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ANTI-REMODELING THERAPY TO PATIENTS WITH CHRONIC HEART FAILURE AND METABOLIC SYNDROME

Abstract. The aim of this work is to study the anti-remodeling efficiency of complex pharmacotherapy of CHF by use of perindopril, spironolacton and bisoprolol in patients with MS. The study involved 106 male patients with chronic heart failure (CHF) II-III FC, with post infarction cardiosclerosis. Depending on the components of MS the patients were divided into 3 groups: Ist group (n=37), patients without MS; Group II (n=34), patients with a combination of dyslipidemia (DLP) with abdominal obesity (AO) and arterial hypertension (AH); Group III (n=35), patients with a combination of AD, AH and DLP with diabetes 2 types. The MS in patients with chronic heart failure reduces the anti-remodeling effectiveness of the combined application of Perindopril, Bisoprolol and Spironolacton, which depends on the representation of its components. The most marked resistance against therapy exists, when there is a combination of AO, AH and DLP with diabetes of 2 types.

Key worlds: chronic heart failure, metabolic syndrome, systolic and diastolic left ventricular dysfunction

A special importance is given to the development of heart failure in patients with metabolic syndrome (MS). This is associated with a high incidence of heart failure after myocardial infarction (MI) in patients with MS [4, 5], as well as the peculiarities of structural and functional changes of the heart. MS is characterized by formation of a distinctive hemodynamic and specific damage of target organs, which then act as an independent risk factor for cardiovascular complications [6, 7]. As shown in studies conducted in recent years, the peculiarities of heart disorders in MS are the development of left ventricular hypertrophy and the inadequate level of blood pressure [8]. Some researchers [9] believe that it is the obesity which plays the main role in the structural and morphological changes of the myocardium. Moreover, there was established a relationship between the character of hypertrophy of the LV and the type of obesity. The eccentric LVH is typical for glyuteofemoral type, while concentric LVH is typical for abdominal type of obesity. Structural modifications and remodeling of the heart are also associated with the other components of the MS, such as insulin resistance, dyslipidemia and hyperinsulinemia [10, 11]. Thus, in a pathological remodeling of the myocardium in CHF in patients with MS not only hemodynamic, but also metabolic factors are being involved.

The aim of this work is to study the anti-remodeling efficiency of complex pharmacotherapy of CHF by use of perindopril, spironolacton and bisoprolol in patients with MS.

Material and Methods

The study involved 106 male patients with chronic heart failure (CHF) II-III functional class (FC), with postinfarction cardiosclerosis. Prescription of myocardial infarction from 6 months to 5 years.

Verification of the diagnosis carried out on the basis of the classification of the New York Heart Association (NYHA), six-minute walk test and due scale assessment scale of the clinical state. The average index six-minute walk testing was detected as 304.7±19,3m (274-338m). Depending on the components of MS the patients were divided into 3 groups: Ist group (n=37), patients without MS; Group II (n=34), patients with a combination of dyslipidemia (DLP) with abdominal obesity (AO) and hypertension (AH); Group III (n=35), patients with a combination of AD, AH and DLP with diabetes of 2 types.

While diagnosingthe MS, the diagnostic criteria of MS International Diabetes Federation (IDF, 2009) was used. Abdominal obesity (AO) (>94 cm for men); level of triglycerides (TG >1.7 mmol/l); the level of lipoprotein cholesterol with high density (HSLPVP <1.03 for men); blood pressure level (systolic blood pressure >130 mm Hg, diastolic blood pressure >85 mm Hg), glucose level on an empty stomach (>5.6 mmol/l) or the presence of diabetes mellitus of type 2 were considered as the main components of the syndrome.

The patients under survey were hospitalized in the cardiology department of the city hospital number 7 in Tashkent. Patients were examined on the basis of the contract with medical diagnostic centre of the Ministry of Health of the Republic of Uzbekistan. All examined patients underwent clinical, laboratory and instrumental methods of research. Echocardiography (EchoCG) was carried out on the machine ***Mindray (China)*** by method of lyingin prone position and the left side of M and B modes in accordance with the requirements of the American Association of Echocardiography (ASE). Wherein the followings were evaluated: the ultimate-diastolic dimension (UDD), the ultimate-systolic dimension (USD), the thickness of the posterior wall of the left ventricle (TPW), the width of the ventricular septal (TVS), the size of the left atrium (LA), ultimate-systolic volume, ultimate-diastolic volume. Concerning the left ventricular (LV) systolic function, the data was assessed due to the level of ejection fraction (EF), which was calculated by the formula Teicholz et al. [8], stroke volume (SV), which was defined as the difference between the UDV-USV, as well as by the degree of shortening of the anterior-posterior size of the left ventricle into systole (% ΔS). Concerning the left ventricular diastolic function, the data was assessed due to the maximum speed of the early peak of diastolic filling (V_{max}Peak E, 0,62 m/s), the maximum speed of transmitral flow during systole of the left atrium (V_{max}Peak A, 0,35 m/s) and the ratio of E/A (1.5-1.6), isovolemic LV relaxation time (IVRT), deceleration time of early diastolic filling (DT). The mass of the myocardium left ventricular (LVMM) was calculated by the formula Devereux RB [9]; index mass of the myocardium left ventricular (LVMMI) as a ratio to the area of the body; the left ventricular hypertrophy criteria was accepted as LVMMI >125 g/m^2 in men and >110 g/m^2 in women. The relative width of walls (RWW) was also calculated.

After a two-week washout period, all patients were taking Perindopril (Prestarium, Servier), Bisoprolol (Concor, Nycomed), as well as Spironolacton (Gedeon Richter) 50 mg/day within the period of three months. Perindopril is titrated at a dose of 4 mg to 8 mg, Bisoprolol was titrated in a dose from 5 mg to 7.5 mg.

Statistical analysis of the received data was performed on a personal computer of IBM PC/AT type by using standard electronic program package «biostatic for Windows, version 6.0" The parameters were described as M±m. While distributing the values, the group comparisons of quantitative variables were performed by using the variational statistical test (t).

The results of the research

The results of echocardiography studies in patients with chronic heart failure, shown in table №1, indicate the presence of features of structural and functional changes in the myocardium in patients with MS. The comparative analysis established that the TPW and TVS were more increased in patients with MS rather than in patients without MS. Whereas the differences according to these indicators between 1st and 2nd groups were not significant, in the third group TVS was greater by 11.9% ($p<0.05$), and TPW by 7.7% ($p<0.05$). It is associated with an increase in ultimate-systolic and ultimate-diastolic size and volume of the left ventricle, which causes an increase in MMLV and IMMLV.

Table№1.

Indicators of echocardiography and Dopler Echocardiography in patients with CHF II-IIIFC and without MS before and after treatment with Perindopril, Bisoprolol and Spironolacton.

Indicators	Treatment periods	1st group (n=37)	2nd group (n=34)	3rd group (n=35)
LA, cm	Before treatment	3,71±0,086	3,94±0,083*	4,16±0,09**
	After 3 months	3,48±0,066°	3,71±0,081°*	4,02±0,089**
LVMM, g	Before treatment	212,78±6,08	235,88±9,58*	283,66±11,58**
	After 3 months	189 ,34±7,18°°	210,57±8,21°	249,14±10,65**
LVMMI, g/m^2	Before treatment	128,58±4,57	130,93±6,23	163,0±6,67**
	After 3 months	114,52±4,89°°	116,53±4,58°	146,38±7,39°**
TVS, cm	Before treatment	1,09±0,028	1,14±0,027	1,22±0,03*
	After 3 months	1,04±0,021	1,09±0,026	1,16±0,026
TPW, cm	Before treatment	1,04±0,021	1,08±0,022	1,12±0,025*
	After 3 months	1,02±0,021	1,07±0,024	1,08±0,021
UDD, cm	Before treatment	4,73±0,071	4,82±0,068	5,15±0,083**
	After 3 months	4,51±0,078°	4,64±0,078	4,9±0,089**

USD, cm	Before treatment	2,95±0,056	3,11±0,057*	3,47±0,085**
	After 3 months	2,67±0,061°°	2,84±0,067°*	3,15±0,089°**
UDV, ml	Before treatment	132,15±3,62	138,42±3,57	159,48±4,39**
	After 3 months	122,07±3,29°	126,21±3,81°	149,44±4,1**
USV, ml	Before treatment	61,78±2,28	68,5±2,22*	91,16±2,91**
	After 3 months	49,96±2,39°°	57,88±2,89°*	79,68±2,91°**
SV, ml	Before treatment	70,37±3,89	69,92±3,28	68,32±2,71
	After 3 months	72,11±1,94	68,33±2,47	69,76±2,05
EF, %	Before treatment	52,56±2,02	50,2±1,53	42,72±1,11**
	After 3 months	59,4±1,13°°	54,39±1,55*	46,90±1,10**
Dt, mc	Before treatment	189,67±8,5	215,08±8,91*	230,83±9,52**
	After 3 months	166,78±6,88°	189,76±8,68	213,8±10,7**
IVRT, mc	Before treatment	85,2±2,05	89,28±2,81*	95,29±2,75**
	After 3 months	78,15±2,51°	81,82±2,53	88,38±2,51*
%ΔS,%	Before treatment	37,16±1,73	35,19±1,34	32,47±1,53*
	After 3 months	40,18±1,88	38,49±1,45	35,66±1,42
PE, м/с	Before treatment	0,59±0,018	0,57±0,019	0,54±0,021
	After 3 months	0,65±0,018°	0,61±0,019*	0,57±0,016**
PA, м/с	Before treatment	0,50±0,016	0,53±0,018*	0,58±0,017**
	After 3 months	0,43±0,018°	0,46±0,019°	0,52±0,015°**
E/A	Before treatment	1,18±0,042	1,08±0,054*	0,93±0,027**
	After 3 months	1,51±0,045°°	1,33±0,041°*	1,10±0,039°**
Heart rate, bpm	Before treatment	75,37±1,72	76,92±1,96	77,4±2,36
	After 3 months	70,04±1,58°	73,29±1,37	74,72±1,99

Note: * - p<0,05; ** - p<0,01 the accuracy of the performance differences compared to the Ist group.
- p<0,05; °° - p<0,01 the accuracy of the performance differences before and after treatment.

The patients in group II compared to patients of group I, have a significant increase in the USD and USV (p<0.05), with little difference in the UDD and UDV. 3rd groups differ with a considerable increase in both ultimate-systolic and ultimate-diastolic volumes and sizes. The UDD amount in these patients was greater by 8.9% (p<0.01), the USD by 17.6% (p<0.01), UDV by 20.6% (p<0.01) and USV by 47% (p<0.01). As a consequence of the above mentioned changes, the LVMM in patients with MS was greater by 10.8% (p<0.05) and 33.3% (p<0.01) in the second and third groups respectively. However, the index points to a significant increase of the current indicator only in the third group.

Along with the structural changes in patients with heart failure, there were identified the left ventricular dysfunctions as well, which is most determined in patients with MS. In particular, in the third group the EF was lower by 18.8% (p <0.01), which particular is due to the decrease in the shortening degree of the anterior-posterior size of the left ventricle into systole by 19.2% (p<0.01). Patients with MS differ by more severe manifestations of diastolic dysfunction as well, which as evident by the significant increase of RA in 2nd group (p<0.05) and the third group (p<0.01) patients within the slight decrease in PE, as well as a decrease in E/A ratio by 7.6% (p<0.05) and 19.5% (p<0.01), respectively. The disturbance of transmitral blood flow is associated with the increasing of left ventricular isovolemic relaxation time by 8.6% (p<0.05); 15.9% (p<0.01), as well as the deceleration time of early diastolic filling by13.4% (p<0.05) and 21.7% (p<0.01) in the 2nd and 3rd groups, respectively. The disorder of systolic and diastolic function of LV leads to strained work of the LA. The received data indicates that the changes revealed by the LV in patients without MS are not reflected on LA condition, while in patients with MS has an increase in its size. Herewith, if this figure in the second group is increased by 6.2% (p<0.05) in the third group the difference reached by 12.1% (p<0.01), which is out of range.

Thus, all patients with heart failure show the signs of structural and functional changes in the left ventricle and left atrium of the heart, the severity of which depends on the presence and severity of MS. The next stage of this work was to study the anti-remodeling efficiency of complex pharmacotherapy using the main set of preparations for the treatment of heart failure.

After 3 months of treatment with Perindopril, Bisoprolol and Spironolacton applied to patients with chronic heart failure, the data obtained (Table №1) shows a significant positive trend by indicators of echocardiography and Doppler Ehocardiography in patients without MS. The weak dynamics of the analyzed indicators was identified in patients with MS, especially of the third group. Despite the positive developments and progress in ultimate-systolic and ultimate-diastolic pressure and size of the left ventricle in patients of the 1st and 2nd groups, which showed statistical veracity, the decrease in TVS and TPW was negligible. In the third group, the statistical veracity was observed in reduction of only USD and USV. Three-month treatment in 1st (p<0.01) and 2nd, 3rd (p<0.05) groups contributed to the reduction of LVMM (p<0.01). However, even if the data of the 2nd and 3rd

groups approached each other and become nearly similar after the treatment, the indicators in the third group still remain significantly higher ($p<0.01$). A similar pattern also appears according to LVMMI.

As a result of the above-mentioned structural changes in patients without MS, a significant improvement of systolic function is observed after the treatment showed, which is evidenced by the increase of ejection fraction ($p<0.01$). The increase of this indicator is also observed in the 2nd and 3rd groups, which did not reach statistical veracity, and lags behind by 8.3% ($p<0.05$) and 21% ($p<0.01$) respectively, compared to the 1st group. Increasing of the degree of anterior-posterior size of the left ventricle into systole is a proof of improvement of its systolic function, which was most, expressed in the 1st group.

There is a difference between surveyed patients according to the results of the effect of the treatment related to the diastolic function of the left ventricular. A significant improvement of this function is observed in patients without MS, which is evident by statistically significant reduction in isovolemic relaxation time of LV, the deceleration time of early diastolic filling and maximum speed of atrial systole, as well as an increase of the maximum rate of early diastolic filling of LV and E/A ratio. However, in patients with MS, especially in the 3rd group, the decrease of Dt and IVRT, the increase of PE were not very significant, and the difference in these indicators between the 1st and 3rd groups remained high, reaching up to 28.2% ($p<0.01$), 13.2% ($p<0.05$) and 12.3% ($p<0.01$), respectively. Along with this, in spite of the decrease in RA ($p<0.05$), it was higher by 20.9% ($p<0.01$) and in spite of the increase in the E/A, this ratio was lower by 27.2% ($p<0.01$) compared to the 1st group.

There are different forms of MS exist depending on the number and combination of symptoms [14]. Besides the classic, there may be alternative options thereof [15]. Based on this, we have identified two groups of patients with MS. In the second group the manifestation of MS was the combination of AO and AH with DLP. Patients of 3rd group had more severe symptoms of MS, in addition to the above mentioned features; they had diabetes of 2 types as well. The currently available published data [16, 17, 18] points to the relationship between MS and the structural-functional changes of the heart. Comparatively high rates of LVMM, LVMMI associated with an increase of TPW and TVS, caused by high USV and UDV were established in patients with MS. There was detected the dependence of these changes on the MS type [15], which is unconditioned by the hemodynamic factors. However, these available data are numerically small and mainly deal with MS in arterial hypertension. According to the results of this study it was established that the structural changes of the myocardium are more uttered in patients with chronic heart failure having AO, AH and DLP than those without MS. In particular, they have much higher LVMM. A severe form of MS in patients with CHF (group III) is characterized by a further increase of this indicator, as well as LVMMI, which is due to TPW and TVS. The LVMMI level in patients of this group exceeds the indicator of the 2nd group by 17.2% ($p<0.05$), which demonstrates an association between the left ventricular hypertrophy level and the severity of MS. Hypertrophy of LV is considered as an independent marker of high risk for cardiovascular disease, including sudden death, and it significantly affects the formation mechanism of diastolic dysfunction of left ventricular heart [19]. In this regard, an important aspect of this problem is - the availability of data on the relationship between diastolic dysfunction and MS [20]. It may be even independently of LV mass. The link between the MS and diastolic dysfunction of LV is also reflected in the results of this study. Patients with the metabolic syndrome (AO + AH + DLP) in contrast to patients without MS are characterized by more severe manifestations of diastolic dysfunction, an increase in IVRT, DT and RA, as well as a decrease in E/A. The accession of diabetes2 to the above mentioned MS manifestations significantly deteriorates the diastolic function, reflected in a further increase of IVRT, DT and the RA, as well as in a decrease of E/A. An important role is assigned to the isovolemic relaxation time of LV, which increases with MS, regardless of LV remodeling and after load severity [21]. For the last a few years, CHF has been more associated with diastolic dysfunction in patients with normal ejection fraction [22, 23]. However, in patients with severe MS symptoms, the CHF is manifested with systolic dysfunction either, which is evident by the decrease of ejection fraction up to 42% and a significant decrease in the degree of shortening of the anterior-posterior size of the left ventricle into systole in the 3rdgroup.

Leading part in the treatment of patients with heart failure is taken by ACE inhibitors, β-adrenoblockers and spironolactones [2]. Three-month treatment with an implement of Perindopril, Spironolacton and Bisoprolol to patients without MS, is characterized by positive dynamics of structural and morphological parameters of LV (decrease in LVMM and LVMMI), left ventricular remodeling, and central hemodynamic (reducing of UDV and USV, increased ejection fraction). It was also detected a positive effect of the therapy on diastolic function of LV, which manifested as a decrease of IVRT and DT, as well as an improvementof transmitral spectrum (reduction of RA, increasing PE and E/A). A similar pattern, but with a little difference of indicators before and after treatmenthas been observed in patients with AO+AH+DLP. LVMM significantly exceeding the indicator of the 1st group, together with LVMMI approached to the level of the 1st group after treatment However, the dynamics of central hemodynamic parameters have considerably conceded. Despite a significant decline, the USD and USV remain statistically and authentically high, whereas ejection fraction stays low compared to the 1st group. After treatment, on the background of significant reduction of PA and increasing of E/A, and according to transmitral spectrum, it was proved that the 2nd group is much inferior to patients without MS. The results of the comparative analysis established that the more severe form of MS (AO+AH+DLP+Diabetes2) in patients with heart failure increasingly reduces the effectiveness of the combined application of Perindopril, Bisoprolol and Spironolacton. Statistically significant positive

changes in these patients after treatment is retraced only according to LVMM, LVMMI, USV, PA, and E/A. Preservation of statistically significant difference according to UDD, USD and EF after treatment between the 1st and the 3rd group represents a significant deceleration of regression of pathological LV remodeling in latter one. This, in its turn, is reflected on the diastolic function of LV. Despite the positive dynamics of transmitral flow indicators, the current function in these patients' remains significantly lower compared to the patients without MS.

Conclusions:

1. The presence of metabolic syndrome in patients with chronic heart failure is an important factor reinforcing the pathological cardiac remodeling and progression of systolic and diastolic dysfunction of LV, which is most manifested within the combination of DLP, AO and diabetes of 2 types.
2. A three-month treatment with an implement of the Perindopril, Bisoprolol and Spironolacton combination in patients suffering from CHF without MS promotes regression of non-adaptive remodeling of myocardial and improvement of systolic and diastolic function of the heart.
3. The MS in patients with chronic heart failure reduces the anti-remodeling effectiveness of the combined application of Perindopril, Bisoprolol and Spironolacton, which depends on the representation of its components. The most marked resistance against therapy exists, when there is a combination of AO, AH and DLP with diabetes of 2 types.

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