GEORGIAN MEDICAL NEWS

ISSN 1512-0112 **No 12 (105) Декабрь 2003**

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ
Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

No 12 (105), 2003

Посвящается юбилейной дате основателя Ассоциации атеросклероза Грузии, заслуженного деятеля науки, академика Нодара Николаевича Кипшидзе

Номер издан под научной редакцией академика Н.Н.Кипшидзе

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ
ТБИЛИСИ - НЬЮ-ЙОРК

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"Georgian Medical News" is a joint publication of GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.). It is listed in the catalogue of The Central Scientific-Medical Public Library of Russian Federation and world-wide catalogues: "*Ulrich's International Periodicals Directory"* and *"Medical and Health Care Serials in Print".* Articles from the bulletin are under review of *scientific and technological informative journal of the Russian Academy of Sciences.*

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"Georgian Medical News" является совместным изданием с Международной Академией Наук, Образования, Искусств и Естествознания (IASEIA) США.

"Georgian Medical News" входит в каталог Государственной Центральной научно-медицинской библиотеки Российской Федерации и Всемирные каталоги *Ulrich's International Periodicals Directory и Medical and Health Care Serials in Print.* Статьи из журнала реферируются в реферативном журнале *Всероссийского института научной и технической информации Российской академии наук (ВИНИТИ РАН)* и хранятся в его базе данных по медицине.

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Ежемесячный совместный грузино-американский научный электронно-печатный журнал
Агентства медицинской информации Ассоциации деловой прессы Грузии,
Академии медицинских наук Грузии, Международной Академии Наук, Индустрии,
Образования и Искусств США.
Издается с 1994 г. Распространяется в СНГ, ЕС и США

Website:
www.geomednews.org.ge
www.geomednews.org
www.viniti.ru

Ассоциация деловой прессы Грузии
зарегистрирована в Ваке-Сабурталинском районом суде
Регистрационный №5/9-525

The International Academy of Sciences, Education, Inducstry & Arts. P.к.Box 390177,
Mountain View, CA, 94039-0177, USA. Tel/Fax: (650) 967-4733

Версия: печатная. **Цена:** свободная.
Условия подписки: подписка принимается на 6 и 12 месяцев.
По вопросам подписки обращаться по тел.: 93 66 78.
Контактный адрес: Грузия, 380077, Тбилиси, ул.Асатиани 7, IV этаж,
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ABOUT GEORGIAN ATHEROSCLEROSIS ASSOCIATION (GAA)

Was founded in 1989.

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BIOGRAPHY OF N.KIPSHIDZE

The famous scientist and physician, academician Nodar Kipshidze was born to the family of highly respectable prominent internist Dr. Nickoloz Kipshidze on the 12th of October, 1923 in Tbilisi, Georgia. After graduating the secondary school Nodar Kipshidze successfully passed admission exams and was enrolled into Tbilisi State Medical Institute. After graduating the institute in 1946 he became the ordinate of the department of Internal Medicine, in 1948 Dr. Kipshidze continued his studies at the postgraduate school of the Institute of Surgery at the Georgian Academy of Sciences. In 1952 Nodar Kipshidze successfully defended the postgraduate dissertation thesis and became the associated professor of the department of Internal Medicine of Tbilisi State Academy of the Physicians.

In 1954 Nodar Kipshidze was successfully enrolled into the PhD program of the Institute of Therapy at the State Academy of the Medical Sciences of Soviet Union. During his fruitful and plentiful work in Moscow during 1954-1957 the young scientist, developed close friendship and professional relationship with academician Miasnikov.

In August of 1957 Nodar Kipshidze was delegated for work to the United Nations Organization in New-York as a doctor. This made him the first Georgian physician to work for the international organization where he performed numerous interesting studies in cooperation with the different scientific centers of US, which enabled him to acquire highly useful experience in the field. The cooperation lasted in

future, as well. In 1959 Nodar Kipshidze returned to Tbilisi and continued working at the Tbilisi State Academy of the Physicians.

In 1960 Nodar Kipshidze founded The Experimental and Clinical Scientific Laboratory of Therapy, in the future (since 1961) The Experimental and Clinical Scientific Institute of Georgia. There were developed several different centers and departments on the base of the Institute: Internal Medicine, Cardiology, Rheumatology, Gerontology, Ultrasound Imaging, Pulmonology, Gasrtoenterology, Hepatology and Scientific Methodology.

In 1963-1965 Nodar Kipshidze was cimmissioned to the WHO in Geneva and worked there as the Director of Biology, Pharmacology and Therapy Departments.

In 1963 Nodar Kipshidze completed and successfully defended the Doctorate Dissertation in Moscow, and a year later he was awarded a degree of Professor.

In 1967 Nodar Kipshidze was awarded the title of the Merited Worker of Science, for his exceptional achievements in his work.

Nodar Kipshidze is the author of 18 monographic works and more than 500 scientific publications. The scientific investigation field of Nodar Kipshidze was always very wide and interesting, he was investigating pathology of myocardial infarction, hypertension, cardiomyopathy, atherosclerosis and geriatry, especially contributing to the new directions in treatment of myocardial infarction, such as: intracardial and intravenous laser-treatment.

In 1981 Nodar Kipshidze was presented with The State Award of the Republic of Georgia for his merit in care for the patients with myocardial infarction; he has organized the Emergency Cardiology Center with modern equipment and highly professional doctors. In 1986 Nodar Kipshidze became the winner of The State Award of Soviet Union for his significant contribution to Medicine.

In 1986 for his scientific monographic works and reports Nodar Kipshidze was awarded the Prize of Academician Miasnikov.

Nodar Kipshidze organized 53 scientific conferences and symposiums, different workshops and training programs.

Nodar Kipshidze had leaded the scientific work in the Institute of Therapy during many years, supervising 30 doctorate and more than 100 candidate dissertations, and is still greatly contributing into scientific medical field.

For the lengthy and successful work in science, in 1975 Nodar Kipshidze was chosen as the Associate Member of the Scientific Academy of Soviet Union and in 1988 he was chosen as the Member of the same Academy. Since 1996 Nodar Kipshidze is the Academician of Georgian Scientific Academy.

The teaching merit of Nodar Kipshidze is very significant as well. Since 1987 he is the Professor of the Chair of Therapy of the Georgian State Medical University.

Since 1963 up-to-day Professor Kipshidze is the expert on staff at the Cardio-Vascular Disease Study Committee of WHO. He is the member of Referring Committee of the scientific journals of Georgia, Russia, Armenia and United States.

In 1984 Nodar Kipshidze was elected Chief of Georgian Gerontology and Internal Medicine Society. He had founded the Georgian Atherosclerosis association and is the President of this organization to the day.

Nodar Kipshidze has been awarded the Prizes of ”People’s Friendship” and “The Red Flag of Work”.

From 2000 Nodar Kipshidze is the chief of the postgraduate department of the National Center of Therapy and still is leading the scientific studies.

In 2003 Nodar Kipshidze was presented the Golden Medal of Academician Chazov of the Committee of Cardiology Association of CIS.

GENETIC FACTORS OF ATHEROSCLEROSIS

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Atherosclerosis is a multifactor disease in development of which both environmental and genetic factors play their parts. At the present there are no doubts that atherosclerosis is laid in childhood and adolescence, and it is pathogenetically connected with the lipid exchange disturbances. Hence, it is of a certain significance to study some risk factors of atherosclerosis among the population of this age.

Lipid exchange is known to be one of the main processes of the human body's vital activity. It is connected with the universal role of lipids in homeostatic function, with the mobile ability of their metabolism to adapt to various states of the body. Lipid exchange significantly affects the activity of membranous enzymes, influences on the level of immunologic reactivity and is connected to the realization of genetic information [1].

Every period of human ontogenesis has certain peculiarities of lipid exchange. A child's birth is followed by a considerable change in metabolism. Lipids being an energy source of a greatest importance take part in the process of homeostasis maintenance and promote the realization of reactions of a neonate when it passes to the extrauterine way of existence.

In this connection the aim of the study was to reveal dyslipoproteinmia (DLP) and to determine blood ground of ABO system in neonates and to present as well as to make lengthy observation (10 years observation) on the chosen group of neonates predisposed to atherosclerosis development at different periods of their lives.

Ten-year long prospective genetic-epidemiologic observations on the population of children and teenagers in Tbilisi can be used when planning and carrying out general prophylactic medical examination of the urban population as when choosing the contingent for a constant observation by a general practitioner and a cardiologist.

The studied problem is of great practical importance since atherosclerosis often develops without any symptoms while the period from the beginning of the disease till its manifestation is determined by the personal peculiarities and interaction with the environmental factors. Hence, the most important tendency of atherosclerosis prophylactics seems to be the exposure of persons predisposed to this disease and developing medical-prophylactic measures.

Material and methods. The study presents the results of prospective family-genetic and clinical-laboratory investigations on 660 neonates and their parents during 10 years.

A genealogic map on parents (age, hereditary burden, ill habits, pregnancy course and that of delivery, ABO blood group and RH, etc.) and on neonates (gestational age, atheropometric date, sex, blood group, RH, etc.) While recording parents' anamnesis, particular attention was paid to such diseases which can influence indices of neonatal lipid exchange: myocardial infarction at the young (before the age of 50) age, hypertension, obesity, atherosclerosis.

Investigations were made on the blood serum taken from the cubital vein of the neonate's both parents and on the blood serum from the neonate's umbilical cord immediately after cutting it.

The levels of total cholesterol, B-lipoproteins, triglycerides concentration were determined in the blood serum of the examined subjects. The quantitative estimation of the total fraction of atherogenic B and pre-beta-lipoprotein was performed by means of the turbidimetric method.

Typing of hyperlipoproteinemia was made after WHO classification. With the aim of studying the relationship between lipid levels and blood genetic markers in all the examined persons, blood groups of ABO system were determined with standard hemagglutination serum.

Results and discussions. The results of examination of 660 neonates and their parents have shown that neonatal umbilical blood revealed dyslipoproteinemia - 17,5% (79 cases). Among them Pa type dyslipoproteinemia was found in 25,9% (20 cases), hyperlipoproteinemia PB in 45,6% (136 cases), hyperlipoproteinemia IV type-in 28,5% (23 cases).

It should be noted that all the neonates with hyperlipoproteinemia had hereditary burden to atherosclerosis on the lone of father or mother.

Following are the examples to illustrate the above mentioned.

Neonate S.K. Georgian, weight 3500gr., length 52 cm. Delivery was without complication. Lipid indices are following: XC-148mj%, TG-90mj% to total fraction of beta and prebeta LP-217mj%. When comparing with the data of dick-electrophoregram we revealed PB hyperlipoproteinemia.

A woman in labor - 35 years old teacher, for the last 2 years had tension angina pectoris. PB type of GLP was diagnosed by testing the blood serum. Father of the proband - 42 years old, with no complains, however Pa type GLP was diagnosed. The grandmother of the neonate on the mother's line suddenly died from myocardial infarction at the age of 48. The grandmother's elder brother had myocardial infarction. Mother's elder sister, 46 years old, suffers from hypertension.

As we see, not a single relative of the proband's mother had lived beyond the age of 60 and the cause of death was atherosclerosis incident; we find a big similarity in the patient's age or in the unfavorable outcome.

Neonate M.K. Georgian, weight 4100gr., length-54cm. The test of blood serum revealed hypertriglyceridemia 92mj%, GLP of type IV. Mother - 34 years old, practically in good health. The investigation revealed GLP of type (cholesterin-287mj%, triglycerides-142mj%). The summ of beta and pre-beta LP - 898 mj%. On the electrophoregram fractions of atherogenic beta and prebeta LP prevailed. Father is 40 years old in good health. The indices of lipids and LP are normal. The proband's grandmother on mother's line has

had angina pectoris for 8 years: attacks have become severe during the last years. The proband's grandfather died at the age of 62 from myocardial infarction, his great uncle died at the age of 65 while watching T.V., his great aunt died suddenly in the street at the age 59, the grandfather on father's line died suddenly at 65, had diabetes mellitus. The grandmother suffers from heart failure at 52 years of age. Father's brothers (42-45 years old) mention of angina pectoris of tension. In this family the neonate's hereditary is burdened from the both sides — mother's and father's lines.

When comparing the values of the parents' lipids with those of the neonates, we revealed that in 228 cases (50,7%) the character of the neonates's DLP coincided with the mother's one. Among them in 86 cases (37,5%) the both had Pa type GLP, in 121 cases (53%) of PB type and in 22 cases (9,5%) GLP of IV type.

The same type of GLP in their father was found in 161 cases (36%). Among them Pa type of GLP in 59 cases (32,2%), PB- (40,6%), IV type – in 22 cases (13,2%).

In in 61 cases out of our material (13,3%) GLP of the both parents coincides with GLP of the neonate. When determining the blood group of system ABO, we found that blood group O prevailed in the neonates and their parents and in majority of the cases (80,78%) these persons had normal lipid values. The figure shows a high frequency of correspondence of IIB type GLP with blood group A (93,1%).

A 10 years prospective examination of the babies and their parents with hereditary burden to atherosclerosis has revealed that every year ambulatory examination show DLP in the children and their parents and IIB type GLP frequently correlate with blood group A without changing with age.

The result of our study show that the development of atherosclerosis and ischemic disease of heart begins in childhood and that atherosclerosis is a problem of pediatrics. Because of this the study of umbilical blood lipid spectrum enables us to reveal hereditary forms of GLP, to make early diagnosis and to start therapy of these disturbances in due time from the first days of the human life.

Thus, we can draw the following conclusion from our studies: a 10 years prospective examination of neonates and their parents has shown that among neonates DLP was diagnosed in 17,5% of cases and IIB type of hyperlipoproteinemia was the most frequent to be found (46,6%) GLP of IIB type was revealed in 35,9% and type IV 28,5 of cases. At the repeated examination of the children and their parents, lipid spectrum values almost failed to change, and we found a group of children with a high probability of developing atherosclerosis.

A relationship has been found among the types of GLP and blood groups of ABO system. A correlation GLP of IIA type with the blood group A (93,1%) should be considered an important risk factor predisposing to the development of atherosclerosis.

On the basis of our finding it is possible to make a wide screaning (examination of children with hereditary burden to atherosclerosis) with the aim of revealing the GLP types that will enable us carry out an early prophylaxis (prescription low content of saturated fatty acid diet and vitamins "E", "B6") of atherosclerosis by means their exchange normalization.

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РЕЗЮМЕ

ГЕНЕТИЧЕСКИЕ ФАКТОРЫ АТЕРОСКЛЕРОЗА

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Результаты 10-летнего проспективного обследования новорожденных (660 пациентов) и их родителей показывают, что среди новорожденных дислипидемия наблюдается в 17,5% случаев, в основном (45,6%), II В типа. Гиперлипидемия II А типа выявляется у 25%, а IV типа у 25% новорожденных. При повторном обследовании (спустя 10 лет) новорожденных и их родителей – показатели липидного спектра не изменились. Выделена группа детей с высоким риском развития атеросклероза. Установлена связь между типами гиперлипопротеинемии и группами крови АВО системы. Наличие высокой корреляции между гиперлипидемией II А типа и А группой крови является риском развития атеросклероза. Определение и нормализация показателей липидного спектра (на фоне назначения диеты с ограничением животных жиров и витаминов "Е" и "В 6") с детского возраста дает возможность проведения успешной ранней профилактики атеросклероза.

Key words: Genetic factors of Atherosclerosis, Dyslipoproteinemia, Blood groups.

Научная публикация

PECULIARITY OF MYOCARDIAL MICROCIRCULATORY NET

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Having studied by Komakhidze's injection method the cardiac vessels of humans, from foetus to 85 years of age and dogs, we found that the venous system of myocardium begins in the sinusoids. The sinusoids play an important role in the regulation of myocardial circulation.

The myocardial sinusoids form a particular compartment of the myocardial venous system consisting of vessels with characteristic wall structure and pattern of distribution. Several venous capillaries open brushlike into the peripheral end of the sinusoid. Brown (1965) designated these formations as "Turnip roots", Lunkenheimer and Merker (1973) - as "Hohlraume", stating that their walls are composed of sinusoids containing endothelium as well as a basal membrane, but no pericytes. This peculiarities are noted also by Wearn (1936) and later by Lunkenheimer (1973) and some others.

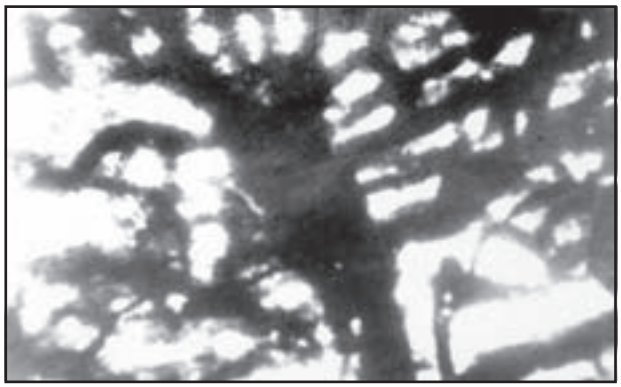
The sinusoid continues in the venula of the myocardium which can have a few dilatations following one another.

The sinusoids acquire particular significance when blood flows through the arteries with some difficulty. It is manifested by age changes of the capillary net of the human myocardium, as well as in experiments. There are sinusoids in the myocardium of human beings of different ages, but it is very difficult to find them in the heart of foetuses or infants, because the dilatations are hardly discernible, the more so as the younger the individual, the denser the capillary net of his myocardium. With age the capillary net is getting more sparce, while the sinusoids become wider and more prominent. After forty-five years of age sinusoids stand out clearly against the background of the surrounding capillary net and with time the difference becomes more and more marked. In aged people, especially in those with cardiosclerosis, sinusoids dominate in the picture of the capillary net of the myocardium. They are not only factually enlarged, but they are more readily distinguishable owing to the thinning of the capillary net.

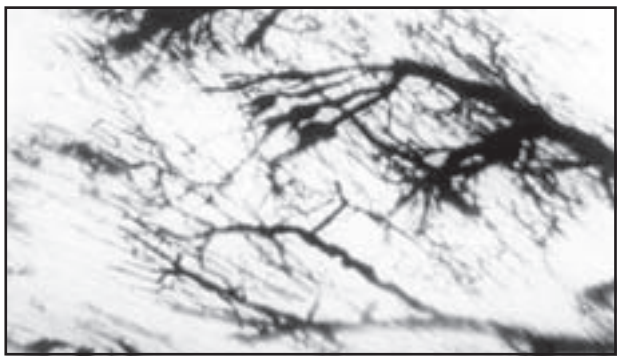
The sinusoids of the myocardium enlarged in experimental ischemia and hypoxic hypoxia too. In the first hours and days after the ligation of the anterior interventricular branch of the left coronary artery of dogs the blood flows to the ischemic area through veins until the new arterial vessels develop. The possibility of the retrograde blood flow is well demonstrated in defective injections of the myocardial vessels - the contrast substance injection into the arteries reaches the capillary net through veins, i.w. via veins, sinusoids and the venous section of the adjacent capillary net, filling them out, while the arteries remain empty. The presence of the injection substance in veins and venous part of the capillary net, its absence from the arteries, which are more peripheral from the ligature, bears evidence for the above assertion. Even after revascularization of the ischemic area the dilation of the sinusoids is well apparent.

The strongly marked enlargement of sinusoids and venules, and increase of their number is obviously the result of the influence exerted thereupon by ligation of the anterior interventricular branch of dogs. By artificial reinforcement of extracardiac sources of vascularization of the heart by means of techniques creating contact between the heart and either lung, intestine or epicardium, and by treatment with coronarodilators in experimental myocardial infarction.

This dilatation of sinusoids and venules is obviously the result not only of ligation of the anterior interventricular branches, but also of treatment of experimental infarction.



Pic. 1. Sinusoid in the myocardium of left ventricle of 8-month's child. x-sinusoid. 20x15.



Pic. 2. Sinusoidal clavate enlargements in left ventricle of 84 years old patient with cardiosclerosis. 8x5.

Our experiments do not confirm the opinion of Beck and Tichy (1935), Demikhov (1958) and a number of other authors that the newly developed vessels grow narrow and lose their importance as an additional source of nourishment of the myocardium due to wrinkling of the cicatrice.

Only the thinnest vessels, such as those in scar tissues, are the result of cardiopexy, whereas the newly-formed sinusoids are much larger.

The fact of dilation of sinusoids with age, and especially in cardiosclerosis, as well as during experimental ischemia and hypoxic hypoxia, confirms that the expansion of volume of the venous channel is inversely proportional to the blood flow in the arteries. The circumstance that the inflow diminishes, while the backflow increases is rather paradoxal. In reality the expansion of the venous channel compensates for the deficiency of the arterial vascularization of the blood supply, bringing nutrients to the myocardium by retrograde blood flow. Vaboril and Schiebler (1969) note that during a certain period of the embrional life of the rat the vascularization of myocardium is accomplished through the sinusoid-venous pathway, however these sinusoids are not identical to the sinusoids of adult mammals.

Since the sinusoids are arranged in groups, the sites of their location during venous stasis are more deeply coloured. In our opinion sinusoids are the formation responsible for the phenomenon of marbling. Several investigators have noted the marbled appearance of the myocardium in the picture of plethoric hearts. We observed this phenomenon in our injection preparations of human and dog hearts. Under the microscope the myocardial capillary net appears as fields of alternating intensity of filling, i.e. as dark and light fields, the latter being devoid of sinusoids.

Sinusoids play an important role in regulation of the blood supply to the myocardium. Owing to the change in their volume they can retain more blood in the venous section, acting as temporary reservoirs thereby slowing down the blood flow and enhancing metabolism.

The above mentioned peculiarities in the arrangement of cardiac venous vessels have been verified only in the ventricular myocardium, whereas we could not detect any sinusoids in the atrium. Evident changes in the venous system of the myocardium in the course of life and under experimental conditions while the blood flow artificially interrupted, testify that venules and sinusoids tend to maintain metabolism at an adequate level.

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РЕЗЮМЕ

СВОЕОБРАЗИЕ МИКРОЦИРКУЛЯТОРНОЙ СЕТИ МИОКАРДА

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Мельчайшие венозные сосуды миокарда человека и собаки начинаются синусоидами, в которые вливаются многочисленные капилляры, наподобие кисточки.

Синусоиды продолжаются в венулы, которые также создают местами расширения. Синусоиды можно обнаружить в миокарде человека всех возрастов, но в печени первого года жизни они очень малого размера и малочисленны. С возрастом постепенно увеличивается их число и размер, особенно в старости и при кардиосклерозе таково же начало венозной системы миокарда собаки. После нарушения проходимости коронарных артерий- экспериментальный инфаркт миокарда, синусоиды резко увеличиваются в объеме и численно.

По факту увеличения сосудов венозного оттока при сокращении коронарного кровоснабжения, предположена возможность кровоснабжения миокарда ретроградным путем, т.е. наличие обратного тока крови из вен в миокард.

Key words: miocardium, sinusoid, retrograde blood flow.

Научная публикация

HELICOBACTER PYLORI INFECTION AND "AGGRESSIVE ATHEROSCLEROSIS"

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The term "Aggressive Atherosclerosis" was introduced by academician Nodar Kipshidze (2000), and means malignant atherosclerosis, caused by destabilization of "unstable atheromatoze plaque", that greatly depends on the inflammatory process taking place in it, and is predisposed to rupture and development of local thrombosis.

In the recent period chronic infections (such as Chlamydia Pneumoniae, Helicobacter Pylori, etc) are considered as provocative factors in developing of coronary heart disease (CHD) and plaque destabilization. Epidemiologic and clinical studies revealed positive correlation between Helicobacter Pylori (HP) infection, CHD and its complications [4,9,10].

At present the concept of the affect of HP on the course of atherosclerosis through prolonged circulation of such weak mediators of inflammation as C-reactive protein (CRP), cytokines, changes in lipids compositions is discussed [7].

The goal of a work was to determine the role of infection in the exacerbation of atherosclerotic process in HP infected CHD patients.

Materials and methods: 25 patients with dyspepsia and HP positive test were studied: 16 patients among them were with CHD - 62,5% males and 37,5% females of the age group 48-70. 9 patients were involved in control group 66,7% males and 33,3% females, age group 31-51.

Blood samples were collected for each person after 12 hour fasting. Non-hemolised serum underwent the following tests: Total cholesterol (TC), Triglycerides (TG), High density lipoproteins Cholesterol (HDLC), Fibrinogen using autoanalyzer Spectophotometre Janway-4500).

TC, TG was perfformed enzimatically using "BIOLABO", France reagents; HDL-Cholesterol was measured after precipitation of VLDL and LDL (using "BIOLABO, France" reagents). ApoB-Lipoproteins were measured by Burstein method [3]. LDL-C was calculated according to Friedwald[5], as Atherogenic index- by accepted formula [6]. Rutberg method was used to measure fibrinogen. CRP was performed by "Human" latex test.

All patents underwent upper GI endoscopies ("Olympus") combined with histology. Type of gastritis was revealed by L.I. Aruine classification (1). The histological study of gastrobioptates was provided by means of Hematyxilin - Eosin and Van-Gieson's stains. Hp status was revealed by urease test of gastric antral and corpus mucosa specimens and histological method by stain of Giemsa. Gastric secretion level was studied by pH-meter.

Semithin and ultrathin slices were used for histo- and ultrastructural examinations of blood formed elements. The electron micro photos were received on the electron microscope "Tesla BS 500" at the accelerated tension of the apparatus 60-70 kv.

Statistical Analysis - Continuous variables are presented as mean(M) +/- standard deviation (SD). Student's T test for data was used to compare values within subject groups; Statistical significance was defined as $P < 0,05$. Correlation (r) were tested by Pearson correlation.

Results and their discussion: The results of investigations indicate association between HP infection and CHD [4,11]. According to the outcomes, 12,9% of HP infected patients with CHD had hyperacidity, in 30,85% of patients gastric acidity was normal; 56,25% - hypoacidity was revealed correspondingly, the data of control group was 22,2%, 22,2% and 55,6%. In 67,3% of CHD patients chronic superficial gastritis and in 32,7% - hypertrophic gastritis were found. In control group the percentage was distributed in the following way 55,6% and 44,4%. It's worth mentioning that there were no cases of atrophic gastritis.

Table. Lipid exchange indices and Fibrinogen in HP infected patients with CHD and without it

	AAge	TC	TG	HDL-C	ApoB-LP	AFb	VLDL-C	LDL-C	IA
M-CG	42	5,0	1,53	1,47	5,3	321	0,31	3,23	2,48
CG Std	15	1,1	0,39	0,31	1,2	61	0,08	0,96	0,80
M- p At	56	6,6	2,18	1,23	7,9	353	0,44	4,94	4,61
At Std	11	1,3	0,50	0,29	1,6	67	0,10	1,33	1,58

CG-controle groupe. CHD- HP infected patients with CHD group. Mean(M), Standard Deviation (SD), Total Cholesterol (TC mmol/l), Fibrinogen(Fb мg/l), High dencity Lipoproteins Cholesterol (HDL-C), Low dencity Lipoproteins Cholesterol (LDL-C), very low dencity Lipoproteins Cholesterol (HDL-C), Atherogenouse Index (IA).

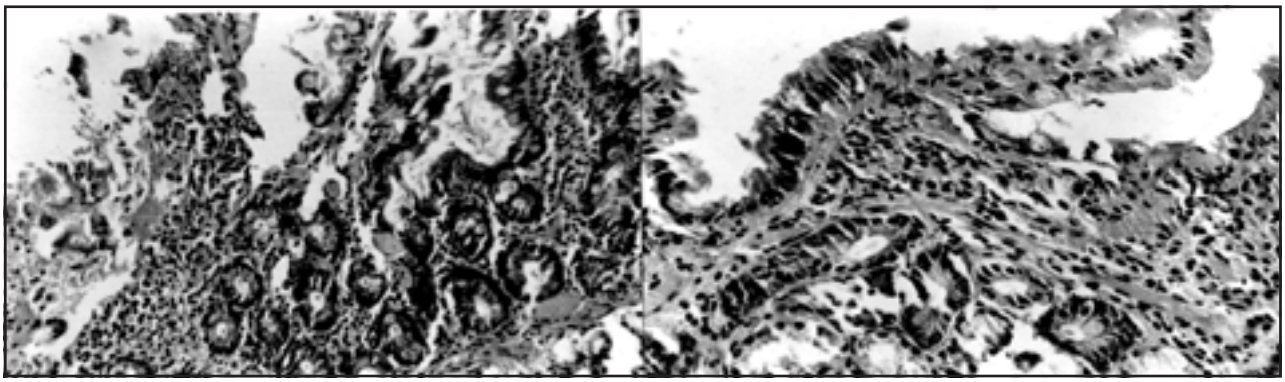

Fig 1. Active phase of gastritis (hypersecrative form of gastritis). Hematyxilin –Eosin stains X

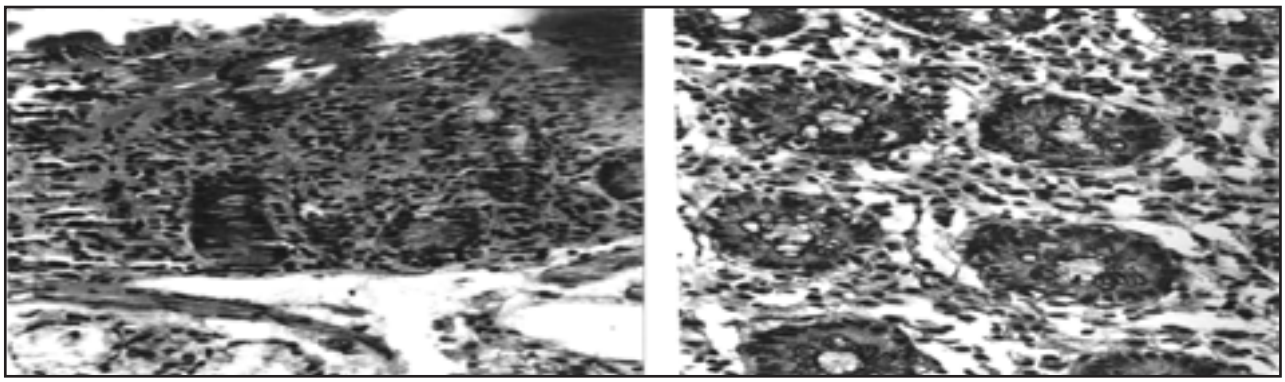

Fig.2 Chronic gastritis. Hematyxilin –Eosin stains X

We consider that one of the causes of CHD exacerbation in HP infected patients is inflammation of atherosclerotic plaque in coronary artery wall that is followed by rupture and thrombosis. The markers of such exacerbation are: increased level of acute phase proteins (fibrinogen and CRP) and of inflammation cell factors. We'd like to present inclusion of leucocytes component in the possible exacerbation of atherosclerosis in case of HP infection and on the background of atherogenesis and existence of inflammation markers.

Active phase of gastritis (hypersecretion form of gastritis) (Fig.1) reveals by existence of macrophages and leukocytes among epithelial cells is connected with HP colonization.

Hystologically (Fig.1) HP chronic gastritis is manifested by proliferative inflammation and deterioration of mucous and submucous layers as well. It is known that lamina propria infiltration with lymphocytes is in close correlation with the level of HP colonization and manifestation of inflammation [8].

Migration of lymphocytes and lamina propria proliferation that is conditioned by HP antigenstimulating affect and cytokines (IL-1, tumor necrosis factor - TNF), produced by antigen presenting cells can explain such correlation. Besides, exfoliation of one layer epithelial, increase of its permeability due to accumulation of leukocytes is also observed. According to the literature sources there exists possibility of HP antigens processing by means of gastric mucocytes. Correspondingly in our material such increase of cells reflects existence of autoimmune disease and among them existence of HP induced gastritis as a necessary component. On the other hand mononuclear infiltration causes progress of inflammatory process and persistence. Such local damage of stomach is very similar for both groups of patients. A chronic local disease, such as chronic active helicobacterial gastritis is a source of activated leucocytes, which getting in the blood flow cause dissemination and chronisation of HP induced process.

What processes take place in blood? Formed elements ultra structure of the PH infected patients with CHD is heterogeneous (active, damaged, apoptotic cells). Vacuolization of cells, autophagocytosis, hypersegmentosis of polymorphic leucocytes nucleus is observed. Monocytes are represented by cells with large nucleus, with numerous fatty inclusions that denote on the existence of scavenger-pathway. Presence of numerous degranular leucocytes explain significant increase of cytokines production, activation of thrombocytic factor and synthesis of "acute phase" proteins.

In full correspondence with this condition aggregates of platelets permanently occur in the blood of CHD patients. They create preconditions for the formation of intravascular thrombosis. Generalization of inflammatory stimulus, in

which pathogenic microbe factor acquires an active role, is manifested by increase of fibrinogen and CRP in HP infected CHD patients.

HP infected patients with CHD increase the inflammatory markers on the background of hyperlipidemia and decrease of HDL is observed (table). This data reliably differ from the data of control group ($p<0,05$). Correlation between cholesterol and apo-B lipoproteins and fibrinogen was observed. Such interrelations didn't take place in control group.

Increase of CRP and fibrinogen is a non-specific phenomenon, which reflects excessive synthesis of these proteins caused by leukocytes produced cytokines in response to liver inflammation and tissue damage. Given data makes possible look at the inflammatory process in the wall of coronal artery (in atheromatouse plaque) from the viewpoint of HP stimulating affect. With this regard it is an interesting fact that HP DNA is manifested in atheromatouse plaques.

Activated leukocytes carry HP and inflammation signal and their interaction with endothelium and atherosclerotic plaque may cause such local complications as rupture of the plaque surface and thrombosis, that is one of the reasons for turning chronic CHD into the acute form.

Presented data shows the significant links between the structural and functional changes in the lipid range, indicators of acute phase proteins and leukocytes in case of atherosclerosis and with the presence of HP infection. Therefore, we think, that HP infection is a predisposing factor for atherogenesis, and in case of atherosclerosis - an aggressive factor, that may induce destabilization and exacerbation of atherosclerotic plaque.

Thus, HP patients with hyperlipidemia make up high-risk group for prevention of atherosclerosis.

CHD patients with HP infection and increased indicators of acute phase proteins are the population under the high risk of possible exacerbation of atherosclerosis.

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РЕЗЮМЕ

HELICOBACTER PYLORI ИНФЕКЦИЯ И «АГРЕССИВНЫЙ АТЕРОСКЛЕРОЗ»

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Понятие «агрессивный атеросклероз», которое по смыслу обозначает атеросклероз со злокачественным течением, причиной которого является дестабилизация «нестабильной атероматозной бляшки, впервые было внесено академиком Н.Н. Кипшидзе в 2000 году.

Целью данного исследования является установление роли геликобактерной инфекции в возможном обострении атеросклеротического процесса.

Обследованы больные с положительным тестом на НР ишемической болезнью сердца (подтвержденным перенесшим инфарктом миокарда и положительным тестом велоэргометрии) и лица контрольной группы (у которых атеросклероз был исключен клиническими исследованиями). Каждому пациенту проведены следующие обследования: общий холестерин (ОХ), триглицериды (Тг), холестерин липопротеинов высокой плотности (Х-ЛПВП), фибриноген (на спектофотометре с помощью тестов "BIOLABO", France). Все пациенты подлежали гастродуоденальной гастроскопии, комбинированной с гистологией и НР статусом (выявляемой уреазным тестом) из мукозной части желудка.

В контрольной группе показатели ОХ, Тг, Х-ЛПРП и Фибриногена не превышали установленных норм, показатели липидного обмена и фибриногена статистически достоверно отличались ($p<0,05$) от таковых у больных ИБС.

Выявлено, что в случае нарушения липидного обмена и персистенции HP создаются благоприятные условия для включения одного из пусковых механизмов атерогенеза: активация моноцит/макрофагов, их хемотаксис, фагоцитоз, нагрузка липидами цитоплазмы, возникновение продуктов перекисного окисления, цитокинов; появляется возможность обострения атеросклероза (включения ответа "острой фазы") с повышением фибриногена.

На основании полученных нами данных рекомендуем пациентов с ИБС и HP инфекцией выделить в отдельную группу с высоким риском обострения атеросклероза.

Key words: Helicobacter pylori, aggressive atherosclerosis.

Научная публикация

LIPID-MODIFYING AND PLEIOTROPIC EFFECTS OF VASILIP (SIMVASTATIN) IN SECONDARY CORONARY DISEASE PREVENTION

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Data from clinical trials have demonstrated strong beneficial effects of the hydroxy-methilglutaryl co-A reductase inhibitors (statins) on both primary and secondary prevention of coronary heart disease (CHD) [1,4]. A growing body of literature suggests that statins have benefits beyond their effect on cholesterol. Pleiotropic (nonlipid) effects of statins may play a role in reducing the incidence of cardiovascular events and include stabilisation of atheromatous plaque, improvement of endothelial function, their anti-inflammatory and anti-platelet activity etc [3]. The complexity and pleiotropism of therapeutic responses to statin therapy suggest the potential value of monitoring strategies more predictive than the cholesterol profile to determine effective therapeutic response before recurrent clinical events.

Statins are the first-line agents in preventive cardiology. In our center where the system of secondary coronary prevention (SCP) has been functioning, simvastatin is one of the mostly used statins. The goal of the present trial was to assess lipid-modifying and some pleiotropic effects of simvastatin (vasilip, KRKA, Slovenia) in CHD patients with and without myocardial revascularization.

Material and methods. At the beginning the study included 98 outpatients. Three patients interrupted to receive vasilip, two-could not recheck blood tests and one-went abroad. 41 patients had undergone coronary artery bypass graft operation, 14 - percutaneous coronary intervention and 37 patients had established CHD without myocardial revascularization. Mean age was 56+3,8 years, only 8 patients were female. All patients were on an antiatherogenic diet at least 4 weeks before and during the whole follow-up. Starting dose of vasilip was 20 mg/day. According to NCEP low-density lipoprotein cholesterol (LDL-C) goal of <100mg/dL [5] the dose of vasilip was titrated. At the end of supervised period mean dose of the drug was 13,3±2,7 mg/day. Fasting lipid profiles – LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC), atherogenic ratio (AR=(TC-HDL-C)/HDL-C) were obtained prior to and after 6 and 12 weeks the initiation of therapy. Besides liver transaminases (AST, ALT), nitric oxide (NO), C-reactive protein, fibrinogen concentrations were examined. Listed parameters were determined by the methods described in our previously published article [2]. Inclusion criteria was: LDL-C>100mg/dL. Exclusion criteria were: TG>400 mg/dL, prior lipid-lowering treatment and contraindications to statin administration.

Results and their discussion. The mean changes from the baseline to the end of study in all parameters of lipid profile are demonstrated in the table.

Simvastatin treatment was associated with marked decreases in TC, LDL-C, TG and AR. Compared with baseline all reductions were statistically significant at the end of the follow-up. In relation to the HDL-C vasilip revealed less efficacy, after 12 weeks of therapy antiatherogenic lipid fraction increased slightly – by only 8%.

Table. Dynamics in lipid parameters during treatment with vasilip (n=92)

Time of the follow-up		Mean and percentage changes versus baseline				
		TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	AR
Baseline	1	251±7,1	156±5,4	39±2,0	194±10,3	5,4±0,16
6 weeks	2	195±6,7-22%	112±4,8-28%	41±1,75%	173±11,2-11%	3,7±0,13-31%
12weeks	3	182±7,3-27%	98±6,1-37%	42±1,98%	163±8,6-16%	3,3±0,11-39%
P-value$_{1-2}$		<0,001	<0,001		-	<0,001
P-value$_{1-3}$		<0,001	<0,001		<0,01	<0,001

According to our data, during 12-week study period vasilip lowered TC, LDL-C, TG and AR by 27%,37%, 16% and 39% respectively. It is noteworthy that more than 60% of the maximum reduction in all lipid parameters was attained in the first 6 weeks after the initiation of simvastatin. During following weeks they were decreasing gradually. Therapy was considered effective in case of achieving the target levels of: TC<200mg/dL, LDL-C<100mg/dL, HDL-C>mg/dL, TG<150mg/dL and AR<3,5 as it is accepted in SCP. They were reached in 95%, 91%, 57%, 48% and 94% of cases respectively.

In 87 patients endothelial function was estimated by examination of plasma nitric oxide (NO) concentrations. During 12 weeks 44 patients were on vasilip treatment and 43 patients – on standard medication therapy. There were observed 4 types of plasma NO levels: extremely low (NO<5mcmol/L), low (NO-5-14 mcmol/L), normal (NO-15-24 mcmol/L) and high levels (NO>24 mcmol/L). In patients with vasilip therapy mean plasma NO concentration was 17±2,9 mcmol/L after 12-week of study period. In patients without statin treatment mean level of the same parameter was 28±2,5 mcmol/L. It is noteworthy that increased plasma concentration of nitric oxide is not less harmful for the vessel wall, than low concentration. Deference between groups was significant (p<0,01). So, patients without statin treatment had impaired endothelial function. On the background of obtained data we can suppose that vasilip improves endothelial function.

By examination of plasma C-reactive protein and fibrinogen concentrations in the same groups of patients there was observed one more pleiotropic effect of simvastatin – anti-inflammatory action. At the end of supervised period - after 12 weeks of therapy mean plasma levels of C-reactive protein were 1,9±0,76 mg/dL and 3,8±0,65 mg/dL in patients with and without statin treatment respectively (p<0,05). Mean plasma fibrinogen concentration at the same stage of the supervision was 3,2±0,4g/L in patients with vasilip therapy whereas in patients without statin treatment it was 6,9±1,1g/L(p<0,01). Hence vasilip had significant anti-inflammatory effect as well.

Therapy with simvastatin was well-tolerated. No serious adverse event occurred during 12-week study period. Mild and asymptomatic elevation of hepatic transaminase levels was observed in one case. One patient reported dizziness. Two patients had muscle pain and weakness of inferior limbs. After dose reductions of the drug to 10mg/day these side-effects disappeared.

In summery, our secondary CHD prevention research demonstrated that treatment with vasilip is beneficial for the correction of dyslipidemia. In addition, vasilip exhibited beneficial effects beyond cholesterol lowering, the so-called pleiotropic effects: it significantly improved endothelial function and revealed anti-inflammatory activity. These nonlipid effects are not less important for the prevention of recurrent ischemic events than modification of lipid fractions. So, the results of the present SCP trial support the use of vasilip in all CHD patients with and without myocardial revascularization.

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РЕЗЮМЕ

ЛИПИДКОРРИГИРУЮЩИЙ И НЕКОТОРЫЕ ПЛЕОТРОПНЫЕ ЭФФЕКТЫ ВАЗИЛИПА (СИМВАСТАТИНА) ВО ВТОРИЧНОЙ КОРОНАРНОЙ ПРЕВЕНЦИИ

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Нами обследованы 92 больных, из них 41-му проведено коронарное шунтирование, 14-и коронарная ангиопластика и 37 пациентам ангиографически установлена ко-

ронарная болезнь сердца. В течение 12 недель больные принимали симвастатин (вазилип, КРКА, Словения) в среднесуточной дозе 13,3±2,7мг, в результате чего понизились показатели общего холестерина, холестерин липопротеинов низкой плотности, триглицеридов и индекс атерогенности на 27%, 37%, 16% и 39% соответственно. Кроме гиполипидемического действия препарат проявил плеотропные эффекты: улучшение эндотелиальной функции, оцениваемое по концентрации оксида азота (NO) в плазме крови и противовоспалительное действие, оцениваемое уровнем С-реактивного белка и фибриногена. Терапия симвастатином сопровождалась минимальными побочными явлениями.

Key words: Lipid-modifying, plrotropic effects, Vasilip (Simvastatin), secondary coronary prevention.

Научная публикация

CORONARY ARTERY DISEASE ABSOLUTE RISK DEVELOPMENT IN SUBSEQUENT DECADE IN TBILISI POPULATION

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Many Coronary Artery Disease (CAD) risk factors are identified but today the most important are "The Primary Three" – hypertension, hypercholesterolemia and smoking [1,3,5]. It is established that effective hypertension treatment reduces the risk of mortality from CAD by 17%, cessation of smoking for people under 65 years of age by 50% and 10% reduction of cholesterol level by 24% [2]. To prevent CAD is more important to estimate the combination of risk factors or the absolute risk of CAD to be estimated, because the absolute risk is an indicator of development of any of clinical manifestations or complications of CAD in the nearest 10 years [4].

Preventive measures or treatment oriented on each risk factor has to be more intensive if the overall risk is high. A person with several mild risk factors has higher CAD risk development, than that having a single risk factor, even it is as much important as hypercholesterolemia.

To estimate the overall risk of CAD development in the nearest 10 years the Framingham diagrams were created, including modifiable risk factors such as hypertension, smoking, hypercholesterolemia and uncontrollable factors such as sex and age.

According to above-mentioned the goal of this work was to estimate CAD risk in Tbilisi population.

Material and methods. 489 randomized persons 20-70 years old, who had not in the past angina pectoris, myocardial infarction, angioplastic surgery or aortocoronary shunting, were studied. The examined persons were divided into age groups according to the Framingham diagrams (table 1).

Table 1. Investigated persons distribution in age groups

Age groups	n	%	Woman	%	Men	%
20-29 years	72	14,7	38	52,7	34	47,2
30-39 years	102	20,8	60	58,8	42	41,2
40-49 years	111	22,6	49	44,1	62	55,8
50-59 years	116	23,7	56	48,2	60	51,7
60-70 years	88	17,9	52	59,1	36	40,9
Whole	489	100	255	52,1	234	47,8

The following was evaluated: arterial pressure measured three times. Serum total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerids and atherogenic index. Smoking.

The absolute risk for the development of CAD was estimated for each studied person by Framingham diagrams. The risk factors of each case were suited to the corresponding graph of the diagram and were compared with the diagram scale, where the absolute risks were given in per sent.

Results and their discussion. On the basis of the USA National Cholesterol Education Program the CAD risk factors are evaluated in the randomized population of Tbilisi.

According to the Framingham diagrams the absolute risk for the development of CAD in subsequent decade was estimated for each studied person. In Tbilisi population in men as well as in women tobacco smoking was the most frequent risk factor. With the age the incidence of risk factors, especially arterial hypertension is growing. After 50 years of age in women and 60 years of age in men the most frequent risk factor is arterial hypertension. Hypercholesterolemia is more frequent risk factor in men than in women, where normal levels of cholesterol are observed more frequently.

Absolute risk of CAD was much higher in men than in women. From 40 years of age men are under great risk. With advanced age the risk of CAD increases and its frequency also increase in subsequent decade (table 2).

Table 2. CAD development absolute risk according to the age groups

Age groups	Woman				Men				
	n	5-10%	10-20%	20-40%	n	5-10%	10-20%	20-40%	>40%
30-39	60	<5%			42	14 (33,3%)	4 (9,5%)		
40-49	49	20 (40%)	7 (14,3%)		62	10 (16,1%)	33 (53,2%)	8 (2,9%)	
50-59	56	11 (16,6%)	24 (42,9%)	5 (8,9%)	60	2 (3,3%)	41 (68,3%)	30 (50%)	
60-69	52	3 (5,8%)	21 (40,4%)	12 (23,1%)	36		3 (8,3%)	18 (50%)	6 (6,6%)
Whole	217	35 (16,1%)	52 (23,9%)	17 (7,8%)	200	26 (13%)	81 (40,5%)	56 (28%)	6 (3%)

For persons, who had normal level of cholesterol and more than two risk factors to measure HDL cholesterol and atherogenic index the recommendation was made to find out risk of CAD development. Because of high frequency of hypercholesterolemia in men over 40 years of age, it is necessary to study blood lipid levels in this age. This will help to implement preventive measures in medical practice.

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РЕЗЮМЕ

АБСОЛЮТНЫЙ РИСК РАЗВИТИЯ ИБС У НАСЕЛЕНИЯ Г. ТБИЛИСИ НА БЛИЖАЙШИЕ 10 ЛЕТ

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Согласно Американской национальной программе изучения холестерина и диаграмм Фремингема, установлены риск-факторы ИБС в рандомизированной популяции г. Тбилиси и определен абсолютный риск развития ИБС на ближайшие 10 лет.

В рандомизированном исследовании участвовали 489 жителей г. Тбилиси, в возрасте от 20 до 70 лет, у которых в анамнезе не отмечались стенокардия, инфаркт миокарда, перенесенная ангиопластика или аортокоронарное шунтирование. Обследование включало измерение артериального давления, определение в сыворотке крови общего холестерина, холестерина липопротеидов высокой плотности, триглицеридов, индекса атерогенности. Выявляли курящих. На основании диаграмм Фремингема для каждого исследуемого определяли абсолютный риск развития ИБС на ближайшие 10 лет.

Выявлено, что независимо от пола, самым частым риск-фактором заболевания являлось курение. У женщин выше 50-и лет, а у мужчин выше 60-и лет на первом месте среди риск-факторов была артериальная гипертензия. Гиперхолестеринемия чаще отмечалась у мужчин, у большинства женщин уровень холестерина был в пределах нормы.

Абсолютный риск развития ИБС у мужчин оказался намного выше, чем у женщин. По мере увеличения возраста увеличивается абсолютный риск развития ИБС на ближайшие 10 лет как у мужчин, так и женщин.

Key words: CAD, risk factors, absolute risk.

Научная публикация

THE VASCULAR WALL FUNCTIONAL ACTIVITY IN CORONARY HEART DISEASE IN HEREDITY FAMILY MEMBERS

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Clinical experience suggests that many physicians harbor a misconception regarding the pathogenesis of thrombotic disorders, particularly, in those individuals with recurrent episodes and Coronary Heart Disease (CHD) risk factor, such as arterial hypertension, smoking, heredity of CHD, body overweight and obesity, hypodynamia [6]. Patients are often evaluated for "hypercoagulation status" with a multitude of coagulation and platelet function tests, as if its detection would account for the cause of the thrombosis. This misperception has the potential of obscuring the true cause of the thrombotic problem, and the investigative approach generates often results in a battery of the coagulation tests, many of which have little bearing on the underlying problem in earlier stage of CHD.

Approaching the pathophysiology of thrombotic disease on the basis of Virchow's triad, rather than on the basis of the primary or secondary abnormalities of haemostasis, provides a better conceptual foundation on which to base an investigation [1,2].

The fibrinolysis system is considered to play an important role in many physiological and pathological processes [7]. In the view of the rapid progress in our knowledge about the fibrinolytic process and its regulation there is a great demand for more specific methods to assay its individual activation at different condition. For plasminogen release from the endothelium study the venous occlusion test of the arm is widely used. In previous period [4,9] there was used venous stasis of 20-min duration. According to other authors results we accepted 10-min occlusion yielded results which were equally informative as those obtained 20-min while causing loss discomfort for the patients. Therefore, the individuals exhibited their peak activity after 10 min. The results come from the same researchers [3] who has shown that venous cuff test using in small groups is equally informative and important for the vascular wall functional activity evaluation and its individual difference detection. Concerning the previous data it has been detected that cigarettes can trigger depression of the vascular wall endothelium prostacycline capacity [5]. Smoking not only chronically increases thrombogenic risk, but it also abrupt short-term risk. Over the long term, CHD heredity, smoking and other well-known risk factors [8] damages the protective factors inside blood vessel, making them more susceptible to plaque formation. More immediately, smoking causes blood vessel to constrict and stimulates platelets to form clots. Therefore, based on the multifactor prospective studies and angiografic investigations it has been detected that smoking, as well as heredity presents the independent risk factors of major vascular diseases.

According to the previous data the main objective of the investigation was to choose more informative blood coagulation parameters to evaluate prothrombotic risk.

Material and methods. In our data the vascular wall functional activity and its reserve capacity have been evaluated in 34 smoker healthy young men in age 18-29 years old-I degree relatives from the families with myocardial infarction history - basic group and in the control group-voluntaries of the same age, but without any indication of CHD, sudden death or stroke in the I or II degree relatives. To determine baseline fibrinolytic activity volunteers have been resting for 30 min. Venous occlusion was obtained by placing at the upper arm of the cuff inflated midway between systolic and diastolic pressure. Prior to and after the stasis for 10 min. a blood sample was occasionally drawn from the same arm. The plasma samples were collected with precaution to prevent any contact activity and care was taken that blood flowed easy to avoid contact phase activator. The blood was centrifuged for 20 min. at 2500 to obtain platelet-poor plasma. The following haemostasis system parameters have been detected: circulated fibrinogen, fibrinogen-B, fibrinolysis activity, antithrombin III activity, kallikrein-kinin frozen test, prothrombin activity. Statistical evaluation was done by the paired Student t-test.

Results and their discussion. Basic fibrinolytic activity in the first group persons has been increased in 23% cases as compared with the control group with the fibrinolysis pronounced increase in 48%. After the venous stasis 71,5% of the CHD family members have shown decrease of the fibrinolysis instead of 16% in the control group, its no change has been detected in 5,5% in the experimental group and in 36% in the control one. The mean basic fibrinolysis activity has been estimated as 23,0±6,07% in the basic group and as 17,5±5,93% in the control. After the venous occlusion all subject of the basic group have shown decrease of the fibrinolysis activity ranging to 16,86±5,92% and in the control group an increase to 19,5±7,51%. Concerning the other haemostasis system parameters (table) it have note that significantly pronounced alteration has been exhibited in the fibrinogen-B basic concentration in the basic group:

(7,55±0,61 g/l instead of 5,51±0,99 g/l in the control), as well as in the antithrombin III level (35,14±3,05% and 43,83±3,41%, accordingly). After the cuff test the difference in fibrinogen-B concentration has been increased to 8,56±0,54 g/l in the first group, so it was significantly higher as among the person without CHD heredity factor existing (5,14±0,31).

Antithrombin- III's level in the post-occlusion period was pronounced increased in the control group ranging to 43,33±2,97% comparing to the basic with antithrombin -III level equal to 34,43±2,69%. There has also been detected kallikrein-kinin's bridge alteration in both groups with the tendency to compensate minimization: 16,71±6,72% prior to and 11,92±3,46 after occlusion in basic group and 18,57±5,96 and 10,02±2,17 in control. Thus, the release of the tissue plasminogen and antithrombotic factors in response to venous occlusion differs considerably when the heredity factor exists. No significant difference has been found out in the prothrombin activity, thrombocytes aggregation, circulate fibrin-monomers or circulate fibrinogen. According this data, it is suitable to choose more informative parameters for the vessel wall functional activity evaluation. It have to be noted, that only in 7,8% healthy person with the heredity abuse the fibrinolytic activity has been increased instead of 21% in control group. The mean basic fibrinolytic activity has been estimated as 18,01±4,23% in I group and as 21,14±6,43% in the control group. Immediately after the venous occlusion the fibrinolytic activity has been decreased to 16,43±5,67% in the basic group. In the control group it was somewhat higher increased to 23,14±6,17%.

Table. Venous occlusion influence on the haemostasis system's parameters

Haemostasis system's parameters	Prior to venous occlusion		After venous occlusion		P_{3-4}
	Basic group	Control group	Basic group	Control group	
Prothrombin activity in %	18,86±0,59	16,67±0,61	18,57±0,46	16,5±0,79	
Thrombocytes spontaneous activity in %	7,7±2,24	9,0±2,04	8,0±0,46	8,5±2,19	
Fibrinogen in g/l	3,67±0,32	3,14±0,44	3,99±0,37	3,47±0,39	
Fibrinogen-B in g/l	7,55±0,61	5,51±0,099	8,56±0,54	6,07±1,01	
Fibrin- monomers in opt,un,	0,35±0,02	0,31±0,05	0,36±0,03	0,32±0,03	0,05
Fibrinolysis activity in %	23±6,07	17,5±5,93	16,86±5,92	19,5±7,51	
Antithrombin activity in %	35,14±3,06	43,83±3,41	34,43±2,69	43,33±2,95	
Kallikrein-kinin bridge in %	16,71±6,72	11,92±3,46	18,57±5,96	10,0±2,17	0,05

The approach to the evaluation of a prothrombotic state can be summarized as follows: multiple risk factors of thrombotic disease development exist. These factors mediate their pathophysiological effect through one or number of the elements of Virchow's triad, and the final common pathway leading to clot formation is through the activation of the haemostatic system. Through a long time it has been known that blood fibrinolytic activity is increased during venous stasis and exercise due to release of the tissue plasminogen activator from the endothelium, probably because of the ultrafiltration and haemo-concentration, as a result of the venous stagnation. Research work has given the possibility to eliminate the fibrinolysis activity decrease after the 10 min. of the stasis in healthy volunteers-first degree relatives in families with myocardial infarction in anamnesis, which was significantly compared to its basic activity. However, there were pronounced individual difference of the vessel's endothelium responsiveness to hypoxia condition in the smoker young family members. It is advisable to conduct 10-min. venous occlusion test, if abnormalities are obtained it remains to be established which prophylaxis provides the normalization of the vascular wall functional activity (physical activity's increase, stop smoking, antioxydants drug therapy, etc.) having a great protective significance in CHD prevention.

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РЕЗЮМЕ

ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ СОСУДИСТОЙ СТЕНКИ У ЛИЦ С ОТЯГОЩЕННОЙ НАСЛЕДСТВЕННОСТЬЮ ПО ИШЕМИЧЕСКОЙ БОЛЕЗНИ-СЕРДЦА

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С целью выявления влияния наследственного фактора ишемической болезни сердца на функциональную активность сосудистой стенки и системы гемостаза, а также определения объективных критериев ее оценки у молодых здоровых лиц- членов семей больных ИБС (первая степень родства) проведена 10-мин. манжеточная венозная окклюзия у 34 добровольцев.. Изучены следующие параметры системы гемостаза: фибриноген, фибриноген-В, общая фибринолитическая активность, холодовая активация калликреин-кининового моста, антитромбин III протамин-сульфатный тест. Оценка активности системы гемостаза в условиях венозной окклюзии выявила достоверное повышение протромбогенного потенциала системы свертывания крови в группе лиц с отягощенной наследственностью по сравнению со здоровыми лицами без указаний в семейном анамнезе на ИБС, что необходимо учитывать при формировании стратегии ранней профилактики сердечно-сосудистых заболеваний.

Key words: vascular wall, coronary heart disease, haemostatic system, heredity.

Научная публикация

SECONDARY PREVENTION OF CORONARY HEART DISEASE IN PATIENTS FOLLOWING MYOCARDIAL REVASCULARIZATION

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All Patients undergoing myocardial revascularization procedures - coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are at high risk for development of further coronary events. Therefore such a category of patients is considered as the top priority for preventive cardiology. This fact is conditioned by ongoing atherosclerotic process, which may cause coronary restenosis and reocclusion as well as new stenosis and occlusion in native coronary arteries and bypass grafts. So, the maintenance of results of PCI and CABG is not less important than namely these methods of myocardial revascularization.

In our clinic where performed approximately 300 operations of CABG and 250 procedures of PCI were carried out and the system of secondary coronary prevention (SCP) was established. The main goals of SCP are: comprehensive risk reduction of subsequent cardiac events, improvement of the quality of life, decrease of the need for recurrent interventional procedures and increase the chances of survival.

Patients and methods. The study population consisted of 303 outpatients who underwent myocardial revascularization in our center between June 2001 and July 2003. Among them 217 patients had CABG, 81 - PCI, 4 - PCI+ CABG and 1 - CABG+PCI. 262 patients were male. Mean age was 57±4,4 years. The frequency of coronary risk factors, medication therapy, mortality rate, recurrent angina, blood lipid profile, plasma concentrations of nitric oxide and fibrinogen, platelets aggregability were studied. Listed biochemical parameters were determined by the methods described in our recently published works [4,5].

Results and their discussion. Modifiable coronary risk factors management is considered as prevention and treatment of the atherosclerotic process itself in coronary arteries and are included as an integral part of any management plan in SCP. This is especially important for patients undergoing CABG and PCI. Frequency of coronary risk factors is presented in table 1.

0-1 risk factor was found in 39% of cases and the majority of patients - 61 % had 2 or more risk factors' combination. Among all coronary risk factors dyslipidemia was most prevalent (77%). It is known that elevated plasma levels of LDL-C and TG, lowered levels of HDL-C are independent risk factors for coronary atherosclerosis(6). Therefore each of them was estimated separately. We observed high quantity of increased LDL-C levels (69%) which is the most important lipid risk factor. More than half the patients had hypertension (systolic blood pressure ≥140 mm.Hg and/or dias-

tolic blood pressure ≥ 90mm.Hg). Frequency of tobacco smoking before myocardial revascularization was high enough (58%) as well. With our effort after CABG and PCI 56% of patients stopped smoking, however braking this addiction over the long-term requires more intensive professional support. The other coronary risk factors occurred less frequently.

The first line agents in SCP following myocardial revascularization are aspirin and statins. Aspirin use was almost universal - 96-100% patients received it. From all prescribed preparations statins are the most expansive and it is noteworthy that despite low social-economic status of our country's patients their use was high enough (80-88%). More than half the patients received ACE inhibitors. In our population the administration of other preparations was less frequent. Patients following PCI received more drugs than after CABG (table 2).

Statins are one of the most important and widely used drugs in preventive cardiology. The efficacy of lipid lowering treatment with statins in delaying the progression of atherosclerosis in native coronary arteries and bypass grafts has been documented with coronary angiography in numerous studies. Besides, despite baseline lipid levels statins have been proven effective in significantly reducing the risk of major cardiac events, coronary death, recurrent interventional procedures and treatment has also been found cost-effective (2,3,7,8). This is associated with statins' pleiotropic effects. It is know that after PCI and acute coronary syndrome the sooner they are initiated the more beneficial they are for clinical outcome (1,3,7.8). Hence, in order to administer statins following direct myocardial revascularization 52 patients' blood lipid status was examined. None of the patients received lipid lowering medications and all of them were on an antiatherogenic diet for at least 4 weeks before operation and during the whole follow-up. In 7 days after bypass surgery there were significant percent reductions in TC, LDL-C, TG and HDL-C by 30%, 31%, 28% and 18% respectively. It is noteworthy that not any lipid lowering medication or strict diet can do it in such a short time. All reductions of lipid fractions were maintained for 4 weeks. At the end of supervised period - 8 weeks after operation all lipid parameters returned to their baseline levels (table 3).

The obtained data suggest that blood lipids should be assessed 4 to 8 weeks after CABG, because all lipid fractions may be depressed after this major surgical procedure. Their increase may start after 4 weeks and return to baseline only 8 weeks post operation. Measurements made earlier than 4 weeks after bypass for initiation of lipid lowering treatment should be viewed with this in mind. We believe from the present trial that the main cause for such a drop of lipids is hemodilution after CABG, wich was proved by the substantial decrease in hematocrit values after a week post operation. But in 4 weeks estimated hematocrit was within normas, whereas lipid parameters were still significantly diminished, so at this time hemodilution could be excluded. May this major surgical procedure stress for liver and result in temporary dysfunction of hepatocytes? More detailed investigations is needed to clarify the question.

Coronary mortality rate in SCP after both methods of myocardial revascularization was 0,3% (1 patient 11 months after CABG). Recurrence of angina was observed in 5 cases following bypass operation. Diagnosis of repeated ischemic events was confirmed by stress test. In 3 patients after 10,8 and 11 months of CABG coronarography was performed. Angiography revealed vein graft occlusions and progression of atherosclerotic lesions in native coronary arteries, however they did not require renewed surgical or endovascular interventions. In other postoperative cases were no symptomatic graft failure. In patients following PCI improvement of Canadian Cardiovascular Society angina class was observed: 52% of patients had no angina, 27% - I functional class and the rest of them - II-III functional class. No angina relapse occurred in 5 patients undergoing PCI and CABG combination.

In order to assess endothelial dysfunction, plasma concentrations of nitric oxide (NO) were examined in 76 patients. 4 types of plasma NO levels were observed: extreme deficite - $<5_{mkmol/l}$ (n=17), low plasma levels - 5-$14_{mkmol/l}$ (n=20), normal levels?15-$24_{mkmol/l}$(n=20) and elevated levels - $>24_{mkmol/l}$ (n=19). Multiple vessel disease was associated with extremely low or increased concentrations of nitric oxide. Also it is noteworthy that from 5 patients with recurrent angina undergoing bypass operation 3 had extreme deficit of plasma NO levels and 2 - elevated levels. Both abnormalities of NO concentrations indicated severe coronary atherosclerotic process which was connected with reappearance of angina. Patients with 0-1 risk factor mainly had normal plasma NO concentrations whereas with 2 or more risk factors' combination - its abnormal levels. We found close relationship between endothelial dysfunction estimated by nitric oxide concentrations and coronary risk factors such as dyslipidemia, especially elevated levels of LDL-C, hypertrigliceridemia and lowered levels of HDL-C as well as hypertension, diabetes, excessive weight and inadequate physical activity. Normal plasma concentrations of NO mostly occurred in patients treated with statins and ACE inhibitors. We examined some parameters of hemostasis as well. Hyperaggregability of platelets was not observed in patients with normal NO levels. Increased concentrations of fibrinogen was mainly found in patients with abnormal plasma levels of nitric oxide. So, the obtained data of our research suggest that plasma nitirc oxide examination have a diagnostic and prognostic value to identify patients at risk and to control the efficacy of pharmacologic interventions in clinical practice. It may be one of the primary targets in the effort to optimize individualized therapeutic strategies in SCP.

Table 1. Frequency of coronary risk factors in patients following myocardial revascularization (n=303)

risk factor 2+ risk factors	119 (39%) 184(61%)
Dyslipidemia LDL-C>100 mg/dL TG>150 mg/dL HDL-C< 40 mg/dL	233(77%) 209(69%) 101(33%) 153(50%)
Hypertension	177(58%)
Diabetes mellitus	72(24%)
Smoking status: Current smokers Past smokers	 6 (2%) 177(58%)
Body composition: Overweight (BMI-25-30 kg/m^2) Obese (BMI >30 kg/m^2)	 88 (29%) 4 (1%)
Sedentary life style	69 (23%)
Family history	75 (25%)

LDL-C - low density lipoprotein cholesterol; TG – triglicerides; HDL-C - high density lipoprotein cholesterol; BMI - body mass index

Table 2. Medication therapy after myocardial revascularization (n=303)

Medications	**Type of revascularization**		
	CABG (n=217)	**PC (n=81)**	**PCI and CABG (n=5)**
Aspirin	211(97%)	78 (96%)	5 (100%)
Statins	188 (87%)	71 (88%)	4 (80%)
ACE inhibitors	133 (61%)	51 (63%)	3 (60%)
β-blockers	87 (40%)	54 (67%)	2 (40%)
Calcium channel blockers	44 (20%)	19 (23%)	0
Other nticoagulants	6 (3%)	14 (17%)	2 (40%)
Nitrates	5 (2%)	23 (28%)	1 (20%)

Table 3. Lipid parameters prior to and some weeks after bypass surgery (n=52)

Weeks		**Mean and percentage changes versus baseline**			
		TC mg/dL	**LDL-C mg/dL**	**TG mg/dL**	**HDL-C mg/dL**
Baseline	1	243±6,5	161±5,8	208±11,2	34±1,8
1 week	2	170±6,1 (30%)	111±6,2 (31%)	150±10,3 (28%)	28±1,4 (18%)
4 week	3	204±7,2 (16%)	123±5,3 (24%)	176±9,9 (15%)	31±1,2 (9%)
8 week		241±8,3	170±7,0	201±10,7	33±1,9
P-value $_{1-2}$		<0,001	<0,001	<0,01	<0,01
P-value $_{1-3}$		<0,001	<0,001	<0,05	<0,05

Conclusion: these are 2 years results of our study, since myocardial revascularization procedures - CABG and PCI are brand new methods of treatment used in our country. The endpoints of secondary prevention following CABG and PCI are: cardiac death, recurrent coronary events and also recurrent myocardial revascularization by surgical or percutaneous means. Our further investigations will include such markers of the progression of coronary atherosclerotic process as plasma levels of lipoperoxides, C-reactive protein, homocysteine, serological parameters of chronic bacterial and viral infections etc. From the scientific point of view they will condition to define more exactly the pathogenesis of restenosis or new stenosis in native coronary arteries and bypass grafts, consequently will help clinicians to establish purposeful medication therapy after successful myocardial revascularization procedures.

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РЕЗЮМЕ

ВТОРИЧНАЯ ПРЕВЕНЦИЯ КОРОНАРНОЙ БОЛЕЗНИ СЕРДЦА У БОЛЬНЫХ ПОСЛЕ РЕВАСКУЛЯРИЗАЦИИ МИОКАРДА

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Под наблюдением находились 303 больных, поступивших в 2001-2003гг. в Центр неотложной кардиологии после хирургической и эндоваскулярной реваскуляризации миокарда. Из них 217 больных после операции коронарного шунтирования (КШ), 81- после коронарной ангиопластики (КА), 4-КА+КШ и 1-КШ+КА. Средний возраст 57±4,4г. У большинства наблюдаемых нами больных (в 61% случаев) отмечалось два или более факторов риска коронарной болезни сердца. Дислипопротеинемия наблюдалась у 77% пациентов, повышение уровня холестерина липопротеинов низкой плотности - в 69% случаев. У больных после операции КШ в течение 4-8 недель отмечалось значительное снижение показателей липидного профиля крови, обусловленное, по нашему мнению, гемодилюцией. Подтверждением тому может служить и факт снижения гематокрита. Исходя из этого, следует полагать, что для липидкорригирующей терапии после хирургической реваскуляризации миокарда липиды крови следует изучать спустя 4-8 недель после операции КШ. При изучении эндотелиальной дисфункции (по уровню оксида азота в плазме крови) выявлено четыре типа концентрации NO: очень низкий - $<5_{мкмоль?л}$ (n=17), низкий - $5\text{-}14_{мкмоль?л}$ (n=20), нормальный - $15\text{-}24_{мкмоль?л}$ (n=20) и повышенный - $>24_{мкмоль?л}$ (n=19). Всем наблюдаемым нами больным, в основном, проводилась терапия аспирином, статинами (в 80-85% случаев) и ингибиторами АПФ (в 60-65%). После эндоваскулярной реваскуляризации миокарда у 52% больных наблюдалось исчезновение, а у остальных 48% - улучшение функционального класса стенокардии. После операции КШ возникновение рекуррентной стенокардии, верифицированной стресс-тестом, отмечено у 5 больных. При повторном ангиографическом исследовании (у 3 больных) в одном случае обнаружены гемодинамически значимые сужения в шунтированных артериях дистальнее коронарных анастомозов, а также в нативном коронарном русле. У двух больных установлены окклюзии в аутовенозных шунтах. Среди больных с ангиографически подтвержденным прогрессированием атеросклеротического процесса двое оказались в группе с критическим дефицитом, а один - в группе с повышенным уровнем NO.

Key words: CABG, PCI, SCP, myocardial revascularization.

Научная публикация

CARDIOVASCULAR DISEASE RISK FACTORS SPREADING IN THE ABKHAZIAN REFUGEES TEMPORARY LIVING IN DIFFERENT REGIONS OF GEORGIA

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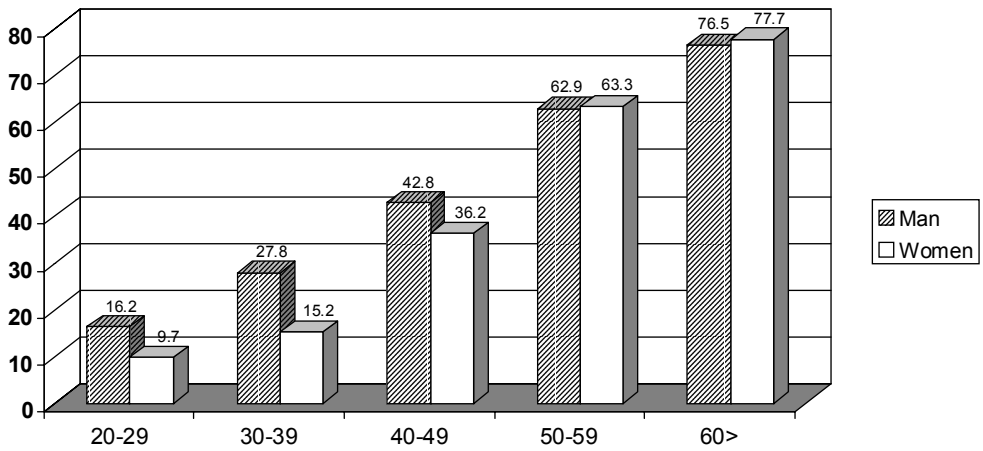
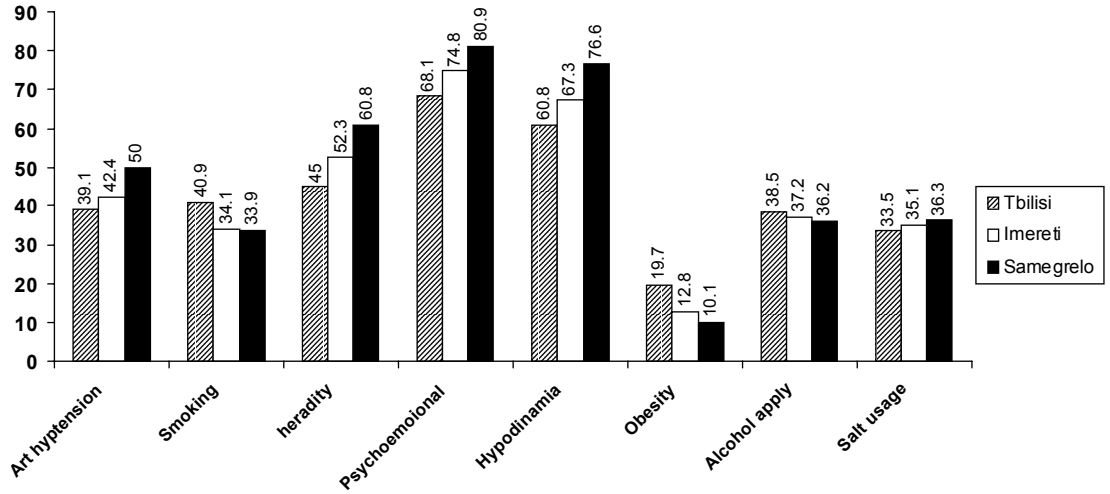
Cardiovascular diseases, particularly Coronary Heart Disease (CHD) and Arterial Hypertension (AH), are the main causes of the disability and mortality in Georgian population [1,3]. Earlier disease identification represents the major strategy policy of National Health protection, as well as disease risk factors exposure, timely prevention and introduction of the healthy life style and the quality of life [1-4]. The preventive strategy is the most important for that part

of Georgian inhabitants, who had suffered hardships and distress, had lost their own home and became social and economical unsecured refugees.

The objective of the research investigation was to discover the major risk factors of CHD and hypertension to disease primary prevention in refugees from Abkahzia temporary living in different regions of Georgia. According to the objectives 4795 persons have been examined (2081 men and 2714 women), aged 18-70 years old. Using the group case excerption method in the organized living refugees (Tbilisi, Kutaisi, Kopitnari, Khobi, Tsalengikha, Zugdidi, Abasha, Photi). There have been discovered very deep outrageous poverty in the refugee population in each region, as well as unemployment, poor life condition, social insecurity. It have to be noted, that basically their social and economical position was better in the big towns, such as Tbilisi, Kutaisi. All of this indicated factors determined psycho-emotional status demonstrated in both sexes of the inhabitants (in 74% in Tbilisi and in 89 % in Samegrelo region). Otherwise, the permanent psycho-emotional factor, itself, determined widespread risk factors, such as arterial hypertension, smoking, and alcohol uptake. The combinations of these risk factors have been disseminated most often in the male population aged 40-60 years old. Most outrageous data have been discovered in hypertension extending in the refugees (table 1). The systolic blood pressure above 140 mm Hg have been extended in 42,8% (45,3% in masculine gender persons and in 40,8% in the females. Spreading of the arterial hypertension in the group of patients about 50 years old was equal higher in males, and vice versa in age above 50 year hypertension in women gets more disseminated (picture 1). Concerning the hypertension degree itself (light, moderate, heavy stages) it have to note that in age 40-49 the light form of hypertension have been extended in mostly, while in the age over 50 year it became heavier and composed with complications, such as cerebral stroke, cardiovascular failure, myocardial infarction. According to the arterial hypertension's regional dissemination it has been extended as follows: 39,1% in Tbilisi, 42,4% in Emereti region, 50% in Samegrelo region, as well as concerning CHD dissemination (worse indication data in Samegrelo region), conformably in 19,2%, 21,7% and 32,1% cases. Extending of the CHD and arterial hypertension had been in the direct proportion with the aggravating heredity in the refugee family members and it has been detected, generally, in 51,1% of the refugees, as well as salt usage (in 35%), obesity and overweight (in 15,5%), while this latter risk factor has been extended in refugees rare in compare with indigenous population. The body-overweight (Ketle index over 29 years old) has been discovered in 14,2% of refugees, that indigenous population in Tbilisi was equal to 32,7%. It might explained by refugees heavy economical and social condition they have a born in one's hand to get a valuable in connection with a strong nervous life style, permanent searching for a job and other different emotional-nervous stresses. This factors probably could be reason for exposed difference in arterial hypertension dissemination in the refugees (42,8%) and indigenous inhabitants (34%). Concerning smoking risk factor dissemination it has to be indicated that in the refugees female population latter it has been discovered in 10,5% in comparison with Tbilisi citizens who, unfortunately, are very much addicted to smoking (46%). Concerning the regional peculiarities in the smoker refugees there had not been discovered any differences (picture 2). Smoking strongly has been disseminated among male population (68%), particularly in the group of age 30-49 years old. The hypodynamia presents one of the most important risk factor of cardiovascular system diseases development. As a result of the massive unemployment in 66,6% they have lost physical activity, other in big towns citizens (Tbilisi, Kutaisi) they are livelier and more active being occupied in "business". Hypodinamia, depression and feeling of deprivation reduce to injurious habits such as alcohol uptake, mostly in male population (70,3%). Concerning different risk factors combination it has to be noted, that in 54,6% refugees have had two risk factors, three factors in 41,3% and more factors combination equal to 27%.



Picture 1. Hypertension frequency in refugees (sex, age)



Picture 2. The frequency of risk factors in according refugees temporary living place

Conclusion. Thus, the preliminary issues of an epidemiological-preventive research investigation in refugees has given the possibility to find out their desperate and considerable condition in the cardiovascular disease and arterial hypertension risk factors pronounced dissemination. Mostly refugees have not the full information of cardiovascular disease and hypertension main risk factors, being unable to get medical advice and to check their own health condition. If at present it dose not seems real to solve refugees disastrous condition prior to their returning home, all the efforts of health services should be focused on bettering refugees health status by prophylaxis and providing them with cardiovascular disease and hypertension risk factors information, as well as health education, enlightening on life style and mostly important, providing free medical advice consultation and drug supply.

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РЕЗЮМЕ

ФАКТОРЫ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ СРЕДИ БЕЖЕНЦЕВ ИЗ АБХАЗИИ, ПРОЖИВАЮЩИХ В РАЗНЫХ РЕГИОНАХ ГРУЗИИ

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В рамках государственной программы (2001-2002 гг.) с целью выявления распространения основных факторов риска сердечно-сосудистых заболеваний, в частности, ишемической болезни сердца (ИБС) и артериальной гипертонии (АГ) проведено эпидемиологическо-профилактическое исследование беженцев из Абхазии, временно проживающих в разных регионах Грузии. Возраст целевой популяции составил 18-70 лет. Результаты исследования выявили неблагоприятные данные и тревожную ситуацию в отношении распространения этих заболеваний и их риск факторов. ИБС выявлена в 19,2% (г. Тбилиси), 21,7% (Имеретия) и 32,1% (Самегрело) случаев. АГ выявлена соответственно в 39,1%; 42,4% и 50% случаев. Достаточно высокими оказались показатели частоты таких значимых риск-факторов, как нервно-эмоциональный фактор, артериальная гипертензия, курение, гиподинамия, наследственная отягощенность, избыточное потребление поваренной соли, частое потребление алкоголя. Результаты исследования оказались более неблагоприятными у беженцев, чем у коренных жителей, а по месту временного проживания – у лиц, проживающих в Самегрело. Следует учесть, что в связи с тяжелым социально-экономическим положением беженцы не имеют возможности получить медицинскую помощь, а также соответствующую информацию относительно факторов риска раннего развития ИБС и гипертензии. Таким образом, считаем крайне необходимой разработку соответствующих мероприятий по первичной профилактике и предотвращению заболеваемости среди беженцев.

Key words: cardiovascular disease, risk factors, refugees.

Научная публикация

PLASMA CONCENTRATION OF SOME ACUTE PHASE PROTEINS IN PATIENTS SEROPOSITIVE TO CHLAMYDIA PNEUMONIAE INFECTION PRESENTING WITH STABLE AND UNSTABLE ANGINA PECTORIS

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Association of Chlamydia pneumoniae (Chl.pn.) with chronic coronary heart disease (CHD) has been detected in several seroepidemiological studies [2,6]. Increased levels of antibodies to Chl.pn. were also verified in the majority of patients with acute myocardial infarction [12]. Moreover, in some investigations the pathogen agent was directly demonstrated from vascular tissue [10] and in atherosclerotic lesion [8]. These findings have been repeatedly verified by others [13,14]. However, seroepidemiology can not prove or disprove a causal association between infection and coronary disease or subsequent coronary events [12].

It is important to note that more publications provide evidence that instability is associated with increased plasma concentration of C-reactive protein (CRP) and fibrinogen - two markers of inflammation, which can predict subclinical atherosclerotic vascular injury [1,15].

In this regard our objective was to compare the diagnostic efficacy of acute phase proteins - CRP, fibrinogen (F), as well as erythrocyte sedimentation rate (ESR) and blood fibrinolytic activity (BFA) in different clinical presentations of CAD, namely in stable and unstable forms of disease and also to identify the role of chlamydial infection in precipitation of acute coronary syndrome.

Material and methods. The study population consisted of 50 patients with documented CHD, seropositive to Chl.pn. antibodies; 32 men, mean age 58,1±2,8 years (range 35 -75 years) and 18 women in post or early menopausal period, mean age 64,7±1,1 years (range 48-75 years). The investigated persons were divided into two groups: 32 patients with relatively stable disease development - chronic stable angina pectoris of NYHA (functional classification according to the New York Heart Association) II and NYHA III - group I, and 18 patients with unstable clinical course - presumed acute coronary syndrome (ACS) - group II. Along with cases of unstable angina pectoris with persistent or transient ST-segment depression or T-wave abnormalities, patients with ischaemic ECG changes but without symptoms (silent ischaemia) were included in this group. Clinical criteria of ACS have been developed according to the definition observed and updated by the European Society of Cardiology in 2000 [5].

Diagnoses were based on medical history, symptoms, rest and exercise electrocardiograms, measures of carotid intimal-medial wall thickness by B-mode sonography. 8 (25%) patients of the I and 13 (72%) patients of the II group had a history of myocardial infarction (MI). 2 and 7 persons of the relevant groups underwent diagnostic coronary arteriography. A sudden cardiac death developed in cases of 2 patients with ACS (in two months period) shortly after the time of investigation.

All participants underwent quantitative measurment of specific IgM, IgA and IgG antibodies to Chl. pn. Infection in serum by immunofluorescence assay (Verotech, Germany). The enzyme immunoassay technique also was used for detection of antibodies as well as for direct quantitative determination of CRP in non-diluted serum at the time of screening was ELISA method (R-biopharm, Germany). Serum creatine kinase MB isoenzyme (CK-MB) activity, as a direct biochemical marker of myocardial damage, was routinely measured at admission at least twice within the first 48 hours by an immunoinhibition assay (CK-MB-NAC, Human, Germany). No patient had trauma or muscle disorders. Excluded were persons with acute MI and cardiac abnormalities, such as rheumatic or congenital heart disease. The data were analyzed by Student t-test, cI test (Pearson), Fisher's test and correlative analysis.

Results and their discussion. Serological profile of Chl. pn. antibodies, reflecting different phases of infective process, of patients with stable (I group) and unstable (II group) forms of CHD is presented in Fig. In the I group (a) IgM antibodies - markers of primary/acute infection were revealed in 21,9% of cases. IgA antibodies, reflecting a prolonged chronic process were detected in 25% of patients. Isolated IgG antibodies as markers of previous infection persisted in 53,1% of cases. No patient of the I group had simultaneous presence of IgA and IgG antibodies, considered as demonstration of reinfection/ reactivation. The obtained data significantly differed from chlamydia specific antibody distribution in the II group, where the above-mentioned combination of IgA and IgG immunoglobulines turned up in the majority (77,8%) of patients.

Table depicts some plasma parameters and immunoglobuline concentration in investigated groups of CHD patients. As it is shown in the table, serum concentration of CRP and F in the II group was significantly ($P<0,01$) higher than the respective concentration in the I group, whereas no significant difference of ESR was found between

the compared groups. This comes in common with some recent reports [3,7]. Increased F levels and high-sensitivity CPR have been reported as risk markers in ACS [11] but the data are not consistent.

Table. Some plasma parameters and immunoglobulin concentration of CHD patients with stable angina pectoris (I group) and ACS (II group)

	I group	II group
C-reactive protein (mg/l)	2,5±1,8	29,1±2,6* "
Fibrinogen (g/l)	3,38±2,1	5,62±0,6 * "
Blood fibrinolytic activity (%)	15,08±1,0*	7,01±1,2 "
Erythrocyte sedimentation rate (mm/per our)	10,75±0,3	13,04±1,1
CK-MB (U/L)	14,02±4,1	39,44±3,8 * "
IgA (gray zone ±0,9-1,1)	1,15±0,78"	2,43±0,9* "
IgG (gray zone ±0,9-1,1)	1,9±0,21"	1,48±1,1"

** - indicates P<0,01 vs another group; " - indicates P<0,01 vs cutoff concentration of biochemical marker*

An average index of CK-MB in the II group has significantly and reliably increased (39,44±3,8) above basal concentration as well as compared with that of the I group (14,02±04,1), though in 33% this parameter did not exceed the cutoff value. This may be explained by the absence of myocardial damage in these cases or limitations of the CK-MB test, as for H-FABP, cardiac troponins and myoglobine are the preferred markers [4,7]. Different time courses of above-mentioned indices determine their different clinical application; H-FABP and myoglobin are the relatively early markers of myocardial necrosis, while elevation in CK-MB or troponin appear later [16], but for detection of re-infarction repeated measurement of CK-MB is more informative and less expensive. All patients with unstable angina consulted with us not earlier than in 5-6 days interval after the onset of chest pain. Because of that, we have chosen CK-MB as biochemical marker of myocardial injury.

Quantitative analysis of Chl.pn. specific antibodies in patients with stable and unstable angina pectoris revealed (table) the elevated serum concentrations of both isolated IgA and IgG immunoglobulines from cutoff values (in I group - 1,9±0,21 and 1,15±0,78 as in II group - 2,43±0,9 and 1,48±1,1), but inter-group comparison of the obtained data showed significant (P<0,01) increase of average values of IgA antibodies in patients with ACS despite the patients with stable disease development. It might be caused by simultaneous presence of IgA and IgG antibodies (72,2%) in the II group and their absence in the patients of the I group, presented in Fig. This clearly demonstrates that infective process in this cases turns from chronic antibody remanence (IgG) to reactivation/reinfection phase (IgG+IgA) and could be considered as an additional triggering factor of CHD activation.

The prognostic value of reactivation/reinfection of Chl.pn. infection seems to be most prominent in CHD patients with previous MI for they form mainly (72%) the II group and constitute only 25% of the I group.

A special attention might be dropped on average serum levels of BFA in the investigated groups. As the table I. shows, in patients with ACS this parameter was below the basal plasma concentration (7,01% with normal range of 14-15%) and significantly differed from the appropriate level in I group (15,08%). Based on our previous investigation [9] we consider such difference as a functional insufficiency of blood fibrinolytic system after a long-term compensatory increase during acute and chronic phases of Chlamydial infection.

Supposedly, in these cases increase of inflammatory markers reflects activation of the concomitant infective process or reactivation of the current chronic infection, which in turn acts as a trigger mechanism for further atherosclerotic vessel injury or threatens stability of atherosclerotic plaque.

Conclusion. The study reveals the complex of disturbances in some plasma parameters in patients with unstable angina pectoris seropositive to Chl.pn. antibodies. This complex encloses significantly elevated levels of CRP, F and CK-MB activity and increased concentration of chlamydia specific IgA antibody titers along with considerable decrease of BFA.

In patients with stable angina pectoris at stable clinical condition seropositive to Chl.pn. antibodies investigated parameters hesitated within the normal ranges.

Elevated levels of isolated IgA or IgG antibody titers and/or appearance of IgA+IgG complex in serum indicate reinfection or reactivation of the current chronic infection, which in patients with ACS obtains an important meaning as an additional risk-factor complicated disease development. Timely detection of mentioned immunoglobulin complex in plasma of ACS patients is important both for prognostic assessment and management.

Assessment of IgA+IgG complex and their serum concentrations along with other biochemical markers of inflamma-

tory activity in patients with ACS, especially in cases of slight and moderate or without any elevation of markers of myocardial damage or disability of their measurement may provide additional insights in the diagnosis of ACS.

A special attention should be given to appearance of IgG+IgA antibody complex or rapid elevation of their serum titers in patients with stable angina pectoris. This may serve as an additional risk-factor for stable development of CHD, and provoke occurrence of acute coronary events.

The prognostic value of appearance of IgG+IgA antibody complex seems to be most prominent in patients with history of MI.

It seems necessary to conduct further researches on the problem to establish new strategies to prevent occurrence of ACS.

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РЕЗЮМЕ

КОНЦЕНТРАЦИЯ НЕКОТОРЫХ БЕЛКОВ ОСТРОЙ ФАЗЫ В ПЛАЗМЕ КРОВИ БОЛЬНЫХ СО СТАБИЛЬНОЙ И НЕСТАБИЛЬНОЙ СТЕНОКАРДИЕЙ, СЕРОПОЗИТИВНЫХ К CHLAMYDIA PNEUMONIAE

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Определялась концентрация некоторых белков острой фазы - С-реактивного белка (СРБ) и фибриногена (Ф), а также фибринолитическая активность крови (ФАК) наряду с маркерами повреждения КК-МВ и специфических иммуноглобулинов IgM, IgG, IgA в плазме крови в двух группах больных ИБС: со стенокардией напряжения с относительно стабильным течением болезни (I группа) и с нестабильной стенокардией (II группа), клиническое течение указанных видов стенокардии оценивалось по рекомендациям Европейского Общества Кардиологов как острый коронарный синдром (ОКС).

Сравнительный анализ исследуемых групп выявил высокие по сравнению с нормальными показателями значения СРБ и Ф и МВ-КК в плазме крови больных с ОКС на фоне достоверного снижения ФАК. Отмечено также значительное повышение уровня антител IgA вместе с появлением в плазме комплекса IgA+IgG у больных II группы, (с ОКС), не отмечающееся у больных I группы.

Повышение титра антихламидийных антител класса IgA при хроническом (IgG) антителоносительстве, а также

комплекса IgA+IgG, наряду с повышением уровня концентрации маркеров воспаления, оценивалось как реинфекция или трансформация хронического инфекционного процесса в рекуррентную фазу, что у больных с острым ОКС приобретает значимость добавочного риск-фактора, осложняющего течение болезни. Выявление комплекса IgA+IgG в плазме крови, одновременно с повышенными титрами маркера воспаления у больных с ОКС, особенно при умеренной или без элевации маркеров повреждения миокарда, или в случаях невозможности их определения, может приобрести добавочную диагностическую ценность.

Key words: Acute coronary syndrome, C-reactive protein, fibrinogen, blood fibrinolytic activity, Chlamydia pneumoniae infection, immunoglobulines.

Научная публикация

EFFECTS OF EXOGENOUS CHOLESTEROL ON THE MICROCIRCULATORY VESSELS AND FORMED ELEMENTS FUNCTIONAL MORPHOLOGY

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The role of blood formed elements has been recently studied in the general theory of atherosclerotic plaque pathogenesis. The stages, dynamics and pathologic process complications are related with changes of some of them [6]. At the same time morphofunctional changes in peripheral blood cells correlated with risk-factors of atherosclerosis development have not been well studied.

The studies on atherosclerosis have revealed the findings indicating a disturbance in lipid exchange and microcirculation promoting changes in various organs of atherosclerosis early stages [5]. Morphogenesis, ultrastructural peculiarities of the histohematic barriers and its role in atherosclerosis pathogenesis have not been studied well enough, neither has been revealed the significance of the changes in blood formed elements from the points of view of systemic approach to atherosclerosis study.

The aim of our study was to examine the character and intensity of structural – functional transformation of blood formed elements at different stages of atherosclerosis development as well as ultrastructural changes of microcirculation in different organs under the conditions at the experimental model of exogenous hypercholesterinemia.

Ultrastructural – functional changes in organ microcirculation (heart, brain, liver, kidneys and lungs) have been studied at atherogenesis early stages prior to development of fibrous changes under the conditions of experimental hypercholesterolemia at the tissue and subcellular level.

Materials and methods. The studies were performed on 80 chinchilla rabbits with an initial body weight of 2,5-3kg. The experimental rabbits (n=60) were on cholesterol diet after N.N. Anichkov. They received cholesterol at a rate of 0,3 g/kg with vegetables; 20 animals of the control group received the same vegetables only. The animals were sacrified with intravenous injections of Thiopental, 300 mg/kg after 15,30,60, 90,120 and 180 days. ApoB-lipoproteins (apoB-LP) and the total amount of Cholesterol in blood serum were estimated after the method of Ilk. The area of aorta atherosclerotic damages was determined after the method of G.G. Avtandilov (1990) on slices dyed in toto with sudan dyes. Semithin and ultrathin slices were used for histo-and ultrastructural examinations. The electron microphotos were received on the electron microscope "Tesla BS 500" at the accelerated tension of the apparatus 60-70 kv.

Resultes and their discussion. According to the literature [5], loading with cholesterol and saturated fatty acids in healthy people as well as in experimental animals after 2-week experimental hypercholesterinemia in blood results in appearance of erythrocyte prehemolitic forms, degranulated polymorphonuclear leucocytes (PNL) and blood platelets. The reaction of PNL results in changes in cell form and plasmolemma activity that is likely to indicate their ability to migration and chemotaxis.

In our case differentiation of PNL into two heterogenous populations was the most visible: active and degranulated cells (foamy cytoplasm, lipid drops and lipid material endocytosis). Degranulation increased in eosinophilic and basophilic granulocytes. Cells with a high nuclearcytoplasmatic ratio, blasts with signs of nucleus activity and granular endoplasmatic network predominated among lymphocyte population.

A systemic damage of endothelium of intraorgan vessels developed at an early stage of the experiment (2 weeks) – edema of endotheliocytes with covering of capillary lumen, endotheliocytes of different density were seen ("light" and "dark" cells). The above mentioned changes, besides pinocytosis, activated additional transport routes: inter – and intraendothelial canals were formed. In cytoplasma of endotheliocytes, mitochondria hypertrophy, that of primary and secondary lysosomas. Analogous changes of endotheliocytes were found in aorta endotheliocytes as well that was observed by other authors too. Plasmorrhagia into basal membranes and pericapillary space was developed that promoted LP insudation and thus the density of capillary basal membranes becomes identical to the density of contents in their lumen and in pericapillary space. In kidneys we found basal membrane laminated structures of capillaries of glomeruli and urinary canals washed away with areas of irregular dilation and homogenization; the typical three- layered structure was lost, amorphous osmiophilic stuff was accumulated in basal membrane depth.

The lengthening of the experimental period (1-2 months) was characterized by on increase in hypercholesterinemia effect (an increase in the amount of vacuoles and lipid inclusions in endotheliocyte cytoplasma, mitochondria destruction) indicating the depletion of their energetic resources. In addition to the cells in balloon dystrophy stage, endotheliocytes with dark citoplasma, irregular luminal surface, dilated pores were available. In capillary lumens from cerebral cortex sensomotor zone were seen endothelium cytoplasma digital processes as a sign of convolute formation – one of the forms of neoangiogenesis. Various structural inclusions were found in the depth of capillary basal membranes from all the organs changing their anatomical peculiarities; these changes acquiring the character of microangiopathy.

Endothelium dysfunction in hypercholesterolemia is regarded as a trigger mechanism for a number of pathologic reactions such as stable adhesion and aggregation of erythrocytes and leukocytes in capillaries, diapedesis and erytrophagia.

The examined organs revealed a capillary plethora (in liver-sinusoid plethora, in lungs – that of interalveolar capillaries), capillary lumen revealed stasis of erythrocytes and leukocytes and their diapedesis resulting in disturbance of organ microcirculation characterizing an acute atherosclerosis stage [7]. Adhesion of monocytes on endothelium surface is believed to be one of the most important components of the inflammatory reaction at atherogenesis early stage. Forty-eight hours later after exposure minimal oxidized low-density LP are known to cause monocyte adhesion to endothelium of aorta, vessels of lungs and heart both in men and in experimental animals [2].

The amount of irreversibly changed forms of erythrocytes, perhaps owing to activation of lipid peroxide oxidation in hypercholesterinemia increased 30 days from the experiment start and further on. Some authors connect this effect with elimination of pathogenic hemoglobin heme [3]. The correlation between PNL degranulation, synthesis and cytotoxin liberation is shown in the works [4]. The platelet degranulation and release of ADF promotes binding of fibrinogene with thrombocyte proteins.

In our study an attention was paid to revealing the morphologic substrate of intercellular cooperation of lymphocytes, blood platelets and PNL. Lymphocyte activation was observed, the formers being attributed to the subpopulation of lymphocyte – killers with numerous phagolysosomes, intercellular cytoplasmatic bridges bound with erythrocytes. This observation indicates the possibility of information exchange among aggregated PNL, degranulated platelets and lymphocytes through the mechanism of superoxide generation exciting chemotaxis of PNL as well via suppression of cytotoxis reactions and participation in the regulation of natural killer population. An increase in morphologically confirmed intercellular interactions observed in the experimental group, compared to the control group, indicates an activation of immune response cytotoxis mechanism. The latter is a compensatory reaction of lymphocytes and PNL to a negligible increase in the contents of atherogenous lipoproteins. An increase in intercellular interactions is also confirmed by activation of monocyte function under the condition of an increased apoB-LP inflow, recognition and their intake by a receptor – mediated mechanism which in these conditions appears to be more efficient than the scavenger – route. Slightly modified LDL promote a release of cytokines (interleukin - 1) whose expression on monocyte plasmolemma results in an increase in lissome contents in the cytoplasm of the latter.

The changes are more intensive in experimental hypercholesterolemia of 3-month duration. Capillary lumen is narrowed and deformed. Endothelium is exfoliated and basal membrane fibrosis is found in some viscera capillaries. The aorta patterns with analogous hypercholesterolemia duration revealed lipid patches confirming atherosclerosis progression.

4-6 months after experimental hypercholesterolemia the changes in the components of viscera histohematic barrier had primarily a qualitative character. The processes of collagenisation and fibrosis of capillary basal membrane dominated with their deformation, rigidity and disturbance in selective permeability. Microcirculation disturbance was also promoted by aggregation and stasis of formed elements edema of endotheliocyte nucleus and cytoplasma, sometimes with bulging of perikarium on area resulting in capillary lumen clogging. Deformed dig-

ital processes of cytoplasma resulted in irregularities of luminal surface relief and in an increase in microplasmatosis. Basal membrane lysis was seen in some places. The area of aortal wall damage with atherosclerosis amounted to 76,7±6,7%.

Thus, damages of micricirculation mediated by changes in histohematic barrier permeability, insudation of plasma rich in LP into pericapillary space with disturbance of organ parenchyma trophism are of great importance in organ dystrophy and fibrosis in experimental hypercholesterinemia. Unidirection and systemicity of the reaction confirms a generalized character of terminal vascular bed damages in response to the effect of one of the atherogenesis risk factors – exogenous cholesterol and dislipidemia. The data received confirm an etiologic importance of exogenous Cholesterol as a starting point of atherogenesis.

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РЕЗЮМЕ

ЭФФЕКТ ВОЗДЕЙСТВИЯ ЭКЗОГЕННОГО ХОЛЕСТЕРИНА НА ФУНКЦИОНАЛЬНУЮ МОРФОЛОГИЮ СОСУДОВ МИКРОЦИРКУЛЯТОРНОГО РУСЛА И ФОРМЕННЫХ ЭЛЕМЕНТОВ КРОВИ В ЭКСПЕРИМЕНТЕ

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Целью исследования являлось выявление параллелизма морфо-функциональных изменений, происходящих в сосудах микроциркуляторного русла и форменных элементах крови при экзогенном введении холестерина.

Эксперимент проводился на кроликах породы шиншилла весом 2,5-3 кг. Введение холестерина осуществлялось холестериновой диетой по Н.Н. Аничкову. Опытная группа состояла из 60 животных, контрольная из 20. Животные забивались на 15,30, 60, 90, 120 и 180 дни от начала эксперимента. Полученные полутонкие и ультратонкие срезы исследовались с помощью электронного микроскопа “ Tesla BS-500” при ускоряющем напряжении 69-70 kv. Полученные данные позволяют судить об этиологической значимости экзогенного холестерина в развитии морфо-функциональных изменений, происходящих в сосудах микроциркуляторного русла и форменных элементах крови и их параллелизме.

Key words: Experimental hypercholesterolemia, blood formed elements, microcirculation.

Научная публикация

NONINVASIVE ASSESSMENT OF ENDOTHELIUM-DEPENDENT VASODILATATION IN SUBJECTS WITH RISK FACTORS OF ATHEROSCLEROSIS AND WITH ISCHEMIC HEART DISEASE AT EARLY STAGE OF TREATMENT WITH STATINS

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Atherosclerosis is considered to be a complex process that is closely linked with alteration of certain cell groups. The early stage of atherosclerotic changes appear in form of endothelial dysfunction (ED), that is why studying ED became very important and topical nowadays [1].

Endothelium is metabollically active structure that controls vascular responses and regulates platelet-wall interaction. Risk-factors of atherosclerosis such as dyslipidemia, hypertension, diabetes mellitus, cigarette smoking, overweight, contribute to ED [2,4,7,9].

Reduced vascular endothelium-dependent vasodilatation (EDV) in response to the physiological or pharmacological stimulation is caused by reduced concentration and/or activity of relaxing factors (NO, prostacycline, c-type natriuretic peptide) or increased contractility of the vessel. These changes of endothelial function play an important role in the initiation, progression and clinical complications of vascular disease. ED is one of the firsts of developments of atherosclerosis and supports and aggravates this process [5].

Recent experimental and clinical studies have suggested reversibility of ED by stopping influence of causes or by treatment [6,8].

The proved link between coronary artery disease and brachial artery ED allows using of this artery as a model for noninvasive study of progression of atherosclerotic process [10].

The aim of our study was to investigate flow-mediated endothelium – dependent vasodilatation (FMD) in patients with risk factors of atherosclerosis and with ischemic heart disease and to evaluate the influence of treatment with HMG-CoA reductase inhibitor simvastatin (Vasilip-KRKA,Slovenia) on impaired endothelial function after 6 week-long treatment.

Materials and methods. 59 patients were studied (males, mean age 50±8years) and divided into 3 groups: I group - 20 patients with risk factors of atherosclerosis (hypercholesterolemia, hypertension, cigarette smoking, overweight et c.), II group–29 patients with ischemic heart disease and III group –10 healthy persons.

Age, family history, lipid profile, body mass index, cigarette smoking, carotid artery alteration were taken into consideration (table 1).

Table 1. Baseline characteristics

	I group	II group	III group
Number of patients	20	29	10
Age, years	50±5	52±8	48±3
BMI	32,4±3,3	28,48±4,1	25,2±3,1
Intima-media of carotid arteries,mm	1,11±0,13	1,3±0,3	0,85±0,11
Atherosclerotic plaque		13	
Risk factors	>3	>4	<1

The TOSHIBA SSH-140A unit was used to measure brachial artery (BA) diameter and blood flow velocity at rest and after occlusion by high pressure cuff twice-before and after treatment with 20 mg Vasilip. To induce flow-mediated endothelium – dependent vasodilatation we used EDRF release test [10] BA was occluded by high pressure cuff for 2 minutes with pressure 50 mmHg higher then systolic blood pressure.

Results and their discussion. In I group BA diameter was 4,76±0,54mm, after occlusion it increased to 5,04±0,66mm. The flow-mediated endothelium-dependent dilatation (FMD) was 5,62±1,8% and grew 8,6±0,6% after treatment.

In patients with iscemic heart desease (II group) BA diameter was 4,58±0,89mm and became 4,88±0,63 mm. FMD was 5,3±0,9% and increased to 8,25±0,76% (table 2). In III group BA diameter was 4,1±0,25mm and increased to 4,51±0,23mm. FMD was normal at baseline-10±0,13%. Blood flow velocity augmentation occurred in both groups after treatment as well.

During investigation we detected enhanced thickness of intima-media complex (I gr. - 1,11±0,13 mm, II gr. - 1,3±0,23 mm) of carotid arteries. The slight reduction occurred after treatment (I gr. - 1,02±0,08 mm, II gr. - 1,15±0,85). Atherosclerotic plaques, observed in 13 patients of I group showed stabilization – size regression and enhanced echogenity, that could be partly caused by improvement of ED.

Table 2. Different cardiological parameters before and after treatment

	I group				II group			
	Before treatment		After treatment		Before treatment		After treatment	
	Before occlusion	After occlusion	Before occlusion	After occlusion	Before occlusion	After occlusion	Before occlusion	After occlusion
BA diameter	4,76±0,54	5,04±0,66	4,69±0,7	5,08±0,3	4,58±0,9	4,88±0,6	4,63±0,7	5,01±0,25
FMD	5,62±1,8		8,6±0,6		5,3±0,9		8,25±0,79	
Blood flow velocity	108,75±4,1		115,43±3,2		102,37±6,3		110,22±4,5	
Intima-media of carotids	1,11±0,13		1,02±0,08		1,3±0,3		1,15±0,85	

Many studies have shown close relationship between ED of BA and coronary atherosclerosis [11], that is why studying endothelial function is very important in order to perform correct and timely treatment.

Conclusions: in present study we investigated endothelium function of BA in patients with risk factors of atherosclerosis and with ischemic heart disease before and after treatment. The ultrasound method enabled us to detect impaired endothelial function and the start of its improvement after treatment with 20mg of simvastatin (Vasilip). The results of study show impairment of endothelium-dependent vasodilatation in both groups, especially in ischemic heart disease group (which is reflection of particular severity of atherosclerosis in this group) and regression of ED after lipid-lowering therapy. Flow-mediated endothelium – dependent vasodilatation increased significantly taking into consideration the short period of treatment (6 week). Further studies are planned through prolonging the treatment.

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РЕЗЮМЕ

НЕИНВАЗИВНАЯ ОЦЕНКА ЭНДОТЕЛИЙЗАВИСИМОЙ ВАЗОДИЛАТАЦИИ У ЛИЦ С ФАКТОРАМИ РИСКА РАЗВИТИЯ АТЕРОСКЛЕРОЗА И ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА НА РАННЕМ ЭТАПЕ ТЕРАПИИ СТАТИНАМИ

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Цель исследования – неинвазивная оценка эндотелийзависимой вазодилатации у лиц с факторами риска развития атеросклероза и ишемической болезнью сердца на раннем этапе терапии статинами. С помощью системы TOSHIBA SSH-140A (датчик с частотой 5 МГц), в триплексном режиме измеряли диаметр плечевой артерии и скорость кровотока в покое и после реактивной гиперемии. Функцию эндотелия оценивали по стандартной методике (D. Celermajer, 1992) до и после 6-недельной терапии симвастатином (Вазилип, фирма KRKA6 Словения) в дозе 20 мг. Обследованы 59 мужчин (средний возраст 50±8года), из них 20 с факторами риска развития атеросклероза (I группа), 29 с ишемической болезнью сердца (II группа) и 10 здоровых мужчин контрольной группы (III группа). Повторно обследованы 36 больных. Результаты исследования свидетельствуют о нарушении эндотелийзависимой вазодилатации в обеих группах (I группа - 5,62±1,8%, II группа - 5,3±0,9%) и о положительном влиянии симвастатина на функциональное состояние эндотелия: эндотелийзависимая вазодилатация повысилась в I группе - до 8,6±0,6%, а во II группе - до 8,25±0,79%. Наблюдение за динамикой этого процесса, при продолжении лечения, станет следующим этапом нашего исследования.

Key words: ED, EDV, FMD, risk-factors of atherosclerosis.

Научная публикация

SOME METABOLIC RISK-FACTORS IN WOMEN WITH ARTERIAL HYPERTENSION

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Essential Hypertension is one of the most prevailed diseases in the world. In 1970s there were registered 60 million such patients in the USA [3]. The number of cases of myocardial infarction caused by essential hypertension made up 1,25 mln, of stroke - 500 000; 1/3 of the total number of cases had a lethal outcome [1]. In 22 000 cases, on the basis of autopsy it was determined that ischemic heart disease was developed in 50%-90% of hypertension cases [2].

Presented data makes obvious the necessity of prevention and study of arterial hypertension. With regard of prevention, correction of risk-factors in women during menopause has crucial importance, as prevalence of hypertension in females of this age group is nearly the same as in males. In women over 50 years of age the prevalence is higher and is connected with the reduction of estrogens after menopause [4-6].

The goal: identification of atherogenic risk-factors (lipids range), fibrinogen, C reactive protein (CRP) and gamaglutamiltransferasa (GGT) in pre-menopause and menopause periods in females with arterial hypertension.

Materials and methods. 83 women were studied. They were divided into two groups - pre-menopause group (I) and menopause group (II) - and subgroups according to the levels of their arterial pressure (basing on the classification adopted by American Association of Hypertension: the marginal hypertension with blood pressure 130/139 - 85/89; mild hypertension - 140/159 - 90/99, moderate hypertension 160/179 - 100/109, severe hypertension 180/209 - 110/119 and very severe hypertension >210->120).

Blood samples were taken from each patient under study after 12 hours of fasting. Lipids range was tested in blood serum by means of spectrophotometer "Janway 4500". Total cholesterol (TC) and triglycerides (TG) were measured by enzyme method using "BIOLABO, France" reagents. The amount of cholesterol in high-density lipoproteins was measured after precipitation of low density lipoproteins cholesterol (LDLC) and very low density lipoproteins cholesterol (VLDLC). Atherogenity Index and low density lipoproteins were calculated by means of Friedwald formula (1972). Fibronigen in blood was measured using the semiautomated procedure offered by "Bio-Fibri". In order to identify C reactive protein "Human" latex test was used.

Table 1. Criteria of disruption of the values of indicators under study is given

systolic arterial pressure	≥140
diastolic arterial pressure	≥90
body mass index	>29,0 kg/m^2
total cholesterol	≥190 mg/dl
cholesterol of low density lipoproteins (LDLC)	≥115 mg/dl
Triglycerides	≥180 mg/dl
high density lipoproteins cholesterol (HDLC)	>43 mg/dl
GGT	in jars<
C reactive protein	>6
Fibrinogen	>4 g/l

Obtained data was processed statistically; M+SD (M-medium, SD-standard deviation) was calculated. Student's t-test for matched data was used in analysis of intergroup information. Reliability rate was determined as P=0,05. Correlation was tested according to Pearson correlation.

Results and their discussion. At present new metabolic risk factors are discussed alongside with "old" ones. These new risk-factors are as follows: estrogens deficiency, homocystein, fibrinogen, blood coagulation factor VII, d-dimer, dislipoproteinemia, C reactive protein.

According to the literature sources in patients with hypertension and metabolic disorders (in comparison with those with hypertension, but without metabolic disorders) average systolic and diastolic pressure is higher, both during day and night hours. At night arterial pressure is significantly higher, that indicates, undesirable course of arterial hypertension in patients with metabolic disorders [8].

The results of our investigation showed that in condition of estrogens deficiency obesity was revealed in 45% of patients. Besides 31% of patients had 1 risk-factor, 33% - two, 26% - three and 10% -four risk-factors.

Comparing the data of 2 groups (table 1) it was revealed that in women with menopause LDLC atherogenity index are reliably elevated, whilst HDLC is decreased (< 0,05). The same was identified by other researchers as well [ ].

Table 2. Indicators of lipid metabolism, C reactive protein (CRP), fibrinogen (Fb), gamaglutamiltransferasa (GGT), body mass index (BMI) in women with hypertension in pre and post menopause periods

Group		age	BMI	SBP	DBP	TC	LDLC	HDLC	VLDLC	TG	IA	Fb	CRP	γ-GT
I	M	44,8	29,2	135,2	81	198,6	112,5	57,8	26,7	129,5	2,7	1,5	6,2	8,95
N=13	SD	5	3,4	19,42	10,6	46,9	40	20,3	7,41	35,7	1,2	1,6	0,6	3,3
II	M	60,7	26,7	161,3	89,6	214,5	138,1	45,3	28,9	141,5	4	3,8	7,7	12,4
n=70	SD	8,6	3,2	19,8	10,4	43,1	47,1	8,3	14	76,7	0,5	0,2	2,7	4,9

Notes: BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood premature; TC - total cholesterol; LDLC - low density lipoproteins cholesterol; VLDLC - very low density lipoproteins cholesterol; HDLC - high density lipoproteins cholesterol; TG - triglycerides; IA - atherogenity index; CRP - C reactive protein; GGT - gama-glutamil transferase.

Excessive fatty tissue in abdominal area is identified as one of the risk-factors for the development of arterial hypertension. The authors consider that it is caused by excessive sensitivity of adipocytes lipolisic enzymes [5], in difference with area of gluteal muscles that is caused by insulin sensitive receptors. It should be mentioned that in our study - estrogens deficiency conditions- obesity was revealed in 45% of patients. The authors consider, that excessive fatty tissue, increased tissue resistance to insulin increases the risk of the development of ischemic heart disease and affects blood coagulation. Correlation between blood components, such as: insulin, fibrinogen and plasminogen activator was identified [6]. It should be mentioned that in our study average indicator of fibrinogen in the patients of group 2 is reliably higher (P<0,05), than in group 1. This result is very important as fibrinogen is atherogenic and thrombogenic risk-factor as well. CRP is also reliably elevated in women with menopause. CRP, just like fibrinogen, is the product of liver acute phase proteins. GGT, that is used as liver pathologic diagnosing test, according to the study is located on the membranes of liver canaliculy epithelial cells with high secretive and absorption ability, is involved in metabolism of lipoproteins, prostaglandins and leucotriens (Pazeles L, et all., 1997). According to the outcomes of our research reliable increase of GGT in group II may indicate liver dismetabolism in condition of estrogen deficiency. It is resulted in lipid misbalance and conditions for oxidative stress are created for the females with hypertension in menopause.

Conclusions: in women with hypertension in menopause misbalance of lipid metabolism takes place, particularly low density lipoproteins cholesterol and atherogenity index are increased, high density lipoproteins cholesterol is reduced; C-reactive protein and fibrinogen are reliably increased in patients with menopause and hypertension; mentioned data is in relation with the elevation of systolic and diastolic blood pressure; increase of metabolic risk-factors in conditions of estrogen deficiency takes place on the background of GGT value elevation, that indicates to the active involvement of liver in hypertension development during menopause.

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РЕЗЮМЕ

НЕКОТОРЫЕ МЕТАБОЛИЧЕСКИЕ РИСК-ФАКТОРЫ У ЖЕНЩИН С АРТЕРИАЛЬНОЙ ГИПЕРТОНИЕЙ

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Цель исследования - установление атерогенных риск факторов: липидного спектра, фибриногена, С-реактивного белка (CRP) и гама-GT во время пременопаузы и менопаузы у женщин.

Исследовано 83 женщин. Исследуемый контингент разделен на две группы: пременопаузы (I) и менопаузы (II)

и подгруппы по уровням артериального давления (по классификации принятой американской ассоциацией гипертонии в1993 году: пограничная 130/139-85/89, мягкая гипертония 160/179-100/109, тяжёлая гипертония 180/209-110/119, очень тяжёлая >210->120).

У исследуемых лиц кровь забирали после 12 часового голодания, полученные данные обработаны статистически.

В состоянии менопаузы у женщин с артериальной гипертонией отмечается дисбаланс липидного обмена, в частности, рост холестерина липопротеидов низкой плотности и индекса атерогенности и уменьшение холестерина липопротеидов высокой плотности; значительно увеличивается С-реактивный белок и фибриноген.

Указанные изменения связаны с увеличением как систолического, так и диастолического артериального давления.

Увеличение метоболических риск факторов в условиях недостаточности эстрогенов происходит на фоне увеличения значений гамаглутамила, что указывает на участие печени в генезе гипертонии во время менопаузы.

Key words: Hypertension, Menopause, Dislipidemia, Metabolism, Fibrinogen, (GT, Astrogan.

Научная публикация

PREVALENCE OF ATHEROSCLEROSIS AND PECULIARITIES OF LIPID METABOLISM AMONG INDIGENT POPULATION

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Currently cardio-vascular diseases are widely spread worldwide, which are related to atherosclerosis. It still remains as one of the most important problem in State, social and medical areas.

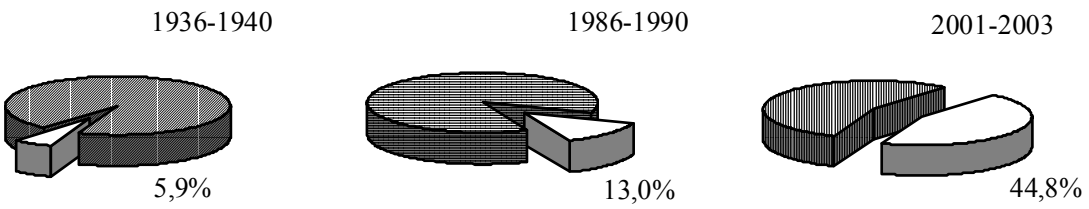
Study of pathogenic mechanism of atherosclerosis and finding of new ways for correction of basic metabolic disorders is a priority direction in medicine. Prevention of cardiovascular diseases is based on modern concept of risk factors, which are divided into variable indicators – total cholesterol amount, density of triglycerides, high and low lipoproteins and correlation of atherogenobe coefficient [1,2,4].

Unfortunately rate of atherosclerosis is quite high. Besides there is no information available about prevalence of the disease and its peculiarities among indigent population.

Our objective was to study prevalence of atherosclerosis among indigent groups of population based on the data obtained at the clinic of Georgian Patriarchate for the period of 2001-2003.

Material and methods. We investigated 388 patients – 210 female (54,1%) and 178 male (45,9%). Age varied between 15 – 87 ages. As the study showed 174 patients (44,8%) had ischemic heart disease.

Below is given the diagram reflecting prevalence of ischemic heart disease by years at therapeutic clinic.



Prevalence of ischemic heart disease by years at therapeutic clinic

Diagnoses were made based on clinical and laboratory-instrumental investigations. Peculiarities of lipid metabolism before and after the treatment were studied in 109 patients. Results are given in the table.

Lipid spectrum was studied using automatic method (Boehringer Maunhein for cholesterol and triglycerides). Atherogenobe coefficient was calculated by Klimov formula. Treatment of patients was carried out according to the traditional scheme. Patients were prescribed antiatherosclerosis diet, provided by the European Society for Atherosclerosis Study.

Table. Lipid metabolism index in patients with ishemic deseases befor and after treatment

Indicators	Before treatment	After treatment
Total cholesterol	7,4 ± 0,2	6,5 ± 0,4
High density lipoproteides	1,2 ± 0,1	1,5 ± 0,3
Low density lipoproteides	5,7 ± 0,4	5,6 ± 0,3
Triglycerides	3,0 ± 0,3	2,8 ± 0,1
Atherogenobe coefficient	6,1 ± 0,7	5,5 ± 0,6

Results and their discussion. As the study showed rate of ischemic heart disease prevalence among indigent population is quite high, despite to the fact that part of these patients keep the fast.

It is known from the literature, that one of the most important risk factors of this pathology is the unbalanced diet [3].

Proceeding from above mentioned, we studied peculiarities of diet in indigent population. Assessment of the diet ration of indigent population revealed deficiency of proteins and fats on the background of high carbohydrates consumption (mainly consuming bread and bread products, potato, etc), which possibly promotes metabolism of lipid spectrum and development of atherosclerosis.

It also must be considered the effect of stress factors and hypodinamia in these patients. Among the indigent we found one more fact – they have anemic syndrome.

The amount of hemoglobine in women in average was 116,18 g/litre and in men 110,6 g/litre. It seems that diet deficiency affected the level of hemoglobin. It makes clear, that patients are under permanent hypoxia.

Currently it is proved that hypoxia stimulates the proliferation of artery walls isolated muscle cells, which becomes one of the mechanisms of development of atherogenobe.

Hypoxia also breaks the ability of ferments to split muscle cells of low-density lypoproteids, leading to their accumulation.

It is accompanied with the fact that in experimental animals, being under systematic hypoxia developed the aortic disorder.

It is also proved that in monkeys and rats, receiving the enriched food, accumulation of lipids was more accelerated during hypoxia, rather than without hypoxia.

Based on comparison of literary sources and results of our study we can assume that ischemic heart disease in these patients is connected with permanent hypoxia.

In summary we can say that all above mentioned is connected with diet, hypodynamia and developed hypoxia.

As the table shows mainly the indicators of total cholesterol and low density lipoproteides are increased. Moderate increase of triglycerides is observed. Coefficient of atherogenobe is also increased. After hard diet and treatment slight decrease of indicators of total cholesterol, low density lipoproteids, triglycerides and atherogenobe coefficient is observed. At the same time increased the indicators of high-density lipoproteids. Clinical condition of the patients improved.

Based on the analysis of the study data we can conclude that the rate of atherosclerosis among indigent population is quite high, which is mainly conditioned by their diet.

Antiatherosclerosis treatment and especially medical diet greatly improves the lipid spectrum of patients.

To our opinion correction of diet ration among indigent population will promote decrease of atherosclerosis prevalence, which is connected to the improvement of their social conditions.

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РЕЗЮМЕ

РАСПРОСТРАНЕНИЕ АТЕРОСКЛЕРОЗА И ОСОБЕННОСТИ ЛИПИДНОГО ОБМЕНА СРЕДИ НЕИМУЩИХ

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Изучено распространение атеросклероза среди неимущих в терапевтической клинике для неимущих Грузинского патриаршества в 2001-2003 гг. Обследованы 388 больных, среди них женщин – 210 (54,1%), мужчин – 178 (45,9%). Возраст варьировал в пределах 15-87 лет.

109 больным проведено антиатеросклеротическое лечение с включением соответствующей диеты. В динамике до и после лечения в крови больных определяли основные показатели липидного обмена. После лечения отмечено сравнительное улучшение липидного спектра больных. В частности, содержание общего холестерина в крови снижается на 12,2%; триглицеридов на 6,7%; холестерин липопротеидов низкой плотности на 1,8%; холестерин липопротеидов высокой плотности повышается на 25%; коэффициент атерогенности снижается на 9,8%.

Key words: atherosclerosis, lipid metabolism, indigent population.

Научная публикация

TWENTY FOUR HOUR BLOOD PRESSURE PROFILE, STRUCTURAL AND HEMODYNAMICAL STATE OF HEART AND ENDOTHELIAL FUNCTION IN HYPERTENSIVE SUBJECTS

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Arterial hypertension (AH) is the most widespread disease in the population and the main cause of increased risk of cardiovascular complications, stroke and renal insufficiency. As a consequence of hypertension, myocardium undergoes structural changes that are termed “hypertensive heart disease.” Hypertension-associated left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality, including myocardial infarction, congestive heart failure and even sudden cardiac death [1-3]. LVH depends not only on severity and duration of hypertension, but on various hemodynamical and nonhemodynamical factors.

In addition to the manifested cardiovascular changes, AH is associated with unfavorable central and local neurohumoral disorders. The endothelium which responds to shear stress, controls vascular responses to vasoactive hormones (by releasing relaxing and contracting factors), regulates platelet-vessel wall interaction and modulates smooth muscle cell migration and proliferation, under certain conditions (AH, dyslipidemia, aging, smoking, etc.) can lead to structural changes of vascular wall and clinical complications of vascular diseases. Endothelial dysfunction (ED) in hypertensive patients with left ventricular hypertrophy can reduce coronary reserve.

Casual blood pressure (BP) measurements correlate poorly with LV mass and ED. 24-h measurements are better in this regard [4]. Main advantage of the use of 24-hour blood pressure monitoring (except precise selection of patients requiring drug treatment, evaluation of effects and results of therapy), is that it enables to carry out dynamic control of BP to reveal some correlation with risk factors and to elucidate common and individual reasons of development of hypertension [5,6]. Relationship between some parameters of 24-hour blood pressure measurements, LVH and ED is important but less studied aspects.

The aim of our study was to assess parameters of 24-hour blood pressure monitoring, with reference to heart and carotid artery structural and hemodynamical changes and state of vessel endothelial function in patients with hypertension-assosiated left ventricular hypertrophy.

Material and methods. We studied 25 patients (mean age 58,5±6,6years) - 13 with systolo-diastolic hypertension (I group), 12 with isolated systolic hypertension (II group). The duration of the disease was 7±2,4years. 10 healthy persons formed control group. Age, family history, lipid profile, body mass index, cigarette smoking were taken into consideration.

TOSHIBA SSH-140A unit was employed to investigate left ventricular parameters (internal dimensions and wall thickness), systolic and diastolic function, carotid artery intima-media complex and endothelial function of brachial artery. Twenty- four hour blood pressure monitoring was carried out by the system ABMP-02/0 (Meditech, Hungary).

Results and their discussion. Left ventricular mass (calculated by method suggested R.Devereux, N.Reichek (7,8)) was increased in both groups: I-233,31±21,5gr and II-220,12±23,8gr (in control group 135,8±24,7gr). Diastolic dysfunction occurred in both groups as well: I-E/A-0,85±0,07; II-E/A-0,74±0,09. The results of 24-hour blood pressure monitoring are given in table.

Table. Results of 24-hour blood pressure monitoring

		24-hour			Day			Night		
		I gr	II gr	Control gr	I gr	II gr	Control gr	I gr	II gr	Control gr
Mean pressure mmHg	Syst	156,2± 3,2	162,3± 2,6	110,5± 2,3	158,2± 3,2	165,5± 4,4	125,3± 2,2	142,5± 5,3	158,4± 3,5	108,4± 5,3
	Diast	98,1± 1,2	87,3± 1,1	74,6± 1,3	101,9± 3,3	85,2± 1,5	76,6± 1,4	93,4± 4,2	83,1± 1,1	70,5± 1,1
Time Index %	Syst	67,7± 3,5	67,9± 5,5	6,7± 1,8	66,4± 4,4	81,6± 5,2	7,2± 1,3	69,3± 6,4	86,2± 5,6	6,3± 2,1
	Dias	52,3± 3,6	6,3± 1,6	3,5± 1,3	58,3± 4,3	6,3± 1,2	4,8± 1,4	46,1± 4,3	6,6± 3,3	1,7± 1,1
24-hour Index %	Syst	8,3± 1,8	6,7± 1,1	15,5± 1,7						
	Diast	8,9± 1,5	11,1± 1,3	17,3± 2,8						
Variability mmHg	Syst	15,5± 2,2	15,8± 1,3	10,1± 0,5	16,3± 1,2	18,3± 0,8	10,8± 0,5	13,3± 0,8	12,2± 0,5	9,2± 0,7
	Diast	13,6± 2,0	9,1± 0,9	8,1± 0,7	14,3± 0,8	9,3± 1,8	8,3± 1,4	10,7± 0,5	8,8± 1,7	8,7± 0,4
Pulse pressure mmHg		56,8± 1,3	74,3± 3,3	34,5± 2,2	56,5± 1,8	80,3± 2,3	48,7± 1,8	55,5± 1,8	75,3± 3,1	37,9± 1,9
Heart rate		73,3± 0,8	63,8± 0,5	61,5± 0,4						

In 1st group diurnal and nocturnal systolic/diastolic BP(158,2±3,2/101,9±3,3mm.Hg and 142,5±5,3/93,4±4,2 mm.Hg),time index - BP load (day - 66,4±4,4/58,3±4,3%, night - 69,3±6,4/46,1±4,3%) and variability (d - 16,3±1,2/ 14,3±0,8mmHg, n - 13,3±0,8/10,7±0,5mmHg) were increased, day/night index was decreased (syst - 8,3±1,8%, diast - 8,9±1,5%). 10 patients were "non-dippers", 2 – "dippers", 1- "night-peaker".

In 2nd group mean diurnal and nocturnal systolic BP (165,5±4,4mmHg and 158,4±3,5 mmHg), time index (day - 81,6±5,2%, night - 86,2±5,6%) and variability of only systolic BP (d - 18,3±0,8mmHg, n - 12,2±0,5mmHg) were increased, day/night index of syst BP was decreased 6,7±1,1%. 9 patients were "non-dippers", 1 -"dipper", 2 - "over-dippers".

Reaction of brachial artery to reactive hyperemia (endothelium – dependent vasodilatation in response to increased blood flow after occlusion) was investigated using EDRF release test (Celermajer 1992) [9]. Endothelium – dependent vasodilatation was reduced in both groups: I - 5,5±0,9%, II - 5,2±0,7%. Thickness of intima-media complex (IMC) of carotid arteries was enhanced (I - 1,3±0,01mm; II - 1,2±0,01mm). Atherosclerotic plaques were detected in 3 patients of 1st group and 5 patients of 2nd group. These changes correlated with dyslipidemia, age, body mass index, left ventricular mass, cigarette smoking.

Thus, in patients with hypertension-associated left ventricular hypertrophy we detected diastolic and endothelial dysfunction (impaired endothelium – dependent vasodilatation of brachial artery, thickening of IMC, atherosclerotic plaques). In 1st group these disorders were in correlation with increased diurnal and nocturnal BP, variability and time index - overall BP load. In patients with ISH- with increased diurnal systolic pressure variability, significant BP load of target-organs and enhanced pulse pressure.

These disturbances represent extent of cardiovascular involvement, affect quality of life and prognosis of patients. Dynamic control of BP, LVH and ED will be helpful in optimization of hypotensive therapy.

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РЕЗЮМЕ

СУТОЧНЫЙ ПРОФИЛЬ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ, СТРУКТУРНО-ГЕМОДИНАМИЧЕСКИЕ ОСОБЕННОСТИ ЛЕВОГО ЖЕЛУДОЧКА И ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ СОСУДИСТОГО ЭНДОТЕЛИЯ У ЛИЦ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Целью исследования явилось определение суточного профиля артериального давления и его взаимосвязи с морфо-функциональным состоянием сердца и сосудистого эндотелия у лиц с артериальной гипертензией.

У 25 больных (средний возраст 58,5±6,6) с систоло-диастолической и изолированной систолической АГ (ИСАГ) и гипертрофией левого желудочка проведены суточное мониторирование АД (СМАД), ультрасонография сердца и сонных артерий, исследование эндотелийзависимой вазодилатации (ЭЗВД) плечевой артерии.

Полученные данные свидетельствуют о существовании корреляции между повышенной массой миокарда, диастолической и эндотелиальной дисфункцией (утолщение комплекса интима-медиа – 1,3±0,01мм - I группа; 1,2±0,01мм - II группа; уменьшение степени ЭЗВД - I группа - 5,5±0,9%; II группа - 5,2±0,7%) и такими параметрами СМАД, как среднее систолическое, диастолическое и пульсовое давление, индекс времени (нагрузка давлением) и вариабельность.

У больных с систоло-диастолической гипертензией вышеуказанная взаимосвязь более выражена суточными параметрами как систолического, так и диастолического давления, а в группе больных с ИСАГ выявлена зависимость от пульсового давления, дневной вариабельности и временного индекса систолического давления.

Key words: AH, LVH, ED, 24-hour blood pressure monitoring.

Научная публикация

PECULIARITIES OF CARDIAC LEFT VENTRICULAR CARDIOMYOCYTE DAMAGE BY INFLUENZA VIRUS A AGAINST A BACKGROUND OF EXPERIMENTAL HYPERHOLESTEROLEMIA

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By their social importance, great damage caused to health of population and country economics, influenza and acute respiratory diseases (ARD) take first place among all other diseases and account for 10-50% of temporary invalidity of population [2].

Influenza virus A, affecting various organs and systems, in 5-17% of cases causes severe hypertoxic forms whose lethality amounts to 0,6-2,5% among persons of advanced age. Distinctive clinical features include an early binding and exudative character of catarrhal syndrome, cardio - pulmonary and cardio-cerebral complications (Miura et al, 2001). The findings reveal [7] that the principal cause of lethality in the given population is acute cardiac insufficiency, various types of rhythm and conduction disturbances.

The aim of the study is to investigate cardiomyocyte ultrastructures from the left ventricle of the heart on the model of toxic influenza A in animals with preceding hypercholesterolemia.

Material and methods. An experimental model of atherosclerosis was made on "Chinchilla" rabbits (n=20) with an initial body weight of 2,5-3 kg. The animals of series 1 were controls and received only hypercholesterol diet (0,3 kg/kg) after the method of Anichkov N. N. (1933) [6].

The animals of series II (main) were infected intranasally with suspension (0,5ml) of influenza virus A, strain (H_3N_2) which often affects people of advanced age [2]. Virus inoculation was carried out 30 days after the onset of cholesterol load. According to the reference data [3,5], changes in the aorta wall such as lipid blotches appear a month after atherogenic dieting.

The samples of myocardium tissue were taken: 1) after 30 days in series I animals - n=10; 2) after 3, 7 and 14 days following infecting in series II - n=3 at every stage of the test.

Ultra thin as well as histologic sections from the aorta wall and left ventricle myocardium were studied. Electronograms were received on microscope Tesla BS-500.

Results and their discussion. The ultrastructural analysis of aorta wall cell transformation into foamy cells in series I revealed characteristic for atherogenesis changes, such as squevinger-mediated trapping of low density lipoprotein molecules (m LLD), formation of phagolysosomes in endothelial and smooth-muscle cells with migration into the subintimal layer that corresponds to the transition of a lipid blotch into the stage of an atherosclerotic plaque [4].

Cardiomyocytes of series I animals reveal a significant intracellular swelling, the presence of large lysosomes and lipid inclusions (fig. 1), shifts of Z - bands, but no fragmentation and lysis of myofibrils was revealed.

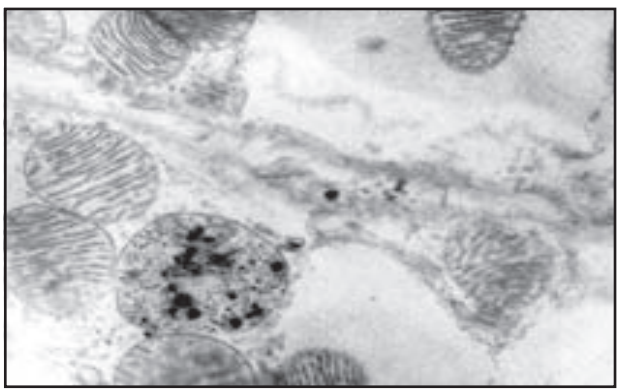

Fig. l. Series I tests. A large lipid inclusion in cardiomyocyte. x 9000

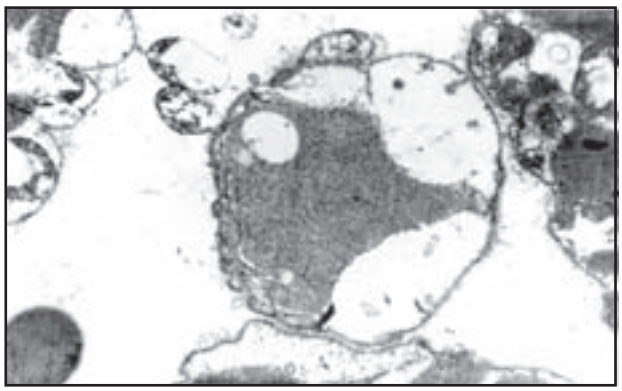

Fig.2. Series II. Hydropic dystrophia of endotheliocytes, x 9000

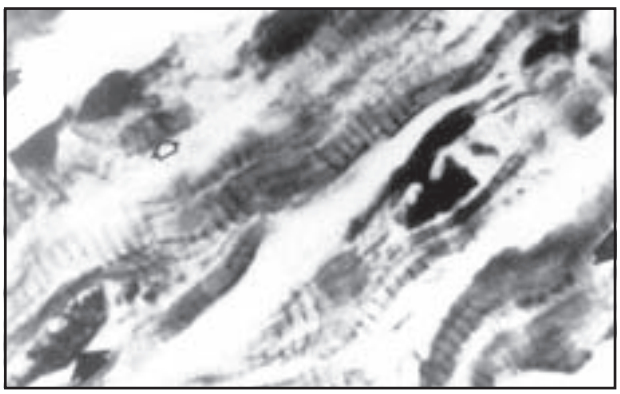

Fig.3. Series II. Coagulative necrosis of myocardial fibers caused by influenza virus A infection; hematoxylin - eosin x 200

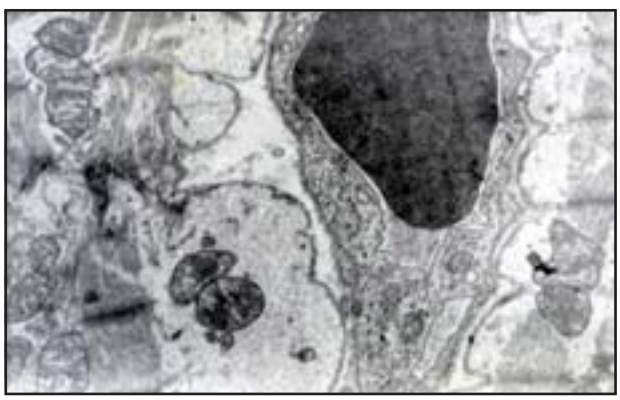

Fig.4. Fragmentation of intercalated disk, lysis of myofilaments, sarcoplasma swelling, x 9000

In series II tests (hypercholesterolemia + influenza) together with the above-mentioned changes, 3 days after infection, we revealed extracellular matrix and capillary endotheliocyte swelling (fig. 2), myofibril lysis.

The 7th and 14th days of the test revealed intercalated disc membrane fragmentation, decomposition of muscular fibers (fig. 3), intracellular swelling (fig. 4).

Mitochondria of unusual structure and of gigantic size, exceeding in size the neighbouring mitochondria, were found among myofibrils. The interior space of such organelles was filled with osmiophilic granules and exclusive membranous structures. According to the reference date, intramytochondrial inclusions, like vacuoles, are modified mitochondria - megamitochondria regarded as the result of mitochondria degeneration.

14 days after influenza virus A infection, cardiomyocytes contained mitochondria with unusual changes in structure. Dystrophic and destructive processes, such as decomposition and reduction of membranous systems, partial or complete cryst lysis, were observed. These changes coincided with laminar complex extension, that of sarcoplasmatic reticulum cavities. The other part of organelles had clearly separated zones, matrix was very decreased compared to neighbouring mitochondria. Besides there were numerous septated mitochondria each of which is separated by its own internal membrane. Mitochondria with such changes develop under hypoxia conditions.

Cardiomyocytes with such mitochondria had characteristic vesicular appearance inherent to cells which underwent apoptosis. Nuclear chromatin, which, when normal, is presented by open and condensed regions, becomes supercondensed and acquires the shape of a crescent round the nucleus periphery. This moment is believed to correspond to the onset of DNA fragmentation [1].

Some authors believe that apoptosis takes part in paroxysmal arrhythmia genesis frequently resulting in sudden death of patients with influenza virus A.

Conclusion. In experimental influenza virus A against a background of hyperholesterolemia, destructive changes in mitochondria are the result of an increased energetic need of a cell in virus infection creating energodeficiency and substrate hypoxia. The death of cardiomyocytes by means of apoptosis takes place in a significant oxygen want of myocardium.

The above mentioned findings enable to conclude that the state of mitochondria ultrastructure is a reliable index enabling to assess the depth of cardiomuscular tissue damage.

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РЕЗЮМЕ

ОСОБЕННОСТИ СТРУКТУРНОЙ ПЕРЕСТРОЙКИ КАРДИОМИОЦИТОВ ЛЕВОГО ЖЕЛУДОЧКА СЕРДЦА ПРИ ИНФИЦИРОВАНИИ ВИРУСОМ ГРИППА А НА ФОНЕ ЭКСПЕРИМЕНТАЛЬНОЙ ГИПЕРХОЛЕСТЕРИНЕМИИ

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Исследована ультраструктура кардиомиоцитов у кроликов с экспериментальной гиперхолестеринемией на 3, 7, 14 день после инфицирования вирусом гриппа А.

Параллельно изучали образцы стенки аорты, как маркера стадии и фаз развития атеросклероза.

В отличие от группы с гиперхолестеринемией при инфицировании вирусом в кардиомиоцитах отмечены вакуолизированные эндотелиоциты капилляров, лизис базальной мембраны и сарколемы сердечно–мышечных клеток, значительный отек экстрацелюлярного матрикса.

Результаты показали наличие коагуляционного некроза и лизиса мембран вставочных дисков в кардиомиоцитах в отличие от неинфицированных животных.

Отличительной особенностью является появление септированных, пузырьчатых мегамитохондрий, что отражает возросшую энергетическую потребность клетки при вирусной инфекции.

Key words: cardiomyocytes, ultrastructure, influenza virus A, hypercholesterolemia.

Научная публикация

LIPID SPECTRUM AND ECG PECULIARITIES UNDER SATURATED FATTY ACID AND CHOLESTEROL LOAD

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Among the various factors that influence CHD dislipidemia is known, the quality of which depends on quality and quantity of accepted food [3], especially saturated fatty acid which represents one of the risk factor of atherosclerosis [4]. In CHD patients correlation between dislipidemia, thrombosis and sudden death is stated [6,20].

The aim of our study is: to reveal the effects of food rich in saturated fatty acid and cholesterol on atherogenic factors (lipid spectrum) and fibrinogen; to state saturated fatty acid test importance for revealing of myocardium electrical instability.

Material and Methods. 11 patients with atherosclerosis (ECG, echocardiography, stress testes and in some cases coronarograpy were used for diagnosing) were examined (57,2±10,19 years)- group I. The control group II - was composed of practically healthy persons 11 (33,7±13,4 years). Atherosclerosis, in this group, was excluded by clinical examination.

Blood samples were taken after 13 hour fasting and 3 hours(the peak of TG and Cholesteremia) after having nutritional load (eggs,200gr 20%sour cream,100gr butter.The total amound of cholesterol=1720mg) (15). Lipid spectrum was studied in blood serum using "Janway 4500" spectrometry. The quantitative determination of total cholesterol (TC) was performed triglycerides (TG) were determined by the enzyme method, while the content of high density lipoprotein-cholesterol (HDLC): low density lipoprotein - cholesterol (LDLC) and very low density lipoprotein - cholesterol (VLDLC) were determined after the precipitation of low density lipoprotein -cholesterol using BIOLABO, France reactive. ApoB lipoprotein content was studied using Burstain method [1], while the Rutberg method [12] was used to study fibrinogen in blood. LDLC were calculated by Friedwald [13], formula and atherogenic index by (IA) formula: TC-HDLC/HDLC [7].

By means of 12 leads ECG on "INNOMED". Dispersion of interval QT (ventricular electric systola) and JT (ventricular repolarization) was defined according the accepted standard formula QTd=QTmax-QTmin [10] and JT=JTmax-JTmin [9].

The received data were analyzed statistically. M±SD(M-mean SD-standard deviation (SD) was calculated. Student-t test was used for the analysis of the data obtained for the groups. Statistical apparance was determined as $p<0,05$. Correlation was tested according to the Person's correlation.

Results and their discussion: There are statistically evident differences of Lipid metabolism, fibrinogen and ECG indices between the groups (1 and 2) before and after nutritional load (table) the same is described in the works of other authors [11].

On the background of changed lipid spectrum, there exists nonhomogenic midst that causes myocardium electric instability the quantity of which represents dispersion of QT interval. The analysis of QT interval spaces variability showed that it is determined by last part (JT) –prolongation of repolarization phase and not the first –the basis of which is destructible of ionic balance on the surface cardiomyocytes membrane.

In the ionic mechanism of electric instability are received claim ionic misbalance which are caused by ferment incompetence [8] and the exact reason of mechanic dispersion is local cellular hypocalcemia, that causes reducement of activation phase of monophase potential [2]. Dislipidemia and cholesterol is calcium signal activation on myocardium electric instability [14].

In the group 1 after nutritional load results in increase: TC-36,6%, Tg-48,6%, apo-BLp-35,2%, Fb-25,9%, VLdL-49%, LDLC-24,7% and IA-65,73%.That is on Statistically increasing and in a tendency for a decrease in HDL-C ($p>0,56$), at the same time electric systolic maximum meaning encreased QTmax 10,26%, QTmin don't chenge. QTd in icreased 66,75% mainly under JTmax 10,34% and JTd 75%.

In group 2 after nutritional load results in increase:TC-20,18%, LDLC-33,6% and Fb-37,6% (statistically evedent $p<0,05$) the above mentioned changes are within the accepted norms.

In control group under nutritional load was observed QTmax 8,57%, QTd 20%, JTmax 7,17%, JTd 66,7% statistically evident increase ($p<0,05$), though significance are within the accepted norms.

In compression of ECG significance appeared electric systole as QTmax ($p<0,002$), also QTmin ($p<0,003$) statistically evident difference among each other, though the difference between QTd significance is statistically unbelievable reduces the dispersion in this group and thus the electric nonstability is less expressed in this group.

Table. Lipid Spectrum(mmol/l), Fibrinogen(mg/dl) and ECG parameters (c)

	Atherosclerosis group n=11, AGE (59,45±7,91)						**pre**	**post**
	Pre	**post**	**P1**	**pre**	**post**	**P2**	**P3**	**P4**
Rrmed	0,85±0,13	0,91±0,15	>0,32	0,81±0,14	0,84±0,13	>0,57	>0,46	>0,22
Qtmin	0,33±0,03	0,33±0,03	>0,88	0,30±0,01	0,31±0,03	<0,24	<0,003	>0,07
Qtmax	0,39±0,04	0,43±0,04	<0,05	0,35±0,01	0,38±0,03	<0,01	<0,002	<0,002
QTd	0,06±0,03	0,1±0,03	<0,001	0,05±0,01	0,06±0,02	<0,05	>0,30	<0,004
JTmin	0,25±0,02	0,25±0,04	>0,63	0,25±0,01	0,26±0,03	>0,52	>0,34	>0,71
Jtmax	0,29±0,01	0,32±0,03	<0,01	0,28±0,01	0,3±0,03	<0,03	<0,18	>36
JTd	0,04±0,02	0,07±0,04	<0,04	0,03±0,04	0,05±0,02	<0,02	<0,08	>0,1
TC	5,52±1,53	7,54±2,08	<0,02	4,36±0,95	5,24±0,5	<0,001	<0,05	<0,002
TG	2,2±0,62	3,3±1,07	<0,01	1,69±0,2	1,99±0,54	<0,09	<0,01	<0,002
HDLC	1,23±0,45	1,2±0,36	>0,56	1,33±0,31	1,31±0,5	>0,85	>0,50	>0,33
B-LP	6,77±1,78	9,15±2,4	<0,02	4,69±1,3	5,91±1,84	>0,09	<0,01	<0,002
FB	352,5±62	444,5±90	<0,01	279,5±39	385±66,2	<0,01	<0,003	<0,01
VLDLC	1,01±0,28	1,49±0,49	<0,01	0,77±0,09	0,91±0,25	>0,09	<0,01	<0,002
LDLC	3,28±0,28	4,9±2,27	<0,05	2,26±0,89	3,02±0,84	<0,05	<0,04	<0,02
IA	3,91±1,93	6,48±3,1	<0,03	2,38±1,07	3,71±2,21	>0,09	<0,03	<0,03

Note: p1 –evidence significance of pre and post nutritional load indices in the GroupI; p2 - evidence significance of pre and post nutritional load in the GroupII; p3 - evidence significance of pre nutritional load in the GroupI and GroupII; p4 - evidence significance of post nutritional load in the GroupI and GroupII; QTmin=QTmin interval; QTmax=QTmax interval; QTd=QT interval dispersion; JTmin= JTmin interval; JTmax=JTmax interval; JTd=JT interval dispersion; pre-before nutrtional load; post- after nutritional load

Atherosclerosis group after nutritional load is expressed between QTmax and JTmax (r=0,61) and also between QTmax and QTd (r=0,70) positive correlation. The latter encased afer nutritional load (r=0,84).It's interesting the existence of positive correlation between QTmin and HDLC (r=0,65), that indicates the HDLC role in electric stable mechanism in practically healthy subjects. After nutritional load there was negative correlation between HDLC and QTmin (r=-0,61), that indicates to the electrodestability features of atherogenic food. It's characteristic in atherosclerosis group without changing QTmin increase of QTmax(10,25%) and in control group before nutritional load between QTmin and QTd (r=-0,67) the disappearance of negative correlation.

In atherogenic patients pre and post (increase of correlation) nutritional load is stated positive correlation between QTmax and QTd (r=0,70, r=0,84).

In group 1 the existence of positive correlation after nutritional load between TC and apo B-Lp and between LDLC and IA (r=0,88; r=0,88 correspondingly) and negative correlation between TC and HDLC (r=-0,61), that indicates the role of atherogenic food in atherosclerosis progress that is expressed between HDLC by JTd (r=-0,63) the depression of negative correlation.

Conclusion: 1. Fatty saturated fatty acid and cholesterol rich food loading causes heart electric instability in investigated patients. 2. Fatty acid and cholesterol rich food causes atherogenic lipids and fibrinogen level statistically increases in atherosclerotic patients and practically healthy persons. 3. In healthy persons before breakfast electric stability is supported by help of space variability minimal increases of depolarization and repolarization, that diminishes the increase of electric systole dispersion and fatal arrhythmia. 4. The persons in control group who have adequate reaction like atherosclerosis patients on food loading must be examined with the help of preventive measurements.

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РЕЗЮМЕ

ОСОБЕННОСТИ ЭКГ И ЛИПИДНОГО СПЕКТРА В УСЛОВИЯХ НАГРУЗКИ ПИЩЕЙ, БОГАТОЙ НАСЫЩЕННЫМИ ЖИРНЫМИ КИСЛОТАМИ И ХОЛЕСТЕРИНОМ

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Одним из главных факторов, влияющих на ИБС и ее осложнения, является дислипидемия, степень которой зависит от количества и качества пищевых продуктов, богатых насыщенными жирными кислотами и холестерином, являющихся риск факторами атеросклероза. Установлена корреляционная связь между дислипидемией, развитием тромбозов и внезапной кардиальной смертью.

Цель исследования - установление влияния пищевой (богатой насыщенными жирными кислотами и холестерином) нагрузки на атерогенные факторы, фибриноген и электрическую нестабильность миокарда.

Исследованы 11 больных атеросклерозом (57,2±10,19 год) и 11 практически здоровых лиц (33,7±13,4 год).

Пищевая нагрузка позволяет выявить локальную электрическую нестабильность миокарда, обусловленную увеличением дисперсии реполяризации желудочков.

Электрическая стабильность у здоровых лиц натощак обусловлена удлинением минимального значения деполяризации и реполяризации желудочков, которое снижает увеличение дисперсии систолы.

Key words: coronary heart disease, atherosclerosis, dyslipidemia, nurtitional load, QT dispersion, JT dispersion.

Научная публикация

THROMBOLYTIC THERAPY AMONG ELDERLY PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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At present thrombolytic therapy represents a pathogenetic method of treatment of acute myocardial infarction. On the basis of many investigations it is determined that application of thrombolytic therapy during 6-8 hours from disease onset reduces hospital and remote lethality [3-5]. In the scientific works that study thrombolytic therapy among elderly patients (over 70) it was shown that in the present group the frequency of hemorrhagic complications is increased [2]. It is know also that there is a high lethality from myocardial infarction among elderly patients [5,6]. Therefore it is actual to determine the expedience of thrombolysis among elderly patients.

Our purpose was the estimation of efficacy and safety of thrombolysis among elderly patients with acute myocardial infarction.

Material and Methods. In research participated 65 patients with acute myocardial infarction aged 70-84 years that went through the course of treatment in the Emergency Cardiology Center from 1999 till 2002. Hence 30 patients with thrombolytic treatment formed group 1, and patients with no thrombolytic treatment – group 2.

As a thrombolytic preparation we used streptokinase (1500.000U) with intravenous administration during 60 min. Research inclusion criteria was 6 hours from myocardial infarction onset, anginal attack >30min and ST segment elevation >0,1mv in two leads. Exclusion criteria was severe trauma during last month, surgical operations during last 6 weeks, circulation disorder of brain or transient ischemia during last 6 months, hemorrhage during last 6

weeks, arterial hypertension in the time of entrance in clinic (TA>180/111 mm Hg), administration of peroral anticoagulants, application of streptokinase in anamnesis. Thrombolytic therapy considered as efficacious in case of>50% reduction of ST segment in lead with the greatest elevation during 3 hours after thrombolytic therapy.

In both the basic and control groups in the absence of contraindications it was carried out the treatment with nitrates, b-blockers, heparin, aspirin, ACE-inhibitors.

Statistic processing was performed by means of X^2 criterion.

Results and their discussion. Basic (group 1) and control (group 2) groups did not differ by sex, age, carried diseases and severity in the time of entrance in clinic (table 1).

Table 1. Characteristic of patients

Indices	Group-1	Group-2
Amount of patients	30	35
Average age, years	71,9	73,4
Women	13(44)	16(46)
Men	17(56)	19(54)
Myocardial infarction in anamnesis	10(33)	12(34)
Diabetes mellitus in anamnesis	4(13)	5(14)
Cardiac insufficiency in anamnesis	8(27)	9(26)

Note: in brackets are indicated percentages of patients.

In thrombolytic group in comparison with the control group noticed an authentic reduction of frequency of mortality and cardiac insufficiency (table 2).

Table 2. Results of thrombolytic therapy

Indices	Group-1	Group-2	P
Amount of patients	30	35	-
Complication of thrombolysis	5(17)	0	-
Development of cardiac insufficiency	12(40)	25(71)	<0,025
Lethality	5(17)	9(26)	<0,05

In thrombolytic group reperfusion registered in 23 cases (77%) – Subgroup-1a. In patients of this Subgroup in contrast to patients of Subgroup-1b (without ECG signs of reperfusion) noticed authentic reduction of hospital lethality (table 3).

Table 3. Results of treatment proceeded from efficacy of thrombolysis

Indices	Patients with reperfusion	Patients without reperfusion	P
Amount of patients	23	7	-
Development of cardiac insufficiency	8(35)	4(57)	<0,025
Lethality	3(13)	4(57)	<0,01

In the subgroup-1b the reason of lethality in all 4 cases was a cardiac insufficiency. In Subgroup-1a 1patient died from arrhythmogenic shock and 2 patients from cardiac insufficiency. Cardiac insufficiency was a basic reason of lethality in control group (in 8 cases from 9).

In the latest recommendations of European and American Association of Cardiologists indicated about high risk of adverse reactions of thrombolysis among elderly patients. There is a high mortality from myocardial infarction among elderly patients that formed 30 per cent during first month [3]. In our research we obtained a similar results in patients without thrombolysis. Treatment with streptokinase reduced lethality. However reduction of lethality was more visually in patients with rehabilitated coronary arteries as a result of thrombolytic therapy.

In this group post-hospital lethality formed 13 per cent that is four times less in comparison group without efficacious thrombolysis ($p<0,01$). These data correspond to ISIS-II [4] and TIMI [5].

Thrombolytic therapy reduced a cardiac insufficiency and despite extreme old age did not observed circulation disorder of brain- the most dangerous complication of thrombolysis. Adverse reactions was not dangerous and did not complicated a clinical trend of disease.

In elderly patients with acute myocardial infarction thrombolytic therapy reduced for certain hospital lethality and cardiac insufficiency. In patients with reperfusion reduction of lethality is more obvious. In elderly patients there is no increase of complications due to a thrombolytic therapy.

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РЕЗЮМЕ

ТРОМБОЛИТИЧЕСКАЯ ТЕРАПИЯ ПОЖИЛЫХ С ОСТРЫМ ИНФАРКТОМ МИОКАРДА

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В настоящее время тромболитическая терапия составляет основу лечения острого инфаркта миокарда. Данные множества исследований показали, что введение тромболитического препарата в первые 6-8 часов заболевания позволяет достоверно сократить сроки госпитализации и отдаленную летальность. Однако, в большинстве исследований тромболитическая терапия проводилась больным в возрасте до 70 лет, тогда как пожилой возраст остается наиболее важным прогностическим фактором летальности в постинфарктном периоде и смертность от инфаркта миокарда в старших возрастных группах является очень высокой.

В связи с этим вопрос о целесообразности проведения тромболизиса больным пожилого возраста до настоящего времени остается спорным. По сей день отсутствуют четкие критерии для проведения тромболитической терапии больным этой возрастной группы.

Key words: acute myocardial infarction, thrombolytic therapy, elderly patients, cardiac insufficiency, lethality.

Научная публикация

USE OF 6-MINUTES WALK TEST FOR THE OBJECTIVIZATION OF THE PATIENTS WITH HEART FAILURE

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Cardiovascular disease, particularly Coronary Heart Disease (CHD), complicated by Coronary Heart Failure (CHF), is the main cause of the disability and mortality through of the wold. Earlier disease detection presents the major medical strategic policy in the disease management. Chronic CHF is most frequently presented at the latest stage of the cardiovascular disease evaluation. It presents one of the wide-spread syndrome (2% in adults population) as an extremely serious health condition and appears to cause hospitalization of the patients above 65 years age. Thus, the right way in that group of the patients treatment have to be chosen according to the disease classification.

Nowadays the NYHA classification is an existed one and its divides patient into four functional classes depended on the load quantity and quality, based on the two main factors as follows : dispnoe, tiredness reduced tolerance of the physical activity, as well as liquid suppression complicated lungs or an extremities oedema.

Table. The New York Association classification of heart failure

Class	Definition	Terminology
I	Patients with cardiac disease but without limitation to physical activity	Asymptomatic left ventricular dysfunction
II	Patients with cardiac disease causing slight limitation to physical activity	Mild heart failure
III	Patients with cardiac disease causing marked limitation to physical activity	Moderate heart failure
IV	Patients with cardiac disease causing inability to carry out any physical activity without discomfort	Severe heart failure

Therefore, that criteria might be non-objective in the health condition evaluation when the clinical symptoms are not yet demonstrative, even the Ejection Fraction (EF) is equal to 30%. Thus, according misbalance between the heart dysfunction and clinical symptoms elucidation emphasizes the diagnostic role of the load test and one of the convenience one is represented by walk-test during 6 minutes.

To choose more convenient and assessable criteria of the CHF evaluation 6- minutes walk-test have been implemented in patient with CHF as an additional criteria in NYHA classification.

Materials and methods. The walk-test has been performed in 23 patients aged 35-70 years. The investigation criteria have been chosen as follows: CHF functional class III-IY, having CHF diagnosis at least 3 months prior the examination, EF less than 40%, stable health condition under the basic treatment during the one week (diuretics, B-blokers, ACE-inhibitors). The 6-minutes walk-test is applied to detect and identify the physical tolerance under the load in patients with CHF to choose the critical load index, as a discordance between the physical efforts and physiological parameters, which will be assessed as the non-adequate blood circulation reaction to the accomplished load. The patients health condition has been evaluated taken in consideration covered distance in the test period. Body weight have to be taken in consideration as well as CHD risk factor and having connection to walking speed, neither sex which does not have any influence on the test results.

At the beginning of he test the patient should have 10-15-minute rest. He/she has been informed about walking distance in advance. It is highly important that there is no contact-dialogues or comments-with the patient during the test. The exact time as well as the frequency of heart contraction and breath per minute should be recorded prior the test. During the test the speed of walking should be maximal. The distance covered by the patient measured (m) and hemodynamic data recorded after six minutes. The test repeated after 15-20 minutes. The obtained data: distance, time and weight, recorded in advance, are put in the following specific formula to calculate the accomplished work.

$$W=mt(39,44+1,19s/t)$$

W - accomplished work (j), m - weight (kg), time (minute), s - distance.

After two repeated tests the index has been calculated.

In case of pain or panting the test has been immediately ceased and time was measured. According to this, index time-recorded during the test has been put into the formula instead of the standard six minutes. If spent time for covering the distance is 6 minutes, the formula have to be calculated that way:

$$W=m(236,64+1,19s)$$

And in case of the ceased test:

$$W=mt(39,44+1,19s/t)$$

For example: Patient, 60 year old, clinical diagnosis-CHD atherosclerosis-cardiosclerosis. Heart failure III (NYHA), diabetes mellitus II type. Ejection fraction 21%; m-90; P-86 and breath per minute-30 was recorded prior the test. During the first test the patient has covered 128 m six minutes, the frequency of pulse had been increased plus ten. After the 20 minutes rest the test have been repeated and lasted for 3 minutes. The criteria of the test ceasing are panting and deep tachycardia. The frequency of the heart contraction has been equal to 115 and the distance covered-74m.

I test: W=90(236,64+1,15*128), W=34546.

II test: W=90*3(39,44+1,19 *74/3), W=18549

End result - W=26547

Results and their discussion. Working ability of the patients with NYHA class III-IV CHF, whose EF varies level between 40-21%, is lowered resulted in short distance by them in six minute (170-100 meters) as well as in panting, breathlessness and strong tachycardia. Five cases were recorded when the patient were unable to accomplish the test due to the presence of above-mentioned symptoms and test was stopped.

According to the obtained data it have to be note that 6-minutes walk-test gives the possibility to evaluate an initial CHF as well to manage medical care process.

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РЕЗЮМЕ

ИНФОРМАТИВНОСТЬ ТЕСТА 6-МИНУТНОЙ НАГРУЗКИ ДЛЯ ОБЪЕКТИВИЗАЦИИ БОЛЬНЫХ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Цель исследования определение информативности теста 6-минутной нагрузки при хронической сердечной недостаточности на специальном контингенте больных. Существующая классификация больных хронической СН (NYHA) часто имеет субъективный характер и не дает возможности качественной оценки стадии заболевания. В настоящем исследовании предпринята попытка определения взаимной корреляции классификации NYHA и данных стандартного теста 6-минутной нагрузки.

Проведено обследование 23 больных ХСН III-IV ФК (NYHA) в возрасте 35-70 лет. Критерии включения в обследование: установление диагноза не менее, чем за 3 месяца до включения в обследование; фракция выброса ниже 40 %, стабильное состояние больного в течение 1 недели на подобранной базисной терапии (диуретики, β-блокеры, ингибиторы АПФ).

С помощью теста 6-минутной нагрузки определялись толерантность к нагрузке посредством хождения по ровной поверхности. За критический показатель принята нагрузка, при которой устанавливается декорреляция между фазнагрузкой и физиологическими параметрами. Статистический показатель декорреляции оценивался как неадекватная реакция кровообращения на осуществленную работу. Состояние оценивалось расстоянием, пройденным за то время, которое коррелирует с пиком насыщения организма кислородом.

Выявлено, что у больных ХСН III-IV ФК (NYHA), у которых Ф-β колеблется в пределах 40-21%, отмечается резкое понижение работоспособности, что выразилось в значительности пройденного расстояния (170-100 м), усилении возникшей одышки, нехватки воздуха и тахикардии. Зафиксировано 5 случаев, когда больные не смогли выдержать 6-минутную нагрузку по причине возникновения вышеупомянутых симптомов, в виду чего тест был прерван.

Таким образом, тест 6-минутной нагрузки достаточно информативен для объективизации пациентов ХСН.

Изучена корреляция между полученными данными и динамикой ФК в процессе лечения.

Key words: 6-minutes walk test; exercise capacity; heart failure.

Научная публикация

RESULTS OF ONE YEAR FOLLOW-UP OF PATIENTS WITH ISCHEMIC CARDIOMYOPATHY TREATED BY EGILOK (METOPROLOL)

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The role of β-blockers in the treatment of patients with ischemic heart disease is well established. Beta blockers have been shown to prolong survival and improve quality of life in patients with chronic heart failure due to ischemic heart disease. It is currently a matter of debate whether any β blocker is superior to the others in terms of improving symptoms, left ventricular function or prognosis and whether adding any β blocker to conventional therapy of heart failure therapy improves patients' symptoms [6,7]. Although the effect of Metoprolol is well-established [8], it is not clear whether any form of Metoprolol have the same effect. Major intervention studies have demonstrated considerable reductions in the risk of stroke and myocardial infarction in all age groups and in both genders after treating with β-blockers [8]. In 1981, results from 3 large randomized placebo-controlled trials documented that β-blockers given to patients after acute myocardial infarction (MI) reduced total mortality by 26% to 36% during long-term follow-up. In total there are currently >50 randomized trials on β-blockers in patients with a history of acute MI.

β-Blockade improves survival, reduces hospitalizations for worsening CHF, and improves left ventricular function when given long-term to patients with CHF [2]. The present analysis was performed to determine whether the subgroup of patients with an ischemic cardiomyopathy benefited from β-blocker therapy.

The aim of the study was to determine the effect of long-term treatment with a β1-adrenergic blocking agent Egiloc (metoprolol) given twice a day in combination with conventional therapy of heart failure to patients with ischemic cardiomyopathy.

Material and methods. Patients were eligible to enroll into the study if they had the symptomatic heart failure (New York Heart Association [NYHA] class II to IV) developed after myocardial infarction.

Patients were randomly assigned to treatment with conventional heart failure therapy (diuretics, ACE inhibitors, digoxin) and combined heart failure therapy and Egilok (metoprolol) of phramaceutical company EGYS ltd (initial dose 12,5 mg daily). All patients have been staying under observation during one year receiving 6,25 mg metoprolol twice a day, and the dose was increased sequentially over the course of 4 weeks at follow-up visits to 12,5 mg twice a day, 25 mg twice daily, and 50 mg twice a day if the prior dose was clinically tolerated. If there were significant signs or symptoms of bradycardia, orthostasis, or worsening congestive heart failure, the metoprolol dose was held constant or reduced and re-evaluated for increase at the following visit. All patients continued to receive their prior heart medications, and diuretic dosages were adjusted as needed when there was evidence of fluid retention.

Ischemic Cardiomyiopathy was diagnosed if patients have had prior myocardial infarct determined by ECG or myocardial SPECT imaging without reversible ischemia on stress-rest SPECT image. Myocardial SPECT was carried out at rest and stress (one-day protocol), 30-45 minutes after intravenous injection of 300 MBq ^{99m}Tc Sestamibi – stress and 750 MBq ^{99m}Tc Sestamibi – rest (Bristol Myers-Squibb). SPECT acquisition was carried out on a single-head large field of view gamma camera (E-Soft, Siemens), were obtained in 64X64 matrices using a step and shoot acquisition over a 180° arc from right anterior oblique to left posterior oblique position. Stress imaging was carried out once ECGs had normalized.

A total of 62 ambulatory patients with heart failure were enrolled in study. Fourteen patients discontinued the study. 48 patients, 29 men and 19 women, aged 49 to 72 years (mean age 58 years) were randomized to the study.

Before enrolment in the study 36 patients had been treated with conventional heart failure treatment – 17 from them were treated with two or three drugs, and 12 patients were untreated. 26 patients continued their conventional treatment and 22 were additionally receiving a ?-adrenergic blocking agent – Egiloc (12.5 – 50 mg daily). Distribution of treatment with ACE inhibitors and diuretics in both groups were the same.

The two groups were similar with respect to variety of demographic and clinical characteristics at baseline (table 1).

Patients have been observed during a year every three months. At the baseline evaluation a complete medical history was obtained, a physical examination was performed. In addition, transthoracic echocardiography and stress-rest myocardial perfusion images were obtained.

Table I. Patient characteristics at baseline according to treatment group

Characteristics	All patients (n = 48)	Conventional Therapy (n = 26)	Metoprolol plus Conventional Therapy (n= 22)
Mean age (y)	52,9±12,1	54,8±10,8	49,9±13,6
Sex (M/F)	29/19	16/10	13/9
Functional class (%. of patients)			
II	25%	22%	27%
III	67%	69%	66%
IV	8%	9 %	8
Left ventricular ejection fraction (%)	36,4±5,7	32,9±3,3	37,4±7,0

Differences between groups at baseline and differences between groups for short- and long-term changes from baseline for hemodynamic parameters were assessed with the use of a Student t test. A value of $p < 0,05$ was considered statistically significant.

Results and discussion. One-year treatment with Egiloc reduces frequency of hospitalizations due to worsening of symptoms of heart failure. Nevertheless we could not find significant improvement in quality of life in patients treated with combination of Egiloc and conventional therapy compared to group treated with conventional therapy alone. As the data in table 2 show, Egiloc didn't cause substantial reductions in seated blood pressures from baseline to after 12 weeks of treatment. The adjusted mean reductions in DBP were 11.3mm Hg and 10.9 mm Hg and the adjusted mean reductions in SBP were 27,5mm Hg and 26,6 mm Hg after treatment with Egiloc + conventional therapy and conventional therapy respectively. Also was found more significant reduction in heart rate in patients treated with combination of Egiloc and conventional HF therapy. The mean seated heart rate in the Egiloc + conventional therapy group was 84 beats/min at baseline and 68±5 beats/min after 12 weeks' treatment, and the corresponding values for patients treated by conventional therapy only were 84 and 75±9 beats/min, respectively. However, this did not result in a significant difference ($p>0,1$).

Table 2. Results of one year follow-up of patients treated with Egiloc+conventional therapy and conventional therapy alone

	Egiloc+conventional therapy of HF	Conventional therapy
EF	42,5±6,3	44,6±7,9
HR	68±5	75±9
Systolic BP	120±12	132±6
Diastolic BP	73±7	75±6
Hospitalization (n)	9	15
Death	0	2

Ejection fraction is the most important marker for predicting of outcomes and survival of patients with heart failure. Patients treated with Egiloc+conventional therapy have showed more significant improvement in ejection fraction than patients treated with conventional therapy.

Myocardial perfusion studies revealed that patients treated with combination of Egiloc and conventional therapy better tolerate physical workload than patients treated with conventional therapy alone and had improvement on perfusion images.

In chronic heart failure, as a response to decreased cardiac output, an activation of several neurohormonal systems occurs to maintain circulation. One of these important compensatory mechanisms is the activation of the sympathetic nervous system. Beneficial effect of treatment with β-adrenergic blocking agents is indicated rather for sympathetic effect than influence on heart rate, cardiac contractility or arteriolar tone. It is well established the effect of long-acting β-blocking agents such as Carvedilol on sustained release Metoprolol in the treatment of patients with heart failure [1,3], but short acting β-blocker Egiloc also looks to have favorable effect during long term treatment. Sympathetic stimulation is the main reason of left ventricular remodeling and cells death after myocardial infarct. So long-term administration of β-adrenergic blocking agents can prevent cells damage by blocking sympathetic stimulation [4,5].

The effect of Egiloc was maintained long term. Patients tolerated initiation and uptitration of Egiloc well. In our patients LVEF was increased during first three months and was not significantly changed during follow-up. It is well established that β-adrenergic blocking agents improve patients' symptoms and functional capacity what was confirmed in our study also. We have found improvement in

NYHA functional class in 23% of patients treated with conventional HF therapy and 36% in treated with Egiloc + conventional HF therapy.

The mortality data obtained from studies on β-blockers are controversial [5]. We can not conclude the favorable effect of Egiloc on mortality because of limited number of patients, but we can indicate that hospitalizations and cardiac deaths are less in patients treated with Egiloc+conventional HF therapy, than in group of patients treated with conventional HF therapy alone.

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РЕЗЮМЕ

РЕЗУЛЬТАТЫ ГОДИЧНОГО ПРИМЕНЕНИЯ ЭГИЛОК (МЕТОПРОЛОЛ) У БОЛЬНЫХ ИШЕМИЧЕСКОЙ КАРДИОМИОПАТИЕЙ

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Обследовано 48 больных ишемической кардиомиопатией с симптомами сердечной недостаточности NYHA II-IV. Проведено стандартное физикальное обследование, ЭхоКГ и исследование перфузии миокарда методом одномоментной эмисионной компьютерной томографии (ОФЭКТ) до начала лечения и через год. 26 больных дополнительно к традиционному лечению сердечной недостаточности получали эгилок в дозе 12,5-50 мг в сутки. 22 больных получали только традиционную терапию сердечной недостаточности (ингибиторы АПФ, диуретики, дигоксин). При лечении комбинацией эгилок+традиционное лечение наблюдалось значимое урежение ЧСС, улучшение симптомов сердечной недостаточности, изменение NYHA класса, а также уменьшение случаев госпитализации и летальности. Применение β-блокаторов при длительном лечении больных ишемической кардиомиопатией улучшает симптоматику сердечной недостаточности.

Key words: Ischemic Cardiomyopathy, Metoprolol, Heart failure, SPECT.

Научная публикация

EFFECTS OF CAPTOPRIL AND ENALAPRIL ON LIPID METABOLISM AND FREE RADICAL OXIDATION ON EXPERIMENTAL HYPERLIPIDEMIA IN RABBITS

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Atherosclerosis plays important role in the pathogenesis of ischemic heart disease, arterial hypertension and congestive heart failure. Ischemic complications which arise therefrom are the leading causes of death at present. Many investigators [7,8,13,15] explain atherosclerosis as a chronic inflammatory response to injury of the endothelium, which leads to complex cellular and molecular interactions among cells derived from the endothelium, smooth muscle and several blood cell components. Inflammatory and other stimuli trigger an overproduction of free radicals, which promote peroxidation of lipids in low-density lipoprotein (LDL) trapped in the subendothelial space. There is now

growing evidence that the oxidative modification of LDL plays a potential role in atherosclerosis [2,10,11]. Products of LDL oxidation are bioactive and they induce endothelial expression and secretion of cytokines, growth factors and several cell surface adhesion molecules. The last-mentioned are capable of recruiting circulating monocytes and lymphocytes into the intima where monocytes are differentiated into macrophages, the precursor of foam cells. Oxidative modification of LDL is a key process for the recognition of LDL by the scavenger receptors on macrophages. The response to the growth factors and cytokines, smooth muscle cells proliferate in the intima resulting in the narrowing of the lumen.

Many investigators [1,5] also have demonstrated a correlation between raised atherogenic serum lipoproteins (VLDL and LDL), decreased antiatherogenic HDL and the incidence of atherosclerosis, as well as the interdependency between hypertension and atherosclerosis. Vasoactive substances such as norepinephrine and angiotensin II as well as oxidised LDL can also activate smooth muscle cell, monocytes, macrophages, that increase free radicals formation [2,9]. In addition, angiotensin II and oxidised LDL inhibit endothelial production of prostacyclin and nitric oxide, two potent autocoids that are vasodilators and inhibitors of platelet aggregation. Increased interest in the prevention and management of atherosclerosis and the identification of hyperlipidemia as a risk factor have stimulated the study of drugs which prevent or reduce this risk.

Aim of the study was to evaluate effects of angiotensin-converting enzyme (ACE) inhibitors-captopril and enalapril on the levels of blood cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and malondialdehyde (MDA) and activity of superoxiddismutase (SOD) in erythrocytes of rabbits with experimental hyperlipidemia.

Material and methods. The experiments were carried out using male rabbits, weighting 2,0-2,5 kg. They were kept in standard conditions and were used after an acclimatization period of at least 15 days. The animals were divided into three groups of seven animals each and were given a daily dose of 500 mg/kg/body weight of cholesterol, dissolving in vegetable oil and 100 mg/kg body weight of methylthiouracil (10% solution).

Group 1 (control): Received cholesterol and methylthiouracil for 45 days per os. Group 2: received captopril 5 mg/kg/day, per os after 1 hours cholesterol and methylthiouracil for 45 days. Group 3: received enalapril 0,5 mg/kg/day per os. After 1 hours cholesterol and methylthiouracil for 45 days. Blood was taken out of marginal ear vein. Serum was analysed for cholesterol, triglyceride, LDL, HDL using commercially available enzymatic assay Kits (Olvex diagnosticum) by a method [4]. Malonic dialdehyde in erytrocytes determined by a method [3]. Activity of superoxide dismutase (SOD) were measured by the spectro-photometry technique [6]. Data was analyzed statistically using Student's t criteria.

Table 1. Effects of captopril and enalapril on the parameters of lipids profile and oxidative metabolism on hyperlipidemia in rabbits with hypothyroidism

	Parameters / Groups	Total cholesterol mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl	MDA mc mol/ml	SOD c,u,/ml erit,
control group	initial	78,2±1,31	85,3±1,81	20,9±1,41	35,2±1,9	2,7±0,04	211,1±1,0
	after 45 days cholesterol+ methylthiouracil	310±11,08	259±5,9	63,4±4,5	24,1±1,15	4,5±0,10	105,6±0,4
	p	p<0,001	p<0,001	p<0,001	p<0,001	p<0,001	p<0,001
group 2	initial	75,1±2,11	82,3±2,5	19,8±2,5	34,2±2,3	2,7±0,06	209,4±1,2
	after 45 days captopril+ cholesterol+ methylthiouracil	254,1±9,0	194,5±4,3	42,2±3,3	31,1±1,54	3,2±0,08	132,0±0,9
	P_1 P_2	P_1<0,001 P_2<0,01	P_1<0,001 P_2<0,001	P_1<0,001 P_2<0,02	P_1<0,001 P_2<0,01	P_1<0,001 P_2<0,001	P_1<0,001 P_2<0,001
group 3	initial	72,0±1,82	82,2±2,0	19,8±2,4	33,8±2,3	2,6±0,4	210,0±1,2
	after 45 days enalapril+ cholesterol+ methylthiouracil	258,2±9,3	205,4±4,3	50,0±3,63	30,2±1,52	3,8±0,04	120,1±0,7
	P_1 P_2	P_1<0,001 P_2<0,01	P_1<0,001 P_2<0,001	P_1<0,001 P_2<0,05	P_1<0,001 P_2<0,01	P_1<0,001 P_2<0,001	P_1<0,001 P_2<0,001

P_1 - compared to initial parameters
P_2 - compared to control group

Results and their discussion. Increase of total cholesterol triglyceride, LDL and decrease of HDL were observed after 45 days of administration of cholesterol and methylthiouracile, compared to initial parameters (table). Furthermore, concentration of malonic-dialdehyde, an indicator of oxidative damage, was higher than activity of antioxidant enzyme, such as SOD was lower compared to initial levels. These data indicate that high-cholesterol diet in rabbits increases atherogenic serum lipoproteins such as LDL and decreases antiatherogenic HDL, produces oxidative stress (reduction of activity of antioxidant enzymes and intensification of lipid peroxidation). The same data has been reported by other investigators [9,12,14].

Methylthiouracile (antithyroid drug) produces hypothyroidism. It is common knowledge that hypothyroidism aggravates atherosclerosis.

The administration of both ACE inhibitors - captopril and enalapril (table) in experimental hyperlipidemia was associated with decreases of serum total cholesterol, triglyceride LDL levels and malondialdehyde level in erytrocytes compared to the control group, whereas HDL level and activity of SOD increased. Our results indicate that ACE inhibition with captopril and enalapril have antioxidant effect and improve lipid profile in hyperlipidemia in rabbits.

It appears that antioxidant effect of captopril was higher than that reached with enalapril. The observed higher than enalapril effect of captopril treatment on malondialdegyde and SOD might be ascribed to the sulfhydryl group in the captopril molecule. However the nonthiol ACE inhibitor enalapril also have the ability to partially protect some targets against oxidative damage. These observations suggest that the presence of a thiol group in the ACE inhibitors structure is not the only determinant for the antioxidant properties.

The effectiveness of ACE inhibitors administration during hyperlipidemia was demonstrated by other investigators [9,12]. Probably it is associated with ACE inhibition that reduce the angiotensin II formation and of bradykinin and substance P degradation. It is known that angiotensin II induces smooth muscle cells proliferation and stimulates oxidation of LDL particles and foam cell accumulation [2]. Inhibition of angiotensin II production leads to decrease in lipid peroxide production and prevent the development of atherosclerosis. Furthermore ACE inhibitors increase of bradykinin and substance P, which improve endothelial function, rise of prostacyclin and nitric oxide production that cause vasodilation and inhibit of platelet aggregation and prevent of atherosclerosis.

It may be concluded that high-cholesterol diet in hypothyroid rabbits is associated with increased total cholesterol, triglyceride, LDL levels and decreased of HDL level. High-cholesterol diet in hypothyroid rabbits produce intensification of lipid peroxidation and reduce activity of SOD. ACE inhibitors-captopril and enalapril decreased total cholesterol, triglyceride, LDL, increased HDL hyperlipidemia induced by the high-cholesterol diet in hypothyroid rabbits. Both of ACE inhibitors captopril and enalapril inhibited the rise of lipid peroxides concentration and increase activity of SOD induced by cholesterol - rich diet, in hypothyroid rabbits. Captopril has higher antioxidant activity than enalapril that might be due to the sulfhydryl group in the captopril molecule. ACE inhibitors can be used as additional drugs in the treatment of hypertensive and hypercholesterolaemic patients.

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РЕЗЮМЕ

ВЛИЯНИЕ КАПТОПРИЛА И ЭНАЛАПРИЛА НА ПОКАЗАТЕЛИ ЛИПИДНОГО СПЕКТРА КРОВИ И СВОБОДНОРАДИКАЛЬНЫЕ ПРОЦЕССЫ ПРИ ГИПЕРЛИПИДЕМИИ В ЭКСПЕРИМЕНТЕ

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Исследовано влияние каптоприла и эналаприла на липидный спектр крови, содержание малонового диальдегида и активность антиоксидантного фермента - супероксиддисмутазы при экспериментальной гиперлипидемии, вызванной вскармливанием гипотиреоидных кроликов холестерином.

Установлено, что каптоприл и эналаприл улучшают липидный профиль при экспериментальной гиперлипидемии, а также обладают антиоксидантной активностью, причем последняя более выражена у каптоприла в сравнении с эналаприлом. Большая антиоксидантная активность каптоприла, очевидно, обусловлена не только уменьшением образования свободных радикалов, связанным с ингибицией АПФ, приводящего к понижению синтеза ангиотензина II, распаду брадикинина и субстанции Р, но и присутствием в его молекуле сульфгидрильных групп, способных нейтрализовать свободные радикалы.

Рекомендуется использовать ингибиторы АПФ в качестве вспомогательных средств для лечения больных с гиперлипидемией.

Key words: high-cholesterol diet, ACE inhibitors, captopril, enalapril, antioxidant activity.

Научная публикация

ROLE OF VEGETABLE FOOD SUPPLEMENTS IN THE DIET THERAPY OF PATIENTS WITH ATHEROSCLEROSIS

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Currently cardio-vascular diseases, such as ischemic heart disease and hypertension, characterized by high prevalence rate, still remain one of the most important problems of contemporary medicine [1,3,5]. Study of pathologic mechanisms of these diseases and finding of new ways for correction of basic metabolic disorders are among the priority directions of medical research. Prevention of cardio-vascular diseases is based on the advanced concept about risk factors, divided into variables – level of total cholesterol, triglycerides, lypoproteides of high and low density, correlation of apo A/ apo B lipoproteids, homocysteines and C-reactive protein and constants (age, gender, family history) [4,8].

Importance of dietological effect in complex prevention and auxiliary therapy of cardio-vascular diseases and their risk factors is out of doubt. Specially developed basic diets and separate components (products of specified chemical composition) allow influencing different mechanisms of pathogenesis. In recent decades special attention of researchers attract food supplements, basically soybean and its products. Effectiveness of soybean protein in correction of disorders in substances exchange processes is detected [6,7].

Objective of the study was to determine the role of soybean protein supplement in diet therapy of patients with atherosclerosis.

Material and methods. Clinical study was carried out on 60 patients (24 male, 36 – female). Observation group included 44 patients (16 – male, 28 – female) 53-80 age group, and control group included 16 patients (9 – female, 7 – male).

Patients were diagnosed after clinical, laboratory and instrumental investigations. Treatment of patients was carried out during 4 weeks: 2 weeks (stage 1) in hospital and 2 weeks in ambulatory environment. On the stage 1 patients were rendered traditional treatment, diet N10 and 15 gr soybean protein supplement daily (5 grams, 3 times a day before meals). On the stage 2 of ambulatory treatment patients were given 30 gr soybean protein supplement daily. 16 patients of control group were on the diet without soybean protein concentrate. In dynamics before and after the treatment indicators of lipid exchange in the blood of patients were measured [2]. Besides in serum of patients we determined the activity of calicrein, d_2 – macroglobuline,

ferments of understomach gland, indicators of cellular and humoral immunity [2].

Results and their discussion. Preliminary study detected increased level of lipids in blood. After the treatment decrease of the level of total cholesterol (by 17,8%), triglycerides (by 32,3%), lipoproteides of low (by 25%) and very low density (by 33,3%) and atherogenesity (by 28%) and increase of lipoproteides of high density (by 36,3%) in patients of basic group was observed (table 1).

Decrease of the indicators of the level of total cholesterol (by 4%), triglycerides (by 13%), lipoproteides of low (by 7%) and very low density (by 17%), coefficient of atherogenesity (6.2%) in blood serum in patients of control group was observed. Increase of lipoproteides of high density (by 7,1%) was also observed, though these indicators didn't have statistically reliable differences.

Table 1. Dynamics of basic indicators of lipid exchange (mmol/l) before and after the treatment

Indicators	Basic group			Control group		
	Observation stage			Observation stage		
	Initial	I	II	Initial	I	II
Total cholesterol	7,9±0,3	7,3±0,4	6,5±0,4	7,5±0,1	7,32±0,15	7,2±0,2
Triglycerides	3,1±0,4	2,5±0,4	2,1±0,3	3,1±0,07	2,9±0,05	2,7±0,1
Low density lipoproteides	6,4±0,5	5,5±0,6	4,8±0,6	6,02±0,2	5,78±0,24	5,6±0,2
Very low density lipoproteides	0,6±0,1	0,5±0,1	0,4±1,07	0,6±0,07	0,56±0,08	0,5±0,05
High density lipoproteides	1,1±0,11	1,2±0,1	1,5±0,12	1,12±0,03	1,14±0,16	1,2±0,08
Atherogenesity coefficient	6,8±0,9	6,0±0,8	4,9±0,7	6,5±0,2	6,24±0,16	6,1±0,2

Thus, based on comparison of data obtained in basic and control groups it was determined that at the end of the study we observed dicrease of total cholesterol (by 13,8%), triglycerides (by 19,3%), lipoproteides of low and very low density (by 18 and 16,7% respectively), coefficient of atherogenesity (by 21,8%) and increase (by 29,2%) of high density lipoproteids in patients of basic group compared to the control group.

It must be mentioned, that during the diet therapy under the effect of soybean protein was noticed the trend towards increase of general inhibitor tripsine (D_2 – antitrpinsin) in blood serum together with the trend of dicrease of tripsinic activity of blood and content of D2 – macroglobuline, which can be connected with presence of inhibitor proteinaz in soybean supplement (table 2), which promote the disturbances of dicrease of the activity of serum protein of tripsine type. Together with this activty of calicrein was obviously increasing and the trend of increasing the activity of precalecrein was taking place.

Table 2. Change of the activity of calicrein system of pacreatic ferments in blood serum before and after of diet therapy

Indicator	Before diet therapy	After diet therapy
Calicrein, mE/ml	80,0±13,0	131,0±15,0
Precalicrein, mE/ml	130,0±22,0	220,0±25,0
d_1 – microglobulin, mE/ml	1,1±0,05	0,9±0,1
d_2 – antitripsine, mE/ml	34,0±6,5	34,0±4,0
BAEE – mmol/ml/min	0,23±0,02	0,2±0,02
tripsine, mEg	3,3±0,5	2,6±0,3
Tripsine inhibitor, mEg	480±20,0	520±10

Difficult symptomocomplex of atherosclerosis is determined not only by different types of exchange disorders, closely connected with the nature of diet, but also by inclusion of cellular-immune reactions in the pathogenesis of the disease. At this time immunopathologic deviations, detected during already developed disease syndrome, further greatly affects course of disease, causing its chronic, progressive development.

In the process of diet therapy, with inclusion of soybean protein in most patients improvement of indicators of cellular immunity was detected (table 3). Particularly it was detected the sensitivity of lypoproteids to polyclonal mitogens with parallel decrease of activity of mononucleids on response to specific antigens. It also must be mentioned the increase of initially decreased level of third component of supplement, and statistically important reduction of titers of orasamucoid (table 4).

Table 3. Change of indicators of T-cellular immunity in patients with atherosclerosis during diet therapy

Indicator	Before diet therapy	After diet therapy
Reaction of blastransformation of lymphocytes (%) under the effect of:		
FGA	53,0±1,2	60,0±1,2
Koi A	55,0±1,3	61,0±1,0
ETC	7,0±0,8	4,0±0,4
EAA	7,0±0,7	4,0±0,5
Index of of break of migration of leukocytes under the effect of:		
FGA	0,8±0,01	0,86±0,01
ETC	0,7±0,01	0,84±0,01
EAA	0,71±0,01	0,85±0,01
Index of cytotoxicity of lymphocytes under the effect of:		
FGA	0,41±0,01	0,33±0,01
ETC	0,23±0,01	0,17±0,01
EAA	0,24±0,01	0,17±0,01

Table 4. Dynamics of separate protein components in blood serum in patients with atherosclerosis during diet therapy

Indicator	Before diet therapy	After diet therapy
reaction of blastransformation of lymphocytes (%) under the effect of:		
FGA	53,0±1,2	60,0±1,2
Koi A	55,0±1,3	61,0±1,0
ETC	7,0±0,8	4,0±0,4
EAA	7,0±0,7	4,0±0,5
Index of break of migration of leukocytes under the effect of:		
FGA	0,8±0,01	0,86±0,01
ETC	0,7±0,01	0,84±0,01
EAA	0,71±0,01	0,85±0,01
Index of cytotoxicity of lymphocytes under the effect of:		
FGA	0,41±0,01	0,33±0,01
ETC	0,23±0,01	0,17±0,01
EAA	0,24±0,01	0,17±0,01

Concentration of immunoglobulines after the course of diet therapy in blood serum did not change.

As it was mentioned above practical application of hypocholesterinemic effect of some vegetable proteins is principally new method of prevention and directed treatment of atherosclerosis. It requires increase of the industrial production of such protein preparations of hypocholesterinemic effect as above mentioned soybean protein supplement.

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РЕЗЮМЕ

РОЛЬ РАСТИТЕЛЬНЫХ ПИЩЕВЫХ ДОБАВОК В ДИЕТОТЕРАПИИ БОЛЬНЫХ АТЕРОСКЛЕРОЗОМ

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У больных атеросклерозом изучали динамику липидных показателей крови, активность калликреин-кининовой системы и иммунологическую реактивность в процессе диетотерапии с использованием соевой белковой добавки. Отмечено гипохолестеринемическое действие соевого белка, коррелирующее с его количеством, Количество общего холестерина в крови снижается на 13,8%; триглицеридов – на 19,3%; холестерина липопротеидов низкой плотности – на 22%; очень низкой плотности – на 16,7%; холестерина липопротеидов высокой плотности повышается на 29,2%; коэффициент атерогенности снижается на 21,8%. Повышение уровня калликреина (на 63,75%) и прекалликреина (на 69,2%) при одновременной тенденции к снижению триптической (на 21,2%) и повышению ингибиторной (на 8,3%), положительные сдвиги в показателях клеточного иммунитета у наблюдаемых больных в процессе диетотерапии.

Key words: lipids serium blood, calicrein-cinin system, trepsine inhibitor active, atherosclerosis.

Научная публикация

RELATION OF LIPIDS, C-REACTIVE PROTEIN AND SOME CYTOKINES WITH CAROTID STENOSIS IN PATIENTS WITH STENOCARDIA

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Some recent fundamental studies on cytokines indicate to their regulatory characters in lipid metabolism. They are assumed to cause atherogenic changes of circulatory lipoproteins[7,9,12,13].

For establishing the relation between multicomponent mechanisms of atherosclerosis and inflammation, the study of cytokines and C-reactive protein(CRP) is of ulmost importance along with the blood lipid spectrum investigation [2,3]. There are some interesting data concerning the relation between blood lipids and main arteries, particalarly extracranial arteries [4,8,10].

Stenocardia is considered to be one of the leading factors for the formation of extracranial carotid stenosis. Hypercholesterolemia and the increase of LDL cholestetrol are precondition for progressing carotid atherosclerosis.

Thus, the aim of our work was to esablish the relation between lipids, interleukin-1 and 6 (IL-1, IL-6), CRP and carotid arteries stenosis.

Material and methods. For this purpose, 46 patients (17 women and 29 men) were examined.They were diagnosed to have stenocardia (II-III functional class). According to carotid stenosis, they were divided into two groups: I group- 20 (patients averege age 57,0±1,3) with hemodynamically insignificant carotid stenosis (<50%), and II - 26 patients(averege age 61,7±1,4) with hemodynamically significant carotid stenosis (>50%).

The control group consisted of 42 practically healthy persons (everage age 52,0±1,8).

For studying carotid arteries we used duplex scanning of exstracranial vessels("PHILIPS SD-800"). The degree of carotid stenosis was determined in transversal and longitudinal sections. Blood investigations were carried out using biochemical analyzer COBAS E MIRA of "ROCHE DIAGNOSTICS" The mentioned studies included: total cholesterol(Tchol), HDL and LDL cholesterol, triglicerides, apolipoproteinA-1(Apo-A-1), apolipoprotein-B(Apo-B), lipoprotein-a (Lp-a), interleukin-1(IL-1) and interleukin –6 (IL-6), and C-reactive protein(CRP). The reagents of ROCHE DIAGNOSTICS and HUMAN were used for our investigation. Statistical analysis was done by the statistical program standard package.Results are given as M±m. The statistical validity of the data was determined by the Student's criterium. Difference was valid when p<0,05.

Results and their discussion. Duplex scaning of carotid arteries revealed that in 67,4% (31 patients) atherosclerotic plaque was localized in the 1st segment of the inner carotid artery, in 17,4% (8 patients) - in the middle part of the inner carotid artery, and in 10,9% (patients)- in the middle part of the common carotid artery, in 4,3% (2 patients) in -various areas. It should be noted that in 63% (29 patients) of the cases the both carotid arteries stenosis was established.

The comparison of CRP parameters obtained by latexagglutiation and immunoturbidimetric methods showed that difference between them is not reliable (P>0,5). This allows to use the both methods equally (table 1).

As for the comparison of parameters of LDL cholesterol determination by direct method and Friedwald formula, the difference between them appeared reliable (P<0,05) (table 2). LDL cholesterol parameters determined by Friedwald formula is higher than that recieved by direct measurement. This has a diagnostic significance for evaluating the lipid atherogenic fraction.

Resulting from the above, it is evident that the direct method of LDL cholesterol valuation significantly increases informativeness of this parameter. Therefore, the direct method of LDL cholesterol evalution by enzimatic reagents is used in the given investigation.

Table 1. Comparison of C-reactive protein parameters estimated by different methods

Methods of determination of CRP	immunoturbidimetric n=46	latexaglutination n=46
mean value mg/l	20,9±3,6	20,5±3,54

Table 2. Comparison of LDL cholesterol evaluated by direct method and Friedwald formula parameters

Methods of determination of LDL cholesterol	Calculation by Friedwald formula n=46	Direct determination n=46
mean value mmol/l	4,21±0,22	3,5±0,26

Table 3. Values of lipids, interleukin-1,6, C-reactive protein in patients with stenocardia

Parameters	Control group	Group I	Group II	Normal values
Total Cholesterol (mmol/l)	5,08±0,038	6,58±0,098	7,34±0,078	3,1 – 5,2
HDL Cholesterol (mmol/l)	1,3±0,03	1,08±0,03	0,9±0,038	>1,42 (male) >1,68 (female)
LDL Cholesterol (mmol/l)	2,44±0,0**	4,29±0,15**	5,39±0,09***	<3,0
Triglicerides (mmol/l)	1,39±0,0**	2,17±0,06**	2,45±0,06	0,45 – 1,86 (male) 0,45 – 1,54 (female)
APO A-1 (mg/dl)	157,40±5,2**	128,65±1,54**	119,25±1,40	115 – 190 (male) 115 – 220 (female)
APO B (mg/dl)	128,1±2,35*	198,85±3,41**	208,39±1,84	70 – 160 (male) 60 – 150 (female)
LP (a) (mg/dl)	4,43±0,36	13,95±0,039**	16,39±0,30***	10 – 17
CRP (mg/dl)	2,0±0,3*	4,4±0,19**	5,11±0,23***	<6
IL – 1 (pg/ml)	1,19±0,03*	6,57±0,09**	7,26±0,05***	0 – 6,7
IL – 6 (pg/ml)	1,02±0,02*	5,01±0,07**	5,99±0,05	0 – 3,3
Mean Frequency of Stenocardia Attack		3,5±2,2	5,7±2,68	

**P<0,05 difference between the control and group* I *values*
***P<0,05 difference between the control and group* II *values*
****P<0,05 difference between group* I *and* II *values*

The findings showed that Tchol (table 3) increased in the both groups as compared with the control one (6,58±0,09 and 7,3±0,07 mmol/l). HDL cholesterol significantly decreased, especially in the group II (0,9±0,03 mmol/l). But in all the patients LDL cholesterol and Apo-B increased, statistically reliable values of triglicerides also increased (P<0,05). However, Apo- A-1 values decresed. It should be noted the tendency of increasing Lp-a, the so-called "independent atherogenic factor" to 13,95±0,39 and 16,33±0,3 mg/dl, and also that the average frequency of stenocardia attacks were twice higher in the group II. This points to the depth of lipidemia and development of atherosclerosis or its severe course. In 68% of cases CRP increased as compared to the control group patients. IL-1 and IL-6 concentration tends to increase in patients with stenocardia who showed hemodynamically significant carotid stenosis. It is worth noting that with the increased IL-1, triglicerides and LDL parameters were much higher that completely agrees with data available in the literature and our findings [1,5,6,11].

The degree of carotid stenosis is in positive correlation with Tchol, LDL cholesterol, Apo-B , CRP, IL-1 and IL-6 parameters, with stenocardia attacks frequency, and in negative correlation with HDL and Apo-1 values.

So, we think that in case of stenocardia , carotid stenosis and the indicies of laboratory parameters are important diagnostic criteria that enable us to use lipid spectrum, CRP,IL-1 and IL-6 as high informative laboratory markers for atherosclerosis diagnosis and its further treatment.

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РЕЗЮМЕ

ВЗАИМОСВЯЗЬ ЛИПИДОВ, С-РЕАКТИВНОГО БЕЛКА И НЕКОТОРЫХ ЦИТОКИНОВ У БОЛЬНЫХ СО СТЕНОКАРДИЕЙ

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46 больных (17 женщин и 29 мужчин) стенокардией (I-II функциональный класс) в зависимости от степени стеноза сонных артерий были разделены на две группы (гемодинамическии незначимый и значимый). Всем пациентам проводили дуплексканирование сонных артерий и биохимические исследования, в частности, изучали липиды различных классов, С-реактивный белок, интерлейкин 1β и 6.

Анализ полученных лабораторных данных показал, что степень стеноза сонных артерий, общий холестерин, холестерин липопротеинов высокой и низкой плотности, апобелки, липопротеин (а), интерлейкин 1β и 6 являются достаточно информативными диагностическими критериями.

Проведена сравнительная оценка иммунотурбидимитрического и латексагглютинационного метода определения С-реактивного белка. Установлена высокая достоверность каждого из них. Сравнение прямого энзиматического метода определения холестерина липопротеинов низкой плотности с так называемой формулой

Фридвальда выявило преимущество прямого метода. Поэтому в данном исследовании был использован энзиматический метод.

Результаты проведенного исследования дают нам право рекомендовать осуществление анализа липидного спектра крови, С-реактивного белка, интерлейкин 1β и 6 в качестве высокочувствительных лабораторных маркеров в мониторинге атеросклеротических поражений различных сосудов.

Key words: atherosclerosis, C-reactive protein, interlrukin-1β, interlrukin-6, HDL, LDL, cholesterol, carotid stenosis.

Научная публикация

LIPID SPECTRUM AND FIBRINOGEN INDICES IN CHD PATIENTS WITH CEREBRAL ATHEROSCLEROTIC ANGIOPATHY

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Cardiac and cerebro-vascular diseases of atherosclerotic origin greatly contribute to morbidity, lethality and disability remaining the most significant cause of problems in modern medicine [1,5].

Dislipidemia is the most important risk factor for coronary hearth disease (CHD) while hypertension and age for cerebral vascular damage, despite the fact of basing on the same systemic disease [2].

The purpose of this study was to investigate lipids and fibrinogen indices in CHD patients with cerebral atherosclerotic angiopathy.

Material and methods: we studied 67 patients (males and females) with CHD accompanied cerebral atherosclerotic angiopathy. All patients having CHD was divided in the following groups: I group: stroke survivors (7 patients); II group: CHD, cerebral atherosclerotic angiopathy and after myocardial infarction (MI) (8); III group: patients with CHD, cerebral atherosclerotic angiopathy and moderate high blood pressure (HBP) (10); IV group: patients with CHD and cerebral atherosclerotic angiopathy (42).

The CHD diagnoses based on the results of history, ECG, Echocardiography, stress-test and in same cases coronarography.

The atherosclerotic cerebral angiopathy diagnoses based on the results of history, cerebrovasculare Triplex Scanning and in same cases brain computerized tomography,

Lipids are measured in serum on "Janway 4500" spectrophotometer. Enzyme methods are used for revealing of levels: total cholesterol (TC) (cholesterol CHOD-PAP Kit, Code SFBC: E6, BIOLABO,France); Triglycerids (TG) (GPO Kit, Code SFBC: KO, BiOLABO, France-bc), High density lipoprotein-cholesterol (HDL-C) after precipitation (HDL Cholesterol –Precipitant, SFBC Code: MI, BIOLABO, France). For blood fibrinogen(Fb) Rutberg's method was used. Atherogenic index (AI) and LDL-C by Friedwald were calculted [3]. Data achieved were processed statistically: M±SD (M-mean, SD-standard deviation), Student-t test was used for the analysis of the data obtained for the groups. Statistical significance was determined as $P<0.05$. Correlation was tested according to the Pearson's correlation test.

Results and their discussion. It was shown that atherogenic lipids levels (TC, LDL-C) and AI are higher than accepted norms [4] in all groups, while HDL-C significance is lower than accepted norms in I, II and IV groups. Statistically confidante differences of HDL-C indices ($p<00,05$) were reached only between III-IV groups (61,9 mg/dl and 45,2 mg/dl accordingly).

Fibrinogen elevation as an atherogenic as well as trombogenic factor is well known [2,3]. The higher indices (570 mg/dl) of fibrinogen were revealed in stroke survivors (I group) patients. Fibrinogen levels differ significantly between I-III group and between I and IV groups ($p<0,05$). From our results and data of other authors [2], we suggest that fibrinogen level is the most dangerous thrombogenic factor among studied risk- factors for stroke survivor patients.

Table. Fibrinogen, lipid spectrum indices in Patients with Cerebral Atherosclerotic Angiopathy (M± SD)

group	age	TC	HDL-C	LDL-C	VLDL-C	TG	Fb	AI	I/M
I	62,6	217,2	39,7	137,9	39,9	180,2	570	4,4	1,3
N=7	10	66,6	5,2	54,3	19,6	110,4	70	2,5	0,2
II	63,9	212,3	42,8	142,6	27	134,8	476,2	4,2	1,4
N=8	6,2	46,4	14,4	32,9	8,4	42,1	64,6	1,4	0,1
III	60,4	230,3	61,9	128,4	26,7	134,2	433,2	3,3	ee,13
N=10	8	57,2	30,3	60,3	7,8	39,4	91,6	0,9	0,25
IV	60,9	215,3	45,2	141,6	32,9	144	415,9	4,2	1,2
N=39	8,6	39,5	12,7	36,5		58,4	105,7	1,4	0,3

TC- Total Cholesterol; TG- Triglycerides; HDL-C-High density lipoprotein cholesterol; VLDL-C-Very low-density lipoprotein cholesterol (mg/dl); LDL-C-Low low-density lipoprotein cholesterol; AI- Atherogenic Index; I/M- intima/media complex artery carotid communis.

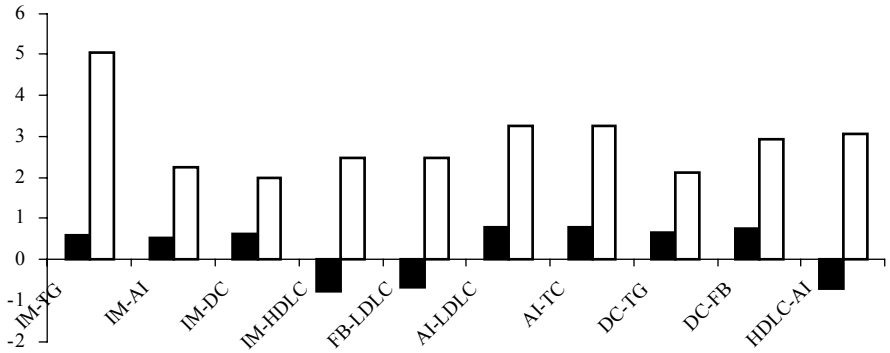

Diagram 1. Correlation of the I group: stroke survivors

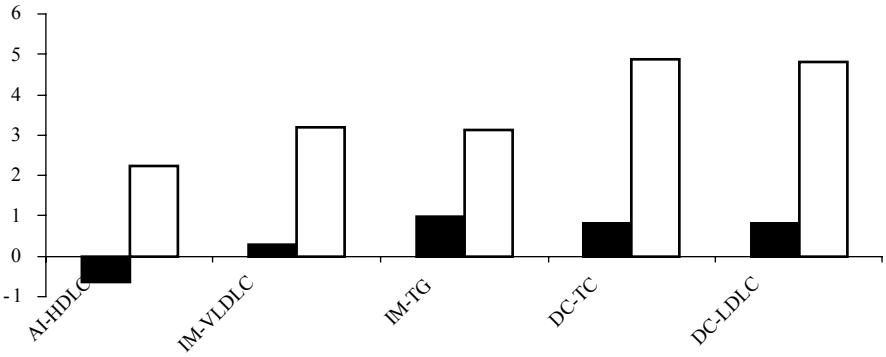

Diagram 2. Correlation of the II group: CHD, cerebral atherosclerotic angiopathy and MI survivors

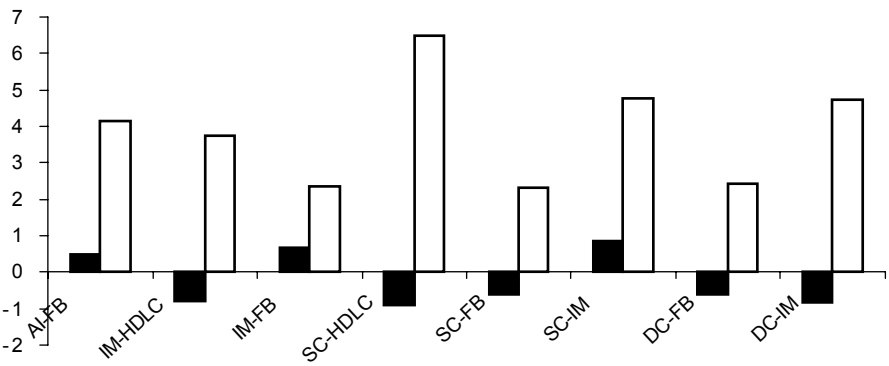

Diagram 3. Correlation of the III group: patients with CHD, cerebral atherosclerotic angiopathy and moderate HBP

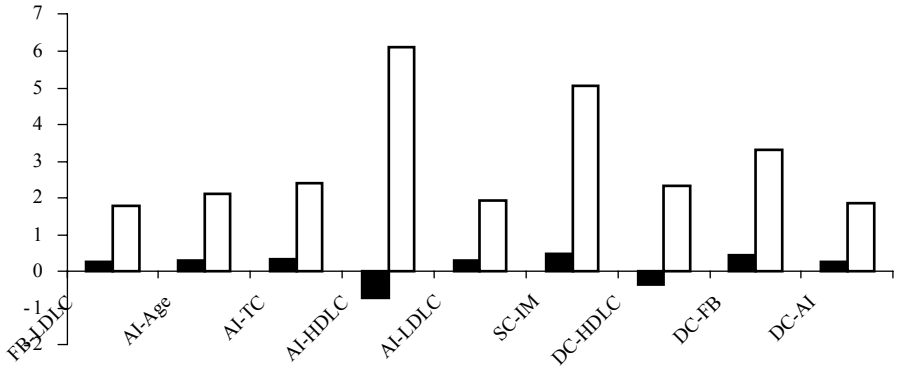

Diagram 4. Correlation of the IV group: patients with CHD and cerebral atherosclerotic angiopathy

Despite that the triglycerides were not elevated in all groups, positive correlation (r=0,89) between triglycerides indices and carotid artery intima-media thickness was observed for the group I (patients after insult). The positive correlation (r=0,647) between triglycerides indices and carotid artery stenosis was established, while the negative correlation (r=- 0,700) was observed between HDL-C and carotid artery intima-media thickness (Diag. 1). The received data show that triglycerdes was a significant lipid component for indication of carotid artery intima-media thickness and stenosis in the patients after insult. The same results were received by other authors as well. In the patients with CHD and HBP (group 3) antiatherogenic HDL-C has a protective effect for development of intracranial arterial stenosis (r=-0,905) (Diag. 3), while in group 4 HDL-C is in negative correlation with extracranial artery stenosis [4].

Atherogenic lipids TC and LDL- C play an important role in patients with MI (group 2), in which positive correlation between extracranial artery stenosis and TC (r=0,542) and from the other hand with LDL-C indices(r=0,870) were observed (Diag. 2). The same results were reached by other authors [6].

In the patients with CHD and HBP (group 3) antiatherogenic HDL-C had a protective effect for development of intracranial arterial stenosis (r=-0,905) (Diag. 3), while in group 4 HDL-C was in negative correlation with extracranial artery stenosis (-0,308) (Diag. 4).

In the group 4 (patients with CHD) positive correlation between age and extracranial artery stenosis has been revealed (Diag. 4).

The received results show the different significance of risk–factors in various clinical events of atherosclerosis.

It may be concluded that : 1. Fibrinogen is significant risk factor for all cerebral angiopathy patients with CHD, but the most important is the thrombogenic factor for stroke survivor patients.
2. Low levels of High-density lipoprotein cholesterol is a significant risk-factor both in the patients with CHD and stroke for extracranial artery stenosis and play an important role in lipid homeostasis when HBP coincidences with CHD.
3.Triglycerides is most significant lipid metabolic component for extracranial arteries stenosis in the stroke survivors.

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РЕЗЮМЕ

ПОКАЗАТЕЛИ ЛИПИДНОГО СПЕКТРА И ФИБРИНОГЕНА У БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА С АТЕРОСКЛЕРОТИЧЕСКОЙ АНГИОПАТИЕЙ ГОЛОВНОГО МОЗГА

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С целью изучения дифференцированного влияния различных атерогенных факторов риска на течение ИБС и нарушение мозгового кровообращения нами обследованы 67 больных с ИБС в возрасте от 40 до 75 лет. Весь контингент больных был распределен на 4 группы: I группа - 7 боль-

ных с перенесенным инсультом, II - 8 больных с перенесенным инфарктом миокарда и атеросклеротической ангиопатией церебральных сосудов, III - 10 больных ИБС, умеренной гипертензией и атеросклеротической ангиопатией церебральных сосудов, IV - 42 больных ИБС и атеросклеротической ангиопатией церебральных сосудов.

Диагноз ИБС, инфаркта миокарда и атеросклеротической церебральной ангиопатии базировался на анамнезе, клинико-лабораторном исследовании, ЭКГ, ЭХО-КГ, стресс-тесте, коронарографии, триплекссонографии сосудов головного мозга и компьютерной томорафии головного мозга.

У всех больных был исследован фибриноген и липидный спектр крови: общий холестерин (ОХ); холестерин липопротеинов высокой плотности (Х-ЛПВП); холестерин липопротеинов низкой плотности (Х-ЛПНП); холестерин липопротеинов очень низкой плотности (Х-ЛПОНП); триглицериды (ТГ).

По результатам исследования можно заключить, что: фибриноген является значимым риск фактором для больных ИБС и церебральной ангиопатией, однако особо следует выделить его тромбогенный риск у больных с перенесенным инсультом.

Понижение показателей Х-ЛПВП представляет общий риск-фактор атеросклеротического поражения экстракраниальных сосудов головного мозга для больных ИБС, перенесших инфаркт миокарда, инсульт и для атеросклеротического поражения интракраниальных сосудов, а также больных ИБС с артериальной гипертензией.

Триглицериды являются важным метаболическим компонентом развития стеноза экстракраниальных сосудов у больных с перенесенным инсультом.

Key words: atherosclerosis, CHD, Lipid metabolism, fibrinogen, Cerebral Atherosclerotic Angiopathy.

Научная публикация

THE ATORVASTATIN'S EFFECTS IN THE PATIENTS WITH CAROTID ARTERY ATHEROSCLEROSIS AND MODERATE HYPERLIPIDEMIA

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The coronary heart disease (CHD) and the cerebral circulation disorders (CCD) are the most fatal diseases in the world population [2,3,5]. These diseases have very high mortality rate decreasing life quality and social activity. The morphological bases of CHD and CCD are the changes of coronary and cerebral vessels, namely: atherosclerotic plaques, endothelial proliferation and stenosis that causes the ischemic disorders in cardiomiocytes and brain cells. Dislipidaemia would be the main reason in pathogenesis of vascular disorders: atherosclerotic plaques, endothelial proliferation and stenosis [1,5].

So the main direction of the treatment and prevention of CHD and CCD is to improve physiological vascular function, which includes: cholesterol level, plaques stabilization, endothelial proliferation and vessels stenosis correction [4].

The aim of the work was the study of Atorvastatin's action on lipid spectrum, vessel lesions and to find atorvastatin optimal doses for treatment of the patients with moderate hyperlipidaemia and carotid vascular lesion.

Material and Methods. For the investigation we have chosen patients at the Department of Cardiology and the Research Center of Atherosclerosis at the National Center of Therapy of Georgia.

The main criteria were: total cholesterol (TC)>160mg/dl, low density lipoprotein - cholesterol (LDLC)>100mg/dl, high density lipoprotein - cholesterol (HDLC) <40mg/dl, triglycerides (TG) >150mg/dl and the presence of atherosclerotic plaques in the carotid arteries, visualized by triplexsonography method, on color Doppler with the 7,5 MHz transducer on "SIEMENS SONOLINE ELEGTA".

We have chosen 9 patients (the age range 52-72), one woman and 8 men. All of them had moderate hyperlipidaemia and atherosclerotic plaques in carotid arteries.

Before beginning of the study, the patients were investigated using biochemical analysis, ECG, ultrasound investigation, Holter monitoring, blood pressure measuring and etc. Lipid spectrum was studied in blood serum using spectrophotometer "Janway 4500". The quantitative determina-

tion of TC was performed. TG were determined by the enzyme method, while the content of high density lipoprotein-cholesterol (HDLC) determined after the precipitation LDLC and very low density lipoprotein using BIOLABO, France reagent. LDLC were calculated by Friedwald method [1].

Using triplexsonography method [4] we were measuring the intima-media complexes and atherosclerotic plaques height. After examination patients were given 20 mg atorvastat daily, orally. The study lasted six mounts, patients were on ambulatory care during this time. Every month in the patients blood lipids were measured and after six months there were visualised carotid arteries with the same method for checking the intima-media complexes and atherosclerotic plaques height.

Figure 1. Case study for lipid spectrum(mg/dl) and vessel lesion parameters; intima-media complex, plaque height (mm) before treatment

TC	LDLC	HDLC	Tg	VLDLC	complex	height
236	179	27	149	30	1.3	2,9
228	182	27	96	19	1.1	2,9
224	149	40	177	35	1.4	2,8
270	180	54	184	36	1.5	2,2
247	181	42	122	24	1	2
263	187	38	192	38	1.6	2,8
236	150	58	140	28	1.1	2,8
247	170	46	157	31	0.9	3,5
229	135	59	178	35	1.1	2,3

Figure 2. Case study of Lipid spectrum (mg/dl) and vessel lesion parameters; intima-media complex, plaque height (mm), after 6 months treatment

TC	LDLC	HDLC	Tg	VLDLC	complex	height
124	61	39	119	24	1.2	2,8
117	59	36	110	22	1	2,7
111	62	30	95	19	1.2	2,6
151	70	54	133	27	1.1	2,1
140	67	55	88	18	1	2,1
159	82	56	104	21	1.1	2,7
175	95	55	126	25	1.1	2,5
152	69	53	149	30	0.9	3
154	71	55	142	28	1.1	2,2

Results and their discussion: The results (see Fig 1 and Fig 2) show lipid data's trend towards improvement: before treatment level of TC was 242,22±15,95 mg/dl and after six months treatment (with atorvastatin 20mg per day orally) the level of TC decreased significantly to 142,56±21,26 mg/dl ($p<0,001$), as level of LDLC (before treatment 168,11±18,60, after treatment 70,67±11,41mg/dl ($p<0,001$), Tg decreased as well (155±31,74 before treatment, 118,44±20,96 after treatment ($p<0,01$). The level of HDLC increased not significantly: 43,44±12,02 mg/dl before treatment and 48,11±10,13 mg/dl after the treatment.

The above-mentioned data showed that atorvastatin improves lipid parameters significantly. The most important is atorvastatin's action on vascular lesion: we observed decrease of intima-media proliferation (intima-media complexes): 1,22±0,24 mm before treatment and 1,08±0,09 mm after treatment ($p<0,05$). Under atorvastatin treatment plaque height diminished statistically confidently: from 2,69±0,45mm to 2,52±0,32 mm ($p<0,05$). These data shows that atorvastatin is able to regress vascular lesion - the main disorder of Atherosclerosis.

Figure 3. Lipid data before and after treatment (M±SD)

	TC (mg/dl)	LDLC(mg/dl)	HDLC(mg/dl)	Tg(mg/dl)	VLDLC(mg/dl)
Before	242,22±15,95	168,11±18,60	43,44±12,02	155±31,74	30,67±6,20
After	142,56±21,26	70,67±11,41	48,11±10,13	118,44±20,96	23,78±4,12

Figure 4. Vessel lesion before and after treatment (M±SD)

	intimae-media complexes(mm)	plaque size (height) mm
Before	1,22±0,24	2,69±0,45
After	1,08±0,09	2,52±0,32

So, the clinical state of patients was improved and the dosage 20mg per day showed the optimal treatment effect. As for the duration of atorvastatin intake, it is different for lipid spectrum and vessel lesion, the improvement of lipid data could be observed in two or three months, but as for vascular lesion, it is a long process and needs longitudinal observation. Our study showed that treatment with 20mg atorvastatin per day during six months established statistically important improvement of vascular lesion.

The patients need to continue the treatment for the improvement of vascular lesion, and they ought to be on the further ambulatory control.

It may be concluded that in patients with atherosclerosis of carotid artery and moderate hyperlipidaemia using of Atorvastatin (20 mg) daily during 6 months decreases TC, LDLC and provokes the trend towards increasing of HDLC; it contributes to the regression of vascular atherosclerotic lesion through decrease of intima-media complexes and plaque height; improves the above mentioned indices through the influence on the normalization of clinical state of patients. Daily 20 mg atorvastatine usage has the optimal treatment effect in the patients with moderate hyperlipidaemia and vascular lesions.

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РЕЗЮМЕ

РЕЗУЛЬТАТЫ ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ АТОРВАСТАТИНА У БОЛЬНЫХ УМЕРЕННОЙ ГИПЕРЛИПИДЕМИЕЙ И АТЕРОСКЛЕРОЗОМ СОННЫХ АРТЕРИЙ

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Ишемическая болезнь сердца (ИБС) и циркуляторные дисфункции церебрального кровообращения (ЦДЦК) являются высоко распространенными заболеваниями в мире и очень опасными для жизни. Гиперлипидемия и атеросклеротические повреждения сосудов являются главным патоморфологическим базисом для ИБС и ЦДЦК.

Целью исследования являлась оценка эффективности применения аторвастатнина у больных (9 случаев) умеренной гиперлипидемией и поражением сонных артерий. Курс лечения составил 20 мг аторвастатина в сутки, в течение 6 месяцев.

Лабораторные показатели (липидный спектр плазмы крови) и данные триплекссонографии (комплексы интима-медии, атеросклеротические бляшки) были улучшены после проведения курса лечения 20 мг аторвастатина в сутки, результаты были статистически подтверждены.

Результаты исследования показали, что применение аторвастатина в дозе 20 мг в сутки, вызывает улучшение клинического состояния больного, снижение липидных показателей, улучшение сосудистых показателей, толщины интима-медия комплексов и высоты атеросклеротических бляшек. Таким образом, пациентам при умеренной гиперлипидемии и атеросклерозе сонных артерий рекомендуется принимать аторвастатин в дозе 20 мг в сутки, в течение 6 месяцев.

Key words: atherosclerosis, dyslipidemia, carotid artery.

Научная публикация

CHLAMYDIA PNEUMONIAE AS A LIKELY RISK FACTOR FOR ISCHEMIC STROKE

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The traditional risk factors, such as dyslipidemia, hypertension, smoking and diabetes mellitus, do not sufficiently explain pathogenesis of the ischemic stroke [5]. Thus new risk factors are being studied intensively. Among them chronic Chlamydia pneumoniae infection appears to be the most important [10]. Chlamydia pneumoniae TWAR is an interacellular gram-negative bacterium that commonly causes respiratory infection [6].

The first suggestion of an association between C.pneumoniae and atherosclerosis was made by Saikku et al in 1988 [12]. A proposed association between C. Pneumoniae and atherosclerosis is based on serologic evidence, pathologic evidence, animal models and therapeutic trials [2,4,9]. Besides there are some studies that did not approve any relations between C. pneumonia and atherosclerosis [15].

The goal of our study was to evaluate possible pathogenetic role of C. pneumoniae in the development of the ischemic stroke.

Matherial and methods. The study was carried out on 47 patients in Neurology department of Tbilisi State Medical University in 2002-2003. The patients' age ranged from 39 to 79. Among them 26 were men and 21 women. The patients were divided into two main groups. The first main group included 24 patients with acute ischemic stroke. Cerebral infarction was diagnosed on the basis of results of CT or MRI. The second main group included 23 patients with chronic cerebrovascular disorders (discircualatory encelophalopathy). The patients with possible cardioembolic stoke were not included in the main group. The following risk factors were reported in both groups of patients: family history of stroke in 34%, lipid disorders in 68%, diabetes in 8%, hypertension in 75%, smoking habits in 52%. The control group was created with 25 healthy persons.

For study persons of both main and control groups IgM and IgG antibodies to C. pneumonia and endothelium- derived relaxing factor (EDRF) were investigated.

Immunoglobin M(IgM) and G(IgG) antibodies to C. pneumoniae were measured using the microiommunofluorescence method. The titers for IgM were positive at a dilution of 1:10 and for IgG 1:16, respectively. The nitric oxide level was determined according to the colorimetric assay in serum with measurement of NO metabolite (NO3) [14].

Results and their discussion. High titers of IgG antibodies to C. pneumoniae were found in 81,4% and 76,1% of study subjects from the first and second groups respectively and IgM antibodies in 53,5% and 39,1% respectively (table).

Table. Prevalence of elevated C. pneumonia antibody titers and no changes among study subjects

N	Ig G	IgM	NO		
			<17 micromol/l.	17-24 micromol/l.	>24 micromol/l.
I	81,4 %	53,5%	49%	5%	46%
II	76,1%	39,1%	41%	29%	30%
III	49%	28%	15%	79%	6%

As we see the seropositivity to C.pneumoniae mostly was observed among patients rather than among persons from the control group. IgM antibody titer was higher in the first group in comparison with the second group (53,5% and 39,1%, respectively). The significant difference of IgG elevated titers was not revealed between first and second groups of patients.

According the nitric oxide level the study subjects were divided into 3 groups: low NO quantity <17 micromol/l, normal 17-24 micromol/l, and high>24 micromol/l (table).

Our results indicate that NO level in healthy patients was considered as normal value that corresponds to the previous studies. For the first group of patients normal value was revealed in 5%, increased value in 49% and NO deficit - in 46% of study subjects. The similar results were found in the second group of patients - normal value of NO was revealed in 9%, increased value in 41% and decreased value in 30%.

The results could be explained by the effects on NO on the vasodilation and inhibition of platelet coagulation.

Low level of NO results in endothelial dysfunction, disturbance of vasodilation and increased adhesion [14]. Excess level of NO has a toxic influence on the vessels wall due to

the formation of peroxynitrate with free radical of oxygen that causes vasonconstriction and thrombosis [8,11,16]. NO level changes were revealed in the first group of patients with acute ischemic stroke in 95%, in patients with discirculatory encephalophaty in 71%, and in healthy persons group in 21%.

The changes of NO in both groups of patients were associated with the frequency of C. pneumoniae seropositivity. This association could be explained by the possible participation of C.pneumoniae in the pathogenesis and clinical manifestation of atherosclerosis [7,13]. A variety of potentially causative mechanisms whereby C.pneumoniae might initiate or accelerate the progression of atherosclerosis have been described. Recent data indicate that specific products of C.pneomoniae, such as the lipopolysaccharide and HSP60 (heat shock protein) may mediate macrophage functions related to arterial inflammation and atherogenesis [3].

It may be concluded that the patients with cerebrovascular disease in most cases have chronic infection caused by C. pneumoniae. The recrudescence of infection is associated with ischemic stroke development.

The patients with cerebrovascular disease have nitric oxide changes that associate with exacerbation of the disease.

Based on our results the treatment of the patients with ischemic stroke could be performed by antichlamydial therapy in addition to the traditional treatment.

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РЕЗЮМЕ

CLAMYDIA PNEUMONIAE КАК ВЕРОЯТНЫЙ РИСК-ФАКТОР РАЗВИТИЯ ИШЕМИЧЕСКОГО ИНСУЛЬТА

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Изучали значение роли хронической инфекции, вызванной Clamydia pneumoniae, в патогенезе ишемического инсульта.

Исследовались уровни титров антител класса IgG и IgM и фактор релаксации эндотелия у 47 больных и 25 практически здоровых лиц. Больные подразделялись на основную группу, перенесших ишемический инсульт (26 случаев), и группу с хроническим нарушением мозгового кровообращения (21 случай).

Результаты исследования показали, что у больных I группы уровень повышения титров IgM наблюдался в 53,5%, IgG - 81,4% случаев, II группы - 39,1% и 76,1% соответственно. В контрольной группе эти показатели соответствовали 49% и 28% случаев. Уровень нарушения NO в группах составил 95% 71% 21% соответственно.

Полученные нами данные позволяют судить о патогенетической роли хронической инфекции C. pneumoniae в дисфункции эндотелия и развитии ишемического инсульта.

Key words: chlamydia pneumoniae, ischemic stroke, risk-factors.

Научная публикация

ROLE OF THE HYPERINSULINEMIA AND HYPERANDROGENIA IN THE STRUCTURE OF REPRODUCTIVE DISEASES CHARACTERIZED BY METABOLIC DERANGEMENTS

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Nowadays, in the recent literature the metabolic syndrome (MS) or x syndrome is quite frequently investigated. According to Reaven G. the MS is the combination of pathogeneticaly related symptoms such as insulin-resistance (IR)/hyperinsulinemia (HI), obesity (O), arterial hypertension (AH), dislipidemia, diabetes mellitus type II or disorders in tolerance toward carbohydrate, atherosclerosis [2,6].

Insulin-resistance/hyperinsulinemia ((IR/HI) is the pathogenetical basis of the MS. At the same time it is the factor of disordered reproductive functions in women, and independent factor for polycystic ovary in particular [4,5].

In literature the concepts of IR and visceral obesity are discussed together (R. Wild, Манухин, Чернух, Finer, Bloom). There are suggestions that IR is detected in the case of universal and gynoid obesity (Poretsry 1994). Virsaladze D. et al. in most of obese patients revealed the HI, which correlates mainly with adipose tissue redistribution and not with the quality of excess body mass [1,3].

The close interrelation of visceral obesity and IR/HI is obvious. Although, investigations of many authors are dedicated to the problem - how to detect which factor is the primary among them IR or HI, the common opinion about the problem is not available.

The aim of our investigations was to detect the role of IR and interrelated HI during reproductive pathologies - the hypothalamic syndrome accompanied with metabolic derangement and insulin-resistant metabolic syndrome (polycystic ovary) [2,7].

Material and methods. Investigations were carried out at the Zhordania Institute of Human Reproduction, clinics of reproductive endocrinology department and the laboratory of hormonal diagnostics.

A total of 211 patients with age from 16 to 40 and 23 healthy women (from the reproductive standpoint) were under observation.

Patients were divided into two major groups - Insulin-resistant metabolic syndrome (IRMS) with secondary polycystic ovary (the group I) and the Hypothalamic syndrome (HS) with secondary polycystic ovary (the group II).

The patients with insulin-resistant metabolic syndrome, secondary polycystic ovary (108 women) were subdivided into two groups - Ia subgroup involved patients with the normal body mass (BMI<25 kg/m^2), in the subgroup Ib were patients with the excess body mass (BMI>25 kg/m^2).

The patients with the hypothalamic syndrome (103 women) were subdivided into two group - The group IIa, patients with normal body mass (BMI<25 kg/m^2); and the group IIb, patients with the excess body mass (BMI>25 kg/m^2).

Anamnesis and state of menstrual and reproductive functions were studied. The objective status - BMI (kg/m^2) and constitutional type were detected as well.

In order to define the type of adipose tissue redistribution the index of lumbar and femoral ratio (I L/F), the hirsutic number and expression quality of other dermatopathies-acne-seborrhea, the partial alopecia of parietal bone, skin dyschromia with “acanthosis nigricans” were studied.

The ultrasonography of pelvic cavity, the hormonal testing - LH, FSH, prolactine, immune-reactive insulin (IRI), free testosterone were carried out.

The received data were analyzed using the Microsoft Excel variation analysis method.

Results and their discussion. Of the 108 patients from the group I, 25 (23%) had the normal body mass (BMI<25 kg/m^2) - the subgroup Ia; and 87 (77%) patients revealed the excess body mass (BMI>25 kg/m^2) - the subgroup Ib;

42% of patients from the group Ia had the visceral redistribution of the adipose tissue (I L/F>0,8); and 58% of patients - gynoid or even redistribution of the adipose tissue (I L/F<0,8). In the subgroup Ib, the 94% of the patients with excess body mass had the I L/F >0,8 or visceral obesity and only 6% of patients were was with (I L/F<0,8) gynoid or even obesity;

The hyperandrogenic markers: hirsutism - 90%, acne - 23%, parietal partial alopecia - in 6 cases indicates high level of androgenia.

Hirsutism - the marker of hyperandrogenia (HA), was mostly expressed in the subgroup Ib especially in patients with

visceral obesity - the hirsutic number 21±0,2. The menstruation was disordered in all cases. Among them in 18% of cases, on the background of the rhythmic menstruation, the anovulation and lutein phase insufficiency was observed, in 47% of cases - oligomenorrhea, in 31% of cases - amenorrhea.

In subgroups, study of menstrual disorder variations revealed the high frequency of oligo-amenorrhea (82%) in patients with visceral obesity.

The results of ultrasonography provided information about polycystic ovary in 100% of cases (in patients from the group I) manifested with central or peripheral multi-folliculosis and thickened capsule of ovary.

According to the hormonal testing, the group I is characterized by increased level of LH (54%), free testosterone and IRI, among them the basal HI - 78% and glucose induced - 22%. The FSH and prolactin levels were in norm.

In the group I patients, positive correlation between frequency and quantitative indices of HI and HA was expressed in both subgroups. The free testosterone 8,41±0,45; IRI - 40,19±1,65.

Objective examination of the group II patients revealed that of the 103 patients 22 (21,4%) had the BMI< 25 kg/m^2 (subgroup IIa).

Almost in all patients (except one) the gynoid or even redistribution of adipose tissue (I L/F < 0,8). Of the 81 patients with BMI>25 kg/m^2 , 38 had the even or gynoid obesity (27,2%) and 43 - visceral obesity (41,7%); (I L/F >0,8). Most of these latter patients mentioned that initially they had the even redistribution of the adipose tissue and gradually underwent transformation into visceral type.

The pathognomonic sign for the group II patients is hypothalamic stigma, which in turn, by essence is the peripheral marker of diencephalic dismodulation. The mentioned sign was not detected in the group I patients, but it was revealed in all patients from the group II (100%).

As for expression of stigmas and activity of dismodulative processes respectively, in the group II 45,6 % of patients had the pink, and 54,4% - the white stigmas. Majority of patients mentioned that initially inactive stigmas were stained, that probably indicates the self-compensation of process. The great amount of active stigmas were revealed in patients involved in the subgroup IIa, however in the subgroup IIb it was expressed with high percent in patients with gynoid obesity as well, and poorly was expressed in patients with visceral obesity.

Among the patients involved in the group II, frequency of the marker of androgenia - hirsutism was high (67%), however it is still less compared to data obtained from the group I. The hirsutism, acne and alopecia were manifested in the IIb subgroup patients.

The variants of menstrual disorders are equally presented among the group II patients. On the background of the rhythmic menstruation, the anovulation and lutein phase insufficiency was observed in 31,1% of cases, oligomenorrhea - in 34,9%, amenorrhea - in 34%. Certain dynamics was detected in the subgroups. In the subgroup IIa light form of menstrual disorders are more expressed, whereas amenorrhea was not detected. The subgroup II was marked with oligo-amenorrhea. Using the ultrasonography, the analogue picture was observed in the subgroup IIa patients. Only 3 patients were with signs characteristic for polycystic ovary. The same parameters were higher in the group IIb patients - 61.2%.

The hormonal testing have shown that the group II patients are characterized with increased level of LH (56,31%), normal level of FSH, hyperprolactinemia (35%) that in the subgroup IIa was mainly detected by increased level of free testosterone concretely in the subgroup IIb (48,5%), and in the same subgroup - by hyperinsulinemia (51,5%).

In the subgroup IIb patients with gynoid and even obesity this latter indicator was expressed by glucose-induced hyperinsulinemia, and patients with visceral obesity - by basal hyperinsulinemia.

Noteworthy and very interesting comparative analysis of the groups I and II. It has shown that by clinical and hormonal manifestations the subgroup Ib and IIb patients with visceral obesity are identical. Hyperandrogenic dermatopathies, free testosterone high level and metabolic disorders - hyperinsulinemia are expressed markedly in these patients.

The difference in these subgroups is expressed by IR/HR and by the probable role of IR/HR related hyperandrogenia in disease structure. The certain predisposition is manifested in the group Ia patients, where the visceral redistribution of the adipose tissue (42%), hyperandrogenia and hyperinsulinemia was detected. So, at the early stage of disease development, when lipogenesis is not well expressed yet and the normal body mass is maintained.

Farther dynamics of process allows exaggeration of lipogenesis and more intensive visceral redistribution of the adipose tissue at the expanse of IR/HI.

The subgroup IIa is not characterized by visceral redistribution of adipose tissue and by increased levels of free testosterone and IRI as well. This fact excludes metabolic

problems in the mentioned group. This group is distinguished by diencephalic dismodulative markers - active stigmas and hyperprolactinemia. Thus, the groups I and II differs by initial pathogenetic origin.

Pathogenesis of the first one includes IR/HI. Farther dynamics of disease exacerbates HA at the expanse of excess amount insulin-dependent free androgens, that eventually results in visceral redistribution of adipose tissue. The vicious circle displays severe IR - metabolic syndrome with secondary polycystic ovary development.

The diencephalic dismodulation is the basis of disease pathogenesis for the group II patients. Peculiarities of feeding habits - increased appetite and alimentary obesity are one of the characteristic hallmarks. The "fate" of the abovementioned obesity to a great extent depends on androgen concentration. Without expressed metabolic derangements it is moderate and does not lead to visceral obesity, however the excess amount of adipose tissue and increased demand for insulin aggravates IR/HI and related processes and in the dynamic of HI the above-mentioned vicious circle displays supporting disease transformation into metabolic syndrome.

According to our investigations and on the basis of literature it is supposed that in the pathogenesis of reproductive diseases accompanied by insulin-resistant metabolic derangements the leading role plays hyperandrogenia, IR and related visceral obesity. The difference is that, initiating factor in the case of IR metabolic syndrome II polycystic ovary is IR/HI, and in the case of neuroendocrine type of hypothalamic syndrome - excess body mass determined by the diencephalic dismodulation.

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РЕЗЮМЕ

РОЛЬ ГИПЕРИНСУЛИНЕМИИ И ГИПЕРАНДРОГЕНИИ В СТРУКТУРЕ РЕПРОДУКТИВНЫХ ЗАБОЛЕВАНИЙ С МЕТАБОЛИЧЕСКИМИ РАССТРОЙСТВАМИ

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Целью данного исследования является установление патогенетической роли инсулинрезистентности (ИР) и связанной с ней гиперандрогении (ГА) в динамике репродуктивных патологий с метаболическими нарушениями – с гипоталамическим синдромом (ГС) и инсулинрезистентным метаболическим синдромом (ИМС) со вторичным поликистозом яичников.

Анатомические, антропометрические, объективные, клинико-гормональные, ультрасонографические исследования проведены 211-и больным и 23-м репродуктивно здоровым женщинам в возрасте 16-40 лет.

В результате сравнительного анализа собственных и литературных данных можно предположить, что в патогенезе репродуктивных патологий с метаболическими нарушениями приоритетную роль играет тандем ИР и ГА и связанное с ним висцеральное ожирение с той разницей, что при ИМС со вторичным поликистозом яичников, инициирующим фактором является ИР/ГИ, а при ГС – избыток массы тела, который является результатом диэнцефальных дисмодуляций.

Key words: Hyperinsulinemia, hyperandrogenia, reproductive diseases, metabolic derangements.

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