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THE EFFECTIVENESS OF TREATMENT WITH MEBICAR IN PATIENTS WITH PERMANENT ATRIAL FIBRILLATION, WHICH STEM FROM ANXIETY AND DEPRESSION.

Lesya Seredyuk, Igor Vakalyuk

Ivano–Frankivsk National Medical University, Ukraine

E-mail: 1992lesias@gmail.com

Resume: The violation of the heart rhythm is widespread at present. Therefore, the study of this nosology is of considerable interest since the etiology and pathogenesis of arrhythmias are the most urgent issues. Anxiety–depressive symptoms and a tendency to chronic stress lead to the depletion of the body, which contributes to the development of cardiovascular disease. Arrhythmia on the nerve tissueappears as a result of frequent psycho–emotional states. Therefore, the treatment is aimed at reducing the risk of cardiovascular mortality and improving the quality of life. The aim of the study is to assess the severity of clinical and hemodynamic indices by using an anxiolytic drug, mebicar. Observations were performed on patients with stable coronary heart disease (SIHD) in combination with atrial fibrillation (AF) using a clinico–psychopathological method of investigation (structured interview).The level of predisposition to stress was determined on the L. Rider scale, while the level of anxiety–depressive symptoms was determined through the hospital scale of anxiety and depression of HADS by means of a survey. The PHQ–15 health questionnaire and the questionnaire for identifying social factors that may have an impact on health were used to assess health status. The study of cardiac hemodynamics was performed using an electrocardiogram (ECG). 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. The determination of cortisol level in serum was carried out by immunoassay (ELISA) on the ER–500 Microplate Reader. The concentration of N–terminal fragment of the brain natriuretic peptide precursor (NTproBNP) in serum was determined by ELISA using a Biosan PST–60HL shaker. The results of the survey showed a direct dependence of the manifestation of AF on the level of psychoemotional stress. We found that in group 1b there were complaints of increased excitability ($p < 0.001$), (p–reliability difference of indices before and after treatment), fatigue ($p < 0.001$), deterioration of memory ($p < 0.01$), loss appetite ($p < 0.05$), sleep disturbance ($p < 0.001$), signs of severe sweating ($p < 0.001$), which indicate the appearance of astheno–vegetative syndrome.The reduction of manifestations of high stress ($p < 0.01$) in patients of group 1b was noted. A similar pattern was detected in the severity of anxiety in men ($p < 0.01$). The manifestations of somatization disorders ($p < 0.01$), ($p < 0.001$) in the corresponding groups of patients under investigation were determined. Among the social factors influencing health are the presence of the nervous atmosphere at home ($p < 0.01$), the influence of the media ($p < 0.01$), and political events ($p < 0.01$). The value of the ECG parameters confirms the violation of the processes of intra–ventricular conduction repolarization ($p < 0.05$), ($p < 0.001$). After analysing the activity of catalase, glutathione peroxidase (GP), and superoxide dismutase (SOD), we can note that the higher the level of psychological distress, the higher the data of the indicators and, accordingly, more distinct signs of antioxidant oxidation are: SOD – 49.87 ± 1.59 and $37.80 \pm 5,37 (p < 0.05)$, catalase – 17.67 ± 1.50 and $11.11 \pm 2.08 (p < 0.05)$. The determination of the content of cortisol also depends on thelevel of anxiety–depressive symptoms ($p < 0.05$). In patients, we observed an elevated serum NT–proBNT level probably against a background of a deteriorated course of the disease ($p > 0.05$).

The application in the complex therapy of patients with SIHD in conjunction with AF anxiolytics of the benzodiazepine series (mebicar) has caused astopping in anxiety–depressive disorders. After the treatment, the clinico–psychopathological examination confirmed the reliably positive dynamics of the psychological status of patients. Indicators of the spectrophotometric method and the titration method indicated that the higher the anxiety–depressive symptoms, the higher the rates of free radical oxidation. Analysing the level of cortisol, we observed its increase depending on the degree of anxiety and depression; NT–proBNT metrics respectively.

Key words: atrial fibrillation, stress, cortisol, mebicar, N–terminal fragment of the precursor of the brain natriuretic peptide (NTproBNP)

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Problem statement and analysis of recent research

Atrial fibrillation (AF) is the most commonly persistent cardiac arrhythmia in clinical practice, which contributes to a deterioration in the quality of life, increased morbidity and mortality [1]. It is projected thatby 2030 due to risk factors such as obesity and diabetes [2], arrhythmia [3], arterial hypertension [4]; more than 23.3 million people will die from acute myocardial infarction (MI), stroke, [2] systemic embolism [3] and life–threatening cardiovascular disorders [5].

Among the population of Ukraine, cardiovascular disease (CVD) accounts for 63.3% of all fatal cases [6]. Significant groups of the population have mental disorders, including post–traumatic stress disorder (PTSD) and disorders of adaptation. Their prevalence in the population is: PTSD–1–3%, adaptive disorders–5–20% of all patients. In the structure of morbidity, non–psychotic mental disorders prevail – neuroses, reactions to stress, personality disorders [7].

Anxiety–depressive symptoms [5], negative emotions [8], and the impact of chronic stress were considered by cardiologists and psychiatrists a long time ago [9]. For many decades, the theory of psychosomatic heart disease has been formed [9]. Clinical trials have been conducted to study the role of depression, anger, anxiety and chronic stress with AF incidents. MESA (Multi–Ethnic Study of Atherosclerosis) has confirmed the association of anxiety–depressive states with an increased risk of AF [10,11]. Therefore, there is a relationship between AF and these states [12], but the spectrum of psychological disorders remains unclear [13].

As a rule, stress–induced rhythm disturbance is manifested by tachyarrhythmias characterized by a pathologically rapid rhythm. Conditionally, they can be divided into organic–associated with any pathology of the heart muscle or vessels; most often it is SIHD, myocardial infarction, myocarditis, cardiosclerosis, cardiomyopathies and inorganic (functional) have no basis for organic lesions; the main causes of their development there are physical and psychological overload, emotional shock, frequent stress situations, intoxication, hypoxia, alcohol, and smoking [9].

It is suggested that personal psychology and the presence of psychological distress may be due to the influence on the sympathetic nervous system, systemic and regional inflammation, and the endothelium function to be factors contributing to the development of AF [13]. The interaction of the cardiovascular and nervous systems is a complicated algorithm in a state of rest, and in the period of stress these reactions become even more complex and dynamic. Negative emotions lead to coronary ischemia, platelet activation, changes in hemodynamics and the release of catecholamines in the blood, as well as cause electrical dissociation in the atria and ventricles [9].

The mechanisms underlying both initiation and the onset of AF are not sufficiently established, but they are believed to include inflammation and oxidative stress [1]. There is strong evidence that there is a strong correlation between inflammation and the pathogenesis of AF [1, 3]. Various inflammatory markers (C–reactive protein, tumor necrosis factor–, interleukin–2, interleukin–6, interleukin–8) were associated with AF. These include the activation and damage of the endothelium, the production of tissue factor from monocytes, increased platelet activation and fibrinogen expression [3]. Oxidative stress is defined as an imbalance between elimination and the elimination of active forms of oxygen (AFC). Excessive development of which can lead to damage to the oxidative tissue of the myocardium.

Natriuretic peptide B–type (BNP) is synthesized by ventricular cardiomyocytes in the form of preproBNP precursor proteins. The main stimulus of its secretion is increased pressure of the myocardium with increasing pressure in the left ventricle of the heart. Subsequently, preproBNP is cleaved and released into the blood in the form of N terminal fragment – NTproBNP and active hormone – BNP. High concentration and stability in the serum allow using NTproBNP to evaluate the function of the myocardium [2]. The content of glucocorticoid hormones in biological fluids, which are objective criteria for the level of acute stress and the type of response of the body to the psycho–emotional stress were investigated. After all, psycho–emotional stress is associated with an increased content of cortisol, which is associated with anxiety–depressive symptoms [6, 8]. A violation of adequate interaction between the cardiac muscle and the above listed structures in response to emotional stress increases the risk of arrhythmia and sudden cardiac death [9].

Therefore, the main task is correction of pharmacological and psychotherapeutic methods of treatment. One of the few drugs that meets these needs is a mebicar, which is used in clinical practice. It has a wide clinical and pharmacological spectrum of action, possessing properties suppresses feelings of fear, emotional tension, and anxiety, as well as improve memory and intellectual activity. Daily dosage –500 mg twice daily, regardless of food intake [11].

The aim of the study is to assess the severity of clinical and hemodynamic indices by using anxiolytic drug,mebicar.

Materials and methods of research

31 medical records of patients undergoing treatment at the cardiology department of the regional clinical cardiology centre in Ivano–Frankivsk were examined.All patients were divided into 2 groups: 1a – patients with SIHD with

a constant form of AF who received standard therapy (16 patients were examined), 1b – patients with SIHD with permanent formof AF form that had anxiolytic therapy in the complex treatment (15 patients were examined).

The criteria for inclusion in the study: signed informed consent to participate in the study; age of patients > 20 years; permanent form of AF which was documented on an electrocardiogram (ECG). The criteria for exclusion from the study: patients were eliminated for the psycho–neurological condition; acute conditions (acute coronary syndrome, myocarditis, pulmonary artery thromboembolism, life–threatening rhythm disturbances (persistent ventricular tachycardia, ventricular fibrillation); reversible causes of AF, such as thyrotoxicosis, or alcohol intoxication.

All surveyed were evaluated for stress according to the methodology of the psychosocial stress scale L. Reeder. Questionnaire L. Reeder included 7 questions and 4 possible answers to each question. The level of stress was assessed as low (0.00–0.99 points), mean (1.00–1.99 points) and high (2.00–3.00 points) stress in men and women (0.00–1.17 points), (1.18–2.17 points) and (2.18–3.00 points) respectively. The PHQ–15 consists of 13 points that are used to diagnose somatoform disorder. The questionnaire for identifying social factors that may affect health includes 28 points. Hospital scale HADS was used to assess the degree of anxiety and depression. The questionnaire for the detection of the status of anxiety and depression presented 7 questions with 3 variants of the answer. Interpretation of these results allows to differentiate 3 categories of the state: norm, subclinical and clinical level. 0–7 points – norm, no dealings; 8–10 – possible case of anxiety / depression; 11 or more is a likely case of anxiety / depression.

ECG were resting in 12 standard leads on the first day of hospitalization, and then in the dynamics after treatment. Electrocardiogram "MIDAS–6/12"was used for ECG recording. The ultrasound examination of the heart was performed on a Canon Aplio 400 (USA) sectoral sensor.

Quantitative determination of catalase by A. Bach and S. Zubkova was carried out by titration using hydrogen peroxide, sulfuric acid, potassium permanganate, distilled water and patient blood. The activity of superoxide dismutase was determined on the apparatus of KFK–2MP, glutathione peroxidase on SPECORDM40.

The quantitative determination of the concentration of total cortisol in serum was determined by ELISA using the ER–500 Microplate Reader. Catalog number –3625–300. Manufacturer – Monobind Inc. (USA). Reagents required for a solid–phase enzyme–linked immunosorbent assay include antibodies, an enzyme conjugate with antigen and a native antigen. When mixing biotinylated antibodies, the enzyme–antigen conjugate and the native antigen contained in the serum, there is a competition between the native antigen of the sample and the enzyme–antigen conjugate for a limited number of immobilized binding sites.

The content of N–terminal fragment concentration of the brain natriuretic peptide precursor (NTproBNP) in serum was determined by ELISA using a SINNOWAER–500 spectrophotometric analyzer using a Biosan PST–60HL shaker. Catalog number is A–9102. The firm – the manufacturer – BEST (Russia).

The statistical analysis of the results was carried out using the STATISTICA–10 program. The level of statistical significance was considered probable at $p<0.05$.

Table 1: Dynamics of clinical indices in patients with a permanent form of AF in the process of treatment with a mebicar

Indicators	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Dynamics of indicators	Before treatment	After treatment	Before treatment	After treatment
The feeling of interruptions	15 (93.75%)	9 (56.25%) p<0.05	10 (66.67%)	1 (6.67%) p<0.001
Accelerated heartbeat	10 (62.50%)	5 (31.25%) p>0.05	7 (46.67%)	1 (6.67%) p<0.001
Shortness of breath at rest	4 (25.00%)	0 (0.00%) p<0.05	5 (33.33%)	0 (0.00%) p<0.01
Overdose pain	5 (31.25%)	0 (0.00%) p<0.05	6 (40.00%)	1 (6.67%) p<0.01
Increase blood pressure	8 (50.00%)	2 (12.50%) p<0.05	7 (46.67%)	0 (0.00%) p<0.01
Fatigue	13 (81.25%)	8 (50.00%) p>0.05	15 (100.00%)	7 (46.67%) p<0.001
Increased excitability	0 (0.00%)	1 (6.25%) p<0.05	10 (66.67%)	1 (6.67%) p<0.001
Deterioration of memory	2 (12.50%)	1 (6.25%) p>0.05	7 (46.67%)	0 (0.00%) p<0.01
Frequent headaches	12 (75.00%)	0 (0.00%) p<0.001	12 (80.00%)	0 (0.00%) p<0.001
Loss of appetite	2 (12.50%)	0 (0.00%) p>0.05	5 (33.33%)	0 (0.00%) p<0.05
Sleep disturbance	5 (31.25%)	1 (6.25%) p>0.05	13 (86.67%)	1 (6.67%) p<0.001
Sweating	5 (31.25%)	0 (0.00%) p<0.01	10 (66.67%)	0 (0.00%) p<0.001
Acrocyanosis / Cyanosis	4 (20.00%)	0 (0.00%) p<0.05	1 (6.67%)	1 (0.00%) p>0.05
Edema of the lower extremities (pastoseness)	13 (81.25%)	0 (0.00%) p<0.001	15 (100.00%)	0 (0.00%) p<0.001

Notes: p- the reliability of the difference in indicators before and after treatment;

The research conducted here among patients of the department of SIHD in the city of Ivano–Frankivsk found that the risk of manifestations of mental disorders in the absence of preventive and corrective measures is significantly increasing. Clinical manifestations occurred within a month after a stressful situation, and the duration of symptoms did not exceed 6 months. Patients expressed complaints about general anxiety,dissatisfaction with life, the adoption of impulsive, and ill–considered decisions. Patients noticed irritability, an increased sense of fear, aggressiveness, and attacks of unfounded anger. Deterioration of attention and memory concentration, poor performance, uncontrollable emotions, depression, and loss of desire to do anything and to strive for something.

After conducting the clinical examination in the respective groups, we obtained the following results. Adaptation disorders (Table 1) in patients of group 1b with a high

level of anxiety–depressive symptoms were characterized by astheno–vegetative syndrome. An analysis of the results confirmed the signs of increased excitability ($p<0.001$), fatigue ($p<0.001$), memory impairment ($p<0.01$), loss of appetite ($p<0.05$), sleep disturbance ($p<0.001$), signs of severe sweating ($p<0.001$), which indicate the significant reliability of these indicators. There was a tendency towards elevated blood pressure (BP) in patients of group 1a ($p<0.05$) and group 1b ($p<0.01$), as well as manifestations of frequent headaches ($p<0.001$).

According to the objective survey, we found that in patients 1a and 1b the symptoms were consistent with heart failure, due to dyspnea alone ($p<0.05$) ($p<0.01$), edema of the lower extremities ($p<0.001$) and acrocyanosis ($p<0.05$).

From the perspective of psychopharmacotherapy, patients noticed the normalization of the mood background, improvement of sleep, restoration of work capacity, restoration of interest inwork, and a reduction of manifestations of astheno–vegetative syndrome. Hence, after analysing the clinical picture, we can note that the commitment to treatment of mebicar in patients in group 1b is decisivelyconfirmed.

A comparison of the obtained data showed that in the 1a group of patients under study, compared with the 1b group, there were more persons with a low level of stress 37.50% and 6.67% – respectively, $p>0.05$. It was established that from the perspective of psychopharmacotherapy patients with cardiopathology noticed the reduction of manifestations of high level of stress in the persons receiving the mebicar ($p<0.01$). It is interesting to note that among men the signs of acute (such as divorce, death or serious illness of a loved one, or a trial of a family member) and chronic (serious financial problems, prolonged difficult relationships with a woman or children) psychosocial stress appeared much more often than among women (Table 2).

Table 2: Dynamics of indicators of psychosocial stress L.Rider in patients with a permanent form of AF in the process of treatment by a mebi??r

Groups of patients	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Level of stress, score	Men			
	Before treatment	After treatment	Before treatment	After treatment
Low	6 (37.50%)	3 (18.75%) p>0.05	1 (6.67%)	1 (6.67%) p>0.05
Average	2 (12.50%)	4 (25.00%) p>0.05	4 (26.67%)	8 (53.33%) p>0.05
High	4 (25.00%)	4 (25.00%) p>0.05	6 (40.00%)	0 (0.00%) p<0.01
Level of stress, scores	Women			
	Before treatment	After treatment	Before treatment	After treatment
Low	1 (6.25%)	1 (6.25%) p>0.05	0 (0.00%)	0 (0.00%) p>0.05
Average	2 (12.50%)	3 (18.75%) p>0.05	3 (20.00%)	6 (40.0%) p>0.05
High	2 (12.50%)	1 (6.25%) p>0.05	3 (20.0%)	0 (0.00%) p>0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

Hospital scale HADS along with an assessment of the level of anxiety can determine the level of depression. In the examined groupsof men, 7 (46.67%) of those with a permanent form of AF who received a meal at the time of the questionnaire marked a clinically expressed anxiety. Substantial improvement of the investigated indexes of anxiety in men of the 1st group is presented (p¡0.01). The reduction of manifestations of clinical anxiety in the subclinical on the background of taking the drug mebicar ($p<0.01$) was noted. Among women with SIHD in combination with AF in 1b groups, a tendency to clinically expressed anxiety was detected ($p<0.05$), however, without a significant difference after treatment. The severity of depression in women was observed in 3 (18.75%) and 2 (13.33%) individuals 1a and 1b groups with subclinical levels of depression ($p<0.05$) and 2 (13.33%) with clinical level, respectively ($p<0.05$) (Table 3).

Table 3: Dynamics of indicators of the hospital scale of anxiety and depression of HADS in patients with a permanent form of AF in the course of treatment with a mebicar

Groups of patients	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Criteria for assessing anxiety, score	Men			
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (norm 0-7 points)	5 (31.25%)	7 (43.75%) p>0.05	1 (6.67%)	1 (6.67%) p>0.05
Subclinical level (possible case) (8-10)	5 (31.25%)	4 (25.00%) p>0.05	1 (6.67%)	8 (53.33%) p<0.01
Clinical level (probable case) (11 or more)	1 (6.25%)	0 (0,00%) p>0.05	7 (46.67%)	0 (0.00%) p<0.01
Criteria for assessing depression, score	Men			
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (norm 0-7 points)	3 (18.75%)	6 (37.50%) p>0,05	0 (0.00%)	2 (13.33%) p>0.05
Subclinical level (possible case) (8-10)	5 (31.25%)	5 (31.25%) p>0.05	2 (13.33%)	2 (13.33%) p>0.05
Clinical level (probable case) (11 or more)	3 (18.75%)	0 (0.00%) p>0.05	7 (46.67%)	5 (33.33%) p>0.05
Criteria for evaluating anxiety, scores	Women			
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (norm 0-7 points)	2 (12.50%)	3 (18.75%) p>0.05	0 (0.00%)	1 (6.67%) p>0.05
Subclinical level (possible case) (8-10)	1 (6.25%)	1 (6,25%) p>0.05	2 (13.33%)	4 (26.67%) p>0.05
Clinical level (probable case) (11 or more)	2 (12.50%)	1 (6.25%) p>0.05	4(26.67%)	1 (6.67%) p>0.05
Criteria for assessing depression, scores	Women			
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (norm 0-7 points)	1(6.25%)	2 (12.50%) p>0.05	1 (6.67%)	2 (13.33%) p>0.05
Subclinical level (possible case) (8-10)	2 (12.50%)	3 (18.75%) p>0.05	1 (6.67%)	2 (13.33%) p>0.05
Clinical level (probable case) (11 or more)	2 (12.50%)	0 (0.00%) p>0.05	4 (26.67%)	2 (13.33%) p>0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

With the use of the PHQ–15 questionnaire, the differences in both before and after treatment were detected in the examined patients. According to the data obtained in men

of 1b group statistically significant moderate ($p<0.01$) and light ($p<0.001$) somatization disorder was recorded. The self–esteem of women's health significantly improved in the group of patients taking mebicar ($p<0.01$). Consequently, we emphasize the presence of connection between the psychoemotional sphere and the cardiovascular pathology: the higher the level of anxiety–depressive symptoms, the worse the health of patients is.

Table 4: Dynamics of indicators of the PHQ–15 health questionnaire in patients with a permanent form of AF in the course of treatment with a mebicar

Groups of patients	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Criteria for evaluation	Men			
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (0-4)	1 (6.25%)	3 (18.75%) p>0.05	0 (0.00%)	1 (6.67%) p>0.05
Light Somatization Disorder (5-9)	7 (43.75%)	8 (50,00%) p>0.05	0 (0.00%)	8 (53.33%) p<0.001
Moderate somatosis disorder (10-14)	3 (18.75%)	0 (0.00%) p>0.05	7 (46.67%)	0 (0.00%) p<0.01
Severe Somatization Disorder (15+)	0 (0.00%)	0 (0,00%) p>0.05	2 (13.33%)	0 (0.00%) p>0.05
Criteria for evaluation	Women			
	Before treatment	After treatment	Before treatment	After treatment
Absence of disorder (0-4)	0 (0.00%)	2 (12.50%) p>0.05	0 (0.00%)	0 (0.00%) p>0,05
Light Somatization Disorder (5-9)	3 (18.75%)	3 (18.75%) p>0.05	0 (0.00%)	6 (40.00%) p<0.01
Moderate somatosis disorder (10-14)	1 (6.25%)	0 (0.00%) p>0.05	4 (26.67%)	0 (0.00%) p<0.05
Severe Somatization Disorder (15+)	1 (6.25%)	0 (0.00%) p>0.05	2 (13.33%)	0 (0.00%) p>0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

After the therapy, there is a decrease in the manifestations of social factors that may have an impact on health, including the presence of a nervous atmosphere at home, the influence of the media, and political events that indicate the reliability of the difference in rates after treatment.

Table 5: The dynamics of social factors that may affect health. in patients with a permanent form of AF in the process of treatment with a mebicar

Groups of patients	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Indexes	Before treatment	After treatment	Before treatment	After treatment
The presence of a nervous atmosphere at home	6 (37.50%)	0 (0.00%) p<0.01	4 (26.67%)	0 (0.00%) p<0.05
Influence of mass media	6 (37.50%)	8 (50.00%) p>0.05	12 (80.00%)	5 (33.33%) p<0.01
Political events	12 (75.00%)	10 (62.50%) p>0.05	10 (66.67%)	2 (13.33%) p<0.01

Note: p- the reliability of the difference between the indicators before and after treatment;

After interpreting the data of the electrocardiogram, it should be noted that the performance of the two groups indicates a violation of the processes of atrial and ventricular repolarization, which is important for the development of heart rhythm abnormalities.

Observations were made that the indices of both groups are statistically different, but all of them indicate changes in the segment ST ($p<0.05$), ($p<0.001$), which is associated with a violation of intraventricular conduction. It is important to note changes in the QRS complex, which may reflect moderate hyperkalemia. Increased heterogeneity of repolarization, manifested by the alteration of the T wave – changes in the amplitude and polarity of the T wave from the complex to the complex, which is a predictor of the appearance of life–threatening arrhythmias ($p<0.05$).

Table 6: Dynamics of the parameters of the electrocardiogram in patients with a permanent form of AF in the process of treatment with a mebicar

Groups of patients	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Indicator dynamics	Before treatment	After treatment	Before treatment	After treatment
R-R	0.83±0.09	0.49±0.09 p<0.05	0.65 ±0.06	0.44±0.07 p<0.01
QRS – D_I	0.15±0.06	0.06±0.001 p<0.05	0.09±0.00	0.08±0.00 p>0.05
QRS – D_{III}	0.13±0.06	0.09±0.01 p>0.05	0.10±0.01	0.05±0.001 p<0.001
QRS – D_{aVF}	0.07±0.004	0.08±0,004 p<0.05	0.09±0.01	0.08±0.00 p<0.05
Сегмент ST	15.5±0.59	11.88±0.63 p<0.001	13.40±0.63	13.20±0.38 p<0.05
ST V_1	13.63±1.00	10.06±0.68 p<0.01	13.00±0.89	12.40±0.57 p>0.05
ST V_6	14.94±0.54	15.19±0.85 p>0.05	13.53±0.63	10.20±0.04 p<0.001
RS-T V5	16.81±0.81	16.75±0.90 p>0.05	16.00±0.73	14.02±0.29 p<0.001
RS-T I	16.31±0.67	13.31±0.84 p< 0.01	14.07±0.66	11.93±0.70 p<0.05
$T_{(-/+)}$ I	0.81±0.27	0.39±0.27 p<0.05	0.67±0.27	0.53±0.45 p>0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

As we can see, the activity of catalase was increased in two groups of patients (15.21 ± 1.29 and 8.74 ± 1.91 mg H2O2 /1 ml of blood) ($p < 0.001$) and (17.67 ± 1.50 and 11.11 ± 2.08 mg H2O2/1ml of blood) compared with the norm ($9.52 - -12.92$ mg H2O2/1ml of blood). When comparing serum superoxide dismutase data, the indicator is statistically higher ($p < 0.05$) and is ($49.87 \pm 1.59\%$) and ($37.80 \pm 5.37\%$), indicating inhibition of the activity of antioxidant enzymes. After our treatment, the activity of catalase and superoxide dismutase decreased in the study group, with a significant difference. We found high levels of glutathione peroxidase activity in patients receiving anxiolytic therapy, with an average of 0.19 ± 0.02 mmol / min / mg. Taking into account the data of the spectrophotometric method and the titration method, it should be noted that the higher the anxiety–depressive symptoms, the higher the rates of free radical oxidation are.

Analysing the levels of cortisol (Table 6), we observed an increase, depending on the level of anxiety–depressive symptoms and stress susceptibility. In patients 1b, this figure is $20.18 \pm 3.79 \mu g/dl$ and $11.99 \pm 1.12 \mu g/dl (p < 0.05)$, which indicates an increased degree of psycho–emotional stress. Thus, we see that the higher the level of psychological stress, the greater the rate of total cortisol in the blood serum is.

Table 7: Dynamics of indicators of activity of catalase, glutathione peroxidase (GP), superoxide dismutase (SOD) of blood serum in patients with permanent form of AF in the course of treatment with mebicar

Indexes	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Indicator dynamics	Before treatment	After treatment	Before treatment	After treatment
Catalase, mg H_2O_2 / 1ml of blood	15.21±1.29	8.74±1.91 p<0.001	17.67±1.50	11.11±2.08 p<0.05
SOD, %	34.81±4.03	27.13±6.04 p>005	49.87±1.59	37.80±5.37 p<0.05
GP, mlmol, min / mg	0.15± 0.02	0.15±0.04 p>0.05	0.19±0.02	0.16±0.03 p>0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

Table 8: Dynamics of serum cortisol index in patients with permanent form of AF in the process of treatment with mebicar

Indexes	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Indicator dynamics	Before treatment	After treatment	Before treatment	After treatment
Cortisol, µg / dL	11.71±1.53	10.59±2.00 p>0.05	20.18±3.79	11.99±1.12 p<0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

As shown by ELISA, the tendency to increase NT–proBNP is also evident. The higher the level of stress, anxiety and depression, the higher the rate is. In patients with high levels of anxiety–depressive symptoms, it was found to be $46.44 \pm 25.18 ng/ml$ and $85.90 \pm 44.84 ng/ml$, which explains the worsening course of this pathology.It is necessary to take into account that there is a significant sensitivity of NT–proBNP when the concentration not exceeding $20 ng/ml$ occurs.

Table 9: Dynamics of the indicator of natriuretic peptide (BNP) and the N–terminal fragment of the precursor of the brain natriuretic peptide in serum (NT–proBNP) in patients with a permanent form of AF in the course of treatment with a mebicar

Indexes	Permanent form of AF (n=16) 1a group		Permanent form of AF with mebicar (n=15) 1b group	
Indicator dynamics	Before treatment	After treatment	Before treatment	After treatment
Natriuretic peptide (BNP) and N-terminal fragment of serum sodium natriuretic peptide precursor (NT-proBNP), ng /ml.	21.58±1.58	56.55±3.50 p>0.05	46.44±25.18	85.90±44.84 p>0.05

Note: p- the reliability of the difference between the indicators before and after treatment;

Conclusion

1. Analysis of the clinico–psychopathological method of the study confirmed the signs of astheno–vegetative syndrome and clinically expressed anxiety and depression.
2. The value of SOD also depends on the level of anxiety–depressive symptoms in patients.
3. The level of cortisol has shown that the higher the anxiety and the level of depression, the higher the given indicator is.
4. Analyzing NT–proBNP data, we observed anincrease depending on the psycho–emotional state.

The prospect of further research is the study of the relationship of psycho–emotional states on the development of paroxysm atrial fibrillation.

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