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FIBROTIC CHANGES IN PATIENTS WITH CHRONIC HEART FAILURE WITH CARDIAC DYSSYNCHRONY AND ASSOCIATED TYPE 2 DIABETES MELLITUS

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The study of fibrosis markers was carried out on 72 observed patients (mean age (69 ± 10.37) years) with chronic heart failure (CHF) of ischemic genesis with manifestations of cardiac dyssynchrony (CD) and concomitant type 2 diabetes mellitus – Galectin 3 and matrix metalloproteinase 1. All patients were divided into 2 groups, depending on the presence of CD. The CD was evaluated according to a conventional technique, the volume fraction of interstitial collagen was measured using the formula of J. Shirani and co-authors, the levels of Galectin-3 and matrix metalloproteinase 1 – by the enzyme-linked immunoassay according to the manufacturer's instructions. The data were processed using parametric and nonparametric statistics. It was revealed that the level of fibrosis development was higher in the group of patients with CD than in the group without CD. This indicates the dependence of the development of myocardial sites asynchronous reduction with the presence of interstitial collagen development. That further requires the study of the effect of anti-fibrotic, anti-ischemic and hypoglycemic agents on the progression of CD to prevent subsequent myocardial remodeling.

KEY WORDS: volume fraction of interstitial collagen, chronic heart failure, cardiac dyssynchrony, Galectin 3, matrix metalloproteinase 1

ФІБРОТИЧНІ ЗМІНИ У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ З ДИССИНХРОНІЄЮ МІОКРАДА ТА СУПУТНІМ ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ

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У 72 обстежуваних (середній вік (69 ± 10,37) років) з хронічною серцевою недостатністю (ХСН) ішемічного генезу з проявами диссинхронії міокарда (ДМ) та супутнім цукровим діабетом 2-го типу проведено вивчення маркерів фіброзу: Галектину 3 та матриксної металопротеїнази 1. Всі пацієнти розділені на 2 групи в залежності від наявності ДМ. ДМ оцінювали за загальноприйнятою методикою, об'ємну фракцію інтерстиціального колагену вимірювали за допомогою формули J. Shirani і співавторів, рівень Галектіна-3 і матриксної металопротеїнази 1 за допомогою імуноферментного методу згідно з інструкцією від виробника. Дані обробляли методами параметричної та непараметричної статистики. Виявлено, що в групі хворих з ДМ рівень розвитку фіброзу був вищим за рівень у групі без ДМ. Це вказує на залежність розвитку асинхронного скорочення ділянок міокарда з наявністю розвитку інтерстиціального колагену, що в подальшому потребує вивчення дії противофібротичних, антиішемічних та гіпоглікемічних засобів на прогресування ДМ для запобігання у подальшому ре моделювання міокарда.

КЛЮЧОВІ СЛОВА: об'ємна фракція інтерстиціального колагену, хронічна серцева недостатність, диссинхронія міокарда, Галектин 3, матриксна металопротеіназа 1

ФИБРОТИЧЕСКИЕ ИЗМЕНЕНИЯ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ С ДИССИНХРОНИЕЙ МИОКРАДА И СОПУТСТВУЮЩИМ САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

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У 72 обследуемых (средний возраст (69 ± 10,37) лет) с хронической сердечной недостаточностью (ХСН) ишемического генеза с проявлениями диссинхронии миокарда (ДМ) и сопутствующим сахарным диабетом 2-го типа проведено изучение маркеров фиброза: Галектина 3 и матриксной

металлопротеиназы 1. Все пациенты разделены на 2 группы в зависимости от наличия ДМ. ДМ оценивали по общепринятой методике, объемную фракцию интерстициального коллагена измеряли с помощью формулы J. Shirani и соавторов, уровень 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 с ДМ уровень развития фиброза был выше уровня в группе без ДМ. Это указывает на зависимость развития асинхронного сокращения участков миокарда с наличием развития интерстициального коллагена, что в дальнейшем требует изучения действия противофибротических, антиишемических и гипогликемических средств на прогрессирование ДМ для предотвращения последующего ремоделирования миокарда.

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

INTRODUCTION

Excessive accumulation of fibrosis has pathological effects on the diastolic function of the myocardium [1]. The number of focal collagen fibers increases in patients with type 2 diabetes mellitus (DM) before the increasing of the total collagen content, that leads to a decrease in myocardial capacity, which is due to glycation of collagen fibers and, as a result, an increase in the weight of the myocardium. Hypertrophy of cardiomyocytes in patients with diabetic cardiomyopathy has been studied for a long time, but its contribution to the ventricular hypertrophy hasn't still been understood completely [1–2]. Detection of new biomarkers of subclinical damage can improve the assessment of the risk of cardiovascular complications. It is becoming relevant to study the fibrosis markers for timely diagnosis of primary changes of extracellular matrix in patients with type 2 DM. Among the manifestations of cardiovascular disease, the main attention is paid to chronic heart failure (CHF) due to the high prevalence of this syndrome, which is associated with an increased risk of mortality among populations throughout the world. There is evidence that plasma levels of galectin (Gal)-3 correlate with the prevalence of type 2 DM and associated metabolic conditions, suggesting that the pharmacological blockage of this lectin can be successful in treating CHF in patients with diabetes [3–4].

The work was carried out according to the plan of research works of the Department of Therapy and Nephrology of the Kharkiv Medical Academy of Postgraduate Education «Optimization of the treatment of chronic heart failure» (SR No. 0117U000585).

OBJECTIVE

To study the features of changes in fibrosis markers – galactine-3 and matrix metalloproteinase-1 in patients with CHF with CD manifestations and associated type 2 DM.

MATERIALS AND METHODS

Complex examination of 72 patients with comorbid pathology – CHF of ischemic origin and type 2 DM was carried out. All patients were on treatment in the therapeutic and cardiology department at Kharkiv City clinical hospital of urgent and emergency aid named after Prof. O. I. Meshhaninov.

Patients were with known CHF, New York Heart Association (NYHA) class I-IV and left ventricular ejection fraction (LVEF) of ≥ 45 % («average» or «preserved» according to the criteria of the European Society of Cardiology, 2016) [5]. The average age of patients was (67.45 ± 10.32) years. Type 2 DM was diagnosed according to the criteria of the American Diabetes Association and the American Diabetes Association Diabetes Care, 2017, and European Association for the Study of Diabetes (EASD). CD was diagnosed according to the recommendations of the European Association of Echocardiography [5–6]. CD was divided into intraventricular, interventricular, atrioventricular and combined.

Instrumental methods – echocardiography with determination of CD indices and electrocardiography (ECG) were performed on all patients with CHF of ischemic genesis and type 2 DM.

The evaluation of myocardial fibrosis was performed with the determination of the content of Gal-3 and matrix metalloproteinase (MMP) 1 in serum using the immune-enzyme method. Galectin-3 was evaluated using Human Galectin-3 kit (Platinum ELISA; eBioscience,

Bender MedSystems, Austria) and MMP-1 content – using the «Human MBZ-1» kit (ELISA, Abfrontier Biotechnology supplier, South Korea).

The volume fraction of interstitial collagen (ICVF) was calculated according to the method, which was determined based on the total voltage of the QRS complex in 12 standard leads, growth, myocardial mass of the left ventricle (LVMM), where the normal level is 1–2 % [7].

ICVF = (1–1,3 * ((total QRS * height) / LVMM)) * 100. Where ICVF is an interstitial collagen volume fraction, %; LVMM – left ventricle myocardial mass, g; height, m; total QRS volt, mm.

To perform the task, the subjects under study (n = 72) were divided into 2 groups. Group 1 (n = 56) with CD and group 2 (n = 16) without CD.

The statistical processing of the obtained results was performed on a personal computer using Microsoft Office Excel 2007 and STATISTICA 6.0. To determine the continuous scale, the mean sample and median were used as indicators of the central trend, the data are presented in the results of the study, as M ± m, where M is the arithmetic mean, m is the mean square (arithmetic) deviation; interquartile range, minimum and maximum value – as measures of spread. The discrepancy was considered reliable if the probability of random difference did not exceed 0.05 ($p < 0,05$).

RESULTS AND DISCUSSION

The mean content of Gal-3 in the studied patients was (7.19 + 0.48) ng/ml, MMP-1 (0.58 + 0.19) ng/ml, and ICVF was (7.22 ± 0.29) %.

Patients were divided into 2 groups to determine the levels of fibroblasts regarding the presence of CD: 1st group included 56 people with DM; 2nd group was represented by 16 persons without signs of DM (Table).

Table 1

The activity of fibrosis markers in patients with type 2 diabetes and CHF of ischemic genesis, depending on the presence of CD (M + m)

Indicator	CD (n = 56)	Without CD (n = 16)
Gal-3, ng/ml	7,49 + 0,6	6,14 + 0,42
MMP-1, ng/ml	0,46 + 0,2	1 + 0,47*
ICVF, %	7,6 ± 4,03	6,52 ± 2,36

**Notes: – the degree of differences probability of in group 2 compared to group 1 ($p < 0,05$)*

The obtained results indicate that the formation of CD leads to an increase in the expressiveness of fibrotic changes. The dependence of levels of fibrosis markers on the degree of development of CD was investigated. The growth of the Gal-3 levels was observed under the condition of the presence of combined CD forms.

Thus, the level of Gal-3 was the highest in patients with simultaneous combination of intraventricular, interventricular or atrioventricular CD (n = 28), while in isolated forms of CD, that is in the presence of one of the forms, the content of Gal-3 was significantly smaller (Fig.). The content of MMP-1 also depended on the combination of CD and was the smallest in patients with combined (n = 28) CD forms. The size of the ICVF also correlated with the forms of CD (Fig.).

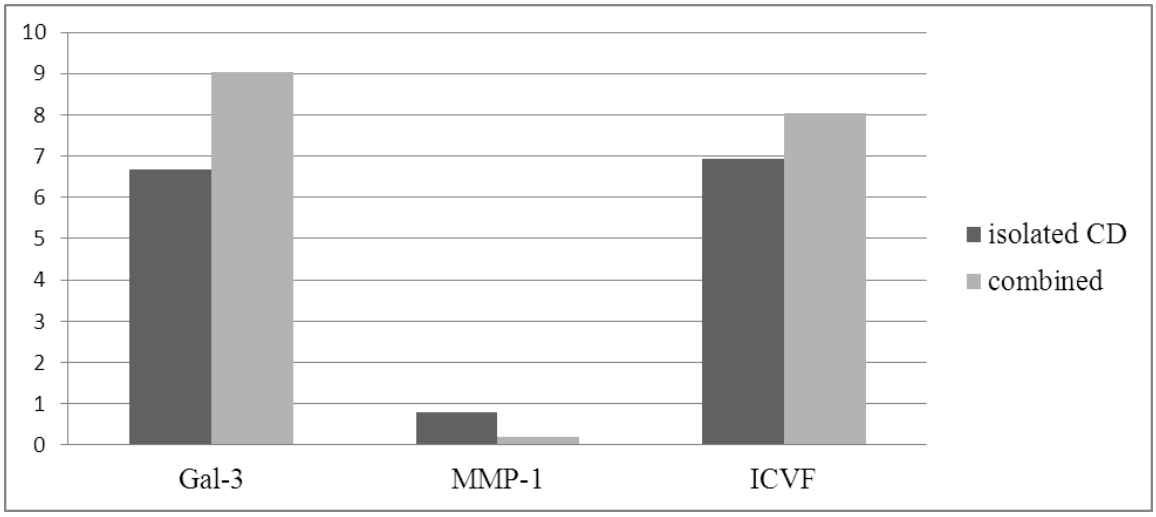

Fig. The activity of fibrosis indicators in patients with CD against the background of CHF

CONCLUSIONS

When type 2 DM combined with CHF of the ischemic genes, the Gal-3 serum level increases, that correlates with the progression of the mechanical CD leading to the myocardial rejuvenation. Content of MMP-1 depends on the form of mechanical CD – decreasing in combined forms.

PROSPECTS FOR FUTURE STUDIES

It remains relevant to further explore the characteristics of changes in the fibrosis markers, depending on the use of hypoglycemic and anti-ischemic therapy, and its effect on CD.

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