CLINICAL HEMORHEOLOGICAL INVESTIGATIONS

Zita Szikszai

Project leader: S.G. Imre, MD, PhD

Department of Immunology
Medical and Health Science Center
University of Debrecen, Hungary

2003

1. INTRODUCTION

Rheology is the science of fluids. Biorheology deals with the flow in the living organism. Hemorheology covers rheological phenomena contributing to physiological as well as pathologically affected functions of the blood and its components. Clinical hemorheological studies deal with pathological hemorheological abnormalities and aim to evaluate their links to diseases, diagnostic as well as to therapeutic approaches. This thesis covers four areas - cerebral ischemia, hemodialysis treatment, diabetes mellitus and carotis interna stenosis and occlusion - from a rheological point of view, in close collaboration with the clinicians examining and treating the patients in the studies.

1.1. Factors contributing to whole blood viscosity

Whole blood is a Non-Newtonian fluid due to the presence of cellular constituents and the interaction of plasma molecules with cells. Hematocrit, plasma viscosity, aggregation of erythrocytes and platelets, deformability of erythrocytes and leukocytes contribute largely to blood viscosity. All of these factors and their constituents can be regarded as hemorheological factors.

- hematocrit

If we consider whole blood as a suspension, hematocrit corresponds to the volume ratio of the suspended particles. The number of erythrocytes is much higher than the number of leukocytes or platelets, therefore under physiological conditions the flow in arteries is affected mainly by the red cells.

- plasma viscosity

Plasma viscosity is mainly determined by the fibrinogen level, the concentration of globulins and the lipid fraction (mostly triglyceride). The concentration of fibrinogen in plasma is relatively low, but its big size and elongated shape affect viscosity highly. Unlike whole blood, plasma is a Newtonian fluid, so measuring and interpreting its viscosity are much simpler.

- aggregation of red cells

The aggregation of erythrocytes determines the size of the suspended particles. Normally, this is a reversible process, depending on the intensity of the flow, i.e. on the forces acting upon the cells. The aggregation of red cells is attained through the interactions of erythrocytes and the large and branchy plasma molecules, fibrinogen and/or globulins.

- deformability of red cells

The normal, biconcave red cell has a surface area about 30-40% in excess of a sphere of an equal volume. This excess surface enables the cell to pass through smaller capillaries than the diameter of the cell itself. Deformability has a role not only in the microcirculation, but in the macrocirculation, too. Deformation makes the cells streamlined, which decreases the resistance to flow. Deformability depends on the geometry, hemoglobin content (inner viscosity) and the structure of the membrane (membrane microviscosity).

- deformability of leukocytes

White blood cells, due to their large size and low deformability, may be trapped in capillaries and cause disturbances in the local flow.

1.2. Rheological factors in disease

The most comprehensive hemorheological study is probably the Edinburgh Artery Study, which followed the cardiovascular events of 1600 persons for 5 years. Whole blood viscosity, hematocrit, plasma viscosity, fibrinogen level were found to be more important risk factors than smoking status, LDL and HDL levels, or systolic blood pressure. The rheological factors were more relevant in men than in women. In the same study, blood viscosity and its major determinants (hematocrit and plasma viscosity) and fibrinogen level were strongly associated with the carotis intima-media thickness (IMT) – an early marker of atherosclerosis – in men. These relationships were independent of three major traditional risk factors: total cholesterol, blood pressure and lifetime smoking history. In contrast, none of these rheological variables showed any significant association with carotid IMT in women. Another result of the Edinburgh Artery Study was that the rheological factors were associated with lower limb ischemia.

The most well-known study concerning plasma viscosity is the MONICA project. In a partial study, 964 middle aged men (45-64 years at entry) were followed for 8 years. The main outcome measure was all-cause mortality. After adjusting for age, smoking, total cholesterol, body mass index, blood pressure and education, a relative risk of 1.41 resulted for one standard deviation increase in plasma viscosity (0.07 mPas).

Polycythemia and polyglobulia are risk factors of stroke, but according to the Framingham study, the upper normal zone of hemoglobin level is also associated with higher risk for cerebral ischemia. A Japanese team examined the pathological material of 432 patients and they found that the cerebral infarction was more prevalent above the hematocrit value of 0.46. German researchers studied the rheological parameters of 523 stroke patients after the period of the acute phase reaction. Patients who suffered

another stroke within two years had higher blood, plasma and serum viscosity, fibrinogen and cholesterol level and more pronounced aggregation of erythrocytes.

In end stage renal failure, cardiovascular diseases are the most frequent causes of death. Atherosclerosis is accelerated in these patients. High blood pressure, hyperuricemia, high parathyroide hormone level (calcium accumulation in the blood vessels), hyperlipidemia are all contributing factors to cardiovascular diseases. Dialysis treatment itself may have deteriorating effect, especially in the case of less biocompatible membranes and solutions. Due to the anemia, blood viscosity is usually not increased in these patients. The deformability of erythrocytes, which is very important in microcirculation, is a more interesting parameter.

The quality of life and the life expectancy of patients suffering in diabetes mellitus are largely affected by angiopathy. The Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes Study have proved the role of normoglycemia in preventing diabetic angiopathy. Nevertheless, many other factors contribute to the development of angiopathy, such as oxidative stress, endothelium injury, increased platelet aggregation and rheological abnormalities. Although a good deal of data has been collected about diabetic angiopathy, we cannot conclude that every detail is clear. It is usually accepted that there are various rheological impairments in diabetes, but there is no consensus about which factors are affected. Results relating to angiopathy are also controversial.

1.3. Aims of the investigations

Our purpose was to answer the following questions:

❖ Is there any difference between the rheological parameters of ischemic stroke and transient ischemic attack (TIA) patients and those of control subjects? Is there any difference in erythrocyte lipid peroxidation? Does the autooxidative test (incubation under air at 37 °C in a pH 7.4 buffer) provide further information about the oxidative process in red cells?

❖ We wished to determine the deformability and lipid peroxidation of erythrocytes in patients with end stage renal failure, undergoing hemodialysis (HD) treatment. Is there any change during HD? Can we find any relationship between erythrocyte deformability, lipid peroxidaton and the other data available about the patients?

❖ Our purpose was to assess the rheological parameters, erythrocyte and plasma lipid peroxidation in patients with type 1 and 2 diabetes mellitus (DM). Is there any difference between the two types of diabetes in these parameters? How does angiopathy affect these factors?

❖ We aimed to investigate the rheological profile and erythrocyte lipid peroxidation of patients with internal carotis artery stenosis and occlusion compared to controls with no plaques or stenosis on the carotis arteries under the age of 55 years.

2. SUBJECTS AND METHODS

Blood samples were collected into ethylenediaminetetracetic acid (EDTA) vacuum tubes (1.5 mg/ml blood), and rheological measurements were completed within 4 hours after venipuncture.

Plasma viscosity

Plasma was separated by centrifugation and plasma viscosity was measured with a microviscosimeter (Haake, Germany) at 37 °C and expressed in mPas.

Erythrocyte deformability

Erythrocyte deformability was determined by filtering erythrocyte suspension through a Nuclepore® Polycarbonate filter of 5 μm pore size (Whatman Inc., NJ, USA), using a St. George type filtrometer (Carat Diagnostics, Hungary). The erythrocyte suspension was diluted in PBS buffer to obtain a hematocrit of 5%. Filtration results were expressed as relative cell transit time (RCTT).

Erythrocyte lipid peroxidation

LP in erythrocytes was measured with the thiobarbituric acid color reaction. The assay was performed under the optimum conditions for reproducibility as defined by Stocks and Dormandy, measuring the difference in absorption between 532 and 600 nm as the basis for calculating MDA concentrations, but without exposure to hydrogen peroxide. Results were expressed as nanomoles of MDA per gram hemoglobin.

2.1. Ischemic stroke, TIA

We screened patients admitted for acute cerebral ischemia. Patients were classified as having TIA (n = 31) or acute ischemic stroke (n = 33) based on the duration of symptoms and the complete clinical and laboratory assessment of ischemic event. The control group consisted of 33 patients (nonvascular neurological inpatients).

Venous blood was drawn from patients after an overnight fast and within 72 hours of the onset of cerebral ischemic symptoms. The sample was drawn prior to the administration of any medication that might interfere with laboratory parameters. Exclusion criteria consisted of recent (< 1 month) myocardial infarction, clinically detectable infection, malignancy, renal failure or deep venous thrombosis. All patients had head computed tomography (CT) scans; patients with intracerebral hemorrhage or tumor were excluded from the study.

Plasma viscosity, erythrocyte deformability and lipid peroxidation were measured as mentioned above. Lipid peroxidation was assessed not only in the fresh sample (LP_0), but after 24h incubation under air at 37 °C in a shaking water bath (LP_{24}), too (autooxidative test). Lipid peroxidation capacity (LPC) was calculated as follows: $LPC = LP_{24} - LP_0$

Hematocrit and hemoglobin values, platelet and leukocyte count, total protein, albumin and fibrinogen content, ESR, cholesterol and triglyceride levels were obtained using standard laboratory methods. The globulin concentration and the albumin:globulin (A/G) ratio was calculated from the total protein content, albumin and fibrinogen values using the following formulas:

Globulin = total protein content minus albumin and fibrinogen value,

A/G ratio = albumin divided by globulin value.

2.2. Hemodialysis

Forty-five patients (20 females, 25 males) aged between 18 and 77 (mean ± SD 55 ± 15) years undergoing HD and 30 healthy volunteers (13 females, 17 males) aged between 22 and 77 (54 ± 13) years participated in the study. Patients had been on dialysis for 4-179 (32 ± 33) months. HD was carried out for 3.5 h 3 times a week, with polysulfone membranes. Renal failure was attributed to chronic glomerulonephritis, polycystic kidney disease, nephroangiosclerosis, nephrocalcinosis and interstitial nephritis. Diabetic patients and patients with clinical symptoms of blood loss were not included.

2.3. Diabetes mellitus

Twenty-seven type 1 diabetic patients (7 females, 20 males) aged 36 ± 14 years, twenty-seven type 2 diabetic patients (18 females, 9 males) aged 56 ± 10 years and 23 healthy volunteers (11 females, 12 males) aged 35 ± 15 years participated in the study.

Plasma viscosity, erythrocyte deformability and lipid peroxidation were measured as mentioned above.

Plasma lipid peroxidation was determined by measuring the total antioxidant status (TAS), which is the inverse of the lipid peroxidation. We used a kit manufactured by the Randox Laboratories Ltd. (UK).

Endothelium injury was assessed by measuring the serum level of the von Willebrand factor (ELISA method).

Fibrinogen was measured within the routine hemostasis laboratory assessments.

2.4. Carotis stenosis and occlusio

Patients were recruited at the Neurosonological Laboratory of the Department of Neurology, University of Debrecen. The upper age limit was set at 55 years. Those with an at least 30% internal carotid artery stenosis at screening were included in the study. An age- and gender matched control group without arteriosclerotic disease and without any severe organic disease was recruited from outpatients or from the inpatient wards of the Department of Neurology, University of Debrecen. These controls – like the patients with occlusive carotid disease – could have been smokers, could have had hypertension or well controlled diabetes, i.e. we did not want to compare the patients to an absolutely healthy control group without any risk factors for atherosclerosis. Instead, we attempted to use a control group that resembles the patient group as much as possible, except for the presence of an occlusive carotid artery disease. Most of these controls were treated primarily for tension-type headache, anxiety disorder or low back pain. Ultrasound examinations were performed immediately after blood sampling using a color-coded HP SONOS 2000 (Hewlett Packard) carotid duplex equipment with a 7.5 MHz linear transducer.

Statistical analysis

Data are presented as mean ± SD. Normality of continuous variables was checked by the Saphiro-Wilk test. The unpaired and paired t tests were used for comparison between controls and HD patients and between before and after HD, respectively. When more than two groups were compared, one-way ANOVA was performed. Two-way ANOVA was used to control for smoking in group comparisons in the carotis atherosclerosis study. Pearson's r correlation coefficient was used to determine the relationship between variables.

3. RESULTS

3.1. Ischemic stroke, TIA

	Kontroll	TIA	Stroke
Hematocrit	0.42 ± 0.04	0.41 ± 0.04	0.43 ± 0.04
Hemoglobin (g/l)	140 ± 14	138 ± 12	142 ± 13
Thrombocytes (G/l)	200 ± 63	257 ± 111[*]	275 ± 88[**]
Leukocytes (G/l)	5.90 ± 1.64	6.43 ± 1.59	8.26 ± 2.56[***††]
Fibrinogen (g/l)	3.1 ± 0.7	3.5 ± 1.1	5.4 ± 3.2[***††]
Total protein (g/l)	70.4 ± 4.7	66.9 ± 6.4	70.0 ± 6.2
Albumin (g/l)	44.4 ± 4.1	43.3 ± 5.4	42.0 ± 4.8
Globulin (g/l)	23.1 ± 5.8	19.1 ± 7.1	21.6 ± 5.8
A/G ratio[a]	2.1 ± 0.7	2.6 ± 0.12	2.1 ± 0.8
Cholesterol (mmol/l)	6.16 ± 1.36	6.11 ± 0.85	6.07 ± 1.22
Triglyceride (mmol/l)	1.79 ± 1.16	1.75 ± 0.62	1.70 ± 0.74
ESR (mm/h)	13 ± 9	18 ± 15	24 ± 19[**]
Plasma viscosity (mPas)	1.30 ± 0.06	1.31 ± 0.07	1.36 ± 0.08[**†]
Erythrocyte RCTT	6.55 ± 0.67	6.92 ± 0.85	7.18 ± 0.75[**]

[*]$p < 0.05$ [**]$p < 0.01$ [***]$p < 0.001$ versus control
[†]$p < 0.05$ [††]$p < 0.01$ [***]$p < 0,001$ versus TIA
[a]Calculated

There was no significant difference among the study groups in measured levels of hematocrit and hemoglobin values, albumin, total protein and globulin content, A/G ratio, cholesterol and triglyceride levels. Platelet number, ESR and erythrocyte RCTT were elevated in stroke patients as compared to control subjects ($p < 0.01$). The platelet count was the only value that was elevated in TIA patients ($p < 0.05$). The fibrinogen level,

leukocyte count and plasma viscosity of stroke patients were significantly higher not only vs. control, but also vs. the TIA group.

Plasma viscosity positively correlated with the triglyceride level in controls ($r = 0.514$, $p < 0.01$). In TIA, plasma viscosity positively correlated with the fibrinogen level ($r = 0.422$, $p < 0.05$), total protein concentration ($r = 0.476$, $p < 0.01$) and ESR value ($r = 0.507$, $p < 0.01$). In stroke patients, plasma viscosity positively correlated with the globulin concentration ($r = 0.543$, $p < 0.01$) and ESR value ($r = 0.462$, $p < 0.01$). There was no significant correlation with erythrocyte deformability or the other parameters in any of the groups.

Lipid peroxidation:

	Control	TIA	Stroke
Erythrocyte LP_0 (nmol MDA/g Hb)	2.2 ± 2.6	3.1 ± 2.7	4.3 ± 3.3[*]
Erythrocyte LP_{24} (nmol MDA/g Hb)	3.7 ± 2.7	5.0 ± 2.6	6.3 ± 3.3[**]
Erythrocyte LPC (nmol MDA/g Hb)	1.4 ± 1.2	1.9 ± 1.0	2.1 ± 1.4

[*]$p < 0.05$ [**]$p < 0.01$ versus control

Lipid peroxidation was elevated in the erythrocytes of stroke patients compared to control. This difference was even more marked after the autooxidation test as the higher level of significance shows, but the difference after the autooxidative test was mainly due to the original differences. We conclude that the auotooxidative test does not provide further useful information. The values in TIA were higher than in controls, but the difference did not reach the level of significance.

3.2. Hemodialysis

The deformability and LP of erythrocytes in uremic patients were impaired in comparison to controls before and after HD. After HD no significant difference was noted in the mean value of patients. Before HD the MDA content of erythrocytes was found to be highly increased in patients compared to the healthy subjects. There was no significant decrease after HD. No correlation between MDA and RCTT was found.

	Control n = 30	Before HD n = 45	p control – before HD	After HD n = 45	p before HD – after HD
RCTT	6.47 ± 0.64	7.01 ± 0.78	< 0.01	7.04 ± 0.65	*NS*
LP	1.7 ± 1.8	4.5 ± 2.5	< 0.001	4.0 ± 2.4	*NS*
(nmol MDA/g Hb)					

We found a weak negative correlation between RCTT and the dosage of EPO ($r = -0.29$, $p < 0.05$) as well as between RCTT and the daily amount of urine ($r = -0.29$, $p < 0.05$). The RCTT values of patients were divided into groups according to the dosage of EPO and the amount of urine. Patients receiving at least 4000 IU/week EPO had significantly better deformable erythrocytes ($p < 0.05$) than patients receiving less or no EPO. This demonstrates indirectly the beneficial effect of EPO on erythrocyte deformability. Erythrocytes in patients with urine at least 450 ml/day also showed better deformability than in patients with less or no urine ($p < 0.01$). This indicates the importance of residual renal function. Iron status, mean corpuscular hemoglobin concentration and mean cell volume were not different in the four groups, so they cannot be responsible for the

differences in deformability. Although polycystic patients (n = 5) had lower RCTT values than other patients (6.33 ± 0.74), this did not affect the results concerning EPO and urine groups because they represented only a small proportion of patients and they were distributed evenly among the four groups. We found a weak positive correlation between RCTT and parathormone (PTH) level (r = 0.29, p < 0.05). The correlation between RCTT and PTH was stronger in patients with higher PTH. In patients with PTH < 12.2 pmol/l (sample median), there was no correlation, whereas in patients with PTH > 12.2 pmol/l, a positive correlation of r = 0.54, p < 0.01 was observed.

3.3 Diabetes mellitus

Results are presented in the following table:

	Control	Type 1 DM	Type 2 DM
Plasma viscosity (mPas)	1.27 ± 0.06	1.28 ± 0.09	1.32 ± 0.10
Fibrinogen (g/l)	2.5 ± 0.9	3.1 ± 1.2	3.6 ± 1.9
Von Willebrand factor (U/l)	0.75 ± 0.32	1.04 ± 0.58	1.24 ± 0.71[*]
Erythrocyte RCTT	6.55 ± 0.67	7.36 ± 0.80[**]	7.00 ± 0.79[**]
Erythrocyte LP (nmol MDA/g Hb)	1.9 ± 1.2	3.4 ± 1.9[*]	4.0 ± 1.7[**]
Total Antioxidant Status (mmol/l)	1.22 ± 0.28	0.74 ± 0.20[***]	0.83 ± 0.27[***]
HgbA1c (%)	5.2 ± 0.2	8.9 ± 2.7[***]	9.3 ± 2.4[***]

[*]p < 0.05   [**]p < 0.01   [***]p < 0.001 versus control

Plasma viscosity was similar across the groups. The elevation of the fibrinogen concentration in type 2 DM was close to the significance level ($p = 0.06$). The concentration of von Willebrand factor was slightly elevated in type 2 DM.

Plasma viscosity positively correlated with the duration of the disease in type 1 DM ($r = 0.445$; $p < 0.05$). In type 2 DM, plasma viscosity positively correlated with the percentage of HgA1c ($r = 0.410$; $p < 0.05$), and with the fibrinogen level ($r = 0.499$; $p < 0.05$). In type 2 DM, we also found a positive relationship between the concentrations of fibrinogen and von Willebrand factor ($r = 0.626$; $p < 0.01$).

Erythrocyte deformability was reduced in both patients groups compared to controls. Erythrocyte lipid peroxidation was increased in diabetic patients. Serum TAS level was decreased (i.e. plasma lipid peroxidation was increased) compared to controls. TAS correlated negatively with HgbA1c in type 1 DM ($r = -0.630$; $p < 0.05$), and the duration of the disease in type 2 DM ($r = -0.641$; $p < 0.05$).

The analysis by the severity of angiopathy was performed in the two diabetic groups together since there was no difference between the groups in our study.

Although there was no difference between the mean value of patients and controls regarding plasma viscosity, we found high plasma viscosity in macroalbuminuria (1.45 ± 0.10 mPas). In macroalbuminuria, fibrinogen level was also highly elevated (5.1 ± 2.2 g/l). The difference was significant compared to microalbumiuria, too.

We also found high plasma viscosity in prolipherative retinopathy (1.45 ± 0.10 mPas). This value was significantly different not only from the control values but versus retinopathy, too.

In diabetic foot syndrome, fibrinogen level was higher compared to patients without this state (3.9 ± 0.4 g/l).

3.4. Carotis stenosis and occlusio

Rheological and erythrocyte lipid peroxidation data are presented in the following table:

	Control	Stenosis	Occlusio
Fibrinogen (g/l)	3.4 ± 0.8	4.2 ± 0.9[**]	4.1 ± 1.2[*]
Plasma viscosity (mPas)	1.36 ± 0.09	1.37 ± 0.09	1.37 ± 0.07
Erythrocyte RCTT	8.13 ± 1.44	8.43 ± 1.27	7.79 ± 1.14
Erythrocyte LP (nmol MDA/g Hb)	3.3 ± 1.7	3.5 ± 2.2	3.5 ± 1.7

[*]$p < 0.05$ [**]$p < 0.01$ versus control

There was no significant difference among the groups in plasma viscosity, erythrocyte deformability and lipid peroxidation.

Fibrinogen was elevated in the patients groups. Smokers had higher fibrinogen level than nonsmokers (4.2 ± 2.1 ill. 3.4 ± 0.8 g/l). As more patients than controls were smokers ($p < 0.001$), patient smoking status had to be controlled for in data analysis. The difference in fibrinogen between groups was entirely due to the effect of smoking on the basis of the 2-way ANOVA (group effect: $p = 0.41$; smoking effect: $p = 0.0098$).

4. SUMMARY AND CONCLUSIONS

Tissue perfusion depends on the perfusion pressure, the diameter of the vessel and the viscosity of blood. Microcirculatory failure may thus result from inadequate perfusion pressure, vessel narrowing or reduced blood fluidity. Whatever the pathophysiology, the net effect of reduction or cessation of tissue perfusion is ischemia or infarction. However, the clinical presentation may be a pointer to the basic pathology. The oxygen transport system is a complex multi-linkage chain and it is only as strong as its weakest link. On this basis, hemorheology has been increasingly gaining interest in a number of disease states.

The aim of the present work was to evaluate the hemorheological profile of patients in four clinical studies. Plasma viscosity and red cell deformability, as well as red cell lipid peroxidation to consider oxidative stress, were measured in addition to standard blood parameters of rheological interest. Results were interpreted in the frame of complex clinical and laboratory assessments.

In comparison with controls, fibrinogen content, erythrocyte sedimentation rate, platelet and leukocyte count, erythrocyte filtration transit time (RCTT) and lipid peroxidation (LP), as well as plasma viscosity were significantly higher in ischemic stroke patients. In transient ischemic attack (TIA), the elevation of these values was not significant with the exception of platelet count. Our results suggest that the hemorheological alterations observed in TIA and stroke are largely non-specific findings and associated with the atherosclerotic disease of patients. The significant elevation of leukocytes, fibrinogen and plasma viscosity in acute stroke versus TIA probably reflects the systemic acute phase response of organism to cerebral infarction.

In uremic patients on hemodialysis (HD), RCTT and LP were significantly higher before and after HD compared to controls. The mean values of results suggest that HD does not affect erythrocyte injury. Nevertheless, the individual modifications of RCTT and LP during dialysis

were found noteworthy. Residual renal function and erythropoietin treatment seemed to be beneficial on red cell deformability.

We found increased erythrocyte LP and decreased serum total antioxidant status, as well as reduced red cell deformability in both type 1 and type 2 diabetic patients compared to healthy subjects. Patients with severe diabetic angiopathy had additional rheological impairments (elevated fibrinogen level and/or plasma viscosity).

Rheological factors were much the same across the groups (carotid stenosis, occlusion, control subjects with no plaques or stenosis of the carotid arteries) in the study of early-onset carotid atherosclerosis; therefore we conclude that these factors probably do not have a major role in the early formation of carotid atherosclerosis.

PUBLICATIONS OF THE AUTHOR

I. Szikszai Z, Fekete I, Imre SG. A comparative study of hemorheological parameters in transient ischemic attack: Possible predictive value. Clin Hemorheol Microcirc 2003;28(1):51-7   IF: 0,297

II. Szikszai Z, Ujhelyi L, Imre SG. Effect of hemodialysis on the deformability and lipid peroxidation of erythrocytes in chronic renal failure. Clin Hemorheol Microcirc, accepted for publication.   IF: 0,297

III. Káplár M, Paragh Gy, Szikszai Z, Imre S, Huszka M, Udvardy M. Haemorheologiai tényezők változása diabetes mellitusban, szerepük az angiopathia kialakulásában. Metabolizmus, accepted for publication.
(in Hungarian)

IV. Magyar MT, Szikszai Z, Balla J, Valikovics A, Kappelmayer J, Imre S, Balla G, Jeney V, Csiba L, Bereczki D. Early-onset carotid atherosclerosis is associated with increased intima-media thickness and elevated serum levels of inflammatory markers. Stroke 2003;34(1):58-63   IF: 5,33

PUBLISHED ABSTRACTS

1. Imre SG, Szikszai Z, Fekete I. Comparative study of hemorheological parameters in TIA and ischemic stroke. Perfusion 2000;13:362
   III. International Symposium on Myocardial Cytoprotection, Pécs, Hungary, 2000

2. Imre SG, Szikszai Z, Farkas T, Fekete I. Deformability and lipid metabolism in red blood cells of cerebrovascular patients. Biorheology 1999;36(1-2):50
   10th International Congress of Biorheology and 3rd International Conference of Clinical Hemorheology, Pécs, Hungary, 1999

3. Szikszai Z, Imre SG, Kappelmayer J, Huszka M, Káplár M, Szabó K, Udvardy M: Leukocyte-platelet adhesion, endothelium derived relaxing factor-NO production, deformability of red blood cells and the antioxidant system in patients with diabetes mellitus. Biorheology 1999;36(1-2):50
   10th International Congress of Biorheology and 3rd International Conference of Clinical Hemorheology, Pécs, Hungary, 1999

4. Fekete I, Imre SG, Szikszai Z, Telek B, Mikita J, Magyar T, Valikovics A, Bereczki D. Hemorheology and Cerebral Blood Flow Velocity (CBFV) in patients with ischemic stroke and essential thrombocytemia. Cerebrovasc Dis 1998;8(4):CLI48
   7th European Stroke Conference, Edinburgh, UK, 1998

5. Szikszai Z, Imre SG, Ujhelyi L. Lipid peroxidation and deformability of erythrocytes in hemodialysed patients. Pathophysiology 1998;5(1):59
   III. International Congress of Pathophysiology, Lahti, Finland, 1998

6. Imre SG, Szikszai Z, Fekete I. Free radical reactions in erythrocytes of stroke patients. Pathophysiology 1998;5(1):84
   III. International Congress of Pathophysiology, Lahti, Finland, 1998

7. Imre S, Szikszai Z, Fekete I. Cerebrovaszkuláris betegek hemorheologiai változásainak új értelmezése. Magyar Belorvosi Archivum 1997;50(1)34
(In Hungarian)
XVI. Congress of the Hungarian Society of Hematology and Transfusion, Szeged, Hungary, 1997

8. Szikszai Z, Imre S, Ujhelyi L. Vörösvérsejtek deformálhatósága és lipid-peroxidációja hemodializált betegekben. Magyar Belorvosi Archivum 1997;50(1)52 *(In Hungarian)*
XVI. Congress of the Hungarian Society of Hematology and Transfusion, Szeged, Hungary, 1997

9. Imre SG, Szikszai Z, Fekete I. Relationship between erythrocyte lipid peroxidation capacity and deformability in vascular patients. Boletim da Sociedade Portuguesa de Hemorreologia e Microcirculação 1997;12(1):111
10th European Conference on Clinical Haemorheology, Lisbon, Portugal, 1997

10.Dörp E, Holdt B, Korten G, Knuth A, Hickstein H, Szikszai Z, Imre S. Hemorheology in relation to hemodialysis. Boletim da Sociedade Portuguesa de Hemorreologia e Microcirculação 1997;12(1):161
10th European Conference on Clinical Haemorheology, Lisbon, Portugal, 1997

11.Szikszai Z, Imre SG, Ujhelyi L, Dörp E, Holdt B, Korten G, Knuth E, Hickstein H. Deformability and lipid peroxidation in hemodialysed patients. Boletim da Sociedade Portuguesa de Hemorreologia e Microcirculação 1997;12(1):111
10th European Conference on Clinical Haemorheology, Lisbon, Portugal, 1997