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EFFECT OF L-ARGININE L-GLUTAMATE ON THE MORPHO-FUNCTIONAL STATE ON THE HEART AND LIVER IN PATIENTS WITH POSTINFARCTION CARDIOSCLEROSIS

Summary. The liver and heart functional tests in patients with postinfarction cardiosclerosis were evaluated.
The aim of the study – to evaluate the effect of l-arginine l-glutamate on the morpho-functional state of the heart and liver in patients with postinfarction cardiosclerosis.
Materials and Methods. All patients were divided into 2 groups: group 2 (n = 49) – patients continued to make basic therapy of CHD, while patients of the group 1 (n = 50) received an additional drug – L-arginine L-glutamate (5 ml 40 % IV 7 days, then IV therapy changed to oral: 0.75g three times a day for 3 weeks. All patients underwent the following studies: a 24-hour holter monitoring, echocardiography, liver ultrasonography scanning and liver function tests (including alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), and bilirubin levels), lipid profiles (including total cholesterol, triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein levels (LDL)). All analyses were performed with the Statistical Package for "STATISTICA® for Windows 6.0" (StatSoft Inc.), Microsoft® Excel 2010 (Microsoft®).
Results and Discussion. L-arginine l-glutamine inclusion into the standard therapy of CHD demonstrated the reliable improvement of liver function: Level of total bilirubin was decreased by 26.3 %, ALT – by 48.5 %, and ALP – by 33 %. Level of total cholesterol was decreased by 16 %, LDL cholesterol – by 20.1 % and TG – by 24.4 %. Besides, level of HDL cholesterol was increased by 19.2 %. It was established, that on the background of L-arginine l-glutamine treatment took place statistically reliable improvement of the ultrasound liver parameters: liver size normalized in 35 % of patients, the structure of the capsular contour was restored – in 37 %. Normalized liver parenchymal echogenicity was noted in 29 % of patients and clear liver vascularity – in 41 %. LA size was decreased by 13.8 % , EDV by 12.5 %, ESV by 19.3 % and ejection fraction (EF) increased by 6.7 % in comparison with the initial data. The number of ischemic episodes per day decreased by 52.4 % in the group 1, the total duration of ischemic episodes per day decreased by 41 % in the group 1, the average duration of ischemic episodes decreased by 27.1 % in the group 1.
Conclusions. Inclusion into the standard therapy of CHD demonstrated the reliable improvement of liver function. A reliable lipidogram improvement was observed only in a group of patients who additionally took L-arginine L-glutamate.
Anti-ischemic activity was higher in the group of patients with additional use of L-arginine L-glutamate. Thus, correction of the morpho-functional state on the heart and liver in patients with postinfarction cardiosclerosis by L-arginine L-glutamate is considered to be pathogenetically substantiated and clinically relevant.

Key words: coronary heart disease; comorbidity; liver; postinfarction cardiosclerosis.

INTRODUCTION Coronary heart disease (CHD) is a major cause of death and disability in developed countries. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years (1). The 2016 Heart Disease and Stroke Statistics update of the American Heart Association has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD, whilst the reported prevalence increases with age for both women and men and it has been estimated that approximately every 42 seconds, an American will suffer for an myocardial infarction (2)

Comorbidity of chronic liver disease with cardiovascular diseases might be of particular interest to the study of cardiac problems. In this case the pathogenic mechanisms could be started and progress the condition of each disease.

Use of metabolic drugs that pathogenetically correct hepatotoxicity risks could improve the prognosis of two comorbid diseases.

L-arginine L-glutamine is a metabolic corrector (3). Due to the presence of these two amino acids, the drug focuses on the pathogenesis of atherosclerosis. On the one hand, the presence of L-arginine, nitric oxide sources (4), can restore endothelium vasodilation and on the other – glutamic acid as a glutathione transferase (5) and glutathione peroxidase enzymes precursor can regulate lipid peroxidation in the body.

The aim of the study – to evaluate the effect of L-arginine L-glutamate on the morpho-functional state of the heart and liver in patients with postinfarction cardiosclerosis.

MATERIALS AND METHODS This study was carried out in the union sanatorium "Khmilnyk", Khmilnyk, Ukraine**.** It is included 99 patients of 58.05±1.28 yr. (71 % male and 29 % female) admitted to the rehabilitation department for cardiac patients with postinfarction cardiosclerosis, stable exertional angina FC II-III.

Exclusion criteria were as follows: oncological diseases, acute cerebrovascular event in history up to 6 months, severe aortic stenosis, atrioventricular blockade of II-III degree, severe cardiac rhythm disorders, vascular thrombosis, liver cirrhosis, diabetes mellitus, decompensated thyroid disease, acute and chronic kidney diseases, acute heart failure, the intake of any metabolic drugs for 1 month before inclusion in the study. The study protocol was approved by the university ethics committee. Patients were grouped according to their treatment: group 2 (n = 49) continued to make basic therapy of CHD, while patients of the group 1 (n = 50) received an additional drug – L-arginine L-glutamine (5 ml 40 % IV 7 days, then IV therapy changed to oral: 0.75g three times a day for 3 weeks.

All subjects underwent the following studies: a 24-hour holter monitoring, echocardiography, liver ultrasonography scanning and liver function tests (including alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), and bilirubin levels), lipid profiles (including total cholesterol, triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein levels (LDL)).

All analyses were performed with the Statistical Package for "STATISTICA® for Windows 6.0" (StatSoft Inc.), Microsoft® Excel 2010 (Microsoft®). Non-parametric statistics methods were used to analyze the data. The data obtained are presented as a mean and standard error of the mean. The Wilcoxon test was used to compare the values of the two dependent groups. Statistically significant differences were found using Student's test.

RESULTS AND DISCUSSION. All patients completed the study according to the protocol. The analysis of the baseline characteristics in both groups was described in Table 1 and did not differ statistically.

The initial findings of the biochemical blood test revealed insignificant cytolytic and cholestatic activity with moderate increase of total bilirubin, ALT, AST, and ALP levels in all patients with postinfarction cardiosclerosis. L-arginine L-glutamine inclusion into the standard therapy of CHD demonstrated the reliable improvement of liver function: Level of total bilirubin was decreased by 26.3 %, ALT – by 48.5 %, and ALP – by 33 %.

The baseline lipid profile of the patients in both groups was impaired. A reliable lipidogram improvement was observed only in a group of patients who additionally took L-arginine L-glutamine. Thus, level of total cholesterol was decresed by 16 %, LDL cholesterol – by 20.1 % and TG – by 24.4 %. Besides, level of HDL cholesterol was increased by 19.2 %.

Primary ultrasound revealed hepatomegaly in combination with increased echogenicity of the liver parenchyma and complicated visualization of vascular pattern in more than 90 % of patients in both groups (Table 2). It was established, that on the background of L-arginine L-glutamine treatment

Table 1. Clinical and biochemical characteristics of patients

Parameters	Groups of study					
	Group 1 (n=50)			Group 2 (n=49)		
	Visit 1	Visit 2	p	Visit 1	Visit 2	p
Age (yr)	61.2±3.1			60.6±4.2		
Gender: female, % male, %	 15 (29 %) 35 (71 %)			 16 (32 %) 33 (68 %)		
BMI (kg/m^2)	32.6±2.1	30.6±1.8	>0.05	34.8±2.1	33.9±1.9	>0.05
Waist circumference (cm)	99.1±7.3	96.3±5.8	>0.05	89.3±9.2	86.9±7.5	>0.05
ALT (mM/l)	0.66±0.14	0.34±0.11	<0.05	0.70±0.13	0.63±0.08	>0.05
AST (mM/l)	0.51±0.08	0.29±0.06	<0.05	0.49±0.07	0.41±0.06	>0.05
ALP (mM/l)	1.36±0.02	0.91±0.06	<0.05	1.24±0.14	1.19±0.12	>0.05
Total bilirubin (mM/l)	19.06±1.03	14.04±1.30	<0.05	19.15±2.02	18.75±1.11	>0.05
Total protein g/l	66.49±0.41	68.10±0.23	<0.05	64.12±3.13	64.35±1.91	>0.05
Total cholesterol (mM/l)	6.90±0.19	5.81±0.19	<0.05	5.95±0.23	5.70±0.18	>0.05
LDL cholesterol	4.03±0.24	3.20±0.22	<0.05	3.85±0.19	3.66±0.21	>0.05
HDL cholesterol (mM/l)	0.84±0.06	1.05±0.05	<0.05	0.91±0.03	0.96±0.03	>0.05
Triglyceride (mM/l)	4.46±0.19	3.37±0.21	<0.05	4.28±0.17	4.01±0.19	>0.05

Table 2. Morpho-functional characteristics of patients

Parameters	Groups of study					
	Group 1 (n=50)			Group 2 (n=49)		
	Visit 1	Visit 2	p	Visit 1	Visit 2	p
Ultrasound of the liver						
Hepatomegaly, n(%) -partial -total	47 (94 %) 11 (22 %) 36 (72 %)	30 (59 %) 9 (17 %) 21 (42 %)	<0.05	44 (90 %) 12 (24 %) 32 (66 %)	43 (88 %) 12 (24 %) 31 (64 %)	>0.05
Capsular contour: -rounded, n(%) -normal, n(%)	 43 (85 %) 7 (15 %)	 24 (48 %) 26 (52 %)	<0.05	 40 (81 %) 9 (18 %)	 39 (79 %) 10 (21 %)	>0.05
Parenchymal echogenicity: -increased, n(%) -normal, n(%)	 47 (94 %) 3 (6 %)	 38 (65 %) 12 (35 %)	<0.05	 44 (90 %) 5 (10 %)	 44 (90 %) 5 (10 %)	>0.05
Vascularity: -blurred, n(%) -normal, n(%)	 46 (92 %) 4 (8)	 25 (51 %) 25 (49 %)	<0.05	 43 (88 %) 6 (12 %)	 42 (86 %) 7 (14 %)	>0.05
Echocardiography						
Left Atrium, ml	48.4±2.24	41.7±2.19	<0.05	49.1±3.21	46.1±2.04	<0.05
EDV, ml	178.3±5.91	156.1±7.42	<0.05	169.1±4.11	162.7±6.22	<0.05
ESV, ml	78.2±3.44	63.1±2.42	<0.05	81.4±2.56	79.1±2.18	<0.05
Ejection fraction (%)	56.8±2.91	60.6±1.45	<0.05	54.6±2.12	56.1±1.45	<0.05
24-hour Holter monitoring						
The number of ischemic episodes per day	8.23±0.9	3.92±1.2	<0.05	7.63±1.2	5.66±1.1	<0.05
Total duration of ischemic episodes per day, min	28.32±1.8	16.74±1.5	<0.05	27.22±2.3	19.84±1.9	<0.05
Average duration of ischemic episodes, min	5.72±0.8	4.17±0.9	<0.05	4.82±1.3	3.87±0.9	<0.05

took place statistically reliable improvement of the ultrasound liver parameters: liver size normalized in 35 % of patients, the structure of the capsular contour was restored – in 37 %. Normalized liver parenchymal echogenicity was noted in 29 % of patients and clear liver vascularity – in 41 %.

Baseline echocardiographic indices were significantly reduced in both study groups (Table 2). After the course of therapy, positive changes in the parameters of end-diastolic volume (EDV), end-systolic volume (ESV), and size of left atrium (LA) were observed in patients of both groups. The index of the contractile function, the ejection fraction (EF), was also improved at the end of the study. However, additional use of L-arginine L-glutamate significantly increased the effectiveness of traditional therapy of CHD. Thus, LA size was decreased by 13.8 % , EDV by 12.5 %, ESV by 19.3 % and EF increased by 6.7 % in comparison with the initial data.

Analysis of the dynamics of 24-hour ECG monitoring was showed a statistically significant decrease in the mean values for each of the indices in patients of both groups (Tables 2). Anti-ischemic activity was higher in the group of patients with additional use of L-arginine L-glutamate. Thus, the number of ischemic episodes per day decreased by 52.4 % in the group 1 and by 25.9 % in the group 2. The total duration of ischemic episodes per day decreased by 41 % in the group 1 and by 27 % in the group 2. The average duration of ischemic episodes decreased by 27.1 % in the group 1 and by 19.7 % in the group 2.

Discussion Thus, patients with postinfarction cardiosclerosis got worse the liver morpho-functional state and lipid profile. According to the literature (6,7,8,9), CHD in association with chronic liver disease triggers pathogenetic mechanisms of the emergence and progression of each pathology and have aggravating influence on the clinical dynamics.

It was found that L-arginine L-glutamine inclusion into the standard therapy of CHD demonstrated the reliable improvement of liver function. These findings coincided with study of Virstiuk and Cherkashyna (10), who investigate the effects of complex treatment with glutargin on the functional state of the liver in patients with CHF. The results revealed that the inclusion of glutargin in treatment of patients CHF improves overall liver function reducing the degree of cytolytic and cholestatic syndromes and improving detoxification and protein-synthesizing functions of hepatocytes.

An important antiatherosclerotic effect arginine obtained in this study is consistent with the findings obtained in the study of the comparative efficacy of the combination of L-arginine with simvastatin with monotherapy simvastatin in patients with advanced IHD (11). Inclusion of L-arginine resulted in a significant increase in endothelial-protective efficacy of statin (especially in the group of patients with triglyceridemia and elevated levels of ADMA).

It is well known that L-arginine is a nitric oxide source and can restore endothelium vasodilation, which is a key link of pathogenesis of CHD. The clinical efficacy of L-arginine in the complex treatment of patients with stable angina pectoris was investigated by Smuglov in 2015 (12). The study included 50 patients with stable angina pectoris. The authors found that the use of L-arginine as a supplement to standard medical therapy improves the clinical course of CHD and quality of life due to the high antianginal and antiischemic action, that confirms the results of our study: the number of ischemic episodes per day decreased by 52.4 % , the total duration of ischemic episodes per day decreased by 41 %, the average duration of ischemic episodes decreased by 27.1 %.

In a double-blind, cross-randomized, clinical trial (13) involving 21 patients with CHF (NYHA II-III), an increase in load time from (70±99) to (99±106) ($P < 0.05$) was noted after treatment with L-arginine (9 g per day) for 1 week. Our study also shows that additional use of l-arginine l-glutamate, decreased LA size was by 13.8 %, EDV by 12.5 %, ESV by 19.3 % and EF increased by 6.7 % in comparison with the initial data.

CONCLUSIONS Inclusion into the standard therapy of CHD demonstrated the reliable improvement of liver function.

A reliable lipidogram improvement was observed only in a group of patients who additionally took L-arginine l-glutamine.

Anti-ischemic activity was higher in the group of patients with additional use of l-arginine l-glutamate.

Thus, correction of the morpho-functional state on the heart and liver in patients with postinfarction cardiosclerosis by L-arginine l-glutamate is considered to be pathogenetically substantiated and clinically relevant.

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ВПЛИВ L-АРГІНІНУ L-ГЛУТАМАТУ НА МОРФОФУНКЦІОНАЛЬНИЙ СТАН СЕРЦЯ І ПЕЧІНКИ У ПАЦІЄНТІВ ІЗ ПОСТІНФАРКТНИМ КАРДІОСКЛЕРОЗОМ

Резюме. У дослідженні було оцінено функціональний стан печінки і серця у пацієнтів із постінфарктним кардіосклерозом.
Мета дослідження – оцінити вплив L-аргініну L-глутамату на морфофункціональний стан серця і печінки у пацієнтів із постінфарктним кардіосклерозом.
Матеріали і методи. Обстежено 99 пацієнтів, яких поділили на 2 групи залежно від проведеної терапії. Хворі другої групи (n=49) продовжували отримувати основну терапію ІХС, разом з тим, як пацієнти першої групи (n=50) додатково приймали L-аргінін L-глутамат (5 мл 40 внутрішньовенно 7 днів із переходом на таблетовану форму: 0,75 г три рази на день протягом 3 тижнів). Усі пацієнти пройшли наступні дослідження: 24-годинний холтерівський моніторинг, ехокардіографію, УЗД печінки, біохімічні показники функції печінки (АЛТ, АСТ, ЛФ, білірубін), ліпідограму (загальний холестерин, ТГ, ЛПВЩ, ЛПНЩ). Статистичну обробку даних проводили за допомогою пакетів програм STATISTICA® for Windows 6.0 (StatSoftInc.), Microsoft® Excel 2010 (Microsoft®).
Результати досліджень та їх обговорення. Включення L-аргініну L-глутамату в стандартну терапію ІХС продемонструвало достовірне поліпшення функції печінки: рівень загального білірубіну зменшився на 26,3 %, АЛТ – на 48,5 %, а ЛФ – на 33 %. Рівень загального холестерину знизився на 16 %, холестерину ЛПНЩ – на 20,1 %, а ТГ – на 24,4 %. Крім того, рівень холестерину ЛПВЩ збільшився на 19,2 %. Встановлено, що на тлі лікування L-аргініном L-глутаматом статистично достовірно покращилися УЗ-показники печінки: розмір печінки нормалізувався у 35 % пацієнтів, структуру контуру відновлено у 37 %. Нормалізація паренхіматозної ехогенності печінки була у 29 % пацієнтів, судинний малюнок візуалізований у 41 %. Розмір ЛП зменшився на 13,8 %, КДО – на 12,5 %, КСО – на 19,3 %, ФВ – на 6,7 % порівняно з вихідними даними. Число ішемічних епізодів у день зменшилось на 52,4 %, загальна тривалість ішемічних епізодів у день знизилася на 41 %, середня тривалість ішемічних епізодів зменшилася на 27,1 %.
Висновки. Включення у стандартну терапію ІХС продемонструвало достовірне поліпшення функції печінки. Достовірне покращення ліпідного профілю спостерігалося тільки у групі пацієнтів, які додатково приймали L-аргінін L-глутамат. Антиішемічна активність була вищою в групі пацієнтів із додатковим використанням L-аргініну L-глутамату. Таким чином, корекція морфофункціонального стану серця і печінки у пацієнтів із постінфарктним кардіосклерозом L-аргініном L-глутаматом вважається патогенетично обґрунтованою і клінічно значущою.

Ключові слова: ішемічна хвороба серця; коморбідність; патологія печінки; постінфарктний кардіосклероз.

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ВЛИЯНИЕ L-АРГИНИНА L-ГЛУТАМАТА НА МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ СЕРДЦА И ПЕЧЕНИ У ПАЦИЕНТОВ С ПОСТИНФАРКТНЫМ КАРДИОСКЛЕРОЗОМ

Резюме. В исследовании было оценено функциональное состояние печени и сердца у пациентов с постинфарктным кардиосклерозом.
Цель исследования – оценить влияние L-аргинина L-глутамата на морфофункциональное состояние сердца и печени у пациентов с постинфарктным кардиосклерозом.
Материалы и методы. Обследовано 99 пациентов, которых разделили на 2 группы в зависимости от проведённой терапии. Больные второй группы (n=49) продолжали получать основную терапию ИБС, в то время, как пациенты первой группы (n=50) дополнительно принимали L-аргинин L-глутамат (5 мл 40 % внутривенно 7 дней с переходом на таблетированную форму: 0,75 г три раза в день в течение 3 недель). Все пациенты прошли следующие исследования: 24-часовой холтеровский мониторинг, эхокардиографию, УЗИ печени, биохимические показатели функции печени (АЛТ, АСТ, ЩФ, билирубин), липидограмму (общий холестерин, ТГ, ЛПВП, ЛПНП). Статистическую обработку данных проводили с помощью пакетов программ STATISTICA® for Windows 6.0 (StatSoftInc.), Microsoft® Excel 2010 (Microsoft®).
Результаты исследований и их обсуждение. Включение L-аргинина L-глутамата в стандартную терапию ИБС продемонстрировало достоверное улучшение функции печени: уровень общего билирубина уменьшился на 26,3 %, АЛТ – на 48,5 %, а ЩФ – на 33 %. Уровень общего холестерина снизился на 16 %, холестерина ЛПНП – на 20,1 %, а ТГ – на 24,4 %. Кроме того, уровень холестерина ЛПВП увеличился на 19,2 %. Установлено, что на фоне лечения L-аргинином L-глутаматом статистически достоверно улучшились УЗ-оказатели печени: размер печени нормализован у 35 % пациентов, структура контура восстановлена у 37 %. Нормализация паренхиматозной эхогенности печени отмечалась у 29 % пациентов, сосудистый рисунок визуализирован у 41 %. Размер ЛП уменьшился на 13,8 %, КДО – на 12,5 %, КСО – на 19,3 %, ФИ – на 6,7 % по сравнению с исходными данными. Число ишемических эпизодов в день уменьшилось на 52,4 %, общая продолжительность ишемических эпизодов в день снизилась на 41 %, средняя продолжительность ишемических эпизодов уменьшилась на 27,1 %.
Выводы. Включение в стандартную терапию ИБС продемонстрировало достоверное улучшение функции печени. Достоверное улучшение липидного профиля наблюдалось только у группе пациентов, которые дополнительно принимали L-аргинин L-глутамат. Антиишемическая активность была выше в группе пациентов с дополнительным использованием L-аргинина L-глутамата. Таким образом, коррекция морфофункционального состояния сердца и печени у пациентов с постинфарктным кардиосклерозом L-аргинином L-глутаматом считается патогенетически обоснованной и клинически значимой.

Ключевые слова: ишемическая болезнь сердца; коморбидность; патология печени; постинфарктный кардиосклероз.