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INTRACARDIAC HEMODYNAMICS, FIBROBLAST GROWTH FACTOR-2 AND OXYPROLINE LEVELS WITH MITRAL VALVE PROLAPSE IN COMBINATION WITH TYPE 1 DIABETES MELLITUS

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Abstract

The purpose. The aim of the study was a comparative analysis of basic echocardiographic parameters, fibroblast growth factor-2 and free and peptide-bounding oxyproline indicators in young patients with mitral valve prolapse, type 1 diabetes mellitus and the combination of both indications.

Materials and methods. 93 patients between 19 and 33 years old with either mitral valve prolapse, type 1 diabetes and the combination of both indications were examined. There are 24 people with diagnosed mitral valve prolapse, 33 patients with type 1 diabetes mellitus and mitral valve prolapse and 36 patients with the monomorbid type 1 diabetes melli-

tus. The establishment of the diagnosis of mitral valve prolapse implemented by echocardiographic criteria L. Freed et al. (2002). The concentration of fibroblast growth factor-2 in blood plasma was determined by the enzyme immunoassay using a Quantikine reagent kit (Human FGF basic Immunoassay), manufactured by R&D Systems, Inc. (USA) and expressed in pg/ml. Free and peptide-bounding oxyproline as the markers of connective tissue metabolism were determined by the method of P. N. Sharaev and expressed in $\mu\text{mol/L}$.

Results. In patients with mitral valve prolapse and ype 1 diabetes mellitus, the higher values of l left ventricular posterior wall thickness and intraventricular septum have been revealed in comparison with the groups of patients with monomorbid mitral valve prolapse and ype 1 diabetes mellitus. Fibroblast growth factor-2 was higher in group with combination of both indications, where it was $[23.7 \pm 0.25]$ pg/ml compared to the control group $[14.20 \pm 0.22]$ pg/ml ($p < 0.01$). There was also a significant difference in the levels of fibroblast growth factor-2 between group with either mitral valve prolapse $[15.33 \pm 0.24]$ pg/ml and combination of mitral valve prolapse and type 1 diabetes $[23.71 \pm 0.25]$ pg/ml ($p < 0.01$). The level of peptide-bound oxyproline, just as the level of free oxyproline, significantly increased in patients with comorbid pathology, compared to the control group: $[16.06 \pm 1.54]$ $\mu\text{mol/l}$ versus $[8.7 \pm 0.81]$ $\mu\text{mol/l}$ ($p < 0.01$) respectively.

Conclusions. The most significant differences in the indices of intracardiac hemodynamics, fibroblast growth factor-2 and free and peptide-bounding oxyproline compared with control were observed in patients with combination of mitral valve prolapse and type 1 diabetes, which may indicate the influence of diabetic metabolic processes on further structural changes in the mitral valve.

Keywords: mitral valve prolapse; diabetes mellitus; fibroblast growth factor-2; free and peptide-bound oxyproline; cardiac valve degeneration; echocardiographic parameters of left ventricular hemodynamic.

INTRODUCTION

Dysplasia of connective tissue (CT) is formed in the embryonic and postnatal periods due to disambryogenetic chsnge in the morpho-functional properties of connective tissue [1]. Mitral valve prolapse (MVP) is one of the most common cardiac manifestations of the undifferentiated dysplasia of connective tissue. In the presence of the development of myxomatous degeneration of the valve apparatus of the heart, damage to the spongy layer of the valves is observed due to a violation of the process of fibrillogenesis, which leads to further edema of the extracellular matrix, changes in the microstructure of the valve itself and affects its func-

tional ability [2]. MVP can lead to a deterioration in the quality of life [3], the development of heart failure, syncope [4], prognostically unfavorable fatal arrhythmias [5]. The methods of echocardiography take a leading place in the diagnosis of MVP, assessment of its dysfunction, the severity of mitral regurgitation and the indices of intracardiac kinetics caused by them. In the beginning of remodeling of the connective tissue carcass of the left ventricle (LV), informative is the Index of the relative LV wall thickness, which is calculated as the ratio of the sum of values in mm of the thickness of the interventricular septum (IVS) and the thickness of the left ventricular posterior wall (LVP) to the end-diastolic size of the LV (LV EDD) [6]. The cellular component of CT is largely represented by fibroblasts, the extracellular matrix - by collagen, elastin and proteoglycans [1, 7].

Fibroblast growth factors (FGF) take their place in the regulation of metabolic processes of connective tissue, among which fibroblast growth factor-2 (FGF-2) is tropic to the heart valve apparatus. Some research is being done on the role of FGF-2 in relation to its direct participation in the formation of pathological disorders of connective tissue of cardiac structures during embryogenesis and in the postnatal period [8]. However, the studies of the role of FGF-2 in the development of morphofunctional changes in valves and myocardium due to dysmetabolic change, in comparison with proteoglycan parameters of connective tissue metabolism combined with mitral valve prolapse are insufficient.

Oxyproline is one of the main aminoacids of collagen, which makes free oxyproline and peptide-binding oxyproline one of the most significant biomarkers of collagen metabolism [9]. In the presence of CT dysplasia, the physicochemical properties of collagen change, there is an activation of proteolytic enzymes that produce CT cells - mainly fibroblasts, which leads to pathological changes in the structure of collagen fibers [10]. An increased content of free oxyproline in the blood may indicate collagen hypercatabolism. Peptide-binding oxyproline is a product of incomplete collagen decay. It is indirectly associated with the presence of atypical pathological forms of collagen and the processes of degradation of connective tissue. Accordingly, the ratio of the free and peptide-binding oxyproline to a certain extent reflect the tendencies of increased synthesis or pathological decomposition of collagen, which can take place simultaneously [11].

In case of diabetes mellitus (DM), dysmetabolic processes of connective tissue and of the carbohydrate metabolism develop simultaneously and are interdependent. Connective tissue dysplasia can be a background for the development and progression of diabetes. In turn, microvascular damages that are inherent in diabetes can deepen degenerative processes in the heart valve apparatus. Thus, the relationship between connective tissue dysplasia, the main

cardiac manifestation of which being MVP, and the development of diabetes may be quite expected [12].

The purpose: to perform a comparative analysis of basic echocardiographic parameters, fibroblast growth factor-2 and free and peptide-bounding oxyproline indicators in young patients with mitral valve prolapse, type 1 diabetes mellitus and the combination of both indications.

2. MATERIALS AND METHODS

93 patients between 19 and 33 years old with either MVP, type 1 diabetes mellitus (DM1) and the combination of both indications were examined (average age of the examined patients was $[26.3 \pm 0.94]$). Overall 69 patients suffered from diabetes. Group 1 was represented by 36 patients with the monomorbid DM1. Group 2 consisted of 33 patients with DM1 and MVP. The comparison group included 24 people with diagnosed MVP. In group 1 the average age was $[27.43 \pm 1.17]$ years, in group 2 it laid by $[26.88 \pm 1.05]$ years, in comparison group it was $[23.9 \pm 1.3]$ years. The control group included 22 virtually healthy individuals. The patients were in inpatient treatment in the endocrinology department of the CNC KhRC «Regional Clinical Hospital». The research conducted during 2017 - 2020 period. During the study the principles of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association (1964–2000), the Council of Europe Convention on Human Rights and Biomedicine (1997), the relevant provisions of the WHO, the International Council of Medical Scientific Communities, the International Code of Medical ethics (1983) and the laws of Ukraine were followed. It was approved by ethics committee at Kharkiv Medical Academy of Postgraduate Education (protocol No. 8 of 27.09.2017). All patients voluntarily signed an informed

consent before starting the study.

The diagnosis of type 1 diabetes was established according to the order of the Ministry of Health of Ukraine No. 1021 from 27th of June, 2014 [13]. The diagnosis of MVP and the main indicators of EchoCG were established according to the echocardiographic criteria of L. Freed et al. (2002) and Bonow R.O. et al., (2006) [14].

The concentration of FGF-2 in blood plasma was determined by the enzyme immunoassay using a Quantikine reagent kit (Human FGF basic Immunoassay), manufactured by R&D Systems, Inc. (USA) and expressed in pg/ml. The level of free and peptide-bounding oxyproline in blood serum were determined by the method of P. N. Sharaev [11] and expressed in $\mu\text{mol/L}$. Furthermore, the ratio of free and peptide-bounding oxyproline was calcu-

lated.

Statistical data processing was implemented using the methods of variation statistics and the Statistica 6.0 software package. Unpaired Student's t-test was used when comparing the results, depending on the normality of the distribution, to identify significant differences. The significance level for testing statistical hypotheses when comparing groups was < 0.05 .

3. RESULTS

Impaired metabolism of connective tissue affects the structural and functional changes in the LV and its valvular apparatus [2, 15], but there is insufficient information on the influence of the presence of type 1 diabetes on the development of MVP complications among young people, when early diagnosis of MVP complications and the establishment of the risk of myxomatous degeneration of the valvular apparatus of the heart is crucial.

We investigated echocardiographic parameters (ECP) of intracardiac kinetics in persons with MVP and type 1 diabetes (group 2) in comparison with isolated MVP (group 1).

Significant differences in ECP indices in the 2nd group of patients compared with the control concerned the thickness of the LVP (8.7 ± 0.11) mm versus (8.2 ± 0.17) mm ($p < 0.05$) and LV stroke volume (55.3 ± 1.52) ml versus (60.6 ± 1.84) ml ($p < 0.05$), also the thickness of the IVS in comorbid pathology was higher than in isolated MVP (8.8 ± 0.14) mm versus (8.3 ± 0.20) mm ($p < 0.05$).

There were no significant differences between such parameters of ECP as end-diastolic size and volume (EDS and EDV) of the LV, end-systolic size and volume (ESS and ESV) of the LV, the degree of prolapse of MV valves in relation to various groups and subgroups of patients (Table 1).

Fibroblast growth factor-2 was higher in group 2, where it was [23.7 ± 0.25] pg/ml and in the comparison group, where it was equal to [18.11 ± 0.21] pg/ml, compared to the control group [14.20 ± 0.22] pg/ml ($p < 0.01$). There was also a significant difference in the levels of FGF-2 between groups 1 and 2 in diabetes patients. It was equal to [15.33 ± 0.24] pg/ml and [23.71 ± 0.25] pg/ml respectively, probably due to the presence of MVP in the group with comorbid pathology ($p < 0.01$).

The content of free oxyproline, which is the marker of collagen synthesis and degradation, significantly increased in patients of group 2 with a combination of type 1 diabetes mellitus and mitral valve prolapse, compared to the control group, ($p < 0.05$) (Table 1).

Table 1 - Indices of intracardiac hemodynamics in isolated mitral valve prolapse and in combination with type 1 diabetes mellitus.

Indices	Group 1 (monomorbid DM1) (n=24)	Group 2 (DM1 + MVP) (n=29)	Control group (n=22)
Average age	23,9 ± 1,3	26,5 ± 1,1	23,1 ± 1,15
EDS LV, mm	45,6 ± 0,57	44,1 ± 0,51	46,0 ± 0,86
ESS LV, mm	29,8 ± 0,41	29,3 ± 0,39	30,7 ± 0,67
EDV LV, mm	92,6 ± 2,4	88,8 ± 2,37	93,9 ± 2,23
ESV LV, mm	34,8 ± 1,12	33,4 ± 1,06	36,5 ± 0,98
IVS, mm	8,3 ± 0,15 ²	8,8 ± 0,14 ¹	8,3 ± 0,20
thickness of the LVP, mm	8,1 ± 0,10	8,7 ± 0,11 ³	8,2 ± 0,17 ²
stroke volume, ml	59 ± 1,10	55,3 ± 1,52 ³	60,6 ± 1,84 ²
the degree of prolapse of MV valves, mm	4,8 ± 0,09	4,8 ± 0,08	-
RTI LV	0,36	0,39	0,36

Note.¹– differences are significant for 1 group; ²– differences are significant for 2 groups; ³– differences are significant relative to the control group (p < 0.05).

When comparing groups of patients with each other, no significant differences were found in terms of free oxyproline. The value reflects the process of collagen degradation. An increase in the content of free oxyproline in patients with concomitant pathology may indicate an increase in the intensity of destructive processes in the collagen metabolism, which corresponds to the presence of a subclinical chronic inflammatory process of low intensity and is a pathological part of the development of vascular complications of diabetes (Table 2).

The peptide-bound oxyproline was more informative as a marker of pathological synthesis and incomplete collagen decomposition. The level of peptide-bound oxyproline, just as the level of free oxyproline, significantly increased in patients with comorbid pathology in group 2, compared to the control group: [16.06±1.54] μmol/l versus [8.7±0.81] μmol/l (p<0.01) respectively. Also, a significant increase in measured values of peptide-bound oxyproline in this group could be determined in comparison with group 1 [12.38±1.34] μmol/L and the comparison group [10.18 ± 1.85] μmol/L (p<0.05).

Table 2 - Levels of free oxyproline and peptide-bound oxyproline in the blood serum of patients with MVP, DM1 and the combination of both

Indicators	Group 1 (monomorbid DM1)	Group 2 (DM1 + MVP)	Comparison group3 (monomorbid MVP)	Control group
free oxyproline, μmol/l	15,10±1,21	17,98±2,01 ⁴	14,37±2,69	13,2±1,16 ²
peptide-bound oxy- proline, μmol/l	12,38±1,34 ⁴	16,06±1,54 ^{1,4}	10,18±1,85 ²	8,7±0,81 ^{1, 2}
The ratio of free oxy- proline and peptide- bound oxyproline	1,22	1,12	1,41	1,52

Note.¹– differences are significant relative to indicator 1 of the group; ²– differences are significant relative to the indicator of group 2; ³ – differences are significant relative to the indicator of group 3; ⁴– differences are significant relative to the control group (p <0,05)

The ratio of free oxyproline and peptide-bound oxyproline levels, which reflects the balance of collagen synthesis and degradation, was [25.9%] lower in patients of group 2 than in the comparison group and significantly lower than in the control group by [35.7 %] due to the relative increase in the proportion of peptide-bound oxyproline. The data obtained indicate a relative imbalance of the connective tissue anabolism and catabolism in case of a combination of diabetes and MVP. Furthermore, it is an indication for the increased pathological changes in the connective tissue metabolism, which can lead to remodelling and myxomatous degeneration of its structure.

4. Discussion

Thus, the data obtained regarding the levels of free and peptide-bound oxyproline indicate a high severity of destructive processes in individuals with MVP combined with type 1 diabetes. Indicators of the level of peptide-bound oxyproline were informative, which were significantly higher in conditions of combined pathology than in isolated MVP and type 1 diabetes (p <0.05). In patients with MVP with clinical manifestations of type 1 diabetes, significant differences (p <0.05) were found in the ECP indices, the thickness of the IVS and LVP compared with the control and the group with isolated MVP. FGF-2 indices were significantly higher in the group with comorbid pathology, probably due to the presence of MVP (p<0.01).

Prospects for further research. Will further continue the study of collagen metabolism indicators and compare it with indicators of intracardiac kinetics of the left ventricle.

5. Conclusions

1. Significant differences in ECP indices in the 2nd group of patients compared with the control concerned the thickness of the LVP (8.7 ± 0.11) mm versus (8.2 ± 0.17) mm ($p < 0.05$) and LV stroke volume (55.3 ± 1.52) ml versus (60.6 ± 1.84) ml ($p < 0.05$).

2. The thickness of the IVS in comorbid pathology was higher than in isolated MVP (8.8 ± 0.14) mm versus (8.3 ± 0.20) mm ($p < 0.05$).

3. FGF-2 in patients of group 2 were significantly higher compared to the control group, group 1 and the comparison group. They were also significantly lower in group 1 compared to the comparison group.

4. The content of free and peptide-bound oxyproline in the blood serum of the examined patients compared with the control group was significantly higher in patients with type 1 diabetes combined with MVP ($p < 0.05$).

5. A significant increase of peptide-bound oxyproline in group 2 in comparison to group 1 and the comparison group was identified (12.38 ± 1.34) $\mu\text{mol/L}$ and (10.18 ± 1.85) $\mu\text{mol/L}$ respectively ($p < 0.05$).

Conflict of interests

The authors declare that they have no conflicts of interest.

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