Cavinton -Forte to the improvement of cerebral blood flow.

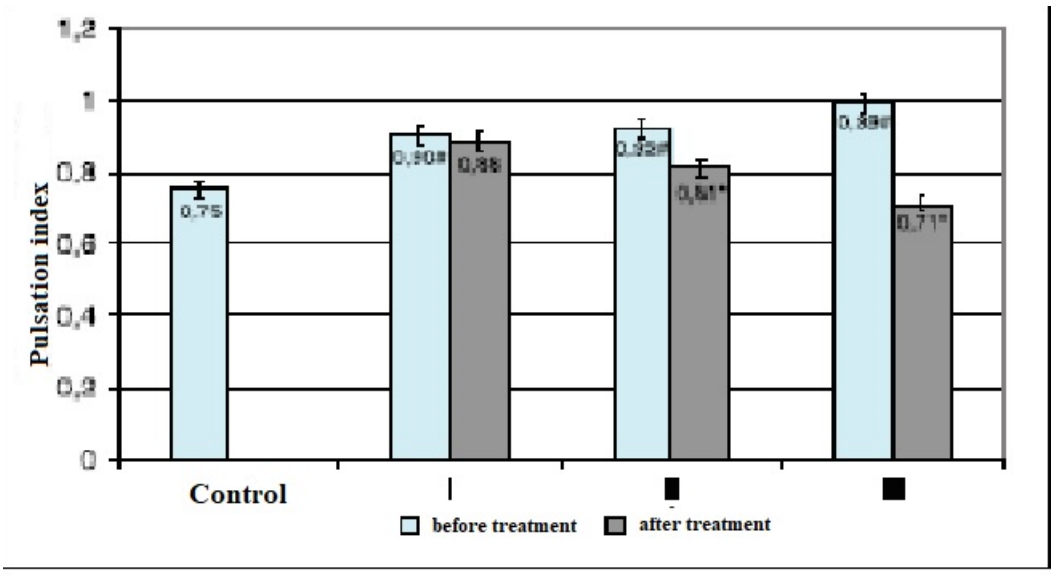
In order to assess the vasodilating function of the endothelium, the level of NO metabolites in the blood serum was examined, the results of which are presented in Figure 2. In the control group, the NO concentration was 23.4 ± 1.6 μmol /l. In HD patients during GC, there was a 1.5–2-fold decrease in NO, amounting to 17.3±1.9 μmol /l, 21.1±1.6 μmol /l and 16.8±2.2 μmol /l in the 1st, 2nd and 3rd groups, respectively. At the same time, the lowest level of NO was observed in the group of patients with the highest speed indicators of cerebral hemodynamics. This may be due to the contribution of a secondary vascular reaction to the release of vasoactive substances during the development of cerebral vasospasm . Therefore, the initial decrease in NO also contributes to the development of the vasospastic reaction of the brain vessels [12]. According to the study protocol, NO levels were re-measured after 12 weeks of therapy. The concentration of nitric oxide significantly increased in all groups of subjects, but the greatest increase (45.2%) was observed in patients taking combination therapy with Normodipine and Cavinton - forte. It is believed that blockade of Na + channels using Cavinton can counteract oxidative stress by eliminating the factor that worsens cellular ionic and metabolic disorders, since if Na + accumulates in neuronal GM, then oxidative stress has a more pronounced damaging effect.

As noted earlier, in recent years it has been proven that systemic inflammation is involved in the pathogenesis of cardiovascular diseases [14]. We studied some parameters of the immune status, presented in Table 2. During the observation process, we did not detect any significant changes in the level of cytokines in the blood serum. Thus, the level of IL-6 was 1.85 mg/l, 2.86 mg/l and 2.1 mg/l in groups 1, 2 and 3, respectively, which was comparable to the control - 2.3 mg/l. The concentration of IL-10 in group 1 was 3.81 pg /l, in group 2 – 2.95 pg /l and in group 3 – 3.45 pg /l, which did not differ significantly from the control group . TNF levels in hypertensive patients also did not differ from normotensive patients, amounting to 1.9 mg/l in group 1, 1.9 mg/l in group 2 and 1.13 mg in group 3. /l. This may be due to the fact that in our young and mature patients with moderate or mild arterial hypertension, associated diseases accompanied by systemic inflammation were excluded.

However, we completed the study and found that during antihypertensive therapy, the level of cytokines decreased, which may indicate a decrease in the intensity of the immune response under the influence of antihypertensive therapy. No significant differences were found in the 1st, 2nd, 3rd group of patients (Fig. 3).

Conclusions

1. During the period of hypertensive crisis, a disturbance of cerebral hemodynamics is observed in the form of a vasospastic reaction with a significant increase in the linear velocity of blood flow and a decrease in the NO content in the blood serum.
2. Antihypertensive therapy for 12 weeks leads to a significant antihypertensive effect and an increase in NO levels in all groups of subjects, most pronounced in patients receiving Normodipine as monotherapy and in combination with Cavinton -Forte.
3. A significant decrease in the peripheral resistance of cerebral vessels according to transcranial Dopplerography occurs only in patients receiving BMCC and especially in combination with Cavinton -Forte.
4. The additional prescription of Cavinton -Forte to antihypertensive therapy is justified in patients with crisis headache, since this significantly improves blood flow parameters in the cerebral vessels in the form of an increase in the linear velocity of blood flow, a decrease in peripheral resistance and an increase in NO in the blood serum.
5. In patients with hypertension, there were no significant changes in the levels of IL-6, IL-10, TNF, which can be associated with the young and middle age of the patients and the absence of associated diseases.



Rice. 1. Dynamics of pulsation index indicators.

Notes:

1) group 1 of patients receiving therapy without BMMK and Cavinton -forte;
2) group 11 of patients receiving monotherapy with Normodipine ;
3) group of patients receiving Normodipine and Cavinton-Forto ;
4) the differences are significant between the control group and patients with hypertension during GC at p<0.05; 5) the differences are significant in the group before and after treatment at p<0.05

Table 1. Linear velocity of blood flow in the middle cerebral artery

Groups of subjects	Indicators of LSC in SMA					
	V_{maxs}, см/с		V_{mean}, см/с		V_{endd}, см/с	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Healthy	95,8±3,7	–	56,1±8,1	–	45,2±4,5	–
I	124,4±6,1#	116,5±2,2	78,3±7,8#	68,9±7,9	58,8±5,1#	54,2±4,9
II	135,6±2,9#	96,2±1,4*	80,4±8,1#	61,5±7,8*	63,5±4,9#	46,3±5,0*
III	148,8±1,1#	97,3±1,5*	88,7±9,6#	60,1±8,6*	64,9±5,6#	47,1±5,5*

Notes:

1) group 1 of patients receiving therapy without BMMK and Cavinton-forte; 2) Group II of patients receiving monotherapy with Normodipine; 3) Group III of patients receiving Normodipine and Cavinton-forte; 4) - maximum systolic blood flow velocity; 5) Vmean is the average blood flow velocity; 6) is the final diastolic blood flow velocity; 7) the differences are significant between the control group and patients with hypertension during GC at p<0.05; 8) * differences are significant in the group before and after treatment at p<0.05

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