Seromarkers of synthesis and collagen degradation, electrophysiological heart parameters among patients with syndrome of preexcitation of ventricles

Seromarcadores de síntesis y degradación de colágeno, parámetros cardíacos electrofisiológicos entre pacientes con síndrome de preexcitación de ventrículos

Vasilets L. M.[1], Krivaya A. A.[2], Vustina V. V.3, Khlynova O. V.[4], Nekrutenko L. A.[5], Tuev A. V.[6]
[1]Professor of the Hospital Therapy Department, Doctor of Medical Sciences, E. A. Wagner Perm State Medical University, Perm, Russia
[2]Arrhythmologist of Perm Regional Cardiologic Dispensary, Candidate of Medical Sciences, E.A. Wagner Perm State Medical University, Perm, Russia
[3]Cardiologist of Perm Regional Clinical Hospital, Candidate of Medical Sciences. E. A. Wagner Perm State Medical University, Perm, Russia
[4]Head of the Department of Hospital Therapy, Doctor of Medical Sciences, Professor, Member of the Russian Academy of Sciences (RAS), E.A. Wagner Perm State Medical University, Perm, Russia
[5]Professor of the Hospital Therapy Department, Doctor of Medical Sciences, E.A. Wagner Perm State Medical University, Perm, Russia
[6]Professor of the Hospital Therapy Department, Doctor of Medical Sciences, E.A. Wagner Perm State Medical University, Perm, Russia

Abstract

The results of examination of 43 patients with syndrome of preexcitation of ventricles are introduced in the article. The aim of the study was to optimize diagnostics and prediction of the development of arrhythmia in this cohort and to find out the possible role of disorder of fibrous matrix in the development of disorder of cardiac arrhythmias. The main group consisted of 43 patients with syndrome of preexcitation of ventricles (phenomenon WPW, syndrome WPW) and 15 practically healthy people of the same age were in the group of comparison. The average age of the examined patients from the main group was 25,3±9,15 years old, among them 29 men (67%) and 14 women (33%). The average age in the comparison group was 27,9±7,9 years old. All groups included into the examination were comparable by gender distribution (p=0,45, Fisher's test) and by age (p=0,27, U-criterion). The highest figures of matrix metal proteinase-9 (MMP-9) were found among patients with syndrome WPW – 96,1±33,2ng/ml and in the group of phenomenon WPW (54,3±21,8ng/ml; p=0,0003). Practically healthy people had minimal values of the MMP-9 - 27,4±10,9ng/ml (p=0,00014; p=0,000002). Maximal values of tissue inhibitor of matrix metal proteinase (TIMP-1) are introduced in the group of phenomenon WPW and in the group of practically healthy people (418,5±69,8 ng/ml and 461,7±72,2ng/ml; p=0,27). Patients with syndrome WPW have lower TIMP-1 – 341,1±90,1 ng/ml (p=0,002; p=0,00012). The level of propeptideprocollagenof the type I(PICP) among patients with syndrome WPW was 179,9±76,2ng/ml and 97,8±31,7 ng/ml (p=0,00014) in the group of phenomenon WPW. All examined patients according to the level of PICP differed from practically healthy people 69,4±23,9ng/ml (p<0,05, U-criterion). The examined patients have changes of fibrous matrix. That includes an increasing the concentration of MMP-9, PICP and reducing TIMP-1. The syndrome WPW is characterized by more expressed disbalanceof seromarkers of synthesis and collagen degradation than phenomenon is. It is possible that the examined seromarkers of fibrosis take place in forming disorders of cardiac arrhythmias in actual syndromes.

Keywords: arrhythmia, arrhythmogenesis, markersof fibrosis.

Resumen

En el artículo se presentan los resultados del examen de 43 pacientes con síndrome de preexcitación de ventrículos. El objetivo del estudio fue optimizar el diagnóstico y la predicción del desarrollo de arritmia en esta cohorte y descubrir el posible papel del trastorno de la matriz fibrosa en el desarrollo del trastorno de las arritmias cardíacas. El grupo principal consistió en 43 pacientes con síndrome de preexcitación de ventrículos (fenómeno WPW, síndrome WPW) y 15 personas prácticamente sanas de la misma edad estaban

en el grupo de comparación. La edad promedio de los pacientes examinados del grupo principal fue de 25,3±9,15 años, entre ellos 29 hombres (67%) y 14 mujeres (33%). La edad promedio en el grupo de comparación fue de 27,9±7,9 años. Todos los grupos incluidos en el examen fueron comparables por distribución de género (p=0,45, prueba de Fisher) y por edad (p=0,27, criterio U). Las cifras más altas de matriz metálica proteinasa-9 (MMP-9) se encontraron entre pacientes con síndrome WPW - 96,1±33,2ng / ml y en el grupo de fenómeno WPW (54,3±21,8ng/ml; p =0,0003). Las personas prácticamente sanas tenían valores mínimos de MMP-9: 27,4±10,9ng/ml (p = 0,00014; p=0,000002). Los valores máximos del inhibidor tisular de la proteinasa de matriz metálica (TIMP-1) se introducen en el grupo de fenómeno WPW y en el grupo de personas prácticamente sanas (418,5±69,8 ng/ml y 461,7±72,2ng/ml; p=0,27). Los pacientes con síndrome de WPW tienen menor TIMP-1 - 341,1±90,1 ng/ml (p=0,002; p =0,00012). El nivel de propéptidoprocolágeno del tipo I (PICP) entre los pacientes con síndrome WPW fue 179,9±76,2ng/ml y 97,8±31,7 ng/ml (p=0,00014) en el grupo de fenómenos WPW. Todos los pacientes examinados de acuerdo con el nivel de PICP diferido de personas prácticamente sanas 69,4±23,9ng/ml (p<0,05, criterio U). Los pacientes examinados tienen cambios de matriz fibrosa. Eso incluye aumentar la concentración de MMP-9, PICP y reducir TIMP-1. El síndrome WPW se caracteriza por un desequilibrio más expresado de los seromarcadores de síntesis y degradación del colágeno que el fenómeno. Es posible que los seromarcadores examinados de fibrosis tengan lugar en la formación de trastornos de arritmias cardíacas en síndromes reales.

Palabras clave: arritmia, arritmogénesis, marcadores de fibrosis.

Introduction

Most of electro physiologists view the syndrome of Wolff-Parkinson-White (WPW) as a classical substrate for disorders of cardiac arrhythmias. However, an actual syndrome still remains a complicated issue when choosing a tactics for treatment such patients. In most cases its clinical manifestation happens at the age from 10 to 20 years old and very rarely among people of elderly age[5]. In 40-80 per cent the syndrome WPW is clinically developed by various forms of disorders of cardiac arrhythmias (DCA). Approximately half of discovered arrhythmias do not only make worse the quality of life but they are often fatal[2]. $^1/_3$ of patients have paroxysms of atrial fibrillation (AF). In most cases it is a reason of cardiovascular accidents. The combination of the AF with high heart rate (HR) and with a short effective refractory period (adiaphoria) (ERP) of additional way of conducting (AWC) creates an ability for development of flutterand fibrillation of ventricles (FV). The conducting the impulses to the ventricles in the ratio of 1:1 up to 340 per minute during episode MA provides transformation of the AF into the FV which is a main mechanism of sudden cardiac death (SCD) of patients with syndrome WPW[1,6,17,20].

The possibility to have a sudden death during 10 years with the syndrome of preexcitation of ventricles exceeds a general risk and it is from 0.15 to 0.39 per cent. In some cases the SCD can be the first clinical demonstration of masymptomatic preexcitation of ventricles[6,8,16].

Nowadays, the non-invasive and endocardialelectrophysiological study (EPS) of cardiac conduction system hasthe key point in the diagnosis the syndromes of preexcitation of ventricles and prediction of the DCA[4]. The results received during the EPS determine the further tactics of treatment of patients[3,6,18]. However, even the non-invasive EPS has a set of contra-indications and restrictions for usage: advisability of its usage among asymptomatic patients and during childhood is still discussed[11,12,14,15,19].

The development of the DCA is connected with progressive structural and functional and electric remodeling of atrial myocardium. The mechanisms of structural remodeling and progression of selective atrial fibrosis are still not studied in detail. An interstitial fibrosis of myocardium is characterized by proffered accumulation of collagen of the 1sttype. The multitude products of metabolism of this protein are terminal propeptideprocollagen type I (PICP), matrix metal proteinase-9 (MMP-9), tissue inhibitor of matrix metal proteinase-1 (TIMP-1)[12,13]. Consequently, the level of PICP, MMP-9 and TIMP-1 can indirectly reflect the degree of synthesis and collagen degradation of type I normally and pathologically.

In that wayserumal biomarkers of fibrosis give a certain mark to a structural reconstruction of extracellular matrix that allows to specify mechanisms of arrhythmogenesis, to optimize early diagnosis and to determine tactics of treatment of patients with the DCA[9,10].

The above mentioned positions give a basis of the aim and tasks of this examination.

The aimis to examine markers of synthesis and collagen degradation, parameters of electrophysiological condition of myocardium among patients with syndrome and phenomenon WPW and to establish possible correlations between them.

Materials and methods

There were examined 43 patients (the main group) with syndromes of preexcitation of ventricles in the specialized cardiological clinic. Among them there were 29 men and 14 women with the average age of 25,3±9,15 years old. Among patients of the main group two subgroups were formed. The patients with phenomenon WPW (n=16) were in the first subgroup, the patients with syndrome WPW (n=27) were in the second subgroup. The both cohorts were comparable by gender distribution (F-criterion, p=0,52) and age (U-criterion, p=0,42). The following DCAs were discovered during the examination among patients with syndrome WPW: atrioventricular reentrant tachycardia (AVRT) among 8 people (30%), atrial flutter (AF) among 6 patients (22%), atrial fibrillation and atrial flutter among 13 patients (48%). The comparison group consisted of 15 practically healthy people comparable by sex and age.

The inclusion criteria were defined to form the main group: men and women at the age from 17 to 45 years old, presence among patients the clinical and instrumental data that testified the syndrome or phenomenon WPW. The ECG criterion includes: contraction of the interval PQ<120msec, presence of the A-wave, confluent character and complex broadening QRS>110-120msec, change of the segment ST and T-wave discordant to the direction of the complex QRS, presence of the DCA, features of additional conducting ways (ACW) discovered during the EPS.

In order to form homogeneous groups the exclusion criteriawere introduced: age younger than 17 and older than 45, illnesses of organs of hepatobiliary zone, diabetes mellitus I and II types (DM), carbohydrate intolerance, hard obstructive pulmonary disease, bronchial asthma, pneumofibrosis, chronic kidney disease, connective tissue diseases, malignant neoplasms, patients with implanted cardioverter defibrillator, electric cardiac pacemaker, hypertensive disease, symptomatic arterial hypertension (AH), patients with chronic cardiac failure (CCF) II FC NYHA, various forms of coronary artery disease (CAD), non-coronarogenic myocardial diseases, acquired affections of valvular apparatus and congenital heart diseases, sick sinus syndrome(SSS) and thyroid function abnormality.

During the examination all patients had general and clinical examination that included analysis of complaints, gathering of medical history and life and physical examination. General and biochemical blood tests and determination of thyroid level were valued. Electrocardiography in 12 leads, long ECG monitoring with defining the cardiac rhythm variability, echocardiography and also electrophysiological study were included in the program of instrumental examination. The quantitative tissue inhibitor of metalloproteinase-1 (TIMP-1) and carboxyterminal propeptide (PIP) - procollagen type I in the blood serum were studied to value the indices of fibrosis factors. The level of TIMP-1 was defined with the help of panels "Human-TIMP-1ELISA" (BenderMedSystems, Austria) by the method of immune-enzyme analysis (IEA) that was realized in several stages. On the first stage antibodies to TIMP-1 adsorbed in the tablet cells are connected with TIMP-1 that is in the samples. Added biotinylated anti-TIMP-1 antibodies are connected with TIMP-1 caught by sorbed antibodies in the wells. After incubation and washing unconjugated biotin conjugate- TIMP-1 is removed from the cells and conjugate streptavidin peroxidase is added. After incubation unconjugated biotin conjugate is removed and substrate solution is added. It forms colouring when interaction with enzyme system. The intensity of colouring is directly proportional to the concentration of TIMP-1. The estimation of PICP was realized by using diagnostic set of "MetraCIPCEIAKit" (QuidelCorporation, the USA). The method is based on the "sandwich" immune-enzyme analysis in micromonoclonal variant with the use of monoclonal anti-PICP antibodies, immobilized in the wells of microplates, rabbit anti-PICP antiserum, conjugate of goat anti-rabbit antibodies with alkaline phosphatase and substratepNPP for quantitative evaluation of PICP in human serum. The antibodies to PICP have 100 per cent of cross-responsiveness with PICP of human blood serum.

Electrophysiological study of the heart conducting system is realized by the method of transesophageal electrostimulation of the auricles with the use of electrostimulator "Astrocard-PolysystemEP/L" (CAS "Meditec", Russia) and multipolar electrode WEFCA-2, Kamenetz-Podolsk. A number of patients had an examination by the method of transvenous electrocardiac stimulation. A universal diagnostics electrocardiac stimulator "Biotok- esophagogastroduodenoscopy (EGD) 01 ml" (OOO "L.M.E. "Biotok", Russia) and multipolar electrodes RFMarinrMC (Medtronic, the USA) were used. The procedures were carried out according to the standard methods. The generally accepted electrophysiological parameters were registered during the examination.

Results

The highest indices of MMP-9 were defined among patients with syndrome WPW – 96,1±33,2ng/ml, noticeably lower they were in the group with phenomenon WPW (54,3±21,8ng/ml; p=0,0003). Practically healthy people had minimal indices MMP-9 - 27,4±10,9 ng/ml (p=0,00014; p=0,000002). Maximum level TIMP-1 is defined among patients with phenomenon WPW and practically healthy people (418,5±69,8 ng/ml and 461,7±72,2 ng/ml; p=0,27). Patients with syndrome WPW TIMP-1 had low indices – 341,1±90,1 ng/ml (p=0,002; p=0,00012). The level PICP among patients with syndrome WPW was 179,9±76,2 ng/ml and with phenomenon WPW – 97,8±31,7 ng/

ml (p=0,00014). All examined patients according to the level PICP differed from practically healthy coevals by 69,4±23,9 ng/ml (p<0,05, U-criterion).

All examined patients had electrophysiological study (EPS). Among all patients with syndromes of ventricles' pre-excitation the features of anthesystole were discovered. Among patients from the main group the shortening of the interval PQ is observed and besides the patients with syndrome WPW (106,18±16,5msec) have it more in comparison with the phenomenon WPW (115,25±19,54msec, p=0,004). When having syndromes of preexcitation the average adiaphoria according to the duration is determined,that is from 220 to 300msec: when having the syndrome WPW it is 240,0±47,9msec and when having the phenomenon WPW it is 241,25±30,84msec. Patients with the syndrome WPW had a shorter adiaphoria (p=0,049). Both groups have the inverse correlation withfibrosisbioindicators - MMP-9 and PICP. From the received data we can indicate the influence of markers' disbalance that characterizes homeostasis of extracellular matrix (EN) on electrophysiological properties of the ACW.

The function of the automatismof sinoatrial node was evaluated with the help of the following parameters: time of functional restoration of the sinoatrial node and corrected time of this indicator, values did not exceed the bounds of the set standards. The speeding up of atrioventricularconductivity (AC) was observed: Wenckebach point was 219,63±30,57 imp/min, patients with the syndrome WPW had shorter adiaphoria of the atrioventricular node (278,15±27,7msec). At that the index of adiaphoria of the atrioventricular conductivity correlated with MMP-9 concentration (R=-0,57; p=0,002). Among patients with phenomenon WPW arrhythmogenic vulnerability of myocardium was low, the DCA was not provoked. Patients with syndrome WPW without MA are provoked by the DCA by type of the AF, the AVRT with orthodromic and antidromic conductivity on ventricles and their combinations. Thus people with diagnosed additional atrioventricular connection (AAVC) have changes of electrophysiological properties of conductive system of the heart, electric instability of myocardium in the form of high arrhythmogenic vulnerability that can be determined by ascending current through atrioventricular node and by hyperexpressionof factors that reflect rearrangement of the EN at the ultrastructural level.

Conclusions

1. Patients with syndrome of preexcitation of ventricles have changes of fibrous matrix: the increasing of concentration of MMP-9, PICP and reducing of TIMP-1 in the blood serum. The syndrome WPW is characterized by more expressed disbalance of seromarkers of synthesis and collagen degradation than the phenomenon WPW. The effective adiaphoria of additional ways of conducting correlated back with MMP-9 and PICP indices.
2. The received results show the possible participation of fibrous disorganization and myocardial inflammation in the formation of the DCA when having syndromes of preexcitation of ventricles.

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