



FEATURES OF HEART FAILURE IN PATIENTS WITH THYROTOXICOSIS

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ABSTRACT

Hyperfunction of the thyroid gland (thyroid gland) – thyrotoxicosis – is a widespread condition associated with an increase in the level of free thyroxine (fT₄) and/or free triiodothyronine (fT₃) with well-known clinical symptoms. In countries without iodine deficiency, it is detected in 0.5–3.9% of the population, while in older age groups, the frequency of occurrence is given the state reaches 11.8%. In regions with iodine deficiency, including in Russia, the incidence is even higher. Most often thyrotoxicosis develops in patients with diffuse toxic goiter (DTZ), multi-node toxic goiter and toxic thyroid adenoma. Bolshin the majority of such patients are elderly and senile, which both complicates clinical diagnosis and leads to more severe consequences. Thyrotoxicosis in them can manifest itself only by nonspecific symptoms: loss of body weight, arrhythmias, sometimes apathy, and be masked associated with symptoms of other diseases – atherosclerosis, arterial hypertension (AH), diabetes mellitus, chronic heart failure (CHF), etc.. On the contrary, young patients may remain able to work for a long time and not consult a doctor until the development of significant cardiovascular pathology.

Keywords: chronic heart failure, coronary heart disease, thyrotoxicosis, vegetative imbalance, threshold level NT-proBNP, left ventricular remodeling.

INTRODUCTION

The main adverse effect of thyrotoxicosis has on the cardiovascular system. The developing changes are reversible in most cases with adequate treatment. Nevertheless, long-term studies of both overt and subclinical forms of thyrotoxicosis have revealed an increase in cardiovascular mortality. According to the data of the Framingham study, in 2007 people with an initial sinus rhythm aged 60 years and older during the 10-year follow-up period, a decrease in the level of thyroid hormone (TSH) was accompanied by a 3-fold increase in the volume of the frequency of atrial fibrillation (AF). A retrospective study that included 7209 patients with thyrotoxicosis, revealed an increase in mortality from cardiovascular and cerebrovascular causes, and both in successfully treated patients with obvious thyrotoxicosis in the anamnesis, and in patients with subclinical hyperthyroidism





not associated with taking levo thyroxine sodium preparations. A recent study showed, that an increase in the level of fT₃ in the blood serum increases the probability of cardiovascular complications by 2.6 times. Prevalence of thromboembolic complications of AF in patients with thyrotoxicosis, it reaches 15%. AF is an independent predictor of the development of ischemic stroke, while its frequency in AF exceeds that in patients with thyrotoxicosis with sinus rhythm. Chronic heart failure is a clinical syndrome in some diseases, accompanied by characteristic symptoms (shortness of breath, decreased physical activity, fatigue, edema, etc.) associated with inadequate perfusion of organs and tissues at rest or during exercise, accompanied by fluid retention in the body and its accumulation in soft tissues. The main causes of CHF include: arterial hypertension (95.5%), coronary heart disease (69.7%), myocardial infarction (15.3%), diabetes mellitus (15.9%). The combination of coronary heart disease and arterial hypertension occurs in most patients with CHF. COPD (chronic obstructive pulmonary disease) accounts for 13% of all causes of CHF, chronic and paroxysmal atrial fibrillation – 12.8%, acute cerebral circulation disorder – 10.3%. Ischemic heart disease is a myocardial lesion caused by a disorder of the coronary circulation, resulting from a violation of the balance between the coronary blood flow and the metabolic needs of the heart muscle. In other words, the myocardium needs more oxygen than it receives from the blood. Coronary heart disease can occur acutely (in the form of myocardial infarction), as well as chronically (periodic attacks of angina pectoris). Thyrotoxicosis is a syndrome caused by hyperfunction of the thyroid gland, manifested by an increase in the content of hormones: triiodothyronine (T₃), thyroxine (T₄). Depending on the level of occurrence of the disorder, the following types of hyperthyroidism are distinguished: primary – thyroid gland, secondary – pituitary gland, tertiary – hypothalamus. The prevalence of chronic heart failure (CHF) in Uzbekistan is 7-10%, and in recent years the number of patients with preserved and intermediate left ventricular ejection fraction (LVEF) has been increasing. In this regard, in modern recommendations for the diagnosis and treatment of CHF, in addition to assessing clinical symptoms and signs, performing echocardiographic examination (EchoCG), much attention is paid to determining the concentration of natriuretic peptides (NPS). At the same time, the results of a number of studies indicate that, that with increased secretion of thyroid hormones, there is also an increase in the concentration of sodium - uretic peptides (NPS). According to the data available in the available literature, there is no consensus whether the level of NUP increases in response to structural and functional changes in the myocardium with thyroid hyperfunction, or thyroid hormones have a direct stimulating effect on the secretion of NUP. The frequency of occurrence of





thyrotoxicosis and cardiovascular diseases (CVD) in elderly patients determines the need to study the features of the diagnosis of ser - heart failure in polymorbid patients with hyperthyroidism.

The aim of the study was to evaluate the diagnostic significance of the criteria of CHF and to study the features of structural and functional remodeling of the left heart in patients with coronary heart disease (CHD) and thyrotoxicosis.

MATERIALS AND METHODS

The open comparative clinical study included 69 patients (mean age 58.3 ± 5.6 years), who were divided into 4 groups: the main group consisted of 16 patients with thyrotoxicosis, coronary heart disease and CHF of functional class II-III (FC) and 3 comparison groups (group 1 – 18 patients with coronary heart disease and CHF II-III FC, without thyroid pathology; Group 2 – 18 patients with thyrotoxicosis without CVD; Group 3 – 17 patients with thyrotoxicosis and coronary heart disease, without clinical symptoms and signs of CHF). The control group consisted of 8 people without signs of CVD and thyroid pathology. Clinical The characteristics of patients are presented in Table 1.

The 2nd, 3rd and main groups included patients with manifest thyrotoxicosis on the background of diffuse toxic goiter or nodular/multinodular goiter with functional autonomy. All patients with coronary heart disease had II-III FC of angina pectoris. Diagnosis and treatment of coronary heart disease, CHF and thyrotoxicosis were carried out in accordance with modern recommendations.

To assess the clinical symptoms and signs of CHF, a clinical condition assessment scale (SHOCK) was used, exercise tolerance was assessed according to the 6-minute walk test (6MTH). The concentration of NT-proBNP in blood serum was determined using reagents (Biomedica, Austria) on the automatic enzyme immunoassay MAX. Holter ECG monitoring (XM ECG) was performed using a wearable eight-channel cardiomonitor "Cardiotechnika-08", echocardiographic examination (EchoCG). They were carried out on the MyLab 70 ultrasound machine in B and M modes, pulse-wave Doppler mode.

All studies were performed prior to the appointment of thyrostatic therapy. Exclusion criteria from the study: hemodynamically significant heart defects; myocardial infarction or acute cerebrovascular accident <6 months old; unstable angina; severe pathology of the liver, kidneys; presence of an artificial pacemaker; inflammatory and infectious diseases; malignant neoplasms; other thyroid diseases, including iatrogenic thyrotoxicosis.

The study was performed in accordance with the standards of good clinical practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The protocol





of the study was approved by the local independent ethics committee, all patients signed an informed consent to participate in the study.

Statistical processing was carried out using the Statistica 10.0 program (StatSoft, USA). It was determined with a normal distribution of quantitative features – the mean and standard deviation ($M \pm SD$), with an abnormal distribution – median and quartiles ($Me [LQ; UQ]$). The normality test was carried out using the Kolmogorov Smirnov criterion. Qualitative variables were described by absolute (n) and relative values (%), compared by Pearson's chi-square criterion. Reliability of differences in independent values The difference between several groups was determined by the Kraskell-Wallis criterion, taking into account the number of groups, $p < 0.0085$ was considered reliable. Pairwise comparison of groups was performed using the nonparametric Mann-Whitney criterion. Correlation analysis was carried out using Spearman's method. The new threshold value of NT-proBNP was calculated using ROC analysis. Differences in values in pairwise comparison, as well as correlations, were recognized as reliable at a significance level of $p < 0.05$.

RESULTS

Assessment of clinical symptoms of CHF on a scale SHOCK did not reveal significant differences between patients of the main and 1 comparison group (with coronary heart disease and CHF without thyroid hyperfunction), however, exercise tolerance in the patients of the main group was significantly lower - by 15.4% ($p = 0.01$).

Analysis of the results of the XM ECG showed that patients of the main group more often than patients of group 1 revealed cardiac arrhythmias (LDC): atrial fibrillation (32% vs 20%, $p = 0.01$), sinus tachycardia (36% vs 22%, $p = 0.01$), supraventricular extrasystole (31% vs 18%, respectively, $p = 0.01$).

The highest heart rate (HR) per day was observed in group 2 patients: 43.2% higher than in patients of the main group ($p = 0.0002$), 60.7% higher than in group 1 patients ($p = 0.0001$) (Table 2). The patients of the main group showed the lowest value of the median circadian index (CI), the absence of a significant decrease in heart rate at night. Assessing the parameters of heart rate variability (HRV), the patients of the main group revealed the lowest values of time indicators – SDNN, rMSSD, pNN50 ($p < 0.05$), the lowest value of the total power of the spectrum – TP ($p < 0.05$), especially due to a decrease in HF ($p < 0.05$), and the highest LF/HF ratio compared to the result in comparison groups 1, 2 and 3 ($p < 0.05$), which indicates a decrease in the activity of the parasympathetic link and hyperactivation of the sympathetic link of the autonomic nervous system (ANS).





In the patients of the main group, reliable correlations were established: between the level of T4 and the HF indicator characterizing a decrease in parasympathetic activity against the background of concomitant thyrotoxicosis ($r=-0.41$, $p=0.045$); between the level of NT-proBNP and SHOCK data ($r=0.39$; $p=0.001$) and 6MTH ($r=-0.45$; $p=0.001$).

Analysis of EchoCG parameters revealed significantly lower values of linear and volumetric LV parameters in patients of the main group.

Thus, in patients with coronary heart disease, CHF and thyrotoxicosis compared with the results of patients with coronary heart disease and CHF without thyroid hyperfunction index The final diastolic LV size (ICDR) was less by 10.9% ($p=0.03$), the indices of the final systolic (ICSO) and diastolic (ICDO) LV volumes were less by 15.03% ($p=0.01$) and 5.92% ($p=0.03$), respectively. It should be noted that two types of LV remodeling were identified in patients with CHF (main and comparison group 1): concentric (KGLJ) and eccentric (EGLJ) LV hypertrophy, and KGLJ was significantly more often determined in the main group (84% vs 70%, $p=0.03$), and EGLJ – in 1 comparison group (16% vs 30%, $p=0.01$). Analysis of the parameters of transmittal blood flow showed that in group 2 patients, normal LV diastolic function was determined in 90% of cases, and LV diastolic dysfunction (LVD) was determined in 10% of cases Type I (relaxation slowdown). In patients of group 3, type I LDL occurred in 65.4% of cases. In the main group, in 100% of cases, type I DL was determined. In group 1, type I DL was found in 86.7% of cases, type II DL (pseudonormalization) – in 10% of cases, type III DL type (restrictive relaxation) – in 3.3% of cases.

The highest LVEF index was determined in patients of the 2nd comparison group. It is important to note that in patients of the main and group 1, the LV LV values did not significantly differ ($p=0.1$) and corresponded to the intermediate type of CHF, which indicates the need to determine NT-proBNP for the diagnosis of HF in polymorbid patients with concomitant thyroid hyperfunction.

A comparative analysis of the concentration of NT-proBNP revealed an increased level of the indicator (>125 pg/ml, according to current recommendations) in all studied groups of patients, including those with thyrotoxicosis without CVD. The level of NT-proBNP in patients with coronary heart disease and thyrotoxicosis without CHF exceeded the threshold value by 2.8 times ($p=0.001$), in patients with thyrotoxicosis without CVD - by 2.04 times ($p=0.001$). There were no significant differences between the values of NT-proBNP in comparison groups 1 and 3 ($p=0.88$), and the highest level of NT-proBNP was determined in polymorbid patients with coronary heart



disease, CHF and thyrotoxicosis – 2.2 times higher than in patients with coronary heart disease and CHF without hyperthyroidism ($p=0.0001$).

During further observation, against the background of therapy with the inclusion of thyrostatics and the achievement of persistent euthyroidism, significant correlations were revealed between the dynamics of TSH concentration and NT proBNP ($r=-0.53$; $p=0.000$), sv.T4 and NT-proBNP ($r=0.43$; $p=0.001$), sv.T3 and NT-proBNP ($r=0.35$; $p=0.01$).

The data obtained allowed us to judge the low diagnostic significance of the recommended level of NUP for the detection of CHF with preserved and intermediate LV LV in hyperfunction conditions. They prompted a revision of the threshold value for this category of patients.

With the help of ROC analysis, based on the determination of the maximum sum of the values of diagnostic sensitivity and specificity (DH+DS), the cut-off threshold was determined, which was 556.4 pg/ml. Thus, according to our data, in patients with thyrotoxicosis and coronary heart disease at the level of NT proBNP >556.4 pg/ml, a decision is made in favor of the presence of CHF with 72% DC, 100% DC, 87.2% diagnostic accuracy ($p<0.001$), while the values of NT proBNP <556.4 pg/ml do not allow to confirm the presence of CHF using this criterion. Area under The ROC curve was 0.942 ± 0.0298 ($p<0.001$), which indicates the excellent quality of the model, and the resulting indicator can be recommended for use in clinical practice.

RESEARCH RESULTS AND THEIR DISCUSSION

The obtained results allowed us to identify the features of the clinical picture in patients with CHF of ischemic genesis in combination with hyperthyroidism. Lower exercise tolerance and more frequent occurrence of cardiac arrhythmias in this category of patients are obviously due to the additional effect of thyroid hormones on the cardiovascular system.

When evaluating the results of spectral and temporal analysis of HRV indicators in patients with coronary heart disease, CHF and thyrotoxicosis revealed a more pronounced predominance of the sympathetic link of the ANS in the regulation of heart rhythm compared with those in patients with coronary heart disease and CHF without thyroid hyperfunction, which indicates an increase in vegetative imbalance with the development of concomitant thyrotoxicosis. The hyperactivation of the sympathetic link of the ANS can also be judged by the features of the daily heart rate profile in patients of the main group: higher values of the maximum daily and the maximum daily heart rate, as well as the absence of a significant decrease in heart rate at night, which is a sign of daily desynchronization.





The influence of thyroid hormones on the structural and functional parameters of the heart in hyperthyroidism is described in sufficient detail in the literature, however, the study of the features of heart remodeling in polymorbid patients with thyrotoxicosis remains relevant. In this study, the features of structural and functional remodeling of the left heart in the presence of concomitant thyrotoxicosis in patients with CHF of ischemic genesis were determined: significantly lower values of indexed linear and volumetric LV parameters, the development of LVL type I in 100% of cases, a more frequent occurrence of LVH compared with the indicators in patients with CHF without thyroid pathology, due to the influence of an excess of thyroid hormones and, above all, hyperactivation of the sympathetic link of the ANS.

Elevated levels of NT-proBNP (>125 pg/ml) were detected both in patients with CHF and in all patients with thyrotoxicosis, regardless of the presence of CVD, which is consistent with the results of previously published studies indicating a stimulating effect of excess thyroid hormones on the secretion of NUP.

Comparative analysis of NT-proBNP results He showed the absence of a significant difference between the indicators in patients with coronary heart disease and CHF without hyperthyroidism and in patients with coronary heart disease and thyrotoxicosis without clinical manifestations of CHF, which allows us to think about a comparable contribution to the increase in the level of NUP as LV remodeling in CHF and hypersecretion of thyroid hormones. The revealed highest level of NT-proBNP in polymorbid patients with coronary heart disease, CHF and thyrotoxicosis, apparently reflects the combined effect of LV morpho-functional changes on the secretion of NUP and hyperfunction of the thyroid gland.

The obtained reliable correlations between the dynamics of TSH and thyroid hormones and the concentration of NT-proBNP against the background of therapy with the inclusion of thyrostatics in patients of the main group indicate the stimulating effect of thyroid hyperfunction on the secretion of NUP. In addition, the revealed correlations between the value of NT-proBNP and the indicators of SHOCK and 6MTH, as well as the absence of significant differences when comparing the clinical manifestations of CHF in patients of the main group and comparison group 1, suggest that the higher level of NTproBNP in patients with ischemic CHF and thyrotoxicosis is due precisely to the influence of increased concentrations of thyroid hormones.

It is important to note that for the diagnosis of CHF with preserved and intermediate LV LV in patients with coronary heart disease and thyrotoxicosis, it is necessary to use a higher threshold level of NT-proBNP, according to this study — 556.4 pg/ml. Determination of the NT proBNP value of the above in polymorbid patients with a





combination of CVD and thyroid hyperfunction will make it possible to diagnose CH (PM 72%, DS 100%). However, the results of NT proBNP below the calculated threshold level do not allow us to confirm the development of CHF using this criterion, but do not exclude its presence. Apparently, in such cases, a more thorough assessment of clinical symptoms and signs, as well as structural and functional parameters of LV, taking into account the features of remodeling in conditions of polymorbidity, is necessary.

CONCLUSION

It is important to note that for the diagnosis of CHF with preserved and intermediate LV LV in patients with coronary heart disease and thyrotoxicosis, it is necessary to use a higher threshold level of NT-proBNP, according to this study – 556.4 pg/ml. Determination of the NT proBNP value of the above in polymorbid patients with a combination of CVD and thyroid hyperfunction will make it possible to diagnose CH (PM 72%, DS 100%). However, the results of NT proBNP below the calculated threshold level do not allow us to confirm the development of CHF using this criterion, but do not exclude its presence. Apparently, in such cases, a more thorough assessment of clinical symptoms and signs, as well as structural and functional parameters of LV, taking into account the features of remodeling in conditions of polymorbidity, is necessary.

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