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BIOLOGICAL AND PHYSICAL MECHANISMS OF CEREBRAL ANEURYSMS FORMATION, GROWTH AND RUPTURE

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ABSTRACT

According to various researchers, the prevalence of unruptured cerebral aneurysms (CAs) in the general population varies from 2 to 5 %. In the vast majority of cases, CAs do not have clinical and neurological manifestations and are discovered incidentally during routine neuroimaging studies. CAs can cause intracranial hemorrhage. As a rule, hemorrhages of this type occur in patients aged 40–60 years. It has been established that about 10–15 % of patients die from an aneurysmal hemorrhage before they receive specialized medical care. Recurrent aneurysmal intracranial hemorrhage is the main cause of high mortality and disability in this group of patients. The search for literature sources in the scientific databases PubMed/Medline, EMBASE, Cochrane Library and eLibrary demonstrated the existence of numerous studies devoted to the study of molecular biology and biophysical mechanisms of formation, growth and rupture of CAs. Combining the results of these studies was the motivation for writing this literature review. The paper reflects in detail the role of inflammation and molecular genetic factors in the growth and rupture of the CAs, and presents the biophysical factors of the rupture of the CAs. The authors pay special attention to the shape, size and coefficient of the CAs as the most important geometric risk factors for the formation and rupture of the CAs. This review presents current data on mathematical modeling of various types of CAs with an assessment of the risk of rupture of the latter, which has found its application in wide clinical practice. The authors also attempted to describe the hemodynamic features in various types of CAs. In turn, the type of blood flow in the CAs cavity largely depends on the size and shape of the latter and the geometry of the carrier artery, which is the basis for preoperative planning and the choice of tactics for surgical treatment of patients with unruptured CAs.

Key words: *cerebral aneurysms, formation, growth, rupture, inflammation, biology, biophysics, mathematical model*

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БИОЛОГИЧЕСКИЕ И БИОФИЗИЧЕСКИЕ МЕХАНИЗМЫ ФОРМИРОВАНИЯ, РОСТА И РАЗРЫВА ЦЕРЕБРАЛЬНЫХ АНЕВРИЗМ

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РЕЗЮМЕ

По данным различных исследователей, распространённость неразорвавшихся церебральных аневризм (ЦА) в общей популяции варьирует от 2 до 5 %. В подавляющем большинстве случаев ЦА не имеют клинико-неврологических проявлений и обнаруживаются случайно при выполнении плановых нейровизуализационных исследований. ЦА может явиться причиной внутричерепного кровоизлияния. Как правило, кровоизлияния такого типа встречаются у пациентов в возрасте 40–60 лет. Установлено, что около 10–15 % пациентов умирают от аневризматического кровоизлияния до оказания им специализированной медицинской помощи. Повторное аневризматическое внутричерепное кровоизлияние выступает основной причиной высокой летальности и инвалидизации указанной группы пациентов. Проведённый поиск литературных источников в научных базах данных PubMed/Medline, EMBASE, Cochrane Library и eLibrary продемонстрировал наличие многочисленных исследований, посвящённых изучению молекулярной биологии и биофизических механизмов формирования, роста и разрыва ЦА. Объединение результатов указанных исследований и явилось побудительным моментом к написанию данного литературного обзора. В работе детально отражена роль воспаления и молекулярно-генетических факторов в росте и разрыве ЦА, представлены биофизические факторы разрыва ЦА. Особое значение авторами уделено форме, размерам и коэффициенту ЦА как важнейшим геометрическим факторам риска формирования и разрыва ЦА. В настоящем обзоре представлены современные данные о математическом моделировании различных типов ЦА с оценкой степени риска разрыва последних, что нашло своё применение в широкой клинической практике. Также авторами предпринята попытка описания гемодинамических особенностей в различных типах ЦА. В свою очередь тип кровотока в полости ЦА во многом зависит от размера, формы последней и геометрии несущей артерии, на чём основано предоперационное планирование и выбор тактики хирургического лечения пациентов с неразорвавшимися ЦА.

Ключевые слова: *церебральные аневризмы, формирование, рост, разрыв, воспаление, биология, биофизика, математическая модель*

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INTRODUCTION

According to autopsy data, the prevalence of cerebral aneurysms (CAs) is 1–5 % of all deaths [1]. Morphologically, CAs are characterized by fragmentation of the internal elastic lamina with damage to the endothelial lining of the vessel, which eventually leads to changes in all layers of the vascular wall in the form of aneurysmal bulge formation, which can be considered as a pathological formation and, at the same time, a compensatory mechanism to reduce the local hemodynamic load on the vascular wall [2, 3]. In the vast majority of cases, CAs do not have clinical and neurological manifestations and are discovered incidentally during routine neuroimaging studies. However, CA can be a cause of intracranial hemorrhage. As a rule, hemorrhages of this type occur in patients aged 40–60 years [4]. The incidence of CA rupture has been shown to increase from 3 per 100,000 population in the group under 30 to 30 per 100,000 population among people over 60 [5]. It has also been established that about 10–15 % of patients die from an aneurysmal hemorrhage before they receive specialized medical care. The mortality rate during the first 3 weeks after CA rupture is 20–30 %, within 30 days it reaches 46 %, and more than 30 % of the population is deeply disabled [6, 7]. It is important to emphasis that recurrent aneurysmal intracranial hemorrhage is the main cause of high mortality and disability in this group of patients [7, 8].

The search for literature sources in the scientific databases PubMed/Medline, EMBASE, Cochrane Library and eLibrary demonstrated the existence of numerous studies devoted to the study of molecular biology and biophysical mechanisms of formation, growth and rupture of CAs. Undoubtedly, knowledge of these mechanisms will allow optimizing existing and developing new methods of treatment for patients with CA in the near future.

THE AIM OF THE STUDY

Analysis of current literature data devoted on the study of biological and biophysical mechanisms of formation, growth and rupture of cerebral aneurysms.

MOLECULAR BIOLOGY OF CA

Role of inflammation

Some studies have shown that vascular wall inflammation plays a crucial role in the formation and growth of CA [9]. Thus, N. Chalouhi et al. [10] noted in their study that constant pronounced hemodynamic impact on the vascular wall leads to the activation of inflammatory process in the latter with the participation of matrix metalloproteinases (MMPs), smooth myocytes, macrophages and the development of oxidative stress. Endothelial dysfunction resulting from a number of modifiable and non-modifiable risk factors (smoking, arterial hypertension, local blood flow disturbance in cerebral vessels, genetic factors) represents the initial stage of CA formation. Oxidative stress initiates the process of vascular wall destruction due to the accumulation of free radicals and destruction of structural elements of the endothelial lining [10, 11].

The next stage of vascular wall destruction is activation of the inflammatory process that involves macrophages, mast cells, T-lymphocytes and a number of proinflammatory mediators and cytokines [12]. A long-lasting inflammation process leads to changes in the phenotype of smooth muscle cells and remodeling of the vascular wall towards the synthesis of extracellular matrix components in the middle coat of the vessel [13]. Changes in the phenotype of smooth muscle cells contribute to the degradation of the internal elastic lamina, impaired collagen synthesis and dysregulation of the synthesis of extracellular matrix components [13]. Vascular wall remodeling is directly related to the degree of nitric oxide (NO) production [13, 14]. It is well known that NO is the most important angioprotector, but only if it is synthesized in adequate amounts. Inadequate NO content in the vascular endothelium may determine the development of endothelial dysfunction and a number of pathological conditions [14]. Thus, NO hyperproduction may result from excessive activation of endothelial NO synthase (eNOS). NO, formed as a result of this process, when interacting with superoxide anion radical can be converted into very toxic substances (peroxynitrite, nitrotyrosine), which have a number of pathogenic effects on the vascular wall (increased oxidation of proteins and lipids, inactivation of enzymes, including mitochondrial enzymes, increased permeability of cytoplasmic membranes, damage to nucleic acids and activation of apoptosis). According to modern concepts, impaired NO bioavailability is the main cause of endothelial dysfunction in the presence of risk factors (arterial hypertension, coronary heart disease, diabetes mellitus, metabolic syndrome) [15].

The final stage of CA formation is apoptosis of smooth muscle cells, which leads to thinning of middle coat of the vessel and increased risk of vessel rupture [16]. In addition, macrophages, attracted by proinflammatory mediators and cytokines into the vascular wall thickness, begin to produce large amounts of MMPs, which break down collagen and other components of the extracellular matrix [17]. All this inevitably leads to additional thinning of the vascular wall, potential formation of CA with its subsequent rupture and development of intracranial hemorrhage. A schematic representation of the role of inflammatory factor in CA growth and rupture is shown in Figure 1.

Role of genetic factors

The genetic disposition to CA formation is well studied. The association of CA with various hereditary nosological forms has been proved, genes responsible for the synthesis of structural components of the vascular wall have been identified, and mutations in the latter among patients with CA have been analyzed in detail [18]. There is a high incidence of CA in some families in the absence of evidence of any systemic pathological conditions [18, 19]. Thus, the presence of the following chromosome loci is statistically significantly associated with familial CA:

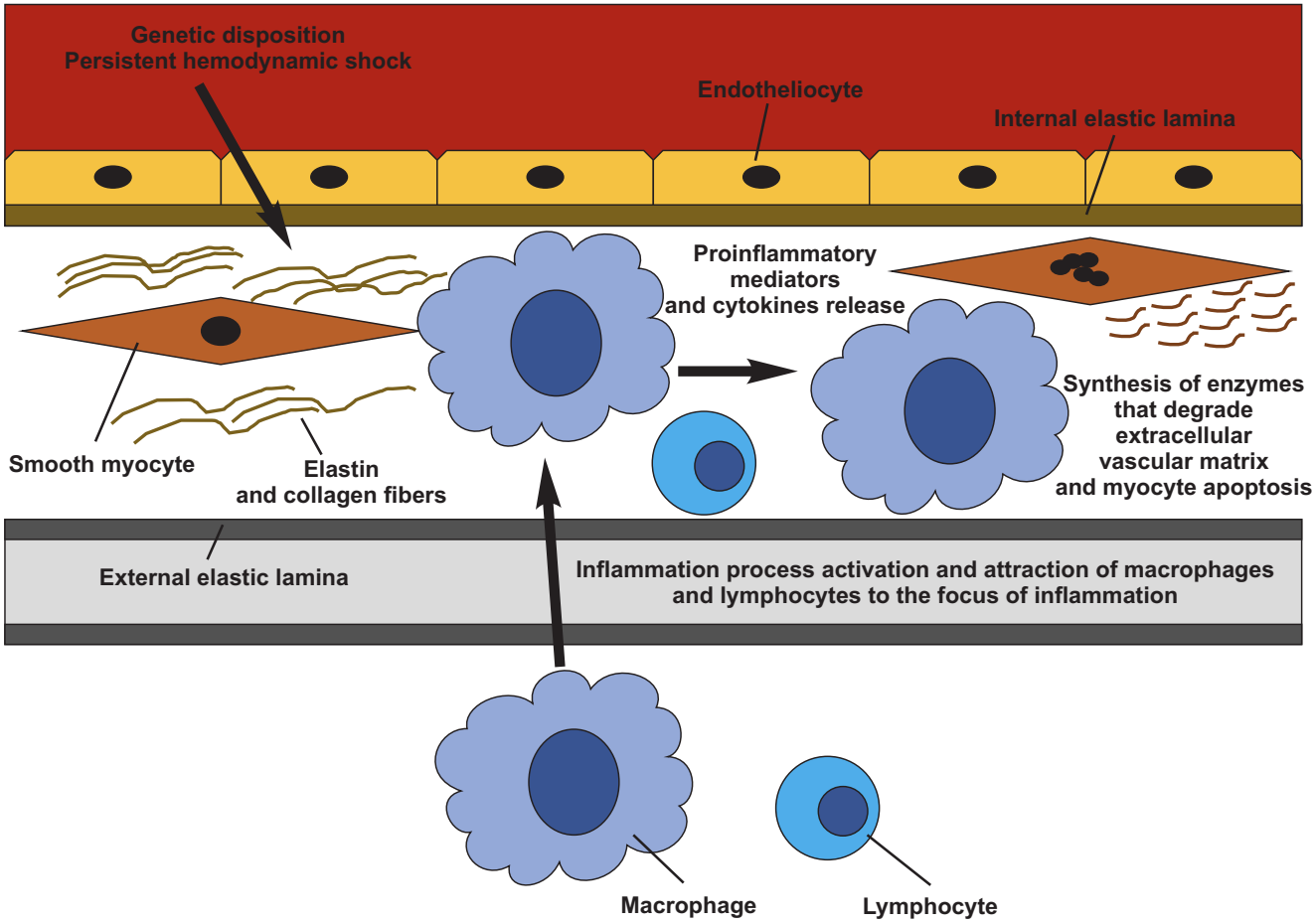

FIG. 1.
Schematic representation of the role of the inflammatory process in CAs growth and rupture

1p34.3-p36.14, 19q13.3, Xp22 and 7q11[20]. The 7q11 locus contains the *COL1A2* gene, the product of which is collagen type I, as well as an adjacent gene responsible for elastin synthesis. In turn, collagen type I and elastin represent the structural basis of the vascular wall [21]. C.B. Theodotou et al. [22] showed in their systematic review that the loci of 9p21/CDKN2 chromosomes are responsible for the process of the vascular wall remodeling and are statistically significantly associated with CA rupture. The study of K. Bilguvar et al. [23], involving more than 2000 patients with CA and 8000 control group respondents, demonstrated that the presence of single-nucleotide polymorphisms in the loci of 2q33.1, 8q11.23 and 9p21.3 chromosomes is statistically significantly associated with cases of sporadic and familial CA. Other potential genetic targets for study on CA formation and growth are MMPs, angiotensin-converting enzyme (ACE), phospholipase C, eNOS and other genes [23]. At the same time, the authors of these studies do not exclude the role of external factors in the formation and rupture of CA.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) analyzed unruptured CAs taking into account patient demographics and the localization of multiple CAs. It was found that more often multiple CAs are localized in the region of the middle cerebral artery (28.6 %) and posterior communicating arteries (13.7 %) [24]. The risk of developing CA is statistically significantly higher in families with a history of CA, especially in Japan and Finland. Globally, about 3 % of the population suffers from CA, but the incidence of aneurysms in Finland is twice as high. Three new loci on 18q11.2 and 10q24.32 chromosomes associated with CA were identified among the Finnish population. Three loci were associated with CA (2q23.3; 5q31.3; 6q24.2) and one with the number of CA (7p22.1). The 7p22.1 locus was more frequent in Finland (4.6 %) than in the Netherlands (0.3 %). Five loci account for 2.1 % of inherited CA in Finland [25]. The previously mentioned *COL1A2* gene has been associated with aneurysms among patients from Japan, China, and South Korea. Nevertheless, this does not fully explain the formation of most CA [25].

Currently, a number of inherited diseases are known to be associated with CA formation, growth and rupture. They include Ehlers-Danlos syndromes (types I and IV), Fabry disease, Osler – Weber – Rendu disease, Pompe disease and autosomal dominant polycystic kidney disease (ADPKD) [1, 25]. Hereditary diseases associated with CA are summarized in Table 1. ADPKD is associated with mutation of *PKD1* and *PKD2* genes [1, 25]. The frequency of occurrence of CA among patients with ADPKD is 10–13 %, and at least 25 % of this number have a positive family history of CA with/without the development of intracranial hemorrhage [25].

TABLE 1

HEREDITARY DISEASES ASSOCIATED WITH CEREBRAL ANEURYSMS [1]

Disease	Type of inheritance	Chromosome locus	Gene
Alkaptonuria	Autosomal recessive	3q2	*AKU*
Thoracic aortic aneurysm	–	9q, 3p8, 1p	–
Autosomal dominant polycystic kidney disease (ADPKD)	Autosomal dominant	16p13.3 4q21	*PKDI* *PKD2*
Achondroplasia	Autosomal dominant	4p16.3	*FGFR3*
Osler – Weber – Rendu disease	Autosomal dominant	9q34.1 12q	*HHT1* *HHT2*
Pompe disease	Autosomal recessive	17q23	GAA
Fabry disease	Autosomal recessive, X-linked	Xq22.1	*GLA*
Osteogenesis imperfecta (type I)	Autosomal dominant	17q22.1 7q22.1	*COL1A1* *COL1A2*
Neurofibromatosis (type I)	Autosomal dominant	17ql1.2	*NF1*
Wermer's syndrome	Autosomal dominant	llql13	*MEN1*
Kahn syndrome	Autosomal recessive	9	0
Cohen syndrome	Autosomal recessive	8q21	*CHSI*
Marfan syndrome	Autosomal dominant	15q21.l	*FBNI*
Noonan syndrome	Autosomal dominant	12q22	9
Rembaud syndrome	Autosomal recessive	9	9
Williams – Beuren syndrome	–	7q11	–
Ehlers – Danlos syndrome (type I)	Autosomal dominant	9q	*COL5A1*
Ehlers – Danlos syndrome (type IV)	Autosomal dominant	2q31	*COL3A1*
Tuberous sclerosis	Autosomal dominant	9q34.1 16ql3.3	*TSC1* *TSC2*
Chronic obstructive pulmonary disease (COPD)	–	19p13.3 14q32	–
Pseudoxanthoma elasticum (PXE)	Autosomal dominant Autosomal recessive	9	9

Analysis of the significance of biochemical markers of connective tissue protein breakdown is a promising area of the study of the pathophysiology of CA formation and growth. Currently, some amino acids and their various forms (oxyproline, hydroxyproline), as well as glycosaminoglycans are the main markers of connective tissue disorder [26–29]. Thus, the study by M.A. Nokhsorova et al. [26] showed that the parameters of the content of some amino acids and their various forms can act as markers of early diagnosis of connective tissue dysplasia (CTD). Similar results were obtained by T.A. Siraeva et al. [27] in their study on pediatric patients with glomerulonephritis. The study by L. Wang et al. [28] and Y. Guo et al. [29] demonstrated the dependence of the level of some amino acids in plasma and urine of patients with aortic dissection and aortic aneurysm. B. Sokół et al. [30] point to a statistically significant correlation between the level of certain amino acids in the cerebrospinal fluid (CSF) and the risk of CA rupture.

BIOPHYSICS OF CEREBRAL ANEURYSMS

Geometric factors

Sizes of cerebral aneurysms

The maximum size of CA is generally considered to be the main risk factor for CA rupture. According to J. Beck et al. [31] and M. Korja et al. [32], in 70–80 % of cases the maximum diameter of unruptured aneurysms is 10 mm. Large (16 to 25 mm) and giant (more than 25 mm) CAs are less common. The clinical and experimental observation of J. Suzuki and H. Ohara [33] showed that the wall of CA, the size of which is not more than 3 mm, is formed by endothelial lining and fibrous tissue, and at the size of CA 4 mm and more, a large number of coarse collagen fibers appear in the wall of the latter. Such morphological changes in the vascular wall significantly reduce its elastic properties with the formation of thinning areas [33]. The changes reduce the degree of resistance of the vascular wall to hemodynamic loads. On the other hand, some authors claim that the difference between the diameters of ruptured and unruptured CA is no more than 1.5 mm and has no statistically significant effect on the risk of CA rupture [34].

A detailed study of the dependence of large CA rupture without taking into account other factors is an extremely difficult problem due to the fact that the analysis of the influence of hemodynamic risk factors gives ambiguous and, in some cases, contradictory results. According to the study of P.B. Canham and G.G. Ferguson [35], CAs with a size of 5 to 9 mm have the highest risk of rupture. However, it is known that the blood flow velocity in the CA is inversely proportional to its dome diameter squared, i. e., as the CA size increases, the blood flow velocity in the cavity of the latter will decrease. A decrease in blood flow velocity will lead to a decrease in the hemodynamic load on the vascular wall. Similar data were obtained by S. Tateshima et al. in their study [36].

Shapes of cerebral aneurysms

It has been proven by numerous studies that the shape of CA has a greater impact on the risk of CA rupture as opposed to its size. Oval, oblong or lobulated CAs have been shown to have a high risk of rupture [36]. According to S. Tateshima et al. [36], in the CA dome region the greatest wall shear stress is noted. The prevalence of ruptured multicameral CAs is statistically significantly higher by 2–7 times [37]. The irregularity of CA contours according to the data of digital subtraction angiography (DFA) is an important risk factor of CA rupture, which confirms thinning of the CA wall, disturbance of its elastic properties and presence of thrombotic masses [38]. C. Sadasivan et al. [39] in their clinical observation noted that CA of the indicated type is statistically significantly associated with rapid growth and a high risk of rupture.

The average CA wall thickness is 16–400 μm [40]. It is known that the CA wall has less pronounced elastic properties in contrast to the arterial wall. At the same time, the stretchability of the CA wall differs in its different parts [40]. The study by J.G. Isaksen et al. [41] clearly showed that in hemodynamic systole the maximum degree of stretching of the CA wall occurs in the region of its *locus minoris resistentia* – the dome wall. The lobular structure of the CA wall confirms the heterogeneity of elasticity of its different sections and correspondingly lower resistance to hemodynamic shocks in comparison with CA of the correct spherical shape [42].

Ratio of cerebral aneurysms

The CA ratio is the ratio of the CA dome height to the width of its neck. Comparison of the values of the ratios of ruptured and unruptured CA indicates a statistically significant predominance of this parameter in the group of ruptured CA (2.4 vs 1.6, respectively) [43]. The clinical case series by H. Ujiie et al. [44], including 129 respondents with ruptured CA and 72 respondents with unruptured CA, showed that the value of the ratio of ruptured CA exceeds 1.6. The unruptured CA ratio, in turn, does not exceed 1.6 [44]. The authors of this study conclude that if the ratio value is less than 1.4, it is safe to say that the risk of CA rupture is low; if the ratio is more than 3, the risk of CA rupture increases significantly [44].

Ratio of CA dome height to the diameter of the parent artery

The ratio of CA dome height to the diameter of the parent artery as a risk factor for its rupture was proposed for the first time by M. Tremmel et al. [45]. The authors statistically significantly found that in 77 % of cases of ruptured CA the ratio of CA dome height to the diameter of the parent artery exceeded 2.05, in contrast to unruptured CA – less than 2.05 [45]. The authors also clearly showed that a 5 mm CA located on the anterior communicating artery with a diameter of 2 mm has a ratio of 2.5, which indicates a very high risk of its rupture, while a CA of similar size but located on the internal carotid artery with a diameter of 4 mm has a ratio of 1.25 and a much lower risk of rupture (about 10 times) [45]. The prospective clinical study by M. Rahman et al. [46] noted that the ratio of CA dome height to the diameter of the parent artery is a sta-

tistically significant risk factor for CA rupture (OR = 2.12; 95% CI: 1.09–4.13).

Mathematical models of cerebral aneurysms

Currently, there are a number of studies on the predictive value of mathematical models of CA growth and rupture risk and its formation. Thus, A.L. Rogozin [47] presented and studied in detail the prognostic value of a mathematical model of the risk of rupture of the internal carotid artery CA. The authors have developed the following formula:

$$P = \frac{1}{1+e^{-z}},$$

where P is the probability of CA rupture, $z = b_1 \times X_1 + b_2 \times X_2 + ... + b_n \times X_n + a$, X – values of independent variables, b – regression ratios, a – constant, e – base of natural logarithm. A more extended mathematical model with several parameters was developed and studied in detail by H. Meng et al. [48]. The researchers presented the final formula as follows:

$$\eta(\lambda,\mu) = \frac{\mu\left(1+\sqrt{1-\mu^2}\right)}{4} \times \frac{\left(1+\lambda^2\right)}{\lambda},$$

where μ is the ratio of CA neck to the parent artery radius, λ is the CA ratio, η is the value of the CA stress factor, which is a function of the ratio of CA neck to the parent artery radius and the CA ratio. In contrast to previous mathematical models, R. Berguer et al. [49] presented a trigonometric model of CA formation, where special attention is paid to the angle between daughter arterial branches forming a bifurcation CA:

$$\cos\theta = \sqrt{\frac{1}{2\beta}},$$

where β is the ratio of the CA neck area to the diameter of the parent artery, θ is the angle between the daughter arterial branches forming the bifurcation CA.

It is clear that the presented mathematical models cannot fully characterize all the processes occurring in the CA cavity and statistically significantly assess the risk of its rupture. Nevertheless, some neurosurgical clinics in the world actively use mathematical models as a rationale for selecting surgical treatment tactics for CA patients in a particular clinical situation.

Hemodynamics of cerebral aneurysms

Blood flows in the CA cavity into simple steady and complex unsteady, or turbulent blood flows [1]. Simple steady blood flow in the CA cavity has a unidirectional constant motion during a single cardiac cycle and may rarely have a single vortex with a constant or changing localization. The turbulent flow is usually unsteady and has a multidirectional motion with many swirls of different localizations in the CA cavity [1, 3].

The type of blood flow in the CA cavity depends largely on the size, shape of the CA and the geometry of the parent artery [1, 16]. In some cases, the blood flow directed into the CA cavity has a high velocity, small width and has a significant hemodynamic effect on certain regions of the CA wall. In other cases, the blood flow is wider and slower, and exerts less hemodynamic shock on the CA wall [1, 16].

Particular attention should be paid to hemodynamic features in bifurcation CAs. Thus, the blood flow velocity in a narrow-neck CA is significantly lower than in the parent artery. The blood flow velocity is higher in a wide-neck CA than in a narrow-neck CA. In a wide-neck CA, blood exchange with the cavity of the parent arterial trunk occurs in greater volume than in a narrow-neck CA [1, 50]. Moreover, the risk of thrombosis is much higher in narrow-neck CA [50].

CAs, which are located at asymmetric arterial bifurcations, have individual hemodynamic characteristics. The part of the CA neck that is adjacent to the larger-diameter daughter artery is subjected to the highest blood pressure, while the part of the neck belonging to the smaller daughter arterial trunk experiences a large degree of stretching under the pulsatile blood flow [51]. The blood volume in the smaller daughter arterial branch comes from the CA cavity, while the larger daughter branch is filled from the parent artery [51].

As for the hemodynamic features of lateral CAs, the filling of the CA cavity with blood is carried out in the distal part of the CA neck. The process of constant change of the blood flow direction occurs in the CA cavity, and the blood exit is verified in the proximal part of the CA neck [52]. The hemodynamic pressure on the distal part of the CA neck is higher than on the proximal part and on the CA dome [53, 54]. According to C.M. Strother et al. [55], lateral CA grows in the direction of blood flow due to the stretching of the CA wall in the distal part of the neck.

The report by D.D. Dolotova et al. [56] showed that a vessel branching from the neck or dome of CA causes their classification as "complex" not only because of the difficulties of surgical intervention, but also because an additional vascular branch and its disconnection from the blood flow can have a significant effect on the change in the parameters of local hemodynamics. The nature of these changes may be determined by such factors as the diameter of the vessel arising from the CA and the location of the CA relative to the parent vessel [56]. The authors of the study also noted that the hemodynamic parameters of bifurcation CAs were much less susceptible to changes: virtual "removal" of the vessel had an insignificant effect on the neck wall and the CA dome located on the flow path from the parent vessel. In lateral CAs, the behavior of the velocity profile and wall shear stress was more diverse, which can be explained by taking into account the totality of local and systemic factors [56].

CONCLUSION

Currently, a great number of studies on the biological and biophysical mechanisms of CA formation, growth, and rupture has been conducted. The role of the inflammatory process, molecular genetics and hemodynamic factors

has been confirmed by numerous experimental and clinical studies. The analysis of risk factors for CA growth and subsequent rupture allows to predict the course of this disease, to choose optimal methods of surgical treatment of this group of patients or to monitor patients with unruptured CA. Undoubtedly, further study of the indicated mechanisms of CA growth and rupture will allow to study in depth the peculiarities of this nosological form from the positions of both fundamental and applied science. This kind of multidisciplinary approach opens up new opportunities in terms of development and introduction of the latest methods of diagnosis and surgical treatment of patients with CA into widespread clinical practice in the near future.

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Conflict of interest
The authors declare the absence of a conflict of interest.

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