УДК 616.12-008.331.1+616.12-005.4]-06-07-037(048.8) https://doi.org/10.26641/2307-0404.2020.4.221225

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THE CONSEQUENCE OF BIOMARKERS OF MYOCARDIAL FIBROSIS IN THE PREDICTION OF ARRHYTHMIAS IN PATIENTS WITH HYPERTENSION IN COMBINATION WITH CORONARY HEART DISEASE (LITERATURE REVIEW)

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Цитування: Медичні перспективи. 2020. Т. 25, № 4. С. 22-31
Cited: Medicni perspektivi. 2020;25(4):22-31

Key words: *markers of fibrosis, galectin-3, aldosterone, transforming growth factor β-1, hypertension, coronary heart disease, ventricular extrasystole*
Ключові слова: *маркери фіброзу, галектин-3, альдостерон, трансформуючий фактор росту β-1, гіпертонічна хвороба, ішемічна хвороба серця, шлуночкова екстрасистолія*
Ключевые слова: *маркеры фиброза, галектин-3, альдостерон, трансформирующий фактор роста β-1, гипертоническая болезнь, ишемическая болезнь сердца, желудочковая экстрасистолия*

Abstract. The consequence of biomarkers of myocardial fibrosis in the prediction of arrhythmias in patients with hypertension in combination with coronary heart disease (literature review). Ivanov V.P., Shushkovska Yu.Yu., Afanasiuk O.I., Pentiuk L.O. *The main morphological structural lesion substrate is myocardial fibrosis. The processes of fibrosis in a certain way are associated with the severity of a variety of cardiac arrhythmias. Myocardial fibrosis may be manifested by prolongation of the QRS complex, frequent ventricular arrhythmias and ventricular tachycardia on the electrocardiogram. Echocardiography is the main tool used to assess the structure and function of the heart, it reveals an increase in the left ventricle, and decrease in ejection fraction and diastolic dysfunction of the left ventricle and an increase in filling pressure. Biological markers are quantitatively defined biological parameters that, as indicators, determine the norm, pathology and result of medecinal correction of the disease (definition of experts from the Biomarkers Definitions Working Group, USA). Changes of biomarkers can be controlled to determine the individual risk of cardiovascular diseases development and measures to normalize them. Among the main causes of fibrosis activation, hyperactivation of the renin-angiotensin-aldosterone system and, as a consequence, the excessive formation of angiotensinogen and aldosterone are considered; increased levels of galectin-3, which contributes to the migration of macrophages, proliferation of fibroblasts and collagen synthesis in cardiomyocytes. Recently, much attention is paid to the study of biochemical markers such as aldosterone, galectin-3 and transforming growth factor-beta-1. Thus, these markers were determined in hypertension, metabolic syndrome, congestive heart failure, hypertrophic cardiomyopathy, myocardial infarction, atrial fibrillation. However, to date studies considering association between frequent ventricular premature beats, as a marker of electrical instability and plasma levels of biomarkers of fibrosis, such as aldosterone, galectin-3and transforming growth factor beta-1, in patients with essential hypertension without / or in combination with coronary heart disease are absent. Based on the aforesaid material,, further thorough study of this problem is promising.*

Реферат. Место биомаркеров фиброза миокарда в прогнозировании аритмий у пациентов с гипертонической болезнью в сочетании с ишемической болезнью сердца (обзор литературы). Иванов В.П., Шушковская Ю.Ю., Афанасюк О.И., Пентюк Л.А. *Основным морфологическим субстратом структурного поражения миокарда является фиброз. Процессы фиброзирования определенным образом ассоциируются с тяжестью различных нарушений сердечного ритма. Фиброз миокарда может проявляться удлинением комплекса QRS, частой желудочковой экстрасистолией и желудочковой тахикардией на электрокардиограмме. Эхокардиография – основной инструмент, используемый для оценки структуры и функции сердца, выявляет увеличение левого желудочка, снижение фракции выброса, диастолическую*

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дисфункцию левого желудочка и повышение давления наполнения. Биологические маркеры - это количественно определяемые биологические параметры, которые как индикаторы определяют норму, патологию и результат лекарственной коррекции заболевания (определение экспертов специальной рабочей группы Biomarkers Definitions Working Group, USA). Изменения биомаркеров можно контролировать для определения индивидуального риска развития сердечно-сосудистых заболеваний и разработки мер по их нормализации. Среди основных причин активации фиброза указывают гиперактивацию ренин-ангиотензин-альдостероновой системы как следствие избыточного образования ангиотензиногена и альдостерона; повышение уровня галектина-3, что способствует миграции макрофагов, пролиферации фибробластов и синтезу коллагена в кардиомиоцитах. В последнее время большое внимание уделяется изучению таких биохимических маркеров, как альдостерон, галектин-3 и трансформирующий фактор роста-β1. Так, данные маркеры определяли при гипертонической болезни, метаболическом синдроме, хронической сердечной недостаточности, гипертрофической кардиомиопатии, инфаркте миокарда, мерцательной аритмии. Однако на сегодня отсутствуют исследования по изучению связи между наличием частой желудочковой экстрасистолии, как маркера электрической нестабильности, и плазменным уровнем биомаркеров фиброза, таких как альдостерон, галектин-3 и трансформирующий фактор роста β-1, у больных с гипертонической болезнью без/и в сочетании с ишемической болезнью сердца. Исходя из вышеизложенного материала, перспективным является дальнейшее тщательное изучение этого вопроса.

Biological markers are quantifiable biological parameters, which as indicators determine the norm, pathology and the result of drug correction of the disease (defined by experts of the special working group Biomarkers Definitions Working Group, USA) [6, 20, 45, 54]. Changes in biomarkers can be controlled to determine the individual risk of preclinical signs of cardiovascular disease and the development of biomarker-controlled pharmacotherapy for their normalization, which are being intensively studied currently [11, 18].

The aim of the work is to establish the possibility of predicting the development of arrhythmias in patients with hypertension in combination with ischemic heart disease on the basis of the results of published scientific studies of biomarkers of fibrosis (aldosterone, galectin-3, transforming growth factor β-1).

Malignant ventricular arrhythmias (VA) and sudden cardiac death are subsequently caused by electrical instability of the myocardium, as a result of which changes in the electrical and physiological properties of the heart are exposed to various pathogenic factors [36]. Frequent ventricular extrasystolias (VE) are considered one of the clinical manifestations of myocardial electrical instability and may indicate the presence of a pathological substrate in the myocardium [43].

The fibrotic process involves increasing the synthesis and activity of various extracellular matrix (ECM) proteins secreted by fibroblasts, including fibronectin, which is underpinned early and forms a framework for fibroblast adhesion and ECM production; procollagen, which is converted into mature collagen; collagen binding agents such as lysyl oxidase; and enzymes that modify ECM, such as matrix metalloproteinases (MMPs) and tissue MMP inhibitors [59, 51].

Myocardial fibrosis (MF) is characterized by excessive accumulation of stromal cells and ECM proteins in the myocardium [44, 50]. Fibroblasts and myofibroblasts are the cells that are most involved in fibrotic processes in the heart, producing excess of ECM proteins, such as collagen types I and III [16, 49]. Increased myocardial fibrosis is associated with left ventricular (LV) remodeling, resulting in electrical inhomogeneity and arrhythmia. Thus, MF can be manifested by prolongation of the QRS complex, frequent VE and ventricular tachycardia (VT) on the electrocardiogram (ECG) [25, 41]. Echocardiography, the main tool used to assess the structure and function of the heart can detect LV enlargement, decreased ejection fraction, LV diastolic dysfunction, and increased filling pressure. However, these data are not specific to MF [14, 19].

Among the main causes of fibrosis activation are: hyperactivation of the renin-angiotensin-aldosterone system [9, 26] and, as a consequence, excessive formation of angiotensinogen II (AT II) and aldosterone [7, 24]; increase in the level of galectin-3 (gal-3) which promotes the migration of macrophages, fibroblasts proliferation and collagen synthesis in cardiomyocytes [3, 42].

In MF the synthesis of collagen types I and III prevails over its degradation, so the detection of high volume fraction of collagen types I and III [38, 55] and/or the ratio of the volume fraction of collagen types I and II in endomyocardiac biopsy with histopathological analysis of tissues is the main method of diagnosing MF. As a non-invasive method of MF diagnosis, magnetic resonance imaging can be used to detect an increase in extracellular connective tissue volume [8]. Therefore, the evaluation of biochemical markers of MF is an alternative method of its determination. Today, there are a large number of markers of fibrosis in the myocardium but their interpretation, clinical significance, prognostic value remain debatable [53].

In our article we will talk about diffuse MF without a previous myocardial infarction.

Currently there is no single classification of fibrosis markers. Serum markers of collagen metabolism can be classified as follows [10]: 1) markers of collagen synthesis (carboxyterminal propeptide of procollagen type I, carboxyterminal propeptide of procollagen type III (PIIIP)); 2) markers of collagen degradation (carboxyterminal telopeptide of type I collagen); 3) markers of inhibition of collagen degradation (tissue inhibitor of MMP type 1); 4) markers of fibroblast activity (transforming growth factor β1 – TGF-β1). The ratio of carboxyterminal propeptide of type I procollagen to PIIIP in serum is associated with malignant ventricular arrhythmogenesis in heart failure (HF), whereas the serum concentration of PIIIP correlates with the content of type III collagen. Gonzalez A. et al. (2018) determined a decrease in the level of PIIIP in patients receiving an antagonist of mineralocorticoid receptor (AMR) – spironolactone, [23, 38]. Accordingly, with a decrease in aldosterone levels, there is a decrease in markers of fibrosis which can be used for pharmacotherapy.

The main cellular form of connective tissue of the body is fibroblast. The process by which epithelial cells acquire the phenotype of mesenchymal (epithelial-mesenchymal transition) contributes to the accumulation of mature fibroblasts. It has been shown that the TGF-β1 protein is a catalyst for the epithelial-mesenchymal transition and, accordingly, promotes the development of cardiac fibrosis [31, 32, 39].

MMP – endopeptidases that can destroy all types of ECM proteins. MMP-1 breaks down more than 40% of collagen, mainly types 1, 2 and 3 [21, 59]. The increase in pressure stimulates the expression of the procollagen gene and the synthesis of collagen protein which causes excessive collagen deposition and the development of fibrosis [37, 40]. In arterial hypertension (AH) under the action of various neurohumoral factors the level of MMP-1 decreases which leads to the accumulation of collagen in the ECM [56].

The TGF-β family includes more than 40 species. Three different isoforms of TGF-β have been described [29, 58]. The marker of fibroblast activity – TGF-β1 is a multifunctional profibrotic cytokine that controls the composition of the cell matrix [30, 29]. Activation of TGF-β1 leads to the proliferation of fibroblasts and the production of ECM proteins, for example it increases the level of collagen and fibronectin [22, 28, 48]. The synthesis of TGF-β1 is activated by AT II which proves the connection of hypertension with MF [26]. In response to AT II, cardiac fibroblasts migrate to the site of the damaged myocardium where they undergo transdifferentiation into myofibroblasts. Fu B. et al. demonstrated that scoparone (a biologically active component isolated from Artemisia capillaris) in culture of rat cardiac fibroblast results in the restoration of ECM remodeling induced by AT II by inhibiting TGF-β1 [33]. Accordingly, by lowering the level of AT II it is possible to reduce the severity of fibrosis in the myocardium.

The European-Commission-funded FIBROTARGETS is a multinational research and production consortium whose task is to identify preclinical data related to interstitial MF in order to change and improve antifibrotic therapy. Examples of biomarkers studied in the FIBROTARGETS consortium [53]: 1) products of collagen metabolism (carboxyterminal telopeptide of collagen type I, N-terminal PIIIP, MMP type 1); 2) cellular matrix proteins (mimecan (osteoglycine), secreting acidic protein with a high content of cysteine (osteonectin), biglikan, thrombospondin 2, osteopontin, lumican); 3) biomarkers associated with major profibrotic mediators (aldosterone, TGF-β1, neutrophilic gelatin-associated lipocalin, gal-3, cardiotropin 1, apelin); 4) inflammatory molecules (15 differentiation growth factor, soluble growth stimulating factor ST-2, tumor necrosis factor of CD40-ligand, Agouti-bound protein); 5) circulating endogenous small (19-25 nucleotides) single-stranded ribonucleic acids.

There are some strategies for the treatment of MF which require further research [38]: 1) at the level of stimulating stimuli: antagonism of relaxin 2 receptors (serelaxin); partial agonism of the adenosine A1 receptor (capadenosone); monocytic chemoattractant receptor blockade protein-1 (cenicrivikor); 2) at the level of myophoblast generation and profibrotic activation: genetic modulation (histone deacytylase inhibitors, peroxide activator-activator receptor agonists); paracrine modulation (antifibrotic growth factors such as insulin-like growth factor-1, major fibroblast growth factor, hepatocyte growth factor; blockade of profibrotic factors (interleukin-10, matrix-cellular connective tissue growth factor); 3) at the level of extracellular fibrogenesis: modulation of bone morphogenetic protein-1-mediated fibrillar collagen formation (bone morphogenetic protein-1 inhibitors); modulation of lysyl oxidase-mediated cross-linking (2-lysyl oxidase inhibitors); stimulation of cardiac lymphangiogenesis (vascular endothelial growth factor-C).

In studies on dogs Magnussen S., Blankenberg S. (2018) showed that AMP (spironolatone and eplerenone) can reduce fibrosis [27]. That is, the use of AMP

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prevents the development of MF. AMP also reduces the risk of both first-onset and recurrent AF [13].

A number of authors believe that if VE is associated with structural remodeling on the background of pro-inflammatory (tumor necrosis factor-alpha, interleukin-6 and 8, C-reactive protein) and profibrotic (TGF-β1, gal-3) changes in LV tissue, it is possible to predict the relationship between gal-3 and the development of VE [36, 47].

Increased levels of TGF-β1 and PIIIP were detected by Polunina EA et al. (2017) in patients with hypertension (H) and LV hypertrophy [1]. That is, the determination of TGF-β1 will predict the development of arrhythmias in patients with hypertension.

In an experiment on rats with created AH, Frangogiannis N.G. (2020) introduced anti-TGF-β1-neutralizing antibodies and found that their introduction contributed to the reverse development of LV diastolic dysfunction due to the reduction of MF and the formation of collagen types I and III. Therefore, TGF-β1 can be used to diagnose MF [32].

Goumans M.J., ten Dijke P. (2018) determined a decrease in LV myocardial mass in rats treated with losartan and tranilast (a nonspecific inhibitor of TGF-β1), and both drugs prevented an increase in perivascular fibrosis by reducing the content of hydroxyproline – an amino acid included in collagen protein composition. Decreased TGF-β1 expression prevented the development of left ventricular hypertrophy and fibrosis even without lowering blood pressure. It is known that the activity of TGF-β1 increases with the stimulation of AT II, so in decrease in the level of the latter the processes of fibrosis in the myocardium can be reduced [39].

In patients with chronic heart failure (CHF) in the analysis of Holter ECG monitoring in decrease in gal-3 there was a 2-fold decrease in the average number of VE per day, while with an increase in gal-3 – an increase in the average number of VE per day by almost 5 times [2]. The analysis of the initial level of gal-3 in patients with CHF revealed a significantly higher level in those who, according to the results of Holter ECG monitoring, had episodes of unstable pulmonary embolism than in those in whom they were not registered [5]. However, Ruzhanska V.O. et al. (2018) did not establish a correlation between gal-3 levels and the number of VE, which were registered in half of patients with hypertrophic cardiomyopathy [12]. According to the HF-ACTION Study (2012), the participation of patients with CHF in a one-dimensional logistic regression model showed an independent effect of gal-3 at a concentration of >17.8 ng/ml on the development of fatal VA, but in a multicenter analysis this association was not preserved [8, 57]. High levels of gal-3 (>17,8 ng/ml) suggest early rehospitalization and mortality regardless of echocardiographic markers of HF severity [46].

Oz F. et al. (2017) determined the level of gal-3 in patients with arrhythmogenic dysplasia of the right ventricle (ADRV) and determined that it was higher (16,9±2.6 ng/ml, $p<0.001$) than in the group of almost healthy individuals (11,3±1.8 ng/ml). Also in patients with ADRV in whom ventricular tachycardia (VT) and ventricular fibrillation (VF) was registered, the level of gal-3 was higher than in those in whom VT and VF was not detected [36]. That is, in patients with ADRV, high levels of gal-3 may indicate the possibility of developing VA.

In patients with atrial fibrillation (AF) the synthesis of collagen fibers and the formation of myocardial fibrosis increases [15]. In the Framingham Offsprin Cohort study, an association between gal-3 concentrations and an increased risk of AF was found [34].

Gong M. et al. (2020), Kang Q. et al. (2018) determined an increase in the level of gal-3 regardless of the type of AF compared with patients in the control group. However, in persistent AF its level was higher than in paroxysmal AF [35, 42]. The highest levels of gal-3 were determined by Tang Z. et al. (2019) in patients with a permanent form of AF [17].

Ionin V. et al. (2016) analyzed the level of gal-3 in patients with metabolic syndrome (MS) and paroxysmal and persistent forms of AF and found that in persistent AF its level is higher than in paroxysmal. The level of gal-3 in the serum of patients with MS and AF is higher than in patients without AF and in the control group of healthy people. A positive correlation was shown between gal-3 levels and AF duration. Patients with frequent paroxysms of AF and ineffectiveness of antiarrhythmic therapy had a higher level of gal-3 than patients with effective antiarrhythmic treatment [4]. When analyzing aldosterone levels in patients with MS and AF, the same data were obtained and a correlation was found between gal-3 levels and aldosterone levels [3].

In patients with CHF with implanted cardioverter-defibrillator, Francia P. et al. (2014) during two years of observation found that the level of gal-3 predicted the development of stable VT/AF [52].

CONCLUSIONS

1. Analysis of the literature shows that the substrate for the development of arrhythmias is MF, which leads to structural and electrical remodeling of the heart. At defeat of cardiovascular system markers of fibrosis allow to define risk of

development of electric instability of myocardium which is a precondition of sudden arrhythmic death.

2. Markers of fibrosis, such as aldosterone, gal-3 and TGF-β1, which were determined in HD, MS, AF, CH, hypertrophic cardiomyopathy, ADRV, make it possible to predict the development of electrical instability of the myocardium. Prediction of the development of VA in patients with HD in combination with coronary heart disease based on the study of the relationship between the presence of frequent VE and plasma levels of MF biomarkers (aldosterone, gal-3 and TGF-β1) has not been established in studies. The above requires priority in-depth study of this issue.

Conflict of interest. The author declares no conflict of interest.

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The article was received
2019.12.29