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## КОМОРБИДНОСТЬ ТИРЕОТОКСИКОЗА С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

**For citation:** M. A. Khusainova, M.S. Bekmuradova, M.T.Ergasheva, D.Dj.Kamolova/COMORBIDITY THYROTOXICOSIS WITH CORONARY HEART DISEASE. Journal of cardiorespiratory research. 2023, vol 1.1, issue 47, pp.230-237.

### АННОТАЦИЯ

Цель: оценить влияние тиреостатиков на клинические симптомы, частоту сердечных аритмий и морфофункциональные показатели левого сердца у пациентов с сочетанием тиреотоксикоза и ишемической сердечной недостаточности. Материалы и методы: в исследовании принял участие 51 пациент. I группа — пациенты с ХСН II–III функционального класса (ФК) на фоне ишемической болезни сердца и сопутствующего тиреотоксикоза (n=24), средний возраст — 58,6±4,6 года; II группа — пациенты с манифестным тиреотоксикозом без сердечно-сосудистой патологии (n=27), средний возраст — 46,7±4,1 года. При включении в исследование и после 6 месяцев терапии с добавлением тиреостатиков оценивали клиническое состояние пациентов и физическую активность, проводили ежедневный мониторинг электрокардиограммы и эхокардиографическое исследование (ЭхоКГ). Результаты: после 6 месяцев комбинированной терапии с включением тиреостатиков на фоне достигнутого стойкого медикаментозно-индуцированного эутиреоза у коморбидных пациентов (I группа) повысилась толерантность к физическим нагрузкам (p <0,001), уменьшилась выраженность клинических симптомов ХСН, достоверно снизилась частота сердечных аритмий (p <0,05). Анализ динамики результатов ЭхоКГ у пациентов I группы выявил достоверное увеличение индекса ударного выброса (p=0,04), фракции выброса левого желудочка (p=0,01), ударного объема (p=0,03), снижение величины напряжения миокарда (p=0,02) и параметров характеризующий трансмитральный кровоток (E/A, p <0,05), который позволил нам судить об улучшении систолической и диастолической функции левого желудочка (ЛЖ) в условиях медикаментозной компенсации тиреотоксикоза. Заключение: включение тиреостатиков в комбинированную терапию и нормализация функции щитовидной железы способствовали уменьшению клинических симптомов сердечной недостаточности, частоты нарушений сердечного ритма, улучшению систолической и диастолической функции ЛЖ у коморбидных пациентов с ишемической ХСН и сопутствующим тиреотоксикозом.

**Ключевые слова:** ишемическая болезнь сердца; хроническая сердечная недостаточность; тиреотоксикоз

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## COMORBIDITY THYROTOXICOSIS WITH CORONARY HEART DISEASE

### ANNOTATION

Objective: to evaluate the effect of thyrostatics on clinical symptoms, the frequency of cardiac arrhythmias and morpho-functional parameters of the left heart in patients with a combination of thyrotoxicosis and ischemic heart failure. Materials and methods: 51 patients participated in the study. Group I — patients with CHF of functional class II–III (FC) on the background of coronary heart disease and concomitant thyrotoxicosis (n=24), average age — 58.6±4.6 years; group II — patients with manifest thyrotoxicosis without cardiovascular pathology (n=27), average age — 46.7±4.1 years. When included in the study and after 6 months of therapy with the addition of thyrostatics, the clinical condition of patients and physical activity were evaluated, daily monitoring of an electrocardiogram and an echocardiographic study (EchoCG) were performed. Results: after 6 months of combined therapy with the inclusion of thyrostatics against the background of achieved persistent drug-induced euthyroidism in comorbid patients (group I), tolerance to physical exertion increased ( $p < 0.001$ ), the severity of clinical symptoms of CHF decreased, the frequency of cardiac arrhythmias significantly decreased ( $p < 0.05$ ). The analysis of the dynamics of EchoCG results in group I patients revealed a significant increase in the shock ejection index ( $p=0.04$ ), left ventricular ejection fraction ( $p=0.01$ ), shock volume ( $p=0.03$ ), a decrease in the value of myocardial stress ( $p=0.02$ ) and parameters characterizing the trans-mitral flow (E/A,  $p < 0.05$ ), which allowed us to judge the improvement of systolic and diastolic function of the left ventricle (LV) in the conditions of drug compensation for thyrotoxicosis. Conclusion: the inclusion of thyrostatics in the combination therapy and normalization of thyroid function contributed to the reduction of clinical symptoms of heart failure, the frequency of heart rhythm disturbances, improvement of systolic and diastolic LV function in comorbid patients with ischemic CHF and concomitant thyrotoxicosis.

**Key words:** coronary heart disease; chronic heart failure; thyrotoxicosis

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## TIREOTOKSIKOZNI YURAK ISHEMIK KASALLIGI BILAN KOMORBIDLIGI

### ANNOTATSIYA

**Maqsad:** tirotoksikoz va yurak ishemik kasalligi komorbid kechgan bemorlarda tirostatiklarning klinik simptomlarga, yurak aritmiyalarining chastotasiga va yurakning morfo-funksional parametrlariga ta'sirini baholash. Materiallar va usullar: tadqiqotda 51 nafar bemor ishtirok etdi. I guruh – yurak yetishmovchiligi bilan birga keladigan tireotoksikoz (n=24) fonida yurak ishemik kasalligi funksional sinf II–III bilan og'riqan bemorlar, o'rtacha yoshi-58,6 ±4,6 yosh; II guruh-yurak-qon tomir patologiyasi bo'lmagan manifest tirotoksikoz bilan og'riqan bemorlar (n=27), o'rtacha yoshi — 46,7±4,1 yil. Tadqiqotga kiritilganda va tirostatiklar qo'shilgan 6 oylik terapiyadan so'ng bemorlarning klinik holati va jismoniy faolligi baholandi, elektrokardiogrammaning kunlik monitoringi va exokardiografik tadqiqot (ExoKG) o'tkazildi. Natijalar: komorbid bemorlarda erishilgan doimiy dori-darmonli eutireoz fonida tirostatiklarni kiritish bilan 6 oylik kombinatsiyalangan terapiyadan so'ng (I guruh), jismoniy zo'riqishlarga chidamlilik oshdi ( $p < 0.001$ ), yurak yetishmovchiligi klinik belgilarining og'irligi kamaydi, yurak aritmiyalarining chastotasi sezilarli darajada kamaydi ( $p < 0.05$ ). I guruh bemorlarida ExoKG natijalari dinamikasini tahlil qilish natijasida zarba chiqarish indeksi ( $p=0,04$ ), chap qorincha qon otish hajmi ( $p=0,01$ ), zarb

hajmi ( $p=0,03$ ), miokard stress qiymatining pasayishi ( $p=0,02$ ) va parametrlar sezilarli darajada oshdi bizga tirotoksikoz uchun dori kompensatsiya sharoitida sistolik va chap qorincha (LV) diastolik funktsiyasi takomillashtirish uchun qilish uchun ruxsat trans-mitral oqimini (E/a,  $p < 0,05$ ), tavsiflovchi. Xulosa: tirostatiklarni kombinatsiyalangan terapiyaga kiritish va qalqonsimon bez funktsiyasini normallashtirish yurak yetishmovchiligining klinik belgilarini kamaytirishga, yurak ritmining buzilishining chastotasiga, ishemik SYuYe va birgalikda tirotoksikoz bilan og'riqan bemorlarda sistolik va diastolic ChQ funktsiyasini yaxshilashga yordam berdi.

**Kalit so'zlar:** koronar arteriya kasalligi; surunkali yurak yetishmovchiligi; tirotoksikoz

**Introduction.** Hyperfunction of the thyroid gland, as is known, has a significant effect on the activity of the cardiovascular system (CVS). Patients with thyrotoxicosis and pre-existing cardiovascular pathology deserve special attention, since this combination often leads to the progression of pathological remodeling of the heart, increases the risk of heart rhythm disturbances (LDC) and decompensation of chronic cardiac insufficiency-sufficiency (CHF). According to the literature, the opinion of researchers remains ambiguous about the possibility of regression of changes in the cardiovascular system when euthyroidism is achieved. In a number of studies, it has been proved that changes in the cardiovascular system in patients with thyrotoxicosis can be reversible against the background of timely prescribed adequate therapy and the achievement of persistent euthyroidism. However, the question of the contribution of timely thyrostatic therapy to the treatment of CHF in comorbid patients with coronary heart disease (CHD) and thyrotoxicosis remains insufficiently studied.

The aim of the study was to evaluate the effect of thyrostatics on clinical symptoms, the frequency of cardiac arrhythmias and morpho—functional parameters of the left heart in patients with a combination of thyrotoxicosis and ischemic heart failure.

**Materials and methods.** 51 patients were included in a comparative clinical study: patients with coronary heart disease and CHF of functional class II-III (FC) and concomitant thyrotoxicosis were group I ( $n=24$ , average age —  $58.6 \pm 4.6$  years), patients with manifest thyrotoxicosis without cardiovascular diseases (CVD) - group II ( $n=27$ , the average age is  $46.7 \pm 4.1$  years). Patients with coronary heart disease had angina pectoris of tension II–III FC. The cause of thyrotoxicosis syndrome in all the studied patients was diffuse toxic goiter or nodular/multi-nodular goiter with functional autonomy. The levels of thyroid-stimulating hormone (TSH), free thyroxine (sv.T4) and free triiodothyronine (sv.T3) in both groups did not significantly differ ( $p < 0.05$ ). 93.8% of group II patients had arterial hypertension (AH). In group I of patients, symptomatic hypertension of endocrine genesis occurred in 72% of cases. All patients with coronary heart disease and CHF had already received therapy in accordance with current recommendations before being included in the study. To assess the severity of clinical symptoms and signs of CHF, a clinical condition assessment scale (SHOCK) was used, and a 6-minute walk test (6MTH) was used to determine exercise tolerance. The concentration of thyroid-stimulating hormone and thyroid hormones (sv.T3, sv.T4), the level of antibodies to thyroperoxidase (At-TPO) and antibodies to TSH receptors (At-RTG) were determined by radioimmunological method. Holter ECG monitoring (XM ECG) was performed on an eight-channel cardiomonitor "Cardiotechnika-04" (Incant CJSC, St. Petersburg), echocardiographic examination (EchoCG) was performed on an ultrasound machine MyLab70 (Esaote, Italy) in B and M

modes, pulse-wave Doppler mode. Patients of both groups with thyrotoxicosis received thiamazole, the starting dose was 30-40 mg / day, then e` titrated to 10-15 mg / day. All studies were performed twice — before the appointment of thyrostatics and after 6 months of therapy.

The study did not include patients who had suffered a myocardial infarction or acute cerebrovascular accident less than 6 months ago; with unstable angina; with severe pathology of the liver, kidneys; other thyroid diseases, drug-induced thyrotoxicosis; patients with implants- with an artificial rhythm driver; suffering from inflammatory and/or infectious diseases; malignant neoplasms. The study was carried out in accordance with the principles of the Helsinki Declaration and with the standards of Good Clinical Practice. Protocol approved by the local independent ethics committee. Informed consent for voluntary participation in the study is signed by all patients. Statistical data processing performed by- I was in the Statistica 10.0 program (StatSoft, USA). If the signs corresponded to the normal distribution law, the mean and standard deviation ( $M \pm SD$ ) were determined, and if there was a discrepancy, the median and quartiles ( $Me [LQ; UQ]$ ) were calculated. The normality test was performed according to the Kolmogorov-Smirnov criterion. Qualitative variables were described by absolute ( $n$ ) and relative values (%), compared by Pearson's chi-squared criterion ( $\chi^2$ ). Comparison of indicators in groups was performed using the Mann-Whitney criterion, differences in indicators before and after treatment were performed using the paired Wilcoxon criterion. The level of reliability of the differences was considered  $p < 0.05$ .

**Results.** It should be noted that thyrostatic therapy for 6 months allowed to achieve persistent euthyroidism in all patients included in the study. A comparative analysis of the results of daily ECG monitoring showed significant positive dynamics in the form of a decrease in heart rate (HR) at all time intervals in patients of both groups with thyroid hyperfunction. However, in patients with thyrotoxicosis without CVD, the dynamics was more pronounced ( $p < 0.05$ ) than in patients with comorbid pathology (Fig. 1). It should be borne in mind that patients with coronary heart disease and CHF were taking beta-blockers even before being included in the study, and therefore they had lower initial heart rate values. Probably, this can explain the lower degree of heart rate reduction in this group of patients. In addition, after 6 months of thiamazole therapy, a decrease in the frequency of cardiac arrhythmias was noted in patients with both- their groups.

In group II patients (with thyrotoxicosis without CVD), after 6 months of treatment, the number of supraventricular (from 23% to 5% of cases,  $p=0.001$ ) and ventricular extrasystoles (from 18% to 2% of cases,  $p=0.001$ ) significantly decreased and episodes of atrial fibrillation (from 14% to 0% of cases,  $p=0.001$ ).

Table 1

EchoCG results in patients with thyrotoxicosis without CVD

Indicators	Initially	After 6 months	The value of p
ICDO LV, ml/m	261,51 [56,01; 64,75]	54,19 [52,68; 54,98]	0,01
IMMLJ, g/m	2104,81 [87,62; 119,12]	76,17 [74,47; 79,96]	0,001
TMJP LV, mm	10,72 [10,03; 11,12]	9,20 [8,91; 9,47]	0,02
IOTS LJ	0,41 [0,38; 0,42]	0,40 [0,36; 0,41]	0,71
UO, ml	75,60 [74,18; 78,69]	61,75 [61,52; 63,25]	0,01
PUV, ml/g	0,39 [0,37; 0,41]	0,42 [0,42; 0,43]	0,04
MTS, g/cm	2158,19 [154,12; 162,45]	141,11 [139,36; 145,05]	0,01
FW, %	67,0 [60,0; 70,0]	60,9 [59,8; 61,7]	0,08
E/A lv	1.21±0.01	1.24±0.02	0.2

**Abbreviations:** ICDO — index of the final diastolic LV volume; IMLJ — LV myocardial mass index; TMJP — thickness of the interventricular septum; LV IOTS — index of the relative thickness of the LV wall; UO — shock volume; PUV — shock ejection index; MS — myocardial stress; PV — LV ejection fraction; E/A — velocity ratio early to late diastolic filling rate (characteristic of transmittal flow).

The dynamics of the incidence of LDC in group I patients (with thyrotoxicosis and comorbid pathology) is shown in Fig. 2. It should also be noted that in group I patients (with comorbid pathology), the addition of the introduction of thyrostatics to standard therapy of coronary heart disease and CHF led to a statistically significant decrease in clinical manifestations of CHF (the average score for SHOCK decreased from 7.08 to 6.06 — by 15.3%,  $p < 0.001$ ) and increased exercise tolerance (the distance during the 6-minute walk test increased from 254 m to 297 m — by 18.2%,  $p < 0.001$ ). A comparative assessment of EchoCG parameters after 6 months of combined therapy with the inclusion of thyrostatics also revealed a statistically significant positive dynamics of the parameters of the left ventricle in patients of both groups. In patients with thyrotoxicosis without CVD, the final diastolic volume (BWW) significantly decreased by 11% ( $p=0.01$ ) and, accordingly, the index of the final- the total diastolic volume (ICDO) — by 12% ( $p=0.01$ ), the thickness of the ventricular septum (LV TMJ) — by 14.2% ( $p=0.04$ ), the LV myocardial mass index (LVMI) — by 27.3% ( $p=0.001$ ). In this group of patients, the indicators of myocardial stress (MS) also statistically significantly decreased by 11% ( $p=0.01$ ), the shock volume (UO) — 18.3% ( $p=0.01$ ), the shock ejection index (PUV) increased by 8% ( $p=0.04$ ) (Table 1). The analysis of the results of EchoCG in patients with a combination of thyrotoxicosis and CHF of ischemic genesis also revealed a statistically significant increase in the indicators of PUV, UO and a decrease in the value of MS. It is especially important to note an increase in the LV ejection fraction (LV) in this group of comorbid patients, which characterizes an improvement in the functional activity of

the myocardium in the conditions of the achieved euthyroid state (Fig. 3). In addition, in group I of patients (with thyrotoxicosis, coronary heart disease and CHF), there is an improvement in LV diastolic function: an increase in E/A by 13% ( $p=0.03$ ) and a decrease in IVRT by 15% ( $p=0.01$ ). However, it should be noted that the indicators of linear and volumetric LV parameters in this group did not significantly change, which is probably due to the existing concomitant cardiovascular pathology in these patients. A comparative assessment of EchoCG parameters after 6 months of combined therapy with the inclusion of thyrostatics also revealed a statistically significant positive dynamics of the parameters of the left ventricle in patients of both groups. In patients with thyrotoxicosis without CVD, the final diastolic volume (BDO) significantly decreased by 11% ( $p=0.01$ ) and, accordingly, the index of final diastolic volume (ICDO) — by 12% ( $p=0.01$ ), the thickness of the ventricular septum (LV TMJ) — by 14.2% ( $p=0.04$ ), LV myocardial mass index (LVMI) — by 27.3% ( $p=0.001$ ). In this group of patients, the indicators of myocardial stress (MS) also decreased statistically significantly — by 11% ( $p=0.01$ ), stroke- the total volume (UO) was 18.3% ( $p=0.01$ ), the impact ejection index (PUV) increased by 8% ( $p=0.04$ ) (Table 1). Analysis of EchoCG results in patients with a combination of thyrotoxicosis and CHF of ischemic genesis also revealed a statistically significant increase in PUV, UO and a decrease in values of MS. It is especially important to note an increase in the LV ejection fraction (LV) in this group of comorbid patients, which characterizes an improvement in the functional activity of the myocardium in the conditions of the achieved euthyroid state (Fig. 3). In addition, in group I of patients (with thyrotoxicosis, coronary heart disease and CHF), there is an improvement in LV diastolic function: an increase in E/A by 13% ( $p=0.03$ ) and a decrease in IVRT by 15% ( $p=0.01$ ). However, it should be noted that the indicators of linear and volumetric LV parameters in this group did not significantly change, which is probably due to the existing concomitant cardiovascular pathology in these patients.

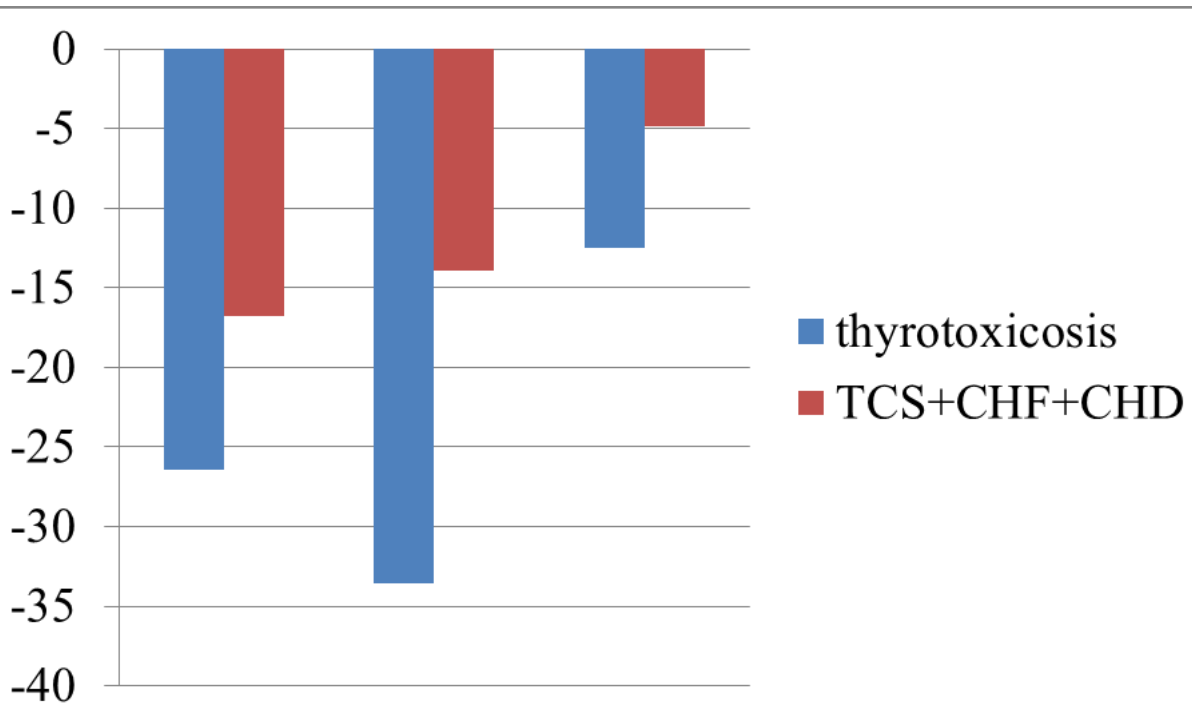


Figure 1. Dynamics of heart rate indicators in patients of both groups with thyrotoxicosis through 6 months of therapy

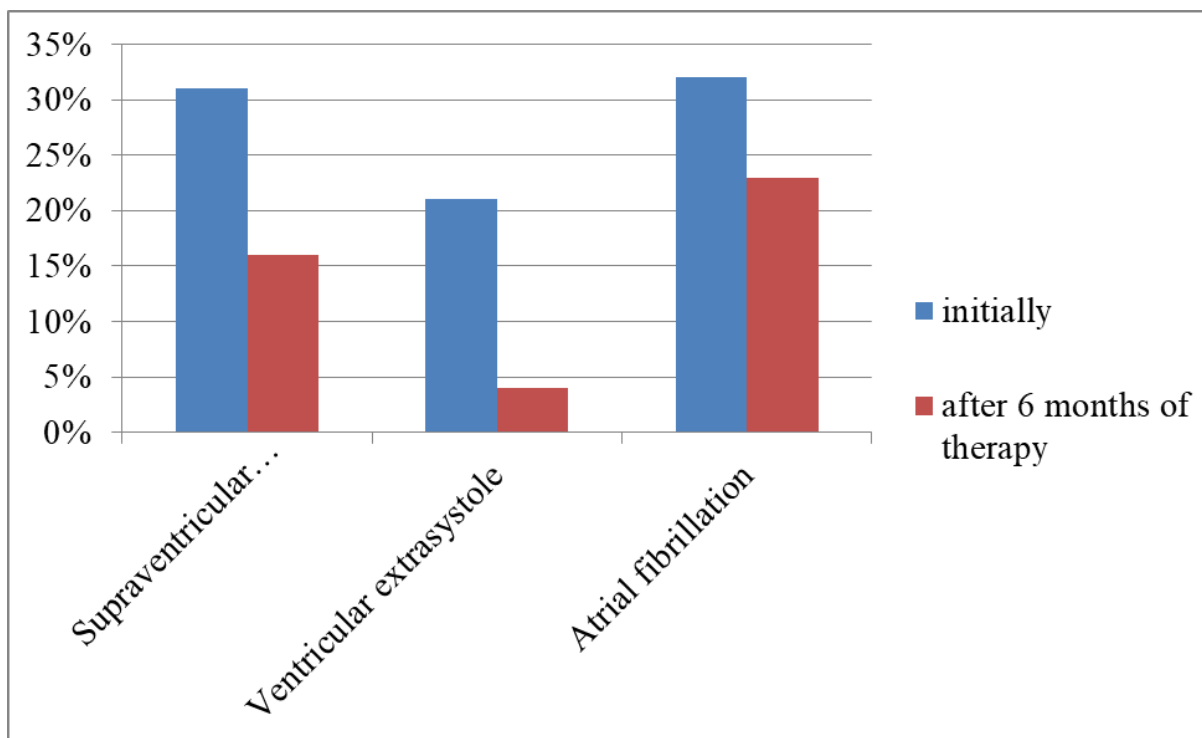
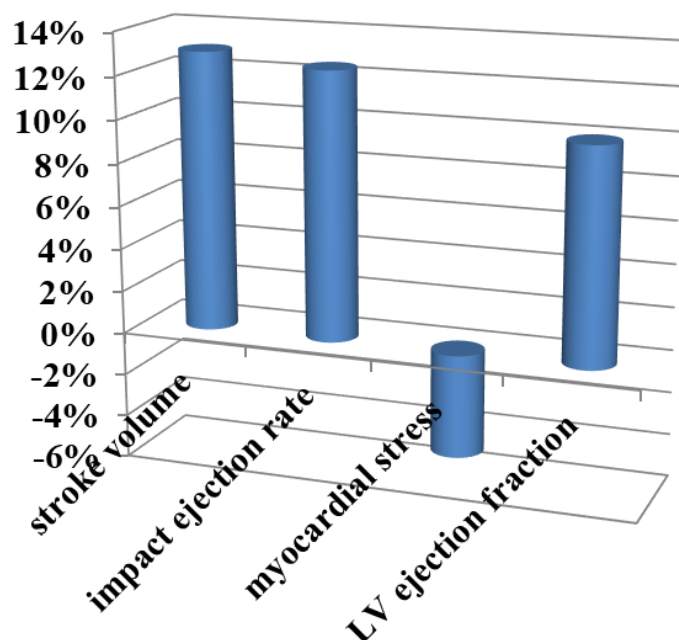


Figure 2. Dynamics of the frequency of occurrence of cardiac arrhythmias in patients with thyrotoxicosis and CHF of ischemic genesis on the background of therapy.

## Dynamics of LV echocardiographic parameters in patients with thyrotoxicosis and CHF of ischemic genesis after 6 months of therapy.



■ Dynamics of LV echocardiographic parameters in patients with thyrotoxicosis and CHF of ischemic genesis after 6 months of therapy.

**DISCUSSION.** It is known that in patients with hyperthyroidism, achieving an euthyroid state does not guarantee the disappearance of symptoms of thyrotoxic cardiopathy. The duration of the disease and the lack of compensation, as well as concomitant pathology, especially of the cardiovascular system, reduce the likelihood of recovery of sinus rhythm and regression of heart remodeling processes in patients with thyrotoxicosis. However, some researchers in their works indicate the possibility of normalization of the morpho-functional parameters of the heart, provided timely and adequate thyrostatic therapy is prescribed. Despite the studies conducted in this direction, it is still relevant to assess the effectiveness of thyrostatic therapy in treatment- research institutes of patients with cardiovascular pathology and thyrotoxicosis. In our study, in patients with thyrotoxicosis who did not have concomitant CVD, against the background of the achieved compensation of the functional activity of the thyroid gland, there was a significant positive dynamics of such clinical symptoms as a decrease in heart rate during the day, a decrease in the incidence of LDC, as well as an improvement in the morpho-functional parameters of the left ventricle in the form of a decrease in LV myocardial remodeling, which is consistent with the results of previously published studies. It should be noted that initially in this group of patients LV LV was elevated and corresponded to the initial, hyperkinetic, stage of thyrotoxic heart disease. The achievement of euthyroidism led to a decrease in LV LV and the restoration of normal LV systolic function. The inclusion of thyrostatics in the scheme of combination therapy in group

I patients who had a combination of ischemic CHF and thyrotoxicosis also contributed to a decrease in the incidence of LDC and a decrease in heart rate, but in this group of patients the dynamics was not so pronounced. It is important to emphasize that the achievement of persistent euthyroidism in patients with combined pathology led to an increase in physical activity and a decrease in the clinical symptoms of CHF. Special attention should be paid to the statistically significant positive dynamics of the structural and functional parameters of the left ventricle, which made it possible to judge the regression of pathological remodeling, improvement of systolic and diastolic function of the left ventricle against the background of therapy. Considering that patients with coronary heart disease and CHF have already received treatment in accordance with clinical recommendations, it can be argued that it was the inclusion of thyrostatics in the combination therapy that led to such a pronounced positive dynamics of the analyzed indicators.

**CONCLUSION.** The results of the study showed that the inclusion of thyrostatics in combination therapy and the achievement of a stable euthyroid state in patients with a combination of ischemic CHF and thyrotoxicosis leads to increased exercise tolerance, reduced symptoms of HF, reduced incidence of LDC, improved systolic and diastolic function of the left ventricle. In practical healthcare, timely detection of thyroid hyperfunction in patients with CVD and optimal drug correction with the achievement of euthyroidism will certainly contribute to improving the effectiveness of therapy in such patients.

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