TODAY'S DAOLLING PROBLEMS OF CEREBRAL CIRCULATION AND COGNITIVE FUNCTION DISORDERS

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Abstract. The history of the study of autoregulation of cerebral blood flow began with its denial in accordance with the Monro-Kellie statement , the essence of which is that the total volume of intracerebral blood, cerebrospinal fluid and intracranial blood is constant, and a decrease in one of them leads to an increase in the other two

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The study of mycocirculatory brain science began with W. Harvey and A. van Leeuwen hoek in 1628 and 1674 respectively [1]. In that period dominated The notion of the supply of the brain substance by the “terminal arteries ” [2], and the quantitative assessment of brain mycocyoculation was limited by the lack of appropriate - MICROSCOPY TECHNIQUES [1]. The results of the study of only THE SPEED indicators of BLOOD FLOW in the vessels of the brain lead to the conclusion about constant circulation . BLOOD [3]. The term " autoregulation " in relation to cerebral blood flow was proposed by NA Lassen in 1959 [4]. Despite this, A. I. Ostroumov in 1876 described the reaction of the muscular membrane of the arteries to an increase in intravascular pressure [6]. The classical Starling theory [7] formed the basis of the capillary blood flow hypothesis, according to which there is a dynamic equilibrium between the volume of fluid filtered at the arterial end of the capillary and the volume of fluid reabsorbed at the venous end (and removed by the lymphatic vessels). The concept of peripheral vascular resistance HD Green has served as evidence of the need for a quantitative assessment of peripheral vascular tone. These studies formed the basis of a model according to which blood flow is regulated by the caliber of arterioles, the volume of blood flow in organs is determined by venules and veins, and the distribution of blood flow in capillaries occurs in accordance with the metabolic needs of the brain [1].

In experiments on animals, data were obtained on changes in the rate of blood flow in the vessels of the brain during manipulations on the cervical sympathetic nerve. HS Forbes (1938) and other authors established the role of blood pressure, osmotic pressure, choline-like substances, adrenaline and CO4 levels [2]. Studies of brain microcirculation were carried out by introducing coloring agents into the carotid arteries of animals with an assessment of the time of their appearance in the retina [8]. Further studies in vivo demanded microsco - 96
pic technology, which was first used on the brain by H. Florey and described by M. Fog

[9]. Assessment of the state of the vessel diameter was carried out by photometric scanning [1]. The first experimental data on the nature of the blood flow in the superficial vessels of the brain were obtained using the "transparent skull" technique [6]. The microelectrode technique for measuring local cerebral blood flow [10], as well as the electroplethysmographic method, the thermoelectric method, and techniques with intravascular tensoresistor sensors , were widely used . Registration of blood filling of cerebral vessels based on impedance has been developed in the form of rheoencephalography and rheoplethysmography [11].

In the 40s of the last century, SS Kety and C. F. Sehmidt presented a method for quantifying the rate of cerebral blood flow [11, 12] using blood gases as indicators. Subsequently, the methods became widespread in various modifications and served as an impetus for the development of methods based on the saturation of the brain tissue with diffusible indicators [13]. The Kety - Sehmidt method subsequently became the reference method for measuring cerebral blood flow [14]. The method for assessing blood flow velocity according to the Kety - Sehmidt principle with a diffusing - radioactive indicator krypton was introduced by V. M. Lewis [15]. JR Rees (1970) established the difference in blood flow velocity in the gray and white matter [16]. HI Glass and AM Harper developed a technique for measuring xenon clearance [17, 18]. Non-invasive techniques based on the inhalation of radioactive inert gases have become widespread in the study of cerebral blood flow [16].

The next step was the transition to nondiffusing contrast agents [6, 16]. The theoretical basis of the indicator washout method was prepared by KL Zierler [19]. He found that the average transit time of the indicator through the tissue is the ratio of the area under the curve (A) and its first peak (H), i.e. t = A/H per minute [20]. R Meier and KL Zierler [21] provide a mathematical substantiation of the indicator dilution theory and demonstrate that the mean transit time is the ratio of blood volume to blood flow velocity. According to the principle of central volume, which is common to all methods of assessing tissue perfusion, these parameters are related by the ratio CBV (cerebral blood volume; cerebral blood volume) = CBF (cerebral blood flow; cerebral blood flow) ^{x} MTT (mean transit time; mean transit time). Based on the works of K. L. Zierler a direction was formed to study the speed indicators of blood flow in the brain according to the dynamics of the density of non-diffusing radiopaque indicators. A great contribution was made by S. K. Hilal [22], who developed the technique of X-ray densitometry for calculating the blood flow velocity in the arteries. NA Lassen at that time quite fully presented an overview of methods for assessing cerebral blood flow in the review [23].

For a short time, the quantitative assessment of cerebral blood flow was based on X-ray videodensitometry [24]. The first use of video densitometry for assessing blood flow was with the use of analog densitometers. The technique of fluorescent excitation

was also used [25].

Current methods for studying tissue and cellular perfusion of the brain. Physical principles, advantages and disadvantages

A new stage in the development of techniques based on the principle of the first pass of a contrast agent became possible after the introduction of X-ray perfusion computed tomography (PCT) into clinical practice [26]. L. Axel (1980) studied the theories of indicator dilution based on the central volume principle and developed a technique for assessing brain tissue perfusion using dynamic PCT [27]. The latter is a series of images obtained during the passage of a bolus of a contrast agent through the brain tissue [28].

In PCT, after an intravenous injection of a contrast agent, it spreads through the venous and then through the arterial network, resulting in an increase in X-ray density on CT sections. The enhancement of CT density after contrast injection can be divided into two phases based on its distribution: intravascular and extravascular. At the initial stage after injection of a contrast agent, an increase in density is associated with the presence of contrast within the vascular bed. During the second stage, when the contrast passes through the basement membranes of the capillaries, there is an increase in density from both vessels and extravascular tissues. Thus, at the first stage, the increase in densitometric parameters is determined by the level of systemic and regional blood flow, and at the second stage, the increase depends on the blood volume and capillary permeability. By obtaining a series of rapid sequence images in the selected area, it is possible to measure the time of “washing out” of the contrast from the tissue after its intravenous injection. Perfusion scores are calculated using mathematical modeling techniques that use native tissue and vascular densitometric scores.

The two most commonly used analytical methods for quantifying perfusion parameters from a dynamic series of sections are: compartment analysis and deconvolution. Both methods require data to be obtained between the "arterial entry" of the contrast agent and its "washout" to assess tissue vascularization [29].

Compartment analysis is a mathematical modeling technique based on comparing one or two parts of a volume. The first model is used to assess tissue perfusion with the presence of a contrast agent only in the vascular bed. This model is based on the Fick principle [30] and calculates tissue perfusion values based on the mass conservation principle. Perfusion values are calculated from the maximum slope (the tangent of the slope at a given point) or the peak height of the contrast agent concentration versus time curve. The second model is used to evaluate capillary permeability and calculate blood volume. This model assumes that in addition to the intravascular space there are additional areas of accumulation of contrast agent, calculations are made using a method called Patlak analysis . This method calculates the quantitative indicators of the passage of the marker from the intravascular space to the surrounding tissues [31].

The inverse convolution method is based on the use of density-time curves to

calculate the residual impulse function for tissue. The plotting of curves is possible under the condition of a linear dependence of tissue density on the concentration of the contrast agent in the incoming artery at a constant blood flow. After flow correction, the height of the curve shows the amount of tissue perfusion, and the area under this curve shows the relative blood volume. An extended inverse convolution model is used to assess capillary permeability [31].

Both methods are generally equivalent, but differ in terms of theoretical assumptions of susceptibility to noise and movement, which is why the compartment analysis method is preferable for the analysis of blood flow in organs with a complex system of vascularization [32]. For reliable calculation and correct interpretation of perfusion parameters, certain conditions must be met : rapid administration of a contrast agent with a high iodine content (bolus), patient immobility during the study [33], knowledge of the specifics of the scanning device.

Given the unified principle of calculating the parameters of tissue blood flow, all research methods provide comparable information:

- CBV is the total blood volume in the selected area of the brain tissue. This concept includes blood both in capillaries and in larger vessels - arteries, arterioles, venules and veins. This indicator is measured in milliliters of blood per 100 g of medulla (ml / 100 g); CBV is a functional parameter that reflects the mechanisms of autoregulation - changes in vessel diameter;
- CBF is the rate of passage of a certain volume of blood through a given volume of brain tissue per unit of time. CBF is measured in milliliters of blood per 100 g of brain matter per minute (mL/100 g min); is the most significant indicator of cerebral perfusion. The stability of the CBF index is maintained by the mechanisms of autoregulation , manifested in a change in the diameter of cerebral vessels depending on the level of systemic arterial pressure. Thus, at the limit of autoregulation mechanisms in pathological changes in blood pressure, the CBF index may decrease [34];
- MTT is the average time during which blood passes through the vascular bed of a selected area of brain tissue, measured in seconds (s). This indicator has limited specificity, since its lengthening may be due to significant stenosis of the main arteries of the neck and head, as well as vasospasm [34].

the time to peak contrast agent concentration can also be calculated (time to peak , TTR). TTR is a complex indicator consisting of two parts: the time of arrival of a contrast agent from the cubital vein to the brain and from the beginning of the entry of this substance into the brain to its maximum concentration in the studied areas of the brain. The first component directly depends on the inotropic and chronotropic functions of the heart. TTR is more sensitive to changes in activity in the left hemisphere than in the right.

Tissue blood flow is assessed using the maps constructed for each of the parameters,

as well as their absolute and relative [35] values in the corresponding areas of the brain.

The absolute perfusion parameters on devices from different manufacturers differ due to the difference in the analytical calculation methods (Table).

The regional transit time of the contrast agent and the velocity of blood flow through a unit of vascular volume are measured. After a delay due to the passage of the indicator through the pulmonary circulation, it reaches a peak and decreases sharply with a second peak of lower amplitude due to recirculation [36]. The software of the CT scanners makes it possible to obtain curves of the density of the contrast agent as a function of time. The dynamics of tissue density after contrast injection is linearly dependent on the concentration of the contrast material [37].

A significant breakthrough in the diagnosis of cerebral microcirculation disorders in cerebrovascular pathology was achieved with the introduction of radionuclide methods into medical practice. Positron emission tomography (PET) is a technique for obtaining tomographic images and quantitative parameters of regional blood flow, including blood flow velocity, metabolic level of oxygenation and oxygen extraction, as well as cell viability, proliferation and metabolic activity of tissues. Images are obtained using biological substances labeled with radioisotopes that release positrons [44]. However, the routine use of PET is limited by the small number of scanners, the cost and complexity of the procedure [36].

Certain hemodynamic characteristics can be obtained by single photon emission computed tomography (SPECT), which is a noninvasive technique for assessing the distribution of a radiopharmaceutical that reflects regional hemodynamics [45] covering the entire brain volume. However, the possibility of obtaining quantitative data is limited in this case [36].

Dynamic perfusion magnetic resonance imaging (PMRI) also provides information on CBF, CBV, and MTT. The method is based on the change in the relaxation time T1 or T2 during the first passage of a contrast agent (gadolinium-based contrasts are usually used) through the capillary bed. PMRI has both advantages over PCT (better spatial resolution, no radiation exposure) and disadvantages (longer scanning time, dependence on motion artifacts, and the fact that PMRI parameters are semiquantitative [46]).

An alternative to methods for assessing cerebral blood flow based on contrast technologies today is the method of non-contrast MR perfusion - labeling of arterial spins (arterial spin labeled - ASL), which does not require the introduction of a contrast agent, since an endogenous marker is used to create a bolus of "labeled" arterial blood [47]. This method was first proposed in the early 1990s and has since been used primarily in research activities. The signal in ASL is roughly proportional to cerebral blood flow (CBF), which is significantly reduced in the core of an ischemic infarct when a large artery is affected. The maintenance of CBF is often provided by the movement of blood through collateral vessels, which leads to an increase in the time of arrival of

arterial blood. The principles of ASL are similar to those of CBF assessment in PET [48], since both methods are fundamentally based on the use of freely diffusing radioactive tracers, which makes it a method for assessing cellular perfusion, like PET and SPECT, and not a method for studying tissue microcirculation, like PCT and contrast media. PMRT. However, during PET, a radioactive tracer is injected, while during the ASL technique, blood itself acts as an indicator. In PET, the half-life of the radiotracer is approximately 2 minutes, while in ASL, when liquid blood becomes demagnetized at a magnetic field strength of 1.5 T (tesla), this figure is about 1.2 seconds. However, when performing the procedure in conditions of high magnetic fields (3.0T and 7.0T), it increases to approximately 1.7 and 2.5 s, respectively, which is similar to the longitudinal relaxation time or T1 of liquid blood. The relatively rapid loss of magnetization of the "endogenous indicator" during ASL makes it possible to carry out repeated measurements within a short period of time (4-8 s), as well as to evaluate changes in CBF in response to neurological or vascular tests [49]. However, because the magnetic labeling disappears during the blood T1 relaxation time (typically within 1.2-1.8 s at the strength of the magnetic field used in clinical settings), the ASL signal may not accurately reflect CBF in ischemic , but viable areas (penumbra) [50]. Nevertheless, the technique, taking into account the absolute safety in the absence of external contrast, with the introduction of tomographs with a higher field into medical practice (today, healthcare has mainly tomographs with a power of 1.5 T, less often - 3 T), probably has serious chances for clinical application in the near future.

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