MAGNESIUM IN IDIOPATHIC MITRAL VALVE PROLAPSE

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UPOTREBA MAGNEZIJUMA KOD IDIOPATSKOG PROLAPSA MITRALNOG ZALISKA

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ABSTRACT

The aim of our research was to increase the effectiveness of the therapy administered to the patients with idiopathic mitral valve prolapse by pharmacological correction of magnesium deficiency. 79 patients (23 females and 56 males with average years of age 35.7±4.3) with undifferentiated connective tissue dysplasia and mitral valve prolapse of the 1st and 2nd degree were examined. The control group consisted of 20 healthy individuals, comparable by sex and age. A test by the UNESCO Institute for Microelements was used for the preliminary diagnostics of magnesium deficiency. Daily ECG monitoring with heart rate variability analysis, echodopplercardiography with the assessment of left ventricular diastolic function and determination of magnesium concentration in blood serum were performed. For the demonstration of autonomic dysfunction "the test for detection of the signs of vegetative changes" was used (10). For the assessment of situational and personal anxiety an "anxiety test" by Ch. D. Spielberg and Y. L. Hanin (25, 26) was used. The succeeding study was performed after 6 months. It was found that complex therapy with magnesium orotate in patients with idiopathic mitral valve prolapse helps to reduce the frequency of clinical manifestations of neurovegetative disturbances in the majority of examined patients contributing to harmonization of the autonomic nervous system function. It has a favorable effect on dysplastic changes and the state of bioelectrical activity of the heart, as well as correction of the psychoemotional state.

Keywords: *valvular disease, magnesium deficiency, treatment*

SAŽETAK

Cilj našeg istraživanja bio je povećanje efikasnosti terapije koja se primenjuje kod pacijenata sa idiopatskim prolapsom mitralnog zaliska farmakološkom korekcijom nedostatka magnezijuma. Ispitivano je 79 pacijenata (23 žene i 56 muškaraca, prosečne starosne dobi 35,7 ± 4,3 godina) sa nediferenciranom displazijom vezivnog tkiva i prolapsom mitralnog zaliska I i II stepena. Kontrolnu grupu činilo je 20 zdravih pojedinaca, uporedivih po polu i starosti. Test UNESCO Instituta za mikroelemente korišćen je za preliminarnu dijagnostiku nedostatka magnezijuma. Vršeni su dnevni EKG monitoring sa analizom varijabilnosti srčanog ritma, ehokardiografija sa procenom dijastoličke funkcije leve komore i određivanje koncentracije magnezijuma u serumu. Za demonstraciju autonomne disfunkcije korišćen je „test za otkrivanje znakova vegetativnih promena" (10). Za procenu situacione i lične anksioznosti korišćen je Ch. D. Spilbergov i Y. L. Haninov „test anksioznosti" (25, 26). Naredna studija izvršena je nakon 6 meseci. Utvrđeno je da složena terapija magnezijum orotatom kod pacijenata sa idiopatskim prolapsom mitralnog zaliska pomaže da se smanji učestalost kliničkih manifestacija neurovegetativnih poremećaja kod većine pregledanih pacijenata koja doprinosi usklađivanju funkcije autonomnog nervnog sistema. Terapija povoljno utiče na displastične promene i stanje bioelektrične aktivnosti srca, kao i na psihoemocionalno stanje.

Ključne reči: *oboljenje valvule, manjak magnezijuma, lečenje*

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INTRODUCTION

Mitral valve prolapse (MVP) or mitral valve prolapse syndrome is considered to be one of the most common cardiac valve anomalies. The results of population-based studies on prevalence of MVP are inconsistent. In the Framingham Heart Study (1) the prevalence of MVP syndrome in the population of 26 to 84 years of age (average age 56.7±1.5) was 2.4% with no differences in sex and age. The maximum prevalence of this pathology (17-38%) was observed in women (twice as often as men) and young people (2). Moreover, severe mitral regurgitation was observed in males with MVP over 50 years old more often than in young women with this pathology. It was demonstrated that the frequency of MVP detection with young people (18-27 years old) starts from 4.3% to 8.1% and increases with athletes up to 11-18% (2, 3).

At present, there is no universal terminology and classification of MVP. It is generally accepted to classify MVP by etiology as primary (idiopathic, congenital) and secondary one (4). Primary MVP should be considered in the context of genetically determined mesenchymal anomaly and respectively within the nosological frame of undifferentiated connective tissue dysplasia (CDT). The conventionality of the term "primary" or "idiopathic" in connection to MVP should be mentioned. Pathogenetically, it is associated with a specific cause – a congenital generalized defect of connective tissue. In addition, mitral valves in differentiated hereditary syndromes and undifferentiated CDT, differing etiologically, are virtually identical in pathogenesis. Secondary MVP is found in ischemic heart disease, chronic rheumatic heart disease, myocarditis, hypertrophic cardiomyopathy, congenital heart disease, etc.

MVP may appear as a clinically mild "phenomenon of echocardiography", as clinically significant complication occur in 2-4% of cases, and almost in the absolute case (95-100%) in the presence of myxomatous degeneration of the valves, i.e. in MVP syndrome (5). Sudden death is a rare complication of MVP, occurring in less than 2% of patients with MVP during prolonged follow-up with an annual mortality of less than 1% (6). In most cases, sudden cardiac death in MVP is of arrhythmogenic genesis and is caused by the occurrence of idiopathic ventricular tachycardia (fibrillation) or in the QT prolonged interval syndrome (7). The risk factors for sudden cardiac death in patients with MVP are the presence of severe mitral regurgitation and LV (left ventricle) systolic dysfunction.

Particular importance in the development of CTD is the deficiency of magnesium, which leads to disruption of the formation of connective tissue structures of the supporting and trophic carcass of the heart. This causes chaotic distribution of collagen fibers, disturbance of collagen synthesis and its biodegradation. Thus, in conditions of magnesium deficiency, fibroblasts produce incomplete collagen of the mitral valve flaps (8). On the other hand, magnesium deficiency leads to an increase in the total activity of matrix metalloproteinases and more aggressive degradation of collagen fibers, which also worsens mechanical resistance of connective tissue (9). We should not forget that the disturbance of the structure and function of connective tissue in MVP affects not only the chordal and valvular apparatus of the valve, but also the connective tissue stroma of the myocardium. In some cases, this leads to the disruption of the synchronicity of contractions of both separate muscle fiber groups and the whole myocardium, and possibly it leads to a decrease in its inotropic reserve, remodeling and, as a result, to the manifestation of heart failure signs. The problems of the relevant treatment and methods of correction of idiopathic MVP remain poorly studied. In connection to this, our goal was to increase the effectiveness of the therapy for the patients with idiopathic prolapse of the mitral valve via pharmacological correction of magnesium deficiency.

MATERIALS AND METHODS

The study involved 79 patients of 18-40 years of age with MVP and phenotypic signs of undifferentiated CTD (Table 1). According to echodopplercardiography, MVP of the 1st degree was diagnosed in 46 patients and MVP of the 2nd degree in 33 patients. Mitral regurgitation was not found in 12 patients. It should be mentioned that 37 patients had mitral regurgitation of the 1st degree and 30 patients had mitral regurgitation of the 2nd degree.

The initial examination was made by applying a specially prepared test including a detailed collection of complaints, anamnesis and physical examination for phenotypic signs of undifferentiated CTD.

Inclusion criteria: males and females ≥18 years old; presence of idiopathic mitral valve prolapse; informed patient consent to participate in the study.

Table 1. Clinical characteristics of the examined patients

Index	General group (n=79)
Average age, years	35.7±4.3
Males/Females	56/23
MVP I degree/II degree	46/33
Mitral regurgitation	
I degree/II degree	37/30
Smoking, n (%)	34
Family history of early cardiovascular events, n (%)	21
BMI (body mass index), kg/m²	24.3±1.6
Height, cm	171.5±1.8

Exclusion criteria: foci of chronic infection, congenital or acquired heart disease, degenerative-inflammatory myocardial lesions, hemodynamic disturbances, thyroid gland pathology, coronary heart disease, arterial hypertension, concomitant diseases of internal organs, differentiated forms of

CTD (Marfan syndrome, etc.); patients younger than 18 years of age.

The control group consisted of 20 healthy individuals without CTD, comparable by sex and age (10 males and 10 females, average age 35.3±4.6) without morphofunctional features of the heart structure according to echocardiography study.

All examined patients underwent standard clinical, biochemical and instrumental studies. For the detection of autonomic dysfunction "the test for detection of the signs of vegetative changes" was used (10). The sum of the scores, if equal to or more than 15, suggested the presence of autonomic dysfunction.

Daily ECG monitoring was performed with the "CARDIOSENS" equipment ("XAI-Medica", Ukraine). Cardiac arrhythmias and conduction disorders, coronary insufficiency and heart rate variability (HRV) were assessed (11). The registration and automated processing of ECG signals were made by the calculation of the parameters of time and spectral analysis, as well as by the indexes obtained on their basis and suggested by P.M. Baevsky (12). For the analysis of vegetative regulation, the following parameters were used:

TI is the tension index of regulatory systems (TI=AMo/2×BP×Mo), where Mo (mode) is the most frequent value of RR, AMo (mode amplitude) is the number of cardio intervals corresponding to the mode range (in %); VR (variation range) is the difference between the maximum and minimum values of RR;

SDNN is a standard deviation in the duration of normal intervals R-R; pNN 50 is the percentage of all analyzed cardio intervals; RMSSD is the square root of mean squares of the difference between adjacent RR-intervals – activity index of parasympathetic link of vegetative regulation. The higher is the value of RMSSD, the more active is the link of parasympathetic regulation (12).

LF/HF is the index of the vagosympathetic interaction, – the ratio of high-frequency and low-frequency components of the heart rhythm. It indicates the change of vegetative balance to the sympathetic or parasympathetic division.

Structural and functional parameters of the left ventricle were assessed using echodopplercardiography (EchoCG) with the ultrasound scanner "Vivid 3" (Japan) and a 3.5MHz probe in prone position on the left side from the parasternal and apical four-chamber views.

The following indices of EchoCG were assessed: aortic diameter, aortic, mitral (MV), tricuspid valve opening amplitude, the hole area of all these valves. Morphometry and evaluation of mitral valve function were performed in M-mode in the standard position II; in the mode of two-dimensional echocardiography – in the parasternal projection of the LV long axis and the LV transverse axis at the level of the mitral valve; and in the apical four-chamber position. EchoCG showed that the sign of mitral valve prolapse was the displacement of the valve (s) to the left atrial cavity by more than 3mm. The systolic deflection of one or both valves of the MV (mitral valve) in the LA (left atrium) in the parasternal longitudinal position by 3.0-5.9 mm is defined as I degree MVP, by 6-8.9 mm – II degree MVP and by more than 9 mm – III degree. Normal values of the MV anterior cusp length were taken as 21-24 mm and of the posterior one as 12-14 mm.

The degree of the severity of myxomatous degeneration was assessed on the ground of the thickness of the MV leaflet during the diastole phase in the middle part outside the chord zone, creating a false impression of its thickening. Common standards for leaflet thickness are 2-4 mm; an increase by more than 5 mm indicates a pathological change (myxomatosis, etc.) (4); by less than 5 mm – non-classical MVP and by 5 mm or more – classical MVP.

The morphology of the valve apparatus, as well as the presence and extent of regurgitation were evaluated. During the assessment of the degree of regurgitation on the mitral valve, the LA depth, the area of mitral regurgitation, the percentage ratio of the jet area, and the LA area were taken into account (13).

LV dimensions and volumes, LV stroke volume and ejection fraction, the thickness of the LV posterior wall and the interventricular septum were also measured during EchoCG examination. Disturbances in the LV local contractility were outlined by the recommendations of the American Society of Echocardiography. The type of LV architectonics was determined by the following parameters: myocardial mass, myocardial index, relative wall thickness, and sphericity index. It was mandatory to determine the size of the LA, RV (right ventricle) and RA (right atrium) cavities, pericardial condition and pressure in the pulmonary artery. The character and flow rate on the valves in systole and diastole pressure gradient were determined with Doppler echocardiography. The diastolic function was assessed by transmittal flow in the pulse-wave Doppler mode, as well as by the analysis of the motion of the fibrous ring of the mitral valve by the method of tissue Doppler imaging. In the Doppler study, LV diastolic function was evaluated according to the time of isovolume relaxation, the deceleration time for the early LV diastolic filling (DT), the maximum rate of LV early filling (peak E), the maximum rate of the atrial systole A and the E/A ratio.

For the assessment of situational and personal anxiety, an "anxiety test" by Ch. D. Spielberg (1973), adapted by Y. L. Hanin (containing 40 questions), was used. The result was assessed as follows: up to 30 points – low anxiety, 31-45 points – moderate anxiety, 46 points and more – high anxiety.

For the preliminary diagnostics of magnesium deficiency, a test by Trace Element Institute for UNESCO was used. The test results were read as follows: 0-9 points – no magnesium deficiency, 10-19 points – risk group for magnesium

deficiency, 20-29 points – moderate magnesium deficiency, 30-39 points – magnesium deficiency, 40-56 points – significant magnesium deficiency (14). The concentration of magnesium in blood serum was evaluated with the automatic biochemical analyzer "Humalyzer 2000" (Germany, the range of normal oscillations is 0.85-1.2mmol/l).

After initial screening, the patients were randomly divided into 2 groups: 39 patients (group 1) received complex therapy including β-adrenoblocker and magnesium orotate 500 mg 3 times a day for 6 months. The second group included 40 people who received monotherapy with a β-blocker. Its administration was preconditioned by the presence of clinical signs of an increase of the sympathetic nervous system tone (cardialgia, palpitations, irregular heart function, dyspnea, etc.) in all examined patients. These groups of patients with MVP were comparable by age, sex and the presence of magnesium exchange disorders. The follow-up study was performed after 6 months of observation.

The effectiveness of the therapy in each patient was assessed as clinically significant with a decrease of the severity (in points) of the analyzed parameters by 50% or more from the baseline.

Statistical processing of the results was made with the program Statistica 6.0. For the quantitative indices measured on an interval scale the mean value, standard deviation and mean error were calculated. For "qualitative" and "ordinal" indices, the index detection frequency in percents and the frequency of registration of different index rank score respectively were defined. The Student's t-test was used in the analysis of the inter-group index differences. In case of the indices measured at the nominal scale, the reliability of the differences in the frequency of index detection in two compared groups was assessed by the Student's t-test and the Fisher transform, linear correlation coefficients and rank correlations were calculated. The reliability of the relationship between the indices measured on a nominal or rank scale was further evaluated using contingency tables – with the calculation of several modifications of the Pearson chi-square test and Cramer's conjugacy coefficients. Differences in mean values and correlations were considered reliable at a significance value of $p<0.05$.

RESULTS AND DISCUSSION

Undifferentiated CTD is characterized by the polymorphism of anomalies of disembriogenesis ("stigma"), which are represented in a phenotype with different frequencies. During the analysis of external phenotypic features of the patients with MVP the most informative were CTD markers, shown in Table 2.

It has been previously observed that different clinical symptoms in MVP patients also depend on magnesium deficiency (3, 14). The study of some aspects of magnesium exchange and its influence on the dynamics of the MVP course has been of great importance. In the analysis of clinical signs of magnesium deficiency it was observed that in the patients of groups I and II, moderate deficiency of magnesium was diagnosed in 74.4% and 70%, the risk of magnesium deficiency development was recorded in 15.4% and 20%, and the signs of magnesium deficiency were absent in 10.2 % and 10%, respectively. Consequently, the majority of patients with MVP of 1st and 2nd degree exhibited clinical signs of magnesium deficiency of varying severity . Differences were statistically significant comparing to the control group – $p<0.01$. During the evaluation of magnesium concentration in blood serum, hypomagnesemia was diagnosed in 82% (32 patients) of group I and 80% (32 patients) of group II. Consequently, the values of serum magnesium were within normal limits in 18% (7 patients) in group I and in 20% (8 patients) in group II.

Table 2. Prevalence of external phenotypic markers in patients with idiopathic MVP (n=79)

Phenotypic markers	Detection frequency,%
Ectomorphy	67.0
Hypotrophy	54.4
Radial-lacunar type of the iris	54.4
The predominance of the length of the 4th hand digit over the length of the 2nd one	50.6
Varicose veins of the lower extremities, developed in adolescence	46.8
Scoliosis	41.8
Chest deformation	39.2
The predominance of the length of the 2nd toe above the length of the 1st one	32.9
Curved little fingers	29.1
Platypodia	29.1
Protruding ears	25.3

The concentration of magnesium in blood serum is the most commonly used marker of magnesium exchange in the body (15). However, the level of magnesium in the serum provides only proximate information about the presence or absence of magnesium deficiency. Hypomagnesemia clearly indicates magnesium deficiency, but its absence does not exclude significant magnesium deficiency in tissues. The concentration of magnesium in the blood serum is not associated with the content of this trace element in other biomaterials (16).

It is expected that in the pathogenesis of diverse clinical symptoms and signs in patients with primary MVP, a leading role is played by the disturbances in the function of the autonomic nervous system with an increase of the sympathetic tone. The predominance of adrenergic effects in MVP is associated both with an increase in the sensitivity of adrenoreceptors to stimulation and with an increase of their total number (17). Changes in vegetative homeostasis are so common in patients with primary MVP that most researchers consider

it an obligate manifestation of this pathology (2, 3). The manifestations of autonomic dysfunction were observed in 75 (94.9%) patients (Table 3).

Table 3. Prevalence of manifestations of autonomic dysfunction in patients with idiopathic MVP (n=79)

Symptoms	Detection frequency,%
Heartache	94.9
Heart palpitations and disturbances	73.4
Headache	74.7
Dizziness	73.4
Hyperventilation syndrome	63.3
Dysfunction of the gastrointestinal tract	45.6
Raynaud's syndrome	37.9
Disturbances of thermoregulation	27.8
Syncope	15.2

At baseline, the examined patients with MVP showed average score on the "test for the signs of vegetative changes" of 45.9±2.1 points whereas the scores of healthy individuals reached 12.3±2.3 ($p<0.001$) points. The study of vegetative homeostasis during the analysis of HRV (heart rate variability) showed the prevalence of simpathicotonia in 70.9% of the examined patients. The data obtained confirm the significant contribution of the autonomic nervous system disorders to the structure of the main clinical manifestations of idiopathic MVP.

The autonomic nervous system is currently being considered to play an important role in the emergence of various heart rhythm disorders (2). It is known that the parasympathetic link inhibits negative adrenergic effects on the heart (18). Decreased vagal activity and/or increased sympathetic activity may lead to the development of prognostically unfavorable cardiac rhythm disorders (19).

Analysis of HRV parameters at the baseline allowed us to diagnose the presence of vegetative disorders in the examined patients with MVP.

At baseline, in patients with MVP, the mode amplitude twice exceeded the results of healthy individuals, the stress index –was increased 3.5 times (all $p<0.001$), and the variation range was reduced by 1.4 times ($p<0.05$) indicating the prevalence of sympathetic activity in the autonomic nervous system. In addition, compared with the control group, a significant decrease in the total heart rhythm variability (SDNN) by 1.3 times and a decrease of the parasympathetic component of cardiac rhythm regulation (RMSSD) by 1.3 times (all $p<0.001$) were observed in patients with MVP. The predominance of sympathetic influences over vagal ones in patients with idiopathic MVP probably indicates an initially high level of adrenergic stimuli in this pathology.

One of the common symptoms of CTD is arrhythmic syndrome. Pathogenetic factors of cardiac arrhythmias are myxomatous degeneration of the conduction system of the heart and valves, especially the posterior one, as well as mitral regurgitation. In the genesis of supraventricular arrhythmias, a special emphasis is placed on the stimulation of the subendocardial areas of the left atrium with regurgitating blood stream, leading to the development of the foci of ectopic excitation. Atrial fibrillation usually develops in patients with atriomegaly caused by hemodynamically significant mitral regurgitation. Among the causes of ventricular rhythm disturbances, hypersympathicotonia, i.e. an abnormal traction of papillary muscles, (20) is taken into consideration.

The existence of a causal relationship between ventricular and atrial arrhythmias and intracellular magnesium content has been established (14). It is expected that hypomagnesemia may contribute to the development of hypokalemia (21). In this case, the membrane resting potential is increased, the processes of depolarization and repolarization are interrupted and the cell excitability decreases. The conductivity of electric impulse slows down contributing to the development of arrhythmias (14, 21). In addition, intracellular magnesium deficiency increases the activity of the sinus node, reduces absolute refractoriness and extends a relative one [22].

Detection frequency of various types of cardiac rhythm and conduction disturbances in the examined patients according to daily ECG monitoring is presented in Table 4.

The inclusion of magnesium orotate in complex therapy for 6 months in patients with idiopathic MVP of the 1st and 2nd degree led to a significant increase of magnesium content in blood serum from 0.61±0.02mmol/l to 0.97±0.03mmol/l ($p<0.001$). Moreover, magnesium concentration in blood serum in patients of group I did not differ significantly from the control group, which apparently indicates the compensation of magnesium deficiency in the studied patient population. At the same time, in the patients of group II no significant changes in magnesium content of blood serum were observed after therapy.

After the treatment, there was a significant ($p<0.05$) decrease in the frequency of clinical manifestations of neurovegetative disorders in the majority of the patients examined. Assessing the effect of magnesium therapy on symptomatology and the severity of all clinical manifestations in patients with MVP, it is necessary to emphasize the significant improvement of the general state of patients and reduction in the frequency and severity of all clinical syndromes and symptoms of the disease.

Table 4. Changes in the findings of daily ECG monitoring on treatment

Indicators	Group II (n=39)		Group II (n=40)	
	Initially	After treatment	Initially	After treatment
Heart rate, bpm	83.6±3.6	68.8±2.3**	82.7±3.2	73.2 ± 2.3*
Supraventricular arrythmia	32.8±10.7	8.9±4.9*	34.6±10.3	27.3±4.6
Ventricular arrhythmia	198±13.8	26±11.6**	179±11.3	44±10.5**
Paroxysmal supraventricular tachycardia,%	7.7	0	12.5	7.5
Blockade of the right leg of the bundle of His,%	30.7	30.7	30.0	30.0
Syndrome of early repolarization of ventricles,%	33.3	0*	35	35

* – statistical significance in comparison to the original data, $p<0.05$; ** – $p<0.001$.

At the same time, the most significant was the dynamics of asthenic complaints ($p<0.05$) of cardialgia, palpitations, cardiac disruptions, headaches, dizziness; tolerability of moderate physical activity ($p<0.05$) in comparison with the patients of group II also improved. Clinically significant decrease in the severity of vegetative dystonia syndrome was observed in 69.2% of patients during the course of magnesium orotate and in 47.5% in the comparison group ($p<0.05$).

Analysis of the effectiveness of drug therapy in the patients with autonomic dysfunction showed positive dynamics of clinical status. The data on A.M. Wayne (10) self-evaluation scale of general state (16) showed that the sum of scores in group I decreased from 45.9±2.4 to 16.8±2.1 points ($p<0.001$) and from 45.8±2.2 to 29.8±2.1 ($p<0.001$) points in group II. The reduction of the total score by 50% after the treatment was considered a positive result. The sum of scores decreased in group I by 63.4% and in group II by 34.9% (all $p<0.001$) indicating a significant decrease of vegetative signs during the administration of complex therapy with magnesium orotate.

After the treatment the patients of both groups showed a decrease in the rate of sympathetic activity. Thus, the stress index in group I decreased at 67.7% ($p<0.001$) and in group II – at 47.3% ($p<0.001$); the mode amplitude – by 33.6% ($p<0.001$) and 16.5% ($p<0.01$); the variation range increased by 64.3% ($p<0.01$) and 38.4% ($p<0.01$), respectively, indicating an improvement in vegetative tone in the patients of group II and reactivation of vegetative balance in group I. In patients with MVP, who additionally received complex therapy with magnesium orotate, a significantly better result was observed in comparison with the experimental group on the stress index (by 62.7%, $p<0.001$) and the variation range (by 21.6%, $p<0.05$). Thus, in the group which additionally received magnesium orotate, harmonization of the function of the autonomic nervous system was observed.

General heart rate variability (SDNN) and parasympathetic regulation of the cardiovascular system (RMSSD) increased simultaneously. In particular, the SDNN index, representing the overall effect of the autonomic regulation of blood circulation, increased in the patients of group I by 27.3% ($p<0.01$), and in group II – by 8.8% ($p>0.05$).. The RMSSD index indicating the activity of the parasympathetic link of vegetative regulation in group I increased by 27.7% ($p <0.01$) and in group II by 8.47% ($p>0.05$).. pNN 50 index showing the degree of the prevalence of the parasympathetic link in group I increased by 27.1% ($p<0.01$) and in group II – by 11.7% ($p>0.05$) (Table 4). Thus, in the patients with arterial hypertension and autonomic dysfunction, the combined therapy with magnesium orotate both led to a more significant increase in general rhythm variability and decreased activity of the sympathetic part of the autonomic nervous system and reactivation of the vegetative balance.

The indices of the structural-functional state of the left ventricle are presented in Table 5.

The analysis of the parameters of intracardiac hemodynamics (Echo-CG findings) showed that in patients of group I there was a significant decrease in the size of the left atrium in comparison with the initial data by 6.6% (all $p<0.05$). In the patients of both groups there was a slight increase in the end-systolic and end-diastolic size of the left ventricle,which was marginally more significant in the comparison group. That corresponded to a slight increase in the stroke volume and ejection fraction of the left ventricle in group I patients, whereas in contrast in group II patients the stroke volume did not change and the left ventricular ejection fraction even slightly decreased but stayed within the normal range. The data obtained reflect the favorable effect of magnesium orotate on dysplastic changes, which conforms to the previously obtained results (23).

Table 5. Dynamics of the structural-geometric condition of LV in the examined patients during treatment

Index	Group I (n=39)		Group II (n=40)	
	initially	6 months	initially	6 months
LA (left atrial diameter), cm	3.51±0.07	3.28±0.05*	3.52±0.06	3.46±0.07
ESD (end-systolic dimension), cm	3.34±0.06	3.35±0.03	3.36±0.04	3.37±0.03
EDD (end-diastolic dimension), cm	4.72±0.05	4.74±0.03	4.74±0.06	4.76±0.04
ESV (end-systolic volume), ml	40.3±1.2	41.3±1.3	40.7±1.3	42.5±1.3
EDV (end-diastolic volume), ml	112.0±1.5	113.5±1.7	112.4±1.6	113.9±1.6
SV (stroke volume), ml	71.9±1.4	73.5±1.2	71.7±1.2	71.6±1.3
EF (ejection fraction), %	63.3±0.7	64.7±0.6	63.5±0.8	62.6±0.6
E/A (peak early filling (E-wave) and late diastolic filling (A-wave) velocities)	0.96±0.06	1.22±0.03*	0.97±0.06	1.08±0.04
Degree of mitral regurgitation	1.08±0.13	0.62±0.11*	1.09±0.16	1.03±0.11

* – statistical significance compared with the initial data $p < 0.05$.

The analysis of the diastolic function characteristics showed that after the treatment,the rate of LV early diastolic filling (peak E) increased by 14.9% ($p<0.05$) in group I and by 7.8% ($p<0.05$) in group II. The maximum rate of atrial systole A after the end of the treatment in group I decreased by 9.6% ($p<0.05$) and by 7.1% ($p<0.05$) in the patients of group II. As a result of the observed changes in these velocity streams in group I patients, the E/A peaks significantly increased by 27.1% ($p<0.05$), indicating improvement in left ventricular relaxation and an increase of the blood volume accepted in the first phase of diastole. At the same time, the increase in the ratio of E/A by 11.5% ($p<0.05$) exceeded the results of the comparison group, where the changes of this index became a tendency. Additionally, a significant ($p<0.05$) decrease in the degree of mitral regurgitation was observed in group I patients (Table 6). In general, the data obtained are the results of the improvement of the connective tissue diffusivity and its architectonics, determining the improvement of its elasticity and extensibility.

After the treatment the patients of group I (Table 5) experienced a significant reduction in the heart rate, in the number of ventricular extrasystoles and supraventricular extrasystole. The antiarrhythmic activity of magnesium orotate is apparently preconditioned by its component magnesium, a natural calcium antagonist, which has a membrane-stabilizing effect, prevents a loss of potassium by the cell, reduces the dispersion of QT interval and also weakens the sympathetic effect on the heart (24).

At baseline the patients with MVP showed an increase in anxiety levels on the scale by Ch. D. Spielberg and Y. L. Hanin, (25, 26) which is explained by the peculiarities of patients' response to the emergence of the disease and associated psychological changes, as well as premorbid features of the patients' personalities. Thus, the degree of reactive and personal anxiety was respectively (49.2±2.3) and (48.8±2.6) in group I and (48.2±2.4) and (47.7±2.6) in group II. High and moderate levels of reactive and personal anxiety were distinct for the majority of patients with MVP (Table 6).

In the patients of group II with low, moderate and high levels of reactive and personal anxiety at baseline no significant changes were observed after the treatment. At the same time, the patients of group I showed a significant decrease in the level of reactive anxiety by 36.8% ($p<0.001$) and personal anxiety by 38.6% ($p<0.001$). Moreover, magnesium orotate proved to be the most effective in the group with high and medium anxiety level, as indicated by the shift of 64.1% and 69.2% in patients reaching a lowlevel of reactive and personal anxiety respectively. At the same time, in the patients with a low degree of anxiety no significant changes were observed at baseline. The difference in the change of the levels of situational and personal anxiety in groups I and II was found to be statistically significant (39.1%, $p<0.001$ and 46.6%, $p<0.001$ respectively). Consequently, after the complex treatment with magnesium orotate the patients with MVP showed positive change of situational and personal anxiety, which indicated an improvement in the psychoemotional state of the patients.

Table 6. Changes of indices of reactive and personal anxiety in patients with idiopathic MVP (M ± m)

Index	Level	Group	Initially	After treatment
Reactive anxiety	low	I	28.2±1.3 (n=2)	28.1±1.2 (n=25)
		II	28.4±1.3 (n=2)	28.5±1.4 (n=3)
	moderate	I	42.6±2.5 (n=16)	33.9±2.3* (n=11)
		II	40.8±2.6 (n=17)	37.2±2.4 (n=18)
	high	I	56.3±2.9 (n=21)	46.1±2.7* (n=3)
		II	56.1±2.5 (n=21)	51.4±2.3 (n=19)
Personal anxiety	low	I	28.5±1.5 (n=2)	28.1±1.4 (n=27)
		II	28.6±1.6 (n=2)	28.2±1.3 (n=3)
	moderate	I	42.8±2.6 (n=17)	33.6±2.4* (n=9)
		II	42.1±2.7 (n=19)	39.3±2.3 (n=21)
	high	I	55.9±2.8 (n=20)	45.6±2.6* (n=3)
		II	55.3±2.7 (n=19)	53.1±2.3 (n=16)

* – statistical significance in comparison with the original data, p <0.05.

CONCLUSION

1. The majority of patients with idiopathic MVP of 1st and 2nd degree have clinical signs of magnesium deficiency of different severity and hypomagnesemia associated with the disturbances of autonomic regulation of the cardiovascular system in the form of relative increase of sympathetic influences and weakening of parasympathetic ones. Patients with MVP showed a decrease in the level of psychological health, manifested as a growth of the number of people with high and moderate levels of reactive and personal anxiety.
2. Complex therapy with magnesium orotate for 6 months in the patients with idiopathic MVP of 1st and 2nd degree led to the improvement of clinical symptoms and signs, to a decrease in the severity of the vegetative dystonia syndrome, toa decrease in the degree of mitral regurgitation and inthe size of the left atrium, as well as to the improvement in the diastolic function of the left ventricle along with the replenishment of magnesium deficiency according to the content of this trace element in the blood serum.
3. Administration of the combined therapy with magnesium orotate in the patients with MVP and autonomic dysfunction led to an improvement in HRV parameters and state of bioelectrical activity of the heart, as well as to a decrease in the level of reactive anxiety, which enables an increase of functional capacities of the body based on the improvement of the psychoemotional state.

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