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Recanalization of Embolized Endovascular Intracranial Aneurysms and Changes in the Blood Viscosity: A Pilot Study

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The purpose of our research was to evaluate the relationships between blood viscosity and recanalization of coiled intracranial aneurysms.

Material/Methods: The study included consecutive patients treated endovascularly by a team of experienced neurosurgeons and neuroradiologists due to brain aneurysm. A total of 50 patients (the average age was 57.48 years, SD=13.71) were assigned to 2 groups: group A with recanalization (4 male and 8 female patients) and group B without recanalization (10 male and 28 female patients) were examined. All patients underwent a 6-month follow-up of the whole-blood viscosity test with a Brookfield DV III+pro cone-plate viscometer using the Rheocalc program. Differences between groups were assessed using the Statistica 12 computer program (StatSoft Inc., Tulsa, OK, USA).





Results: Studies have shown no significant difference in the age range between group A and B ($P=0.31$). In group A, higher viscosity values were found for whole blood [median: 4.14 dyn×sec/cm² (mPa×sec) quartile range 0.42], compared to group B [median: 3.92 dyn×sec/cm² (mPa×sec); quartile range 0.40; ($P=0.04$)]. This difference was significant ($P=0.04$). Additionally, the level of hematocrit was positively related with recanalization, the higher the hematocrit, the more frequent recanalization. A very strong and statistically significant relationship occurred between the frequency of recanalization and smoking ($P<0.001$).

Conclusions: The occurrence of higher values of whole blood viscosity which increase turbulent flow through the vessels may be a risk for recanalization of the coiled intracranial aneurysm.

MeSH Keywords: **Angiography • Intracranial Aneurysm • Neurosurgery • Rheology**

Abbreviations: **DSA** – digitally subtraction angiography; **WSS** – wall shear stress, **SAH** – subarachnoid hemorrhage

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Background

Cerebral aneurysms as dilations may be defined events that happens at weak points along the length of arteria circulation in the brain. They may be various sizes from as small as 5 to 6 mm to medium size of 25 mm or even larger than 25 mm [1]. The majority are saccular (berry) which is associated with the absence or thinness of the tunica media, as well as a nonpresence or noticeable fragmentation of the internal elastic lamina [2,3].

Cerebral aneurysm formation is caused by various factors, including genetic factors such as fibromuscular dysplasia, autosomal dominant polycystic kidney disease, tuberous sclerosis, and arteriovenous malformations (AVM), as well as environmental factors such as smoking and alcohol abuse, and other influence such as atherosclerosis, hypertension, or advanced age [4].

Studies conducted by epidemiologists have revealed the rate of incidental aneurysms to be 7% (95% confidence interval [CI]) [5–9], with a corresponding occurrence of clinoid segment aneurysms at 3% (95% CI) [2–4]. Globally it is estimated to be roughly 3.2%, at an average age of 50 years, and with the overall gender ratio of 1: 1. After the age of 50 years, a significant change in this rate can be observed, with an increase in the predominance of female cases rising to 2: 1. It is believed that this is associated with a reduced level of estrogen, and thus a decrease in collagen content in vascular tissue [5].

It has been suggested that multifactor processes in nature result in saccular aneurysm formation. With time, the internal elastic lamina experiences a breakdown as a result of hemodynamic stress. In conjunction with a turbulent blood flow, this results in structural exhaustion. It has also been shown that T-cell and macrophage-mediated inflammation can be responsible for vascular-wall histologic changes, leading to aneurysmal formations and growths. Accentuating these changes are the aforementioned risk factors. Fusiform aneurysms are, conversely, the result of atherosclerosis and mycotic aneurysms derived from the septic emboli found in infectious endocarditic [6,7].

Neurosurgical (classic) protection of the brain aneurysm against subarachnoid hemorrhage (SAH) is a craniotomy, which slows reaching the location of the brain malformation and closing the aneurysm lumen with a metal clip (clipping) [8]. This is an invasive procedure and, therefore, its use is associated with the risk of potential serious complications. Since the 1980s, less invasive methods of treatment have been developed, such as endovascularly implantation of metal coils, which avoids potential complications related to an open surgical method [9–12]. This method, although much less invasive, is not free of risks,

as some of the coiled aneurysms undergo recanalization, something that is reported to occur in a significant percentage of treated patients [13–16].

Therefore, scientific studies have been conducted to detect various recanalization risk factors that could reduce the incidence of recurrent subarachnoid hemorrhage [17]. Studies confirming the role of hemodynamic factors in the initiation, development, and rupture of this brain malformation have been reported in the literature and it should be noted that unruptured aneurysms with residual necks following endovascular treatment pose a very low risk of rupture (0.6%) [8]. The blood flow of partially occluded aneurysm and hemodynamic disturbances on the recanalization of the aneurysm are rare [18]. Such characteristics of blood flow were studied by Luo et al. using a computer analysis of fluid flow dynamics in recanalized aneurysm previously partially occlude [19].

There are even fewer studies devoted to the recanalization of the embolized brain aneurysm with blood viscosity. In our review of world literature, we found only a few studies devoted to the relation of blood viscosity and recanalization of the embolized brain aneurysm. In one study, the authors discuss important risk factors, such as the high peak systolic wall shear stress (WSS), OSI, and the velocity observed around the aneurysm neck areas following embolization of para-clinoidal aneurysms [16].

Other authors have discussed problems with the measurement of blood viscosity, arguing that blood is not a Newtonian fluid and the measurements of viscosity coefficients create considerable experimental as well as interpretative difficulties [20]. Some articles have discussed the theoretical models developed regarding this issue using digital models that indirectly describe blood behavior in embolized brain aneurysm [21,22].

Therefore, there is a need to understand the effect of blood rheological properties and their relationship to recanalization of brain aneurysms. This knowledge may contribute to more effective endovascular treatment.

The purpose of our research was to evaluate the relationships between blood viscosity and the recanalization of coiled intracranial aneurysms.

Inclusion and exclusion criteria

We included in this study patients with only 1 aneurysm, detected by chance during neuroimaging. Patients with a history of blood clotting disorders, diabetes, cancer, more than 1 aneurysm, and polycystic kidney disease were excluded.

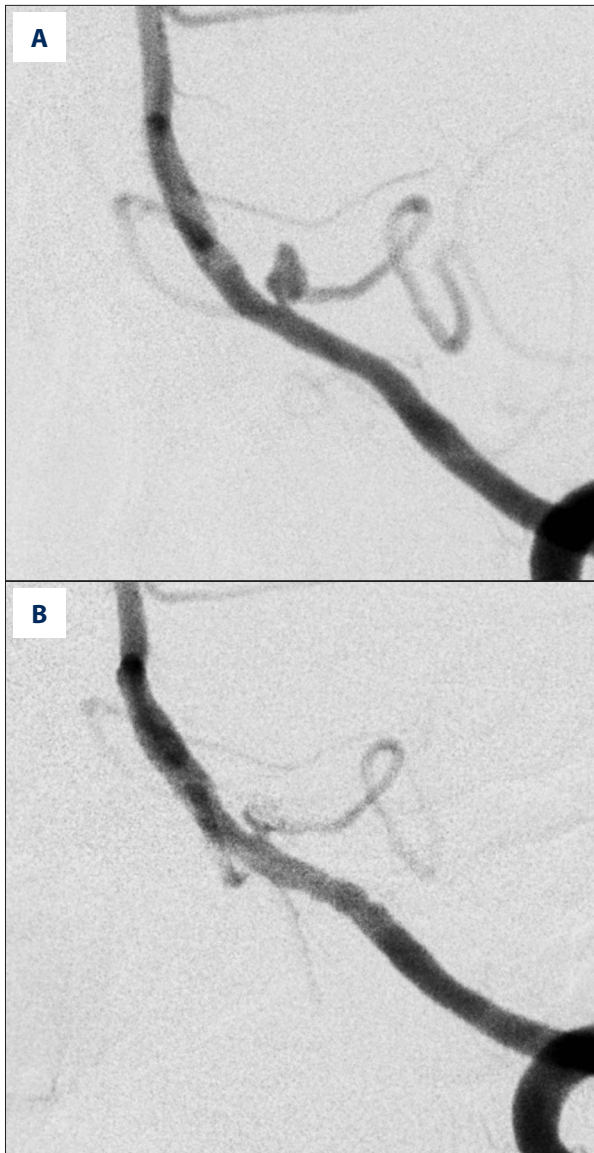


Figure 1. Examples of the angiographic image (DSA) of the initial segment of the lower left posterior cerebellar artery with aneurysm treated with coil embolization; (A) before the embolization; (B) microcoils in the lumen of the aneurysm. In control DSA, the aneurysm was almost completely closed except for a narrow space adjacent to the wall, which was contrasted (Class III b according the Modified Raymond-Roy Classification). The aneurysm remained incompletely occluded at first follow-up immediately after coiling; (C) Control angiography after 6 months. Performed examination showed the enlargement of a posterior leakage into the bag of previously embolized aneurysm (currently 3×1.5 mm). Source: own material.

Embolization technique

Embolization procedures were performed in our Interventional Neuroradiology Laboratory. Directly before each operation, we performed digitally subtraction angiography (DSA). One of the common femoral arteries was punctured according to the Seldinger method with a 6F catheter inserting. Then, the end of the guiding catheter was inserted in the proximal part of one of the internal or vertebral carotid arteries. Subsequently, the microcatheter was inserted coaxially and its end was placed in the aneurysm lumen. In the procedure, we used embolization microcoils, which shape, size, and number were depended on morphological features (size and anatomical conditions) of the aneurysm sac. The embolization procedure was modified through the use of intermediate catheters and balloon microcatheters according to the brain vessels tortuosity,

atherosclerotic lesions, the morphology of the aneurysm, the shape and the position in relation to the mother vessel, as well as the width of the neck of the aneurysm.

The effectiveness of embolization was monitored by DSA during the procedure and immediately after its completion, as well as at 6-month follow-up (Figure 1A–1C).

After the procedure, each patient underwent 12 to 24 hours of observation and monitoring of vital signs in the intensive care unit (ICU) recovery room. Each enlargement of the inflow of the aneurysm to the embolized aneurysm described by the radiologist was considered a recanalization. For the assessment of the degree of recanalization of the previously closed aneurysm, we used the Modified Raymond-Roy Classification (MRRC).

Material and Methods

The studies included all patients treated endovascularly in 2016–2018 due to brain aneurysm by a team of experienced

Table 1. Biographic characteristics of the examined patients.

Number of patients	Group A+B		Group A		Group B	
	n	%	n	%	n	%
Total	50	100%	12	24%	38	76%
Male	14	28%	4	8%	10	20%
Female	36	72%	8	16%	28	56%
Age	x	SD	x	SD	x	SD
Total	57.48	13.71	55.83	7.07	58.00	15.26
Male	60.00	10.45	53.00	3.46	62.80	11.10
Female	56.50	14.79	57.25	8.15	56.29	16.32

SD – standard deviation.

neurosurgeons and neuroradiologists, at the Department of Neurosurgery and Neurotraumatology of the Jagiellonian University Medical College in Cracow. All patients signed the informed consent to participate in the study. The analysis of medical records included age, sex, accompanying diseases, previous subarachnoid hemorrhage, (arterial hypertension, cancer, atherosclerosis, dyslipidemia), smoking, brain aneurysms (quantity, location), laboratory tests (hematocrit, hemoglobin, erythrocytes, leukocytes).

Biographical characteristics of the patients are presented in Table 1. A total of 50 patients were examined, including 14 male patients and 36 female patients. Age ranged from 20 to 83 years old; the average age was 57.48 years, standard deviation (SD)=13.71 years. In group A, there were 12 people (4 males and 8 females), or 23% of the study population, aged 50–69 years; the average age was 55.83 years, SD=7.07. In group B there were 38 people (10 males and 28 females), aged 20–83 years old; average age was 58.00 years, SD=15.26 years.

Examination procedure

In all patients, 6 months after the procedure, a full blood viscosity test was performed. Whole blood was examined. It was collected from the ulnar vein in the morning between 7.30 AM and 8.30 AM in patients who remained fasting for at least 10 hours. Blood was collected into anticoagulants (calcium disodium ethylenediaminetetraacetate, Ca-EDTA), using Vacutainer vacuum collection devices (Vacutainer system, BD Diagnostics, Plymouth, UK). Using a flow thermostat, the viscosity of whole blood and plasma was determined at a constant temperature of 37°C using a Brookfield DV III+Pro Cone-Plate Viscometer (Brookfield Engineering Labs Inc., Middleborough, MA, USA) using the Rheocalc program. The blood viscosity was determined at shear rates: 100, 200 and 400, 600 s⁻¹, and the plasma viscosity at shear rates of 100, 200 and 400 s⁻¹ according to accepted standards and test methodology used in other studies using the Brookfield viscometer.

Statistical methods

Statistical analysis was performed using the Statistica 12 computer program (StatSoft Inc., Tulsa, OK, USA). The chi-square independence test was used to check the relationship between the qualitative features. The normality of the distribution was verified using the Shapiro-Wilk test. Comparing the quantitative variables in which no normality of distribution or homogeneity of variances between the compared groups was observed; 2 non-parametric Mann-Whitney U tests were used. The categorized variables were presented by frequency, while the quantitative variables when the assumptions of the normal distribution were met by the mean and SD, and in other cases by the median and quartile range. The dependence between the viscosity of whole blood and the recanalization of the embolized aneurysm was examined using logistic regression analysis. Statistical significance was determined at the level $P=0.05$.

Results

The possible impact of demographic data on the recanalization of the embolized aneurysm were checked first. The Mann-Whitney test did not show a statistically significant difference in age between group A, in which recanalization occurred, with respect to group B, which was not recanalized ($P=0.31$). There was no correlation between gender and recurrence (chi square $P=0.64$).

Table 2 shows the characteristics of the studied groups A and group B due to qualitative data: sex and the occurrence of coexisting diseases. There was no significant relation between hypertension ($P=0.596$), atherosclerosis ($P=0.119$), and dyslipidemia ($P=0.665$) and recanalization of the coiled aneurysm. However, nicotine use was associated with recanalization of the coiled aneurysm: more frequently occurred in smokers ($P\leq 0.001$).

Table 2. Characteristics of the studied groups A and B: sex and co-morbidities.

Feature	Group A n/(%)	Group B n/(%)	P
Sex	Vide Tab1	Vide Tab1	0.637
Hypertension	6/12 (50%)	14/34 (41%)	0.596
Atherosclerosis	0/12 (0%)	6/34 (18%)	0.119
Dyslipidemia	2/12 (17%)	4/34 (12%)	0.665
Nicotinism	8/12 (67%)	4/34 (12%)	<0.001

Table 3. The location and morphological features of aneurysms.

Factor	Aneurysm group				P value
	Group A (with recanalization)		Group B (without the recanalization)		
Location					
Parent vessel	N	%	N	%	
ACoA	5	10	17	34	0.392
ICA	4	8	14	28	0.811
VBS	2	4	5	10	0.090
MCA	1	2	2	4	0.989
Morphological features					
Feature	N	%	N	%	
Plaque in aneurysm	3	6	11	22	0.439
Plaque in parental vessel	5	10	13	26	0.290
Irregular shape	2	4	11	22	0.197
Daughter sac	2	4	13	26	0.772
Size of aneurysm					
Parameter	Size (inmm)	SD	Size (inmm)	SD	
Depth	4.82	±2.54	4.21	±2.01	0.321
Width	4.31	±2.01	4.92	±2.04	0.095
Neck width	4.97	±1.53	4.01	±2.16	0.041
Maximum diameter	6.11	±2.84	5.82	±3.09	0.209
Depth/width ratio	1.52	±0.54	1.25	±0.43	0.031
Aspect ratio	1.82	±0.90	1.37	±0.91	0.042

ACoA – anterior communicating artery; ICA – internal carotid artery; VBS – vertebro-basilar system; MCA – middle cerebral artery; SD – standard deviation.

The characteristics of patients regarding the location and morphological features of recanalized aneurysms are shown in Table 3. Most patients had an aneurysm localized in the anterior communicating artery (ACoA) or internal carotid artery (ICA).

Plaque in aneurysm occurred in 3 patients (6%) in group A, and in 11 patients (22%) in group B. Plaque in parental vessel occurred in 5 patients (10%) in group A, and in 13 patients (26%) in group B. Irregular shape of the sac occurred in

Table 4. Characteristics of the studied groups A and B due to quantitative data.

Feature	Group A Median (IQR)		Group B Median (IQR)		P
Age	53.50	(9.00)	62.00	(22.00)	0.306
Ht	41.85	(6.00)	39.00	(4.30)	0.120
RBC	4.57	(0.43)	4.38	(0.35)	0.189
Hb	13.90	(1.40)	12.85	(1.80)	0.014
WBC	8.80	(3.86)	7.18	(3.38)	0.046
Whole blood viscosity	4.14	(0.42)	3.92	(0.40)	0.041
Plasma viscosity	1.57	(0.31)	1.58	(0.32)	0.695

Ht – hematocrit; RBC – red blood cells; HB – hemoglobin; WBC – white blood cells.

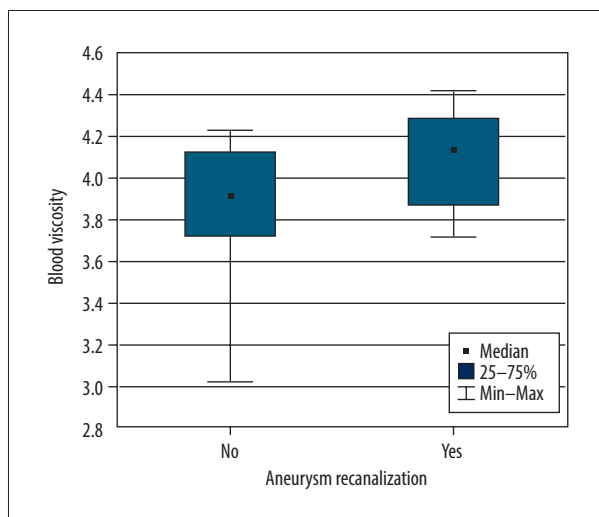


Figure 2. Blood viscosity and aneurysm recanalization in group A and B.

2 patients (4%) in group A, and in 11 patients (22%) in group B. We also found Daughter sac in 2 patients (4%) in group A, and in 13 patients (26%) in group B.

The analysis of the size of aneurysms shows that we recanalized more cases with a wider aneurysm neck, and with a higher depth/width ratio and aspect ratio (depth/neck width). Characteristics of the studied groups A and B included age and morphological elements (hematocrit, red blood cell count, hemoglobin, white blood cell count, blood and plasma viscosity as shown in Table 4.

We found that the level of hemoglobin was significantly higher in group A compared to group B ($P=0.014$). Also, the number of white blood cells was significantly higher in group A compared to group B ($P=0.046$), and the blood viscosity was significantly higher in group A compared to group B ($P=0.041$).

The next step was to examine the differences in laboratory results between the 2 groups using Mann-Whitney tests. There were no significant differences in hematocrit ($P=0.120$) and the number of red blood cells ($P=0.189$). However, in the group of patients with recanalization, higher values of hemoglobin ($P=0.014$) and white blood cell counts ($P=0.041$) were observed.

The comparison of blood viscosity in groups A and B

The comparison of blood viscosity in groups A and B is illustrated in Figure 2. Higher values of blood viscosity were associated with recanalization. In group A, higher blood viscosity values were found: median: 4.14 dyn×sec/cm² (mPa×sec) (Système international d'unités, SI) quartile interval 0.42. While in group B, lower blood viscosity values were found: median: 3.92 dyn×sec/cm² (mPa×sec) quartile range 0.40; ($P=0.04$). The difference between blood viscosity results obtained in group A compared to group B was statistically significant ($P=0.04$).

Regression analysis showed the effect of whole blood viscosity on recanalization. Viscosity increase by 1 dyn×sec/cm² (mPa×sec) increases the risk of recanalization up to 27 times (CI 1.10–666.6). The viscosity of the blood thus influences the recanalization, as the differences between groups A and B are statistically significant ($P=0.044$).

Discussion

We confirmed the hypothesis that blood viscosity increase was correlated with recanalization. A greater level of blood viscosity favors cerebral vessel turbulent blood flow, and this may result in complications in the form of cerebral artery aneurysm recanalization following coiling. Turbulent blood flow may promote leaching of the thrombus created after coil clogging, i.e., aneurysm recanalization despite any earlier closure using coils [23]. This kind of flow also exacerbates wall shear

stress (WSS) and probably might result in an increase in the mobility (expansion) of the vibrating vessel wall, possibly rinsing out the thrombus from the aneurysm.

In the literature on vascular blood flow studies, attention is drawn to the fact that blood is a non-Newtonian fluid. Therefore, when comparing the effect of non-Newtonian with Newtonian fluids in the conditions of pulsed flow assessed by the micro-interlaced velocimetry (PIV) method, the authors showed that non-Newtonian fluid can bring about endothelial damage not caused by Newtonian fluid [24]. The marked oscillating WSS observed during the pulsatile phase may be attributed to a bluntness of flow under the same wall shear rate condition as seen with the Newtonian fluid. In addition, a highly viscous flow accentuates the variation in the WSS after passing through the stenosed structures.

A similar tendency is also displayed in the mathematical simulation of the WSS mechanism. It was found that such a tendency is connected with plaque instability or tissue layer rupture and damage. These results, connected with the damage impact to the internal wall of the vessel, and the narrowing of the artery, may help clinicians to better comprehend the relevant mechanisms. These results related to the endothelial damage effect can aid clinicians in understanding the relevant recanalization mechanisms [25,26].

More detailed studies explaining the WSS mechanism, using particle image velocimetry (PIV) were carried out by Walker et al. [27]. The study results found the differences between flows of non-Newtonian and Newtonian fluids, and confirmed the mechanism described earlier – that the increased at peak pulsatile flow of a non-Newtonian fluid may lead to damage to the vessel wall.

These observations, although not proven in our research, may be one of the reasons for the recanalization of coiled aneurysm. However, what we did find was 2 important mechanisms underlining the recanalization of cerebral aneurysms: 1) the increased level of hemoglobin correlated with the recanalization rate such that the higher the level of hemoglobin, the greater the probability of recanalization (see Table 3). We did not find in the literature any explanation for this phenomenon. 2) The increase in white blood cells had a direct proportional correlation with the recanalization rate such that the higher the number of white blood cells, the greater the likelihood there was of recanalization.

As is known, leukocytosis correlates with the body's inflammatory status [28]. The high level of leukocytosis may be connected with local and systemic inflammatory response syndrome (SIRS) resulting from the coagulation in the aneurysmal sac and inflammation of the vessel wall by the thrombus with a

weakening of its secondary wall. To date, not all the reactions and mechanisms that occur in the thrombus in the coiled aneurysm have been examined, though it may be assumed that, in a way similar to the inflammatory reaction in other tissues, the migration of leukocytes, thrombus dissolution, and finally the recanalization of the aneurysm is stimulated.

Therefore, aneurysms formation and the frequency of the recanalization of the coiled intracranial aneurysms are associated with disorders of elasticity in the elastin and collagen fibers that form the vascular wall. The reasons for this are exogenous (e.g., the inflammatory state) and endogenous factors (e.g., genetic disorders). Therefore, in future research, it will be important to broaden research into these factors. It should be considered that small-sized aneurysms (<7 mm) have a predisposition to major recanalization through growth following coil embolization, as opposed to coil compaction, as was implied in earlier literature [29].

In addition, a significant relationship has been noted between smoking and aneurysm recanalization. Our results are in accordance with the latest research by Futchko et al. [30]. They examined a total of 247 patients who underwent endovascular treatment of 296 documented intracranial aneurysms. In smokers, the relapse rate was 26.3%, while in non-smokers it was only 17.2%. A multifactor analysis showed that after checking for potential factors interfering with smoking itself – regardless of whether this was now or in the past – it was connected with a significantly increased risk of aneurysm relapse. The odds ratio for recurrent aneurysm in current and ex-smokers was 2.739 (95% CI: 1.1227–7.0, $P=0.0308$) and 2.698 (95% CI: 1.078–7.22, $P=0.0395$) respectively compared to non-smokers. Our study showed that smoking was associated with a significant increase of aneurysm recanalization: patients who smoked had recanalization more often than patients who had never smoked; similar to other studies [31,32].

Tabuchi suggested that postmenopausal estrogen deficiency might skew results [33], and an unbalanced distribution of male/female numbers and differences in the age of females (pre and post menopause) (as was the case in our study) may distort study results [34].

It should be emphasized that the research we carried out revealed at least partially those factors that may affect the efficiency of intracranial aneurysms coiling. This information can be used to modify the procedure in future research, with particular attention placed on the evaluation and reduction of the blood viscosity in order to minimize turbulent flow in the cerebral vessels. Thus, it will be possible to partially prevent the recanalization of the embolized cerebral aneurysm which constitutes the adverse effect of the procedure. This will promote reduction in the frequency of subarachnoid hemorrhages,

and thus the need for any possible re-coiling procedure and even the possibility of reduced patient death. Subsequently, this will minimize the adverse medical, social, and economic effects of aneurysm recanalization.

Strengths of study

There are few clinical pieces of research devoted to the connection between blood viscosity and recanalization of the coiled intracranial aneurysm. Consequently, our research is most valuable and has, at least partially, identified factors that may affect the efficiency of intracranial aneurysms coiling. This will allow us to modify the procedure in the future, with particular emphasis on the evaluation and reduction of blood viscosity to minimize turbulent flow in the cerebral vessels. This will make partial prevention of the recanalization of the embolized intracranial aneurysm possible, which constitutes the adverse effect of the procedure. This will also promote reduction in the frequency of subarachnoid hemorrhages, and thus the need for any possible re-coiling procedure and even the possibility of patient death. Subsequently this will minimize the adverse medical, social, and economic effects of aneurysm recanalization.

Additionally, we discovered another important factor connected with coiled aneurysm recanalization. And that is the increase in the number of white blood cells, directly proportionally correlated with the recanalization rate itself: the higher the number of white blood cells, the greater is the likelihood of recanalization.

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Study limitations

We are aware of the potential limitations of our study. The most important factor here being the small number of patients and the patients being recruited from a single center. This is connected with the exact selection of study participants. We only included unruptured brain aneurysm patients; in future research there would need to be patients with subarachnoid hemorrhage included. The other weak point of this research was neglecting the WSS measurement. This was passed over due to the lack of precise methodology in our department. We did not equally take into account other inflammatory factors such as those of C-reactive protein (CRP) and fibrinogen.

In order to deepen the statistical analysis, we are planning to extend the future scope of the research. The number of patients undergoing recanalization of aneurysms and several tests of blood viscosity included in it will be larger, which will allow us to better assess and understand the mechanisms underlying the fact that blood viscosity is associated with aneurysms recanalization. Therefore, in future research, whole blood should be analyzed as a non-Newtonian fluid, which has a turbulent flow and can cause recanalization of the aneurysm.

Conclusions

The occurrence of higher values of whole blood viscosity which increase turbulent flow through vessels may be a risk for coiled cerebral aneurysm recanalization. The research results of this study provide information useful to clinicians to better understanding the mechanisms of recanalization of coiled brain aneurysms, as well as broadening our knowledge on this subject in general.

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