ORIGINAL ARTICLES

The influence of the degree of cerebral atherosclerosis on the changes in hemostatic system in patients with ischemic brain disease and atherosclerotic encephalopathy

Major Assist. **Ranko Raičević**[*], MD, PhD, Lt. General Prof. **Aco Jovičić**[*], MD, PhD, **Slavka Mandić-Radić**[†], BSc, Major-General Assist. Prof. **Momčilo Krgović**[‡], MD, PhD, Col. Assist. Prof. **Bratislav Magdić**[*], MD, PhD, Lt. **Ljubo Marković**[‖], MD, MA, **Dragan Hajduković**[§], MD, Assist. Prof. **Pavle Jović**[†], MD, PhD

Military Medical Academy, [*]Clinic of Neurology, [†]Central Laboratory of Clinical Chemistry, [‖]Institute of Radiology, [§]Clinic of Endocrinology, [‡]Clinic of Cardiology, **Belgrade**

Vascular brain diseases are ranked the third as the cause of morbidity and mortality, in spite of the progress in diagnostic, therapeutic and preventive procedures. In the majority of cases of vascular brain diseases, it is ischemic brain disease, which is the final and the most severe stage of cerebral arteries atherosclerosis. Etiopathogenesis of atherosclerosis is not closer defined yet, but oxidative hypothesis is distinguished among the numerous theories. Within this theory, main place is attached to oxidative modification of LDL and Lp(a), together with numerous physiopathologic facts with the central role of reactive oxidative matters, where endothelial dysfunction is the main disorder responsible for the onset of numerous impairments, such as changes in coagulation-anticoagulation system. Considering these facts, it was established the hypothesis that in patients with IBD existed changes in hemostatic system, which were in positive correlation with the degree of cerebral atherosclerosis. The study comprised 36 patients with acute IBD and 28 patients with atherosclerotic encephalopathy. Control group was comprised of 30 patients with non-vascular diseases of similar characteristics. We investigated the correlation of the changes in hemostatic system (platelet aggregation, antithrombin III, D-dimer, protein C, factor VII, factor VIII, PAI-1) compared to the degree of cerebral atherosclerosis (ultrasonographically) and compared to the observed groups of patients. On the basis of all, the results of this study revealed significant increase of procoagulant factors concentration in patients with IBD, and similar changes were observed in patients with atherosclerotic encephalopathy, but less pronounced. All these changes in the total sample of patients, and particularly in patients with the pronounced cerebral atherosclerosis, are of primary and chronic character.

Key words: **cerebral arteriosclerosis; atherosclerosis; cerebral ischemia; hemostasis.**

Introduction

Vascular brain diseases are ranked the third as the cause of morbidity and mortality in the majority of countries, independently of their medical technological progress and socio-economic status. In about 80 % of the cases of vascular brain disease, it is ischemic brain disease (IBD) (1-5).

Primary disease responsible for the development of IBD is the atherosclerosis of cerebral arteries. A certain number of hereditary and habitual factors influence the

progression of this process. Since etiopathogenesis of atherosclerosis is still unclear, in this study we will present current processes that are causing atherosclerotic cerebral changes, particularly hemorrheologic and coagulation disorders (1-11).

Lipid oxidation is one of the theories most frequently used for the explanation of this process. Oxidation of LDL and Lp(a) occurs under the activity of free radicals and enzymatic reactions. This influences the modification of apo B 100 (apoprotein specific for LDL), which results in an uncontrolled takeover of LDL from monocytes and macrophages, in which occurs degradation and deposition of cholesterol with foam cell formation. This is the initial pathological event in the atherogenesis and is, therefore, responsible for IBD (1-3).

This, we can say, "cascade" system that includes extremely complex changes is responsible for atherosclerosis, which consequently leads to IBD that is the most severe and final complication of the atherosclerosis of cerebral arteries. The main event in this system is the change in hemorrheologic mechanisms, primarily because we are dealing with the factors influencing cerebral microcirculation (1-5, 12-28).

Examining these changes, we can get an insight in fine molecular changes at the level of ionic currents in ischemic tissue. Shortly, from physiologic aspect, system of hemostasis represents dynamic equilibrium between the processes of coagulation and anti-coagulation, which provides liquid state of the blood. From biochemical point of view, it is a multi-component, fermentative and auto-catalytic process that is developing in the form of a "cascade" (1-3, 29-31).

It is important to understand that three main triggers of platelet activation are released during endothelial dysfunction as a factor in the development of atherosclerosis: platelet activating factor (PAF), thrombin and contact with collagen. Further more, platelet factor 3 is released from activated platelets, which represents thrombokinase and can initiate the process of coagulation. Thus thrombosis is a complex interaction between platelet activation and coagulation cascade, with endothelial dysfunction as the initial trigger (1-3, 11-31).

Dynamic equilibrium of these processes, which provides liquid state of the blood, is maintained by anticoagulation system that includes antithrombin III, proteins C and S , as well as fibrinolytic system.

Hypercoagulable state is defined as the state in which changes of coagulation, platelet activity and anticoagulation mechanisms favor thrombogenesis (1-3, 17-28).

Recent studies show that signs of coagulation are present in acute phase of IBD, while signs of fibrinolysis are present in subacute and chronic phases (1-5, 11-31).

Currently accepted opinion is that platelet hyperactivity is of the utmost importance in IBD pathogenesis. Platelet hyperactivity was present in patients with brain atherosclerosis without clinical signs of IBD, in patients with transient ischemic attacks (TIA) and brain infarction in all phases. Thus it is a primary hemorrheologic disorder with a central role in the onset of IBD, as well as in its evolution, and it is also a risk factor for a relapse (1, 2, 14-37).

In the patients with pronounced atherosclerosis, besides the presence of risk factors of atherogenesis, there exist an intensive process of lipid peroxidation in atherosclerotic lesions, reduction of prostacyclin production, increase in free radicals formation and during the aging there is an increase of fibrinogen, antiplasmin, reduction of free heparin, increase in circulating catecholamines with the altered reaction to stress. Actually, all these factors are favorable for IBD development (1, 2, 14-37).

On the other hand, these processes make a disbalance in coagulation-anticoagulation system (1-3, 14-28).

Physiopathologically, an increased platelet activity is the earliest phase of atherogenesis in endothelial dysfunction (33-37).

On the whole, nowadays we do not dispose of the precise facts about the changes in coagulation-anticoagulation system in patients with atherosclerosis and IBD. On the basis of all cited above, we have established the following hypothesis:

1. In patients with cerebral atherosclerosis and acute IBD (AIBD) there are significant changes of coagulation-anticoagulation system;

These changes are in positive correlation with the degree of cerebral atherosclerosis verified by ultrasonography of cervical arteries.

Objects of the study

1. To establish the degree of the severity of clinical syndromes and cerebral atherosclerosis degree (by ultrasonography) in patients with AIBD (n=36);
2. To perform an analysis of blood samples on parameters of coagulation and anticoagulation activity (activated partial thromboplastin time – aPTT), euglobulin test, platelet aggregation, antithrombin III, fibrin degradation products, D-dimer, plasminogen activator inhibitor-1 (PAI-1), protein C and S, factor VII and VIII;
3. To analyze these factors in patients (n=28) with ultrasonographically and laboratory confirmed diagnosis of cerebral atherosclerosis and with symptoms of dyscirculatory encephalopathy, without IBD;
4. To analyze coagulation-anticoagulation parameters in 30 patients without symptoms and signs of atherosclerosis, and immunologic, inflammatory, hematologic and malignant diseases;
5. To analyze the correlation of changes in coagulation-anticoagulation system with the degree of cerebral atherosclerosis compared to ultrasonographic findings and severity of IBD.

Methods

In the study were included 32 patients admitted to the Clinic of Neurology of the Military Medical Academy with

acute attack of ischemic brain disease of transient ischemic attack (TIA) and reversible ischemic attack (RIA) type, as well as cerebral infarction. Control group I comprised 30 patients without symptoms and signs of atherosclerosis, immunologic, inflammatory, hematologic and malignant diseases.

Control group II consisted of 28 patients with atherosclerotic encephalopathy without manifestations of cerebral infarction.

All patients receiving anticoagulant therapy were excluded from the study. Patients with the disorders that might affect coagulation-anticoagulation system as well as patients with hepato-renal failure were also excluded.

Blood samples for determination of sedimentation, fibrinogen, hemostatic factors (aPTT, platelet aggregation, euglobulins, antithrombin III, D-dimer, PAI-1, fibrin degradation products, factor VII and VIII, protein C and S) were taken from all patients immediately after the admission, or at least 72 hours after clinical picture was revealed.

CT or MR examination were performed in all patients with IBD within 3-10th day in order to confirm the nature and severity of ischemic lesion of cerebral parenchyma.

The degree of neurologic and functional deficit was determined before and after acute phase of IBD after the repeated examination by the same neurologist. The severity of IBD using the scale for the estimation of cerebral infarction severity by Grotta and Noreen was determined in all patients on the basis of clinical neurologic findings, results of additional investigations, analysis and the degree of recovery (32).

In 60 patients was performed echoangiography of neck arteries and scaling was done according to international scale (33) (Table 1).

Table 1

Degree of stenosis	Index of stenosis
Normal	0
<= 25%	1
<=50%	2
<=75%	3
>75%	4

All patients with IBD received the same therapy.

Results were analyzed using Student's test, bi-serial correlation, and linear regression analysis.

Coagulation-anticoagulation parameters were analyzed by the same analyst using Dade Behring reagents and Behring coagulation apparatus. Only for D-dimer were used reagents from Boehringer Manheim and Diagnostica Stago.

Results

Ultrasonography was performed in 32 patients with acute IBD (AIBD) and in 28 patients with atherosclerotic encephalopathy (AE).

After the scoring of ultrasonographic findings we analyzed the correlation between ultrasonographic findings and coagulation factors in patients with IBD and in patients with aterosclerotic encephalopathy compared to the controls. No significant differences of general characteristics were found between the observed groups (Table 2).

Table 2

General characteristics of examinees from experimental and control groups

	Sex		Age	Patients (No)
	Male	Female	(Year ± SD)	
AIBD	18	14	65.56 ± 7.11	32
AE	16	12	64.34 ± 6.21	28
Control group	19	11	61.89 ± 8.56	30

Patients from control group were almost 4 years younger then the patients in experimental groups, but due to high standard deviation this was not significant.

Degree of atherosclerosis according to ultrasonographic findings is shown on Table 3 compared to the experimental group.

Similar distribution of the degree of atherosclerosis of cervical arteries existed in patients of both groups, while more severe forms of stenosis and occlusion were more significantly pronounced in patients with clinical manifestations of IBD.

Platelet aggregation was accelerated in patients with IBD ($p<0.01$), compared to the control group. This parameter was also significantly lower, i.e., the acceleration was faster, in patients with AE compared to the control group ($p<0.05$). No significant differences were observed between patients with IBD and AE.

Antithrombin III was lower in patients with IBD compared to controls ($p<0.01$). It was also lower in patients with AE ($p<0.05$). Antithrombin III was lower in patients with IBD compared to patients with AE ($p<0.05$).

D-dimer showed high standard deviation in all groups, particularly in patients with AIBD. In spite of this, the results showed that D-dimer had significantly higher concentrations ($p<0.01$) in patients with AIBD compared to the control group. The comparison of this parameter in patients with AE and control group demonstrated higher concentrations in patients with AE, on the border-line sig-

Table 3

Ultrasonographically confirmed degree of atherosclerosis in patients with AIBD and atherosclerotic encephalopathy

Degree of Stenosis	AIBD	AE
Normal	6 (18.7%)	6 (21.4%)
<=25%	4 (12.5%)	3 (11.1%)
<=50%	4 (12.5%)	3 (11.1%)
<=75%	9 (28.1%)	10 (35.7%)
>75%	9 (28.1%)	6 (21.4%)

nificance (p=0.067). Compared to patients with AIBD, this parameter was lower (p<0.05).

Protein C was significantly lower in patients with AIBD, as well as in patients with AE compared to the control group (p<0.05).

Level of factor VIII was higher in patients with AIBD compared to controls (p<0.05). This was also registered in patients with AE but without statistical significance.

PAI-1 had significantly higher concentrations in patients with AIBD compared to controls (p<0.01). The same significant difference was registered between PAI-1 concentrations in patients with AIBD compared to the concentration of this parameter in patients with AE. PAI-1 was higher in patients with AE compared to controls (p<0.05) (Tables 4-8).

2. Significant negative correlation existed between ultrasonographic findings and antithrombin III and platelet aggregation (p<0.05).
3. There was no statistical significance for other coagulation-anticoagulation factors, neither positive, nor negative.
4. No differences between these parameters were observed by the analysis of these relations in the groups.

Discussion

Vascular brain diseases are ranked the third as the cause of morbidity and mortality despite the progress of diagnostic, therapeutic and measures of prevention (1-5). Is-

Table 4

Platelet aggregation

GROUP	PLATELET AGGREGATION	
AIBD	X=7.89	SD=1.456
AE	X=8.88	SD=1.781
Control group	X=10.23	SD=1.876
GROUP	PROTEIN C	
AIBD	X=0.87	SD=0.087
AE	X=0.96	SD=0.098
Control group	X=1.39	SD=0.097
GROUP	FACTOR VIII	
AIBD	X=1.39	SD=0.123
AE	X=1.16	SD=0.132
Control group	X=0.98	SD=0.132
GROUP	ANTITHROMBIN III	
AIBD	X=0.842	SD= 0.098
AE	X=0.987	SD=0.098
Control group	X=1.198	SD=0.119
GROUP	D-DIMER	
AIBD	X=3.30	SD=1.34
AE	X=2.08	SD=1.23
Control group	X=1.79	SD=1.35

Concerning the association of atherosclerosis, i.e., found degree of stenosis or occlusion confirmed by ultrasonographic examination of cervical arteries and the changes in system of hemostasis, in all examinees was determined the following:

1. There was positive correlation of atherosclerosis of cervical arteries and PAI-1 concentrations (p<0.05). For D-dimer it had border-line value (p=0.064).

chemic brain disease is the most frequent of vascular brain diseases, and it represents the most severe and final stage of atherosclerosis of cerebral arteries (1-5). Etiopathogenesis of atherosclerosis is not clear yet and one of acceptable hypothesis is the one concerning lipid oxidation (1-3, 38-43). The main point of this hypothesis is the oxidative modification of LDL and Lp(a) including numerous physiopathological factors with the central role of reactive

oxidative matters, and endothelial dysfunction as the main change leading to coagulation system disorder. According to these facts we have established the hypothesis that in patients with IBD exist changes in hemostasis system that are in positive correlation with the degree of cerebral atherosclerosis (1-3, 44-51).

Etiology and pathogenesis of cerebral atherosclerosis and atherosclerosis in general are not clearly defined yet. On the other hand, numerous epidemiological studies enabled identification of numerous factors, which contribute to the development of atherosclerosis and ranking of their importance was established. These factors are known as atherosclerotic risk factors (1-3).

Lipoprotein a – Lp(a) has an important role in hemostatic dysfunction. Lp(a) is composed of LDL bound with specific apo A in a bending form by disulfide bond. It has a high affinity for scavenger macrophage receptors and there is a close correlation between its plasma concentration and the deposition in atherosclerotic lesions, more pronounced then for apo B (1-5, 44-51, 78-93).

Apo A is structurally similar to plasminogen, which can result in competitive effect against the same substrate with the reduction of plasmin production (1-3).

However, human brain considering the microcirculation has specific autoregulatory mechanisms of hemostatic system. On the other hand, this system is not completely independent of changes in hemostatic system in systemic circulation.

Antithrombotic endothelial characteristics of cerebral circulation are:

1. presence of thrombomodulin (TM), a membrane anticoagulant protein, found at the luminal side of endothelial cells;
2. absence of procoagulant tissue factor (TF) in cerebral endothelium;
3. presence of a barrier that prevents the passage of circulating coagulation factors into the cerebral tissue and the initiation of external coagulation in interaction of TF and astrocytes;
4. physical/chemical characteristics of luminal endothelial membrane that acts preventively by inhibiting the binding of platelets and promoting the contact phase of internal coagulation;
5. prostacyclin production with the adherence of antithrombin III to heparin sulfate that is found exclusively on the albumin side of cerebral capillaries, which results in strong inhibition of platelet aggregation (1-3, 77-79).

However, in states leading to the development of IBD of atherothrombotic etiology, there are conditions for the impairment of hemostatic system with the predomination of pro-coagulation mechanisms.

The trigger of such events in cerebral blood vessels is TF, known as tissue thromboplastin. Normally, TF is not found on the endothelium of hematoencephalic barrier, but when it is damaged as in ischemia, external coagulation is initiated. Further more, an activation of internal coagulation cascade with the propagation of coagulation processes occurs. This process develops in such way: TF is the receptor for factor VII, and this complex activates factor IX and X; factor IXa forms a complex with factor VIIIa and activates factor X; factor Xa forms a complex with factor Va and activates prothrombin. Thrombin degrades fibrinogen, creating a monomer-fibrin, which then polymerizes into fibrin coagulum (1-5, 70-79).

Balance to the coagulation processes is fibrinolytic system, with plasmin as the main component. In a formed thrombus, there is a large amount of plasminogen-together with numerous other plasma proteins. Plasminogen must be activated in order to become plasmin. Plasmin is tripsin-like enzyme with protheolytic ability of lysing fibrin, fibrinogen and factors V, VIII and XII (1-5, 77-79).

Locally, fibrinolysis enables slow clearing of thrombus and re-canalization of cerebral circulatory system. This system is also under fine control of t-PA and PAI-1 as the main factors.

Most of the t-PA concentration in plasma and tissues is considered to be in inactive state, actually as the part of PAI-1 complex, which is the primary endogenous t-PA inhibitor. On the other hand, the fact that a fraction of free t-PA is found in cerebral capillaries imposes the conclusion that cerebral endothelium has the key role in fibrinolytic mechanisms of cerebral circulation (1-3, 71-85).

Apart from this, it is considered that t-PA has the other roles such as the positive influence on sympathetic activity and as a mediator of neuronal degradation. Damaged or stimulated endothelium releases t-PA into cerebral circulation, and it dissolves plasminogen bound to fibrin (71-86).

In this study, we have begun from the fact that physiopathology of atherosclerosis, as well as IBD, can not be assessed according to single disorders responsible for its evolution. The point is that it is a chain-cascade reaction. Our idea was to show the significance of laboratory findings, especially because they represent relatively easy and economical methods.

Hemorrheologic disorder that influences coagulation-anticoagulation system has the key place in this complicated mechanism.

Furthermore, we must not forget the other risk factors that contribute to atherosclerosis. For example, lipoprotein oxidation is a very important event in atherosclerosis. Hypertension on the other hand influences lipoprotein influx. Vessel bifurcations are the loci minoris resistentiae for atherosclerotic deposits. Besides, smoking causes chemical damage of endothelium, which increases the oxidation and influx into arterial intima (1, 85-106).

This influences hemorrheologic disorders significantly and according to our results causes disbalance of hemostatic system in favor of pro-coagubility states.

We registered high concentrations of D-dimer, which was a sensitive marker for active coagulation and PAI-1 as a marker for the activated inhibition of fibrinolysis.

This correlation was the most significant in patients with IBD ($p<0.001$) for both parameters. Also, we registered positive correlation for accelerated platelet aggregation, as well as for low concentrations of antithrombin III.

These results point out that these parameters in acute phase of IBD, especially in the first several days, influence the increased activation of plasma coagulation factors. Platelet activity is the highest in acute IBD phase, but is also present in patients with atherosclerotic encephalopathy without the clinical manifestations of IBD.

Shortly, the conditions for pro-coagulation are created in the acute phase, which was confirmed by our results. Also, it is important to mention, that these changes were statistically significant in a group of patients with atherosclerotic encephalopathy compared to the controls.

Conclusion

1. There is a significant increase in concentration of procoagulant factors in patients with IBD;
2. The same changes, but with a lower significance are observed in patients with atherosclerotic encephalopathy;
3. Results revealed the fact that changes of hemostatic system in cerebral atherosclerosis were chronic and probably of primary character.

REFERENCES

1. *Jovičić A,* editor. Cerebrokardijalni i kardiocerebralni sindromi. Beograd: JP PTT Srbije; 1998.
2. *Jovičić A.* Značaj moždanog krvotoka u cerebrovaskularnim bolestima. In: *Mršulja B, Kostić V,* editors. Biološki osnovi terapije cerebrovaskularne bolesti. Beograd: Medicinski fakultet; 1992. p. 5-30.
3. *Heiss WD.* Cerebral blood flow: physiology, pathophysiology and pharamacological effects. Adv Otorhinolaryngol 1981; 27: 26-39.
4. *Lassmann H.* Adhesion molecules and the blood-brain barrier. In: *Abramsky O, Ovadia H,* editors. Frontiers in multiple sclerosis. London: Martin Dunitz; 1997. p. 161-9.
5. *Frackowiak RS.* The pathophysiology of human cerebral ischemia: a new perspective obtained with positron tomography. Q J Med 1985; 57: 713-27.
6. *Hallenbeck JM.* Inflammatory reactions at the blood-endothelial interface in acute stroke. In: *Siesjo BO, Wieloch T,* editors. Advances in neurology. Philadelphia: Lippincot-Raven Publishers; 1996. p. 281-300.
7. *Lampl Y, Fleminger G, Gilad R, Galron R, Sarova-Pinhas I, Sokolovsky M.* Endothelium in cerebrospinal fluid and plasma of patients in the early stage of ischemic stroke. Stroke 1997; 28: 1951-5.
8. *Jovičić A, Ivanišević V, Marković M, Simović M.* Uloga azotnog oksida u fiziološkim funkcijama i patološkim stanjima. Vojnosanit Pregl 1994; 51: 126-31.
9. *Dawson TM, Dawson VL, Snyder SH.* A novel messenger molecule in brain: the free radical, nitric oxide. Ann Neurol 1992; 32: 297-311.
10. *Lindsberg JP, Hallenbeck MJ, Feuerstein G.* Platelet-activating factor in stroke and brain injury. Ann Neurol 1991; 30: 117-29.
11. *Siesjo BO, Wieloch T,* editors. Advances in neurology. Philadelphia: Lippincott-Raven Publishers; 1996.
12. *Harper AM.* Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. J Neurol Neurosurg Psychiatry 1966; 29: 398-403.
13. *Jovičić A, Đorđević D, Jovanović M.* Mehanizam ekscitoneurotoksičnosti i perspektive terapije antagonistima ekscitatornih aminokiselina. Vojnosanit Pregl 1996; 53: 45-52.
14. *Jovičić A, Gavrilović M, Magdić B, Đorđević D.* Serumski lipidi i ishemični cerebrovaskularni poremećaji. Vojnosanit Pregl 1984; 41: 251-7.
15. *Jovicic A, Ivanisevic V, Ivanovic I.* Lipoprotein(a) in patients with carotid atherosclerosis and ischemic cerebrovascular disorders. Atherosclerosis 1993; 98: : 59-65.
16. *Raičević R, Jovičić A, Veljančić D, Đorđević D, Čedić V, Dinčić E,* et al. Značaj uduženosti faktora rizika od moždane ateroskleroze kod bolesnika sa akutnom ishemijskom bolešću mozga. Vojnosanit Pregl 1998; 55: 255-63.
17. *Hamsten A, Eriksson P, Karpe F, Silveira A.* Relationships of thrombosis and fibrinolysis to atherosclerosis. Curr Opin Lipidol 1994; 5: 382-9.
18. *Fisher M, Miselman JH.* Hemorheological factors in cerebral ischemia. Stroke 1991; 22: 1164-9.
19. *Jovičić A.* Hemoreološki poremećaji i terapijski koncept u infarkta mozga. Vojnosanit Pregl 1987; 44: 44-50.
20. *Qizilbash N, Jones L, Warlow C, Mann J.* Fibrinogen and lipid concentrations as risk factors for transient ischaemic attacks and minor ischaemic stroke. BMJ 1991; 303: 605-9.
21. *Wood JH, Kee DB Jr.* Hemorheology of the cerebral circulation in stroke. Stroke 1985; 16: 765-72.
22. *Thomas DJ.* Whole blood viscosity and cerebral blood flow. Stroke 1982; 13: 285-7.
23. *Jovičić A.* Prilog medikamentoznoj terapiji infarkta mozga u akutnoj fazi [doktorska disertacija]. Beograd: Vojnomedicinska akademija 1981.
24. *Jovičić A, Ristović B.* Određivanje indeksa deformabilnosti eritrocita u bolesnika sa ishemičnim cerebrovaskularnim poremećajima. Vojnosanit Pregl 1986; 43: : 12-5.

25. *Ivanišević V.* Uloga hemoreoloških činilaca u nastanku i evoluciji ishemičnih cerebrovaskularnih poremećaja [doktorska disertacija]. Beograd: Vojnomedicinska akademija; 1992.
26. *Jovičić A, Ivanišević V, Toplaov D, Magdić B.* Korelacija nivoa adenozin trifosfata u krvi i deformabilnosti eritrocita u bolesnika sa tranzitornim ishemičnim atacima i infarktom mozga. Vojnosanit Pregl 1988; 45: 83-7.
27. *Jovičić A, Pavlović G, Ivanišević V.* Hiperkoagulabilnost krvi i ishemična bolest mozga. Vojnosanit Pregl 1992; 49: 351-6.
28. *Joseph R, D'Andrea G, Oster SB, Welch KM.* Whole blood platelet function in acute ischemic stroke. Importance of dense body secretion and effects of antithrombotic agents. Stroke 1989; 20: 38-44.
29. *Feinberg WM, Bruck DC, Ring EM, Corrigan JJ Jr.* Haemostatic markers in acute stroke. Stroke 1989; 20: 592-7.
30. *Lindgren A, Lindoff C, Norrving B, Astedt B, Johansson BB.* Tissue plasminogen activator and plasminogen activator inhibitor-1 in stroke patients. Stroke 1996; 27: 1066-71.
31. *Tohgi H, Suzuki H, Tamura K, Kimura B.* Platelet volume, aggregation and adenosine triphosphate release in cerebral thrombosis. Stroke 1991; 22: 17-21.
32. *Grotta JC, Lemak NA, Gary H, Fields WS, Vital D.* Does platelet antiaggregant therapy lessen the severity of stroke? Neurology 1985; 35: 632-6.
33. *Marić D.* Senzitivnost pojedinih komponenti lipidnog statusa u određivanju povišenog rizika za nastanak i evoluciju moždane ateroskleroze i ishemijske bolesti mozga [magistarski rad]. Beograd: Vojnomedicinska akademija; 1995.
34. *Jovičić A, Veljančić D, Đorđević D, Maličević Ž.* Poremećaj sadržaja i prometa lipida kao faktor rizika za nastanak i razvoj moždane ateroskleroze i ishemijske bolesti mozga. Vojnosanit Pregl 1996; 53: 125-32.
35. *Reed DM, Resch JA, Hayashi T, Maclean C, Yano K.* A prospective study of cerebral artery atherosclerosis. Stroke 1988; 19: 820-5.
36. *McGill HC Jr.* Cerebral artery atherosclerosis and diet. Stroke 1988; 19: 801.
37. *Yatsu FM, Fisher M.* Atherosclerosis: current concepts on pathogenesis and interventional therapies. Ann Neurol 1989; 26: 3-12.
38. *Fogelholm R, Murros K, Rissanen A, Ilmavirta M.* Decreasing incidence of stroke in central Finland, 1985-1993. Acta Neurol Scand 1997; 95: 38-43.
39. *Lanska DJ, Kuller LH.* The geography of stroke mortality in the United States and the concept of a stroke belt. Stroke 1995; 26: 1145-9.
40. *Bots ML, Looman SJ, Koudstaal PJ, Hofman A, Hoes AW, Grobbee DE.* Prevalence of stroke in the general population. The Rotterdam Study. Stroke 1996; 27: 1499-501.
41. *Truelsen T, Prescott E, Gronbaek M, Sehnohr P, Boysen G.* Trends in stroke incidence. The Copenhagen City Heart Study. Stroke 1997; 28: 1903-7.
42. *Bonita R, Beaglehole R.* The enigma of the decline in stroke death in the United States: the search for an explanation. Stroke 1996; 27: 370-2.
43. *Young SM, Fisher M, Sigsbee A, Errichetti A.* Cardiogenic brain embolism and lupus anticoagulant. Ann Neurol 1989; 26: 390-2.
44. *Elinder LS, Walldins G.* Antioxidants and atherosclerosis progression: unresolved questions. Curr Opin Lipidol 1994; 5: 265-8.
45. *Gianturco SH, Bradley WA.* Atherosclerosis: cell biology and lipoproteins. Curr Opin Lipidol 1994; 5: 313-5.
46. *Saxena U, Goldberg IJ.* Endothelial cells and atherosclerosis: lipoprotein metabolism matrix interactions, and monocyte recruitment. Curr Opin Lipidol 1994; 5: : 316-22.
47. *Liu AC, Lawn RM.* Vascular interactions of lipoprotein (a). Curr Opin Lipidol 1994; 5: 269-73.
48. *Dinčić D.* Molekulski pristup u savremenom shvatanju nastanka i razvoja procesa ateroskleroze. Vojnosanit Pregl 1997; 54: 55-60.
49. *Frijns CJ, Kappelle LJ, van Gijn J, Nieuwenhuis HK, Sixma JJ, Fijnheer R.* Soluble adhesion molecules reflect endothelial cell activation in ischemic stroke and in carotid atherosclerosis. Stroke 1997; 28: 2214-18.
50. *Hulthe J, Wikstrand J, Emanuelsson H, Wiklund O, de Feyter PJ, Wendelhag I.* Atherosclerotic changes in the carotid artety bulb as measured by B-mode ultrasound are associated with the extent of coronary atherosclerosis. Stroke 1997; 28: 1189-94.
51. *McCalden TA, Nath RG.* Mechanisms of vascular supersensitivity in hypercholesterolemia. Stroke 1989; 20: 238-41.
52. *Jovičić A, Ivanišević V, Marković M.* Racionalne osnove za primenu antioksidanata u neurologiji. Vojnosanit Pregl 1993; 50: 406-15.
53. *Halliwell B.* Oxidants and the central nervous system: some fundamental questions. Is oxidant damage relevant to Parkinson's disease, Alzeheimer's disease, traumatic injury or stroke ? Acta Neurol Scand Suppl 1991; 126: 23-33.
54. *Jovičić A, Đorđević D, Veljančić D, Dinčić E.* Uloga E i C vitamina u patofiziologiji i terapiji ishemijske bolesti mozga. Arh Farm 1996; 5-6: 227-50.
55. *Albin RL, Grenamyre TJ.* Alternative excitotoxic hypothesis. Neurology 1992; 42: 733-8.
56. *Yue TL, Fuerestein GZ.* Platelet-activating factor: a putative neuromodulator and mediator in the pathophysiology of brain injury. Crit Rev Neurobiol 1994; 8: : 11-24.
57. *Jovičić A, Jovanović M, Đorđević D, Magdić B, Dinčić E, Maličević Ž.* Oksidativna i antioksidativna aktivnost kod bolesnika sa diseminovanim demijelinizacionim oboljenjem centralnog nervnog sistema. Vojnosanit Pregl 1997; 54: 193-202.
58. *Barnet HJ.* Thrombotic processes in cerebrovascular disease. In: *Colman RW, Hirsh T, Marder VJ, Salzman*

EW, editors. Hemostasis and thrombosis: basic principles and clinical practice. 2nd ed. Philadelphia: JB Lippincott Co; 1987. p. 1301-15.

59. *High KA, Roberts HR*, editors. Molecular basis of thrombosis and hemostasis. New York: Dekker; 1995. p. 4-124.
60. *Colman RW.* Hemostasis and thrombosis: basic principles and clinical practice. 2nd ed. Philadelphia: Lippincott; 1994.
61. *Sherry S.* Fibrinolysis, thrombosis and hemostasis: concepts, perspective and clinical applications. Philadelphia: Lea and Febiger; 1992.
62. *Halkier T.* Mechanisms in blood coagulation, fibrinolysis and the complement system. Cambridge: Cambridge University Press; 1991.
63. *Davie EW, Fujikawa K, Kisiel W.* The coagulation cascade: initiation, maintenance, and regulation. Biochemistry 1991; 30: 10363-70.
64. *Furie B, Furie BC.* The molecular basis of blood coagulation. Cell 1988; 53: 505-18.
65. *Esmon CT.* Cell mediated events that control blood coagulation and vascular injury. Ann Rev Cell Biol 1993; 9: 1-26.
66. *Esmon CT.* The protein C anticoagulant pathway. Arterioscler Thromb 1992; 12: 135-45.
67. *Walker FJ.* Protein S and the regulation of activated protein C. Semin Thromb Hemost 1984; 10: 131-38.
68. *Esmon CT.* The roles of protein C and thrombomodulin in the regulation of blood coagulation. J Biol Chem 1989; 264: 4743-6.
69. *Suzuki K, Deyashiki Y, Nishioka J, Toma K.* Protein C inhibitor: structure and function. Thromb Haemost 1989; 61: 337-42.
70. *Fair DS, Marlar RA, Levin EG.* Human endothelial cells synthesize protein S. Blood 1986; 67: 1168-71.
71. *Esmon CT, Taylor FB Jr, Snow TR.* Inflammation and coagulation: linked processes potentially regulated through a common pathway mediated by protein C. Thromb Haemost 1991; 66: 160-5.
72. *Collen D, Lijnen HR.* Fibrinolysis and the control of hemostasis. In: *Stamatoyannopoulos G, Nienhuis AW, Majewrus PW, Varmus H*, editors. The molecular basis of blood diseases. Philadelphia: WB Saunders; 1994. p. 725-52.
73. *Bauer KA, Rosenberg RD.* Role of antithrombin III as a regulator of in vivo coagulation. Semin Hematol 1991; 28: 10-18.
74. *Collen D, Lijnen HR.* Basic and clinical aspects of fibrinolysis and thrombolysis. Blood 1991; 78: 3114-24.
75. *Sprengers ED, Kluft C.* Plasminogen activator inhibitors. Blood 1987; 69: 381-7.
76. *Takada A, Takada Y, Urano T.* The physiological aspects of fibrinolysis. Thromb Res 1994; 76: 1-31.
77. *Zlokovic BV, Wang L, Schreiber SS.* Haemostatic functions of the blood-brain barrier: possible implications in the pathogenesis of stroke. In: *Greenwood J, Begley DJ, Segal MB*, editors. New concepts of a blood brain barrier. New York: Plenum; 1995. p. 141-5.
78. *Zlokovic BV.* Antithrombotic, procoagulant and fibrinolytic mechanisms in cerebral circulation: implications for brain injury and protection. Neurosurg Focus 1997; 2: 6-26.
79. *Strickland DK, Kessler CM.* Biochemical and functional properties of protein C and protein S. Clin Chim Acta 1987; 170: 1-23.
80. *D'Andrea G, Toldo M, Canazi A, Cortelazzo S, Ferro-Milone F.* Platelet behavior in patients with TIA: responsivness to small doses of aspirin. Eur Neurol 1985; 24: 426-32.
81. *Jovičić A.* Aktivnost trombocita u bolesnika sa ishemičnim cerebrovaskularnim poremećajima. Vojnosanit Pregl 1983; 40: 13-6.
82. *Jovicic A, Mandic S.* Circadian variation of platelet aggregability and fibrinolytic activity in healthy subjects. Thromb Res 1991; 62: 65-74.
83. *Jovicic A, Ivanisevic V, Nikolajevic R.* Circadian variation of platelet aggregability and fibrinolytic activity in patients with ischemic cerebrovascular disorders. Thromb Res 1992; 64: 487-91.
84. *van Kooten F, Ciabattoni G, Patrono C, Dippel DW, Koudstaal PJ.* Platelet activation and lipid peroxidation in patients with acute ischemic stroke. Stroke 1997; 28: 1557-63.
85. *Tohgi H, Kawashima M, Tamura K, Suzuki H.* Coagulation-fibrinolysis abnormalities in acute and chronic phases of cerebral thrombosis and embolism. Stroke 1990; 21: 1663-7.
86. *Gronholdt ML, Nordestgaard BG, Nielsen GT, Sillesen H.* Echolucent carotid artery plaque are associated with elevated levels of fasting and postprandial triglyceride-rich lipoproteins. Stroke 1996; 27: 2166-72.
87. *Napoli C, Paterno R, Faraci FM, Taguchi H, Postiglione A, Heistad DD.* Midly oxidazed low-density lipoprotein impairs responses of carotid but not basilar artery in rabbits. Stroke 1997; 28: 2266-72.
88. *Woo J, Lau E, Lam CW, Kay R, Teoh R, Wong HY,* et al. Hypertension, lipoprotein(a), and apolipoprotein A-1 as risk factors for stroke in the Chinese. Stroke 1991; 22: 203-08.
89. *Ostojić M.* Lipidi i ateroskleroza. Bilten odbora za lipide pri kardiološkoj sekciji SLD 1994; (3): 17-23.
90. *Wilt TJ, Rubins HB, Robins SJ, Riley WA, Collins D, Elam M,* et al. Carotid atherosclerosis in men with low levels of HDL cholesterol. Stroke 1997; 28: 1919-25.
91. *Tanne D, Yarri S, Goldbourt U.* High-density lipoprotein cholesterol and risk of ischemic stroke mortality. A 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. Stroke 1997; 28: 83-7.
92. *Nishida K, Markey SP.* Platelet-activating factor in brain regions after transient ischemia in gerbils. Stroke 1996; 27: 514-9.
93. *Satoh K, Imaizumi T, Yoshida H, Hiramoto M, Takamatsu S.* Increased levels of blood platelet-activating

factor (PAF) and PAF-like lipids in patients with ischemic stroke. Acta Neurol Scand 1992; 85: 122-7.

94. *Yamazaki M, Uchiyama S, Maruyama S.* Alterations of haemostatic markers in various subtypes and phases of stroke. Blood Coagul Fibrinolysis 1993; 4: 707-12.
95. *Raimondi P, Bongard O, de Moerloose P, Reber G, Waldvogel F, Bourameaux H.* D-dimer plasma concentration in various clinical conditions: implication for the use of this test in the diagnostic approach of venous thromboembolism. Thromb Res 1993; 69: 125-30.
96. *Hashemi S, Palmer DS, Aye MT, Ganz PR.* Platelet-activating factor secreted by DDAVP-treated monocytes mediates von Willerbrand factor release from endothelial cells. J Cell Physiol 1993; 154: 496-505.
97. *Mettinger KL, Nyman D, Kjellin KG, Siden A, Soderstrom CE.* Factor VIII related antigen, antithrombin III, spontaneous platelet aggregation and plasminogen activator in ischemic cerebrovascular disease: a study of stroke before 55. J Neurol Sci 1979; 41: 31-8.
98. *Feinberg WM, Erickson LP, Bruck D, Kittelson J.* Hemostatic markers in acute ischemic stroke. Association with stroke type, severity and outcome. Stroke 1996; 27: 1296-300.
99. *Lindgren A, Lindoff C, Norrving B, Astedt B, Johansson BB.* Tissue plasminogen activator and plasminogen activator inhibitor-1 in stroke patients. Stroke 1996; 27: 1066-71.
100. *Press RD, Liu XY, Beamer N, Coull BM.* Ischemic stroke in the elderly. Role of the common factor V mutation causing resistance to activated protein C. Stroke 1996; 27: 44-48.
101. *Catto AJ, Grant PJ.* Risk factors for cerebrovascular disease and the role of coagulation and fibrinolysis. Blood Coagul Fibrinolysis 1995; 6: 497-510.
102. *Wu KK, Folsom AR, Heiss G, Davis CE, Conlan MG, Barnes R.* Association of coagulation factors and inhibitors with carotid artery atherosclerosis. Early results of the Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol 1992; 2: 471-80.
103. *Uchiyama S, Yamazaki M, Hara Y, Iwata M.* Alterations of platelet, coagulation and fibrinolysis markers in patients with acute ischemic stroke. Semin Thromb Hemost 1997; 23: 535-41.
104. *Kario K, Matsuo T, Kobayashi H, Asada R, Matsuo M.* 'Silent' cerebral infarction is associated with hypercoagulability, endothelial cell damage, and high Lp(a) levels in elderly Japanese. Arterioscler Thromb Vasc Biol 1996; 16: 734-41.
105. *Franceschini G, Cofrancesco E, Safa O, Boschetti C, Tremoli E, Mussoni L,* et al. Association of lipoproteine (a) with atherothrombotic events and fibrinolytic variables. A case-control study. Thromb Res 1995; 78: : 227-38.
106. *Raičević R.* Promjene u koagulaciono-antiokoagulacionom sistemu kod bolesnika sa ishemijskom bolešću mozga [doktorska disertacija]. Beograd: Vojnomedicinska akademija 1998.

The paper was received on March 16, 1999.

Апстракт

Raičević R, Jovičić A, Mandić-Radić S, Krgović M, Magdić B, Marković Lj, Hajduković D, Jović P. Vojnosanit Pregl 1999; 56(5): 461-470.

УТИЦАЈ ИЗРАЖЕНОСТИ МОЖДАНЕ АТЕРОСКЛЕРОЗЕ НА ПРОМЈЕНЕ У ХЕМОСТАЗНОМ СИСТЕМУ КОД БОЛЕСНИКА СА ИСХЕМИЈСКОМ БОЛЕШЋУ МОЗГА И АТЕРОСКЛЕРОТСКОМ ЕНЦЕФАЛОПАТИЈОМ

Васкуларне болести мозга задржавају трећу позицију у морбидитету и морталитету поред напредовања дијагностичких, терапијских и превентивних процедура. У највећем броју случајева васкуларних обољења мозга ради се о исхемијској болести мозга, а ова представља у већини случајева завршну и најтежу фазу атеросклерозе можданих артерија. Етиопатогенеза атеросклерозе није још увијек ближе дефинисана, али се међу бројним теоријама издваја оксидациона хипотеза. У оквиру ове хипотезе централно мјесто се придаје оксидативној модификацији LDL и Lp(a) уз учешће бројних патофизиолошких чинилаца са централном улогом реактивних оксидативних материја, а гдје дисфункција ендотела представља централни поремећај одговоран за настанак бројних поремећаја, а међу њима и промјена у коагулационо-антикоагулационом систему. У складу са овим чињеницама постављена је радна хипотеза да код болесника са ИБМ постоје промјене у хемостазном систему, које су у позитивној корелацији са степеном израженості мождане атеросклерозе. Испитивањем је обухваћено 36 болесника са акутном ИБМ и 28 болесника са атеросклеротском енцефалопатијом.

Контролну групу је чинило 30 болесника са неваскуларним обољењима сличних општих карактеристика. Испитана је повезаност промјена у хемостазном систему (агрегација тромбоцита, антитромбин три, D-димер, протеин C, протеин S, фактор VII, фактор VIII, PAI-1) у односу на израженост мождане атеросклерозе (ултрасонографски) и у односу на посматране групе болесника. На основу свега и резултати овог испитивања показали су да код болесника са ИБМ постоји значајно повећање концентрације прокоагулантних фактора, а сличне промјене постоје код болесника са атеросклеротском енцефалопатијом, изражене у мањој мјери, а да су ове промјене у укупном узорку болесника, а посебно код болесника са израженом можданом атеросклерозом, примарног и хроничног карактера.

К љ у ч н е р е ч и: **mozak, arterioskleroza; ateroskleroza; mozak, veliki, ishemija; hemostaza.**