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PARTICULARITIES OF THE CELLULAR HEMOSTASIS AND PERIPHERAL BLOOD - VESSEL FUNCTION IN WOMEN WITH MIGRAINE

Summary of the Doctoral Dissertation

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MIGRENA SERGANČIŲ MOTERŲ LĄSTELINĖS HEMOSTAZĖS IR PERIFERINIŲ KRAUJAGYSLIŲ FUNKCIJOS YPATUMAI

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ABBREVIATIONS

ABP	arterial blood pressure
AIx	augmentation index
AIx/HR	adjusted augmentation index
BMI	body mass index
BZ	biological zero
CHD	coronary heart disease
CRP	C reactive protein
CVD	cardiovascular diseases
FID	Flow induced dilation
FRHI	Framingham reactive hyperaemia index
GP	glycoprotein
HDL	high density lipoprotein cholesterol
hs-CRB	high sensivity C reactive protein
LDL	low density lipoprotein cholesterol
M0	migraine without aura
MA	migraine with aura
PAC-1	glycoprotein complex IIb/IIIa antibody (platelet activation complex-1)
PAT	peripheral arterial tonometry
PF	peak flow
PORH	post occlusive reactive hyperaemia
PWV	pulse wave velocity
RF	rest flow
RHI	reactive hyperaemia index
SAA	serum amyloid A
SPSS	statistic analysis program
T. Chol.	total cholesterol
TG	triglycerides

1. INTRODUCTION

Migraine is a chronic disorder characterized by recurrent headaches, usually unilateral, as often as not followed by nausea and increased sensitivity to sound and light. Based on the data of epidemiologic studies its prevalence rate per the whole population is approximately 10-20 percent. This disorder is 3 to 4 times more common in women than in men. People of 25-55 years are most likely to suffer from migraine. Only approximately 10 percent of all people with migraine are able to work, study and do the chores during the migraine attack.

The first publication on possible relation between stroke and migraine came out as early as 1881. In the studies that followed the hypotheses that migraine, especially MA, is related with a 2-3 times greater risk of ischaemic stroke, which is extremely high among young women. It induced the further research on relation between these disorders. The results showed that people with migraine are more likely to be subject to cardiovascular risk factors (high arterial blood pressure, higher concentration of cholesterol, more frequent smoking, etc.). Also, during the attack the changes in blood circulation were detected. Thus, the blood-vessel dysfunction theory was formed that includes not only local changes in the brain arteries but also in other blood - vessels.

Recent studies proved that people with MA are subject to higher risk of both ischaemic stroke and other ischaemic - blood vessel complications (including coronary heart disease). This risk is believed to be determined by the particularities of the pathogenesis of the aura. MA is likely to be related with systemic damage, even with perivascular inflammation. This might stimulate the emission of biologically active agents and platelet aggregation (both during the attacks and between them), as well as formation of microthrombi. Furthermore, secondary activation of coagulation system may additionally induce the ischaemic blood vessel events in different areas. Therefore, by carrying out this research we were seeking to determine more specific and sensitive markers of inflammatory response, their relation not only with MA or M0, but also with the functional activity of platelets and functionality and stiffness of endothelium of blood - vessels of different diameter. The results might help not only to explain the higher risk

of cardiovascular diseases among people with migraine, but it would also allow to identify patients with higher risk and apply appropriate preventive measures.

The Goal of the Research

To determine the connection of migraine with and without aura (in women) not only with common cardiovascular risk factors, but also with particularity of inflammatory markers, particularities of cellular hemostasis and changes in functionality and stiffness of endothelium of peripheral blood vessels of various diameter during period between the attacks.

Objectives of the Research

1. To evaluate the rate of risk factors of common cardiovascular diseases in women with migraine and their relation with different types of migraine attacks.
2. To determine the particularities of inflammatory indicators (C reactive protein and serum amyloid A) and their relations with the types of migraine attacks, as well as with changes in functional activity of platelets.
3. To evaluate the influence of migraine on platelet aggregation, platelet degranulation reaction and formation of platelet - monocyte aggregates during the period between attacks.
4. To evaluate the influence of different clinical types of migraine on functional activity of platelets.
5. To evaluate the influence of migraine attacks, their frequency and intensity platelet aggregation function, platelet degranulation reaction and formation of platelet - monocyte aggregates, as well as their relation with different clinical types of migraine.
6. To determine the changes in stiffness and endothelial function of peripheral blood - vessels of various diameter in patients with migraine during the period between attacks.
7. To determine the influence of the risk factors of common cardiovascular diseases and different clinical types of migraine on stiffness and endothelial function of peripheral blood - vessels.

8. To determine the correlative relation of platelet aggregation, degranulation, formation of platelet - monocyte aggregates with functional and anatomic changes in peripheral blood - vessels in patients with migraine.
9. To evaluate the influence of migraine aura on correlative relation of platelet function activity with changes in stiffness and endothelial function of peripheral blood - vessels of different sizes.

Novelty of the Research

Functional activity of platelets (platelet aggregation function, degranulation phase and formation of platelet - monocyte aggregates) in women with migraine was evaluated during the period between attacks using the new flow cytometry method that is almost not influenced by external factors. Also, the relation between these changes and other traditional risk factors of atherosclerosis, including indicators of the significance of the inflammatory process, was determined. Furthermore, not only the influence of different clinical types of migraine (i.e. migraine with and without aura) on cellular hemostasis and inflammatory indicators was analyzed but also the particularities of these inflammatory markers. For the first time women with migraine (with and without aura) were examined using non-invasive methodologies of blood - vessel analysis (endothelium reliant flow-induced dilation, laser dopplerography, peripheral arterial tonometry, measurement of blood - vessel stiffness using the method of aplanation tonometry). A comprehensive evaluation of functional and anatomic changes in blood-vessels was performed and correlative relations of these changes with inflammatory indicators and changes in platelet functional activity were determined.

2. PARTICIPANTS AND METHODS OF THE RESEARCH

The research was carried out in 2006-2010 in Vilnius University Hospital Santariskes Clinics (VUL SK). In order to perform the research the Permission No. 5/026 of Bioethics Committee of Lithuania was obtained.

Selection of Participants and Formation of Groups

60 women of middle age (from 25 years to menopause) diagnosed with migraine in Neurology Clinic of Vilnius University Hospital Santariskiu Clinics based on International Headache Society classification criteria of 2004 participated in the research. Based on their diagnosis they were divided into two groups: 30 women diagnosed with migraine with aura (MA) and 30 women diagnosed with migraine without aura (M0). Control group consisted of 60 healthy women who agreed to participate voluntarily. Persons with the following features were not involved in the research: women who had or had had diabetes, angina pectoris, myocardial infarction, cerebral infarction, transient ischemic attack, pregnant women, as well as those who were using anticoagulants and antiaggregants. Women were examined not at least in 5 days after the latest migraine attack, in the middle of menstruation cycle, at 8-10 AM; patients were fasting, before morning cigarette and coffee Furthermore, a week before the exam they were not allowed to take medication influencing functional activity of platelets, such as non-steroidal anti-inflammatory drugs, various analgesics, triptanes. In order to carry out the research the Permission of Regional Ethics Committee was obtained, also, all the participants signed the Informed Consent Form.

Course of the Research

Anamnesis data on migraine, CVD risk factors, other diseases and medications used were gathered by interviewing the women. Height, body mass, arterial blood pressure of the participants was measured and samples of venous blood were taken in order to perform biochemical and flow cytometry analysis. During the same visit examinations of endothelium of peripheral blood - vessels and arterial stiffness were performed on the patients.

Methodology of the Research

Traditional Risk Factors of Cardiovascular Diseases and Anthropometric Data

Information about traditional cardiovascular risk factors (arterial hypertension, dyslipidemia, cigarette smoking, physical inactivity, overweight or obesity, family history of premature coronary heart disease (CHD) and Framingham risk scores) and use of antihypertensive medications was evaluated. Mean value of two measurements of blood pressure was recorded. Arterial hypertension was considered then systolic blood pressure (ABP) > 140 mm Hg and diastolic ABP > 90 mm Hg or

history of use of antihypertensive medications was present. Fasting blood lipids (total cholesterol (T. Chol), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and triglycerides (TG)) were evaluated by commercially available kits. Results of blood lipids were categorized into two groups: normal or elevated/low. Current cigarette smoking was defined as any cigarette smoking in the past month.

Physically active person was considered as having activity longer than 30 minutes more than 3 times per week. Height and weight were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Overweight was defined when BMI was > 25-29.9 kg/m. The family history was considered positive for premature CHD if history of clinical CHD or sudden death was positive in first degree male relatives younger than 55 years of age and in first degree female relatives younger than 65 years of age.

In order to evaluate cardiovascular risk of all the participants the ATP III (Adult Treatment Panel II) Framingham risk score recommended by NCEP (*National Cholesterol Education Program),* which helps to estimate a 10 year risk of myocardial infarction and coronary death, was used. Indicators assessed were the following: age, gender, total cholesterol and HDL, systolic ABP (average mean of at least 2 measurements), smoking (current cigarette smoking was defined as any cigarette smoking in the past month), use of antihypertensive medications. Each indicator was evaluated in points that later were converted into risk percentage. Risk can be calculated by using tables or electronic calculation that provides more exact calculations. There are 3 risk categories: less than 10 %, 10-20 % and more than 20 %.

Migraine characteristics (duration of the disease, frequency of attacks, count of days with headache during the last 3 months, average intensity of pain (from 1 to 10 points) during the last 3 months information of the abortive and prophylactic treatment) was collected.

Inflammatory Markers Determination Methodology: C Reactive Protein and Serum Amyloid A

Using standard high-sensitivity methodology C reactive protein (CRP) and serum amyloid A (SAA) in blood were analyzed in the Centre of Laboratory Diagnostics

of VUL SK. CRP was analyzed using the Architect analyzer (Abbott, US), while SAA was analyzed using the BNII analyzer (Dade Behring).

Evaluation of Functional Activity of Platelets Using the Flow Cytometry Method

The functional activity of platelets was determined by the flow cytometry method, using the three-color/three - antibody technique on the FACSCanto machine (BD, US), in unstimulated blood complying with the recommendations for the analysis. Data was analyzed using the BD FACSDiVa software (version 6.1.2).

In order to identify the platelets three antibodies were used: CD42a (GP IX), CD41a (GP IIb) and CD61 (GP IIIa), while in order to evaluate the activity the following antibodies were chosen: PAC-1(*platelet activation complex*) - specifically binding activated GP IIb/IIIa complex (in order to evaluate the aggregation phase) and CD62 - specifically binding with the antigen CD63 (integral membrane protein produced in the lysosomes) expressed on the surface of platelets (in order to evaluate the degranulation phase). The findings were expressed by absolute numbers of cases (how many platelets analyzed had an expressed marker), percentage (evaluating the part of the population with the marker) and average fluorescence intensity (AFI) (the intensity of glow of the platelet population expressing the marker analyzed).

Platelet - monocyte aggregates were found in monocyte population detecting both markers: that of platelets CD42a and monocytes CD14; both percentage of events and an absolute number of events were calculated within the monocyte population.

Non-invasive Analysis of Endothelial Function

The examination of blood - vessel walls was performed in the Department of Preventive Cardiology during morning hours in a room were a stable temperature of 22 ^{o}C was maintained by the same experienced cardiologist who had not been informed about the real diagnosis. Patients were fasting, before morning cigarette, without having had alcohol and coffee for at least 12 hours before the examination and at least 5 days after the latest migraine attack. The examination starts after the woman has been laying in rest for 10–15 minutes.

Ultrasound Endothelial Function Examination in the Brachial Artery: Endothelium dependent Flow induced Dilation

The examination was performed using the ultrasound device (Prosound α-10, Aloka) with 12 MHz frequency electronic linear transmitter. In order to produce flow induced dilation (FID) the cuff of a sphygmomanometer is placed on the middle-proximal third of the forearm (the standard blood pressure measurement cuff for adults was used) which is quickly inflated to 100 mmHg more than the previously measured systolic pressure, then it is suddenly released. The diameter of the brachium at rest and after being fastened for 5 minutes with blood pressure measurement cuff is evaluated. FID is calculated automatically using the software (changes in diameter of the artery during the hyperaemial flow induced dilation are compared to the reference measurement at rest and are expressed in percentage from artery diameter at rest (equaled to 100 percent). FID percentage calculated using this method is a value determining the endothelial function.

Laser dopplerography

Endothelial function in the microcirculation (capillaries, arterioles, venules and shunts) is evaluated using the laser Doppler. PeriFlux System 5000 (Perimed, Sweden) is used. The transmitter of the laser Doppler is placed on the dorsal surface of the middle phalanx of a finger of the non-dominant hand. Post-occlusion reactive hyperemia is registered as change of perfusion at rest as compared to the perfusion after being fastened for 5 minutes with blood pressure measurement cuff 100 mmHg more than the systolic ABP. Peripheral perfusion is expressed in perfusion units (PU) and is calculated using the following formula:

$$\text{Perfusion} = \begin{array}{c}\text{Concentration of}\\ \text{moving blood cells}\end{array} \times \begin{array}{c}\text{Average blood cell}\\ \text{movement speed}\end{array}$$

There are various parameters of microcirculation changes and the most important ones are the following: Rest flow (RF); Biological zero (BZ) - perfusion that is determined when fastening with a cuff; Peak Flow (PF) - highest measured perfusion after releasing the cuff; Time To RF - time needed to restore the rest flow; Time To PF - time needed to reach peak flow; Hyperaemia area and Occlusion area. Also the changes in circulation are calculated and they are expressed in percentage: RF - BZ (difference

between rest flow and biological zero), BZ - PF (difference between biological zero and peak flow) and RF - PF (difference between rest flow and peak flow).

Method of Peripheral Arterial Tonometry

Peripheral arterial tonometry (PAT) (Endo-PAT, Itamar, Israel) is performed at the same time as laser dopplerography. This method is used to evaluate endothelium dependent post - occlusion hyperemia - triggered flow induced vasodilation in arterial area of a finger of a hand. The main parameter evaluated by the PAT is reactive hyperaemia index (RHI), which shows the ratio of signal amplitude before and after occlusion (software calculations are based on the ratio of post-occlusion hyperaemia and change in systemic circulation registered in the reference arm). Maximum hyperemia is observed when 60-90 s have passed after the occlusion. Recent researches showed that reactive hyperemia index calculated by evaluating the circulation 90-120 s after the occlusion (FRHI - Framingham reactive hyperaemia index) correlates better with the traditional CVD risk factors. Thus, in this research both values were evaluated.

Analysis of arterial stiffness using the aplanation tonometry method

Arterial stiffness parameters were measured by one cardiologist. The arterial stiffness was assessed by non-invasive measuring augmentation index (AIx), brachial and aortic pulse wave velocity (PWV), using the SphygmoCor device (Sphygmocor (v.8.) ArtCor Medical, Australia). AIx was calculated from the aortic pressure waveform obtained by applying a transfer function to the radial pressure waveform. Measured AIx was normalized for the heart rate of 75 beats per minute due to the strong dependence of this index on the heart rate (AIx/HR). Pulse wave velocity (PWV) was determined by the sequential acquisition of pressure waveforms from the carotid and the radial arteries (brachial PWV) or carotid and the femoral arteries (aortic PWV) using the same tonometer. The timing of these waveforms was synchronized with that of the R wave on a simultaneously recorded electrocardiogram. PWV was determined by the calculation of the difference in the carotid to radial or to femoral path length divided by the difference in R wave to waveform foot times. The pulse wave velocity was measured over 10 consecutive heartbeats to cover a complete respiratory cycle.

Statistical Methods

Data was processed using the statistical software package SPSS 17.0 (*version for windows*). Descriptive statistics of quantitative variables is delivered in the form of averages - standard deviations (average±SD).

For comparison of two groups in respect of a quantitative variable t -test or non - parametric Man - Whitney test (in case the data is distributed unequally) was applied. For comparison of more than two groups in respect of a quantitative variable unifactorial dispersion analysis (in the case of unequal dispersions Welch test statistics was used) was applied. Paired comparisons were performed using the LSD (*least significant difference*, in the case of unequal dispersions – Tamhane) test. For non-parametric data χ^2 independency criterion was used.

Models of simple logistic regressions, where dependent variable was the variable indicating the disease (migraine - control), were constructed in search of a relation between migraine and reactivity of blood - vessels. Migraine was considered as an event. ROC curves were drawn and the area below the curves was evaluated for indicators with prognostic value.

Correlation coefficients in groups of healthy persons and persons with migraine were calculated in order to analyze the relation between migraine, indicators of blood - vessel reactivity and functional activity of platelets.

Two - sided p values are presented in all the analyses. Significance level is considered .05.

3. RESULTS

3.1. Comparison of Risk Factors of Cardiovascular Diseases and Anthropometric Data

The first task of this Thesis is designed to evaluate the frequency of common cardiovascular diseases in women with migraine and the relation of the mentioned diseases with different types of migraine attacks. The analysis was carried out in two stages:

1) the indicators of all the women with migraine and the control group were compared.

2) the indicators of women with different types of migraine and the control group were compared.

3.1.1. Comparative Analysis of the Group of Women with Migraine and the Control Group

In order to make sure whether the comparison between the experimental (women with migraine) and control group was correct in further analysis of factors, both groups were compared based on sociodemographic and clinical characteristics. In order to carry out the analysis, data of 120 women was used: 60 women suffered from migraine and 60 women constituted the control group. Student's t - test for independent samples was used for the analysis of continuous variables while in the case of discrete variables χ^2 criterion was applied. Characteristics of groups are presented in Table 1.

Table 1. Characteristics of Patients with Migraine and Control Group

Variable*	Patients with migraine (n=60)	Control group (n=60)	p
Age (years)	38.79±9.21	35.60±8.03	.057
BMI (kg/m^2)	23.40±3.91	23.30±3.62	.892
Family anamnesis of an early CHD, n (%)	24 (40)	25 (41.6)	.853
Hypodynamics, n (%)	26 (43.3)	32 (53.3)	.361
Smoking, n (%)	5 (8.33)	6 (10.0)	.752
Systolic ABP (mmHg)	125.72±11.13	122.18±7.81	.051
Diastolic ABP(mmHg)	82.33±10.35	75.25±8.10	<.001
Average ABP (mmHg)	96.79±9.76	90.90±7.27	<.001
T. Chol (mmol/l)	5.16±1.07	5.51±0.91	.065
TG (mmol/l)	1.01±0.62	.97±.40	.752
HDL (mmol/l)	1.62±0.38	1.72±0.29	.120
LDL (mmol/l)	3.07±0.92	3.35±0.79	.099
CRP (g/l)	1.51±2.13	1.61±2.76	.349
SAA (mg/l)	4.16±5.82	4.68±4.19	.387
Risk based on Framingham (%)	1.46± 1.40	1.18±.62	.288

*- averages and standard deviations are presented (Average±SD), grey areas indicate statistically significant differences, n – number; percentage presented is based on total number of participants (N) in the group, BMI - body mass index, CHD - coronary heard disease, ABP - arterial blood pressure, average ABP- calculated 1/3 systolic ABP+ 2/3 diastolic ABP, T. Chol - concentration of total cholesterol, TG – triglyceride concentration, HDL– high density lipoprotein cholesterol concentration, LDL - low density lipoprotein cholesterol concentration, CRP- C reactive protein, SAA - serum amyloid A.

Analysis of the findings of the research shows that the distribution of most of the common atherosclerosis risk factors in both groups was similar. The difference was observed only in the case of arterial blood pressure: higher diastolic ($p = .001$) and average ($p < .001$) blood pressure were statistically significant in the group of patients with migraine, while systolic blood pressure did not reveal any differences ($p = .051$).

3.1.2. Comparative Analysis of Factors of Patients with Different Types of Migraine and Control Group

Based on clinical course two types of migraine can be distinguished: migraine with aura and migraine without aura. 30 out of 60 participants of the research suffered migraine attacks with aura (MA) and 30 suffered from migraine attacks without aura (M0). In order to make sure that both groups analyzed were homogenous they were compared based on control variables. Group of patients with migraine with aura and that of patients without it did not reveal differences based on the duration of the disease, frequency of attacks, count of days with headache during the last 3 months, average intensity of pain (from 1 to 10 points) during the last 3 months (evaluated based on Student's t-test). The results of one more parameter are important in order to interpret the results and that is the comparison of homogenuousness of groups based on the use of triptanes. For this purpose the χ^2 criterion was applied. However, in this case no statistically significant difference was determined**,** either (Table 2).

Table 2. Comparison of Patients with Migraine with Aura and without Aura Based on Characteristics of the Disease

Variable*	Patients with migraine without aura (M0) (n=30)	Patients with migraine with aura (MA) (n=30)	p
Duration of the disease (years)	17.58±9.46	19.89±10.25	.401
Frequency of attacks per month., n (%)	3.80±3.83	3.37±5.40	.747
Use of triptanes, n (%)	6 (20.0)	9 (30.0)	.276
Average duration of pain (days during 3 months)	16.16±11.08	15.65±12.86	.881
Average intensity of pain	6.00±1.47	5.69±1.93	.533

Intergroup comparison of continuous variables was performed using the unifactorial dispersion analysis (ANOVA discrete - χ^2 independency criterion). This methodology was used to evaluate the differences and sameness of common characteristic features of MA, M0 and control group. The results are presented in Table 3.

Table 3. Characteristics of the groups researched

Variable*	Patients with migraine without aura (M0) (n=30)	Patients with migraine with aura(MA) (n=30)	Control group (n=60)	p	Post hoc
Age (years)	38.03±8.62	39.52±9.83	35.60±8.03	.131	
BMI (kg/m^2)	23.43±3.76	23.37±4.11	23.30±3.62	.989	
Family anamnesis of an early CHD, n (%)	11 (36.6)	13 (43.3)	25 (41.6)	.541	
Hypodynamics, n (%)	17 (56.6)	10 (33.3)	32 (53.3)	.024	2<1.3 **
Smoking, n (%)	2 (6.6)	3 (10)	6 (10)	.758	
Systolic ABP (mmHg)	129.67±11.71	121.90±9.20	122.18±7.81	.001	1>2.3
Diastolic ABP (mmHg)	84.47±8.49	80.26±11.64	75.25±8.10	<.001	1>2.3
Average ABP (mmHg)	93.53±8.94	94.14±9.92	90.90±7.27	<.001	1>2.3
T. Chol (mmol/l)	5.13±0.97	5.19±1.18	5.51±0.91	.178	
TG (mmol/l)	.89±.40	1.14±.76	.97±.40	.166	
HDL (mmol/l)	1.59±.30	1.66±0.44	1.72±.29	.221	
LDL (mmol/l)	3.12±.85	3.03±1.01	3.35±.79	.239	
CRP (g/l)	1.37±2.26	1.65±2.02	1.61±2.76	.881	
SAA (mg/l)	4.67±7.75	3.66±3.02	4.68±4.19	.648	
Risk based on Framingham, (%)	1.67±1.8	1.26±.82	1.18±.62	.391	

* - averages and standard deviations are presented (Average±SD), grey areas indicate statistically significant differences, ** χ^2 independency criterion was calculated for each pair of groups

No differences were observed between patients with different types of migraine and the control group based on most of the characteristic parameters, except from arterial blood pressure. Furthermore, patients with migraine without aura were characterized as having a higher blood pressure than MA or control group (systolic ABP M0 vs MA p = .002. M0 vs. Control p = .001; diastolic ABP M0 vs MA p = .020. M0 vs. Control p < .001; Average ABP M0 vs MA p = .015. M0 vs. Control p < .001).

It was established that patients with MA did more excersise than those of control group or patients with M0 based on their interviews (intergroup comparison based on χ^2 independency criterion MA vs Control group p = .007. MA vs M0 p = .048. Control group vs M0 = .379). Groups did not show statistically significant differences based on other indicators.

Summarizing the findings, the conclusion was made that it is not always possible to control the secondary variables. Therefore, stricter methods of control of secondary variables were applied in further research (e.g., not only comparison of groups based on the Student's t-test or Mann-Whitney criteria, but also covariation analysis).

3.2. Changes in Functional Activity of Platelets

Next task of this research was to determine whether there was a relation between migraine and platelet activation markers.This task was solved in two stages:

- Comparison of control and migraine groups without taking into account the type of migraine;
- Comparison of control and migraine groups by dividing patients with migraine based on presence of aura

It is important to point out that before performing the analysis of functional activity of platelets it was established that there was no difference in amount of platelets between groups (migraine group 271.00±58.88 vs 286.80±54.28 control group, p = .146). Thus, the further conclusions are related precisely to the particularity of migraine.

3.2.1. Comparison of Migraine and Control Groups Based on Functional Activity of Platelets

In order to find out whether there is a difference of platelet functional activity between migraine and control groups, amount of different antibodies captured was evaluated. The results were compared using the Student's t - test. The results of the comparison are presented in Table 4.

Table 4. Platelet Activation Indexes in Migraine and Control Groups (Comparison Using the Student's t - test)

Variable*	Patients with migraine (n=60)	Control group (n=60)	p
AFI CD63	75.62±93.27	147.04±82.81	<.001
AFI PAC-1	44.89±7.68	51.80±9.10	<.001
% PAC-1/CD42a	15.13±15.40	5.59± 7.25	.001
Absolute number: PAC-1/CD42a	4347.35± 4447.70	1641.33± 2114.70	.001
% CD63/CD61	.61±.63	.34±.32	.010
Absolute number: CD63/CD61	176.03±178.04	101.78±88.97	.013
% CD63/CD41	.61±.63	.35±.32	.011
Absolute number: CD63/CD41	175.21±178.54	101.80±88.67	.021
% platelet-monocyte aggregates	7.63±1.75	8.48±1.88	.015
Absolute number: platelet-monocyte aggregates	520.13±188.76	543.71±163.05	.485

* - averages and standard deviations are provided, grey areas indicate statistically significant differences; AFI - average fluorescence intensity, % - percentage of platelets that captured both antibodies, Absolute number - number of platelets that captured both antibodies, CD63 - integral membrane protein produced in the lysosomes antibody (in order to evaluate the degranulation phase), PAC-1 - activated glycoprotein IIb/IIIa marker (in order to evaluate the aggregation phase), CD42a, CD61. CD41- particular antibodies used to find platelets.

Analysis of data presented in Table 4 shows that statistically significant differences were found based on basically all of the variables. It was established that there were more platelets (both in percentage and absolute numbers) that captured both PAC-1 and CD63 antibodies in the migraine group. This shows increased functional activity (both aggregation and degranulation) of platelets. On the other hand, the average fluorescence glow intensity both with PAC-1 and CD63 was lower in the migraine group, also, there was a lower percentage of formation of platelet-monocyte aggregates.

The findings of the research induced the analysis of the role of different risk factors of cardiovascular diseases in functional activity of platelets. The role of BMI (whether the women are overweight or not), dyslipidemia (wheter cholesterol levels of the participants comply with the norm), CRP (whether the results comply with the norm, or there is an active inflammatory process) and SAA (low risk of cardiovascular events when SAA < 3.8 mg/l, medium risk, when SAA 3.9-8.2 mg/l and high risk when SAA ≥ 8.3 mg/l) in changes of parameters of functional activity of platelets was evaluated. The results of group comparison are presented in Tables 5-8.

Table 5. Relation between Body Mass Index and Functional Activity of Platelets in Women with Migraine

Variable*	BMI		p
	< 25 kg/m^2 (n = 38)	≥ 25 kg/m^2 (n = 22)	
AFI CD63	82.92±93.86	62.68±92.95	.344
AFI PAC-1	45.26± 7.28	44.23±8.47	.701
% PAC-1/CD42a	13.37±11.75	18.17±20.27	.595
Absolute number: PAC-1/CD42a	3932.24±3477.37	5068.32±5803.44	.754
% CD63/CD61	.64±.58	.56±.71	.431
Absolute number: CD63/CD61	185.36±166.98	159.50±199.16	.367
% CD63/CD41	.64±.58	.56±.71	.431
Absolute number: CD63/CD41	184.31±167.66	159.09±199.45	.404
% platelet-monocyte aggregates	7.46±1.36	7.93±2.29	.857
Absolute number: platelet-monocyte aggregates	512.72±192.52	533.27±185.60	.822

Table 6. Relation between Cholesterol Concentration and Functional Activity of Platelets in Women with Migraine

Variable*	Total cholesterol		p
	< 5.00 mmol/l (n = 31)	≥ 5.00 mmol/l(n = 29)	
AFI CD63	75.72±81.28	75.52±106.42	.800
AFI PAC-1	44.03±7.08	45.83±8.31	.659
% PAC-1/CD42a	12.14±11.01	18.61±18.97	.152
Absolute number: PAC-1/CD42a	3445.96±3166.41	5398.96±5472.27	.123
% CD63/CD61	.54±.48	.68±.76	.636
Absolute number: CD63/CD61	156.09±136.00	198.03±215.61	.554
% CD63/CD41	.54±.48	.68±.76	.636
Absolute number: CD63/CD41	155.59±136.35	196.86±216.32	.578
% platelet-monocyte aggregates	8.09±1.85	7.12±1.51	.024
Absolute number: platelet-monocyte aggregates	557.25±197.27	479.17±173.07	.073

* - averages and standard deviations are provided, grey areas indicate statistically significant differences

Table 7. Relation between C reactive Protein and Functional Activity of Platelets in Women with migraine

Variable*	CRP		p
	< 3.00 g/l (n=51)	≥3.00 g/l (n=9)	
AFI CD63	81.17±93.73	43.56±88.75	.304
AFI PAC-1	44.69±7.62	46.00±8.40	.745
% PAC-1/CD42a	15.01±15.42	15.76±16.34	.872
Absolute number: PAC-1/CD42a	4302.43±4456.14	4594.38±4695.20	.852
% CD63/CD61	.64±.66	.42±.28	.566
Absolute number: CD63/CD61	185.63±188.97	120.56±77.56	.569
% CD63/CD41	.64±.66	.42±.28	.566
Absolute number: CD63/CD41	184.67±189.57	120.56±77.56	.611
% platelet-monocyte aggregates	7.73±1.79	7.03±1.42	.281
Absolute number: platelet-monocyte aggregates	521.10±187.63	514.56±206.72	.699

Table 8. Relation between serum amyloid A and functional activity of platelets in women with migraine

Variable*	SAA			p
	< 3.9 mg/l (n=43)	3.9-8.2 mg/l (n=15)	≥ 8.3 mg/l (n=5)	
AFI CD63	79.30±98.52	68.00±67.03	63.80±120.71	.893
AFI PAC-1	44.65±7.5	45.76±9.42	44.60±3.28	.899
% PAC-1/CD42a	15.42±16.32	14.94±16.18	13.34±5.57	.961
Absolute number: PAC-1/CD42a	4395.75±4720.04	4375.54±4661.49	3941.20±1641.58	.978
% CD63/CD61	.64±.71	.53±.35	.48±.21	.758
Absolute number: CD63/CD61	186.25±203.76	154.53±102.49	144.00±63.75	.787
% CD63/CD41	.64±.71	.53±.35	.48±.21	.758
Absolute number: CD63/CD41	185.46±204.22	153.30±103.67	144.00±63.75	.788
% platelet-monocyte aggregates	7.58±1.74	7.97±20.6	7.10±0.65	.617
Absolute number: platelet-monocyte aggregates	510.55±173.01	559.38±259.22	500.40±109.78	.702

The conclusion was made that women with migraine that are overweight (BMI ≥ 25) did not show difference from those of normal weight (BMI < 25), i.e. overweight does not influence functional activity of platelets (Table 5). The same conclusion was made when evaluating the influence of CRP and serum amyloid A on functional activity of platelets: the increase of inflammatory markers was not statistically significant in functional activity of platelets in women with migraine (Tables 7 and 8). The influence of hypercholesterolemia (total cholesterol ≥ 5.00 mmol/l) on functional activity of platelets was not proved, either (Table 6). However, the results of increased formation of platelet - monoyte aggregates when the level of cholesterol is lower were slightly unexpected.

Values of indicators of functional activity of platelets in migraine and control groups were evaluated using a more complex linear model: covariation analysis. Analysis model also included age, average arterial blood pressure, BMI, total cholesterol, HDL, TG (LDL was not included due to its strong correlation with measurements of total cholesterol ($r = 0.938$; $p < 0.001$), CRP and SAA. (table 9).

Table 9. Functional Activity of Platelets in Migraine and Control Groups (Comparison Using Covariation Analysis)*

Variable*	Migraine group (n=60)	Control group (n=60)	p
AFI CD63	75.68±13.62	144.25±15.31	.004
AFI PAC-1	45.18±1.22	51.33±1.37	.004
% PAC-1/CD42a	15.32±15.49	7.71±11.21	.461
Absolute number: PAC-1/CD42a	4401.94±4474.02	2256.62±3266.01	.436
% CD63/CD61	.57±.08	.38±.09	.149
Absolute number: CD63/CD61	165.63±22.05	112.78±24.79	.162
% CD63/CD41	.58±.08	.38±.09	.152
Absolute number:CD63/CD41	164.53±22.12	113.12±24.86	.175
% platelet-monocyte aggregates	7.66±0.28	8.43±0.31	.107
Absolute number: platelet-monocyte aggregates	515.38±27.17	552.77±30.54	.421

* - averages and standard deviations are provided, grey areas indicate statistically significant differences

Covariation analysis showed that average fluorescence intensity (AFI) of platelets bound with PAC-1 and CD63 antibodies was significantly lower in migraine group than in control group. This shows that only these variables are directly related to the effect of migraine. However, other variables chosen might be influenced by the set of heart and blood - vessel risk factors.

3.2.2. Comparison of Functional Activity of Platelets Based on the Type of Migraine

Assuming that migraine with and without aura had a different effect on functional activity of platelets, the influence of migraine aura on chosen variable was evaluated. The results were compared in two methods: simple unifactorial analysis and covariation analysis. The results of the unifactorial analysis are presented in Table 10 and those of intergroup comparison using the post hoc test are provided in Table 11 (paired comparisons were performed only on those indicators that were different in all the three groups).

Table 10. Functional Activity of Platelets in Patients with Migraine with and without Aura and in the Control Group (Unifactorial Dispersion Analysis)

Variable*	Patients with migraine without aura (M0) (n=30)	Patients with migraine without aura (MA) (n=30)	Control group (n=60)	p
AFICD63	74.37±89.51	76.84±98.23	147.04±82.81	<.001
AFI PAC-1	45.07±7.85	44.71±7.63	51.80±9.10	<.001
% PAC-1/CD42a	16.77±14.96	14.38±15.92	7.06±13.43	.002
Absolute number: PAC-1/CD42a	4763.58±4298.30	4065.89±4563.91	1349.71±1625.26	<.001
% CD63/CD61	.68±.73	.54±.51	.34±.32	.022
Absolute number: CD63/CD61	194.20±206.14	158.45±147.19	101.78±88.97	.024
% CD63/CD41	.68±.73	.54±.51	.35±.32	.025
Absolute number: CD63/CD41	192.53±207.18	158.45±147.19	101.80±88.67	.026
% platelet-monocyte aggregates	7.92±1.96	7.34±1.50	8.48±1.88	.024
Absolute number: platelet-monocyte aggregates	542.00±217.14	498.97±157.29	543.71±163.05	.503

* - averages and standard deviations are provided, grey areas indicate statistically significant differences

Table 11. Paired Comparisons of Groups Based on Platelet Activation (Unifactorial Dispersion Analysis)

Variable /groups*	M0 vs MA	M0 vs Control	MA vs Control
AFI CD63	.914	.001	.001
AFI PAC-1	.868	.001	<.001
% PAC-1/CD42a	.367	.004	.012
Absolute number: PAC-1/CD42a	.326	.003	.032
% CD63/CD61	.304	.005	.090
Absolute number: CD63/CD61	.336	.006	.088
% CD63/CD41	.305	.006	.096
Absolute number: CD63/CD41	.360	.008	.089
% platelet-monocyte aggregates	.216	.183	.007

* - p values of paired comparisons are presented, averages are presented in table 10. grey areas indicate statistically significant differences

Data presented in Tables 10 and 11 on functional activity of platelets did not prove a substantial difference between patients with migraine with aura and patients with migraine without aura. However, in comparison with control group both MA and M0 showed statistically significant difference based on CD63 and PAC-1 average fluorescence intensity, as well as based on number of platelets that captured PAC-1 antibodies. Furthermore, in the MA group both the level of platelets that captured degranulation antibody (CD63) and percentage of platelet-monocyte aggregates was lower than in the M0 group.

The model of covariation analysis included the same factors as previously mentioned: age, average arterial blood pressure, BMI, total cholesterol, HDL, TG, CRP and SAA. The results are presented in Table 12. For statiscically significant differences paired comparison of groups was performed (Table 13).

Table 12. Comparison of Groups based on Platelet Markers Using Covariation Analysis

Variable*	Patients with migraine without aura (M0) (n=30)	Patients with migraine with aura (MA) (n=30)	Control group (n=60)	p
AFI CD63	71.74±17.48	80.99±20.09	143.42±15.54	.015
AFI PAC-1	45.36±1.57	44.93±1.80	51.36±1.39	.015
% PAC-1/CD42a	17.165±3.333	13.168±3.185	7.60±2.66	.114
Absolute number: PAC-1/CD42a	4840.65±783.29	3757.62±748.63	1503.84±624.44	.008
% CD63/CD61	.68±.70	.53±.52	.33±.34	.051
Absolute number: CD63/CD61	184.77±28.16	139.79±32.35	116.25±25.04	.209
% CD63/CD41	.65±.10	.48±.11	.39±.09	.190
Absolute number: CD63/CD41	182.48±28.27	140.30±32.47	116.89±25.13	.239
% platelet-monocyte aggregates	7.83±0.36	7.41±0.41	8.47±0.32	.206
Absolute number: platelet-monocyte aggregates	530.11±34.82	495.48±40.00	555.87±30.96	.575

* - - averages and standard deviations are provided, grey areas indicate statistically significant differences

Table 13. Paired Comparisons of Groups after the Covariation Analysis

Variable / groups*	M0 vs MA	M0 vs Control	MA vs Control
AFI CD63	.719	.005	.033
AFI PAC-1	.851	.008	.014
Absolute number: PAC-1/CD42a	.802	.002	.009

* - p values of paired comparisons are presented, averages are presented in table 12;
grey areas indicate statistically significant differences

Analysis of the data prresented in Tables 12 and 13 showed that in all cases migraine groups did not show a statistically significant difference and total difference of averages was determined by differences with the control group. Both unifactorial dispersion analysis and covariation analysis showed that patients with migraine with and without aura showed a statistically significant difference from the control group based on CD63 and PAC-1 average fluorescence intensity, as well as number of platelets bound with PAC-1 antibodies. Risk factors of cardiovascular diseases did not influence these changes. Thus, this should be related directly to the particularities of course of migraine itself.

3.2.3. Relation between Functional Activity of Platelets and Migraine Intensity

In order to evaluate relation between functional activity of platelets and different parameters of migraine intensity (frequency of headaches (expressed in number of days during the recent three months) and intensity of headaches (evaluated in the scale of 10. where 0 – no pain, 10 – the most intense pain possible) the correlations of these factors in the MA and M0 groups was calculated. The results are presented in Table 14. Analysis shows that the was no statistically significant correlations in MA group. However, there were three statistically significant correlations registered in the M0 group.

Table 14. Relation between Functional Activity of Platelets and Migraine Intensity

Variable***	Patients with migraine without aura (M0) (n=30)		Patients with migraine with aura (MA) (n=30)	
	Frequency of headaches	Intensity of headaches	Frequency of headaches	Intensity of headaches
AFI CD63	.085	.199	.044	.109
AFI PAC-1	.522**	-.130	.336	.235
% PAC-1/CD42a	.406	.256	.353	.149
Absolute number: PAC-1/CD42a	.406	.257	.342	.185
% CD63/CD61	-.013	-.082	.249	.063
Absolute number: CD63/CD61	-.008	-.029	.213	.038
% CD63/CD41	-.013	-.082	.249	.063
Absolute number: CD63/CD41	.009	-.056	.213	.038
% platelet-monocyte aggregates	-.475*	.000	-.378	-.102
Absolute number: platelet-monocyte aggregates	-.469*	-.094	-.245	-.053

* p < .05. ** p < .01

******* correlation coefficients are presented, grey areas indicate statistically significant correlations

More frequent migraine headaches in the group of women with migraine without aura influence higher functional activity of platelets, i.e., higher fluorescence intensity of IIb/IIIa marker. However, the number of platelet-monocyte aggregates expressed both in absolute numbers and in percent, has negative correlation with the frequency of migraine: the more frequent are the headaches, the lower amount of platelet-monocyte aggregates is registered.

3.3. Migraine and Blood - vessel Reactivity

The next task of this Thesis seeks to determine the endothelial function and stiffness of peripheral blood - vessels of various diameter in women with migrain with and without aura, as well as their relation with common risk factors of cardiovascular diseases. In search of an answer to the questions brought the following activities were performed:

- Comparison of control and migraine groups without taking into account the type of migraine;
- Comparison of control and migraine groups separating migraine groups based on the presence of aura (MA and M0).

3.3.1. Comparison of Endothelial Function and Blood-vessel Stiffness in Migraine and Control Groups

In order to compare migraine group and control group based on blood-vessel reactivity, Student's t - test for independent samples was applied. The results are presented in Table 15.

Analysis of data presented in Table 15 shows that there were 4 statistically significant differences between groups found and all of them were determined during the evaluation of microcirculation using the method of laser dopplerometry. The sample of patients with migraine demonstrated worse results for rest flow (RF), also, derivative indicators related to RF were different from those of the control group based on these indicators: lower percent change in circulation from rest flow to biological zero (RF - BZ) and percent change in circulation from rest flow to peak flow (RF - PF). Findings also showed that the occlusion area (PV x s) in the group of women with migraine was statistically significantly smaller. This analysis did not show any difference in endothelial function between migraine group and control group in any of the areas

analyzed. Also, groups did not show differeces based on the indicators of stiffness. Statistically significant differences found show increased tone of small blood -vessels at rest, as well as lower ischaemia induced microcirculation capacity.

Table 15. Comparison of Groups Based on Blood - vessel Reactivity Indicators

Variable*	Patients with migraine (n=60)	Control group (n=60)	p
FID (%)	5.02±3.60	4.38±2.79	.307
PWV of radial artery (m/s)	7.92±0.94	8.26±1.10	.086
PWV of aorta (m/s)	6.76±1.20	6.84±1.02	.735
Alx/HR (%)	16.80±11.29	16.08±14.29	.768
RHI (%)	2.12±.61	1.94±.55	.104
FRHI (%)	.70±.44	.63±.58	.449
RF (PU)	44.61±41.58	55.93±33.55	.019
BZ (PU)	6.09±2.46	6.16±3.71	.464
PF (PU)	201.73±88.56	218.90±93.22	.338
RF - BZ (%)	-80.80±10.29	-85.64±9.63	.015
BZ – PF (%)	3515.52±1771.65	4229.44±2601.31	.108
RF – PF (%)	508.94±353.91	388.78±247.15	.049
Time to RF (s)	32.11±31.52	28.51±17.37	.887
Time to PF (s)	57.33±38.98	45.41±22.74	.071
Occlusion area (PUx s)	11999.90±12698.77	15633.86±11040.62	.029
Hyperaemia area (PV x s)	10766.83±715.59	9914.15±8007.21	.249

* - averages and standard deviations are presented, grey areas indicate statistically significant differences; FID - flow induced dilation, PWV - pulse wave velocity, AIx/HR - adjusted augmentation index, RHI - reactive hyperaemia index, FRHI - Framingham reactive hyperaemia index, RF - rest flow, BZ - biological zero, PF - peak flow, RF - BZ - percent change in circulation from rest flow to biological zero, BZ - PF- percent change in circulation from biological zero to peak flow, RF - PF- percent change in circulation from rest flow to peak flow, time to RF- time needed to recover rest flow, time to PF - time needed to reach peak flow, PU -perfusion units, s - seconds.

Additionally, covariation analysis of all the factors mentioned was performed. As in the analysis of platelet activation particularity, this analysis includes the following factors: age, average arterial blood pressure, BMI, total cholesterol, HDL, TG, CRP and SAA. In order to compare groups based on FID, additionally brachial artery outlet diameter was included. Results are presented in Table 16.

Table 16. Comparison of Groups Based on Blood-vessel Reactivity Indicators Using the Covariation Analysis.

Variable*	Patients with migraine (n=60)	Control group (n=60)	p
FID (%)	5.254±0.459	4.099±0.505	.119
PWV of radial artery (m/s)	7.891±0.143	8.293±0.158	.082
PWV of aorta (m/s)	6.547±0.145	7.102±0.163	.020
Alx /HR (%)	14.805±1.427	18.474±1.587	.114
RHI (%)	2.089±.086	1.972±.093	.399
FRHI (%)	.701±.074	.631±.080	.556
RF (PU)	40.033±5.400	60.872±5.649	.016
BZ (PU)	6.100±0.442	6.146±0.463	.947
PF (PU)	189.293±13.317	232.325±13.930	.042
RF – BZ (%)	-79.417±1.437	-87.134±1.504	.001
BZ – PF (%)	3222.513±321.953	4545.886±336.782	.010
RF – PF (%)	531.307±44.816	364.625±46.881	.020
Time to RF (s)	34.744±3.969	25.417±4.368	.151
Time to PF (s)	58.543±4.871	43.983±5.360	.069
Occlusion area (PVx s)	10316.473±1713.434	17653.978±1909.375	.010
Hyperaemia area (PV x s)	10379.991±1148.593	10378.353±1279.940	.999

* -averages and standard deviations obtained using the model equation are presented, grey areas indicate statistically significant differences

Analysis of the data presented in Table 16 shows that control of secondary variables allowed to reveal more statistically significant differences between migraine group and control group when comparing them based on blood-vessel reactivity. Additionally to the indicators discussed above (worse indicator of rest flow (RF), lower RF - BZ, but higher RF - PF circulation changes, smaller occlusion area) patients with migraine had lower aorta pulse wave velocity (PWV), worse indicator of highest post - ischaemic circulation in microcirculation (PF), as well as lower percent change of circulation from biological zero to peak flow (BZ - PF). Thus, statistically significant differences found during the covariation analysis imply that migraine is related to higher blood - vessel elasticity, unchanged endothelial function of blood - vessels in brachium and finger, however, worse endothelial function of microcirculation, as well as increased tone of skin blood - vessels at rest and lower ishaemia – induced microcirculation capacity.

3.3.2. Comparison of Blood-vessel Reactivity in the Control Group and Migraine Groups, dividing them based on the type of migraine

In order to determine how the particularities of the endothelial function and stiffness of blood-vessels are related with the type of migraine, unifactorial dispersion analysis was performed. Additionally, variables with statistically significant differences were subjet to paired comparison. The results are presented in Tables 17 and 18.

Table 17. Comparison of Groups Based on Blood - vessel Reactivity Indicators Using the Unifactorial Dispersion Analysis

Variable*	Patients with migraine without aura (M0) (n=30)	Patients with migraine without aura (MA) (n=30)	Control group (n=60)	p
FID (%)	3.80±2.51	6.19±4.11	4.38±2.79	.010
PWV of radial artery (m/s)	7.86±.95	7.98±.95	8.26±1.10	.210
PWV of aorta (m/s)	7.05±1.36	6.48±.95	6.84±1.02	.137
Alx/HR (%)	15.73±10.63	17.87±12.00	16.08±14.29	.777
RHI (%)	2.17±.68	2.07±.54	1.94±.55	.223
FRHI (%)	.85±.41	.55±.43	.63±.58	.064
RF (PU)	45.75±50.32	43.63±33.17	55.93±33.55	.316
BZ (PU)	6.01±2.09	6.16±2.77	6.16±3.71	.978
PF (PU)	203.17±102.98	200.49±75.85	218.90±93.22	.629
RF – BZ (%)	-79.83±11.21	-81.63±9.55	-85.64±9.63	.042
BZ – PF (%)	3473.20±1736.97	3552.01±1830.90	4229.44±2601.31	.264
RF – PF (%)	514.74±284.11	503.94±409.68	388.78±247.15	.144
Time to RF (s)	33.11±44.15	31.26±14.46	28.51±17.37	.764
Time to PF (s)	55.18±47.02	59.18±31.19	45.41±22.74	.113
Occlusion area (PV x s)	12226.0±15403.0	11804.99±10089.38	15647.80±10917.67	.317
Hyperaemia are (PV x s)	9315.64±6607.88	12017.85±7770.08	9703.61±8045.47	.343

* - averages and standard deviations obtained using the model equation are presented, grey areas indicate statistically significant differences

Table 18. Paired Comparisons of Groups after the Simple Dispersion Analysis

Variable / groups*	M0 vs MA	M0 vs Control	MA vs Control
FID (%)	.004	.436	.014
RF – BZ (%)	.513	.020	.089

* - p values of paired comparisons are presente, averages are presented in table 17; grey areas indicate statistically significant differences

Analysis of the results presented in the Table 17 shows that there were only two statistically significant differences found between the groups. Intergroup comparison (Table 18) proved that women with migraine with aura had a better endothelial function measured in the brachial artery (higher FID) than women with migraine without aura or

control group. The tendency that women with migraine had worse rest flow in microcirculation remained, however, a statistically significant difference was obtained based on only percent change of circulation from rest flow to biological zero (RF - BZ). Patients with M0 demonstrated statistically higher value than the control group.

In order to find out, whether the control of secondary variables would prove these results, covariation analysis was performed**.** Analysis included the following factors: age, average arterial blood pressure, BMI, total cholesterol, HDL, TG, CRP and SAA. In order to compare groups based on FID, additionally brachial artery outlet diameter was included. The results are presented in Table 19, group comparissions between significant variables – in Table 20.

Table 19. Comparison of Groups Based on Blood-vessel Reactivity Indicators Using the Covariation Analysis

Variable*	**Patients with migraine without aura (M0) (n=30)**	**Patients with migraine with aura (MA) (n=30)**	**Control group (n=60)**	**p**
FID (%)	3.65±0.62	6.71±0.59	4.14±0.47	.001
PWV of radial artery (m/s)	7.86±0.20	7.90±0.19	8.30±0.15	.198
PWV of aorta (m/s)	6.75±.20	6.36±.19	7.09±.16	.025
Alx/HR (%)	14.93±2.02	14.68±1.94	18.46±1.58	.280
RHI (%)	2.14±.12	2.03±.11	1.97±.09	.600
FRHI (%)	.85±.10	.53±.10	.63±.07	.065
RF (PU)	41.68±7.99	39.27±7.09	60.48±5.64	.059
BZ (PU)	6.07±0.65	6.10±0.50	6.15±0.46	.995
PF (PU)	193.88±19.67	185.87±17.46	232.01±13.88	.118
RF – BZ (%)	-77.74±2.11	-80.77±1.87	-87.18±1.49	.002
BZ – PF (%)	3247.67±476.67	3232.75±423.24	4527.36±336.32	.041
RF – PF (%)	569.27±66.08	498.02±58.68	364.94±46.62	.051
Time to RF (s)	37.37±5.94	32.51±5.46	25.39±4.38	.301
Time to PF (s)	58.01±7.30	58.99±6.72	43.98±5.38	.192
Occlusion area (PU x s)	11067.97± 2573.59	9678.20± 2367.22	17647.80± 1918.57	.035
Hyperaemia area (PU x s)	9247.21± 1719.05	11342.09± 1581.20	10387.65± 1281.52	.676

* - averages and standard deviations obtained using the model equation are presented, grey areas indicate statistically significant differences

Table 20. Paired Comparisons of Groups after the Covariation Analysis

Variable / groups	**M0 vs MA**	**M0 vs Control**	**MA vs Control**
FID (%)	.001	.552	.002
PWV of aorta (m/s)	.163	.226	.007
BZ – PF (%)	.981	.042	.024
RF – BZ (%)	.278	.001	.012
Occlusion area (PU x s)	.695	.057	.016

* - p values of paired comparisons are presented, averages are presented in table 19; grey areas indicate statistically significant differences

Analysis of the findings shows that there were 5 statistically significant differences found. Higher flow induced dilation (FID) in the sample of patients with migraine with aura in comparison with M0 and control groups, as well as higher difference based on the estimates of percent change of circulation from rest flow to biological zero among patients with M0 were discussed before, however, differences based on pulse wave velocity (PWV), occlusion are and percent change of circulation from biological zero to peak flow (BZ - PF) were found.

Data presented in the table of paired comparisons also shows that MA group showed differences from the control group based on all the parameters analyzed: higher flow induced dilation, lower pulse wave velocity of aorta and smaller occlusion area were identified. Both migraine groups had dysfunctional circulation at rest and had a statistically significant difference from the control group based on lower changes in circulation: RF - BZ and BZ - PF. On the other hand, MA showed difference from M0 only based on FID.

Analysis of the results proved that there were no statistically significant differences between groups based on the method of peripheral arterial tonometry. Furthermore, migraine with aura is related to a better endotheliai function of brachial artery and lower aortic stiffness. Most of the differences emerged when performing microcirculation analysis using the laser dopplerometry method. As at the moment of ischaemia (BZ) circulation did not differ between groups, however, BZ - PF was statistically significantly lower in both migraine groups, it implies that migraine is related to worse endothelial function in skin blood - vessels. Furthermore, changes typical to both MA and M0 groups are related to increased tone of blood - vessels at rest.

3.3.3. Relation between Blood - vessel Reactivity and Migraine Intensity

In order to evaluate the relation between blood-vessel reactivity and parameters of migraine intensity (frequency and intensity of headaches) correlations of these factors were calculated in M0 and MA groups. The results are presented in Table 21.

Table 21. Comparison of Groups Based on Blood-vessel Reactivity Indicators Using Unifactorial Dispersion Analysis

Variable***	Patients with migraine without aura (M0) (n=30)		Patients with migraine with aura (MA) (n=30)	
	Frequency of headaches	Intensity of headaches	Frequency of headaches	Intensity of headaches
FID (%)	-.161	.621**	-.213	.028
PWV of radial artery (m/s)	.021	-.278	-.108	.157
PWV of aorta (m/s)	.021	-.233	.123	-.075
Alx/HR (%)	.151	.013	-.390*	.104
RHI (%)	-.034	-.085	-.129	.287
FRHI (%)	-.187	-.104	.001	.181
RF (PU)	-.305	-.513*	-.033	-.018
BZ (PU)	.194	.099	-.071	-.266
PF (PU)	-.014	-.351	-.012	.294
RF – BZ (%)	.366	-.696**	.031	-.204
BZ – PF (%)	-.148	-.359	.111	.279
RF – PF (%)	.127	.320	.112	.184
Time to RF (s)	-.099	-.207	-.321	.334
Time to PF (s)	.178	-.143	.211	.043
Occlusion area (PU x s)	-.324	-.574*	-.024	.021
Hyperaemia area (PU x s)	.177	-.072	.249	.276

* $p < 0.05$. ** $p < 0.01$

******* correlation coefficients are presented, grey areas indicate statistically significant correlations

Analysis of data presented in Table 21 shows that there was only one statistically significant correlation registered in the group of patients with migraine with aura: the more frequent the headaches were, the lower was the adjusted augmentation index. Meanwhile, there were four statistically significant correlations within the sample of migraine without aura and two of them at the 0.01 significance level. It was determined that the higher was the intensity of headaches, the higher was the value of flow-induced dilation. Furthermore, the results show that the higher is the intensity of headaches, the the smaller is the occlusiona area and worse rest flow (RF), as well as percent change in circulation from rest flow to biological zero (RF - BZ).

3.4. Relation between Platelet Activation, Blood - vessel Reactivity and Migraine

The eighth and ninth task of this Thesis is to determine correlative relationships of platelet aggregation, degranuation, formation of platelet - monocyte aggregates with functional and anatomic changes in peripheral blood -vessels, as well as their relation with the types of migraine. Therefore, correlation coefficients between all

platelet activation markers and blood - vessel reactivity indicators were calculated in migraine and control groups.

There was no statistically significant correlation between the endothelial function and CD63/CD61 and CD63/CD41 antibodies (in percentage and absolute numbers), as well as average fluorescence intensity (AFI) CD63 results. Thus, these results are not presented in the table. Due to the fact that there was no statistically significant correlation with various platelet functional activity characteristics, the table does not include the following functional indicators of endothelium: pulse wave velocity of radial artery, pulse wave velocity of aorta, Framingham reactive hyperaemia index (FRHI), rest flow (RF), circulation at the moment of ischaemia (BZ), maximum post - ischaemic circulation (PF), percent change in circulation from rest flow to biological zero (RF - BZ), percent change in circulation from biological zero to peak flow (BZ - PF), occlusion area (PU x s). Correlation of the rest of the variables is presented in Table 22.

Analysis of Table 22 show that there were few statistically significant correlations; most of them were in the group of patients with migraine without aura. Furthermore, groups showed differences based on variables with significant correlations. Patients with migraine without aura demonstrated two statistically significant correlations based on platelet - monocyte aggregates expressed in absolute numbers: the higher was the number of platelet - monocyte aggregates, the lower was the reactive hyperaemia index, as well as adjusted augmentation index.

Also, this correlation is the only with the significance level equal to .01. Furthermore, correlation was also determined between time needed to recover rest flow. The longer was the time needed, the lower was glow intensity of activated glycoprotein IIb/IIIa marker (evaluation of aggregation phase), number of platelets bound with PAC-1 antibodies (both in percent and absolute numbers), as well as the higher percentage of platelet - monocyte aggregates.

The only variable of endothelial function within the sample of patients with migraine with aura that correlated with different platelet variables was the occlusion area: the larger was the area, the bigger amount of platelet - monocyte aggregates was found.

Table 22. Correlations of platelet functional activity and endothelial function

Variable***	AFI PAC-1	% PAC-1/CD42a	Absolute number: PAC-1/CD42a	% platelet-monocyte aggregates	Absolute number: platelet-monocyte aggregates
Migraine with aura					
FID (%)	.283	-.109	-.103	.113	.036
Alx/HR (%)	-.105	-.186	-.153	.200	.120
RHI (%)	.358	.239	.246	-.054	-.082
RF – PF (%)	.087	-.127	-.071	-.219	-.260
Time to RF (s)	.035	.149	.171	.080	.078
Occlusion area (PU x s)	.133	.047	.022	.369*	.280
Migraine without aura					
FID (%)	-.205	-.261	-.271	-.118	-.228
Alx/HR (%)	-.089	-.033	-.030	-.130	-.547**
RHI (%)	.050	.068	.078	-.336	-.398*
RF – PF (%)	-.098	.181	.188	.201	-.142
Time to RF (s)	-.443*	-.539*	-.527*	.430*	.091
Occlusion area(PU x s)	-.083	-.198	-.195	.005	.390
Migraine (both groups)					
FID (%)	-.018	-.173	-.182	-.078	-.115
Alx/HR (%)	-.132	-.097	-.082	.003	-.213
RHI (%)	.176	.19	.196	-.213	-.283*
RF – PF (%)	-.007	-.019	.002	-.022	-.156
Time to RF (s)	-.197	-.215	-.192	.253	.070
Occlusion area(PU x s)	.031	-.100	-.099	.203	.301*
Control group					
FID (%)	-.172	.595	.571	.347*	.158
Alx/HR (%)	.009	.611	.619	.078	.055
RHI (%)	.133	.551	.571	.000	.064
RF – PF (%)	-.312*	-.132	-.167	-.051	-.001
Time to RF (s)	-.003	-.100	-.100	-.085	.047
Occlusion area(PU x s)	.159	.270	.321	.190	.132

* $p < 0.05$. ** $p < 0.01$

******* correlation coefficients are presented, grey areas indicate statistically significant correlations

In case the whole migraine group was analyzed, the conclusion would be made that as in the case of migraine without aura, the most important variable of platelet function in the whole group is the number of platelet - monocyte aggregates. It also has a negative relation with the reactive hyperaemia index and positive relation with the occlusion area. Meanwhile, positive relation between flow-induced dilation and percent

of platelet - monocyte aggregates was found in the control group. However, average fluorescence intensity of the PAC-1 marker had a negative relation with percent change of circulation from rest flow to peak flow.

Thus, there is a reason to believe that there is a relation between migraine, the endothelial function and platelet activation markers; it depends on the type of migraine and has a qualitative difference from the relation within the group of healthy patients.

CONCLUSIONS

1. The women with migraine without aura were determined to have a higher both systolic and diastolic arterial blood pressure, as well as hypodynamics. There were no other differences in risk factors of cardiovascular diseases between the groups of migraine with aura and migraine without aura.
2. The relation of serum amyloid A and C reactive protein with types of migraine, as well as with changes in functional activity of platelets and endothelial function and stiffness of peripheral blood - vessels of various diameters was not proved.
3. Women with migraine demonstrated an increased functional activity of platelets between the attacks: higher number of platelets in the surface had expressed aggregation and degranulation antigens, however, the average fluorescence intensity of these expressed antigens was lower and was not influenced by other risk factors of cardiovascular diseases.
4. A relation between platelet activity and clinical type of migraine was determined: there was a higher number of platelets had captured the degranulation antibody within the group of migraine without aura and a lower amount of platelet-monocyte aggregates within the group of migraine with aura.
5. The frequency and intensity of migraine attacks affected the platelet function and was aura-dependant: the frequency of migraine without aura attacks showed inverse correlation with the number platelet - monocyte aggregates and direct correlation with average fluorescent glow of aggregation antibodies.

6. Women with migraine showed dysfunctional endothelial function in microcirculation, however, in both large and small blood - vessels it was normal.

7. Different clinical types of migraine gad different effect on peripheral blood-vessels: better endothelial function during the period between attacks was registered within the group of migraine with aura (i.e., higher flow induced dilation was registered).

8. Disorders in platelet function affects the peripheral blood-vessel function of patients with migraine: direct relation between the number of platelet-monocyte aggregates and ischaemia - induced changes in microcirculation capacity and inverse relation with endothelial function of small peripheral blood - vessels was found.

9. Migraine aura influences correlative relations of the variables analyzed: there was an inverse relationship between the number of platelet-monocyte aggregates and arterial stiffness as well as endothelial function in the small peripheral blood-vessels in the group of migraine without aura, while in the group of migraine with aura there was a direct correlation between platelet aggregates and ischaemia-induced changes in microcirculation capacity.

SUMMARY IN LITHUANIAN

ĮVADAS

Migrena - lėtinis susirgimas, kuriuo sergant skausmo priepuoliai ir juos lydintys reiškiniai sutrikdo ligonių kasdienę veiklą. Be to, sergantiems migrena, o ypač migrena su aura, yra 2-3 kartus padidėjusi išeminių insultų (ypač jauniems), o taip pat kitų išeminių - kraujagyslinių komplikacijų rizika. Pasirodė, kad sergantiems migrena yra dažniau nustatomi kardiovaskulinės rizikos veiksniai, priepuolio metu stebimi kraujotakos kitimai galvos smegenyse. Taip susiformavo kraujagyslinės disfunkcijos teorija, apimanti ne tik lokalius pakitimus galvos smegenų arterijose, bet ir kitose kraujagyslėse Tikėtina, jog MA yra susijusi su sisteminiu kraujagyslių pažeidimu, galbūt ir perivaskuliniu uždegimu. Tai galėtų skatinti biologiškai aktyvių medžiagų išsiskyrimą bei trombocitų agregaciją (tiek priepuolių metu, tiek tarp jų), mikrotrombų susidarymą. Be to, antrinis koaguliacinės sistemos suaktyvėjimas gali nulemti įvairių lokalizacijų išeminių kraujagyslinių įvykių atsiradimą. Tačiau iki šiol atlikti tik pavieniai darbai, vertinę periferinių kraujagyslių pokyčius sergantiems migrena, o ankstesni trombocitų funkcijos tyrimai turi nemažai trūkumų.

Darbo tikslas

Tarp priepuolių nustatyti moterims, sergančioms migrena su aura ir be auros, ryšį ne tik su bendraisiais širdies bei kraujagyslių rizikos veiksniais, bet ir su uždegiminių žymenų specifiškumu, ląstelinės hemostazės ypatumais bei su įvairaus diametro periferinių kraujagyslių endotelio funkcijos bei standumo kitimais.

Darbo uždaviniai

1. Įvertinti migrena sergančiųjų moterų bendrųjų širdies ir kraujagyslių ligų rizikos veiksnių dažnį ir jų ryšį su skirtingomis migrenos klinikinėmis priepuolio pasireiškimo formomis.
2. Nustatyti uždegiminių rodiklių (C reaktyvaus baltymo ir serumo amiloido A) ypatumus ir jų sąsajas su migrena, jos skirtingomis klinikinio pasireiškimo formomis bei trombocitų funkcinio aktyvumo kitimais.

3. Laikotarpyje tarp priepuolių įvertinti migrenos poveikį trombocitų agregacijai, trombocitų degranuliacijos reakcijai bei trombocitų- monocitų agregatų susidarymui.
4. Nustatyti skirtingų migrenos klinikinių formų poveikį funkciniam trombocitų aktyvumui.
5. Įvertinti migrenos priepuolių, jų dažnio ir intensyvumo įtaką trombocitų agregacinei funkcijai, trombocitų degranuliacijos reakcijai bei trombocitų-monocitų agregatų susidarymui ir jų ryšį su skirtingomis migrenos klinikinėmis formomis.
6. Laikotarpyje tarp priepuolių migrena sergančiosioms nustatyti įvairaus diametro periferinių kraujagyslių standumo bei endotelio funkcijos pokyčius.
7. Nustatyti bendrųjų širdies ir kraujagyslių ligų rizikos veiksnių ir skirtingų migrenos klinikinių formų poveikį periferinių kraujagyslių standumui bei endotelio funkcijai.
8. Migrena sergančiosioms nustatyti koreliacinius trombocitų agregacijos, degranuliacijos, trombocitų- monocitų agregatų susidarymo ryšius su periferinių kraujagyslių funkciniais ir anatominiais pakitimais.
9. Įvertinti migrenos auros poveikį trombocitų funkcijos aktyvumo koreliaciniams ryšiams su įvairaus kalibro periferinių kraujagyslių endotelio funkcijos bei standumo kitimais.

Darbo naujumas

Migrena sergančioms moterims įvertinome trombocitų funkcinį aktyvumą (trombocitų agregacinę funkciją, degranuliacijos fazę bei trombocitų - monocitų agregatų susidarymą), šių pokyčių ryšį su tradiciniais aterosklerozės rizikos veiksniais, uždegiminį procesą atspindinčiais rodikliais, o taip pat su klinikinėmis migrenos formomis bei priepuolių intensyvumu ir dažnumu. Pirmą kartą migrena su aura ir be auros sergančioms moterims kompleksiškai ištyrėme arterijų standumą bei skirtingo diametro periferinių kraujagyslių endotelio funkciją, atliekant tėkmės sąlygotos dilatacijos matavimus žasto arterijoje, lazerinę doplerografiją, periferinių arterijų tonometriją. Taip pat nustatėme šių pokyčių koreliacinius ryšius su uždegiminiais rodikliais bei trombocitų funkciniu aktyvumu.

TIRIAMIEJI IR TYRIMO METODAI

60 Į tyrimą įtraukta 120 moterų nuo 25 metų amžiau iki menopauzės: 60 kontrolinės grupės ir 60 moterų sergančių migrena. Migrena sergančiąsias skirstėme pagal migrenos tipą į grupes: migrena su aura (MA) – 30 ir migrena be auros (M0) – 30 moterų. Anamnezės duomenys apie migreną, KVL rizikos veiksnius, kitas ligas ir vartojamus vaistus surinkti apklausiant moteris. Tiriamosioms išmatuotas ūgis, kūno masė, arterinis kraujospūdis bei paimti veninio kraujo pavyzdžiai biocheminiams tyrimams (lipidogramai, CRB ir SAA nustatyti) ir tėkmės citometrijos tyrimams (vertintas agregatinis, degranuliacinis aktyvumas bei trombocitų – monocitų agregatų susidarymas. Taip pat buvo atliekamas arterijų standumo ištyrimas (apskaičiuojant augmentacijos indeksą (AIx), stipininės arterijos ir aortos pulsinės bangos greitį (PBG)) bei periferinių kraujagyslių endotelio funkcijos tyrimai: nuo endotelio priklausoma tėkmės sąlygota dilatacija žasto arterijoje (TSD), nuo endotelio priklausoma pookliuzinės reakcinės hiperemijos sukelta tėkmės sąlygojama vazodilatacija rankos piršto arteriniame baseine (vertinant RHI ir FRHI), lazerinė doplerografija odos mikrocirkuliacijai vertinti.

REZULTATAI

Sergančiosios skirtingomis migrenos formomis nesiskyrė nuo kontrolinės grupės moterų pagal daugumą bendrosios charakteristikos parametrų, išskyrus arterinį kraujo spaudimą: didesniu kraujospūdžiu pasižymėjo M0 pacientės, lyginant su MA ar kontroline grupe (sistolinis AKS M0 vs MA $p = 0,002$, M0 vs Kontrolė $p = 0,001$; diastolinis AKS M0 vs MA $p = 0,020$, M0 vs Kontrolė $p < 0,001$; vidutinis AKS M0 vs MA $p = 0,015$, M0 vs Kontrolė $p < 0,001$). Sergančios MA buvo daugiau sportuojančios (MA vs kontrolinė grupė $p = 0,007$, MA vs M0 $p = 0,048$, Kontrolinė grupė vs M0 = 0,379).

MA ir M0 grupės nesiskyrė pagal ligos trukmę ($p = 0,401$), priepuolių dažnį ($p = 0,747$), tirptinų vartojimą ($p = 0,276$). Nerasta skirtumo ir vertinant trijų mėnesių galvos skausmų stiprumą ($p = 0,533$) bei trukmę ($p = 0,881$).

Trombocitų skaičius tarp grupių nesiskyrė (p = 0,146). Migrena sergančiųjų grupėje trombocitų funkcinis aktyvumas buvo didesnis: daugiau trombocitų prisijungusių CD63 antikūną (% CD63/CD61 p = 0,010, abs. sk. CD63/CD61 p = 0,013) bei PAC-1 (% p = 0,001, abs. sk. p = 0,001), tačiau VFI PAC-1 (p < 0,001) ir VFI CD63 (p < 0,001) buvo mažesni, o taip pat nustatytas mažesnis procentinis trombocitų - monocitų agregatų kiekis (p < 0,015). Sergančioms migrena moterims viršsvoris (KMI ≥ 25), uždegiminių žymenų (CRB ir SAA) padidėjimas bei dislipidemija įtakos trombocitų funkciniam aktyvumui neturėjo. Kovariacinė analizė (atsižvelgiant į amžių, vidutinį arterinį kraujospūdį, KMI, bendrą cholesterolį, DTL, TG, CRB ir SAA) parodė, kad migrena sergančiosioms VFI PAC-1 ir VFI CD63 buvo ženkliai mažesni nei kontrolinėje grupėje (abiem atvejais p < 0,004). Trombocitų funkcinio aktyvumo parametrai MA ir M0 grupėse statistiškai reikšmingai nesiskyrė, o bendras skirtumų vidurkis nulemtas skirtumų lyginant su kontroline grupe: VFI CD 63 MA vs Kontrolė p = 0,033, M0 vs Kontrolė p = 0,005; VFI PAC-1 MA vs Kontrolė p = 0,014, M0 vs Kontrolė p = 0,008 ; abs. sk PAC-1/CD42a MA vs Kontrolė p = 0,009, M0 vs Kontrolė p = 0,002). Be to, M0 sergančiosioms dažnesni migreniniai galvos skausmai tiesiogiai koreliavo su didesniu VFI PAC-1 (p < 0,01), bet atvirkščiai su trombocitų - monocitų agregatų kiekiu (abs. sk p < 0,05, % p < 0,05). MA grupėje negauta nei vienos statistiškai reiškmingos koreliacijos.

Palyginę migrena sergančiąsias ir kontrolinės grupės moteris pagal kraujagyslių reaktyvumą, nustatėme skirtumus pagal mikrocirkuliacijos parametrus. Migrena sergančiosioms buvo blogesnė RF (p = 0,019), bei skyrėsi nuo kontrolinės grupės su RF susiję išvestiniai rodikliai (mažesnis RF – BZ (p = 0,015), RF – PF (p = 0,049), mažesnis plotas po okliuzijos kreive (p = 0,029)).

Atlikę kovariacinę analizę, migrena sergančiosioms, be ankščiau minėtų parametrų, nustatėme mažesnį aortos PBG (p = 0,020), blogesnę PF (p = 0,042) bei mažesnį BZ – PF (p = 0,010). MA, M0 ir kontrolinė grupės tarpusavyje skyrėsi TSD (p = 0,010) ir RF – BZ (p = 0,042) parametrais. MA pasižymėjo geresne TSD nei M0 (M0 vs MA p = 0,004). Po kovariacinės analizės (kai atsižvelgėme į ankščiau naudotus kintamuosius bei papildomai įtrauktas žasto arterijos išeities diametras) grupės skyrėsi pagal TSD (p = 0,001), aortos PBG (p = 0,025), RF – BZ (p = 0,002), BZ – PF (p = 0,041) bei plotu po okliuzijos kreive (p = 0,035). MA ir M0 grupės tarpusavyje skyrėsi

tik TSD atžvilgiu, MA grupėje ji buvo didesnė (p = 0,001). Be to, M0 sergančiosioms, patiriančioms stipresnius galvos skausmus, buvo didesnė tėkmės sąlygota dilatacija, bet plotas po okliuzijos kreive, RF, RF–BZ buvo mažesni. Tuo tarpu dažnesnius priepuolius patiriančioms MA pacientėms buvo nustatytas mažesnis AIx/HR.

Įvertinę trombocitų aktyvumo kitimų koreliacinius ryšius su periferinių kraujagyslių reaktyvumo parametrais, o taip pat ryšį su migrenos tipais, nustatėme, kad: trombocitų – monocitų agregatų skaičius atvirkščiai koreliavo su RHI migrenos ir M0 grupėse (abiem atvejais $p < 0.05$), tiesiogiai su plotu po okliuzijos kreive migrenos ir MA grupėse (abiem atvejais $p < 0.05$), su AIx/HR M0 grupėje (atitinkamai $p < 0.01$) su TSD kontrolinėje grupėje ($p < 0.05$). VFI PAC-1 atvirkščiai koreliavo su RF – PF kontrolinėje grupėje ($p < 0.05$) bei su laiku iki RF M0 grupėje. Pastarasis dar koreliavo M0 grupėje atvirkščiai su % ir abs. sk PAC-1/CD42a (abiem atvejais $p < 0.05$) bei tiesiogiai su trombocitų – monocitų agregatais ($p = 0.05$).

IŠVADOS

1. Sergančioms migrena be auros moterims nustatytas ne tik didesnis sistolinis ir diastolinis arterinis kraujo spaudimas, bet ir hipodinamija. Kiti širdies ir kraujagyslių ligų rizikos veiksniai tarp sergančiųjų migrena be auros ir migrena su aura nesiskyrė.
2. Neįrodytos serumo amiloido A ir C reaktyvaus baltymo sąsajos nei su migrenos pasireiškimo tipais, nei su trombocitų funkcinio aktyvumo kitimais, nei su įvairaus diametro periferinių kraujagyslių standumo ar endotelio funkcijos sutrikimais.
3. Sergančiosioms migrena tarp priepuolių rastas padidėjęs trombocitų funkcinis aktyvumas: didesnis skaičius trombocitų paviršiuje turėjo ekspresuotus agregacijos ir degranuliacijos antikūnus, tačiau vidutinis šių ekspresuotų antikūnų fluorescencinis intensyvumas buvo mažesnis ir jam įtakos neturėjo kiti širdies ir kraujagyslių rizikos veiksniai.
4. Nustatytas trombocitų aktyvumo ryšys su migrenos klinikine pasireiškimo forma: migrenos be auros grupėje didesnis trombocitų skaičių turėjo degranuliacijos antikūną, o migrenos su aura grupėje susidarė mažiau trombocitų - monocitų agregatų.
5. Migrenos priepuolių dažnis ir intensyvumas veikė trombocitų funkciją ir priklausė nuo auros: migrenos be auros priepuolių dažnis atvirkščiai koreliavo su trombocitų -

monocitų agregatų skaičiumi ir tiesiogiai su vidutiniu agregacijos antikūnų fluorescenciniu švytėjimu.

6. Migrena sergančioms moterims endotelio funkcija buvo sutrikusi tik mikrocirkuliacijoje, tuo tarpu tiek stambiosiose, tiek smulkiosiose kraujagyslėse sutrikusi nebuvo.

7. Migrenos skirtingos klinikinės pasireiškimo formos skirtingai veikė periferines kraujagysles: tarp priepuolių nustatyta geresnė endotelio funkcija migrenos su aura grupėje, t.y. didesnė tėkmės sąlygota dilatacija.

8. Trombocitų funkcijos sutrikimai veikia migrena sergančiųjų periferinių kraujagyslių funkciją: nustatytas susidarančių trombocitų monocitų agregatų tiesioginis ryšys su išemijos sukeltais mikrocirkuliacijos talpos kitimais ir atvirkštinis ryšys su endotelio funkcija smulkiosiose periferinėse kraujagyslėse.

9. Migrenos aura yra svarbi koreliaciniams tirtų kintamųjų ryšiams: migrenos be auros grupėje stebėtas atvirkštinis ryšys tarp trombocitų - monocitų agregatų skaičiaus ir arterijų standumo bei endotelio funkcijos smulkiosiose periferinėse arterijose, o migrena su aura sergančiosioms trombocitų agregatų skaičius tiesiogiai koreliavo su išemijos sukeltais mikrocirkuliacijos talpos kitimais.

PUBLICATIONS

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