Effectiveness of Treating Patients with Stable Ischemic Heart Disease and Co-Existent Paroxysmal Atrial Fibrillation with Mebicar

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Abstract
Atrial fibrillation is a disturbance of heart rhythm, which is characterized by frequent contractions of atrial muscle fibers. Stable ischemic heart disease, arterial hypertension, heart failure, obesity are risk factors for progression of atrial fibrillation. Psycho-emotional stress, anxiety and depression can be the cause of atrial fibrillation paroxysm as well.

The objective of the research was to study the effect of mebicar in the treatment of paroxysmal atrial fibrillation considering anxiety-depressive symptoms.

Materials and Methods. Observations were performed on patients with stable ischemic heart disease and co-existent paroxysmal atrial fibrillation using clinico-psychopathological research method (structured interview). The level of stress was determined on the L. Rider scale and the 10-Item perceived stress scale; the level of anxiety and depression was determined by means of the Hospital Anxiety and Depression Scale and the Patient Health Questionnaire-9. The evaluation of the free radical oxidation state was carried out using a spectrophotometric method to determine the activity of catalase, glutathione peroxidase, superoxide dismutase in the blood serum.

Results. As a result of the analysis, it was found that the higher the level of anxiety-depressive disorders, the more frequent paroxysms of atrial fibrillation. High level of stress was found in 37.50% of men (p<0.01) and 31.25% of women (p<0.05) in Group 2b. The manifestations of the clinical level of anxiety and depression in men of Group 2b (p<0.05) were detected.

Conclusions. The analysis of electrocardiogram indices showed the signs of atrial fibrillation (p<0.05), repolarization abnormalities (p<0.001), left ventricular hypertrophy (p<0.05), and the appearance of extrasystoles (p<0.001). Echocardiographic indices showed the signs of diffuse cardioclerosis, severe left atrial dilatation (p<0.05) and reduced myocardial contractility, which was statistically confirmed. The use of anxiolytic medication – mebicar – during treatment helped significantly improve the clinical and hemodynamic parameters, which confirmed treatment effectiveness.

Keywords
atrial fibrillation; stress; cardio neurosis; anxiety; depression; oxidation of free radicals; Macrose index

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Problem statement and analysis of the latest research

Among the population of most developed European countries, cardiovascular disease (CVD) accounts for almost 40% of all fatal cases. According to the World Health Organization, approximately 23.6 million people worldwide will die of CVD, namely arrhythmias and stroke, by 2030 [1].

Atrial fibrillation (AF) is the most common supraventricular arrhythmia with a high risk of sudden death and thromboembolic complications [2]. Paroxysmal form of AF is one of the most dangerous cardiac rhythm disturbances and accounts for 35% of all types of arrhythmias [3]. First off, AF is an independent predictor of mortality due to embolic strokes. The development of paroxysm is preceded by a variety of factors, including stable ischemic heart disease (SIHD), myocardial infarction (MI), infiltrative or inflammatory diseases of the atria, endocrine disorders, congenital heart defects, and surgical intervention. In apparently healthy young people, AF paroxysms often arise as idiopathic AF [3].

Seventy-eighty per cent of patients with rhythm disturbances were found to have borderline mental disorders, namely anxiety and depression, which impaired the clinical course of AF [3]. According to the literature, the main pathogenetic mechanisms of developing cardiac rhythm disturbances under the influence of psycho-emotional stress are the activation of the sympathetic nervous system, the decrease in the variability of the heart rate, changes in the platelet reactivity and platelet serotonin system, instability of the myocardium due to ischemia and vasoconstriction, excessive free radical production and the development of oxidative stress [4]. To date, there are several theories of arrhythmias in cardiology: the theory of re-entry, the type of micro or macro re-entry with the development of functional blockade in different sections of the conducting system, the theory of automatic ectopic excitation, the theory of trace potential, the theory of heterogeneous repolarization of individual structures of the myocardium, the theory of increasing the automatism of the conducting system cells located below the sinus node. Among the main mechanisms, which are mediated by the manifestation of rhythm disturbances under the influence of stress, there is the activity of the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS) [1].

According to Engel C.L., the cause of sudden cardiac death from psycho-emotional stress can be increased activity of the sympathetic and parasympathetic nervous systems [3, 5]. The increase in the sympathetic tone, the decrease in the vagal tone and cardiac anxiety symptoms can be the main provocative factors of AF acting as triggers and modulating ANS [6].

The role of the sympathetic and parasympathetic nervous systems in the development of heart arte variability (HRV) was found to be as follows: during an emotional reaction, anger occurs, sympathetic activity and heart rate (HR) increase; however, HRV, that is an indicator of parasympathetic activity, does not change. Due to this, we can conclude, that this is the mechanism of arrhythmogenesis [5]. There are many research works, that proved the excessive production of free radicals and the development of oxidative stress to be the leading mechanisms of initiation and progression of AF [4].

Oxidative stress is a disturbance in the prooxidant to antioxidant balance towards prooxidants [7, 8]. Prooxidants cause an increase in the formation of free radicals, including smoking, pollutants, activation of oxygen metabolites [7]. The increased level of reactive oxygen intermediates (ROI) in the cell promotes the initiation of negative reactions that initiate lipid peroxidation (LPO) of cell membranes resulting in damage to their structure and increased permeability [9].

The antioxidant system of the body is known to be able to inhibit free radical oxidation of organic substances and products of LPO reactions [7, 9]. Enzyme antioxidants include superoxide dismutase (SOD), which binds to ROI to form hydrogen peroxide; glutathione peroxidase (GP), which reduces lipid hydroperoxides due to the oxidation of glutathione; catalase, which disrupts peroxides in lipid hydroperoxides [7]. As a result of the studies conducted, the intensification of stress oxidation pro-
cesses was proven to have a direct effect on cardiomyocytes, contributing to the arrhythmogenic activity of the myocardium. In modern literature, there are only few research works devoted to the study of oxidative stress in patients with AF [8].

The objectiv of the research was to study and analyze the dynamics of the effect of mebicar in the patients with SIHD and co-existent paroxysmal AF considering anxiety-depressive symptoms.

1. Materials and Methods

Thirty-one patients with paroxysmal AF were examined in the cardiology departments of Ivano-Frankivsk Regional Clinical Cardiology Center and Central City Clinical Hospital. Two groups were formed. Group 2a included 15 patients with SIHD and co-existent paroxysmal AF who received standard therapy. Group 2b consisted of 16 patients with SIHD and co-existent paroxysmal AF who received standard therapy with the addition of anxiolytic drug mebicar. All the patients gave voluntary informed consent to participate in the study.

Inclusion criteria included the presence of paroxysmal AF. Exclusion criteria included the presence of acute, subacute, inflammatory stage of MI, congenital and acquired heart defects, cardiomyopathies of various genesis, intoxication with cardiac glycosides, antidepressants, diuretics, sympathomimetics or toxic substances, thyrotoxicosis, psychiatric disorders (schizophrenia, affective disorders), alcohol addiction and psychoactive substance abuse.

The study was approved by the Hospital Research Ethics Committees and conducted in accordance with the World Medical Association Declaration of Helsinki (1989).

In the course of the study, there was made a comparison between the dynamics of the course of the main cardiological disease against the background of standard and anxiolytic therapy.

In addition to the clinical examination, the following psychometric methods of research were used: L. Rider’s Psychosocial Stress Scale, the 10-Item perceived stress scale (PSS-10), the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire-9 (PHQ-9) for identifying social factors that may have an impact on health.

L. Rider’s Psychosocial Stress Scale is intended to assess susceptibility to stress. In men, stress level was assessed as low (0.00-0.99 points), average (1.00-1.99 points) and high (2.00-3.00 points); in women, it was (0.00-1.17 points), (1.18-2.17 points) and (2.18-3.00 points) respectively.

The PSS-10 included 10 items divided by the level of stress, where PSS-10 scores ranging 0-13 were considered low perceived stress, PSS-10 scores ranging 14-16 were considered average perceived stress, PSS-10 scores ranging 27-40 were considered high perceived stress.

The HADS consists of 14 questions that assess the well-being of patients during the previous week. Patients respond to each question on a 3-point Likert’s scale. Seven of the 14 questions assess the level of depression, and the other seven evaluate the level of anxiety. Evaluations are summed up separately for depression and anxiety, with a range of 0-21 points. Interpretation of results allows to differentiate 3 categories of the state: normal, subclinical and clinical anxiety/depression: 0-7 scores indicate non-cases, no disorders; 8-10 scores indicate possible case of anxiety/depression, 11 scores or more indicate probable case of anxiety/depression. To assess the impact of negative factors, there was used the PHQ-9 for determining social factors that affect health. On the first day of hospitalization and then in the dynamics after treatment, there was performed a standard 12-lead electrocardiogram (ECG) while the patients rested. The MIDAS 6/12 electrocardiograph was used for ECG recording.

The evaluation of linear dimensions and volume parameters of the heart, the state of the valvular apparatus was performed by echocardiography using the Canon Aplio 400 ultrasound machine (USA) by means of sectoral sensor before and after treatment. The end-diastolic index (EDI) and the end-systolic index (ESI) were calculated. In addition, stroke volume (SV) was measured as the difference between the volumes of the left ventricle (LV) in diastole and systole. An important hemodynamic parameter of the contractile function of the LV is the ejection fraction (EF), which characterizes the systolic function of the heart. The myocardial
mass of the LV (MMLV) and its index, i.e., LV volume/mass ratio were determined. The relative LV wall thickness (LVWT) was determined by the formula: LVWT = 2 * LVPWd/EDD, where LVPWd was left ventricular posterior wall thickness in diastole (cm), EDD was end-diastolic dimension (cm). The shortening of the anterior-posterior dimension (D, %) of the LV short-axis is the distance between the E-peak of the anterior mitral valve leaflet coaptation point and the interventricular septum, which characterizes the ratio of diastolic (the apex of the R-wave) to the systolic (the end of the T-wave) LV dimension. The types of LV geometry in case of its hypertrophy were calculated as follows: in the presence of LV hypertrophy (LVH) and LVWT < 0.43, eccentric LVH was diagnosed; in case of LVH and LVWT > 0.43, concentric HLV was diagnosed.

Quantitative determination of catalase according to A. Bakh and S. Zubkova was carried out by titration using hydrogen peroxide, sulfuric acid, potassium permanganate, distilled water and patient’s blood. One ml of diluted solution of blood was added to a test tube containing 2 ml of a 1% solution of hydrogen peroxide and 7 ml of water. After 30 minutes, 3 ml of 10% solution of sulfuric acid were added. The resulting solution was titrated with normal solution of potassium permanganate until a faint pink color appeared. In healthy adults, normal catalase value ranges within 9.52-12.92 mg of hydrogen peroxide per ml of blood.

The SOD activity was determined on the KFK-2MP apparatus. The following reagents were used: 0.15 M phosphate buffer (pH 7.8), incubation mixture - 37 ml of EDTA-Na2 (ethylene diamine tetraacetate acid disodium salt), 330 ml of nitrotetrazole blue, 55 ml of phenazine methisulphate. This mixture was mixed with 300 ml of phosphate buffer and left overnight, filtered in the morning. The calculation was carried out according to the formula: SOD (%): = Ek-Eo: Ek * 100.

The activity of GP was determined on the SPECORD-M40 two-channel spectrophotometer, using a reaction mixture comprising 1 ml of phosphate buffer, sodium azide 12 mM-0.9 ml, 0.5 ml of 2.5 mM reconstituted glutathione, 0.2 ml of the patient’s blood serum, 0.5 ml of H₂O₂. The reaction was started by adding H₂O₂, stopped after 2 minutes, adding 1 ml of 10% TCO. The mixture was centrifuged at 3,000 rpm for 15 minutes. There was determined the extinction of oxidized glutathione at 260 nm. The activity of the enzyme was expressed in micromoles of oxidized glutathione per 1 Hb per minute.

Laboratory blood tests were performed in the morning on an empty stomach after abstaining from food for 14 hours. Blood biochemical tests were performed with the use of a biochemical analyzer. The indicators of coagulation hemostasis were studied.

Statistical data processing was carried out using Statistica-10. P-value less than 0.05 was considered statistically significant.

### 2. Results and Discussion

According to the results of psychopathological examination of the patients with SIHD and co-existent paroxysmal AF, a direct correlation between the level of anxiety-depressive symptoms, stress susceptibility and the appearance of AF paroxysm was revealed. The study allowed us to compare the data before and after treatment.

During the clinical examination, the occurrence of AF paroxysms in the studied groups was found to be associated with acute (unexpected death of relatives, accidents, divorce, conflicts between relatives) and chronic (illnesses of relatives, financial problems) psychosocial stress.

AF paroxysm was accompanied by the feeling of interruptions (p > 0.05), accelerated palpitation (p > 0.05), frequent changes in blood pressure (BP) (p < 0.05), cardiac rhythm disturbance (p < 0.05), signs of autonomic dysfunction, including memory impairment (p < 0.05), sleep disturbance (p < 0.05), sweating (p < 0.01), general fatigue, which could confirm the symptoms of cardiac neurorosis.

It should be noted that the patients had signs of cardiogenic liver congestion due to heart failure in the systemic and pulmonary circulation, which was clinically manifested by hepatosplenomegaly (p > 0.05). In 50.00% of men (p < 0.01) and 25.00% of women (p < 0.01)
Table 1. Dynamics of the PSS-10 indices in patients with paroxysmal AF during treatment with mebicar.

| Groups          | Paroxysmal AF (n=15) | Paroxysmal AF, treatment with mebicar (n=16) |
|-----------------|-----------------------|---------------------------------------------|
|                 | Group 2a              | Group 2b                                     |
| Level of stress, points | before treatment | after treatment | before treatment | after treatment |
| Low             | 0 (0.00%)            | 3 (20.00%)                                  | 0 (0.00%)        | 0 (0.00%)       |
|                 | p>0.05               | p>0.05                                      | p>0.05           | p>0.05          |
| Average         | 7 (46.67%)           | 4 (26.67%)                                  | 3 (18.75%)       | 8 (50.00%)      |
|                 | p>0.05               | p>0.05                                      | p>0.05           | p>0.05          |
| High            | 0 (0.00%)            | 0 (0.00%)                                   | 6 (37.50%)       | 1 (6.25%)       |
|                 | p<0.01               | p>0.05                                      | p<0.01           | p>0.05          |

| Level of stress, points | before treatment | after treatment | before treatment | after treatment |
|-------------------------|-------------------|-----------------|------------------|-----------------|
| Low                     | 0 (0.00%)         | 0 (0.00%)       | 1 (6.25%)        | 2 (12.50%)      |
|                         | p>0.05            | p>0.05          | p>0.05           | p>0.05          |
| Average                 | 8 (53.33%)        | 8 (53.33%)      | 1 (6.25%)        | 4 (25.00%)      |
|                         | p<0.01            | p>0.05          | p<0.01           | p>0.05          |
| High                    | 0 (0.00%)         | 0 (0.00%)       | 5 (31.25%)       | 1 (6.25%)       |
|                         | p<0.05            | p>0.05          | p<0.05           | p>0.05          |

Note: p - the reliability of the difference in indicators before and after treatment.

women (p>0.05) of Group 2b, a high level of stress was found. When studying indicators of the PSS-10 among 16 surveyed patients, high levels of stress were detected in 6 men and 5 women - 37.50% (p<0.01) and 31.25% (p<0.05), respectively. The average level of stress was found in 8 women - 53.33% (p<0.01). After analyzing the data, we can conclude that the indicators of Group 2b significantly differed from the indicators of Group 2a (Table 1).

According to the results of the study, 25.00% of men in Group 2b had a probable case of anxiety and depression (p<0.05), manifested as a feeling of emotional tension, fear, loss of vivacity, sudden feeling of panic, depression, persistent feeling of sadness and unwillingness to live, including suicide. Among women, these symptoms were observed as well; however, without a probable difference between the scores (p>0.05). The assessment of the dynamics of anxiety and depression according to the HADS after treatment showed a statistically significant (p<0.05) decrease in depressive mood and anxiety in men of Group 2b (Table 2).

Analyzing the data of the PHQ-9, we found that men of Group 2b complained of depressive mood, fatigue, sleep disturbance, inability to concentrate, that indicated moderate depression symptoms (p<0.05).

On the background of taking mebicar at a dose of 500 mg twice a day for two weeks, the manifestations of emotional tension, fear, anxiety reduced, and memory, mental capacity (p<0.05) improved. There were no side effects when taking a tranquilizer.

In the patients with paroxysmal AF, statistical accuracy of ECG indices was revealed (Table 3). Slow depolarization of the atrium is the electrophysiological basis of AF, which develops under the mechanism of re-entry.

An important electrocardiographic sign of AF
Table 2. Dynamics of the HADS indicators in patients with paroxysmal AF during treatment with mebicar.

| Groups                          | Paroxysmal AF (n=15) | Paroxysmal AF, treatment with mebicar (n=16) |
|--------------------------------|----------------------|---------------------------------------------|
|                                | Group 2a             | Group 2b                                    |
| Criteria for evaluating anxiety, scores | before treatment     | after treatment                             | before treatment | after treatment |
| No disorder (norm 0-7 scores)  | 2 (13.33%)           | 7 (46.67%)                                 | 1 (6.25%)       | 4 (25.00%)      |
|                                   | p>0.05               | p>0.05                                     | p>0.05          | p>0.05          |
| Subclinical level (possible case) (8-10 scores) | 4 (25.00%)           | 4 (25.00%)                                 | p>0.05          | p<0.05          |
| Clinical level (probable case) (11 scores or more) | 4 (25.00%)           | 1 (6.25%)                                  | p<0.05          | p>0.05          |
| Criteria for assessing depression, scores | before treatment     | after treatment                             | before treatment | after treatment |
| No disorder (norm 0-7 scores)  | 4 (26.67%)           | 9 (60.00%)                                 | 1 (6.25%)       | 3 (18.75%)      |
| Subclinical level (possible case) (8-10 scores) | 3 (20.00%)           | 0 (0.00%)                                  | p>0.05          | p<0.05          |
| Clinical level (probable case) (11 scores or more) | 4 (25.00%)           | 1 (6.25%)                                  | p<0.05          | p>0.05          |
| Criteria for evaluating anxiety, scores | before treatment     | after treatment                             | before treatment | after treatment |
| No disorder (norm 0-7 scores)  | 2 (13.33%)           | 6 (40.00%)                                 | 2 (12.50%)      | 3 (18.75%)      |
| Subclinical level (possible case) (8-10 scores) | 2 (13.33%)           | 2 (13.33%)                                 | p>0.05          | p>0.05          |
| Clinical level (probable case) (11 scores or more) | 4 (25.00%)           | 0 (0.00%)                                  | p>0.05          | p>0.05          |
| Criteria for assessing depression, scores | before treatment     | after treatment                             | before treatment | after treatment |
| No disorder (norm 0-7 scores)  | 3 (20.00%)           | 6 (40.00%)                                 | 2 (12.50%)      | 3 (18.75%)      |
| Subclinical level (possible case) (8-10 scores) | 2 (13.33%)           | 2 (13.33%)                                 | p>0.05          | p>0.05          |
| Clinical level (probable case) (11 scores or more) | 3 (20.00%)           | 0 (0.00%)                                  | p>0.05          | p>0.05          |

Note: p - the reliability of the difference in indicators before and after treatment.
Table 3. Dynamics of ECG parameters in patients with paroxysmal AF during treatment with mebicar.

| Indices | Paroxysmal AF (n=15) | Paroxysmal AF, treatment with mebicar (n=16) |
|---------|----------------------|---------------------------------------------|
|         | before treatment | after treatment | before treatment | after treatment |
| RR      | 0.79±0.07 | 0.90±0.05 | 0.60±0.05 | 0.76±0.07 |
|         | p<0.05   | p>0.05    | p>0.05    | p>0.05 |
| QRS – DI| 0.10±0.01 | 0.09±0.01 | 0.06±0.00 | 0.07±0.01 |
|         | p<0.01   | p>0.05    | p>0.05    | p>0.05 |
| T wave in V2 lead | 2.27±0.56 | 2.43±0.71 | 6.00±0.00 | 2.69±0.82 |
|         | p<0.001  | p>0.05    | p>0.05    | p>0.05 |
| T wave (-/+) in aVL lead | 0.67±0.30 | 0.93±0.32 | 2.00±0.00 | 1.06±0.19 |
|         | p<0.001  | p>0.05    | p>0.05    | p>0.05 |
| T wave (-/+) in V6 lead | 2.27±0.45 | 1.86±0.50 | 4.00±0.00 | 1.31±0.54 |
|         | p<0.001  | p>0.05    | p>0.05    | p>0.05 |
| ST segment | 15.80±0.92 | 16.14±0.51 | 14.31±0.66 | 13.44±1.12 |
|         | p>0.05   | p<0.05    | p>0.05    | p<0.05 |
| ST segment in V1 lead | 13.73±0.89 | 14.93±0.59 | 14.0±0.00 | 11.75±0.96 |
|         | p>0.05   | p<0.01    | p>0.05    | p<0.01 |
| RS-T segment in V6 lead | 15.80±1.02 | 17.36±0.71 | 15.19±0.60 | 14.44±1.16 |
|         | p>0.05   | p<0.05    | p>0.05    | p<0.05 |
| RS-T segment in I lead | 15.73±1.08 | 17.64±0.82 | 13.63±1.06 | 13.38±1.41 |
|         | p>0.05   | p<0.05    | p>0.05    | p<0.05 |
| CVI: R wave in aVL lead + S wave in V3 lead >28mm | 9.13±1.99 | 8.64±2.01 | 14.00±0.00 | 10.31±1.96 |
|         | p>0.05   | p<0.05    | p>0.05    | p<0.05 |
| EI: R1+SIII >17 mm | 12.07±0.97 | 13.14±1.82 | 17.00±0.00 | 12.56±1.35 |
|         | p<0.05   | p>0.05    | p>0.05    | p<0.05 |
| PI=QR* interval /QT interval | 0.10±0.08 | 0.50±0.09 | 0.00±0.00 | 0.00±0.00 |
|         | p>0.05   | p<0.001   | p<0.001   | p<0.001 |
| MI:P wave duration/PQ segment dustion<1.1 | 0.18±0.07 | 0.50±0.09 | 0.14±0.07 | 0.21±0.07 |
|         | p>0.05   | p<0.05    | p>0.05    | p<0.05 |
| P-Q interval | 0.05±0.02 | 0.13±0.02 | 0.04±0.02 | 0.06±0.02 |
|         | p<0.05   | p>0.05    | p>0.05    | p>0.05 |

Note: p - the reliability of the difference in indicators before and after treatment.

is the irregularity of ventricular QRS complexes, an irregular ventricular rhythm reflecting different RR intervals (p<0.05). The T wave in the unipolar leads (aVL) (p<0.001) and in thoracic leads (V2), (V6) (p<0.001) indicates repolarization abnormalities. A high, symmetrical T wave explains subendocardial ischemia of the myocardium. The ST segment represents the ventricular excitation process, where its duration depends on the pulse rate (p<0.05).

An interpreting the Cornell Voltage Index (CVI) and the Endleyden Index (EI), we noted that the indices of both groups indicated the presence of severe LVH, that was statistically proven (p<0.05). The ratio of the coupling interval and the QT interval is called the prematurity index (PI) and explains the emergence of extrasystoles (p<0.001).

Having compared the data of the Macruz Index
Table 4. Dynamics of echocardiographic indicators in patients with AF during treatment with mebicar.

| Indicators, units of measure | Paroxysmal AF (n=15) | Paroxysmal AF, treatment with mebicar (n=16) |
|-----------------------------|----------------------|---------------------------------------------|
| Group 2a                    | Group 2b             |                                             |
| Indicator dynamics          | before treatment     | after treatment                             | before treatment | after treatment |
| EDD, cm                     | 5.01±0.13            | 5.14±0.19                                   | 5.21±0.17        | 5.44±0.22      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| ESD, cm                     | 3.65±0.14            | 3.81±0.19                                   | 3.98±0.08        | 4.01±0.20      |
|                             | p<0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| EDV, ml                     | 120.40±7.84          | 127.25±12.51                                | 133.31±10.88     | 148.40±15.07   |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| ESV, ml                     | 56.47±6.09           | 63.63±8.46                                  | 68.56±8.91       | 73.00±9.06     |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| TIVSd, cm                   | 1.13±0.02            | 1.09±0.02                                   | 1.16±0.04        | 1.07±0.04      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| LVPWd, cm                   | 1.10±0.03            | 1.08±0.04                                   | 1.16±0.02        | 1.10±0.03      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| EDI ml/m                    | 0.37±0.03            | 0.38±0.05                                   | 0.35±0.02        | 0.37±0.03      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| ESI ml/m                    | 0.18±0.02            | 0.19±0.03                                   | 0.23±0.05        | 0.18±0.01      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| SV, ml                      | 62.60±2.53           | 63.63±4.28                                  | 64.88±3.25       | 75.40±6.26     |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| EF (%)                      | 52.07±1.26           | 50.25±1.39                                  | 50.19±1.30       | 51.60±1.24     |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| MMLV, g                     | 210.29±9.16          | 212.13±10.70                                | 240.54±10.85     | 238.30±23.26   |
|                             | p<0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| IMMLV g/m                   | 0.66±0.05            | 0.64±0.06                                   | 1.02±0.38        | 0.61±0.05      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| LVWT (c.u.)                 | 0.44±0.02            | 0.42±0.00                                   | 0.48±0.04        | 0.40±0.01      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| S, %                        | 1.38±0.02            | 1.35±0.02                                   | 1.35±0.01        | 1.36±0.02      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| Concentric hypertrophy      | 10 (66.67%)          | 10 (66.67%)                                  | 10 (87.50%)      | 10 (87.50%)    |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| Eccentric hypertrophy       | 5 (33.33%)           | 5 (33.33%)                                   | 6 (37.50%)       | 6 (37.50%)     |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| LAD cm                      | 3.84±0.15            | 3.89±0.14                                   | 4.29±0.14        | 4.06±0.13      |
|                             | p<0.05               | p>0.05                                      | p>0.05           | p>0.05         |
| RVD, size, cm               | 2.89±0.06            | 2.96±006                                   | 2.96±0.25        | 2.99±0.12      |
|                             | p>0.05               | p>0.05                                      | p>0.05           | p>0.05         |

Note: p - the reliability of the difference in indicators before and after treatment.
Table 5. Dynamics of indicators of catalase, SOD, GP activity in the blood serum of patients with paroxysmal AF during treatment with mebicar.

| Indices                  | Paroxysmal AF (n=15) | Paroxysmal AF, treatment with mebicar (n=16) |
|--------------------------|-----------------------|---------------------------------------------|
|                          | before treatment      | after treatment                            |
| Catalase, mg H2O2/1ml of | Group 2a              | Group 2b                                    |
| blood                    | before treatment      | after treatment                            |
|                          | 14.42±1.46            | 9.92±2.25                                  |
|                          | 15.37±1.55            | 12.18±2.06                                  |
|                          | p>0.05                | p<0.001                                    |
|                          | 34.56±4.87            | 38.00±7.63                                  |
|                          | p>0.05                | p<0.001                                    |
|                          | 0.14±0.03             | 0.10±0.03                                  |
|                          | 0.16±0.02             | 0.11±0.02                                  |
|                          | p>0.05                | p<0.01                                     |
| Note: p - the reliability of the difference in indicators before and after treatment.

(MI) in Group 2a and Group 2b, where the indices were 0.50±0.09 and 0.21±0.07, respectively, we noted that there was a significant difference in the indicators after treatment (p<0.05). Analyzing the PQ interval data, we observed a shortening of its duration depending on the HR (p<0.05).

Table 4 shows the dynamics of echocardiographic parameters in the patients with paroxysmal AF. With the increase in the level of anxiety-depressive symptoms, there was the increase in ESD, EDV, left atrial dimension (LAD) and decrease in EF.

Having analyzed the MMLV, we found that its mass might also depend on the level of anxiety-depressive symptoms. Having compared the data of Group 2a and Group 2b, where the indicators were 210.29±9.16 and 240.54±10.85, respectively, we noted that the indicator of Group 2b was higher, which was statistically confirmed (p<0.05). The value of ESD was significantly higher than that in Group 2a (p<0.05).

Particular attention was paid to the clinical and pathogenetic features of LA state. In hemodynamic overload of the atria, the intra-atrial pressure increases, thereby leading to the atrial wall thinning with the development of diffuse atrial sclerosis, that results in reduced myocardial contractility due to the overflow of its cavities with blood at the end of the systole, which is accompanied by the dilation of cardiac walls. As the LA has the tendency to dilatation, it leads to AF. According to the Framingham Study, increased LA was associated with a twofold increase in AF. The LA indicator in the patients of Group 2b was rather high - (4.29±0.14 cm), whereas, in Group 2a, it was (3.84±0.15 cm), indicating systolic dysfunction.

The study of the dynamics of free radical processes involved the study of antioxidant enzymes. Having analyzed the activity of catalase (Table 5), we found that the value of this indicator depended on the level of psycho-emotional stress. Having compared the data between Group 2a and Group 2b, where the values were 9.92±2.25 mg H2O2/1 ml of blood and 12.18±2.06 mg of H2O2/1 ml of blood, respectively, we noted that the indicator was higher in Group 2b, which was statistically confirmed (p<0.001). After interpreting SOD, we noted that its parameters depended on the level of psycho-emotional state as well, that was statistically proven (p<0.001). The activity of serum GP in the patients receiving anxiolytic therapy was 0.11±0.02, (p<0.01), which explained the positive dynamics of treatment. Consequently, increased anxiety and depression symptoms affected the activity of antioxidant enzymes, which led to the disturbance of free radical oxidation. Free radicals, that modify cardiomyocyte receptors, deepened ischemia and contributed to the arrhythmogenic effect.

There were no significant differences in the levels of total bilirubin, cholesterol, total protein, creatinine, alanine aminotransferase, aspartate amino-
transferease among the examined patients (p>0.05). The analysis of the results of urea level in Group 2a and Group 2b was as follows: 6.67±0.49 mmol/l and 10.09±4.97 mmol/l as compared to the normal range of 1.7-8.3 mmol/l, that might explain the side effects of taking β-blockers or a worsened course of cardiac disease. The indicators of the circulatory system in the patients of Group 2b indicated the signs of hypocoagulation. The reliability of prothrombin time was 14.55±0.77 and 6.85±1.70 (p<0.001) and hematocrit - 0.48±0.01 and 0.43±0.01 (p<0.001) in Group 2a and Group 2b, respectively.

Thus, the results of the study suggested the occurrence of psychosomatic AF, in which the patients develop cardioneurosis symptoms manifesting themselves as repeated episodes of AF paroxysms on the background of psycho-emotional stress. Taking anxiolytic drug mebicar at a dose of 500 mg twice a day allowed reducing the manifestations of anxiety and depression, which led to the positive dynamics in the clinical course of cardiological disease.

3. Conclusions

1. The analysis of the clinical psychopathological method of the study confirmed the symptoms of cardioneurosis, susceptibility to stress and the clinical level of anxiety and depression.
2. Echocardiographic indices showed the signs of diffuse cardiosclerosis, severe LA dilatation and reduced myocardial contractility.
3. The functional state of the antioxidant system showed that the higher the anxiety and the level of depression, the higher the data indicators.

4. Prospects of Further Researches

Prospects for further research are the study of the effectiveness of mebicar in the dynamics.

References

[1] Ermashkin VI. Predполагаемый механизм возникновения аритмий сердца. The Journal of scientific articles “Health and Education millennium” 2013;15(6):1-11.

[2] Filippova MO. Analysis of the indicators of protein and lipid oxidative stress in patients with atrial fibrillation in combination with and without effort angina. Astrakhan Medical Journal. 2018;1(13):1-8. [published in Russian]

[3] Lukaschenko AA. The role of emotional stress in the genesis of life-threatening heart rhythm disorders. RUDN Journal of Medicine. 2014;2:35-41. [published in Russian]

[4] Philippova MO, Polunina OS, Voronina IP et al. The prognosis of development of the paroxysm of atrial fibrillation in patients with post-infarction cardiosclerosis. Kuban Scientific Medical Bulletin. 2017;(3):114-119. [published in Russian] DOI: https://doi.org/10.25207/1608-6228-2017-24-3-114-119

[5] Troshina DV, Volel BA. Stress-induced atrial fibrillation. Zh Nevrol Psikhiatr Im S S Korsakova. 2019;119(1):6-13. [published in Russian] DOI: https://doi.org/10.17116/jnevro20191190116 [PMid:3078024]

[6] Severino P, Mariani V. Triggers for Atrial Fibrillation: The Role of Anxiety. Cardiology Research and Practice. 2019;5. DOI: https://doi.org/10.1155/2019/1208505 [PMid:30906592 PMCid:PMC6398072]

[7] Gorokhova SG. Cardiovascular continuum possibilities of coenzyme Q10 in correction of oxidative stress. Cardiology. 2011;51(10):61-65. [published in Russian]

[8] Filippova MO. Oxidative stress in patients with atrial fibrillation and postinfarction cardiosclerosis. Modern problems of science and education. 2016;6:65. [published in Russian]
Karpukhina OV. Analysis of metal-induced oxidative stress in unicellular organisms. Fundamental research. 2013;11:671-674. [published in Russian]

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