UDC: 616.12-008.313-036.8

A COMPARATIVE ASSESSMENT OF THE EFFECT OF MINERALOCORTICOID RECEPTOR ANTAGONISTS ON CHANGES IN GALECTIN-3 AND MMP-1 FIBROSIS MARKERS IN PATIENTS WITH CHRONIC CARDIAC FAILURE COMBINED WITH TYPE 2 DIABETES MELLITUS WITH MANIFESTATIONS OF MYOCARDIUM DYSSYNCHRONY

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A comparative assessment of the effect of mineralocorticoid receptor antagonists on changes in galectin 3 and matrix metalloproteinase 1 fibrosis markers has been carried out on 106 examinations (average age (69 ± 10.37) years) with type 2 DM and CCF of ischemic nature of I-IV FC according to NYHA with retained systolic function of the left ventricle and manifestations of myocardium dyssynchrony.

All the patients were divided into 3 groups depending on the intake of mineralocorticoid receptor antagonists. Myocardium dyssynchrony was assessed according to the generally accepted technique; the volume faction of interstitial collagen was measured using the formula of J. Shirani et al.; galectin-3 and matrix metalloproteinase-1 levels – using the immunoenzyme method according to the manufacturer's manual. The data was processed using the methods of parametric and non-parametric statistics. It was discovered that the myocardium dyssynchrony development percentage in the group of patients not taking mineralocorticoid receptor antagonists was higher than in the group of patients taking spironolactone or eplerenone. An increase in fibrosis marker levels was shown in the spironolactone intake group compared with the group of patients taking eplerenone. Mineralocorticoid receptor antagonist intake requires blood potassium level control and case monitoring of manifestations of dyssynchrony and myocardial fibrosis.

KEY WORDS: interstitial collagen volume faction, chronic cardiac failure, myocardium dyssynchrony, galectin 3, matrix metalloproteinase 1

ПОРІВНЯЛЬНА ОЦІНКА ВПЛИВУ АНТАГОНІСТІВ МІНЕРАЛОКОРТИКОЇДНИХ РЕЦЕПТОРІВ НА ЗМІНИ МАРКЕРІВ ФІБРОЗУ ГАЛЕКТИН-3 І ММП-1 У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ В ПОЄДНАННІ З ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ З ПРОЯВАМИ ДИССИНХРОНІЇ МІОКАРДА

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На 106 обстежуваних (середній вік (69 ± 10,37) років) з ЦД 2-го типу та ХСН ішемічного генезу I–IV ФК за NYHA зі збереженою систолічною функцією лівого шлуночка та проявами диссинхронії міокарда, проведена порівняльна оцінка впливу антагоністів мінералокортикоїдних рецепторів на зміни маркерів фіброзу галектину-3 і матриксної металлопротеінази-1.

Усі пацієнти були розділені на 3 групи в залежності від прийому антагоністів мінералокортикоїдних рецепторів. Диссинхронію міокарда оцінювали за загальноприйнятою методикою, об'ємну фракцію інтерстиціального колагену вимірювали за допомогою формули J. Shirani і співавторів, рівень галектіна-3 і матриксної металлопротеінази 1 за допомогою імуноферментного методу згідно з інструкцією від виробника. Дані обробляли методами параметричної та непараметричної статистики. Виявлено, що в групі хворих, що не приймали антагоністи мінералокортикоїдних рецепторів відсоток розвитку диссинхронії міокарда був вище ніж в групі хворих, що вживали спіроналактон або еплеренон. Показано підвищення рівнів маркерів фіброзу у групі прийому спіроналактону у порівнянні з групою хворих що приймали еплеренон. Прийом антагоністів мінералокортикоїдних рецепторів вимагає контролю рівня калію крові і динамічне спостереження за проявами диссинхронії та міокардіального фіброзу.

КЛЮЧОВІ СЛОВА: об'ємна фракція інтерстиціального колагену, хронічна серцева недостатність, диссинхронія міокарда, галектин-3, матриксна металлопротеіназа-1

СРАВНИТЕЛЬНАЯ ОЦЕНКА ВЛИЯНИЯ АНТАГОНИСТОВ МИНЕРАЛОКОРТИКОИДНЫХ РЕЦЕПТОРОВ НА ИЗМЕНЕНИЯ МАРКЕРОВ ФИБРОЗА ГАЛЕКТИНА-3 И ММП-1 У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ В СОЧЕТАНИИ С САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА С ПРИЗНАКАМИ ДИССИНХРОНИИ МИОКАРДА

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У 106 пациентов, (средний возраст (69 + 10,37) лет) с СД 2-го типа и ХСН ишемического генеза I - IV ФК по NYHA с сохраненной систолической функцией и признаками диссинхронии миокарда, проведена сравнительная оценка влияния антагонистов минералокортикоидных рецепторов на изменения маркеров фиброза, галектина-3 и матриксной металлопротеиназы-1, у больных с хронической сердечной недостаточностью в сочетании с сахарным диабетом 2-го типа с признаками диссинхронии миокарда. Обследуемые разделены на 3 группы в зависимости от приема антагонистов минералокортикоидных рецепторов. Диссинхрония миокарда оценивалась по общепринятой методике, степень выраженности объемной фракции интерстициального коллагена определяли с помощью формулы J. Shirani и соавторов, вровень галектина-3 и матриксной металлопротеиназы-1 с помощью иммуноферментного метода согласно инструкции от производителя. Данные обрабатывали методами параметрической и непараметрической статистики. Выявлено, что в группе больных, не принимавших антагонистов минералокортикоидных рецепторов, процент развития диссинхронии миокарда был выше, чем в группе больных, употребляющих спироналактон или эплеренон. Также показано повышение уровней маркеров фиброза в группе приема спиронолактона в сравнении с группой больных, принимающих эплеренон. Прием антагонистов минералокортикоидных рецепторов требует контроля уровня калия крови и динамическое наблюдение за признаками диссинхронии и миокардиального фиброза.

КЛЮЧЕВЫЕ СЛОВА: объемная фракция интерстициального коллагена, хроническая сердечная недостаточность, диссинхрония миокарда, галектин-3, матриксная металлопротеиназа-1

INTRODUCTION

An increased aldosterone level tends to promote fibrosis development in hypertrophic heart ventricles, decreases myocardial perfusion and it was discovered [1] based on systematic review of the clinical trials carried out by Ezekowitz et al. [2] that the mineralocorticoid receptor antagonists used decrease mortality among patients with chronic cardiac failure (CCF) by 20 %. It is generally recognized that heart remodeling is the main pathogenic sign of left ventricle dysfunction. [3]

Several clinical trials were carried out to study the potential influence of the drugs in question on heart remodeling in patients with CCF, but comprehensive information on the assessment of this influence is not sufficient. Due to this fact, there is a need to continue research aimed at the study of the peculiarities of changes in heart structure and function in patients with left ventricle dysfunction. [4–5]

According to the recommendations of the European Society of Cardiology, mineralocorticoid receptor antagonists are assigned IA recommendation class as first-line drugs for the treatment of CCF of ischemic origin. [6–9] However, the issue of the wide use of these drugs to decrease myocardial fibrosis is still discussed widely; meanwhile, comparative discussions regarding which drug is to be preferred – spironolactone or eplerenone – are held. [4, 10]

There is still no clear information concerning changes in fibrosis marker activity if mineralocorticoid receptor antagonists are used in patients with CCF of ischemic nature accompanied by type 2 diabetes mellitus and manifestations of myocardium dyssynchrony (MD).

The paper is written according to the «Cardiac and Neurohumoral Mechanisms of Chronic Cardiac Failure Development in Patients with Comorbidities» research plan of the Chair of Therapy and Nephrology of Kharkiv Medical Academy of Postgraduate Education (DR No. 0111U003579).

OBJECTIVE

To carry out a comparative assessment of the influence of mineralocorticoid receptor antagonists on changes in galectin 3 and matrix metalloproteinase 1 fibrosis markers in patients with chronic cardiac failure combined with

type 2 diabetes mellitus with manifestations of myocardium dyssynchrony.

MATERIALS AND METHODS

For the study to be completed, 106 patients with type 2 DM and CCF of ischemic genesis of I–IV FC under NYHA with retained systolic function and manifestations of myocardium dyssynchrony were examined. The average age of all the examinees was (67.45 ± 10.32) years. 43 men (41 %), aged (65 ± 10.62) on average, and 63 women (59 %), aged (69 ± 10.37) on average, were examined in the group. Fibrosis marker activity in the blood serum was determined for 72 examinees.

The criteria of inclusion in the study were as follows: having type 2 DM and CCF of I–IV FC under NYHA. Patients were excluded from analysis if they had an acute coronary distress or chronic kidney failure.

Type 2 DM was diagnosed according to the recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) concerning type 2 DM diagnosing criteria.

Myocardial fibrosis was assessed with the content of galectin 3 and matrix metallo-proteinase (MMP) 1 in the blood serum determined using the immunoenzyme method; galectin 3 based on the Human Galectin-3 kit (Platinum ELISA; eBioscience, Bender MedSystems, Austria) and MMP-1 content based on the Human MM3-1 kit (ELISA; Abfrontier Biotechnology supplier, South Korea). The degree of interstitial collagen volume fraction was calculated from the formula of J. Shirani et al. [11]: ICVF (%) = $(1\text{-}1{,}3*\frac{totalQRS(mm)\,x\,height\ (m)}{LVMM(g)})*100$,

wherein the normal level of ICVF was set within the range of 1 % and 2 %.

Myocardium dyssynchrony was assessed using echocardiography synchronized with electrocardiography according to the generally accepted method of determining myocardium dyssynchrony, where the following was determined: the septal to posterior wall motion delay (SPWMD), the aortic (APEI) and pulmonary (PPEI) pre-ejection interval, the interventricular mechanical delay (IVMD), the left ventricular filling time (LVFT), the registration time of E and A waves, the left ventricular ejection time (LVET), the isovolumic relaxation time (IVRT), the early ventricular filling flow deceleration time (DT), the time from the start of the QRS complex to the start of the peak systolic velocity, the time to the peak systolic velocity (Ts), the root-mean-square time deviation to the peak LV systolic velocity (Ts-SD).

To complete the task set, the examinees (n = 106) were divided into 3 groups. Group 1, (n = 40) people – 38 % of the examinees, did not take any mineralocorticoid receptor antagonists. Group 2, (n = 34) people – 32 % of the examinees, took 50 mg of spironolactone daily. Group 3, (n = 32) people – 30 % of the examinees, took 50 mg of eplerenone daily.

The data were processed after the base was formed using Microsoft Excel and Statistical software. Parametric (M, SD) and non-parametric (absolute and relative (percentages (p, %) and criterion $\chi 2$) of units)) criteria were used for the statistical assessment of results. The probability of differences between the groups was determined using the Mann-Whitney U-test. The expected result was determined by the confidence level of $p < 0.05$.

RESULTS AND DISCUSSION

The results obtained were analyzed in view of whether there is any dyssynchrony in the groups. Mechanical myocardium dyssynchrony was discovered in 83 (78 %) individuals. Among them, the isolated myocardium dyssynchrony type was diagnosed in 52 individuals (49 %): intraventricular myocar-dium dyssynchrony in 49 individuals (46 %), atrioventricular one in 2 individuals (1.8 %), interventricular one in 1 individual (0.94 %), and the combined type in 31 individual (29 %). 8 examinees (20 %) in group 1 had no signs of myocardium dyssynchrony; interventricular MD was observed in 1 individual (2.5 %); 20 individuals (50 %) had intraventricular MD; 11 individuals (27.5 %) had combined type MD. In group 2, 9 (26 %) of the examinees had no signs of myocardium dyssynchrony; intraventricular MD was noted in 12 individuals (35 %); 13 individuals (38 %) had combined type MD. In group 3, 7 examinees (22 %) had no signs of myocardium dyssynchrony; 2 individuals (6 %) had atrioventricular dyssynchrony; 16 individuals (50 %) had intraventricular MD; combined type MD was noted in 7 examinees (22 %).

The highest average values of Gal-3 and MMP-1 were noted in the 2nd group of examinees taking spironolactone. For instance, Gal-3 (9.03 ± 1.06) ng/ml, the lowest Gal-3 in

the group not taking the drugs is (6.68 ± 0.64) ng/ml. MMP-1 in group 1 not taking the drugs was lowest, (0.27 ± 0.05) ng/ml; in group 2 of the examinees taking spironolactone, MMP-1 was (0.72 ± 0.36) ng/ml (Tab). VICF in the 1st group of examinees not taking the drugs was lowest, (6.92 ± 0.47) %. The VICF values did not differ significantly between groups 2 (patients taking spironolactone) and group 3 (patients taking eplerenone) (tab.).

Table

Fibrosis marker activity in patients with type 2 DM and CCF of ischemic nature with manifestations of MD depending on the intake of mineralocorticoid receptor antagonists – spironolactone and eplerenone (M ± m)

Indicator	Group 1 (n=40)	Group 2 (n=34)	Group 3 (n=32)
Gal-3, ng/ml	6.68±0.64	9.03±1.06	7.07±0.93
MMP-1, ng/ml	0.27±0.05	0.72±0.36*	0.64±0.36
VICF, %	6.92±0.47	7.26±0.46	7.55±0.49

Notes: – the degree of probability of differences in group 2 compared with group 1 ($p \leq 0.05$).

Thus, the lowest percentage of combined forms of myocardium dyssynchrony, which aggravate CCF manifestations the most, was noted in the group of the examinees taking eplerenone. Increased MMP-1 levels in patients taking mineralocorticoid receptor antagonists evidence that collagen degradation processes are launched. Increase in myocardium fibrosis increases electric non-homogeneity by strengthening leading heart system dysfunction. In [12–14] early use of spironolactone and eplerenone hinders further development of myocardium fibrosis by improving noradrenaline consumption by the myocardium and increases the pumping function productivity of the myocardium, hindering left ventricle remodeling in patients with CCF. [15–16] For a clearer notion of myocardial fibrosis against the background of spironolactone and eplerenone intake, it is expedient to study galectin 3 and MMP 1 markers in real time for several months more from the start of the treatment.

CONCLUSIONS

Fibrosis marker activity is more expressed in the examinees on spironolactone than in the patients taking eplerenone. Higher myocardium dyssynchrony values and a higher percentage of combined forms of myocardium dyssynchrony are observed in the examinees who have not been taking any mineralocorticoid receptor antagonists than in the examinees taking spironolactone or eplerenone. For a clearer notion of the dynamics of change in myocardial fibrosis against the background of spironolactone and eplerenone intake, it is expedient to study galectin 3 and MMP 1 markers for several months more from the start of the treatment, monitoring the blood potassium level and manifestations of myocardium dyssynchrony against the background of type 2 DM with CCF of ischemic nature.

PROSPECTS FOR FUTURE STUDIES

Further study of the peculiarities of changes in interstitial collagen values depending on the use of therapy aimed towards decrease in myocardial fibrosis and myocardium dyssynchrony phenomena by titrating the daily doses of the drugs remains topical.

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