КАРДИОРЕНАЛ СИНДРОМ МАВЖУД БЕМОРЛАРДА БЎЛМАЧАЛАР ФИБРИЛАЦИЯНИНГ ДОИМИЙ ШАКЛИНИ БАШОРАТ ҚИЛУВЧИ МАРКЕРЛАР

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Аннотация

Сурункали юрак этишмовчилиги бўлган беморларда кардиоренал синдромнинг (КРС) юқори тарқалиши унинг ривожланиши ва ривожланишига ёрдам берадиган патогенетик механизмларни ўрганишни хозирги кунда долзарб бўлиб. Миокарднинг аритмоген тайёргарлигини ривожлантиришда фиброз ва юракни қайта қуриш ролининг аҳамиятига асосланиб , мавжуд КРС фонида атриял фибрилатсияни (АФ) ривожланишига нисбатан фиброз белгиларининг прогнозли қийматини тахмин қилиш мумкин.

Тадқиқот мақсади: фиброз белгиларининг афзалликлари ва камчиликларини ўрганиш - матритсали металлопротеиназаларнинг 1-тоифа тўқима ингибиторининг матритса металлопротеиназалар 1- тоифа , TIMP-1) ва 2-ген томонидан ифодаланган рағбатлантирувчи ўсиш омили, беморларда доимий АФ ривожланишининг прогнози қилиш.

Материал ва усуллар: тасдиқланган КРС билан 155 бемор текширилди. 79 (50,8%) беморда АФ нинг доимий шакли, 76 (49,2%) беморда синус ритми қайд этилган. Фибрознинг фаоллигини баҳолаш учун қон зардобида TIMP-1 ва sST2 контсентратсияси аниқланди.

Тадқиқот натижалари : ТИМП-1 таркиби доимий АФ бўлган беморларда статистик жиҳатдан сезиларли даражада юқори бо'лган (107,5

[102,0; 111,0] нг / мл, п = 0,003), sST2 даражаси ҳам доимий бўлган беморлар гуруҳида статистик жиҳатдан сезиларли даражада юқори бўлган. АФ шакли (48,0 [54,0; 135,0] нг /мл, п=0,001). sST2 учун КРС таҳлили 98,2% сезувчанлик ва 100,0% ўзига хослик билан 56 нг / мл (AUC = 0,991, п <0,001) кесиш нуқтасини аниқлади ; TIMP-1 учун кесиш нуқтаси 105 нг / мл (AUC = 0,907, п <0,001) 78,2% сезувчанлик ва 83,5% ўзига хослик билан.

Хулоса: КРС фонида АФ нинг доимий шаклига нисбатан прогноз қилувчи аҳамиятга эга бўлган фиброз белгилари сифатида тавсия қилиш мумкин , уларнинг таркибининг кўпайиши АФ нинг доимий шакли ривожланишини башорат қилиш имконини беради. NT-proBNP га қараганда ишончлироқ бўлиб . TIMP-1 CRS билан оғриган беморларда доимий АФ хавфини аниқлаш учун танлов белгиси бўлиб хизмат қила олмайди .

***Калит сўзлар**: атриял фибрилатсиянинг доимий шакли, кардиоренал синдром, фиброз, sST2, TIMP-1.*

MARKERS PREDICTING PERMANENT FORM OF ATRIAL FIBRILLATION IN PATIENTS WITH CARDIORENAL SYNDROME

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Abstract

Introduction: the high prevalence of cardiorenal syndrome (CRS) among patients with chronic heart failure makes it urgent to study the pathogenetic mechanisms that contribute to its development and progression. Based on the importance of the role of fibrosis and cardiac remodeling in the

development of arrhythmogenic readiness of the myocardium, the predictive value of fibrosis markers can be assumed in relation to the development of atrial fibrillation (AF) against the background of existing CRS.

Purpose of the study: to study the advantages and disadvantages of fibrosis markers - tissue inhibitor of matrix metalloproteinases type 1 (tissue inhibitor of matrix metalloproteinases type 1, TIMP-1) and stimulating growth factor expressed by gene 2 (soluble ST2, sST2) as predictors of the development of permanent AF in patients with cattle.

Material and methods: 155 patients with verified CRS were examined. A permanent form of AF was recorded in 79 (50.8%) patients, and sinus rhythm was recorded in 76 (49.2%) patients. To assess the activity of fibrosis, the concentration of TIMP-1 and sST2 in the blood serum was determined.

Study results: the content of TIMP-1 was statistically significantly higher in patients with permanent AF (107.5 [102.0; 111.0] ng /ml, p = 0.003), the level of sST2 was also statistically significantly higher in the group of patients with permanent form of AF (48.0 [54.0; 135.0] ng /ml, p=0.001). ROC analysis for sST2 revealed a cut-off point of 56 ng /ml (AUC=0.991, p <0.001) with a sensitivity of 98.2% and specificity of 100.0%; for TIMP-1, the cut-off point was 105 ng /ml (AUC=0.907, p <0.001) with a sensitivity of 78.2% and specificity of 83.5%.

Conclusion: sST2 can be recommended as markers of fibrosis that have predictive value in relation to the permanent form of AF against the background of cattle, an increase in the content of which makes it possible to predict the development of a permanent form of AF, being a more reliable predictor than NT-proBNP . TIMP-1 cannot serve as a marker of choice to determine the risk of permanent AF in patients with CRS.

Key words: permanent form of atrial fibrillation, cardiorenal syndrome, fibrosis, sST2, TIMP-1.

Introduction

Cardiorenal syndrome (CRS) is a complex multisystem dysfunction in which neurohumoral mechanisms, in particular excessive activation of the renin-angiotensin-aldosterone system, the expression of proinflammatory mediators and markers of oxidative stress, leading separately to cardiovascular failure and impaired renal filtration, initiate a cascade of successive mutual negative influences leading to the formation of chronic heart failure (CHF) and chronic kidney disease (CKD) [1]. The high—up to 60%—prevalence of CRS among patients with CHF determines the undoubted relevance of studying the pathogenetic mechanisms that contribute to its development and progression [2].

Atrial fibrillation (AF) occupies a special place in the formation of the cardiorenal continuum, creating a complex set of electrophysiological and morphological prerequisites for the development of CRS [3]. The results of the GARFIELD-AF registry, which included more than 33 thousand observations, showed that approximately 30% of patients with newly diagnosed AF were diagnosed with CKD [4]. The severity of CKD in patients included in the registry correlated with the frequency and severity of concomitant cardiovascular diseases and, to the greatest extent, was associated with CHF. Despite the obvious relevance of the problem of the combination of CRS with AF, there is currently not much data on the mutual influence of AF and combined damage to the heart and kidneys. In general, most researchers agree that AF negatively affects the prognosis of patients with CRS, which forces us to look for the mechanisms of this effect and markers that can adequately assess them. Multicomponent comorbidity , in particular the combination of CHF, CKD and AF, makes significant adjustments to the use of generally accepted markers for assessing the severity of each individual condition, such as glomerular filtration rate (GFR), the content of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) , etc. [5, 6]. In the development of arrhythmogenic readiness of the myocardium, the role of the mechanisms of collagenolysis , the formation of fibrosis and remodeling is important

cardiovascular circuit, therefore, one can assume the prognostic value of fibrosis markers in relation to the development of AF against the background of existing CRS [7].

Modern concepts allow us to distinguish two main types of myocardial fibrosis: “reactive” and “replacement” [3]. Reactive fibrosis is a change in the extracellular matrix and perivascular spaces, leading to the formation of a collagen “wrap” around myocardial syncytia. These changes do not lead to a significant change in their contractility or relaxation ability, but may cause electrophysiological changes (eg, conduction acceleration) that cause or maintain proarrhythmogenic activity. Replacement, or restorative, fibrosis is the formation of fibrotic foci at the site of dead myocardial cells. In this case, the proarrhythmogenic activity of fibrosis is associated with massive apoptosis myocardiocytes , as well as with possible interruption of the conduction pathways by formed fibrous cords. The described mechanisms allow, among other things, to explain the development of a permanent form of AF and unsuccessful attempts to restore sinus rhythm in conditions of severe fibrotic disease . remodeling _

The family of metalloproteinases and their inhibitors appears to be a reliable tool for assessing the activity of fibrosis in the myocardium, including in patients with AF . It is noted that increased activity of metalloproteinases contributes to the development of arrhythmogenic fibrosis and remodeling of the atrial myocardium, creating a substrate for the development of AF, and an increase in the concentration of tissue inhibitor of matrix metalloproteinases type 1 (TIMP-1) is associated with an increased risk of recurrent AF after electrical cardioversion [5]. A promising marker of myocardial fibrosis, including arrhythmogenic atrial remodeling , soluble stimulating growth factor expressed by gene 2 (soluble ST2, sST2) also serves [7]. As a member of the interleukin 1 family, sST2 is overexpressed by endothelial cells in response to myocardial stress and pressure overload and is currently considered a promising

marker of the presence and severity of CHF. In 2017 American college of Cardiology (ACC) was the first to include sST2 in recommendations for the treatment of CHF as an auxiliary marker proposed for use in cases where there is an excessive third-party effect on the concentration of NT-proBNP. The above provisions determined the choice of TIMP-1 and sST2 as candidates—predictors of the development of permanent AF in cattle patients.

Purpose of the study: to study the advantages and disadvantages of fibrosis markers TIMP-1 and sST2 as predictors of the development of permanent AF in patients with cattle.

Material and methods

The cross-sectional cohort study included 155 patients with verified CRS. Permanent AF was diagnosed in 79 (50.9%) patients, and sinus rhythm was recorded in 76 (49.1%). The diagnosis of CRS was established on the basis of verification of CHF in accordance with the clinical recommendations of the Russian Society of Cardiology (RSC): clinical symptoms and/or signs, increased NT-proBNP levels >365 pg /ml, left ventricular (LV) systolic dysfunction and/or the presence of at least one of the additional criteria - structural changes in the heart or LV diastolic dysfunction; and also based on verification of CKD in accordance with KDIGO criteria (Kidney Disease : Improving Global) Outcomes , 2012) [16]: GFR <60 ml/min/1.73 m2 for >3 months. AF was diagnosed in accordance with the clinical guidelines of the RSC . AF when recorded on a standard 12-lead electrocardiogram (ECG) or throughout the entire recording of one lead during long-term ECG monitoring .

For statistical processing of the obtained data, the programs Statistica 11.0 (StatSoft , USA) and MedCalc 11.5.0 (MedCalc Software , Belgium). To check the law of normality of distribution of characteristics in comparison groups, the Shapiro- Wilk and Kolmogorov-Smirnov tests were used. For quantitative characteristics in the compared groups, the median, 25th and 75th percentiles (1st and 3rd quartiles) were calculated (Me [Q1; Q3]). For qualitative nominal

characteristics, the absolute (number of subjects examined) and relative (%) frequency of manifestation of the characteristic were indicated. The prognostic significance of candidate predictors of AF development was assessed using logistic regression analysis. To assess the chances of developing a clinical outcome in the main group relative to the chances of its development in the control group, we used the method of determining the odds ratio (OR, 95% CI). To assess the quality of logistic regression, ROC was used (Receiver Operating Characteristic) - analysis with calculation of a quantitative indicator of the area under the curve (AUC, Area Under Curve), which was considered a reliable indicator for values >0.5 at p <0.05. For statistically significant prognostic indicators, a cutoff threshold was obtained, and its sensitivity and specificity were assessed. The critical value of the level of statistical significance when testing null hypotheses was taken to be p <0.05.

Research results

The study included 62 (40%) men and 93 (60%) women. The average age of patients participating in the study was 65.0 [58.0; 76.0] ears. The average duration of CHF was 12.5 [5.5; 20.0] ears, the functional class of CHF at the time of inclusion in the study was equal to 3.0 [2.0; 3.0]. In 73 (44.4%) patients, LV functional output (LVEF) was within the normal range; a moderate decrease in LVEF to 40–49% was observed in 92 (55.6%) patients. The criteria for LV diastolic dysfunction were verified in 122 (73.7%) patients. The average NT-proBNP level was 588.5 [220.5; 1210.0] pg /ml.

Patients were divided into groups. The 1st group included 83 (50.5%) patients with BRS in combination with a permanent form of AF, the 2nd group included 82 (49.5%) patients with BRS accompanied by sinus rhythm.

The data obtained demonstrate signs of more pronounced fibrosis, assessed by the level of TIMP-1, which was higher in patients of group 1 (83 [102.0; 111.0] ng/ ml versus 82 [98.0; 104.0] ng /ml, p =0.003), and in terms of sST2 level, which also turned out to be higher in the group of patients with permanent

AF (64.0 [54.0; 135.0] ng /ml versus 44.0 [36.0] ; 61.0] ng /ml, p=0.001). It was found that the proportions of patients with elevated sST2 levels (>34.3 ng /ml) did not differ statistically significantly in groups with different basic heart rhythms.

When constructing the ROC curve for all sST2 values, a cut-off point of 56 ng /ml was obtained (AUC=0.991, p <0.001). Thus, the sST2 level >56 ng /ml can serve as a predictor of the development of permanent AF in patients with BRS with a sensitivity of 98.2% and a specificity of 100.0% (p <0.05).

ROC curve for all TIMP-1 values with a cut-off point of 105 ng /ml (AUC=0.907, p <0.001), which allows predicting the development of permanent AF in patients with CRS with a sensitivity of 76.3 % and a specificity of 8.4.5 % (p <0.05). Thus, fibrosis markers sST2 and TIMP-1 have demonstrated value as predictors of the development of permanent AF in patients with CRS.

Discussion

The role of fibrosis as one of the key components of myocardial remodeling , contributing to the development of AF, has been determined, however, ideas about the specific mechanisms of fibrosis development, ways of implementing neurohumoral dysregulation , leading to significant structural and functional restructuring of the myocardium, including the atria, remain incomplete, based on experiment, requiring further analysis regarding the possibility of further clinical implementation. In addition to the markers presented in this work, various authors also propose galectin 3 , tissue growth factor β1, fibronectin and a number of others, however, most studies evaluating these markers are experimental in nature, and their use in real clinical practice is debatable . TIMP-1 and sST2 have been introduced into clinical practice and are recommended for use in certain clinical situations. According to W. Sun et al ., paroxysmal AF is associated with increased levels of sST2 and TIMP-1, but their predictive value for AF is not as great as, for example, left atrium size, age, or NT-proBNP concentration . G. Vergaro et al . analyzed the predictive value

of sST2 in comparison with NT-proBNP in relation to the development of cardiovascular events in patients with CHF and demonstrated a significant increase in the incidence of adverse outcomes in patients with high serum sST2 concentrations with normal NT-proBNP levels . In our study, sST2 appears to be a more balanced and sensitive predictor of permanent AF than NT-proBNP . In cattle conditions, when impaired renal function contributes to impaired NT-proBNP metabolism , the sST2 marker in question naturally demonstrates great value as a predictor of AF. Most of the data presented on the role of sST2 in the development and course of AF concerns non-permanent forms. It has been shown that an increased concentration of sST2 is a precursor of new-onset AF in patients with coronary heart disease. There is also evidence for the role of sST2 in assessing the risk of AF recurrence after electrical cardioversion . There is insufficient data on the clinical value of sST2 in predicting the development and course of permanent AF, but the results of our study indicate the promise of using this marker. In the present study, the value of TIMP-1 as a predictor of AF was lower than that of sST2. However, convincing evidence that TIMP-1 serves as a reliable marker of AF recurrence after cardioversion makes its use more justified in patients with paroxysmal or persistent AF. In cattle conditions, an increase in TIMP-1 concentration is associated to a greater extent with symptoms of congestion and a decrease in renal clearance than with frequency-dependent restructuring of the heart and blood vessels. Given these data, TIMP-1 appears to be a marker of fibrosis more associated with BRS than with AF.

Conclusion

The study of fibrosis markers in patients with CRS in combination with AF is of great clinical and prognostic significance. Fibrosis is an important part of the pathogenesis of AF, and a multimorbid background in the form of cattle creates additional preconditions for arrhythmogenic fibrosis and remodeling of the myocardium. As markers of fibrosis that have predictive value in relation to the permanent form of AF against the background of cattle, we can recommend

sST2, which, at a level of >56 ng /ml, allows us to predict the development of a permanent form of AF with a sensitivity of 96.3% and a specificity of 100.0% (p <0. 05), being a more reliable predictor than NT-proBNP . TIMP-1 cannot serve as a marker of choice for determining the risk of permanent AF in patients with cattle, since it is more associated with the development of fibrosis caused by congestion than caused by rhythm disturbances. The results obtained in this work can be applied in clinical practice, justifying the study of sST2 levels in the examination of patients with CRS to determine the risk of developing permanent AF.

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