Comparative Analysis of the Animal Model and Results of the Clinical Research of the Aneurysm Inclination Angle as the Predisposing Factor for the Occurrence of Rupture

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SUMMARY

Introduction Natural course of aneurysms that occur on blood vessels of the brain singles out the need for understanding the mechanism of the occurrence of aneurysm wall rupture and identification of anatomic characteristics as predictive factors for hemorrhage to occur.

Objective In this study we comparatively present results of our researches and experimental models on animals.

Methods We made a comparative analysis of anatomical characteristics of blood vessels of the brain and aneurysms obtained on the basis of digital subtraction angiography and intraoperative finding. In this article we review recent research in the anatomic characteristics of intracranial aneurysms and parent blood vessels. We present a series of 185 aneurysms (ruptured and unruptured) dissected at the Neurosurgical Clinic of Clinical Center of Serbia in Belgrade.

Results Inclination angle may be considered as the vital predesposing factor for intracranial aneurysm rupture. In aneurysms that ruptured it was 139.748±27.242°, while in unruptured aneurysms it was considerably smaller and amounted to 100.882±22.001° (p<0.01).

Conclusion Inclination angle may be regarded as the vital predisposing factor since it differs considerably in unruptured and ruptured aneurysms. Aneurysms with blood stream angle smaller than 115° have very small probability of rupture, while blood stream angle bigger than 150° presents a high risk of rupture.

Keywords: intracranial aneurysms; inclination angle; risk of rupture

INTRODUCTION

Intracranial aneurysms are relatively frequent and occur according to autopsy and angiographic data in 2-5% of cases in general population [1]. Most often they are found on sites where large blood vessels of the base of the brain and their first bifurcations are joined, and their size ranges from only several millimeters to 3 and more centimeters (80% up to 12 mm). Their ruptures (annual incidence 10-22/100,000 citizens) are the main cause of spontaneous subarachnoidal hemorrhage, with total mortality of around 50% in the first month after rupture. Around 2/3 patients are females, and the largest rupture incidence is between 30 and 60 years of age [2, 3].

Current approach to saccular aneurysms on blood vessels of the brain concerns improvement of diagnostic procedures in early discovery of the existing as well as the recognition of risk factors for appearance of de novo saccular aneurysms on the blood vessels of the brain and the attempt to find a bioactive therapeutic model. Under experimental conditions saccular aneurysms on the blood vessels of the brain in primates and rodents may be induced by the induction of hypertension and by the ligation of the carotid artery on one side (Figure 1) [4-8].

Experiments show that in genesis of the de novo saccular aneurysms on the blood vessels of the brain hemodynamic stress of the arterial pulse wave has an important role leading to the straining of the blood vessel wall. This theory has been confirmed by the application of the mathematical model [9]. Regardless of the results, mechanism of the occurrence of de novo aneurysms on the blood vessels of the brain has not been completely cleared up. It is considered that hemodynamic stress increases the proteolytic activity of enzymes; level of pro-matrix metalloproteinase-2 (MMP2) increases as do proteolytic activities in serum in patients with a ruptured saccular aneurysm. Physiological reaction of arteries to the increase of hemodynamic pressure is seen in hypertrophy of the medial layer, adventitial fibrosis and hyperplasia of the muscle layer. Hyperplasia of the muscle layer is also detected at the site of the normal branching of the blood vessels of the brain [3].

Hemorrhage from the intracranial aneurysm is the consequence of the weakness of the aneurysmal wall and influence of hemodynamic factors (systole impacts of the blood wave,

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turbulent flow of blood inside the aneurysmal cavum, vibrating movements during the passage of the systole wave through the blood vessels of the brain). As the predictive factor for the onset of aneurysm rupture one anatomical detail has been singled out, meaning the direction of the aneurysm orientation and the angle it forms with the carrying artery (Figure 2) [10, 11, 12].
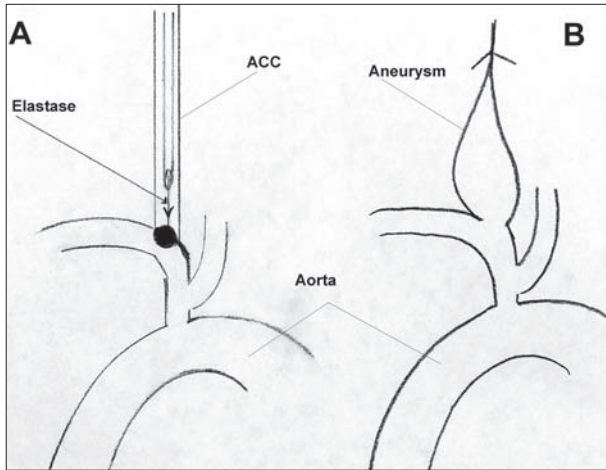

Figure 1. Experimental model of intracranial aneurysm: A) procedure with elastase and balloon occlusion; B) aneurysm after procedure with elastase
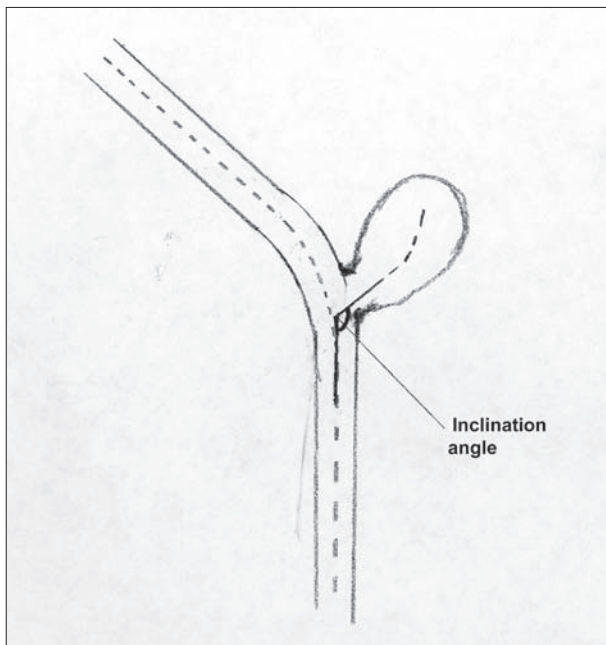

Figure 2. Inclination angle of intracranial aneurysm

OBJECTIVE

In this study we comparatively present results of our researches and experimental models on animals.

METHODS

The analysis included 185 dissected aneurysms (137 ruptured and 48 unruptured) in patients hospitalized at the Clinic for Neurosurgery of the Clinical Center of Serbia in the period from 2006-2008. All patients were subjected to 3D-DSA (Axiom Artis, Siemens). Measuring was performed in such a manner that rotation of the reconstruction was performed in space until the smallest angle of the blood stream (inclination angle) was measured. The angle formed by lobuli and daughter aneurysms in bisaccular and multilobular aneurysms was also measured. For statistical analysis we used the Student t-test.

RESULTS

Mean value of the angle formed by the carrying blood vessel and the central line of the blood stream in the aneurysm (inclination angle) in our group was $129.812 \pm 27.306°$. In aneurysms that ruptured it was $139.748 \pm 27.242°$, while in the unruptured aneurysms it was considerably smaller and amounted to $100.882 \pm 22.001°$. Statistically significant difference in favor of a considerably greater mean value of the inclination angle in the ruptured aneurysms was noticeable ($p<0.01$, $t=9.051$, $DF=183$). Graph 1 presents the distribution of aneurysms according to the blood stream angle.

Mean value of the inclination angle in the ruptured aneurysms that were located on the right side was $138.286 \pm 21.657°$, and on the left $134.722 \pm 24.668°$. When compared no statistically significant difference was found ($p>0.05$, $t=0.637$, $DF=94$). The mean value of the inclination angle in the unruptured aneurysms that were on the right side was $103.078 \pm 26.735°$, and on the left side $98.611 \pm 20.494°$. When compared no statistically significant difference was found ($p>0.05$, $t=0.154$, $DF=38$). When ruptured and unruptured aneurysms on the right side were compared ($p<0.01$, $t=4.585$, $DF=61$), as well as on the left side ($p<0.01$, $t=5.255$, $DF=70$) statistically significant difference in favor of greater values of the angle
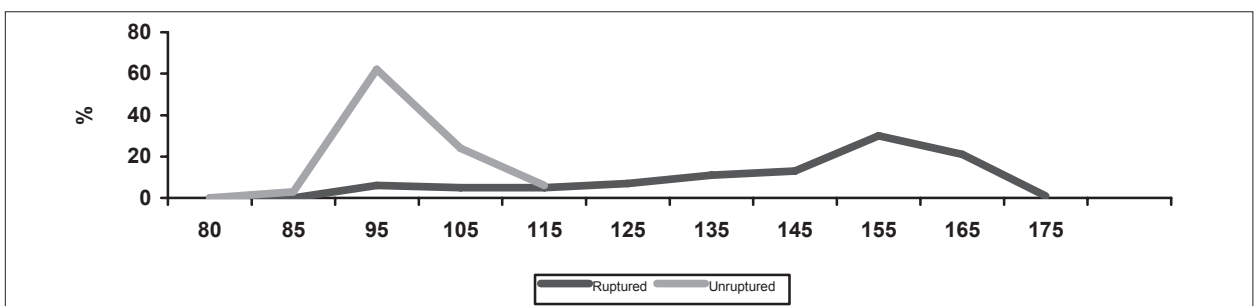
Graph 1. Distribution of aneurysms according to blood stream angle

Table 1. Mean values and standard deviation (SD) of the inclination angle for the most frequent locations of intracranial aneurysms

Localization	Ruptured		Unruptured		Together	
	Mean value	SD	Mean value	SD	Mean value	SD
ACI	123.8	23.817	92.727	3.438	114.306	24.558
ACM	142.5	19.924	101.0714	21.229	131.346	27.334
ACoA	148.478	13.351	105	5	143.462	18.962

ACI – arteria carotis interna; ACM – arteria cerebri media; ACoA – arteria communicans anterior

Table 2. Results of t-test for mutual comparison of the inclination angle of aneurysms ACI, ACM and ACoA

Ratio	Ruptured			Unruptured			Together		
	t	DF	p	t	DF	p	t	DF	p
ACI/ACM	2.996	73	<0.01	1.290	30	>0.05	2.996	115	<0.01
ACM/ACoA	1.276	81	>0.05	0.319	23	>0.05	2.029	106	<0.05
ACI/ACoA	4.377	68	<0.01	4.924	19	<0.01	5.061	89	<0.01

DF – degree of freedom

formed by the carrying blood vessel and the central line of the blood stream in the aneurysm was noticeable.

The mean value of the angle formed by the carrying blood vessel and the central line of the blood stream in the aneurysm (inclination angle) in the vertebrobasilar confluence was 122.941±32.213°. In the aneurysms that ruptured it was 145±18.371°, while in the unruptured aneurysms it was considerably smaller and was 98.125±25.363°. A statistically significant difference in favor of considerably bigger angle in the ruptured aneurysms (p<0.01, t=4.368, DF=19) was noticeable. In the carotid confluence this value was 130.819±26.523°. When only ruptured aneurysms were observed the value was 139.222±21.528°, and it was 101.731±21.258° for the unruptered ones. Here a statistically significant difference was also observed in favor of the considerably bigger angle in the ruptured aneurysms (p<0.01, t=7.844, DF=162).

When compared, the inclination angles in the vertebrobasilary confluence and carotid confluences of the ruptures aneurysms statistically significant difference was not found (p>0.05, t=0.777, DF=135). Comparing the same parameters in the unruptured aneurysms a statistically significant difference (p>0.05, t=0.777, DF=46) was not observed as well. Table 1 presents mean values and standard deviation of the blood stream angle for three most frequent intracranial aneurysm locations (ACI, ACM and ACoA). When the angle ratio of ruptured and unruptured aneurysms was considered, we obtained a statistically significant difference in all three aforementioned locations (p<0.01). In the internal carotid artery the value of t test was 4.307 (DF=48), mid cerebral 6.533 (DF=65) and frontal communicating artery 5.589 (DF=39). Results of t-test of the mutual comparison of the blood stream angles of the abovementioned three locations are presented in Table 2.

DISCUSSION

Impacts of the systole wave are transferred to the wall of the aneurysm according to the principle of the hydraulic pressure transfer in closed vessels (Bernoulli's law). The phenomenon of resonance occurs during the passage of the systole wave through the cerebral arterial network. It is reflected in constant vibration. Arterial pressure height has a direct influence on the intensity of these factors. Due to that, in order to make further research developments were initiated involving experimental models of intracranial aneurysms with induced hypertension and ligature of the carotid artery on one side [4-8]. A study of the computerized simulation of the flow conducted by Szikora et al. [13] pointed to a great significance of the blood stream and geometry of the aneurysm for the risk of rupture.

Review of the animal models of brain tumor researches

Experiments with intraluminal elastase have also been performed to induce formation of aneurysms in rabbits, where the aneurysm occurred due to degeneration of lamina elastica [10, 12, 14]. Experiments on animals have shown that turbulent movement of blood within the aneurysm in certain places leads to the increase of pressure and that hemodynamic stress of the pulse wave causes straining of the blood vessel wall. Direct cause-effect connection of the hemodynamic stress and increase of elastase activity has not been clearly shown, although it has been shown on the animal model that hemodynamic stress increases proteolytic activity of the enzyme. The level of pro-matrix metalloproteinase-2 (MMP2) increases as do the proteolytic activities in the serum in patients with a ruptured saccular aneurysm [15]. Hypoplasia of the muscle layer is detected at the site of normal branching of the cerebral blood vessels [3]. Half-life of elastin is extremely long (around 50 years) thus destruction of lamina elastica in the blood vessel wall when the aneurysm gets formed is the consequence of the increased activity of MMP and other proteolytic enzymes, and is not the sign of physiologic ageing.

Inhibition of MMP activity by doxycycline in rats in whom the internal carotid artery is ligated does not prevent the occurrence of the saccular aneurysm, and this points to the existence of a group of proteolytic enzymes which cause the lamina elastica to become weak and

occurrence of the aneurysm, on the other hand it has been determined that doxycycline is not a universal inhibitor of the proteolytic activity [16]. Experimentally caused atherosclerotic changes in rats may lead to changes in the internal elastic layer of the blood vessel wall and/or to the complete occlusion of the blood vessel, histological analysis identified cells type Th-2 as the cause and for the complete occlusion cells type Th-1 (helper T lymphocytes) [17, 18].

The growth of adventitial capillaries or vasa vasorum provoked by balloon dilation of blood vessels in monkeys accompanies miointimal hyperplasia [19]. Entry of blood into the aneurysm occurs almost exclusively during systole, and the exit of blood is not pulsatile [20]. Aneurysms on bifurcations have a greater risk of rupture as the impact of the systole wave is more direct [21]. In aneurysm where the force of the systole pressure directly empties in the fundus, the probability of the rupture is greater [22]. Also, if the blood vessel itself has an irregular flow, the risk of the rupture of the aneurysm is greater [23]. These results have confirmed that the blood stream direction and the angle that form the vector of the blood stream and the carrying blood vessel is more imported than the angle that is anatomically formed by the aneurysm and the carrying blood vessel [24, 25].

Analysis of the experimental model of aneurysms induced by elastase in rabbits performed by Onizuka et al. [10] have confirmed the fact that the angle between the carrying blood stream and the main axis of the aneurysm is significant for increase and onset of aneurysm rupture.

In our series the mean value of the angle in ruptured aneyrisms was 139.748±27.242° and in unruptured aneurysms it was considerably smaller and was 100.882±22.001° (p<0.01). The angle smaller than 115° was detected in 88.235% of unruptured aneurysms, while

the angle bigger than 150° was observed in only three cases. Contrary to that, 86.869% aneurysms that ruptured had the blood stream angle bigger than 115°, therefore this value could be taken as the threshold. This threshold value for the blood stream angle is very close to results obtained by Dhar et al. Their threshold for somewhat smaller percentage (81.8%) was 112°, but this difference, taking into consideration close values, could be considered almost irrelevant [11, 25]. According to Suga et al. [11], the critical angle for the occurrence of the rupture of the aneurysm is 160-1700.

CONCLUSION

Normal physiology of cerebral blood flow, congenital and acquired flow anomalies, and risk factors for intracranial aneurysm rupture has been widely studied in the last decade *in vitro*, in animals and also in humans since the development of neuroimaging procedures.

The inclination angle (angle formed by the carrying blood vessel and the central line of the blood stream in the aneurysm) may be regarded as the vital predisposing factor since it differs considerably in unruptured and ruptured aneurysms. Aneurysms with blood stream angle smaller than 115° have very small probability of rupture, while blood stream angle bigger than 150° presents a high risk of rupture.

Recognizing risk factors for aneurysm rupture of incidentally appeared anerysms is a challenge for neurosurgeons and neurologists. Prior condition for the reduction of aneurysmal bleeding morbidity and mortality is to use spatial reconstruction of cerebral blood vessels and aneurysms as a standard neuroradiological procedure.

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Упоредна анализа резултата истраживања на животињама и клиничког испитивања угла инклинације интракранијалних анеуризми као предиспонирајућег фактора за настанак руптуре

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КРАТАК САДРЖАЈ
Увод Природни ток анеуризми на крвним судовима мозга наглашава потребу за разумевањем механизма настанка руптуре зида анеуризме и утврђивањем анатомских обележја као предиктивних фактора за настанак крварења.
Циљ рада У овој студији дати су компаративни резултати нашег клиничког истраживања и експерименталних испитивања на животињама.
Методе рада Рађена је упоредна анализа анатомских одлика крвних судова мозга и анеуризми добијених на основу дигиталне суптракционе ангиографије и интраоперационог налаза. Приказана је серија од 185 анеуризми (руптурираних и неруптурираних) код болесника оперисаних на Клиници за неурохирургију Клиничког центра у Београду.

Резултати Угао инклинације може се сматрати важним предиспонирајућим фактором за руптуру интракранијалне анеуризме. Код анеуризми које су руптуриране он је 139,748±27,242°, док је код неруптурираних знатно мањи и износи 100,882±22,001° (*p*<0,01).
Закључак Угао инклинације је битан предиспонирајући фактор, јер се знатно разликује код руптурираних и неруптурираних анеуризми. Код анеуризми с углом инклинације мањим од 115 степени вероватноћа за настанак руптуре је мала, док угао инклинације већи од 150 степени носи висок ризик од руптуре.
Кључне речи: интракранијалне анеуризме; угао инклинације; ризик од руптуре