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Philosophy of medicine

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TIME FOR RADICAL CHANGE OF UNIVERSAL MYOCARDIAL INFARCTION DEFINITION HAS ARRIVED YESTERDAY

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In this manuscript, we discuss a previously introduced definition of the myocardial infarction (MI), and propose to redefine it so it is not limited just to "a necrosis in the setting of myocardial ischemia", which we think is the case only in the deceased individuals that died during the first few hours from the MI onset, but to include a broader description of the acute aseptic coronarogenic inflammation of the cardiac muscle. We suggest that the outcome of the MI to a large extant depends on the synchronization of the necrotic and reparative processes and that their desynchronization ultimately results in the development of MI complications. A better understanding of the MI and the use of appropriate definition is warranted for a development of new therapeutic targets.

KEY WORDS: myocardial infarction, inflammation

ЧАС РАДИКАЛЬНОЇ ЗМІНИ УНІВЕРСАЛЬНОЇ ДЕФІНІЦІЇ ІНФАРКТУ МІОКАРДА НАСТУПИВ УЧОРА

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Підіймається питання визначення інфаркту міокарда (ІМ). Звертається увага на помилкову дефініцію ІМ як некрозу в зоні ішемії серцевого м'яза. Такі випадки можуть мати місце у обмеженої частини померлих, причому в перші години ІМ, коли запалення в зоні інфаркту ще повністю не розвилося. ІМ має постулюватися як гостре коронарогенне асептичне запалення серцевого м'яза в зоні порушеного коронарного кровообігу. Умовою його неускладненого витоку є синхронізація некротичних і репаративних процесів і ускладнення розвиваються при їх десинхронізації. Правильна дефініція ІМ необхідна для його кращого розуміння і розробки ефективних терапевтичних підходів.

КЛЮЧОВІ СЛОВА: інфаркт міокарда, запалення

ВРЕМЯ РАДИКАЛЬНОГО ИЗМЕНЕНИЯ УНИВЕРСАЛЬНОЙ ДЕФИНИЦИИ ИНФАРКТА МИОКАРДА НАСТУПИЛО ВЧЕРА

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Поднимается вопрос определения инфаркта миокарда (ИМ). Обращается внимание на ложную дефиницию ИМ как некроза в зоне ишемии сердечной мышцы. Такие случаи могут иметь место в ограниченной части умерших, причем в первые часы ИМ, когда воспаление в зоне инфаркта еще полностью не развилось. ИМ есть острое коронарогенных асептическое воспаление сердечной мышцы в зоне нарушенного коронарного кровообращения. Условием его неосложненного исхода является синхронизация некротических и репаративных процессов и осложнения развиваются при их десинхронизации. Правильная дефиниция ИМ необходима для его лучшего понимания и разработки эффективных терапевтических подходов.

КЛЮЧЕВЫЕ СЛОВА: инфаркт миокарда, воспаление

In 2000, the First Global myocardial infarction (MI) Task Force presented a new definition of MI in which any necrosis in the setting of myocardial ischemia was labelled as MI. This definition was carried over and introduced again in 2007 and in 2012 [1–4].

We believe that this definition can be partially applied to deceased patients and only to those who died during the first hours after MI before the inflammation in the MI zone has fully developed.

We define MI as an acute coronarogenous aseptic inflammation in the part of a cardiac wall with disrupted coronary circulation. Damage to any part of the body triggers a universal inflammatory response, the very same mechanism that is taking place in the MI setting [1, 5].

The inflammation that develops in the MI zone is aseptic and alterative, and unites both necrotic (the key role belongs to bone marrow granulocytic leukocytes) and reparative (the key role belongs to bone marrow agranulocytic leukocytes) processes.

The most favorable course for the MI is the inflammatory process that develops without any complications, necessary environment for which includes synchronization of necrotic and reparative processes to preserve integrity strength of myocardium in the MI zone with a subsequent formation of fibrotic scar to replace damaged and necrotized tissues [5].

A positive outcome of MI to a large extent depends on the adequate stress responses (also known as eustress).

The major cause of complications in the MI healing is distress (hyperreactive, hyporeactive, or intermittent).

The mechanism of complications, irrespective of a distress type, always remains the same – a desynchronization of necrotic and reparative processes, which leads to a large spectrum of complications, the very first of which is weakening of cardiac wall in the MI zone.

These complications, in many cases, result in cardiac aneurysms and cardiac wall ruptures that develop early in the state of hyperreactive distress and/or when MI covers large areas [5–6].

Therefore, understanding of the MI as an acute coronarogenous aseptic inflammation in the cardiac wall is extremely important for a better understanding of the disease and may provide new therapeutic approaches.

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Clinical researches

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DEVELOPMENT AND PROGRESSION OF OBESITY IN PATIENTS WITH CORONARY HEART DISEASE: EMPHASIS ON LEPTIN GENE POLYMORPHISM (Arg223Gln)

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The article assesses the contribution of leptin gene polymorphism (Arg223Gln) in the development and progression of obesity in patients with coronary heart disease. 222 patients with coronary heart disease and obesity were surveyed. The study of leptin gene polymorphic locus Arg223Gln was performed by polymerase chain reaction of all examined patients. G allele and G/G genotype of the leptin gene polymorphism (Arg223Gln) are more common among the patients with coronary heart disease and obesity and the frequency of their detection increases with the growth of the degree of obesity.

KEY WORDS: leptin gene polymorphism, obesity, coronary heart disease

РОЗВИТОК ТА ПРОГРЕСУВАННЯ ОЖИРІННЯ У ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ: АКЦЕНТ НА ПОЛІМОРФІЗМ ГЕНА ЛЕПТИНУ (Arg223Gln)

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У статті оцінено внесок поліморфізму гена лептину (Arg223Gln) у розвиток і прогресування ожиріння у хворих на ішемічну хворобу серця. Обстежено 222 хворих на ішемічну хворобу серця й ожиріння. Дослідження поліморфного локусу Arg223Gln гена лептину проводили методом полімеразної ланцюгової реакції всім обстеженим хворим. Серед хворих на ішемічну хворобу серця й ожиріння частіше зустрічаються алель G і G/G генотип поліморфізму гена лептину (Arg223Gln), причому частота їх виявлення збільшується відповідно зростанню ступеня ожиріння.

КЛЮЧОВІ СЛОВА: поліморфізм гена лептину, ожиріння, ішемічна хвороба серця

РАЗВИТИЕ И ПРОГРЕССИРОВАНИЕ ОЖИРЕНИЯ У БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА: АКЦЕНТ НА ПОЛИМОРФИЗМ ГЕНА ЛЕПТИНА (Arg223Gln)

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В статье оценено вклад полиморфизма гена лептина (Arg223Gln) в развитие и прогрессирование ожирения у больных ишемической болезнью сердца. Обследовано 222 больных ишемической болезнью сердца и ожирением. Определение полиморфного локуса Arg223Gln гена лептина проводили методом полимеразной цепной реакции всем обследованным больным. Среди больных ишемической болезнью сердца и ожирением чаще встречался аллель G и G/G генотип полиморфизма гена лептина (Arg223Gln), причем частота их выявления увеличивалась соответственно увеличению степени ожирения.

КЛЮЧЕВЫЕ СЛОВА: полиморфизм гена лептина, ожирение, ишемическая болезнь сердца

INTRODUCTION

Obesity is one of the most pressing health and social problems, which is characterized by the world health organization as a non-infectious epidemic. Up to present, the obesity pathogenesis causes debate among scientists. However, after the discovery of leptin the number of studies dealing with the problem increases. In addition, leptin significantly

influences on the atherosclerotic process, the harbingers of which is obesity [1].

Today, the interest of scientists is confined to the definition of the pathogenetic role of gene polymorphisms, especially in the context of combined course of coronary heart disease (CHD) and obesity.

The results of studies examining the influence of leptin gene polymorphism on the development of obesity are controversial [2–3], and Ukrainian populations are not defined.

OBJECTIVE

The aim of the study is to evaluate the contribution of leptin gene polymorphism (Arg223Gln) in the development and progression of obesity in patients with coronary heart disease in the Ukrainian population.

MATERIALS AND METHODS

With the purpose to study the problem the comprehensive examination of 222 patients with coronary artery disease and obesity was carried. The patients included were treated in the Cardiology Department of the Kharkiv Clinical hospital № 27, which is the basic medical institution of Internal Medicine № 2 and Clinical Immunology and Allergology of Kharkiv National Medical University of Ministry of Health of Ukraine. The comparison group consisted of 115 CHD patients with normal body weight. The control group consisted of 35 practically healthy people. Additionally, patients of IHD and obesity were divided into subgroups depending on the degree of the last: the first subgroup consisted of 80 patients with obesity of the 1-st degree, the second group consisted of 71 patients with obesity of the 2-nd degree, the third – 71 patients with obesity of the 3-d degree. Groups were matched in accordance age and sex. The study excluded patients with severe concomitant pathology of the respiratory system, digestive system, kidneys and individuals with cancer.

The diagnosis was established in accordance with the applicable orders of the Ministry of Health of Ukraine.

All patients were undergone general clinical and instrumental examination. For the characteristics of obesity body mass index (BMI) (Quetelet index), which was calculated with the formula: weight (kg)/height (m2), was determined.

The study of leptin gene polymorphic locus Arg223Gln was performed by polymerase chain reaction with electrophoresis detection of the results using sets of reagents «SNP-EXPRESS» produced by NPF «Ltah» (RF). Extraction of DNA from whole blood was performed using a reagent «DNA-Express-blood» produced by NPF «Ltah» (Russian Federation) according to the instructions. The correctness of the distribution of genotypes was determined under Hardy-Weinberg equilibrium ($pi2 + 2\ pipj + pj2 = 1$). In accordance with the Helsinki Declaration, all patients were informed about the clinical trial and gave consent for determination of polymorphism of the studied gene.

Statistical data processing was performed using Statistica package, version 6.0. For comparison of the frequency distribution of alleles and genotypes between groups $\chi 2$ Pearson and Fisher criteria were used. To determine the relative risk odds ratio (OR) was calculated. As the lack of association VSH=1 was considered; as a positive association – VSH > 1; negative association of allele or genotype with the disease (low disease risk) VSH < 1 was considered. Confidence interval (CI) is an interval of values within which with 95 % probability the predictive value of VSH presents. Statistically significant differences were considered at $p < 0.05$ were considered.

RESULTS AND DISCUSSION

The development of obesity in patients with coronary artery disease in the Ukrainian population was connected due to the results of our study with G allele and G/G genotype leptin gene polymorphism (Arg223Gln) (Table. 1).

The presence of G allele and G/G genotype of the leptin gene polymorphism (Arg223Gln) in CHD patients was associated with the development of obesity, respectively (OR = 1,70, 95 % CI = [1,26–2,31], $\chi 2$=11.8, $p < 0.05$) and (OR = 2,77; 95 % CI = [1,50–5,12], $\chi 2$=10,9; $p < 0.05$).

Table 1

The value of G allele and G/G genotype of leptin gene polymorphism (Arg223Gln) in the development of obesity in CHD patients

Genetic markers	OSH (95 % CI)
The G Allele of	1,70 (1,26–2,31)
	$\chi^2 = 11,8$; $p < 0,05$
Genotype of G/G	2,77 (1,50–5,12)
	$\chi^2 = 10,9$; $p < 0,05$

We carried out the determination of the frequency of alleles and genotypes of leptin gene polymorphism (Arg223Gln) depending on BMI in patients with CHD and obesity based on the previous data (tab. 2).

32 patients with coronary artery disease and obesity of the 1-st degree were carriers of A allele, that was equal to 40 %, G allele – 48 patients (60 %). A/A genotypes, G/A and G/G genotypes had 18 (22,5 %), 30 (37,5 %) and 32 (40 %) patients with CHD and obesity of the 1-st degree accordingly. In the group of patients with obesity of the 2-nd degree the following frequency distribution of alleles and genotypes of leptin gene polymorphism (Arg223Gln) took place: 23 people, that is worth to 32.39 %, were the carriers of A allele, 48 patients (67,61 %) – G allele; 13 (18,31 %), 24 (33,80 %) and 34 (47,89 %) respectively had A/A, G/A and G/G genotypes. In the group of patients with combined CAD and obesity of the 3-d degree 16 patients (22,54 %) were carriers of A allele: 55 people (of 77.46 %) - G allele; 8 (11,28 %), 25 (35,2 %) and 38 (of 53.52 %) – A/A, G/A and G/G genotypes, respectively.

17,46 % and 9,85 % more patients with CHD and obesity of the 3-d degree were carriers of the G allele in comparison with patients of the groups 1 and 2, as A allele , conversely, was more common in individuals with obesity of the 1-st and 2-nd degree. G/G Genotype was significantly more prevalent in patients with coronary artery disease and obesity of the 3-d degree on 13.52 % and 5,63 %, and A/A genotype – less on 11.22 % of 7.03 %, compared to patients with obesity 1-st and 2-nd degree, respectively.

Table 2

Frequency of alleles and genotypes of leptin gene polymorphism (Arg223Gln) depending on BMI in patients with CHD and obesity

Genetic markers group 1	group 1 Obesity of the 1-st degree (n = 80)	group 2 Obesity of the 2-nd degree (n = 71)	group 3 Obesity of the 3-d degree (n = 71)
Allele A	32 (40 %)	23 (32,39 %)*	16 (22,54 %)*#
Allele G	48 (60 %)	48 (67,61 %)*	55 (77,46 %)*#
Genotype A/A	18 (22,5 %)	13 (18,31 %)	8 (11,28 %)*
Genotype G/A	30 (37,5 %)	24 (33,80 %)	25 (35,2 %)
Genotype G/G	32 (40 %)	34 (47,89 %)*	38 (53,52 %)*#

Thus, G allele and G/G genotype of the leptin gene polymorphism of (Arg223Gln) are more common among the patients with coronary artery disease and obesity, and the frequency of their detection increases with the growth of BMI in the Ukrainian population.

These data match the results obtained by V. S. Mattevi et al. in 2002 [4] in the Brazilian population, A. Portoles et al in 2006 [5] in the Spanish population, Y. Y. Yako in 2012. [6] among the people of Africa, proves, that the carriage of this genotype is associated with the development of obesity. However, in the studies of T. Gotoda et al [7] in the British population, A. Constantin et al. [8] and the results of the meta-analysis, performed by

M. Neo et al. [9] in romanes, these linkages were not obtained. Moreover, N. Yiannakouris et al. in 2001 found that homozygote is more dominant than 223 R allele among people with normal body weight significantly than in patients with overweight and obesity [10]. Research results are contradictory and require further research.

CONCLUSIONS

G allele and G/G genotype of leptin gene polymorphism (Arg223Gln) were associated with the development of obesity in CHD patients, and the frequency of their detection increases with the growth of BMI in the Ukrainian population.

PROSPECTS FOR FUTURE STUDIES

Given the urgency of the comorbid pathology problem further research should be directed towards the study of other associations of gene polymorphisms with the development and progression of cardiovascular diseases and obesity.

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TYPES OF IMMUNE RESPONSE FOR VARIOUS ESTHTEIN-BARR FORMS OF VIRAL INFECTION

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In 321 patients with different forms of EBV infection in the age range from 19 to 57 years (mean age 33,1 ± 11,7 years) different types of immune response were isolated and studied. All participants in the study were divided into groups of comparable sex and age: patients with infectious mononucleosis (n = 138); patients with various forms of chronic EBV infection (n = 183); clinically healthy volunteers (n = 20). During the study all ethical norms were observed in accordance with international and Ukrainian protocols. Clinical examination of patients and healthy volunteers included examining complaints, an epidemiological history, a history of illness and life, an objective examination, instrumental and laboratory studies in dynamics. Statistical processing of the results of the study was carried out by parametric and nonparametric methods using the program Statistika 6.0, for each variational series, the absolute values (n), the arithmetic mean (M), the mean error of the arithmetic mean (m) were calculated. It was found that patients with different forms of EBV infection have a reliable cytokine imbalance. Four main types of immune response were identified: normoreactive, dissociative, hyporeactive and hyperreactive. The revealed types of immune response testify to inadequate cellular-humoral reactivity of the organism in conditions of prolonged persistence of EBV, which is manifested by a tendency to suppress cell-mediated and enhancing humoral mechanisms of the immune response and is reflected in the clinical and biochemical manifestations of the disease and leads to a protracted undulating course of the disease.

KEY WORDS: Epstein-Barr virus, types of immune response, course of the disease

ТИПИ ІМУННОЇ ВІДПОВІДІ ПРИ РІЗНИХ ФОРМАХ ЕПШТЕЙНА-БАРР ВІРУСНОЇ ІНФЕКЦІЇ

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На 321 пацієнті з різними формами ВЕБ-інфекції у віковому діапазоні від 19 до 57 років (середній вік 33,1 ± 11,7 років) були виділені і вивчені різні типи імунної відповіді. Всі учасники дослідження були розділені на зіставні за статтю та віком групи: пацієнти з інфекційний мононуклеоз (n = 138); пацієнти з різними формами хронічної ВЕБ-інфекції (n = 183); клінічно здорові добровольці (n = 20). В ході роботи були дотримані всі етичні норми згідно з міжнародними і українськими протоколами. Клінічне обстеження пацієнтів і здорових добровольців передбачало вивчення скарг, епідеміологічного анамнезу, анамнезу захворювання і життя, об'єктивний огляд, інструментальні та лабораторні дослідження в динаміці. Статистична обробка результатів дослідження проводилася параметричними і непараметричних методами з використанням програми Statistika 6.0, для кожного варіаційного ряду розраховували абсолютні значення (n), середнє арифметичне (M), середню помилку середнього арифметичного (m). Встановлено, що пацієнти з різними формами ВЕБ-інфекції мають достовірний цитокіновий дисбаланс. Було виділено чотири основних типи імунного реагування: нормореактівний, діссоціативний, гіпореактивний і гіперреактивність. Виявлені типи імунного реагування свідчать про неадекватну клітинно-гуморальної реактивності організму в умовах тривалої персистенції ВЕБ, що проявляється схильністю до пригнічення клітинно-опосередкованих та посилення гуморальних механізмів імунної відповіді і відображається в клініко-біохімічних проявах хвороби і призводить до затяжного хвилеподібний перебіг захворювання.

КЛЮЧОВІ СЛОВА: вірус Епштейна-Барр, типи імунної відповіді, перебіг хвороби

ТИПЫ ИММУННОГО ОТВЕТА ПРИ РАЗЛИЧНЫХ ФОРМАХ ЭПШТЕЙНА-БАРР ВИРУСНОЙ ИНФЕКЦИИ

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На 321 пациенте с различными формами ВЭБ-инфекции в возрастном диапазоне от 19 до 57 лет (средний возраст 33,1 ± 11,7 лет) были выделены и изучены различные типы иммунного ответа. Все участники исследования были разделены на сопоставимые по полу и возрасту группы: пациенты с инфекционным мононуклеозом (n = 138); пациенты с различными формами хронической ВЭБ-инфекции (n = 183); клинически здоровые добровольцы (n = 20). В ходе работы были соблюдены все этические нормы согласно международным и украинским протоколам. Клиническое обследование пациентов и здоровых добровольцев предусматривало изучение жалоб, эпидемиологического анамнеза, анамнеза заболевания и жизни, объективный осмотр, инструментальные и лабораторные исследования в динамике. Статистическая обработка результатов исследования проводилась параметрическими и непараметрическими методами с использованием программы Statistika 6.0, для каждого вариационного ряда рассчитывали абсолютные значения (n), среднее арифметическое (M), среднюю ошибку среднего арифметического (m). Установлено, что пациенты с различными формами ВЭБ-инфекции имеют достоверный цитокиновый дисбаланс. Было выделено четыре основных типа иммунного реагирования: нормореактивный, диссоциативный, гипореактивный и гиперреактивный. Выявленные типы иммунного реагирования свидетельствуют о неадекватной клеточно-гуморальной реактивности организма в условиях длительной персистенции ВЭБ, что проявляется склонностью к подавлению клеточно-опосредованных и усилением гуморальных механизмов иммунного ответа и отображается в клинико-биохимических проявлениях болезни и приводит к затяжному волнообразному течению заболевания.

КЛЮЧЕВЫЕ СЛОВА: вирус Эпштейна-Барр, типы иммунного ответа, течение болезни

INTRODUCTION

The relevance of the Epstein-Barr virus infection (VEB) is due to a high degree of infection of the population not only in Ukraine but worldwide, since specific antibodies to this virus are detected in almost 95 % of the adult population. Specific tropism of VEB to immunocompetent cells, systemic damage to internal organs, a wide range of clinical forms of the disease, and the absence of specific prevention is the subject of research by many scientists [1–2]. Thus, many clinical forms of VEB (tumor and non-tumor) have been described, in which the virus plays the role of an etiological factor: chronic active EBV infection; X-linked lymphoproliferative disease; nasopharyngeal carcinoma; Burkett's lyphoma; Hodgkin's disease; lymphoproliferative disease [2].

It has been established that VEB has a large set of genes, which allows it to escape to a certain extent from the human immune system. In particular, VEB generates proteins – analogues of a number of human interleukins and their receptors that change the immune response [3–4]. In addition, VEB is highly mutually beneficial, which allows him for a certain time to avoid exposure to specific immunoglobulins and cells of the host's immune system.

The prognosis of the outcomes of VEB infection depends on the presence and severity of immune dysfunction, the genetic predisposition to certain VEB-associated diseases, as well as on the presence of a number of external factors damaging the immune system.

A number of studies have shown that the predominant part of cytokines produced by Th-2 lymphocytes, is associated with long-term viral persistence and chronic process, while activation of the Th-1 type - with spontaneous recovery from acute forms of VEB [5–7]. It is of interest to identify and study the production of basic regulatory cytokines with the establishment of immunological response types in patients with VEB infection.

OBJECTIVE

The aim of the study was to study the dynamics of multidirectional synthesis of cytokines (IL-1β, TNF-α, IL-6, IL-2, IL-4 and IL-10) and to determine the types of immune response for predicting the clinical course of

the disease in patients with various forms of VEB-infection.

MATERIALS AND METHODS

The work was carried out on the basis of the Department of General and Clinical Immunology and Allergology of the Medical Faculty of the V. N. Karazin Kharkiv National University in 2009–2015.

The study involved 321 patients with VEB infection, the average age was 33,1 ± 11,7 years. Based on the purpose of the study, all patients were conditionally divided into the following groups: the first group - patients with infectious mononucleosis (IM, n = 138) with laboratory-proven signs of primary viral infection; the second group includes patients with various forms of chronic VEB infection (n = 183), among them: serous meningitis (n = 8), chronic tonsillitis (n = 32), nonspecific lymphadenopathy (n = 48), prolonged subfebrile condition n = 54), reactive arthritis (n = 16), chronic fatigue syndrome (n = 25). The comparison group consisted of 20 clinically healthy young people with no signs of acute or any chronic pathology, the mean age was 24.1 ± 3.2 years.

During the study, the provisions of the Helsinki Declaration of the World Medical Association, the ethical code of the doctor of Ukraine were observed, in addition, all participants received informed consent.

During the study, complaints, an epidemiological history, a history of the disease and life, an objective examination, instrumental and laboratory methods of investigation, as well as detection of the presence of atypical mononuclear cells, detection of specific antiviral antibodies (VCA-IgM, EA-IgM and EBNA-IgG) in the blood serum by ELISA (IBL, Germany) and Vector-Best (RF), the detection of VEB DNA by polymerase chain reaction (PCR) in the blood and saliva, the activity of aspartic and alanine transferase (AsAT, AlAT), lactate dehydrogenase (LDH) and creatinine phosphate kinase (CKF), fibrinogen in the course of the disease were assessed. To confirm the diagnosis as a screening express blood test for the presence of VEB, a heterophile test was used in the Hoff-Bauer modification (Chireshkina N. M. 1973). In a part of the patients, serological examinations for the herpes simplex virus type 1 + 2 (HSV-1 + 2), cytomegalovirus (CMV), toxoplasma, hepatitis viruses (A, B and C), HIV were performed for differential diagnostics. For this, anti-CMV-IgM, anti-toxo-IgM, anti-HAV-IgM, HBsAg, anti-HBc-total and anti-HIV-1 + 2 total test systems were used.

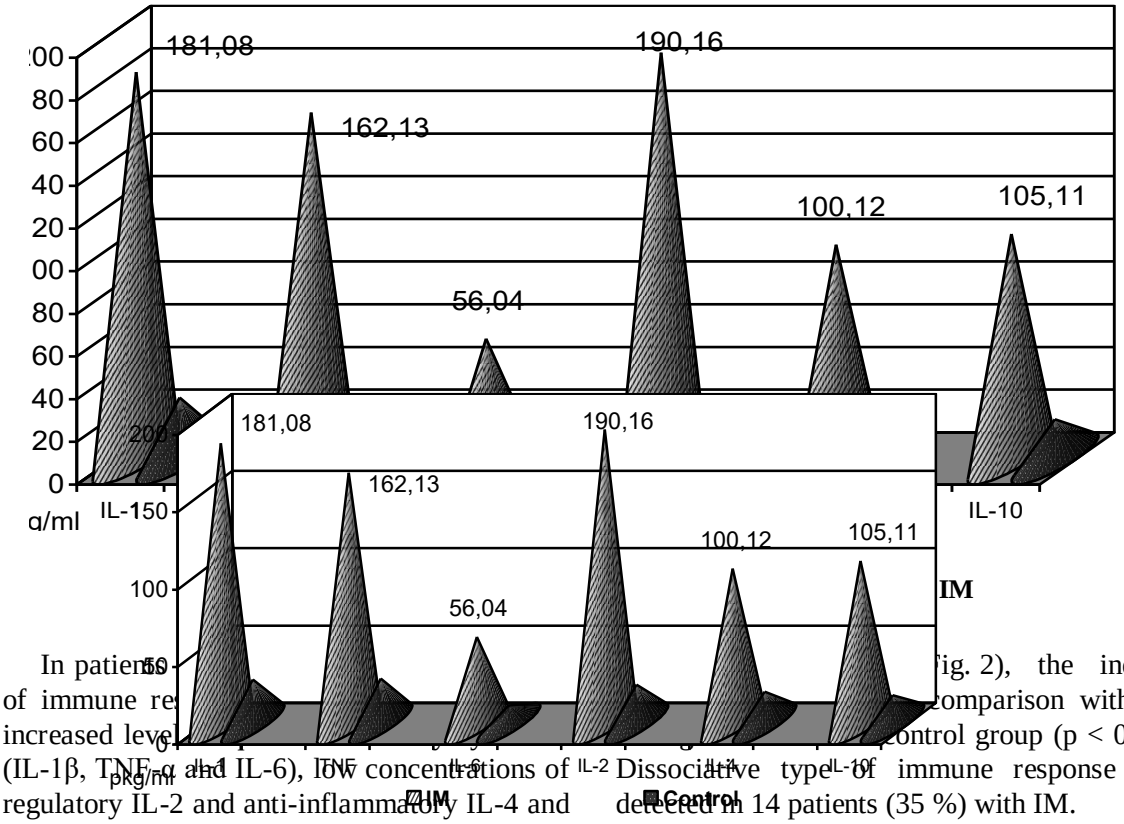
Molecular genetic studies included the determination of VEB replicative activity based on detection of DNA in the blood serum by PCR, in addition serum concentrations of the cytokines studied were determined: IL-1β, IL-6, IL-6, IL-2, IL-4, IL- 10, using the manufacturer's instruction with the use of a ELISA. Technical analysis was carried out in the clinical diagnostic laboratory of the Kharkov Regional Clinical Infectious Diseases Hospital and the Sinevo Medical Laboratory.

The statistical processing of the results of the study was carried out by parametric and nonparametric methods using the Statistika 6.0 for Windows program (Stat Soft Inc, USA) on a PC with a Pentium II Celeron 850 PPGA processor. For each variational series, the absolute values (n), the arithmetic mean (M), the mean error of the arithmetic mean (m) were calculated.

RESULTS AND DISCUSSION

Analysis of the dynamics of the cytokine profile in patients with VEB showed multidirectional changes in the synthesis of the investigated proinflammatory and anti-inflammatory cytokines, which was the basis for the establishment of four types of immune response: I – normoreactive type (significant increase in proinflammatory and anti-inflammatory cytokines), II – dissociative (high rates of pro-inflammatory cytokines background of low values of regulatory IL-2 and anti-inflammatory cytokines), III – hyporeactive (low concentrations of inflammatory and anti-inflammatory cytokines) and IV – hyperreactive (high concentrations of both pro-inflammatory and anti-inflammatory cytokines).

Analysis of proinflammatory (IL-1β, TNFα, IL-6), regulatory (IL-2) and anti-inflammatory cytokines (IL-4, IL-10) production data in patients with IM with normoreactive type of immune response (Fig. 1) revealed reliable increase in all the studied parameters in 5,2–7,7 times ($p < 0.05$) in comparison with the control levels. This type of immune response was detected in 17 patients (42.5 %) with IM.



In patients with IM (Fig. 2), the indices of immune response were characterized by comparison with the increased levels of pro-inflammatory cytokines control group ($p < 0.05$). (IL-1β, TNF-α and IL-6), low concentrations of Dissociative type of immune response was regulatory IL-2 and anti-inflammatory IL-4 and detected in 14 patients (35 %) with IM.

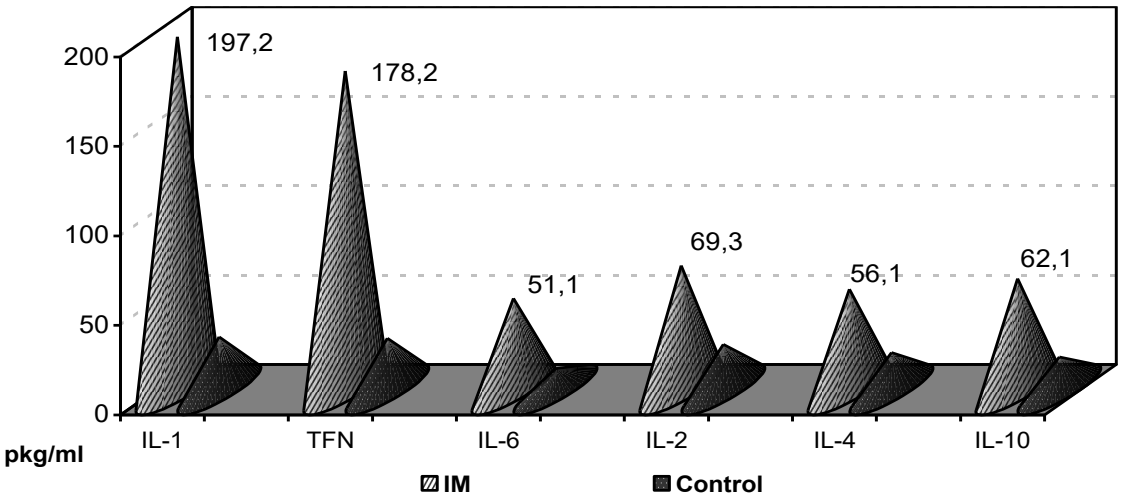


Fig. 2. Dissociative type of immune response in patients with IM

The presented results of the study with a hyperreactive type of immune response in patients with IM (Fig. 3) were characterized by reliably high levels of the studied parameters in comparison with similar parameters in patients with normoreactive type (on average in 1,5–2 times) and control group data (on average in 8–10 times) ($p < 0.05$). This type was detected in 22,5 % (9 patients) with IM.

When comparing the severity and duration of the main clinical and biochemical indices in patients with IM with different types of immune response, we found some differences presented in Table 1.

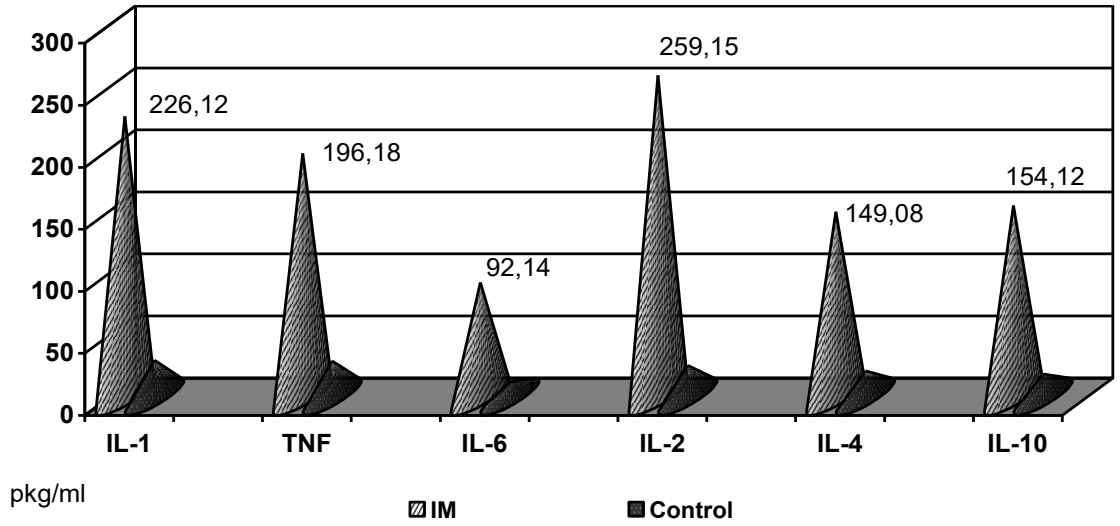


Fig. 3. Hyperreactive type of immune response in patients with IM

Table 1

The duration of individual clinical symptoms, depending on the type of immune response in patients with MI (n = 40)

Clinical symptoms	Duration of symptoms for different types of immune response (M ± m) days		
	Normoreactive type n = 17	Dissociative type n = 14	Hyperreactive type n = 9
General weakness	7,1 ± 1,3	9,9 ± 1,8 [1,2]	8,6 ± 1,2 [3]
Fever	8,4 ± 1,4	13,9 ± 2,1[1, 2]	10,9 ± 1,8 [3]
Headache	5,8 ± 1,7	6,4 ± 1,8	6,2 ± 1,3
Sleep disturbance	6,9 ± 1,4	8,2 ± 2,2	7,4 ± 1,5
Nausea	4,8 ± 1,7	5,7 ± 1,2	5,6 ± 1,3
Pain in the throat	5,4 ± 1,8	6,9 ± 1,7 [1]	6,2 ± 1,5
Lymphadenopathy	10,7 ± 1,2	18,9 ± 1,5 [1,2]	14,8 ± 1,1 [3]
Hepatolienal syndrome	9,5 ± 2,1	12,9 ± 1,8 [1,2]	10,8 ± 2,2
Bed-days	11,9 ± 1,8	15,9 ± 1,4 [1,2]	12,9 ± 1,7

Note: 1 – p < 0.05 between normoreactive and dissociative types of immune response; 2 – p < 0.05 between dissociative and hyperreactive types of immune response; 3 – p < 0,05 between normoreactive and hyperreactive types of immune response.

As can be seen from the presented data, in patients with IM with established normoreactive type of immune response, the main clinical symptoms were characterized by a shorter duration than in the patients with dissociative type and hyperreactive type against the background of antiviral therapy.

Thus, the general weakness in patients with dissociative type of immune response lasted 9,9 ± 1,8 days, whereas in patients with normoreactive and hyperreactive type – 7,1 ± 1,3 and 8,6 ± 1,2 days, respectively ($p < 0.05$). The duration of the fever was also longer in patients with a dissociative type of immune response – 13,9 ± 2,1 compared with the rates of patients with normoreactive and hyperreactive type – 8,4 ± 1,4 and 10,9 ± 1,8 days, respectively ($p < 0.05$). The duration of intoxication symptoms in the form of headache, sleep disturbances and nausea was not statistically significant between groups ($p > 0.05$). The presence of pain in the throat was more prolonged in patients with dissociative type of immune response 6,9 ±

1,7 days ($p < 0.05$) compared with those of patients with normoreactive and hyperreactive type – 5,4 ± 1,8 and 6,2 ± 1,5 days, respectively. Significant differences were also observed in the duration of lymphadenopathy in patients with a dissociative type of immune response of 18,9 ± 1,5 days ($p < 0.05$) compared with the data of the 1st and 3rd groups, with the groups also differing among the groups reliability. The duration of hepatolienal syndrome was significantly higher with a dissociative type of immune response – 12,9 ± 1,8 days ($p < 0.05$), compared with other groups. The length of stay of patients with MI on inpatient treatment also was longer in patients with dissociative type of immune response – 15,9 ± 1,4 days ($p < 0.05$), compared to similar data of patients with normoreactive and hyperreactive type – 11,9 ± 1,8 and 12,9 ± 1,7 days, respectively.

Levels of concentrations of the studied parameters in patients with chronic forms of EBV infection are presented in Fig. 4 and 5.

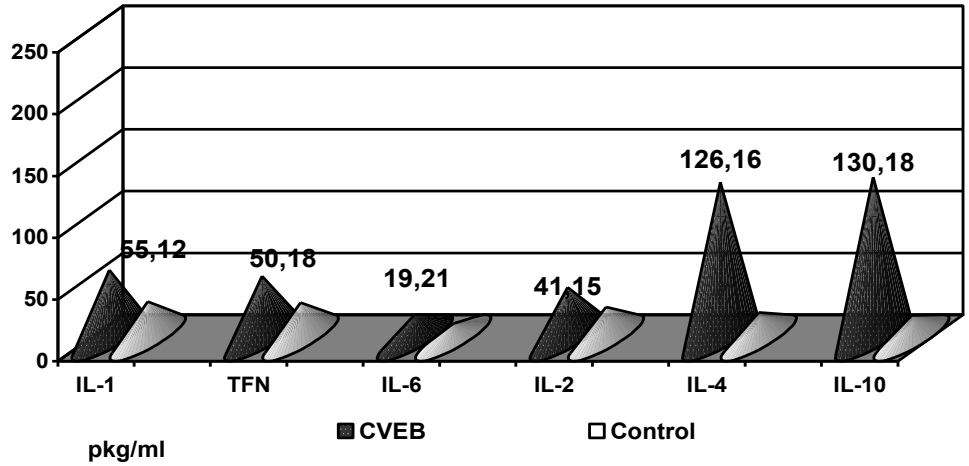


Fig. 4. Dissociative type of immune response in patients with HVEB infection

Thus, in patients with a dissociative type of immune response, low production of pro-inflammatory cytokines and regulatory IL-2 was observed, whereas levels of anti-inflammatory IL-4 and IL-10 significantly increased in accordance with the activity of the process. The level of IL-4 exceeded in 5.7 times the parameters of the control group, and IL-10 was 6 times higher than the mean values of the control group ($p < 0.05$).

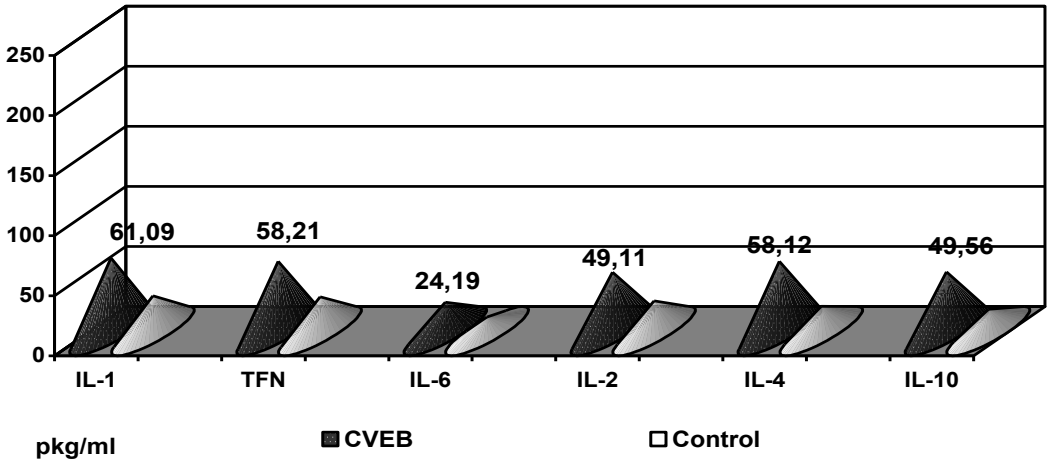


Fig.5. Hypoactive type of immune response in patients with HVEB infection

Among the patients with HVEB with the revealed hyporeactive type of immune response, the synthesis of proinflammatory and anti-inflammatory cytokines was characterized by low concentrations, the indices were practically within the values of the control group and did not differ statistically ($p > 0.05$).

The established types of immune response to the clinical course of HVEB are given in Table. 2.

Table 2

The duration of the main clinical symptoms, depending on the type of immune response in patients with HVEB (n = 80)

Clinical symptoms	Duration of symptoms for different types of immune response (M ± m) days	
	Hyporeactive type n = 33	**Dissociative type n = 47**
General weakness	5,6 ± 1,2	10,1 ± 1,3*
Arthralgia, myalgia	4,6 ± 0,9	8,9 ± 1,0*
Lymphadenopathy	4,8 ± 1,1	9,7 ± 1,2*
Subfebrile condition	5,9 ± 1,8	10,4 ± 1,4*
Hepatolienal syndrome	18,8 ± 2,2	26,5 ± 2,0*

*Note: * - p <0.05 between the hypotreactive and dissociative type of immune response.*

As can be seen from the presented data, in patients with HVEB with established hyporeactive type of immune response, the main clinical symptoms were characterized by a shorter duration than in the patients with a dissociative type against the background of antiviral therapy.

Thus, the general weakness in patients with a dissociative type of immune response lasted 10,1 ± 1,3 days, whereas in patients with a hyporeactive type it was 5,6 ± 1,2 days, respectively ($p < 0.05$). The phenomena of arthralgia and myalgia were also less pronounced in a group of patients with a hyporeactive type of immune response and were 4,6 ± 0,9 and 8,9 ± 1,0 days, respectively. The duration of peripheral lymphadenopathy was also lower in patients with a hyporeactive type of immune response: 4,8 ± 1,1, compared with data in patients with dissociative type 9,7 ± 1,2 ($p < 0.05$). The subfebrile condition was significantly shorter in patients with a hyporeactive type of immune response (5,9 ± 1,8 days) than in the dissociative type (10,4 ± 1,4 days), ($p < 0.05$). Hepatolienal syndrome was the longest clinical symptom in HVEB patients with both hyporeactive (18,8 ± 2,2 days) and dissociative (26,5 ± 2,0 days) immune response ($p < 0.05$).

Despite the significant achievements of modern medicine, many questions about the nature of the cytokine-producing ability of immunocompetent cells and their immunopathogenetic characteristics in HVEB infection are still unclear, and the literature data do not contain unambiguousness and sufficient justification.

Studies of recent years [5–7] found that the cytokine spectrum in VEB infection depends on the balance of the immune response of the body. Most researchers agree that the predominant participation of cytokines produced by Th-2 lymphocytes is associated with viral persistence and process chronization, and Th-1 with spontaneous recovery and elimination of the pathogen.

We found that in patients with VEB four types of immune response are observed: normoreactive, dissociative, hyporeactive and hyperreactive. These types of immune response testify to inadequate cellular-humoral reactivity of the organism in conditions of long-term persistence of EBV, which is manifested by a tendency to suppress cell-mediated and enhancing humoral mechanisms of the immune response and is reflected in the clinical and biochemical manifestations of the disease and leads to a protracted undulating course of the disease.

CONCLUSIONS

In patients with different forms of EBV infection, there is a significant cytokine imbalance. In patients with VEB, four types

of immune response are observed: I – normoreactive type (significant increase in proinflammatory and anti-inflammatory cytokines); II – dissociative (high proinflammatory cytokines against low values of regulatory IL-2 and anti-inflammatory cytokines); III – hyporeactive (low concentrations both pro-inflammatory and anti-inflammatory cytokines) and IV – hyperreactive (high concentrations of both pro-inflammatory and anti-inflammatory cytokines). The established types of immune response testify to the inadequate cellular-humoral reactivity of the organism under conditions of prolonged persistence of EBV, which is manifested by a tendency to suppress cell-mediated and amplified humoral mechanisms of the immune response and is reflected in the clinical and biochemical manifestations of the disease and leads to a protracted undulating course of the disease.

PROSPECTS FOR FUTURE STUDIES

Interesting and promising are the studies aimed at drug correction of the revealed disorders with established types of immune response in patients with HVEB and studying the influence of the latter on the outcomes of the disease, the development of complications and the activity of the process, which will be the subject for our further study.

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THE EFFECTIVENESS OF CHRONOTHERAPY IN HYPERTENSIVE PATIENTS WITH AN INSUFFICIENT DEGREE OF SLEEP-TIME SYSTOLIC BLOOD PRESSURE DECLINE

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Blood pressure (BP) circadian rhythm violation, manifested as an insufficient degree of its sleep-time relative decline, is an independent cardiovascular risk factor. The main method of the correction is chronotherapeutic approach, when at least one antihypertensive drug is taken at bedtime. However, most researchers focus on normalizing the daily profile of systolic blood pressure (SBP) and do not pay enough attention to changes in the daily profile of diastolic blood pressure (DBP) and blood pressure in general. The aim of the study was to evaluate the influence of the chronotherapeutic approach on the SBP and DBP levels and the DBP daily profile in hypertensive patients with an insufficient degree of sleep-time relative SBP decline. The study included 12 patients with arterial hypertension (AH) with an insufficient degree of sleep-time relative SBP decline. Participants were divided into two groups: group 1 included patients who take at least one antihypertensive drug at bedtime, group 2 – patients who take all antihypertensive drugs in the morning. All patients underwent 24-hour blood pressure monitoring using the computer system «Cardiosens» (KhAI Medica, Ukraine, with the oscillometric method of BP measuring) when enrolling in the study and after 3 months. The type of SBP and DBP diurnal profile, the mean values of SBP, DBP and hyperbaric indices were determined and compared between groups 1 and 2 at each visit, as well as within groups between visits. The results showed that the SBP daily profile normalization in patients with insufficient degree of sleep-time relative SBP decline from group 2 was achieved only in 11 % of cases, and in group 1 SBP and DBP daily profile normalized in 1/3 patients. In some patients from group 2 SBP and DBP daily profile converted into the overdipper type, while in group 1 overdippers did not appear at the end of the study. It was concluded that conversion of daily DBP profile to overdipper as a consequence of bedtime drug administration requires a review of the accepted treatment strategy.

KEY WORDS: arterial hypertension, chronotherapy, daily blood pressure profile, nondipper

ЕФЕКТИВНІСТЬ ХРОНОТЕРАПИИ ГІПЕРТОНІЧНОЇ ХВОРОБИ У ПАЦІЄНТІВ З НЕДОСТАТНІМ СТУПЕНЕМ НІЧНОГО ЗНИЖЕННЯ СИСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ

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Порушення добового ритму артеріального тиску (АТ), що проявляється у недостатній мірі його нічного зниження, є незалежним чинником ризику серцево-судинних захворювань. Основним методом його корекції є хронотерапевтичний підхід, коли хоча б один антигіпертензивний препарат призначається на ніч. Однак більшість дослідників фокусуються на нормалізації добового профілю систолічного артеріального тиску (САТ) і не приділяють достатньої уваги змінам добового профілю діастолічного АТ (ДАТ) і АТ в цілому. Метою дослідження було оцінити вплив хронотерапевтичного підходу на рівень САТ і ДАТ та добовий профіль ДАТ у пацієнтів з гіпертонічною хворобою (ГХ) з недостатнім ступенем нічного зниження САТ. У дослідження увійшли 12 хворих на ГХ з недостатнім ступенем нічного зниження САТ. Учасники були розділені на дві групи: до групи 1 увійшли пацієнти, що приймають хоча б один гіпотензивний препарат на ніч, в групу 2 – пацієнти, що приймають все гіпотензивні препарати вранці. Всім пацієнтам проводилося добове моніторування АТ з використанням комп'ютерної системи «Кардіосенс» (ХАІ Медика, Україна, з осцилометричним методом вимірювання АТ) на початку дослідження та через 3 міс. Визначали тип добового профілю САТ і ДАТ, середні значення САТ, ДАТ та показників навантаження підвищеним тиском і порівнювали між собою в групах 1 та 2 на кожному візиті, а також всередині груп між візитами. Результати показали, що нормалізація добового профілю САТ у пацієнтів з недостатнім ступенем його нічного зниження з групи 2 було досягнуто лише в 11 % випадків, а в групі 1 добовий профіль САТ і ДАТ нормалізувався у 1/3 пацієнтів. В групі 2 у частині пацієнтів добовий профіль САТ і ДАТ

перейшов в тип овердіпер, в той час як в групі 1 овердіперів по закінченню дослідження не виявилося. Зроблено висновки, що зміна типу добового профілю ДАТ на овердіпер як наслідок призначення гіпотензивних на ніч вимагає перегляду прийнятої лікувальної стратегії.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, хронотерапія, добовий профіль артеріального тиску, нондіпер

ЭФФЕКТИВНОСТЬ ХРОНОТЕРАПИИ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ У ПАЦИЕНТОВ С НЕДОСТАТОЧНОЙ СТЕПЕНЬЮ НОЧНОГО СНИЖЕНИЯ СИСТОЛИЧЕСКОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ

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Нарушение суточного ритма артериального давления (АД), проявляющееся в недостаточной степени его ночного снижения, является независимым фактором риска сердечно-сосудистых заболеваний. Основным методом его коррекции является хронотерапевтический подход, когда хотя бы один антигипертензивный препарат назначается на ночь. Однако большинство исследователей фокусируются на нормализации суточного профиля систолического АД (САД) и не уделяют достаточного внимания изменениям суточного профиля диастолического АД (ДАД) и АД в целом. Целью исследования было оценить влияние хронотерапевтического подхода на уровень САД и ДАД и суточный профиль ДАД у пациентов с гипертонической болезнью (ГБ) с недостаточной степенью ночного снижения САД. В исследование вошли 12 больных ГБ с недостаточной степенью ночного снижения САД. Участники были разделены на две группы: в группу 1 вошли пациенты, принимающие хотя бы один гипотензивный препарат на ночь, в группу 2 – пациенты, принимающие все гипотензивные препараты утром. Всем пациентам проводилось суточное мониторирование АД с использованием компьютерной системы «Кардиосенс» (ХАИ Медика, Украина, с осцилло-метрическим методом измерения АД) при включении в исследование и через 3 мес. Определяли тип суточного профиля САД и ДАД, средние значения САД, ДАД и показателей нагрузки повышенным давлением и сравнивали между собой в группах 1 и 2 на каждом визите, а также внутри групп между визитами. Результаты показали, что нормализация суточного профиля САД у пациентов с недостаточной степенью его ночного снижения из группы 2 была достигнута лишь в 11 % случаев, а в группе 1 суточный профиль САД и ДАД нормализовался у 1/3 пациентов. В группе 2 у части пациентов суточный профиль САД и ДАД перешёл в тип овердиппер, в то время как в группе 1 овердипперов по окончанию исследования не оказалось. Сделаны выводы, что изменение типа суточного профиля ДАД на овердиппер как следствие назначения гипотензивных препаратов на ночь требует пересмотра принятой лечебной стратегии.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, хронотерапия, суточный профиль артериального давления, нондиппер

INTRODUCTION

With the introduction of ambulatory blood pressure monitoring (ABPM) into clinical practice, the daily variability of blood pressure (BP) and its changes become important in the management of patients with arterial hypertension (AH) [1–3]. The BP circadian rhythm is considered normal, when its daily values exceed the night ones by 10–20 % [4].

In 1988, O'Brien and co-authors first showed that the violation of the BP circadian rhythm, manifested in an insufficient degree of its nightly decline, increases the risk of stroke in patients with AH [5]. This type of BP profile was called «nondipper». Further studies conducted in this direction confirmed that an insufficient reduction in systolic BP (SBP) at night is an independent risk factor for cardiovascular diseases [3]. According to the data of different authors, the frequency of occurrence the «nondipper» type of BP profile among patients with AH is about 50 % [6–7].

The main method of correction of this circadian rhythm disruption is the chronotherapeutic approach, when at least one antihypertensive drug in a full daily dose is prescribed at bedtime [8]. It is believed that the shift of the intake of antihypertensive drugs of all major groups from morning to evening time allows restoring the normal daily BP rhythm in 30–60 % of «nondippers» according to the data of different authors [8–9]. However, most researchers focus on the normalization of SBP daily profile and do not pay enough

attention to changes in diastolic blood pressure profile [9].

OBJECTIVE

To assess the impact of the chrono-therapeutic approach on the level of SBP and ВИЗ daily profile in patients with AH with insufficient degree of sleep-time relative SBP decline.

MATERIALS AND METHODS

The research was carried out within the framework of the research work «Pharmacological and interventional approaches to the treatment of patients with cardiac arrhythmias, arterial hypertension», state registration number 0116U000973.

In the settings of the outpatient clinic № 24 in Kharkiv, 44 patients with AH aged from 41 to 78 years were examined. For further analysis, patients with an insufficient degree of sleep-time relative SBP decline (< 10 %) according to ABPM were selected.

The study included 12 people with the «nondipper» type of SBP daily profile – 7 women (58 %) and 5 men (42 %). The first stage of AH was diagnosed in 1 patient (8 %), the second – in 8 (67 %), the third – in 3 (25 %). The first degree of AH was diagnosed in 7 patients (58 %), the second – in 2 (17 %). Three patients (25 %) had controlled AH, with preserving the target values of SBP and DBP throughout the 24 hours. Nocturnal hypertension was diagnosed in 9 cases (75 %).

Participants were divided into two groups. Group 1 included 3 patients (25 %) taking at least one antihypertensive drug at bedtime, group 2 included 9 patients (75 %) taking all antihypertensive drugs in the morning. To achieve target BP levels, patients, if necessary, underwent correction of antihypertensive therapy – increasing the dose, replacing or adding drugs. The regimen of antihypertensive drugs intake was not changed.

Exclusion criteria were secondary arterial hypertension, hemodynamically significant valvular heart disease, cardiomyopathy of any origin, chronic heart failure of III clinical stage or IV functional class by NYHA, any acute conditions (infections, trauma, operations) during the previous 3 months, chronic diseases in decompensated stage or exacerbation, oncological diseases, as well as any circumstances that make it difficult to perform ABPM.

All patients underwent ABPM when included in the study – 1 visit, and after 3 months – 2 visit. The monitoring was carried out using the computer system «Cardiosens» (KhAI Medica, Ukraine) with an oscillometric method of BP measurement. The monitoring was performed in the conditions of a typical patient day, with the preservation of domestic physical and psychoemotional loads. The cuff was placed on the non-dominant hand. According to Ambulatory Blood Pressure Monitoring International Recommendations 2013 [4], BP was measured with an interval of 15 minutes during the period of awake and 30 minutes during the sleep time. Periods of the day and night was defined on the basis of the patient's diary. When assessing ABPM data, in accordance with Ambulatory Blood Pressure Monitoring International Recommendations 2013 [4], manual data extraction was performed – the following measurements were excluded from the analysis: SBP > 250 or < 70 mm Hg; DBP > 150 or < 40 mm Hg; pulse pressure > 150 or < 20 mm Hg; heart rate > 200 or < 20 per minute.

The results of ABPM were excluded from analysis in the following cases: ≥ 30 % of invalid measurements; absence of BP measurements for 2 hours or more; unusual for the patient daily activity during monitoring; a night sleep period of less than 6 or more than 12 hours [4].

The degree of relative sleep-time BP decline was calculated using the formula: *(100 × [mean daily BP – mean BP] / mean daily BP)*.

Depending on the value of this ration the following types of daily BP profile were defined: «dipper» - physiological decrease in BP during the night – sleep-time relative BP decline 10–20 %; «overdipper» – an excessive fall in BP at night, sleep-time relative BP decline > 20 %; «nondipper» – the lack of BP reduction at night, sleep-time relative BP decline < 10 %; «night-peaker» - night-time BP more than during daily activity, sleep-time relative BP decline < 0 [4].

The mean values of SBP, DBP and hyperbaric indices for SBP and DBP were determined for 24 hours and periods of day and night and compared in groups 1 and 2 at each visit, as well as within groups between visits.

For each ABPM parameter the arithmetic mean (M), the median (Me), and the standard deviation (Sd) were determined. Proportions of

types of the daily BP profile were determined in percent (P).

A comparison of the data obtained in groups 1 and 2 at each stage of the study was performed using the unpaired Student's t-test for parameters with normal distribution and the Mann-Whitney U-test for free-distributed parameters. Comparison of data obtained at the beginning and at the end of the study in groups 1 and 2, and in general for all enrolled patients was performed using paired Student's t-test for parameters with normal distribution and Wilcoxon signed-rank test for parameters with a free distribution. To compare the proportions the angular transformation method with F-test was used.

RESULTS AND DISCUSSION

At the first visit, the mean sleep-time values of SBP and DBP exceeded the recommended threshold levels in both groups (Table 1), as well as the 24-h SBP mean in group 2 and 24-h DBP mean in group 1. The awake means of SBP and DBP remained within the normal range in both groups. The values of pulse pressure (PP) exceeded the recommended levels in both groups during all monitoring periods. The awake, sleep-time and daily mean values of the SBP and DBP time index (TI) were higher than normal in both groups, and all of them in both groups were higher at night than in daytime. The mean values of SBP and DBP hyperbaric index (HBI) exceeded recommended values during all monitoring periods in both groups.

It was noteworthy that the mean values of SBP, PP and SBP hyperbaric indices during all monitoring periods were higher in group 2, but mean values of DBP and DBP hyperbaric indices – in group 1.

The mean values of SBP and DBP sleep-time relative BP decline did not exceed 10 % in both groups, but were mostly reduced in group 2– both for SBP and DBP.

When comparing the studied indices of ABPM in the awake, sleep-time and 24-h periods no significant differences between the groups were seen (Table 1).

Table 1

ABPM indices in groups 1 and 2, visit 1

Monitoring periods	ABPM indices	Patients groups					
		group 1, n = 3			group 2, n = 9		
		M	Me	Sd	M	Me	Sd
24 hours	SBP, mm Hg	130	129	11.5	132	130	12.3
	DBP, mm Hg	81	83	7.2	75	73	9.7
	PP, mm Hg	49	46	9.5	56	57	7.0
	SBP TI, %	45	42	29.1	52	48	27.1
	DBP TI, %	44	46	28.5	29	29	22.0
	SBP HBI, mm Hg / h	134	89	143.0	178	146	149.8
	DBP HBI, mm Hg / h	97	109	84.1	68	51	63.4
Awake	SBP, mm Hg	131	130	12.1	133	128	12.8
	DBP, mm Hg	82	84	6.7	77	73	10.4
	PP, mm Hg	49	45	9.6	56	55	8.4
	SBP TI, %	40	31	31.6	45	29	30.5
	DBP TI, %	40	44	28.1	24	31	25.2
	SBP HBI, mm Hg / h	73	25	95.5	98	8	104.3
	DBP HBI, mm Hg / h	47	61	37.2	36	13	42.4
Sleep- time	SBP, mm Hg	126	126	10.0	129	131	11.2
	DBP, mm Hg	76	77	7.1	71	72	8.1
	PP, mm Hg	51	48	8.3	58	60	6.2
	SBP TI, %	53	61	27.0	65	65	29.1
	DBP TI, %	51	49	29.2	45	60	27.6
	SBP HBI, mm Hg / h	60	64	52.0	80	73	63.7
	DBP HBI, mm Hg / h	50	48	48.2	31	28	24.3
Sleep-time relative SBP decline,%		4	3	1.1	3	5	5.5
Sleep-time relative DBP decline,%		9	9	1.0	7	11	7.4

Notes: M – mean value, Me - median, Sd – standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, PP – pulse pressure, TI – time index, HBI – hyperbaric index

In group 1, all patients had a daily DBP profile nondipper. In group 2, frequencies of the daily DBP profiles dipper and nondipper were approximately the same. The overdipper daily profile at the first visit was not met in any of the groups (Table 3).

After 3 months all patients underwent repeated ABPM. Overall, we achieved a reduction of all ABPM parameters the target values of SBP and DBP for all monitoring periods, except sleep-time DBP values, which have been reduced, but did not normalize. Statistically significant differences at the level of $p < 0.05$ were achieved for awake, sleep-time and 24-h means of DBP, sleep-time SBP means and DBP HBI. Sleep-time relative SBP and DBP decline has improved as compared with the initial data, but they are still did not exceed 10 % (Table. 2).

Table 2

Comparison of the main ABPM indices at visits 1 and 2

Monitoring periods	ABPM indices	Visits					
		visit 1, n = 12			visit 2, n = 12		
		M	Me	Sd	M	Me	Sd
24 hours	SBP, mm Hg	131	130	11.6	128	127	9.2
	DBP, mm Hg	77	76	9.2	74 *	75	7.4
	PP, mm Hg	55	56	7.9	54	54	6.5
	SBP TI, %	50	45	26.4	42	38	25.8
	DBP TI, %	33	33	23.3	27	22	23.4
	SBP HBI, mm Hg / h	167	118	143.0	112	116	78.3
	DBP HBI, mm Hg / h	75	59	66.3	51	30	51.4
Awake	SBP, mm Hg	133	129	12.1	130	129	10.0
	DBP, mm Hg	78	79	9.7	75 *	76	7.8
	PP, mm Hg	54	55	8.9	54	54	7.9
	SBP TI, %	43	30	29.4	38	25	30.3
	DBP TI, %	28	23	25.7	23	19	20.8
	SBP HBI, mm Hg / h	92	29	98.5	58	30	58.7
	DBP HBI, mm Hg / h	39	26	39.8	27	20	23.7
Sleep- time	SBP, mm Hg	128	129	10.5	123 *	125	9.8
	DBP, mm Hg	72	73	7.9	68 *	67	8.4
	PP, mm Hg	56	57	7.2	54	53	6.4
	SBP TI, %	62	63	27.9	49	46	33.5
	DBP TI, %	47	54	26.7	41	35	36.7
	SBP HBI, mm Hg / h	75	69	59.3	54	60	45.8
	DBP HBI, mm Hg / h	36	38	30.4	25 *	8	32.2
Sleep-time relative SBP decline,%		3	4	4.7	5	6	8.2
Sleep-time relative DBP decline,%		8	10	6.4	9	11	8.9

*Notes: M – mean value, Me – median, Sd – standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, PP – pulse pressure, TI – time index, HBI – hyperbaric index; * p < 0.05*

At the second visit in group 1 daily and awake SBP and DBP target values were achieved, while sleep-time SBP and DBP means normalization was failed, and the average values of SBP over the night period did not change at all (tab. 4). Changes in the PP were insignificant – within 1–2 mm Hg. The hyperbaric indices decreased in comparison with the initial values, but did not restore to normal. A statistically significant decrease was achieved only for 24-h values of DBP TI at the level of $p < 0.05$. Awake mean values of SBP and DBP hyperbaric indices were able to decrease as close as possible to the recommended standards, and sleep-time DBP hyperbaric indices – to transfer to borderline values. The daily SBP and DBP profile succeeded to normalize in 1/3 patients (Table. 3).Mean values of sleep-time relative SBP and DBP decline decreased, to a greater extent for SBP (Table 4).

Table 3

BP daily profiles in groups 1 and 2 at the 2nd visit

Type of daily BP profile		Patients groups			
		group 1, n = 3		group 2, n = 9	
		visit 1	*visit 2*	*visit 1*	*visit 2*
SBP	**dipper**	-	33 %	-	11 %
	nondipper	100 %	67 %	100 %	78 %
	night-picker				
	overdipper	-	-	-	11 %
DBP	**dipper**	-	33 %	56 %	56 %
	nondipper	100 %	67 %	44 %	33 %
	night-picker				
	overdipper	-	-	-	11 %

Table 4

ABPM indices in groups 1 and 2, visit 2

Monitoring periods	ABPM indices	Patients groups					
		group 1, n = 3			group 2, n = 9		
		M	**Me**	**Sd**	**M**	**Me**	**Sd**
24 hours	**SBP, mm Hg**	126	127	1,2	129	131	10,7
	DBP, mm Hg	78	76	4.0	73^{i}	73	7.9
	PP, mm Hg	48	49	3,6	57*	55	5,8
	SBP TI, %	29	78	15,1	47	49	27,9
	DBP TI, %	34$^{\bullet}$	38	29,5	25	22	22,5
	SBP HBI, mm Hg / h	78	37	58,1	124	128	83,7
	DBP HBI, mm Hg / h	67	107	66,9	46	28	49,0
Awake	**SBP, mm Hg**	126	58	2,5	131	130	11,3
	DBP, mm Hg	80	126	3,8	74^{i}	74	8,4
	PP, mm Hg	47	47	4,5	57*	55	7,2
	SBP TI, %	17	16	3,2	45	46	32,4
	DBP TI, %	25	27	22,0	22	14	21,8
	SBP HBI, mm Hg / h	19	19	9,1	71	35	62,9
	DBP HBI, mm Hg / h	27	28	25,3	26	19	24,7
Sleep- time	**SBP, mm Hg**	126	129	8,5	122^{i}	121	10,5
	DBP, mm Hg	74	71	8,3	66	65	8.0
	PP, mm Hg	52	49	5,2	55	53	6,8
	SBP TI, %	51	67	40,7	48	43	33,6
	DBP TI, %	49	52	44,0	38	12	36,4
	SBP HBI, mm Hg / h	60	88	49,8	53	36	47,4
	DBP HBI, mm Hg / h	39	30	42,0	20	2	29,6
Sleep-time relative SBP decline, %		1	- 4	8,5	7	6	7,9
Sleep-time relative DBP decline, %		8	8	6,8	10	11	9,8

*Notes: M – mean value, Me – median, Sd – standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, PP – pulse pressure, TI – time index, HBI – hyperbaric index; *p < 0,05 comparing groups 1 and 2 at visit 2, $^{\bullet}$p < 0,05 comparing visits 1 and 2 of group 1, p < 0,05 comparing visits 1 and 2 of group 2*

In group 2, at the second visit, it was possible to reduce and achieve the target values of SBP and DBP during all monitoring periods, except the mean sleep-time values of SBP. Concerning 24-h and awake values of DBP and sleep-time SBP values a statistically significant decrease was achieved at the level of $p < 0.05$. Mean sleep-time PP values decreased in comparison with baseline, but did not return to normal, but, on the contrary, daily and awake PP means increased, albeit insignificantly. Also, it was possible to reduce the hyperbaric indices. DBP TI and HBI, as well as SBP TI succeeded to transferee to the borderline values during all monitoring periods, but SBP HBI even decreased in comparison with the baseline, but remained high throughout the 24 hours (Table 4). The sleep-time relative SBP and DBP decline increased, and for DBP it was reached the level of 10 %, which already corresponds to the dipper type. The number of SBP non-dippers in group 2 decreased by 22 % and DBP non-dippers by 11 % (Table 3).

Thus, it was possible to achieve the target SBP and DBP 24-h and awake means in both groups, while sleep-time SBP and DBP mean values were failed to normalize in group 1. In group 2 the sleep-time SBP and DBP mean values decreased, although we achieved target values only for DBP (Table 4). A more pronounced decrease in sleep-time relative SBP and DBP decline was found in group 2. In group 1 the 24-h SBP values were reduced to a greater extend then in group 2.

It was notable the PP changes. In group 1, at the second visit, there was a PP decrease in daytime and an increase at night, in group 2, on the contrary, an increase in daytime and a decrease in night. When comparing the PP levels in groups 1 and 2 on the second visit, the differences were statistically significant at the level of $p < 0.05$ (Table 4). In general, in group 1, PP decreased compared to baseline, and in group 2 increased.

In group 2 at the second visit it was possible not only to reduce the main ABPM indices, but also to achieve lower values in comparison with group 1 (Table 4).

Sleep-time relative SBP and DBP decline succeeded to increase and made close to dipper profile only in group 2, while in group 1, on the contrary, it increased, aspiring to an even more unfavorable night-picker type of daily BP profile. Although normalization of the SBP and DBP daily profile was achieved in a larger proportion of patients in group 1, these differences were statistically insignificant (Table 3–4).

It is believed that in patients with AH, the administration of at least one antihypertensive drug at bedtime leads to more pronounced BP decrease at night and contributes to the daily profile normalization [8–9]. Hermida et al., 2005, 2007 [10–11] provide data on the daily SBP profile normalization in 75 % of patients with AH in those who takes drugs at bedtime. But it does not take into account that as a result of antihypertensive therapy DBP is also reduced, and this both BP indices are important in management and prognosis in patients with AH [12].

In our study, the normalization of SBP daily profile in patients with an insufficient sleep-time relative SBP decline from group 2 was achieved only in 11 % of cases. Patients of group 1 had better results – the daily profile of SBP and DBP was normalized in 1/3 of patients. Also, at the end of the study, it was found that in group 2 in a part of the patients the daily profile of both SBP and DBP converted to the overdipper type, while in the group 1 there were no overdippers at the end of the study.

In accordance with these results, the question of antihypertensive drugs administration at bedtime in hypertensive patients with SBP non-dipper profile should be considered open, since in some cases this leads not to normalization of the daily BP profile, but to its transition to the overdipper type.

The data obtained in our study show that the chronotherapeutic approach in management of patients with AH should not consist in the strict antihypertensive drugs administration at bedtime, but be based on a thorough evaluation of the patient's chronoprofile and the daily profile not only of the SBP, but the DBP also.

CONCLUSIONS

1. Hypotensive therapy in patients with AH with SBP nondipper profile irrespectively of the medication regimen leads not only to a decrease in BP, but also to the normalization of its daily profile.

2. The use of antihypertensive drugs at bedtime in such patients to a greater extent

reduces sleep-time BP, and morning administration – awake BP, and SBP daily profile normalization is better in patients, who takes antihypertensive drugs in the morning then at bedtime.

3. Transition of diurnal DBP profile into overdipper as a consequence of the bedtime antihypertensive drug administration requires revision of this treatment strategy.

PROSPECTS FOR FUTURE STUDIES

It seems advisable to study the administrating time effects on the daily DBP profile in hypertensive patients with an insufficient sleep-time relative DBP decline.

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ALLELE STATUS OF ALDOSTERONE SYNTHASE (CYP11B2) GENE POLYMORPHISM AND CARDIAC REMODELING AFTER ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

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Aldosterone plays an important role in the development of reparative and reactive fibrosis and cardiac remodeling (CR) after myocardial infarction. The objective of the study is to investigate the structural and functional parameters of the myocardium, heart rate variability (HRV), exercise intolerance, levels of sST2 in association with polymorphism of CYP11B2 gene of aldosterone-synthase in ST-myocardial infarction (STEMI) patients during a 6-months follow-up period. 85 STEMI patients were enrolled: 68 (80 %) male and 17 (20 %) female, mean age was 58,94 ± 10,16 years. Examinations were performed twice: during 1–3 days after PCI with infarct-related artery stenting and included clinical assessment, ultrasound diagnostic, immunofermentative blood analyses (sST2), polymerase chain reaction in real time (polymorphism –T344C of the CYP11B2 gene). After 6-months of observation, 57 patients were reexamined – clinical assessment, ultrasound diagnostic, HRV were performed. CYP11B2 TT-genotype in 6 months after STEMI is associated with a maladaptive character of after infarction remodeling.

KEY WORDS: STEMI, CYP11B2 gene polymorphism, cardiac remodeling

АЛЕЛЬНИЙ СТАТУС ПОЛІМОРФІЗМУ ГЕНА CYP11B2 АЛЬДОСТЕРОН-СИНТАЗИ ТА СЕРЦЕВЕ РЕМОДЕЛЮВАННЯ ПІСЛЯ ІНФАРКТУ МІОКАРДА З ЕЛЕВАЦІЄЮ СЕГМЕНТА ST

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Альдостерон відіграє важливу роль в розвитку репаративного та реактивного фіброзу та кардіального ремоделювання після інфаркту міокарда. Метою роботи стало визначити асоціації морфофункціональних та біохімічних показників з різними генотипами поліморфних варіантів гена CYP11B2 альдостерон-синтази в динаміці спостереження протягом 6 місяців. В дослідження включено 85 пацієнтів з ГІМпST, з них 68 (80 %) чоловіків та 17 (20 %) жінок, в середньому віці 58,94 ± 10,16 років. Дослідження проводилось двічі: протягом 1–3 дня після стентування інфаркт-залежної артерії та включало клінічну оцінку, ультразвукову діагностику, імуноферментний аналіз sST2, полімеразну ланцюгову реакцію поліморфізма –T344C гена CYP11B2. Через 6 місяців спостереження до клініки звернулось 57 пацієнтів, яким було проведено клінічну оцінку, ультразвукову діагностику, дослідження варіабельності серцевого ритму. Поліморфний генотип TT гена CYP11B2 асоціюється з мальадаптивним характером ремоделювання після інфаркту міокарда.

КЛЮЧОВІ СЛОВА: ГІМпST, поліморфізм гена CYP11B2 альдостерон-синтази, ремоделювання серця

АЛЛЕЛЬНИЙ СТАТУС ПОЛИМОРФИЗМА ГЕНА CYP11B2 АЛЬДОСТЕРОН-СИНТАЗЫ И РЕМОДЕЛИРОВАНИЕ СЕРДЦА ПОСЛЕ ИНФАРКТА МИОКАРДА С ЭЛЕВАЦИЕЙ СЕГМЕНТА ST

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Альдостерон играет важную роль в развитии репатативного и реактивного фиброза и ремоделирования сердца после инфаркта миокарда. Целью работы явилось определить ассоциации

морфофункциональных и биохимических показателей с различными генотипами полиморфных вариантов гена CYP11B2 альдостерон-синтазы в динамике наблюдения в течение 6 месяце. В исследование включено 85 пациентов с ОИМпST, из них 68 (80 %) мужчин и 17 (20 %) женщин, в среднем возрасте 58,94 ± 10,16 лет. Исследование проводилось дважды: в течение 1–3 дня после стентирования инфаркт-зависимой артерии, что включало клиническую оценку, ультразвуковую диагностику, иммуноферментный анализ sST2, полимеразную цепную реакцию полиморфизма –T344C гена CYP11B2. Через 6 месяцев наблюдения в клинику обратилось 57 пациентов, которым была проведена клиническая оценка состояния, ультразвуковую диагностику, исследование вариабельности сердечного ритма. Полиморфный генотип TT гена CYP11B2 ассоциируется с мальадаптивным характером ремоделирования после инфаркта миокарда.

КЛЮЧЕВЫЕ СЛОВА: ОИМпST, полиморфизм гена CYP11B2 альдостерон-синтазы, ремоделирование сердца

INTRODUCTION

Cardiac Remodeling (CR) is defined as a change in genes expression, molecules, cells, and interstitial which have a clinical manifestation in altering the size, shape and function of the heart after an injury [1]. Most of the geometric changes that have been formed during an early CR (less than 72 hours) were significantly limited by the area of the infarction and included stretching, spreading of the damaged zone and regional myocardial thinning. Whereas the late CR (more than 72 hours) involved myocardial stretching of the whole left ventricular (LV), including border zone infarcts, non-ischemic areas with subsequent hypertrophy, deformation of the LV shape and deterioration of systolic function [2].

Aldosterone plays an important role in the development of reparative and reactive fibrosis and CR in ST-segment elevation of myocardial infarction (STEMI) and after infarction cardiosclerosis [3–5]. There is convincing evidence about the local intracardiac formation of the hormone in acute myocardial infarction (AMI) and chronic heart failure (CHF) patients, along with the aldosterone synthesis activation by the adrenal glands and its flow into the bloodstream. Aldosterone is an inducer of inflammation in the vascular endothelium and perivascular zones of the myocardium. Aldosterone inhibits the release of NO, reduces expression of the vascular endothelial growth factor, causes proliferation of fibroblasts with the formation of collagen type I and type III and affects apoptosis that promotes interstitial myocardial fibrosis, its remodeling and dysfunction [4–6].

The relationship between aldosterone and sST2, which belongs to the IL-1 receptor family, was detected. sST2 blocks the cardioprotective effect of IL-33 and promotes the development of myocardial fibrosis [7–8].

The final stage of the aldosterone synthesis from desoxycorticosterone catalyzes the aldosterone synthase enzyme, whose primary structure is the CYP11B2 gene. In the literature association of the polymorphism of the promoter region of the aldosterone synthase gene CYP11B2 (–T344C) with cardiovascular risk is widely discussed.

The dynamics of morphofunctional changes in the myocardium in the acute period of STEMI and 6 months after the event, depending on the genotypes of polymorphous variants of the CYP11B2 gene TT, TC and CC have not been studied well [9]. One of the aldosterone properties is the ability to reduce baroreceptor's sensitivity, increase sympathetic and decrease parasympathetic activity [4]. The most informative method for a quantitative estimation of the cardiac autonomic regulation is the heart rate variability (HRV).

Decreased HRV as a background of significant increase in sympathetic and decrease of parasympathetic activities in AMI are important pathogenetic components of ventricular arrhythmias and arrhythmic death were shown in the North American groups' study [10].

In patients with after infarction cardiosclerosis, the deterioration of time and spectral analysis, sympathetic and parasympathetic imbalances became a prognostic factor in the risk of ventricular arrhythmias and sudden death [11–16]. Works devoted to the HRV study, depending on polymorphous variants TT, TC and CC of CYP11B2 gene were not found.

OBJECTIVE

To investigate the structural and functional parameters of the myocardium, HRV data, exercise intolerance, the different sST2 blood levels depending on the polymorphism of the aldosterone synthase gene CYP11B2 in STEMI patients during a 6-months follow-up period.

MATERIALS AND METHODS

In the Government institution «L. T. Malaya Therapy National Institute of the National Academy of Medical Science of Ukraine» 85 STEMI patients were enrolled in the first three days: 68 (80 %) male and 17 (20 %) female, mean age was 58, 94 ± 10, 16 years. The examination of all the patients with selective coronary angiography and stenting of the infarct-related artery were held in the Governmental institution of general and emergency surgery N.A. V. T. Zaitsev.

According to the European guidelines for the diagnostics and treatment of STEMI (2012) the diagnosis was established. The study protocol was confirmed by the Commission of Ethics and Deontology of the GI «L. T. Malaya Therapy National Institution of NAMS of Ukraine» in accordance with the thesis of the Helsinki Declaration, the study was performed. All patients had signed the informed consent.

The follow-up period was for 6 months and after that period 57 patients were examined again. All subjects have received standard therapy for 6 months. During the hospital period, 2,4 % patients died, after 6 months – 3,5 % patient.

End-diastolic (EDV), end-systolic (ESV) volume of left ventricle (LV), end-systolic (ESD) and end-diastolic (EDD) diameter of LV, LV myocardial mass (LV MM), LV ejection fraction (LV EF) (Simpson formula), and diastolic dysfunction has been determined as the maximal speed of early diastolic filling E (m/s), maximal velocity of atrial diastolic filling A (m/s), their E/A ratio were evaluated by ultrasound diagnostic.

With the Holter monitor «Cardio Sens «KhAI-Medica»» 6 months after the index event, HRV was investigated. The following data were evaluated: SDNN is the standard deviation of normal to normal R-R intervals, RMSSD the root mean square differences of successive R-R (heart beat) intervals, pNN50 is the proportion of NN50 divided by the total number of NN (R-R) intervals, TP is the total strength of the spectrum, ULF is an ultra-low-frequency component of HRV, VLF is the spectral strength in the very low-frequencies, LF is the power of low frequency oscillations, HF is the power of the spectrum of high-frequency oscillations, LF / HF – the ratio. To determine physical activity tolerance, all patients were given a six minute walk test.

Investigation of allele polymorphism –T344C of the CYP11B2 gene was performed by polymerase chain reaction in real time. The level of sST2 using the Presages ST2 Assay (Critical Diagnostics, USA) reagent enzyme immunoassay method was determined. The control group included 30 practically healthy persons; the average value of sST2 for those patients was 19.4 [15.9–29.1] ng/ml.

This work is the fragment of scientific research were done in the department of acute myocardial infarction of Government institution «L. T. Malaya Therapy National Institute of the National Academy of medical science of Ukraine»: «To investigate modern models of risk stratification and personification preventive measures of sudden cardiac death in patients after acute coronary syndrome», registration № 0114U001167, code: 02/14.

The study was planned as the only-case design. The statistical processing of the obtained data using the Statistica 8.0 software package (Statsoft Inc, USA), Microsoft Office Excel 2003 was performed. The data is presented as Median (Me), upper (UQ) and lower (LQ) quartile sampling. U-Criterion Mann Whitney to assess intergroup differences was used. A statistically significant difference was considered if P-value is lower than 0.05.

RESULTS AND DISCUSSION

The analysis of the alleles and genotypes distribution of the CYP11B2 aldosterone synthase gene shows the following frequencies of T and C alleles in patients with STEMI – 52 % and 48 %, the frequency of homozygous TT, heterozygous TC and homozygous CC – n = 22 (25,9 %), n = 46 (54,1 %) and n = 17 (20 %), respectively. The observed frequency of genotypes was in Hardy-Weinberg equilibrium ($X^2 = 0,63$; $p > 0,05$).

Characteristics of myocardial infarction depending on genotypes of polymorphic variants-T344C of the aldosterone synthase CYP11B2 gene are presented in Table 1.

Table 1

Clinic-instrumental characteristic of myocardial infarction of researched patients depending on polymorphous variants -T344C of the CYP11B2 gene aldosterone synthase

Data	TT N 22 (25,9 %)	TC N 46 (54,1 %)	CC N 17 (20 %)	χ^2 P_{1-2}, P_{1-3}, P_{2-3}
Complicated STEMI	8 (36,4 %)	16 (37,8 %)	6 (35,3 %)	0,02 p = 0,89 0,07 p = 0,79 0,07 p = 0,79
Anamnesis of MI	1 (4,5 %)	4 (8,6 %)	3 (17,6 %)	0,43 p = 0,46 0,73 p = 0,20 0,30 p = 0,28
Anterior STEMI	15 (68,2 %)	26 (56,2 %)26	11 (64,7 %)11	0,85 p = 0,36 0,01 p = 0,91 0,34 p = 0,56
Posterior STEMI	7 (31,8 %)	20 (43,5 %)	6 (35,3 %)	0,43 p = 0,51 0,01 p = 0,91 0,09 p = 0,77
Data of selective coronaroangiography				
1 CA>50%	6 (27,3 %)	8 (17,4 %)	3 (17,6 %)	0,39 p = 0,53 0,11 p = 0,75 0,12 p = 0,73
2 CA>50%	2 (9,1 %)	7 (15,2 %)	5 (29,4 %)	0,10 p = 0,75 1,49 p = 0,22 0,83 p = 0,36
3 CA>50%	2 (9,1 %)	8 (17,4 %)	1 (5,9 %)	0,29 p = 0,59 0,05 p = 0,82 0,57 p = 0,45
Types of coronary flow				
Right	11 (50 %)	17(40 %)	9 (52,9 %)	1,05 p = 0,31 0,02 p = 0,89 0,73 p = 0,39
Left	1 (4,5 %)	4 (8,7 %)	3 (17,6 %)	0,01 p = 0,91 0,65 p = 0,42 0,30 p = 0,58
Balanced	1 (4,5 %)	1 (2,2 %)	2 (11,8 %)	0,05 p = 0,82 0,05 p = 0,82 0,85 p = 0,36

Regarding to table 1, all patients with STEMI were compatible above coronary atherosclerosis but significant differences had not observed.

The changes in the morphofunctional state of the LV, which occurred within 6 months after STEMI, depending on genotypes of polymorphic variants-T344C of the aldosterone synthase CYP11B2 gene, are presented in Table 2.

Table 2

Dynamics of morphofunctional myocardial changes 6 months after STEMI depending on polymorphous variants -T344C of the CYP11B2 gene aldosterone synthase

Parameters		TT	TC	CC
LV EDV, ml	1	124,00 [96,00-144,00]	118,00 [103,00-159,00]	118,00 [107,00-144,00]
	2	155,60 [133,00-182,00]	135,00 [96,00-182,00]	143,50 [120,00-176,00]
	P	0,030	0,668	0,074
LV ESV, ml	1	63,00 [44,00-67,00]	58,00 [45,00-92,00]	60,00 [50,00-79,00]
	2	61,00 [56,00-90,00]	55,00 [42,00-75,00]	58,00 [43,00-82,00]
	P	0,526	0,851	0,827
LV EDD, sm	1	5,00 [4,60-5,40]	5,16 [4,90-5,60]	5,15 [4,70-5,40]
	2	5,42 [5,02-5,70]	5,25 [4,65-6,00]	5,30 [5,10-5,90]
	P	0,033	0,645	0,120
LV ESD, sm	1	3,70 [3,30-4,00]	3,70 [3,23-4,05]	3,59 [3,20-4,22]
	2	3,80 [3,60-4,00]	3,60 [3,20-4,10]	3,80 [3,20-4,30]
	P	0,483	0,869	0,580
Left atrium, sm	1	3,98 [3,70-4,30]	4,27 [3,87-4,70]	4,30 [3,80-4,60]
	2	3,80 [3,60-4,20]	4,30 [3,80-4,70]	4,00 [3,70-4,20]
	P	0,479	0,762	0,193
EF, %	1	50,65 [46,00-55,00]	54,00 [47,00-58,00]	51,00 [48,00-54,00]
	2	53,50 [49,00-60,00]	56,50 [47,50-60,50]	57,00 [52,00-59,00]
	P	0,309	0,311	0,078
E/A	1	1,13 [0,66-1,20]	1,00 [0,75-1,40]	1,15 [0,50-1,40]
	2	0,85 [0,65-1,10]	1,20 [1,00-1,67]	1,00 [0,80-1,45]
	P	0,049	0,329	0,563
LV MM, g	1	242,50 [198,50-258,50]	258,50 [201,00-300,50]	246,00 [205,00-292,50]
	2	269,00 [234,00-305,00]	219,50 [160,00-265,50]	229,00 [170,30-231,00]
	P	0,046	0,095	0,089
Mitral valve regurgitation, stage 1–2	1	22,7%	8,7%	17,6%
	2	45,5%	4,3%	5,9%
sST2, ng/ml	1	40,73 [30,69-55,41]	51,47 [33,64-122,17]	44,93 [35,68-115,58]
	2	34,52 [25,86-35,49]	32,96 [24,78-42-58]	25,07 [21,37-40,20]
		0,11	0,004	0,052

Note: 1 – hospital period of STEMI, 2 – 6 month after STEMI

Comparison of the cardiac hemodynamics parameters during the hospital period and 6 months after the event, depending on the polymorphous variants of the CYP11B2 (–T344C) gene, shows the following tendency of the course of LV CR: the

significant increase of LV EDV in patients with TT genotype in 6 months after STEMI (p = 0,030), a tendency for increase of LV EDV in CC homozygote (p = 0,074), for heterozygous TC there was no significant increase of the parameter (p = 0,668). A significant increase in LV EDD in the group with the genotype TT was observed (p = 0,033), the variance of TC and CC showed no significant changes. There was the statistical tendency to LV EF increase in patients with CC genotype (p = 0,078). In the groups of patients with heterozygote TC and homozygous TT, the level of LV EF increased nonsignificant.

The increase of the LV MM has occurred in the group with the TT genotype, unlike the variants of the TC and CC, there was a tendency to its reduction. The E/A ratio has been compared, its significant decrease in patients with polymorphous variant TT was observed (p = 0,049), in patients with TC and CC variants, E/A values remained within the normal limits. The number of patients with mitral valve deficiency whose genotype was TT has been increased twice, while in patients with variants of TC and CC genotypes frequency of occurrence of mitral regurgitation was rare. There are no significant changes in LV ESV, LV ESD, and LA diameter dynamic 6 months after STEMI.

The group of patients with the genotype TT had the lowest tolerance to physical activity and was 385,5 [312,0–482,5] m, in the group with TC – 480,0 [439,0–519] m, CC-495 [468,0–530,0] m (pTT-TC = 0,05, pTT-CC = 0,02, pTC-CC = 0,44). In the acute period of STEMI, increase in the level of sST2 was found in comparison with the control group regardless of the genotype (TT, TC and CC variants, p1 = 0,003, p2 = 0,002, p3 = 0,001, respectively). After 6 months, in patients with TT genotype the sST2 level decrease by 15,2 % (p = 0,11), in the TC group – 35,7 % (p = 0,004), in the CC – 44,2 % (p = 0,052), table 3.

Table 3

Data of cardiac rhythm variability depending on genotypes of polymorphous variants – TT, TC and CC of the aldosterone synthase CYP11B2 gene

Parameters	TT (1)	TC (2)	CC (3)	P
SDNN, msec	50,0 [41,0-57,0]	53,5 [45,25-57-50]	52,50 [49,50-70,00]	P_{1-2} = 0,088 P_{1-3} = 0,049 P_{2-3} = 0,290
RMSSD, msec	17,0 [11,5-24,5]	25,5 [18,75-31,50]	22,0 [14,50-39,50]	P_{1-2} = 0,001 P_{1-3} = 0,07 P_{2-3} = 0,442
pNN50, msec	0,9 [0,35-5,10]	4,15 [1,48-9,93]	2,8 [1,20-5,70]	P_{1-2} = 0,004 P_{1-3} = 0,034 P_{2-3} = 0,406
TP, $msec^2$	2343,5 [1676,0-3197,0]	2815,0 [2024,0-3467,5]	2598,5 [1854,0-3941,5]	P_{1-2} = 0,230 P_{1-3} = 0,211 P_{2-3} = 0,762
ULF, $msec^2$	566,5 [347,0-815,0]	511,5 [341,5-725,5]	489,5 [375,00-1046,00]	P_{1-2} = 0,706 P_{1-3} = 0,254 P_{2-3} = 0,190
VLF, $msec^2$	1125,0 [827,0-1664,0]	1365,0 [1074,5-1788,0]	1569,0 [1036,0-2475,0]	P_{1-2} = 0,169 P_{1-3} = 0,050 P_{2-3} = 0,158
LF, $msec^2$	532,0 [463,0-1198,0]	545,0 [346,5-894,5]	432,0 [202,0-625,0]	P_{1-2} = 0,650 P_{1-3} = 0,039 P_{2-3} = 0,081
HF, $msec^2$	107,5 [67,5-241,5]	250,0 [113,0-423,0]	123,0 [51,0-251,0]	P_{1-2} = 0,038 P_{1-3} = 0,044 P_{2-3} = 0,019
LF/HF	4,20 [3,20-4,60]	2,40 [1,76-3,65]	3,20 [2,03-3,60]	P_{1-2} = 0,001 P_{1-3} = 0,041 P_{2-3} = 0,266

The analysis of HRV data revealed a decrease in the time and frequency in all three groups of patients in comparison with the normal [10]. However, when the group of patients with the genotype of TT was compared, the lowest values of time domain data – SDNN (p1-2 = 0,088, p1-3 = 0,049), RMSSD (p1-2 = 0,001, p1-3 = 0,07), pNN50 (p1-2 = 0,04, p1-3 = 0,034), and frequencies - VLF (p1-3 = 0,050, p2-3 = 0,081), HF (p1-2 = 0,038, p1-3 = 0,044, p2-3 = 0,019) were observed. Spectral analysis revealed a significant difference between the LF components and the ratio of LF/HF in the TT genotype group compared to other groups (p1-3 = 0,089, p2-3 = 0,081) and (p1-2 = 0,001, p1-3 = 0,041) respectively. There was no significant difference between indicators TP and ULF.

Aldosterone synthase (CYP11B2) catalyzes the final stage of the aldosterone formation from a desoxycorticosterone. Beyond the adrenal gland expression of the CYP11B2 gene in smooth myocytes of blood vessels and cardiomyocytes, the existence of tissue-specific activation of myocardial aldosterone synthase in MI was shown. A significant increase in the expression of CYP11B2 mRNA in the myocardium in patients with chronic heart failure, and its positive correlation with the fraction of collagen in the myocardium, the severity of LV dysfunction was found [17–18]. Therefore, the gene aldosterone-synthase is considered as a candidate genome, which depends not only on the synthesis of aldosterone, but also on the course of CR. Regarding to the association of the polymorphism of the CYP11B2-T344C gene with the risk of MI, its following remodeling, and clinical course, the literature data are ambiguous: thus, Hengstenberg C. et al., 2000, according to the results of a 5-year follow up for patients with MI, did not find associations between the alleles of the CYP11B2 gene, the severity of myocardial dysfunction and CP indices [19].

Hautanen A. et al., 1999, showed that in male carriers of 344C-alleles, in those who are smoking and have dyslipidemia, the risk of MI increases compared to carriers of 344T-alleles [20]. According to Korneva V.A., 2011, the presence of the genotype of T-alleles in the homozygous state almost increased the risk of cardiovascular disease by 2 times [21]. In a study by Lobach L.E. et al., 2017, patients with TP + CT polymorphism of the CYP11B2 gene had an increased risk of MI [22]. In patients with ischemic genesis CHF, including a post-myocardial infarction cardiosclerosis, allele T, and the genotype TT of the polymorphic locus-T344C of the CYP11B2 gene were associated with the severe clinical manifestation of CHF, and the genotypes ST and allele T were more commonly recorded in patients with an unfavorable course of the disease [23].

The presented work was conducted to patients with myocardial infarction. In our study, the structural and functional parameters of the myocardial condition were obtained during the period of hospitalization (acute phase of the disease), and their changes within six-months of follow-up. Primary indicators of hemodynamics in STEMI patients with homozygote TT and CC, and heterozygote TC weren't significantly different. In the post-infarction period, the TT genotype carriers had a significant increase in the size and extent of LV (EDD, EDV), the degree of its hypertrophy (LVMM). These changes were accompanied by diastolic dysfunction with a significant slowing of the filling of the LV (reduction in E/A), an increase in the number of patients with regurgitation at the mitral valve, indicating an unfavorable maladaptive heart remodeling. Unlike patients with TT genotype, in patients with CC-genotype there was a tendency to increase inotropic function of the left ventricle, a significant decrease in the hypertrophy formation, a lack of significant changes in the parameters of LV dilatation, diastolic function and decrease the number of patients with mitral valve regurgitation, hence, indicating a favorable flow of structural and functional changes in the LV after the MI after 6 months. In patients carrying heterozygotes TC there was a tendency to decrease LVMM, and other hemodynamic parameters did not differ statistically.

Differences in cardiac remodeling after STEMI were reflected in the functional reserve of the cardiovascular system – in TT carriers compared to CC, the results of the 6-minute walk test revealed a significantly lower physical activity tolerance.

In all polymorphic variants of the CYP11B2 (-T344C) gene, there was a decrease in parasympathetic tone (SDNN, RMSSD, PNN50, HF), an increase in sympathetic activity (LF), a sympatho-parasympathetic index (LF/HF), but the most significant changes components of HRV in patients with the genotype of TT in comparison to the CC genotype were observed.

Excessive activation of the sympathetic component of the spectrum (LF) and reduction of the activity of the parasympathetic regulation mechanisms (HF) is the basis for the development of the maladaptation reaction and indication of an unbalanced function of the autonomic nervous system. The high LF/HF index characterizes the decrease in the sympathetic and parasympathetic balance in favor of the prevalence of the sympathetic VNS. Reducing the level of the very low-frequency spectrum (VLF) indicates the energy-deficient state of the autonomic nervous system, the strength of VLF-oscillations is a sensitive indicator of the metabolic processes management in a myocardium with disturbed geometry and metabolism and fibrotic changes. Changes in HRV in the patients after MI are associated with the development of the general adaptive syndrome and with significant structural and functional reorganization of the myocardium [11–12]. In our study, patients with the TT genotype were associated with an inadequate HR course with more pronounced changes in the time and frequency parameters of HRV, which suggests that this variant is unfavorable for the subsequent course of the after infarction period.

Interest in determining the sST2 level arose due to the following reasons: we diagnosed MI by the increased level of the specific biomarkers, which is associated with the degree of myocardial damage, HR, the risk of progression of CHF and the risk of sudden death [7]. Weir R.A.P et al., 2010, found the relationship between sST2, the evolution of MI, HR, aldosterone levels, and the efficacy of eplerenone in patients with high levels of sST2 [5]. Analysis of the relationship between the concentration of aldosterone and –T344C polymorphism of the CYP11B2 gene showed that T-allele associated with higher levels of hormone [24]. In our study, patients with the TT genotype compared with the TC and CC variants revealed a lower degree of reduction of sST2 after STEMI which connected to the adverse prognosis for those patients, and also demonstrated the possible relationship between elevated aldosterone, sST2 and pathological myocardial remodeling.

CONCLUSIONS

1. Patients with STEMI - carriers of homozygotes TT of the CYP11B2 gene in 6 months after the index event are associated with the occurrence of hypertrophy and left ventricular dilatation, diastolic dysfunction with violation of LV relaxation, and decreased tolerance to physical activity that indicates a maladaptive character of after infarction remodeling.

2. After the HRV data were compared in patients after STEMI. A decrease in the parasympathetic tone component, an increase in sympathetic activity, and sympathetic parasympathetic index in carriers of the TT genotype of the CYP11B2 gene indicated more pronounced autonomic imbalance than that in CC-genotype carriers.

PROSPECTS FOR FUTURE STUDIES

Prospects for future studies are to observe investigated patients to 1–3 years to do more reliable conclusions.

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PULSE PRESSURE CLASSES AND DOSAGE OF THE MAIN GROUPS OF CARDIAC MEDICATIONS IN PATIENTS AT THE ANNUAL FOLLOW-UP PERIOD AFTER PACING

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Dose factor of the main groups of cardiac medications in five pulse pressure (PP) classes was studied in 220 patients (110 men and 110 women) at the annual stage after pacing, the average age 70 ± 9 years. Patients with the IV and V class of PP require the administration of higher doses of antiarrhythmics, diuretics, calcium channel blockers and ACE inhibitors.

KEY WORDS: pulse pressure, cardiac pacing, cardiac medications

КЛАСИ ПУЛЬСОВОГО АРТЕРІАЛЬНОГО ТИСКУ І ДОЗУВАННЯ ОСНОВНИХ ГРУП КАРДІОЛОГІЧНИХ ПРЕПАРАТІВ У ПАЦІЄНТІВ НА РІЧНОМУ ПЕРІОДІ ПІСЛЯ ПОСТІЙНОЇ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЇ

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Вивчено коефіцієнт дози кардіологічних препаратів в п'яти класах пульсового артеріального тиску (ПАТ) на річному періоді спостереження після імплантації електрокардіостимуляторів (ЕКС) у 220 пацієнтів (110 чоловіків і 110 жінок) у віці 70 ± 9 років. Пацієнти з імплантованими ЕКС в IV і V класах ПАТ вимагають призначення антиаритмічних препаратів, діуретиків, антагоністів кальцію та інгібіторів ангіотензіперетворюючого ферменту в більш високих дозах.

КЛЮЧОВІ СЛОВА: пульсовий артеріальний тиск, постійна електрокардіостимуляція, кардіологічні

КЛАССЫ ПУЛЬСОВОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И ДОЗИРОВКА ОСНОВНЫХ ГРУПП КАРДИОЛОГИЧЕСКИХ ПРЕПАРАТОВ У ПАЦИЕНТОВ НА ГОДОВОМ ПЕРИОДЕ ПОСЛЕ ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИИ

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Изучен коэффициент дозы кардиологических препаратов в пяти классах пульсового артериального давления (ПАД) на годовом периоде наблюдения после имплантации электрокардиостимуляторов (ЭКС) у 220 пациентов (110 мужчин и 110 женщин) в возрасте 70 ± 9 лет. Пациенты с имплантированными ЭКС в IV и V классах ПАД требуют назначения антиаритмических препаратов, диуретиков, антагонистов кальция и ингибиторов ангиотензипревращающего фермента в более высоких дозах.

КЛЮЧЕВЫЕ СЛОВА: пульсовое артериальное давление, постоянная электрокардиостимуляция, кардиологические препараты

INTRODUCTION

Pulse pressure (PP) is an important component in blood pressure control and outcomes predicting, especially in patients with chronic heart failure (CHF), ischemic heart disease, atrial fibrillation (AF) [1–2]. Pacemaker implantation, changing the pumping function of the heart, influences the PP, which should be taken into account in the pharmacological support of patients [3–4]. However, changes in the major groups of cardiac medication doses depending on the PBP class in patients at the annual follow-up period after pacemaker implantation has not yet been studied.

OBJECTIVE

The goal of our work was to evaluate the changes in the doses of medications in different classes of PBP in patients at the annual follow-up period after pacemaker implantation.

MATERIALS AND METHODS

220 patients (110 men and 110 women) aged 70 ± 9 years before and after pacemaker implantation and cardiac resynchronization therapy (CRT) were examined: DDD (R) regimen – 132 patients, VVI (R) - 69, CRT (P / D) – 19. Indications for pacing were atrioventricular (AV) block – 125 patients, bundle branches block – 55 patients, sick sinus syndrome (SSS) – 51 patients, permanent atrial fibrillation (AF) – 70 patients, dilated cardiomyopathy (DCM) – 16 patients.

Exclusion criteria were: age less than 40 years, the presence of concomitant angina pectoris of IV functional class (FC), chronic heart failure (CHF) of IV FC, stimulation of the right and / or left ventricle (RV/LV) less than 50 % for the entire observation period.

Before and after pacing, drug therapy was represented by next medications, with average therapeutic doses:

– B01AA anticoagulants – warfarin 5 mg, including new anticoagulants B01AE – direct thrombin inhibitors – dabigatran etexilate (pradaxa 300 mg) and B01AF – direct Xa factor inhibitors – rivaroxaban (xarelto 20 mg);

– B01AC antiplatelet agents – clopidogrel and acetylsalicylic acid 75 mg;

– C01BD antiarrhythmic drugs - amiodarone 200 mg;

– C03 diuretics – hydrochlorothiazide 12.5 mg, furosemide 40 mg, torasemide 5 mg, indapamide 2.5 mg, spironolactone 50 mg;

– C07A β- blockers – metoprolol 100 mg, bisoprolol 5 mg, nebivolol 5 mg, carvedilol 6,25 mg, betaxolol 5 mg, atenolol 50 mg;

– C08 Ca-channel blockers – C08CA dihydropyridine derivatives – amlodipine 10 mg, nifedipine 90 mg and C08DA phenylalkylamine derivatives – verapamil 80 mg;

– C09A angiotensin converting enzyme (ACE) inhibitors – enalapril 10 mg, lisinopril 10 mg, ramipril 5 mg, fosinopril 10 mg;

– C09C angiotensin II receptor blockers (ARB) – losartan 50 mg, candesartan 8 mg;

– C10AA inhibitors of hydroxyl-methylglutaryl (HMG) coenzyme A (CoA) reductase – simvastatin 20 mg, atorvastatin 20 mg, rosuvastatin 10 mg.

For each group of drugs, the dose factor was calculated as the average therapeutic dose for the drug taken as 1,0.

Patients were classified into five classes of PP: I – very low PP - less than 20 mm Hg, II – low PP – more than 20 but less than 40 mm Hg, III – normal PP – 40 – 60 mm Hg , IV – high PP – more than 60 but less than 80 mm Hg, V – very high PP – more than 80 mm Hg.

The dose factor was defined in each class of PP for drugs, mentioned above, prior to pacing, in the early period (3–5 days), 6 months and 1 year after pacemaker implantation.

Statistical analysis was performed using Microsoft Excel (for parametric data M – mean value, sd - standard deviation). The significance of differences between groups was determined by a nonparametric Mann-Whitney U-test. The expected result was defined confidence level $p < 0.05$.

RESULTS AND DISCUSSION

In the table the dose factor of the major groups of cardiac drugs in the PP classes in patients in a year after pacing is presented.

Initially, the dose factor of anticoagulants, antiaggregants, ARBs and HMG CoA reductase inhibitors was at the average therapeutic level in all PP classes and did not change at the follow-up stages after pacing.

The dose factor of antiarrhythmic drugs (amiodarone) was equally smaller in II and III classes and greater in the V class of PP. In the early postoperative period, the dose factor was increased in all classes - the higher the PP class, the greater the dose factor - and it subsequently decreased to the initial values in IV, V and, to a greater degree, in II, III PP classes.

Initially, the dose factor of diuretics was equally smaller in II, III and greater in the V classes of PP. It increased in all classes of PAD and, to a greater extent, in IV and V at all stages of follow-up after pacing.

The dose factor of β-blockers was smaller in II and equally greater in IV, V classes of PP. In the early postoperative period, it increased to an equal degree in the IV, V classes and to a lesser degree in the III and II classes of the PP, respectively, and did not change after.

Initially the dose factor of Ca-channels blockers did not change in the early

postoperative period in all PP classes. Six months after pacing it decreased in IV, V classes to the average therapeutic level and, to a greater degree, in class III of PP and remained at the same level. In the II class of PP, Ca-channels blockers were not used throughout the observation period.

Initially, the lowest dose factor of ACE inhibitors was observed in II PP class and the largest in IV and V classes of PP. The dose factor did not change in all classes in the early postoperative period but decreased in 6 months and a year after pacing – to a greater degree in II and III PP classes and to a lesser degree - in IV and V classes of PP.

Table

The dose factor of the main groups of cardiac medications in PP classes in patients in a first year after pacing (M ± sd)

Meds	Classes of PP															
	II				III				IV				V			
	Before pacing	After 3-5 days	After 6 months	After 1 year	Before pacing	After 3-5 days	After 6 months	After 1 year	Before pacing	After 3-5 days	After 6 months	After 1 year	Before pacing	After 3-5 days	After 6 months	After 1 year
anticoagulants	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
antiplatelets	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
antiarrhythmics	1.2 ± 0.3	1.5 ± 0.5	1.3 ± 0.2	1.1 ± 0.4	1.2 ± 0.3	1.5 ± 0.5	1.3 ± 0.2	1.1 ± 0.4	1.6 ± 1.4	1.8 ± 1.2	1.7 ± 1.3	1.6 ± 1.2	1.8 ± 0.2	2 ± 0.2	1.9 ± 0.1 x#	1.8 ± 0.2
diuretics	1 ± 0.2	1.1 ± 0.2	1.1 ± 0.4	1.1 ± 0.4	1 ± 0.2	1.1 ± 0.3	1.1 ± 0.5	1.1 ± 0.4	1.3 ± 0.5	1.4 ± 0.6	1.5 ± 0.4	1.6 ± 0.2	1.5 ± 0.5	1.6 ± 0.3	1.7 ± 0.2	1.8 ± 0.4
β- blockers	0.6 ± 0.1	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.8 ± 0.4	0.9 ± 0.4	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.5	1.0 ± 0.5	1 ± 0.2	1 ± 0.4
Ca-channel blockers	-	-	-	-	1 ± 0	1 ± 0	0.9 ± 0.1	0.9 ± 0.1	1.2 ± 0.2	1.2 ± 0.2	1 ± 0	1 ± 0	1.3 ± 0.2	1.3 ± 0.2	1 ± 0	1 ± 0
ACE inhibitors	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.3	0.7 ± 0.3	1 ± 0.3	1 ± 0.3	0.9 ± 0.2	0.8 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.4	1 ± 0.3	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.3	1.1 ± 0.2
ARBs	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
Statins	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0

*Note: *p <0.05 - between values in III and II, IV, V PP classes, ^{x}p<0.05 - between values in II and IV, V PP classes, ^p <0.05 - between values in IV and V PP classes, $^{\#}$ p<0.05 - between values in the same PP class before and after pacing.*

The change of the dose factor in groups of cardiac medications in patients at the annual follow-up period after pacing has been studied previously in regard to the duration of the QTc interval, the QRS complex and the functional class of chronic heart failure [5–7]. However, there appears to be no data on dose factor changes dependently on the PP class.

In our work, the increase in dose of diuretics and β-blockers with an increase in the PP class in patients at the annual follow-up period after pacing was shown. Our data is indirectly confirmed by the results of other

authors [8], showed the direct relations between the PP level and the prescribed dose of medications in patients without pacing.

The increase in the dose factor of antiarrhythmic drugs in the early period after pacing with subsequent reduction of their dose, as well as the dose of Ca-channels blockers and ACE inhibitors, indirectly correlates with the data presented in the literature [6–8].

The absence of changes in the dose factor of anticoagulants, antiplatelets, ARBs and HMG CoA reductase inhibitors in all PP classes after pacing is indirectly confirmed by data of some authors [5, 8].

Our study has showed that the dose factor of antiarrhythmic drugs, diuretics, Ca-channels blockers and ACE inhibitors in patients at different follow-up periods after pacing increases with the PP class, which confirms the great importance of assessing the PP class when choosing the doses of cardiac medications.

CONCLUSIONS

1. In patients after pacing, the dose factor of the main groups of cardiac medications correlates with the PP classes and, the greater the PP class, the greater the dose rate of the medications.

2. After pacing an increase of the dose factor of antiarrhythmic drugs (amiodarone) in the early period and diuretics and ß-blockers throughout the observation period with an increase in the PP class is required.

3. The long term period of pacing contribute to reduction of the dose factor of antiarrhythmic drugs (amiodarone), Ca-channel blockers and ACE inhibitors in all classes of PP, to a greater extent - in II and III classes.

4. The dose factor of anticoagulants, antiplatelet agents, ARBs and HMG CoA reductase inhibitors does not depend on the PP class and does not change over the entire observation period.

5. Patients after pacing with IV and V classes of PP require the higher doses of antiarrhythmics, diuretics, Ca-channel blockers and ACE inhibitors.

PROSPECTS FOR FUTURE STUDIES

It seems rational to study the optimization of drug therapy in patients after pacing in various classes of PP in a period of more than one year with correction of the frequency of administration and the doses of various medications.

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PROTEOLYTIC DEGRADATION OF POLY (ADP-RIBOSE) POLYMERASE IN RATS WITH CARRAGEENAN-INDUCED GASTROENTEROCOLITIS

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The aim of the research was to study the activity of poly (ADP-ribose) polymerase in small intestinal homogenate of rats with chronic carrageenan-induced gastroenterocolitis, as well as mechanisms of regulation of the enzyme in this pathology. Twenty Wistar Albino Glaxo rats were divided into two groups. Animals of group 1 (n = 10) consumed 1 % carrageenan solution for 28 days, which resulted in the development of gastroenterocolitis confirmed morphologically. The control group consisted of intact animals (n = 10). The activity of poly (ADP-ribose) polymerase (PARP) in the homogenate of small intestine, as well as caspase-3, matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) serum levels were determined. Obtained data were statistically processed using the Mann-Whitney U test and calculating median and interquartile range (Me, 25th–75th percentile) with the help of the GraphPad Prism 5 application. The development of carrageenan-induced gastroenterocolitis was accompanied by an increase in caspase-3, MMP-2, MMP-9 concentrations in blood serum and a decrease in the activity of PARP in small intestinal homogenates. The reduced activity of PARP in chronic carrageenan-induced gastroenterocolitis may be due to the proteolysis of this enzyme under the action of caspase-3, MMP-2, and MMP-9.

KEY WORDS: gastroenterocolitis, carrageenan, rats, poly (ADP-ribose) polymerase, caspase-3, matrix metalloproteinases

ПРОТЕОЛІТИЧНА ДЕГРАДАЦІЯ ПОЛІ (АДФ-РИБОЗА) ПОЛІМЕРАЗИ ЩУРІВ ПРИ КАРАГЕНАНОВОМУ ГАСТРОЕНТЕРОКОЛІТІ

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Метою дослідження стало вивчення активності полі (АДФ-рибоза) полімерази у гомогенаті тонкого кишечника щурів з хронічним карагенан-індукованим гастроентероколітом, а також механізмів регуляції даного ферменту при зазначеній патології. Двадцять щурів популяції Wistar Albino Glaxo були розділені на дві групи по десять тварин у кожній. Тварини дослідної групи вживали 1 % розчин карагенану протягом 28 днів, що призводило до розвитку гастроентероколіту, який було підтверджено морфологічно. Контрольна група складалася з інтактних тварин. Визначали активність полі(АДФ-рибоза) полімерази (ПАРП) у гомогенаті тонкого кишечника та рівні каспази-3, матриксної металопротеїнази-2 (ММР-2) і матриксної металопротеїнази-9 (ММР-9) у сироватці крові. Отримані дані статистично оброблялися з використанням тесту Манна-Уїтні і розрахунку медіани і межквартільного діапазону (Me, 25-й-75-й процентилі) за допомогою програми «GraphPad Prism 5». Розвиток карагенан-індукованого гастроентероколіту супроводжувався підвищенням сироваткових каспази-3, ММР-2, ММР-9 на тлі зниження активності ПАРП у гомогенаті тонкого кишечника тварин. Зниження активності ПАРП при хронічному карагенан-індукованому гастроентероколіті може бути обумовлено протеолізом даного ферменту під дією каспази-3, ММР-2 і ММР-9.

КЛЮЧОВІ СЛОВА: гастроентероколіт, карагенан, щури, полі (АДФ-рибоза) полімераза, каспаза-3, матриксні металопротеїнази

ПРОТЕОЛИТИЧЕСКАЯ ДЕГРАДАЦИЯ ПОЛИ (АДФ-РИБОЗА) ПОЛИМЕРАЗЫ КРЫС ПРИ КАРРАГЕНАНОВОМ ГАСТРОЭНТЕРОКОЛИТЕ

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Целью работы стало изучение активности поли (АДФ-рибоза) – полимеразы в гомогенате тонкого кишечника крыс с хроническим каррагинан-индуцированным гастроэнтероколитом, а также механизмов регуляции данного фермента при указанной патологии. Двадцать крыс популяции Wistar Albino Glaxo были разделены на две группы по десять особей в каждой. Животные опытной группы употребляли 1 % раствор каррагинана в течение 28 дней, что приводило с развитию гастроэнтероколита, подтвержденного морфологически. Контрольная группа состояла из интактных животных. Определяли активность поли (АДФ-рибоза) – полимеразы (ПАРП) в гомогенате тонкого кишечника и уровни каспазы-3, матриксной металлопротеиназы-2 (ММР-2), матриксной металлопротеиназы-9 (ММР-9) в сыворотке крови. Полученные данные статистически обрабатывались с использованием теста Манна-Уитни и расчета медианы и межквартильного диапазона (Me, 25-й-75-й процентили) с помощью приложения «GraphPad Prism 5». Развитие каррагинан-индуцированного гастроэнтероколита сопровождалось повышением каспазы-3, ММР-2, ММР-9 в сыворотке крови и снижением активности ПАРП в гомогенате тонкого кишечника животных. Снижение активности ПАРП при хроническом каррагинан-индуцированном гастроэнтероколите может быть обусловлено протеолизом данного фермента под действием каспазы-3, ММР-2 и ММР-9.

КЛЮЧЕВЫЕ СЛОВА: гастроэнтероколит, каррагинан, крысы, поли (АДФ-рибоза) – полимераза, каспаза-3, матриксные металлопротеиназы

INTRODUCTION

Poly (ADP-ribose)-polymerase (PARP) is a fairly large protein consisting of 1014 amino acid residues, which is involved in the regulation of a number of intracellular functions [1], including DNA repair, cell proliferation and differentiation, apoptosis, necrosis, gene expression [2], and the degradation of PARP occurs under the influence of various intracellular proteases such as caspases, calpaines, granzymes, cathepsins, and matrix metalloproteinases [3].

The role of PARP in the development of inflammatory processes seems to be quite controversial. PARP has been shown to regulate the expression of certain pro-inflammatory proteins, in particular, tumor necrosis factor-α (TNF-α) and inducible NO-synthase (iNOS). It has been known that inflammation results in the development of oxidative stress, which is accompanied by DNA damage. In response to oxidative damage to DNA, PARP activation occurs, which in turn potentiates upregulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) whose action mediates the expression of proinflammatory factors [2, 4]. Thus, PARP is considered to exert pro-inflammatory effects, however, taking into account the pleiotropic effects of this enzyme, it is important to note that the impaired delicate balance of PARP inside the cell in the direction of both hyper- and hypoactivation can make the pathological process more severe.

OBJECTIVE

Nowadays the activity and role of PARP in the development of chronic carrageenan-induced inflammation of the gastrointestinal tract have not been studied, therefore the aim of the research was to study the activity of PARP in small intestinal homogenates of rats with chronic carrageenan-induced gastroenterocolitis, as well as the mechanisms of its regulation.

MATERIALS AND METHODS

Twenty female white WAG rats, which were kept in standard conditions of the vivarium, were used in the experiment. The animals were randomly divided into 2 groups. Group 1 consisted of animals exposed to the food additive λ-carrageenan for 4 weeks (n = 10). Group 2 served as a control group and included ten intact animals. Long-term oral administration of λ-carrageenan led to the development of chronic gastroenterocolitis confirmed morphologically [5, 6].

All experimental procedures were performed in accordance with the provisions of the European Convection for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes and Directive 2010/63/EU on the protection of animals used for scientific purposes adopted on September 22, 2010.

Laboratory animals were removed from the experiment by decapitation. Fragments of small intestine were taken immediately after

decapitation. They were perfused with a cooled saline solution. Powdered and shredded small intestine was used to prepare a homogenate in 0.25 M Tris-HCl buffer (pH = 7.4) containing 0.32 M of sucrose. After 15-minute centrifugation at 3,000 rpm. (1,200 g), the supernatant was obtained in which the PARP activity was determined using the method based on the electrophoretic separation of poly-ADP-ribosylated histone proteins from nuclei followed by the quantitative determination of poly-ADP-ribose in them [7]. Caspase-3 blood serum concentrations were measured using ELISA kit manufactured by *eBioscience* (Vienna, Austria). The content of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) in blood serum was determined using ELISA kits produced by *Quantikine* (Minneapolis, USA). The Awareness Technology Stat Fax 303 Plus Microstrip Reader was used to register the optical density of solutions.

The statistical processing of the data obtained in our research was carried out using the GraphPad Prism 5 application. Median and interquartile range (Me, 25th–75th percentile) were calculated. To assess the differences in quantitative characteristics between independent groups, the Mann-Whitney U test was used. The results were statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

It was established that the development of chronic carrageenan-induced gastro-enterocolitis was accompanied by a decrease in the activity of PARP in small intestinal homogenates. In animals of group 1 whose representatives had been administered with carrageenan solution, the activity of PARP was 3-fold reduced compared to the control group (Fig. 1).

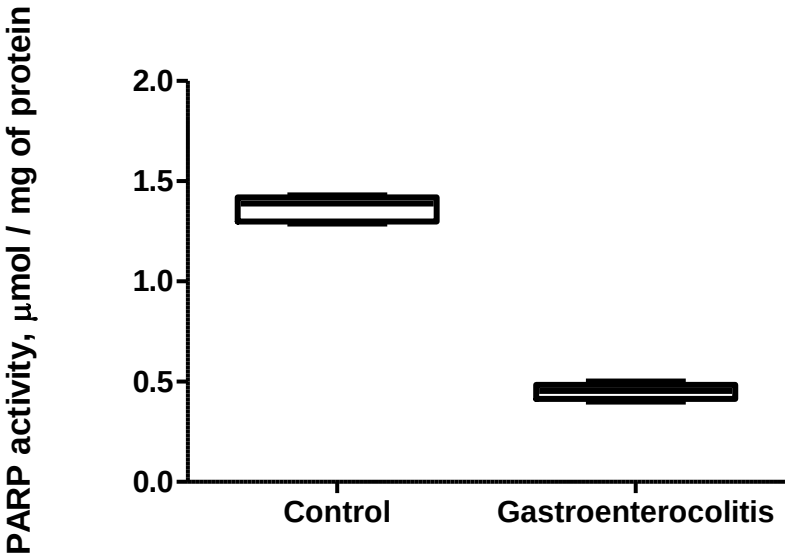

Fig. 1. The activity of poly (ADP-ribose) polymerase in small intestinal homogenates of rats with carrageenan-induced gastroenterocolitis

Among the proteases that are potentially capable of participating in the proteolytic degradation of PARP, we have selected MMP-2, MMP-9, and caspase-3. The four-week oral intake of the food additive λ-carrageenan was found to cause the upregulation of caspase-3 whose level statistically significantly exceeded the same parameter of the control group ($p < 0.001$) more than 38 times (Fig. 2).

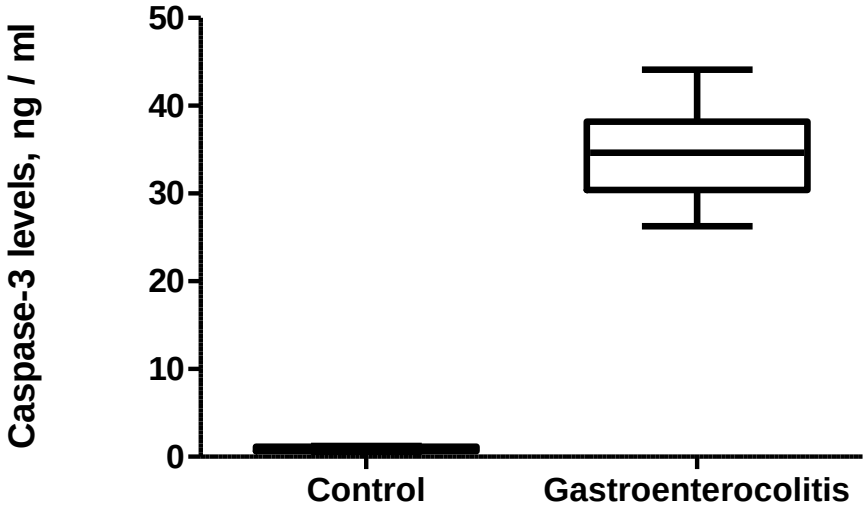

Fig. 2. Caspase-3 blood serum levels in animals with carrageenan-induced gastroenterocolitis

The comparison of the content of metalloproteinases in blood serum of rats with carrageenan-induced gastroenterocolitis and their serum levels in healthy animals allowed us to find out that the disease was accompanied by a significant increase in both MMP-2 and MMP-9 serum levels ($p < 0.01$). For instance, we found a 1.5-fold increase in serum MMP-2 concentrations in animals from group 1 compared to the control animals (Fig. 3).

At the same time, the concentration of MMP-9 was statistically significantly 3.7 times higher ($p < 0.01$) in blood serum of rats with gastroenterocolitis (Fig. 4).

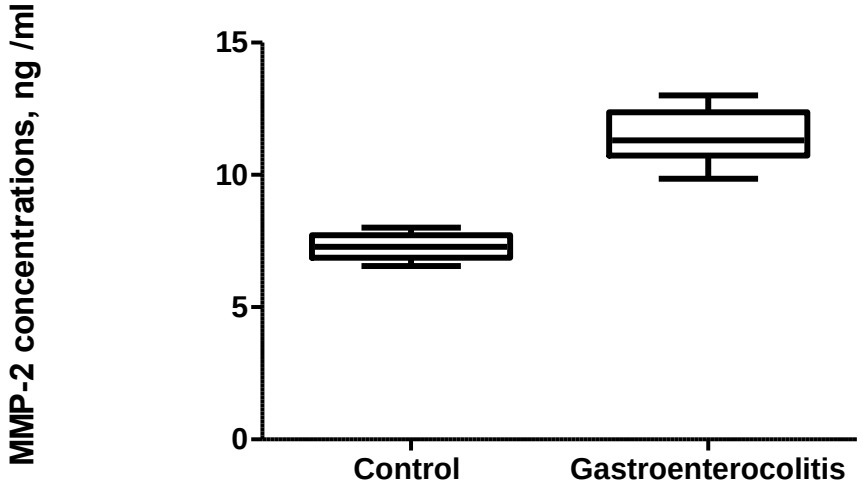

Fig. 3. Matrix metalloproteinase-2 blood serum concentrations in animals with carrageenan-induced gastroenterocolitis

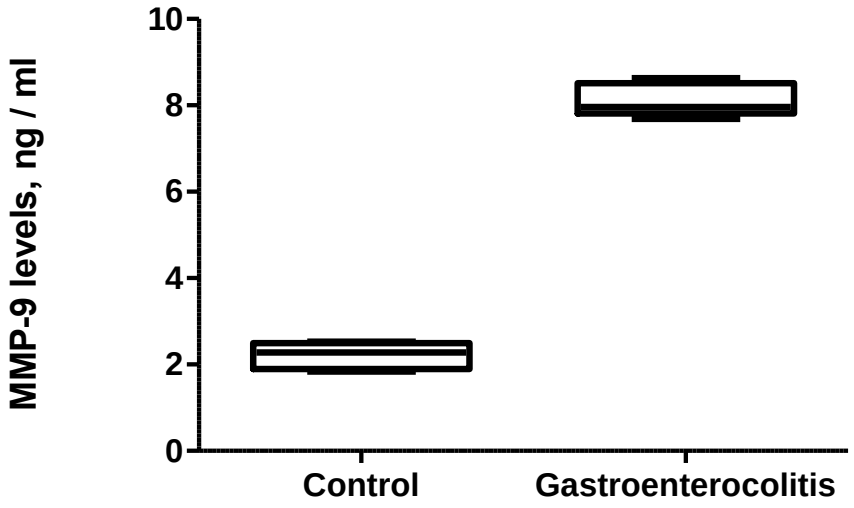

Fig. 4. Matrix metalloproteinase-9 blood serum levels in rats with carrageenan-induced gastroenterocolitis

Taking into account the reported data on the involvement of MMP-2, MMP-9, and caspase-3 in the degradation of PARP [3, 8], the observed decrease in PARP activity might be explained by the cleavage and inactivation of this enzyme by caspase-3 and metalloproteinases. However, we presume that the effect of MMP-2 and MMP-9 on the breakdown of PARP in carrageenan-induced inflammation is less pronounced compared to caspase-3, since only a slight elevation of blood metalloproteinases is observed in the animals from group 1 against the background of considerable activation of caspase-3.

The involvement of PARP in the regulation of the expression of proinflammatory factors makes it possible to explain the early decrease in the activity of inducible NO synthase [9, 10], one of the reasons of which is probably the abnormal PARP-dependent regulation of NF-κB. As a result, NF-κB-mediated expression of inducible NO synthase is affected.

Nowadays, there is no doubt that chronic inflammation is connected with malignant transformation of cells. It has been known that the prolonged oral exposure to carrageenan results in the development of not only chronic inflammation but also gastrointestinal tumors [11]. We assume that the PARP deficiency may serve as one of the factors of tumor transformation, since a decrease in the PARP activity reduces the reparative DNA ability, which is the cause of malignancy.

CONCLUSIONS

1. Chronic gastroenterocolitis developed due to a 4-week consumption of carrageenan is accompanied by a decrease in the activity of PARP and elevation of MMP-2, MMP-9 and caspase-3 in blood serum of animals.

2. Reduction of the PARP activity in chronic carrageenan-induced gastroenterocolitis can be explained by proteolysis of this enzyme under the influence of caspase-3, MMP-2 and MMP-9.

3. Diminished DNA reparative abilities in case of PARP deficiency may serve as one of the factors of malignization in chronic carrageenan-induced intestinal inflammation.

PERSPECTIVES OF FURTHER RESEARCH

It is promising to study other proteolytic enzymes that can participate in the degradation of poly (ADP-ribose) polymerase in chronic carrageenan-induced gastroenterocolitis, affecting the rate of DNA repair, apoptosis, and cell proliferation in this way.

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CHARACTERISTIC OF PARAMETERS OF HEART RATE VARIABILITY IN PATIENTS WITH DIFFICULT-TO-CONTROL AND CONTROLLED ARTERIAL HYPERTENSION

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Parameters of heart rate variability (HRV) were studied in 112 patients with arterial hypertension (AH) aged 58.5 ± 9 years (60 patients with difficult-to-control arterial hypertension (DTCAH) and 52 patients with controlled arterial hypertension (CAH)). The control group was consisted of 20 conditionally healthy persons of the same sex and age. It has been established that patients with AH were characterized by decrease in the level of total power of the HRV spectrum, the power of the high-frequency (HF) and low-frequency (LF) domains of the spectrum, and increase in the level of the very low-frequency spectrum (VLF) and value LF/HF that reflect sympathovagal balance. It has been established that there were more significant disorders in neurohumoral regulation in patients with DTCAH in comparison with patients with CAH, which consist of the predominant adrenergic activation, primarily due to the sympathetic link of the autonomic nervous system. HRV can be used as an effective non-invasive method for the diagnosis and control of DTCAH.

KEY WORDS: difficult-to-control arterial hypertension, heart rate variability

ХАРАКТЕРИСТИКА ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ХВОРИХ НА ВАЖКОКОНТРОЛЬОВАНУ ТА КОНТРОЛЬОВАНУ АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ

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Вивчено показники варіабельності серцевого ритму (ВСР) у 112 пацієнтів з артеріальною гіпертензією (АГ) у віці 58,5 ± 9 років (60 пацієнтів з важкоконтрольованою артеріальною гіпертензією (ВАГ) і 52 пацієнта з контрольованою артеріальною гіпертензією (КАГ)). Групу контролю склали 20 умовно здорових осіб такої ж статі і віку. Встановлено, що для пацієнтів з АГ характерно зниження рівнів загальної потужності спектра ВСР (ТР), потужності високочастотного (HF) і низькочастотного (LF) доменів спектра при більш високих рівні потужності дуже низькочастотного спектра (VLF) і значенні LF/HF, яке відображає симпатовагальний баланс. Встановлено, що у пацієнтів з ТАГ в порівнянні з пацієнтами з КАГ спостерігаються більш суттєві порушення в нейрогуморальної регуляції, які складаються в переважній адренергічній активації, перш за все, за рахунок симпатичної ланки вегетативної нервової системи. Робиться висновок, що ВСР може використовуватися як ефективний неінвазійний метод з метою діагностики та контролю ТАГ.

КЛЮЧОВІ СЛОВА: важкоконтрольована артеріальна гіпертензія, варіабельність серцевого ритму

ХАРАКТЕРИСТИКА ПАРАМЕТРОВ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА У ПАЦИЕНТОВ С ТРУДНОКОНТРОЛИРУЕМОЙ И КОНТРОЛИРУЕМОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Изучены показатели вариабельности сердечного ритма (ВСР) у 112 пациентов с артериальной гипертензией (АГ) в возрасте 58,5 ± 9 лет (60 пациентов с трудноконтролируемой артериальной гипертензией (ТАГ) и 52 пациента с контролируемой артериальной гипертензией (КАГ)). Группу контроля составили 20 условно здоровых лиц такого же пола и возраста. Установлено, что для пациентов с АГ характерно снижение уровней общей мощности спектра ВСР (ТР), мощности высокочастотного (HF) и низкочастотного (LF) доменов спектра при более высоких уровне мощности очень низкочастотного спектра (VLF) и значении LF/HF, которое отображает симпатовагальный

баланс. При этом установлено, что у пациентов с ТАГ в сравнении с пациентами с КАГ наблюдаются более существенные нарушения в нейрогуморальной регуляции, которые состоят в преобладающей адренергической активации, прежде всего, за счет симпатического звена вегетативной нервной системы. Делается вывод, что ВСР может использоваться как эффективный неинвазивный метод с целью диагностики и контроля ТАГ.

КЛЮЧЕВЫЕ СЛОВА: трудноконтролируемая артериальная гипертензия, вариабельность сердечного ритма

INTRODUCTION

Difficult-to-control arterial hypertension (DTCAH) is arterial hypertension in which the level of blood pressure (BP) remains above the target value despite the use of a combination of three or more antihypertensive drugs, including a diuretic, in conjunction with the lifestyle modification [1]. The prevalence of DTCAH in the population of people with arterial hypertension (AH) is from 15 to 30 % [2].

Inadequate effectiveness of pharma-cotherapy of DTCAH causes the search for additional non-pharmacological inter-ventions. In particular, one of such methods is heart rate variability (HRV) [3].

HRV is a noninvasive method for the study of regulatory systems in physiological and in pathological conditions, which allows to estimate a neuro-humoral regulation and its constituent elements, its stress resistance and physiological responses to stress [4]. It is known that observed in case of AH imbalance of the autonomic and humoral regulation, may be assessed using analysis of HRV. Studies have demonstrated the decrease in values of parameters of HRV in individuals with AH compared with those with normal blood pressure [5]. However, publications devoted to the study of HRV parameters in patients with DTCAH have not been revealed.

OBJECTIVE

Identify the features of the HRV parameters in patients with DTCAH in comparison with patients with controlled hypertension (CAH).

MATERIALS AND METHODS

On the clinical base of the Kharkov city outpatient clinic № 24 and the State Institution «Kharkov Clinical Hospital for Railway Transport No. 1» 112 patients with AH were examined (63 men and 49 women). Average age is 58,5 ± 9 years. There were 56 patients with DTCAH and 56 patients with CAH. The control group was consisted of 20 healthy persons of the same sex and age.

The inclusion criteria in the study were any stage and degree of AH. The criterion of DTCAH was the presence of a persistent increase in BP above the target level, despite the simultaneous use of three or more antihypertensive drugs of various classes in adequate therapeutic doses, including a diuretic.

Exclusion criteria were heart failure functional class IV, acute coronary syndrome, rhythm and conduction disorders, diabetes mellitus, chronic respiratory insufficiency, bronchial asthma, chronic obstructive pulmonary diseases, peptic ulcer and duodenal ulcer at the stage of exacerbation, systemic diseases of connective tissue, tumors.

Analysis of HRV was carried out on the computer diagnostic complex CardioLab 2009 («HAI-Medica», Ukraine). The study was conducted in the sitting position after 15 min rest. The computation of HRV indices was performed in real time within the 7-minute session on the background of the ECG in the first standard lead with a sampling rate of the signal at 1000 Hz. There were allocated 3 types of waves using the fast Fourier transform: slow (VLF, 0,0033–0,05 Hz), medium (LF, 0,05–0,15 Hz), fast (HF, 0,15–0,40 Hz).

The following parameters of HRV were determined in all subjects in 5-minute intervals to assess the state of regulatory systems [6]: TP – total power of the spectrum, a measure of the power of the effects of neurohumoral reactions (ms2); VLF – the absolute power of the very low-frequency spectrum is associated with thermoregulation, renin-angiotensin system and sympathetic nervous system (ms2); VLF – the relative power of very low frequency spectrum (%); LF – the absolute power of the low-frequency spectrum is associated mainly with the sympathetic and partially parasympathetic links of regulation (ms2); LF – the relative power of low frequency spectrum (%); HF – the absolute power of the high-frequency domain of the spectrum is associated mainly with the parasympathetic regulating unit (ms2); HF – the relative power of high frequency spectrum (%);

LF/HF – measure display sympathovagal balance.

Statistical analysis was performed in the program Statistica 10. An analysis was conducted of the data for outliers (Grabs test) and compliance data the hypothesis about the normal distribution (Kolmogorov-Smirnov test): after exclusion of cases with emissions data for further calculations used the sample of 50 patients with DTCAH and 50 patients with CAH. For statistical evaluation of the results were used parametric tests: M – mean value, sd – standard deviation. The significance of differences between groups was determined using nonparametric T-Wilcoxon test.

RESULTS AND DISCUSSION

Mean values of HRV parameters in patients with DTCAH and CAH are presented in Table 1.

Table 1

The parameters of HRV in patients with DTCAH and CAH (M ± sd)

The parameters of HRV	Control group	Groups of patients	
		DTCAH	CAH
TP, ms2	1635 ± 145*	1150 ± 493	1052 ± 388
VLF, ms2	446 ± 67	414 ± 161**	537 ± 188#
VLF', %	27	36	51
LF, ms2	710 ± 63	335 ± 155**	244 ± 121#
LF', %	43	29	23
HF, ms2	386 ± 26*	200 ± 121	150 ± 77#
HF', %	24	17	14
LF/HF	1,8 ± 0,2	2,21 ± 0,93	1,95 ± 0,89

*Notes: * – P < 0,05 – between the control group and the group DTCAH, ** – P < 0,05 – between the groups of patients with DTCAH and CAH, # – P < 0,05 - between the control group and the CAH.*

In patients with AH compared with healthy individuals of the control group there were changes of the regulation systems, which were manifested with low levels of TP, HF, LF, and high level of VLF and value LF/HF. Whereas there were differences within the group of persons with AH between patients with DTCAH and CAH.

At lower TP in both groups of patients with AH, in patients with DTCAH it was higher by 1.09 times than in patients with CAH. The contribution of TP in patients with DTCAH was (36 %) less than in patients with CAH (51 %). In contrast, the proportion of LF and HF in TP in patients with DTCAH (29 % and 17 %) was more than its share of patients with CAH (23 % and 14 %). The ratio VLF:LF:HF in patients with DTCAH was 2.1:1,7:1, and in patients with CAH – 3,6:1,6:1.

The value LF/HF in patients with DTCAH was higher by 1.13 times than in patients with CAH. It indicated a more expressed imbalance of sympatho-vagal regulation in the first group.

The obtained results confirm existing ideas about the changes of HRV indexes in case of AH [7–9]. We had found that patients with DTCAH had less significant reducing in the total power spectrum of HRV than in patients with CAH, accompanied by more significant decrease in VLF and increase in LF and HF. Greater deviation of the value LF/HF was the evidence of a greater imbalance of regulatory systems and of more severe disease.

These results show a more significant violations of neurohumoral regulation in patients with DTCAH in comparison with patients with CAH, which are the predominant adrenergic activation, especially due to the sympathetic link of vegetative nervous system and explain the difficulties in achieving the target BP in this group of patients [10–11].

The data obtained should be taken into account in the conduct of the patient and the choice of therapeutic tactics.

CONCLUSIONS

1. Patients with AH was characterized by decrease in levels of TP, HF and LF, higher levels of VLF and the value of LF/HF.
2. Patients with DTCAH in comparison with patients with CAH were observed more significant abnormalities in neurohormonal regulation, which were the predominant adrenergic activation, especially due to the sympathetic link of vegetative nervous system.
3. HRV can be used as an effective non-invasive method of diagnostics and control of DTCAH.

PROSPECTS FOR FUTURE STUDIES

In the future, it seems appropriate to study the dynamics of parameters of HRV in patients with the DTCAH at various stages of treatment.

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TYPES OF RADIOFREQUENCY ABLATION AND CLINICAL SYMPTOMS IN PATIENTS WITH ATRIAL FIBRILLATION AND FLUTTER

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The study involved 76 patients with atrial fibrillation and atrial flutter (AF/AFL) who were divided into groups depending on conducted surgery (radiofrequency ablation of pulmonary veins (RFA PV), cavo-tricuspid isthmus (CTI), a combined strategy (PV + CTI)). We evaluated the sex and age of patients, AF and AFL form, duration of AF/AFL, classification of AF / AFL by the different scales, stage and degree of hypertension (AT); types of coronary heart disease (CHD); diabetes mellitus type 2; acute cerebrovascular accident history; functional class and stage of chronic heart failure (FC CHF). The frequency distribution of basic cardiovascular diseases and their clinical signs are observed equally in patients with AF/AFL, regardless of the type of surgery carried out and they do not influence the choice of the latter. Male patients often held RFA CTI and women – RFA PV. Patients with persistent AF often require alternative treatments, especially catheter ablation of arrhythmic substrate.

KEY WORDS: clinical features, atrial fibrillation and flutter, surgery, catheter ablation, cavo-tricuspid isthmus, pulmonary veins

ТИПИ РАДІОЧАСТОТНОЇ АБЛЯЦІЇ І КЛІНІЧНІ ОЗНАКИ У ПАЦІЄНТІВ З ФІБРИЛЯЦІЄЮ ТА ТРІПОТІННЯМ ПЕРЕДСЕРДЬ

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Обстежено 76 пацієнтів з фібриляцією та тріпотінням передсердь (ФП/ТП) в групах в залежності від проведеного оперативного втручання (радіочастотна абляція легеневих вен (РЧА ЛВ), каво-трикуспідального істмусу (КТІ), комбінована стратегія (ЛВ+КТІ)). Оцінювалися стать та вік пацієнтів, форма ФП та ТП, тривалість перебігу ФП/ТП, класифікація ФП/ТП за різними шкалами, стадії та ступені артеріальної гіпертензії (АГ); типи ішемічної хвороби серця (ІХС); наявність цукрового діабету 2 типу; гостре порушення мозкового кровообігу в анамнезі; функціональний клас та стадія хронічної серцевої недостатності (ФК ХСН). Частота поширення основних кардіоваскулярних захворювань та їх клінічних ознак спостерігаються однаково в групах пацієнтів з ФП/ТП незалежно від типу проведеного оперативного втручання і вони не впливають на вибір останнього. Пацієнтам чоловічої статі частіше проводиться РЧА КТІ, і жіночої – РЧА ЛВ. Пацієнти з персистуючою формою ФП частіше потребують альтернативних методів лікування, в першу чергу катетерної абляції субстрату аритмії.

КЛЮЧОВІ СЛОВА: клінічні ознаки, фібриляція та тріпотіння передсердь, оперативне втручання, катетерна абляція, каво-трікуспідальний істмус, легеневі вени

ТИПЫ РАДИОЧАСТОТНОЙ АБЛЯЦИИ И КЛИНИЧЕСКИЕ ПРИЗНАКИ У ПАЦИЕНТОВ С ФИБРИЛЛЯЦИЕЙ И ТРЕПЕТАНИЕМ ПРЕДСЕРДИЙ

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Обследованы 76 пациентов с фибрилляцией и трепетанием предсердий (ФП/ТП) в группах в зависимости от проведённого оперативного вмешательства (радиочастотная абляция легочных вен (РЧА ЛВ), каво-трикуспидального истмуса (КТИ), комбинированная стратегия (ЛВ + КТИ)). Оценивались пол и возраст пациентов, форма ФП и ТП, длительность течения ФП/ТП, классификация ФП/ТП по различным шкалам; стадии и степени артериальной гипертензии (АГ); типы ишемической болезни сердца (ИБС); наличие сахарного диабета 2 типа; острое нарушение мозгового кровообращения в анамнезе; функциональный класс и стадии хронической сердечной недостаточности (ФК ХСН). Частота распространения основных кардиоваскулярных заболеваний и их клинических признаков наблюдаются одинаково в группах пациентов с ФП/ТП независимо от типа проведённого оперативного вмешательства, и они не влияют на выбор последнего. Пациентам мужского пола чаще проводится РЧА КТИ, женского – РЧА ЛВ. Пациентам с персистирующей формой ФП чаще требуются альтернативные методы лечения, в первую очередь, катетерная абляция субстрата аритмии.

КЛЮЧЕВЫЕ СЛОВА: клинические признаки, фибрилляция и трепетание предсердий, оперативное вмешательство, катетерная абляция, каво-трикуспидальный истмус, легочные вены

INTRODUCTION

Despite progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world [1–2].

With the introduction of catheter interventions methods the opportunity to radically eliminate the arrhythmia substrate revealed itself, which is particularly important for young patients.

In general, catheter ablation is effective in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent and probably long persistent AF (AFL) as second-line therapy after failure or intolerance to antiarrhythmic therapy. In paroxysmal AF as catheter ablation was considered first-line therapy, randomized study showed only a slight improvement results rhythm control compared with antiarrhythmic therapy [3].

Patients with documented right-atrial isthmus-dependent flutter, undergoing ablation due to AF, the right atrial isthmus ablation is recommended [1].

The above requires a careful approach to assess the main clinical characteristics of patients requiring surgical treatment for arrhythmia, which is not enough studied at the moment.

OBJECTIVE

To establish clinical features of patients with AF and AFL depending on the type of conducted radiofrequency ablation.

MATERIALS AND METHODS

76 patients aged 59 ± 8 (p (M ± sd)) (44 male and 32 female) were examined, from them – 21 patients with radiofrequency ablation of pulmonary veins (RFA PV), 30 - cavo-tricuspid isthmus (CTI), 25 – a combined strategy (PV + CTI), which were distributed to the appropriate group.

We evaluated the sex and age of patients, AF and AFL forms (paroxysmal, persistent, permanent); duration of AF/AFL (> or < 1 year); classification of AF / AFL by scales: EHRA (I–IV), CHA2-DS2-VASc (0–5), HAS-BLED (1–3); stage (I–III) and degree (1–3) of arterial hypertension (AH); types of ischemic heart disease (IHD) (angina of effort and functional classes (FC), X-syndrome, variant angina (VA), silent myocardial ischemia (SMI), atherosclerotic heart disease (ASHD), past myocardial infarction (PMI)); diabetes mellitus (DM) type 2; acute cerebrovascular accident history (CVA) ; FC and stages of chronic heart failure (CHF) according NYHA classification, stages of CHF according Strazhesko M.D. and V. H. Vasilenko in the Association of Cardiologists of Ukraine recommendations (2012) [4–5].

The data obtained after the formation of the database processed in Microsoft Excel. For statistical evaluation of the results were used parametric criteria's (mean – M, standard deviation – sd), non-parametric criteria's (absolute (n, number), relative (percentage (p, %) and the average error rate (sP)). The level of statistical significance of differences between groups was assessed using non-parametric Friedman ANOVA and Kendall coefficient of Concordance test and additionally performed a Wilcoxon Matched Pairs Test for parameters that showed a statistical difference between the groups to identify differences between couples. Friedman nonparametric test

was considered statistically significant at $p < 0.05$, Wilcoxon test was considered statistically significant when $W < 0.05$.

Calculations were performed using the software package STATISTICA 10.

RESULTS AND DISCUSSION

Table 1 present's data on the distribution of patients by age and sex in different groups conducted surgery with the evaluation of statistical significance.

Table 1

Distribution of patients by age and sex in different groups conducted surgery with the evaluation of statistical significance

Indicator			**RFA PV**	**RFA CTI**	**RFA PV+CTI**
Total (n, % ± sP)			21, 28 ± 5	30, 39 ± 6	25, 33 ± 5
Gender (n, % ± sP)	Males		7, 33 ± 5	23, 77 ± 5	14, 56 ± 6
	Females		14, 67 ± 5	7, 23 ± 5	11, 44 ± 6
	The level of statistical signify-cance of differences between groups	Friedman test result	p = 0,0023		
		Value of coefficient of Concordance	W = 0,2888		
		Wilcoxon test result	p = 0,0033	No significant differen	No significant differen
Age (M ± sd, years)			53 ± 9	64 ± 7	59 ± 6
	The level of statistical signifi-cance of differences between groups	Friedman test result	No significant difference p = 0,2231		
		Value of coefficient of Concordance	W = 0,075		

Notes: M – mean; n – number; sd – standard deviation; sP – the average error rate.

Revealed significant differences between groups in the ratio of male/female ($p < 0.05$), where the group CTI dominated by men, in the group PV – women; group PV + CTI ratio had no significant difference.

Table 2 presents data of main characteristics of the clinical course and the underlying rating scale AF/AFL with the assessment of the level of statistical significance.

The persistent form of the AF surpassed the RFA PV group ($p < 0.05$), between CTI and PV + CTI groups statistically difference was not revealed. The significant difference was detected between all groups by the types: paroxysmal form predominated in PV + CTI group, persistent – in CTI group.

Figure shown the distribution of data for group's duration of AF/AFL with assessment of statistical significance.

Table 2

Main characteristics of the clinical course and the underlying rating scale AF/AFL

Main characteristics of heart rhythm disturbances			**RFA PV**	**RFA CTI**	**RFA PV+CTI**
AF (n, % ± sP)	Total		21, 100	14, 47 ± 6	25, 100
	Paroxysmal		3, 14 ± 4	1, 7 ± 3	16, 64 ± 6
	Persistent		18, 86 ± 4	11, 79 ± 5	9, 36 ± 6
	Permanent		0	2, 14 ± 4	0
	The level of statistical significance of differences between groups	Friedman test result	p = 0,0083		
		Value of coefficient of Concordance	W = 0,2279		
		Wilcoxon test result	p = 0,0082	No significant difference	p = 0,0071

Continuation of the table

AFL (n, % ± sP)	Total		4, 19 ± 5	30, 100	25, 100
	Paroxysmal		0	3, 10 ± 3	14, 56 ± 6
	Persistent		4, 100	25, 83 ± 4	11, 44 ± 6
	Long-persistent		0	2, 7 ± 3	0
	The level of statistical significance of differences between groups	Friedman test result	p = 0,00001		
		Value of coefficient of Concordance	W = 0,5493		
		Wilcoxon test result	p = 0,0002	p = 0,0071	p = 0,0014
Classification of AF/AFL and scales (n, % ± sP)	EHRA	I	0	0	0
		II	1, 5 ± 2	1, 3 ± 2	2, 8 ± 3
		III	19, 90 ± 3	27, 90 ± 3	23, 92 ± 3
		IV	1, 5 ± 2	2, 7 ± 3	0
	The level of statistical significance of differences between groups	Friedman test result	No significant difference p = 0,246		
		Value of coefficient of Concordance	W = 0,666		
	CHA2-DS2-VASc	0	4, 19 ± 5	3, 10 ± 3	4, 16 ± 4
		1	6, 29 ± 5	9, 30 ± 5	9, 36 ± 6
		2	7, 33 ± 5	8, 27 ± 5	8, 32 ± 5
		3	2, 10 ± 3	6, 20 ± 5	3, 12 ± 4
		4	1, 5 ± 2	3, 10 ± 3	1, 4 ± 2
		5	1, 5 ± 2	1, 3 ± 2	0
	The level of statistical significance of differences between groups	Friedman test result	No significant difference p = 0,793		
		Value of coefficient of Concordance	W = 0,011		
	HAS-BLED	1	8, 38 ± 6	7, 23 ± 5	8, 32 ± 5
		2	10, 48 ± 6	18, 60 ± 6	13, 52 ± 6
		3	3, 14 ± 4	5, 17 ± 4	4, 16 ± 4
	The level of statistical significance of differences between groups	Friedman test result	No significant difference p = 0,3817		
		Value of coefficient of Concordance	W = 0,458		

Notes: n – number; sd – standard deviation; sP – the average error rate.

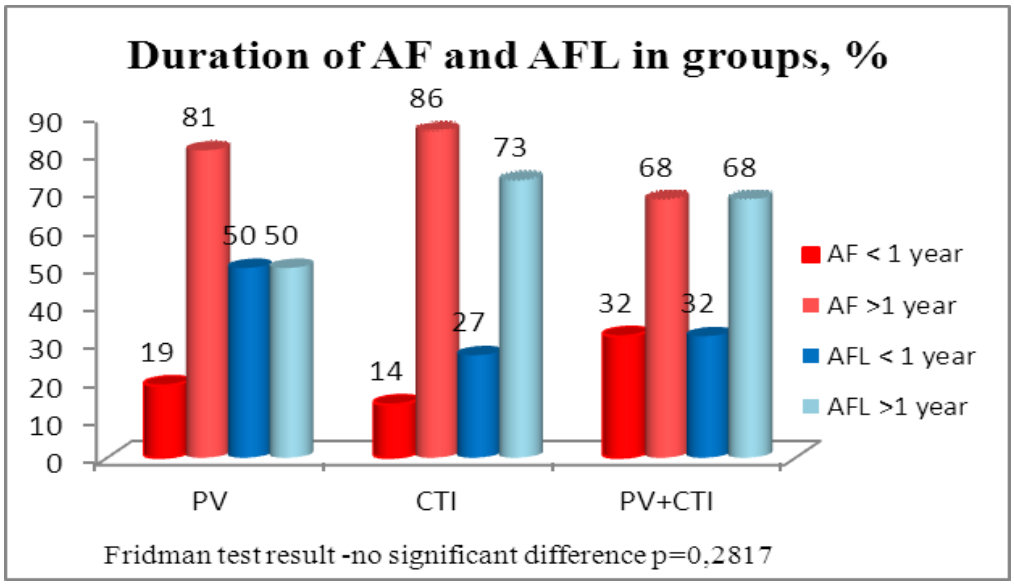

Fig. Distribution of data for group's duration of AF/AFL

The significant difference between the groups in duration of AF/AFL groups is absent, so the duration of the course of a particular type of arrhythmia did not influence the selection of the type of surgery.

These basic clinical indicators of patients who were carried various types of intervention are presented in Table 3.

Table 3

Basic clinical indicators of patients who were carried various types of intervention

Clinical features				**RFA PV**	**RFA CTI**	**RFA PV+CTI**
Total number of patients, part from the total number (n, % ± sP)				21, 27 ± 9	30, 39 ± 6	25, 33 ± 5
Diseases		Total		12, 57 ± 6	20, 67 ± 5	16, 64 ± 6
		Stage	I	0	0	0
			II	9, 75 ± 5	15, 75 ± 5	14, 88 ± 4
			III	3, 25 ± 5	5, 25 ± 5	2, 12 ± 4
		Degree	1	0	3, 15 ± 4	0
			2	6, 50 ± 6	6, 30 ± 5	9, 56 ± 6
			3	6, 50 ± 6	11, 55 ± 6	7, 44 ± 6
		The level of statistical significance of differences between groups	Friedman test result	No significant difference p = 0,5044		
			Value of coefficient of Concordance	W = 0,0325		
	IHD (n, %± sP)	Total		10, 48 ± 6	21, 70 ± 5	14, 56 ± 6
		Angina of effort		2, 20 ± 5	10, 48 ± 6	3, 22 ± 5
		FC of angina	I	0	0	0
			II	2, 67 ± 5	3, 30 ± 5	2, 67 ± 5
			III	1, 33 ± 5	7, 70 ± 5	1, 33 ± 5
			IV	0	0	0
		X-syndrome		1, 10 ± 3	0	0
		VA		0	0	0
		SMI		0	0	0
		ASHD		7, 70 ± 5	8, 38 ± 6	10, 71 ± 5
		PMI		0	3, 14 ± 4	1, 7 ± 3
		The level of statistical significance of differences between groups	Friedman test result	No significant difference p=0,6294		
			Value of coefficient of Concordance	W = 0,022		
	DM (n, % ± sP)	Total		1	6	3
		Type	2	1, 100	6, 100	3, 100
	Acute CVA (n, % ± sP)	Total		3, 14 ± 4	3, 10 ± 3	3, 10 ± 3
	CHF (n, % ± sP)	Total		16, 76 ± 5	26, 87 ± 4	15, 60 ± 6
		FC	I	7, 43 ± 6	7, 27 ± 5	6, 40 ± 6
			II	6, 38 ± 6	11, 42 ± 6	7, 47 ± 6
			III	3, 19 ± 4	8, 31 ± 5	2, 13 ± 4
			IV	0	0	0
		Stages	I	8, 50 ± 6	8, 31 ± 5	8, 53 ± 6
			IIA	8, 50 ± 6	14, 54 ± 6	7, 47 ± 6
			IIB	0	4, 15 ± 4	0
			III	0	0	0
		The level of statistical significance of differences between groups	Friedman test result	No significant difference p = 0,3492		
			Value of coefficient of Concordance	W = 0,1597		

Notes: n – number; sP – the average error rate.

Based on the results presented in tables, age, class EHRA, scale CHA2-DS2-VASc and HAS-BLED, duration of course of arrhythmia, the stage and degree of AH, types of IHD, DM, acute CVA, stage and FC CHF in groups RFA PV, CTI and PV+ CTI statistical differences were absent and therefore did not influence on the choice of the type of surgical intervention, that was not reflected in the literature.

We have identified as J. Romero et al. [6], the prevalence in the structure of sex men in the group RFA CTI due to higher prevalence of AFL among male gender. The presence in some patients with AFL concomitant AF, by the same data [6] should be regarded as a separate disease.

The predominance of women in the group RFA PV are explained by the data [7] about more symptomatic AF course in females, when medical intervention ineffective and ablation of arrhythmia substrate comes to the fore in the treatment strategy.

According to the data [8], persistent form of AF is associated with a poor control of the rhythm using drug therapy; therefore, these patients often require alternative therapies, especially RFA of arrhythmia substrate.

CONCLUSIONS

1. The frequency distribution of main cardiovascular diseases and their clinical characteristics (stage and degree of AH, types of IHD, DM, acute CVA, stage and FC CHF) observed equally in patients with AF/AFL regardless of the type conducted by surgical intervention and therefore they do not affect its choice.
2. Male patients often carried RFA CTI and women – RFA PV, due to the greater prevalence of AFL among the first and more severe clinical course of AF among second.
3. Patients with persistent form of AF more often require addition of medical therapy by alternative methods, especially catheter ablation of arrhythmia's substrate.

PROSPECTS FOR FURTHER RESEARCHES

It seems to be appropriate to study further clinical course of AF and AFL depending on the type of surgical intervention and characteristics of drug therapy.

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Clinical case

UDC 612.1: 616.02/06

DIAGONAL EARLOBE CREASE: FRANK'S SIGN IN ISCHEMIC HEART DISEASE

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The article emphasizes the necessity of meticulous physical examination of the patient in the modern clinical practice. Two clinical examples of diagonal earlobe crease, also known as Frank's sign, are given. Both cases describe patients with ischemic heart disease, but age of patients and severity of Frank's sign differ. The literature data about its frequency in different groups of population as well as the clinical significance and possible underlying pathophysiological mechanisms of Frank's are shown.

KEY WORDS: diagonal earlobe crease, Frank's sign, atherosclerosis

ДІАГОНАЛЬНА СКЛАДКА МОЧКИ ВУХА: ОЗНАКА ФРАНКА ПРИ ІШЕМІЧНІЙ ХВОРОБІ СЕРЦЯ

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У статті підкреслюється необхідність ретельного фізичного обстеження хворого в сучасній клінічній практиці. Дано два клінічні приклади діагональної складки мочки вуха, також відомої як ознака Франка. Обидва випадки описують хворих із доведеною ішемічною хворобою серця, але різного віку із різною виразністю ознаки Франка. Наведено літературні дані про її частоту в різних популяційних групах, а також клінічне значення та можливі основні патофізіологічні механізми виникнення ознаки Франка.

КЛЮЧОВІ СЛОВА: діагональна складка мочки вуха, ознака Франка, атеросклероз

ДИАГОНАЛЬНАЯ СКЛАДКА МОЧКИ УХА: ПРИЗНАК ФРАНКА ПРИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА

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В статье подчеркивается необходимость тщательного физического обследования больного в современной клинической практике. Даны два клинических примера диагональной складки мочки уха, также известной как признак Франка. Оба случая описывают больных з доказанной ишемической болезнью сердца, но различного возраста и с различной выраженностью признака Франка. Приведены данные литературы о его частоте, а также о клиническом значении и возможных патофизиологических механизмах развития признака Франка.

КЛЮЧЕВЫЕ СЛОВА: диагональная складка мочки уха, признак Франка, атеросклероз

INTRODUCTION

Despite the widespread introduction of modern laboratory and instrumental methods for diagnosing cardiovascular diseases (CVD), especially of atherosclerotic origin, careful interviewing and physical examination of the patient continue to play an important role in the diagnosis of ischemic heart disease (IHD).

The physical examination of a patient with suspected atherosclerotic CVD should include an assessment of whether a patient looks younger or older than his or her actual age [1–3]. This approach assumes that the perceived age of a patient correlates with age-related disease and mortality, and thus that patients appearing older than their chronological age are more likely to have poor health status, compared with those appearing their actual age [4]. Previous studies have found that male pattern baldness, grey hair, and facial wrinkles as well as presence of arcus cornea are all markers of looking old for one's age [1, 5–7]. Earlobe crease, xanthelasmata, and arcus cornea are appearance factors, which similarly to the common age-related signs occur more frequently with increasing age. Cardiovascular disease is one of the most common age-related diseases, and also the leading cause of death worldwide [1].

According to the literature data earlobe crease (ELC) has been shown to be associated with CVD or risk factors for CVD and could be a marker of predisposition to CVD.

CLINICAL CASE

Case 1 presentation. A 61-year-old man presented to the emergency department with 5-hour burning chest pain non-responsible to sublingual nitroglycerin, irradiating to the left shoulder, associated with dyspnea. His has a history if long-standing hypertension, positive family history for hypertension and cerebrovascular disease. Physical examination noted diagonal (Frank's sign) and pre-auricular creases in both earlobes (Fig. 1).

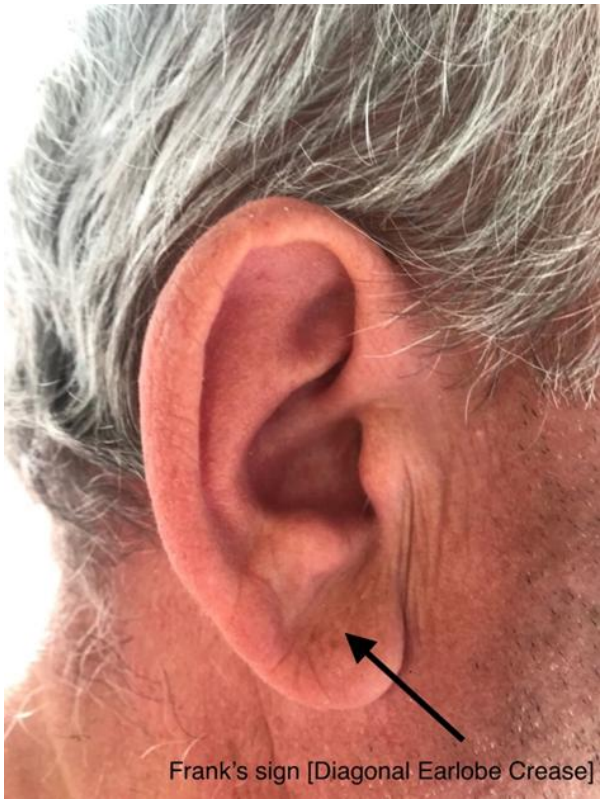

Fig. 1. Photograph shows the diagonal earlobe and preauricular creases

An electrocardiogram revealed horizontal ST-segment depression with negative T wave in I, AVL and V5–V6 leads. Cardiac enzymes (troponin T, MB fraction of creatine kinase) were markedly elevated. Coronary angiography revealed occlusion of marginal branch of

circumflex artery, and one stent was placed. The following diagnosis was made: IHD. Acute (13.10.2017) myocardial infarction without Q wave of the basal and lateral left ventricle wall. Occlusive atherosclerosis of circumflex artery (Corona-roangiography with stenting 13.10.2017). Essential hypertension III stage 3 grade, very high total cardiovascular risk. HF I stage with preserved systolic function II FC.

This clinical case demonstrates Frank's sign in patient slightly older than 60 years with proven CVD. Although it has limited sensitivity, the sign is more useful diagnostically in persons younger than 60 years of age than in older persons [8].

The next clinical case demonstrates this sign in older patient with proven CVD but without arterial hypertension.

Case 2 presentation. A 73-year-old man who complaints of general fatigue with a past medical history of non-Q-wave myocardial infarction, confirmed by cardiac enzymes, dyslipidemia, paroxysmal form of atrial fibrillation according to results of electrocardiographic Holter monitoring is under our following-up with the diagnosis IHD. Postinfarction (non-Q-wave anterior infarction 10.09.2014) cardiosclerosis. Atrial fibrillation, paroxysmal form. EHRA I, CHA2DS2-VASc - 3, HAS-BLEED-2. HF I stage with preserved systolic function II FC. Condition after mild amiodarone-induced thyroid dysfunction with spontaneous restoration of euthyroidism. The case of amiodarone-induced thyroid dysfunction was described previously [9]. This patient was noted to have bilateral Frank's sign with 2 diagonal earlobe creases (Fig. 2).

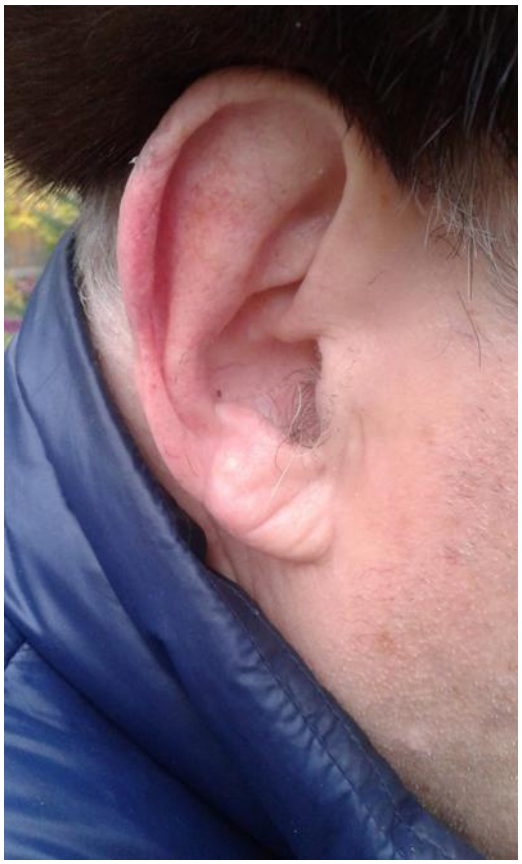

Fig. 2. Photograph shows two diagonal earlobe creases

Both cases demonstrate an association between ELC and proven atherosclerosis of the coronary arteries regardless of patients' age. According to some literature data, the frequency of ELC has been shown to be high in patients with IHD, which was shown in our clinical cases.

DISCUSSION

In Raman study, the prevalence of ELC, a sign of coronary heart disease was observed in nearly 60 % of patients with diabetes more than 40 years old [10]. In Australia, Davis et al. [11] reported that the sensitivity and specificity of

ELC for detecting IHD were 60 % and 48 % but this sign was of little value as a sign of the presence of diabetic vascular complications. According to another study [12] of 520 forensic autopsy cases, the existence of an ELC was noted in 55 % of cases. ELC was found to be the strongest independent risk factor for coronary artery disease and sudden cardiac death apart from age and body mass index for both genders.

ELC runs from the lower pole of the external meatus, diagonally backward to the edge of the lobe at approximately 45 degrees. In 1973, Frank first reported the association of the presence of ELC with IHD [13]. It was deemed as the Frank sign. However, a consensus for the routine use of ELC in IHD patients is yet to be formed [14].

Preliminary observations by ancient Chinese traditional doctors suggesting that a 'positive ear-lobe sign' is associated with the development of premature coronary artery atherosclerosis have been heralded [15–16]. Prior to Frank's description, aficionados of Roman sculpture might have seen but not grasped the significance of busts portraying the emperor Hadrian prominently displayed bilateral ear lobe creases [17–18]. Classical writings suggest that the Roman emperor Hadrian, born in Italia, 10 km from present day Sevilla, died from congestive heart failure resulting from hypertension and coronary atherosclerosis. This diagnosis is supported by the identification of bilateral diagonal ear creases on sculptures of several busts of Hadrian as well as literary evidence of behavior pattern A. Roman portrait sculpture is considered to be highly accurate and detailed (Fig. 3) [15, 18–19].

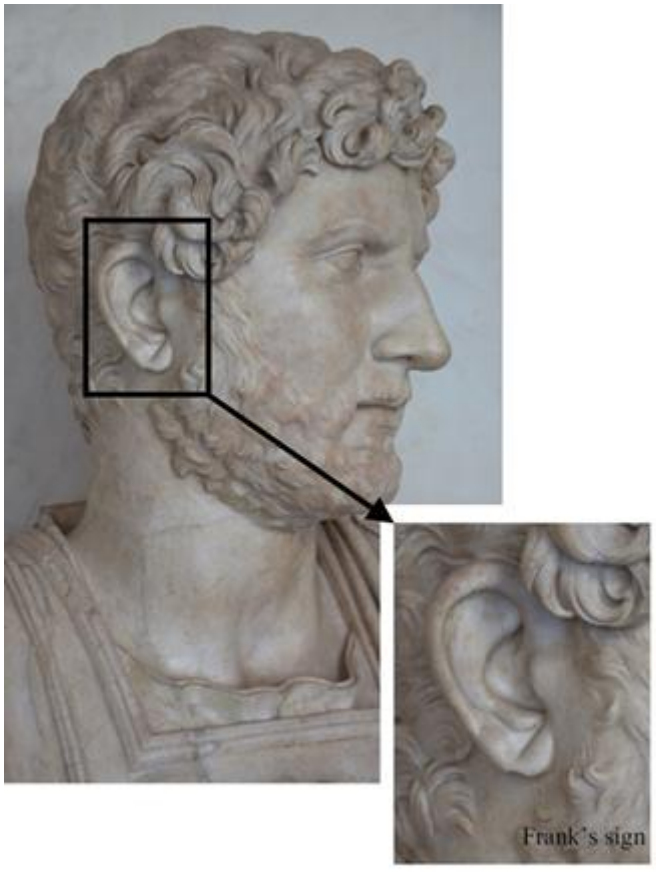

Fig.3. Colossal head of Hadrian. Rome, Vatican Museums, Pius-Clementine Museum, Round Room, 7 (Musei Vaticani, Museo Pio-Clementino) [19]

The etiologic basis of ELC is not clear and the underlying pathophysiological mechanisms are still under discussion. The suggested explanation might include degeneration of elastin as well as unbalanced ratio of collagen to elastin, as these traits reflecting

microvascular disease were similarly seen in biopsy specimens taken from the earlobes and the coronary bed. Similarly to the heart, earlobes have an end-artery-type of microcirculation without collaterals and become quickly anoxic if end-arteries are occluded [20]. Thus, the postulated theory suggests that any pathological condition influencing the microvasculature such as IHD, diabetes mellitus, metabolic syndrome and arterial hypertension may contribute to the formation of Frank's sign [14]. Moreover, diffuse loss of elastin and elastic fibers were observed in biopsy specimens taken from earlobe creases depicting the vasculature morphology present in the coronary bed, pathognomonic of IHD. A conclusion that elastin degeneration in the skin may be a marker of abnormalities in vessel walls with similar elastic properties was made [21]. Therefore, risk factors for CVD associated with abnormal microcirculation might cause ELC due to a local microvascular alteration associated with atherosclerosis [22].

Moreover, a possible association between Frank's sign and carotid arteries atherosclerosis has been demonstrated recently by clinical, autopsy, and angiography studies though not finally confirmed. Some authors supposed that Frank's sign might be the earliest manifestation of a generalized vascular disease and subclinical atherosclerosis [23–25]. The ELC was also associated with such IHD surrogates as brachial-ankle pulse wave velocity and aortic intima-media thickness in subjects without clinically overt CVD. A common patho-physiologic relation between ELC and IHD has been shown in the molecular biology research, which may be explained by structural similarity: earlobe collagen consists of peptide chains resembling those present on scavenger macrophages receptor used for the ingestion of atheromatous cholesterol [24, 26].

The relation between Frank's sign and ageing is still controversial. The primary role of ageing was discussed due to the rarity of ELC among infants and because Japanese male patients having ELC had shortened telomeres in peripheral white blood cells, again implicating aging [23–24]. Embryologic and vascular supply disorders are also suggested by the same genetically originated end-arterioles and similar leukocyte antigen subtypes for both ELC and coronary artery atherosclerosis [24–25, 27].

Thus the majority of clinical, angiographic and postmortem reports support the idea that ELC can be a valuable extravascular physical sign able to highlight those patients who are predisposed to atherosclerotic CVD. Along with the patient's medical history and meticulous physical examination Frank's sign may be helpful in evaluation of atherosclerotic risk.

CONCLUSIONS

The goal of any medical procedure is to achieve the best clinical result with the maximal possible improvement in the quality of life and life expectancy of the patient while minimizing the cost of evaluation. The basis of the approach is the meticulous physical examination of the patient [28].

Most cardiovascular risk factors require specific laboratory investigations (i.e. lipid profile, glucose) and might not be highly available in low or middle-income countries, where access to health resources is sometimes limited. That is why the identification of simple clinical signs associated with an increased risk of cardiovascular disease cannot be overestimated. Thus appropriate integration of patient symptoms, demographics, clinical characteristics, and examination findings remains essential for the clinician to accurately determine the likelihood of atherosclerotic cardiovascular diseases to distinguish those patients who need further meticulous investigation.

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THE PICKWICKIAN SYNROME CASE

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The article demonstrates a clinical case of Pickwickian syndrome. The clinical manifestation of the syndrome, a diagnostic approach including instrumental methods, and the up-to-date treatment based on the literature data are shown. The significance of maintaining lifestyle modification with accent on a normalization of body mass is emphasized.

KEY WORDS: the Pickwikian syndrome, obesity-hypoventilation syndrome, lifestyle modification

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У статті представлена клінічна картина синдрому Піквікіка. Показані клінічні прояви синдрому, діагностичний підхід, включаючи інструментальні методи, та наведено сучасне лікування на підставі літературних даних. Наголошено на важливості підтримки модифікації способу життя з акцентом на нормалізації маси тіла.

КЛЮЧОВІ СЛОВА: синдром Піквіка, синдром ожиріння-гіповентиляції, модифікація способу життя

СЛУЧАЙ СИНДРОМА ПИКВИКА

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Данная статья демонстрирует клинический случай синдрома Пиквика. Показаны клинические проявления синдрома, диагностический подход, включающий инструментальные методы, и современное лечение на основе литературных данных. Подчеркивается важность сохранения модификации образа жизни с акцентом на нормализацию массы тела.

КЛЮЧЕВЫЕ СЛОВА: синдром Пиквика, синдром ожирения-гиповентиляции, модификация образа жизни

INTRODUCTION

Obesity and its consequences lead to increase of morbidity and negatively influence on quality of life with increased healthcare expenses. One of these repercussions is obesity-hypoventilation syndrome (OHS), or alveolar-hypoventilation in obesity [1]. It has been named as the «Pickwickian syndrome» after Joe, the fat, red faced boy in Charles Dickens' The Pickwick Papers [2]. The diagnosis of this syndrome can be made in the presence of three key components such as obesity if body

mass index (BMI) exceeds 30 kg/m^2, obstructive sleep apnea and daytime or wakefulness hypoventilation resulting in chronic hypercapnia in the absence of alternative causes explaining the hypoxemia-hypercapnia. These signs are known as the Pickwickian triad, too. Although it has been revealed that approximately 10–20 % of obese patients with daytime somnolence have hypercapnia the precise prevalence of OHS really is unknown [1]. Moreover, its prevalence has been markedly increasing during the last three decades, probably due to the present «epidemic» of obesity [1]. OHS often remains undiagnosed until the late stage of the disease. Early detection of the OHS is of greatest importance, as effective treatment can lead to significant improvement in patient outcomes [3].

CLINICAL CASE PRESENTATION

A 50-year old man was admitted to the Institute of Therapy with complaints of dyspnea and chest tightness during moderate physical activity, leg edema, fatigue, daytime sleepiness and weight gain. His wife told that her husband had disturbed sleep at night as well as snoring and short-term pauses during sleeping.

ANAMNESIS MORBI

Patient developed all symptoms two years ago when dyspnea and chest tightness during moderate physical activity occurred. The hypertension (HTN) was diagnosed at the same time. The maximal blood pressure (BP) was 170/100 mm Hg. The patient was prescribed drug treatment with bisoprolol, indapamide and lisinopril but without marked efficacy.

ANAMNESIS VITAE

Patient denies tuberculosis, sexually transmitted infections, traumas, hereditary diseases. He had an appendectomy and surgical intervention because of left-side inguinal hernia in the childhood. Allergic history is negative. The patient smokes a pack of cigarettes in a day and denies alcohol abuse.

OBJECTIVE EXAMINATION

Patient's conciseness is clear, general condition is of moderate severity, posture is active. Patient is orientated in place, time and his personality. Patient is obese with BMI 41,62 kg/m^2. Face is hyperemic. Thyroid gland is slightly enlarged, smooth, elastic, mobile, non-tender to palpation. Peripheral lymph nodes are non-palpable. Respiratory rate is 18 per minute. Lung percussion reveals resonant sounds. Dry rhonchi at the background of the weakened vesicular breathing were auscultated. Heart borders are shifted 2 cm to the left. Heart auscultation: heart rhythm is regular, heart sounds are muffled. Pulse rate is 68 beats per minute. BP is 140/90 mm Hg on both arms. Abdomen is symmetrical, increased in its size due to subcutaneous fat, participates in breathing. Tenderness to palpation is absence. Blumberg sign is negative. Liver edge is palpable 5 cm below the left costal margin without tenderness to palpation. Spleen is non-palpable. Pasternatsky sign is negative on both sides. Moderate feet and shins pitting edema are detected.

LABORATORY AND INSTRUMENTAL TESTS

In CBC (13.09.17) elevated erythrocytes sedimentation rate (ESR) – 16 mm/h with unremarkable other parameters.

Urinalysis (13.09.17): no abnormalities were found.

Blood biochemistry (13.09.17): mild hyperglycemia (fasting glucose level 6,09 mmol/L (normal range is 3,3–5,5 mmol/L), but glycosylated hemoglobin is within normal limits (5,7 %; normal range is 4,5–6,1 %); increased level of ALT (55 U/L, normal limits less than 45 U/L), a high-sensitivity C-reactive protein (hs-CRP) is 4,5 mg/L (normal limits less than 3 mg/L), elevated levels of total cholesterol (5,39 mmol/L, normal limits less than 5,2 mmol/L) and low density lipoprotein cholesterol (LDL-C) (3,78 mmol/L, normal limits less than 3,1 mmol/L). Increased level of thyroid-stimulating hormone (TSH) up to 7,88 mcIU/ml (normal range is 0,23–3,4 mcIU/ml) with normal level of the thyroid hormone free T4 (13,0 nmol/L, normal range is 10,0–23,2 nmol/L) were detected.

Chest X-ray (14.09.17): sings of the left ventricle hypertrophy and dilatation of the left atrium, compaction of the aortic wall and calcification of the left coronary artery, high level of diaphragm position.

ECG (12.09.17) sinus rhythm with heart rate 64 beats per minute, non-specific repolarization abnormalities in the lateral and inferior segments of the left ventricle wall.

Echocardiography (12.09.17): ejection fraction (EF) is 60 %. Contractility function is preserved. Enlargement of the left atrium up to 4, 2 cm (norm less than 4,0 cm). Left ventricle: end-diastolic diameter is 5,2 cm (norm is 3,5–5,6 cm), end-systolic diameter is 3,5cm (norm is 2,3–4,0 cm), posterior wall thickness is 1,12 cm (norm is 0,6–1,1 cm) – increased. Intraventricular septum thickness is increased up to 1, 13 cm (norm is 0, 6–1, 1 cm). Right ventricle: diameter is 2, 6 cm (norm less than 3,0 cm). Right atrium is 3, 8 cm (norm is 2, 0–3,8 cm). The systolic pressure in a pulmonary artery is 35 mm Hg (norm is 30 mm Hg) – increased. Valve apparatus is not changed. Conclusion: thickening of aortic wall and aortal valve leaflets, mild dilatation of the left atrium cavity, the left ventricle hypertrophy and the blockade-type dyskinesia of the inter-ventricular septum. Pulmonary hypertension I degree.

Ultrasonography of the thyroid gland (12.09.17): diffuse goiter, II degree.

Abdominal ultrasonography (12.09.17): diffuse changes of the liver, enlarged gall bladder, sings of chronic pancreatitis.

Consultation of endocrinologist (18.09.17): Diffuse goiter II degree, subclinical hypothyroidism. Obesity 3 degree of mixed etiology. Impaired glucose tolerance. Levothyroxine 12, 5 mcg per day was recommended.

Consultation of neurologist (18.09.17): Diffuse hypertensive encephalopathy II degree.

CLINICAL DIAGNOSIS

IHD: Stable effort angina II functional class. Essential arterial hypertension II stage, 2nd degree, very high total cardiovascular risk. Hypertensive heart (left ventricle hypertrophy). HF II A stage with preserved systolic function of the left ventricle (EF 60 %), II functional class by NYHA. Diffuse goiter II degree, subclinical hypothyroidism. Obesity 3 degree of mixed etiology. Impaired glucose tolerance. Diffuse hypertensive encephalopathy II degree. Pickwickian syndrome.

TREATMENT

Lifestyle modification, with a reduction of energy intake and an increase in physical activity, is essential in all treatment strategies for obesity. Patient received recommendation to follow hypolipidemic low-caloric diet with carbohydrates and salt restriction. Rational physical activity should include at least 30 min/day, 5 days/week of moderate intensity physical activity. Smoking cessation was highly recommended [4].

Drug therapy: acetylsalicylic acid 75 mg/day, atorvastatin 20 mg/day with LDL cholesterol goal level less than 1.8 mmol/L or LDL cholesterol reduction by no less than 50 % when the target level cannot be reached; bisoprolol 2, 5 mg/day in the morning under the heart rate control with target level of 55–60 beats per minute at rest; torasemide 5 mg/day under close urine output control, ramipril 5 mg/day under BP control with target level less than 140/90 mm Hg, L-thyroxin 12, 5 mcg/day under TSH level control. Patient condition was improved: dyspnea did not disturb in the hospital setting, leg edema disappeared.

DISCUSSION

The feature of this case is the combination of obesity with respiratory complications during nighttime sleeping, sleepiness and fatigue in daytime which allow thinking about Pickwickian syndrome, or OHS. We also can assume that hypofunction of thyroid gland has contributed to the development of obesity.

Radiographic features in OHS may be heterogeneous. Patients with OHS may either have normal chest radiographs or exhibit cardiomegaly and/or abnormal pulmonary vascularity, i.e. signs of pulmonary hypertension. Typically, subtle radiographic signs of pulmonary vascularity are difficult to evaluate given the patient body habitus [5]. These literature data can explain the absence of lung abnormalities in chest X-ray in our patient. Presence of high level of diaphragm position which has been seen in our patient can be due to severe abdominal obesity.

According to the literature data OHS is generally observed in subjects over 50 years. Comorbidities, favored by obesity, such as arterial hypertension, left heart diseases, diabetes are very frequent in these patients [3]. All these clinical manifestation are present in described clinical case.

The other interesting feature which is present in our patient is elevated level of hs-CRP. From our point of view this abnormal laboratory marker can be explained by the presence of low-grade inflammation specific to obesity. Increased visceral adiposity has

been shown to activate the important pathways connecting low-grade chronic inflammation, oxidative stress and blood coagulation [6]. The expansion of adipose tissue produces a number of bioactive substances, known as adipocytokines or adipokines, which trigger chronic low-grade inflammation and interact with a range of processes in many different organs. Although the precise mechanisms are still unclear, dysregulated production or secretion of these adipokines caused by excess adipose tissue and adipose tissue dysfunction can contribute to the development of obesity-related metabolic diseases [7].

Chronic inflammation is pivotal in heart disease; studies have shown that high levels of CRP, measured by hs-CRP, can be a marker of atherosclerosis. hs-CRP is an important predictor for adverse cardio-vascular events including myocardial infarction, cerebrovascular events, peripheral vascular disease, and sudden cardiac death in individuals without a history of heart disease [8]. Relative risk of future cardiovascular events based on hs-CRP testing is estimated as follows: low risk: CRP < 1.0 mg/L; intermediate risk: CRP 1.0–3.0 mg/L; high risk: CRP > 3.0 mg/L [9].

The patient did not undergo a spirography. But it may be recommended for such patients, because it typically reveals a restrictive pattern with a reduction in forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) but normal FEV_1/FVC ratio. This restrictive pulmonary physiology is further impaired in OHS. Chest wall compliance is reduced and respiratory resistance is increased, likely secondary to the reduction in functional residual capacity and expiratory reserve volume. As a result, the work of breathing in OHS patients is twice that of obese eucapnic individuals and increases further when these patients are positioned supine from sitting as a result of the cephaled shift of abdominal contents [10].

CONCLUSIONS

There are two tasks in the treatment of Pickwickian syndrome: maintaining a healthy body weight and oxygen therapy. Weight loss is achieved first of all by the lifestyle modification, which means a hypocaloric diet, rational physical activity and also drugs therapy, which opportunities are rather limited. If conservative treatment for obesity is non-effective the expediency of the surgical intervention should be taken into account. Bariatric surgery has been shown to be the most effective modality of reliable and durable treatment for severe obesity. In practice, several mini-invasive and invasive surgical approaches exist to achieve the optimal weight in obese patients with or without obesity-hypoventilation syndrome. According to the guidelines issued by the National Institutes of Health, patients with body mass index greater than 35 kg/m^2 and an obesity-related comorbid condition (including obesity-hypoventilation syndrome) or patients with a body mass index greater than 40 kg/m^2 can be referred for surgical treatment. The second task can be achieved by noninvasive ventilation bi-level positive airway pressure (inspiratory and expiratory positive airway pressure) [11]. The value of timely and effective treatment of Pickwickian cannot be overestimated because in the absence or non-efficacy treatment the mortality caused by respiratory arrest during sleep and the abnormalities in heart and lungs can reach 70 %. On the other hand, Pickwickian syndrome is entirely reversible if it is diagnosed and treated properly. If the problem goes undiagnosed or untreated, the outcome can be fatal due to adverse cerebrovascular or cardiovascular events including sudden cardiac death.

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DERMATOPOLYMIOSITIS OR WHEN CLINICAL DIAGNOSIS MUST BE ON SYNDROME LEVEL

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The patient with the severe course of dermatopolymiositis served as an example for diagnostics, clinical syndromes establishment, and treatment tactics. The importance of the syndrome but not of the nosological diagnosis was marked.

KEY WORDS: dermatopolymiositis, syndrome diagnosis, cancer intoxication

ДЕРМАТОПОЛІМІОЗИТ АБО КОЛИ КЛІНІЧНИЙ ДІАГНОЗ ПОВИНЕН БУТИ НА СИНДРОМНОМУ РІВНІ

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На прикладі клінічного спостереження пацієнтки з важким перебігом дерматополіміозиту розглянуто діагностику, встановлення клінічних синдромів, тактику лікування. Підкреслено важливість не нозологічного, а синдромного діагнозу.

КЛЮЧОВІ СЛОВА: дерматополіміозит, синдромний діагноз, ракова інтоксикація

ДЕРМАТОПОЛИМИОЗИТ ИЛИ КОГДА КЛИНИЧЕСКИЙ ДИАГНОЗ ДОЛЖЕН БЫТЬ НА СИНДРОМНОМ УРОВНЕ

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На примере клинического наблюдения пациентки с тяжелым течением дерматополимиозита рассмотрено диагностику, установление клинических синдромов, тактику лечения. Подчеркнута важность не нозологического, а синдромного диагноза.

КЛЮЧЕВЫЕ СЛОВА: дерматополимозит, синдромный диагноз, раковая интоксикация

INTRODUCTION

Dermatopolymiositis (DPM) is the system progressive disease and/or clinical syndrome revealing itself mainly by striated and smooth muscle loss with movement disorders as well as skin in the form of erythema, edema and not pronounced but often met visceral pathology [1–2].

Dermatopolymiositis is met in 0,2–0,8 cases per 100 000 of population. Predominant age: two peaks – 5–15 and 40–60 years. Predominant sex: female – 2:1 thousands of population [3–4].

Predisposing factors: cooling, insolation, stresses, physical overstrain, vaccination, medications.

The debut in late life appears due to the secondary nature (tumors, infections, etc.) [1–5].

The clinical study of the patient with severe dermatopolymiositis is offered to your attention.

CLINICAL CASE

The patient, female, 69 years old, complains about generalized weakness, weakness in lower extremities, dizziness, movement difficulties,

food swallowing difficulties, enunciation difficulties, mouth dryness, fever, skin rash. Retarded in the consciousness. It's difficult for her to answer the questions.

Anamnesis Morbi. The disease lasted 2–3 weeks when the mentioned complains appeared. The beginning of the disease was connected with hypothermia. The state became worse progressively, from 19.12.2016 to 26.12.2016 the patient was at hospital treatment. Diagnosis: Polyneuropathy with preferential injury of proximal section of lower extremities to moderate paresis, elements of bulbar syndrome. Neuroborreliosis? Hypertonic angiopathy of the retina of both eyes. Heart failure of the II-A stage, II FC. The carried out therapy: soda buffer IV drip, reosorbilact IV drip, glucose + ascorbic acid IV drip, saline solution, ceftriaxone 2 g/daily IV jet. Despite the carried out therapy the state of the patient was not better. She was hospitalized to neurological department because of worsening of her state.

The daughter mentioned a bite of an insect (which one is unknown) in the right forearm.

Anamnesis vitae. The patient was a conductor, now a pensioner. The working conditions were connected with frequent emotional stress; bad habits are denied; drug anamnesis is not burdened; allergy anamnesis is not burdened; from toxically factors the contact with poison for mice (arsenic based) is mentioned. Tuberculosis, virus hepatitis A, sugar diabetes, mental and venereal diseases are denied. Operations are denied. Rare respiratory diseases are marked during the lifetime.

Objective status. The state is hard, the consciousness is clear, the position is recumbent, enunciation is violated. The patient had correct physique, adequate nutrition, height – 163 sm, weight – 74 kg, BMI – 27,82 kg/m^2; skin had conventional color. Hyperemic spots (periorbital) are found on the face. Erythema spots are found on the forearms and shoulders, unit ones – on the hands. These are small plum-alike formations not rising above the surface of the skin, painless on palpation. The tongue is dry, covered by white fur. Lymphatic nodes accessible for palpation are not enlarged. Thyroid is not enlarged. Joints are painless, unconverted. Muscles are painless on palpation. Muscular power is reduced in proximal areas of lower extremities to 4 marks. Clear pulmonary sound is heard over lungs on percussion, auscultator breathing is vesicular. RR is 18 /min. AP (right) – 150/90 mm Hg, AP (left) – 150/90 mm Hg, HR – 74/min. The borders of approximate thickness are extended to the left +1,0 sm, tones are muted, rhythmic, the accent of the 2 tone on aorta. Belly is not distended, takes part in breathing, soft, painless. Liver is at the age of costal arch, soft, painless. Spleen is not palpated; Costovertebral angle tenderness is negative on both sides; edemas of the lower legs are absent. On the back side of both lower legs varicose veins are found.

Neurological status: the consciousness is clear. Enunciation is clear. Meningeal signs are absent. Eye sockets and pupils D=S. The movement of eyeballs is not limited aside, painless. The pupils' reaction on the light is normal. Convergence is lowered. Horizontal nystagmus is adjusting at outlook. Constitutional asymmetry of the face. Symptoms of oral automatism. Exit points of the trigeminal nerve are painless. The tongue is on the middle line. Pharyngeal reflex is lowered. Dysphonia. Muscular atrophies are not found. Muscular tone is not changed. Muscular power is reduced in proximal areas of lower extremities to 4 marks. Tendinous and periosteal reflexes from hands S=D are reduced. Sensitivity is preserved. Finger-nose probe is satisfactory.

Examination plan: Clinical blood analysis; Clinical urine analysis; Biochemical blood analysis (glucose, bilirubin, creatinine); Coagulogram; Lipidogram; Blood analysis for Borrelia burgdorferi; Electrocardiogram (ECG); Echocardiogram (EchoCG); US of thyroid gland, kidneys; Electroneuromyography (ENMG).

Results of the investigation. Clinical blood analysis: neutrophilic leukocytosis with the left shift of leukocyte formula. Increased ESR. **Biochemical blood analysis:** increased calurea; Increased AsAT, AlAT. **Activity of blood serum enzymes:** increased Creatine phosphokinase (CPhK) CK- NAC, Creatinekinase MB (CK- MB). **Coagulogram:** increased soluble fibrin-monomer complexes (SFMC). **Clinical urine analysis:** Moderate turbidity, much slime. **Blood analysis for Borrelia burgdorferi (blot analysis):** positive. **ECG:** Conclusion: HR 95 b/min. The electric heart axis is 26 degrees, horizontal position. Sinus rhythm, myocardium changes (V1, V2, V3, V4). Negative notch T (V1, V2, V3). **Chest organs radiography:** EED – 0,4 mSv; Focal and infiltrative changes in lungs are not found. Fibrose tightness is found in right lower areas.

Lung roots are structural, not enlarged. Sinuses are free. The diaphragm is clearly delineated. The heart is extended to the right, the aorta is sclerotized in the arch region. **US:** Sclerotic changed of aorta walls and mitral and aortal valves flaps. Dilation of ascending aorta, cavities of both auricles. Myocardium hypertrophy of both ventricles. Thyroid diffuse changes. Thyroid hyperplasia. Diffuse changes of kidneys parenchyma. Left kidney cyst. Incomplete duplication of the left kidney. Kidneys microcalculosis. **ENMG:** the data testify in favor of muscular injury (inflamematory myopathy – dermatomyositis).

Medical consultation: Considering the anamnesis, complains, objective examination data only the syndrome diagnosis can be stated: Secondary dermatopolymiositis; inflammatory syndrome; Bulbarian syndrome; Differentiate possible infection and neoplastic nature.

Clinical syndromes: Dermatopolymiositis; Infection syndrome; Bulbarian syndrome.

Therapy: Diet № 15, Dexamethasone 12 mg I/V, Reosorbilact 200,0 ml, Glucose 200,0 ml, Ceftriaxone 2g I/M, Suprastin 1,0 mg, Demidrol 0,3 mg, Analgin 2,0 mg, Omez 20 mg.

Results: Despite the carried out therapy the state of the patient remained hard. 11.01.2017 at 02:28 came respiratory and circulatory arrests. Resuscitation measures gave no result. 11.01.17. at 03:05 biological deaths was stated.

Post mortal diagnosis: Endometrium carcinoma with metastasis into stuffing gland. Secondary dermatopolymiositis. Cancer intoxication.

CONCLUSIONS

1. The clinical case confirms that the gold standard of the diagnosis is the morphological one.
2. The cause of the secondary dermatopolymiositis was stated – neoplastic disease. The rest accentuated clinical syndromes are included into the clinic of neoplastic disease.
3. The example shows that not the nosological but the syndrome diagnosis is correct until the nature of the disease is stated.

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CLINICAL CASE OF PATIENT WITH MYOCARDIAL «BRIDGE» OR WHAT CAN BE HIDDEN BEHIND A TYPICAL CLINIC OF ANGINA PECTORIS

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The article presents a clinical case, when the myocardial bridge was manifested with symptoms typical for angina pectoris. It is also emphasized the importance of carrying out of coronary angiography for such patients, and the effectiveness of stenting in cases of hemodynamically significant muscle bridges is noted.

KEY WORDS: myocardial «bridging», tunneled artery, angiography, ischemic disease, angina pectoris, atherosclerosis, anomalies of coronary vessels

КЛІНІЧНИЙ ВИПАДОК ПАЦІЄНТА З МІОКАРДІАЛЬНИМ МОСТИКОМ, АБО ЩО МОЖЕ ПРИХОВУВАТИСЯ ЗА КЛІНІКОЮ ТИПОВОЇ СТЕНОКАРДІЇ

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У статті розглядається клінічний випадок, коли миокардиальний місток маніфестував симптомами, що типові для стенокардії. Також підкреслюється важливість проведення у таких пацієнтів коронарографії, та зауважується ефективність у випадках гемодинамічно значущих міокардиальних містках.

КЛЮЧОВІ СЛОВА: міокардиальний місток, тунельна артерія, ангіографія, ішемічна хвороба, стенокардія, атеросклероз

КЛИНИЧЕСКИЙ СЛУЧАЙ ПАЦИЕНТА С МИОКАРДИАЛЬНЫМ МОСТИКОМ ИЛИ ЧТО МОЖЕТ СКРЫВАТЬСЯ ЗА КЛИНИКОЙ ТИПИЧНОЙ СТЕНОКАРДИИ

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В статье представлен клинический случай, когда мышечный мостик манифестировал симптомами, типичными для стенокардии. Также подчеркивается важность проведения у таких пациентов каронарографии и отмечается эффективность стентирования в случаях гемодинамически значимых мышечных мостиков.

КЛЮЧЕВЫЕ СЛОВА: миокардиальный мостик, тунельная артерия, ангиография, ишемическая болезнь, стенокардия, атеросклероз

INTRODUCTION

The myocardial «bridge» at first was recognized at autopsy by Reyman in 1737 and first described angiographycally by Portmann and Iwig in 1960 [1–3].

In 1995, R. Stables conducted the first stenting of the tunneled segment. Myocardial bridging is a congenital anomaly in which a

segment of a coronary artery takes a «tunneled» intramural course under a «bridge» of overlying myocardium [4]. The true frequency of MB is unknown. Numerous authors give a variety data – from 5 to 87 % [5].

There are reasons to think that the myocardial «bridges» are present in almost a one third of adults [5].

Hemodynamically significant myocar-dial «bridges» during coronary angiography are found in 0.5–4.9 % of patients [5–6].

The MB is usually described for the left anterior descending artery, and besides the middle segment of the LDA being considered as the most common location, but other large coronary arteries may also be involved in the process. Myocardial bridging does not produce any symptoms in the majority of patients. However, deeper bridging (> 2 mm) or MB with significant compression can manifest with myocardial ischemia, acute coronary syndromes, coronary spasm, exercise-induced dysrhythmias (such as supraventricular tachycardia, ventricular tachycardia, or atrioventricular block), myocardial stunning, transient ventricular dysfunction, syncope, sudden death [6].

Coronary angiography remains the most common technique for MB diagnostic [6–7].

It gives complete information about the anatomy of the coronary arteries, the localization of MB and about the degree of narrowing of the CA in systole and in diastole. Asymptomatic patients with MB do not need treatment. In patients with symptoms, medicines such as beta-blockers and calcium channel blockers are usually the first line of treatment. But in refractory to medication cases or in cases with significant systolic compression of coronary artery (more than 70 %) stent implantation can be one of the method for surgery management of MB. The purpose of our work is to present a clinical case when MB induced the symptoms of angina pectoris and to emphasize the importance of coronary angiography and stent implantation in diagnostic and treatment of symptomatic MB.

OUR CASE

Patient: female, 67 years old.

Complaints: was admitted to the cardiologycal department with complaints of pressing retrosternal pain, connected and without connection with physical exertion, relieved at rest. These complaints had noted first about six months ago.

History of the disease: patient has been suffering from hypertension since 1989, the maximum level of BP was 210/100 mm Hg. Because of hypertension periodically she was hospitalized in the cardiologycal department. She regularly takes medicine: equator 20/10 mg, bisoprolol 5 mg, roxera 20 mg.

Objective examination: active position, skin and visible mucous without changes. Above the lungs: by percussion clear pulmonary (resonant) sound, by auscultation – vesicular breathing. Auscultation of the heart – rhythmic heart sounds, accentuated II tone over the aorta. Pulse – 61 beats per minute, BP - 140/80 mm Hg. The abdomen is soft, painless, the liver is at the edge of the costal arch. Pasternatsky syndrome is negative at both sides. There are no signs of peripheral edema.

Preliminary diagnosis: Hypertension II stage 3 degree, hypertensive heart. HF 0-I. Moderate additional risk IHD. The diagnosis of stable angina was on discussion. To clarify the diagnosis of stable angina, in addition to the standard plan of investigation for patients with hypertension, a treadmill test was prescribed.

RESULTS OF THE SURVEY

General blood and urinary tests: didn't show significant pathological changes. ***Biochemical blood tests***: total bilirubin – 7.76 μmol / l, ALT 29 U \ L, creatinine – 93.95 μmol / l, glucose 6.64 μmol / l. Lipid spectrum: triglycerides 3.3 mmol / l, total cholesterol – 7.93 mmol /l, HDL – 1.43 mmol / l, LDL – 0.77 mmol / l, atherogenic coefficient – 5.4. The conclusion is: mild hyperlipidemia.

ECG: sinus rhythm with heart rate 81 beats / min. ECG signs of left ventricle hypertrophy (Fig. 1).

ECHO-CG: diameter of aorta – 32mm (20–37 mm), mitral valve opening – 29mm(26–35 mm), left atrium – 32 mm, left ventricle end diastolic diameter – 40 mm (35–55), end systolic diameter – 25 mm (23–38 mm), ejection fraction – 65 % (55–78 %), systolic fraction 34 % (28–44 %), interventricular septum – 11.8 mm (6–11 mm), right atrium – 28 mm, right ventricle – 18 mm (9–26), thickness of LV posterior wall – 12.7 mm (6–11 mm). Conclusion: there are atherosclerotic changes of the aorta, hypertrophy of the left ventricle. EKG-monitoring + BP-monitoring: the heart rate corresponds to age norm. During

24 hours submaximal heart rate was not achieved (63 % of the maximum possible for patient's age). Ventricular and atrial ectopic activity was not revealed. Levels of systolic and diastolic blood pressure are corresponded for mild hypertension.

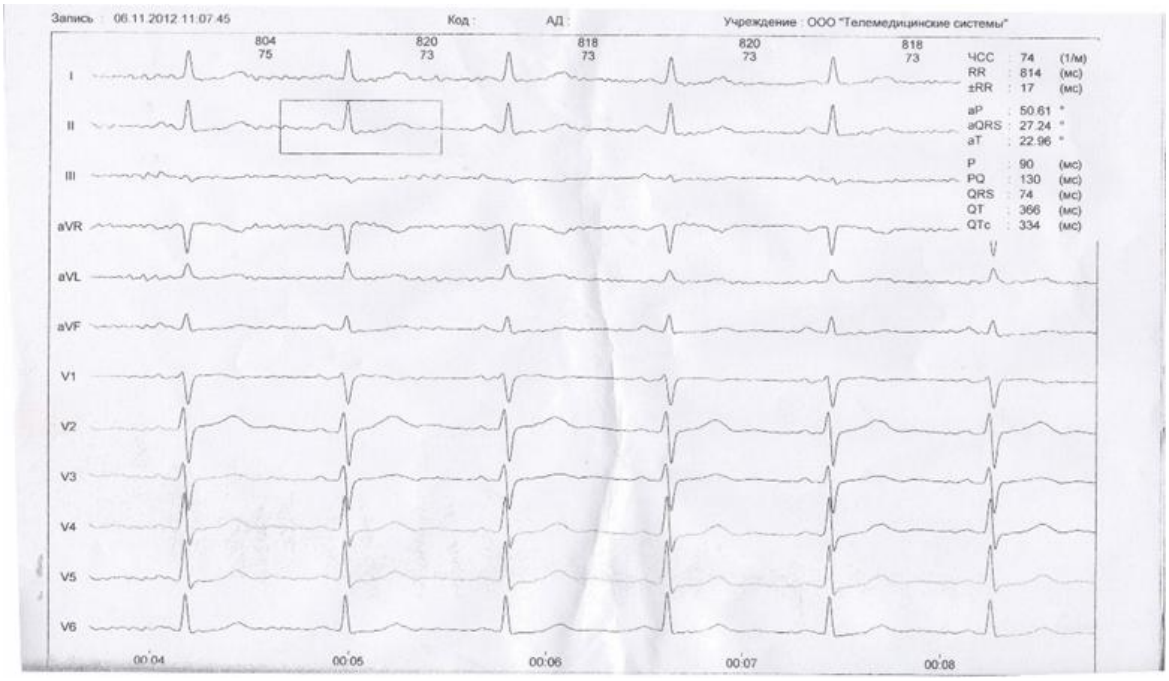

Fig. 1. ECG

Treadmill test: while doing exercise treadmill test (by Bruce protocol) blood pressure, heart rate and 12-leads ECG were recorded during several steps with increased physical exertions (from 4,6 METs) (Fig. 2). The ECG and ST-segment were continuously displayed and measured automatically by a computer-assisted system in all 12 leads. Max reached BP was 180/100 mm Hg, max HR 127 bpm. At heart rate of 120 beats per minute (7,0 METs), the ST segment showed progressive depression more then 1,0 mm in leads II, III, aVF, V4, V5, V6 that necessitated termination of the test (Fig. 3). The patient complained only on mild dyspnea and tiredness. During 4 minutes of restitution period there was complete recovery of ST-segment. Conclusion: test is positive.

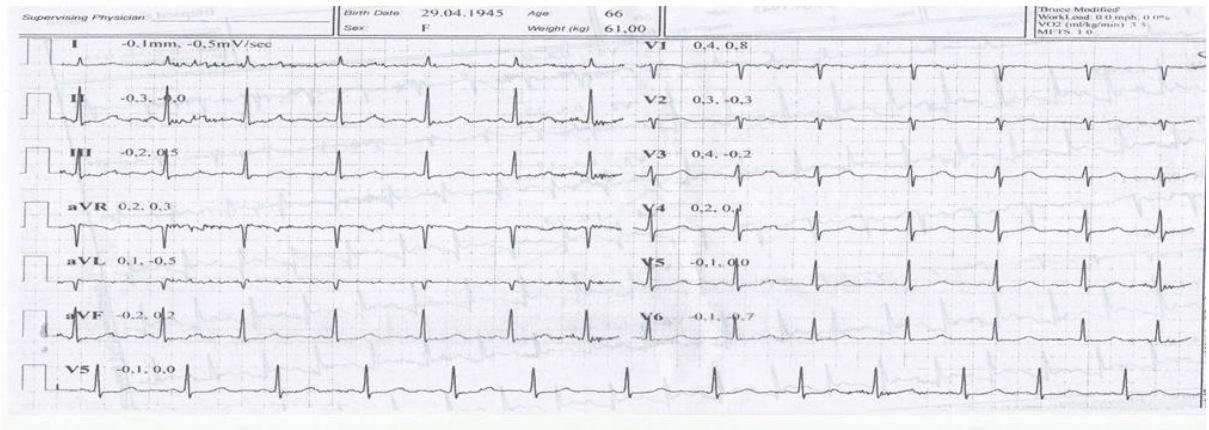

Fig. 2. (Early stage 4,6 METs)

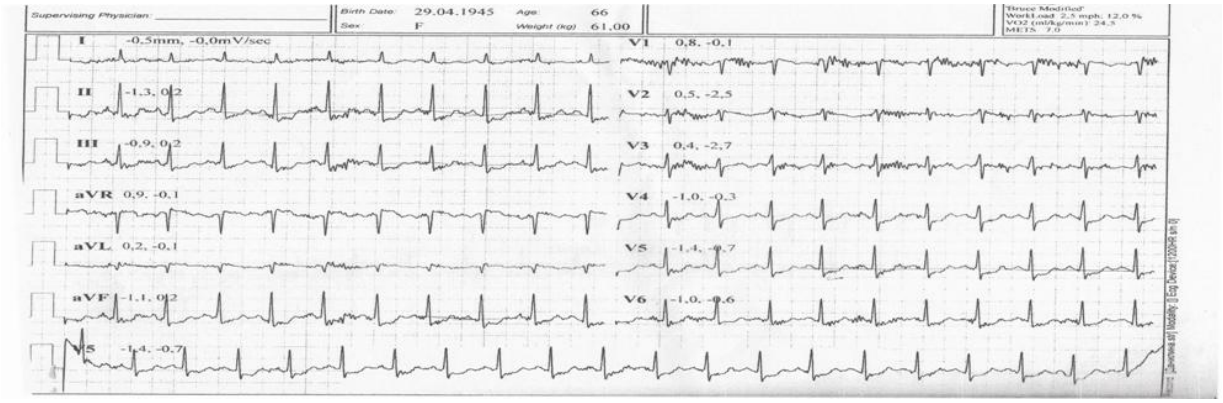

Fig. 3. (The 3-d minutes of 7,0 METs (ST depression)

Taking into account the positive treadmill test, retrosternal pain, coronary angiography was recommended to clarify coronary arteries condition and to decide about further tactic of the patient's management. Indication class-1.

Coronary angiography conclusion: the right type of coronary blood supply. Significant coronary tortuosity. Left coronary artery – prolonged myocardium bridging in the middle segment of the left anterior descending coronary artery (LAD) with systolic compression 90 % (Fig. 4A, 4B). The circumflex artery branches of the left coronary artery and right coronary artery have signs of atherosclerotic lesions without hemodynamic significance. Direct stenting with DES resolute integrity stent 3.0×38 mm was performed (Fig. 4C, Fig. 5).

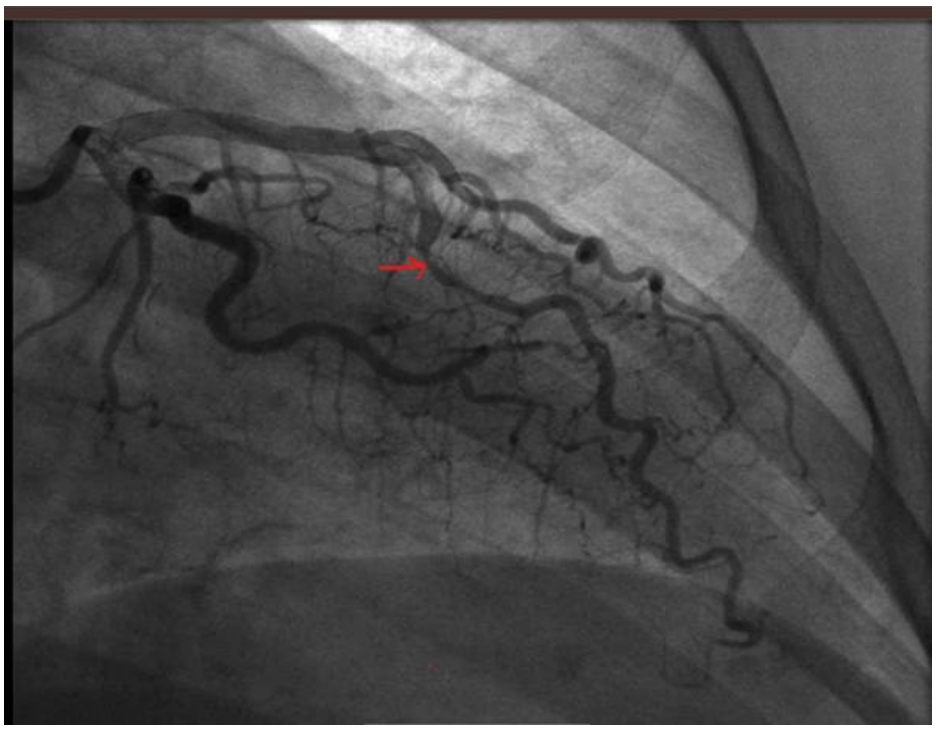

Fig. 4A. Compression of the average segment of the LAD into systole

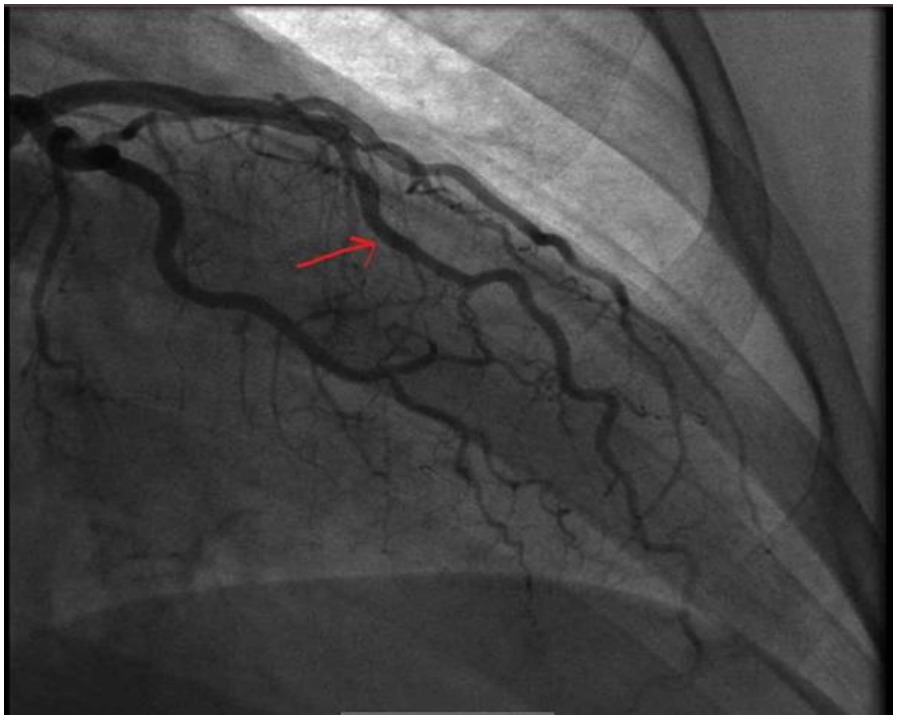

Fig. 4B. Condition of the average segment of the LAD in diastole

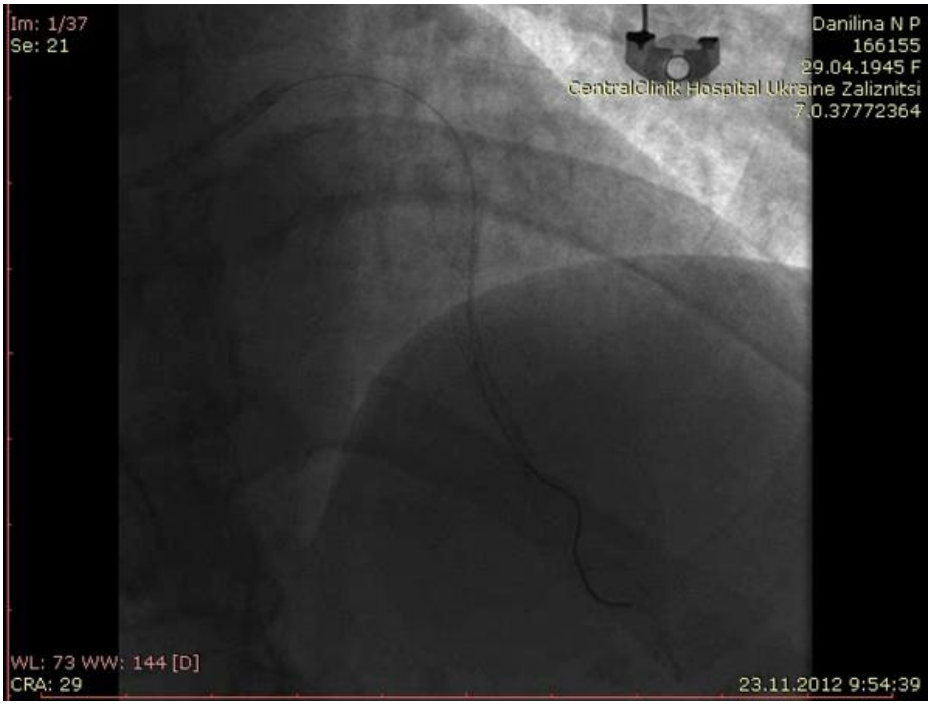

Fig. 4C. Stage of stenting

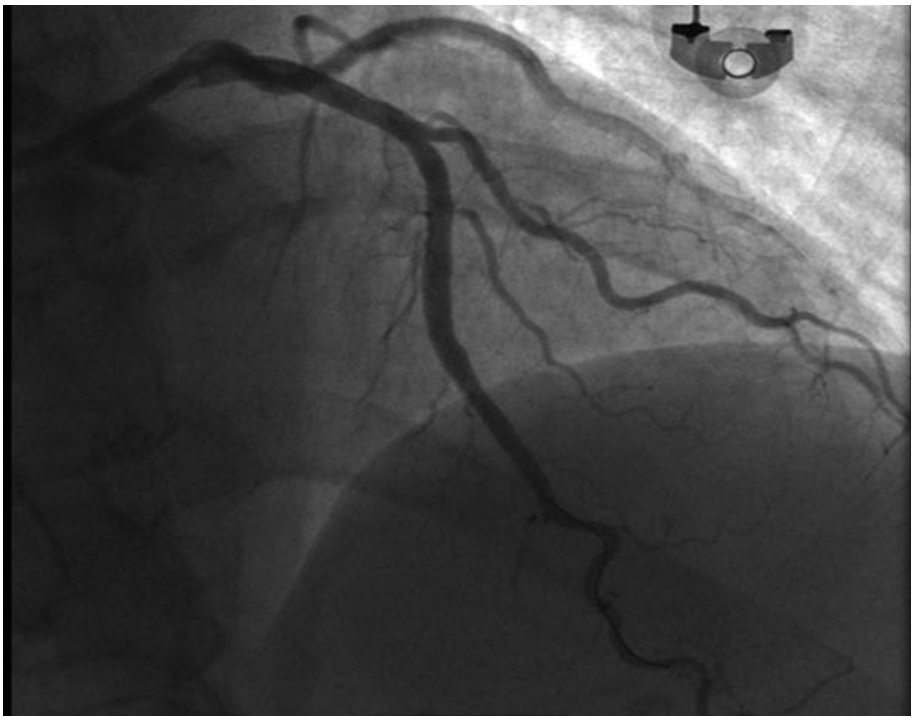

Fig. 5. After stenting (systole)

RECOMMENDATIONS

– Ramipril 5 mg, bisoprolol 5 mg
– Rosuvastatin 40 mg
– Plavix 75 mg
– Aspirin 100mg
– Repeat test with physical exertion after 3 months.

FOLLOW-UP IN 3 MONTH AFTER STENTING

Complaints: none.

Data of the second treadmill test: the test was conducted by Bruce protocol (Fig. 6–7). The test was negative (there was no any ischemic dynamic of the ST segment). Tolerance to physical activity was 10,1 METs. Maximum BP was 160/80 mm Hg.

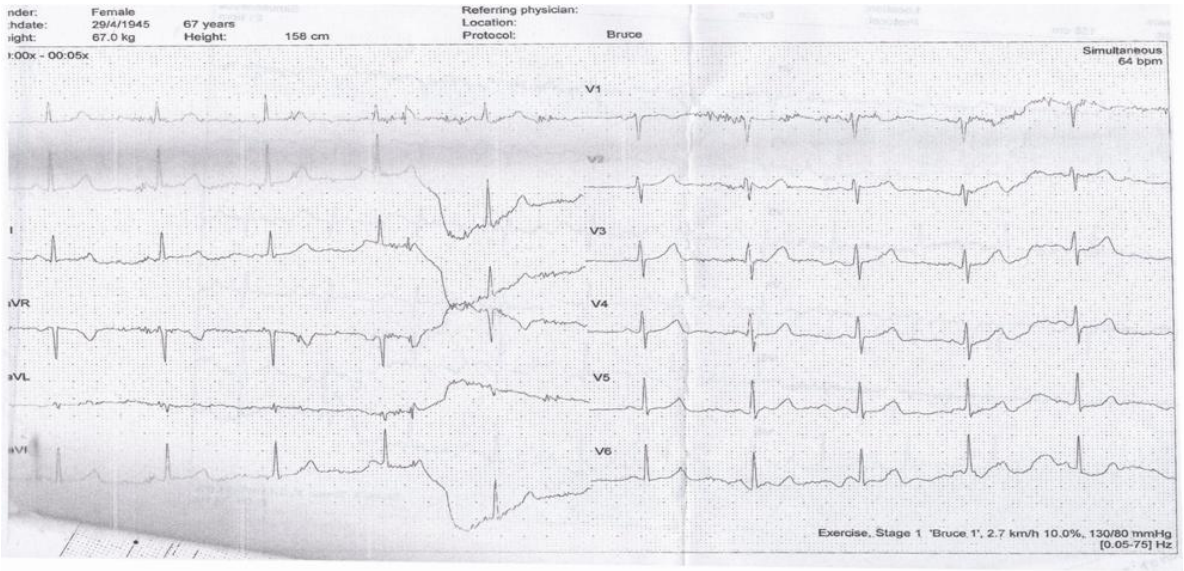

Fig. 6. Early stage.

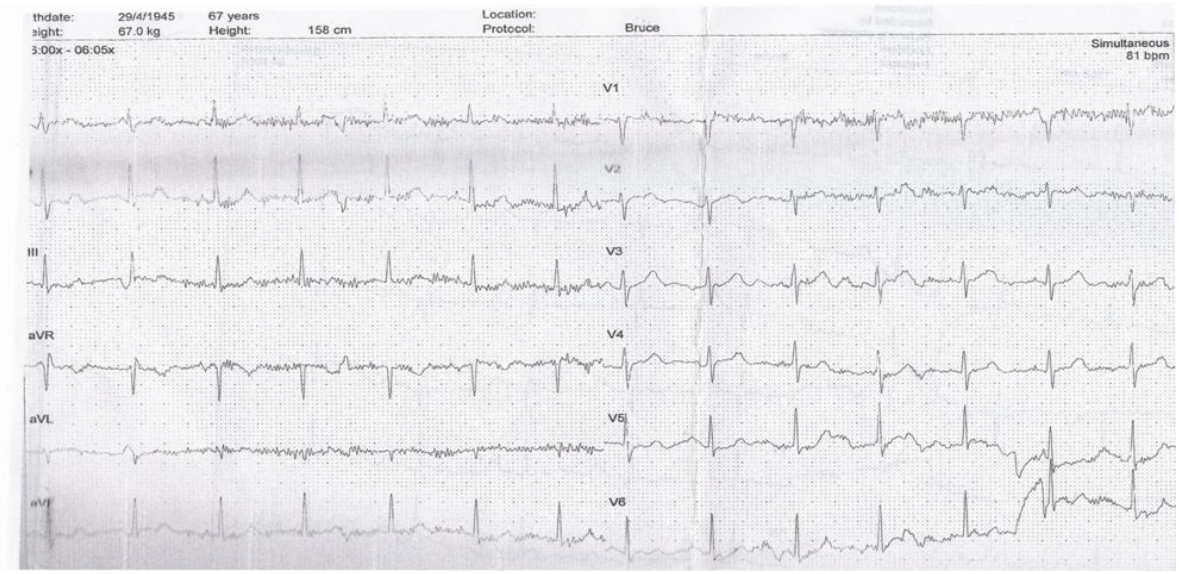

Fig.7. Stage of 10,1 METs.

CONCLUSIONS

The presented clinical case shows that MB should be taken into account in differential diagnosis in patients with symptoms of angina pectoris. Before coronary angiography was conducted (in presented patient), MB was hidden behind the typical for angina pectoris symptoms (including positive results during stress test). In addition, coronary angiography shown the localization and hemodynamic significance of the myocardial «bridge» and changed the treatment tactic from drug therapy to the stenting. The negative treadmill test and no clinical manifestations of angina pectoris after stenting confirm correctness of the chosen treatment strategy.

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