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THE DILEMMA OF USE OF THE LEVOTHYROXIN IN PATIENTS WITH HEART FAILURE (literature review and own data)*

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Currently, the pathogenesis of heart failure (HF) is considered as a unique scenario of a change in systemic homeostasis, in which the dysfunction of the myocardium, peripheral organs, and disruption of the neuroendocrine and immune systems form chronic cross-connections between stressful stimuli with constant activation of the stress response [1]. Interest in the role of thyroid hormones (TH) in HF has increased over the past decades [1]. Pantos S. et al. published a series of animal studies on the effects of TH on the heart, especially during ischemia or myocardial infarction (MI) [2–6]. They showed that both short-term and long-term use of a combination of triiodothyronine (T_3) and tetraiodothyronine (T_4) in rats with MI leads to improvement of left ventricular (LV) function and prevents pathological remodeling of the myocardium. It should be noted that this group of researchers did not observe any changes in the remodeling of scars in the necrotic zone associated with the treatment of TH [1]. Interventions affecting post-MI scar remodeling may lead to aneurysm or cardiac rupture. It is known that TH have an antifibrotic effect, however, treatment with these drugs does not lead to an increase in the risk of these complications [1].

It should be noted that T_3 and/or T_4 replacement therapy has never been tested in humans after MI, despite the existence of a clear relationship between low thyroid function and poor prognosis after MI. In many animal studies, similar changes and improvements have been demonstrated with the treatment of TH. Today, the problem of using T_3 and T_4, or their combination, is fully described, depending on specific clinical situations. For example, it seems logical that T_4 treatment may work better in primary hypothyroidism, but not in impaired peripheral conversion of T_4 to T_3 (low triiodothyronine syndrome — LT_3S), when T_3 appears to be more beneficial.

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The aim of this article is to systematize literature data on to use of levothyroxin (LT) in patients with a heart failure and to present the results of own research.

MATERIALS AND METHODS

The narrative review represents an assessment of the most pertinent literary sources published in English language from 1990 to 2021, which dealt with the issues of to use of thyroid gland hormones in patients with heart failure. Also, the results of own research were presented.

Our study protocol was approved by the local Ethics and Deontology Committee of Government Institution «L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine». The study procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. Patients were included in the study on the time of hospitalization in the cardiology department due to decompensation of the HF. In the study were 218 patients with HF (60 women and 158 men), with a median age of 58.0 [54.0: 67.0] years. Criteria of inclusion: signing informed consent, history of myocardial infarction, verified diagnosis of HF II–IV functional class (FC) by NYHA, autoimmune thyroiditis. Exclusion criteria: no informed consent, severe valvular heart defects, HF of other etiology than myocardial infarction, thyro-suppressive treatment, other serious pathologies (tumor, tuberculosis) which could complicate treatment or reduce life expectancy.

Diagnosis and treatment of HF were performed in accordance with the recommendations of the European Society of Cardiologists [18].

Serum levels of thyroid-stimulating hormone (TSH) (normal range 0.3–4.0 mIU/L), free T_3 (T_{3f}) (normal range 2.5–5.8 pmol/L) and free T_4 (T_{4f}) (reagent range 10–25 pmol/L) were determined using reagent kits («TSH-ELISA», «T4f» and «T3f» by Hema, Ukraine). Levels of reversible triiodothyronine (T3r) (normal range: 90–350 pg/mL), and the N-terminal fragment of the prohormon of the Brain natriuretic peptide (NT-proBNP) (norm < 125 pg/mL), as well as thyroid peroxidase and thyroglobulin antibody titers were determined using an ELISA kit (Elabscience®, China). Immunoenzymatic studies were performed on a semiautomatic enzyme-linked immunosorbent analyzer «Immunochem-2100» (High technology, USA) No. 501322057FSE. Certificate of last verification № 08-421 / 2 dated 26.11.2018).

Doppler echocardioscopic examination was performed using the VIVID-3 ultrasound diagnostic system (General Electric, USA). End-diastolic and end-systolic dimensions (EDD and ESD, respectively) of the left ventricle (LV), the thickness of the interventricular septum (IVS) and the LV posterior wall (LVPW), the diameter of the left atrium (LA), right ventricle (RV), other options were determined. The end-diastolic and the end-systolic volumes of the LV (LV EDV, LV ESV, respectively), the LV ejection fraction (LV EF), the LA index (ILA), the myocardial mass of the LV (MM LV) and its index (IMM LV) were calculated.

The ultrasound examination of a thyroid gland was performed. IAT was diagnosed by ultrasound criteria [4] and by thyroid peroxidase and thyroglobulin antibody titers, in the absence of signs of thyroid hyperfunction.

109 (50%) patients (group I) with AIT received LT due to hypothyreosis in past. These patients intaked LT during 2 years before included in the study and have euthyreosis.

Group II included 109 patients with HF without LT treatment. Patients in both groups did not differ by age and gender (Table 1). The median time of LT treatment before inclusion in the study was 12.0 [10.0; 16.5] months. After hospital discharge, patients were monitored for 2 years, taking into account the presence of re-hospitalization (RH) for decompensation of the HF, mortality. The combined endpoint (CE) was determined according to these indicators.

The normality of indicators distribution was checked using the Shapiro-Wilk test. Data are given as the median (Me) and interquantile (25% and 75%) ranges (for non-normally distributed variables), and as the mean (M) and the standard deviation (± SD) (for ANOVA). Quantitative indicators comparison was performed using a non-parametric criterion of Mann-Whitney. Frequency of groups was evaluated by the Pearson chi-squared test (χ^2). The odds ratio (OR) with 95% confidence interval

(CI) was calculated. For comparison of LV EF values in the groups of patients taking different doses of LT a one-way ANOVA was performed with posterior multiple comparison by the Sheffe method. A ROC analysis was used to determine the effect of LT dose on HF over two years. P-value < 0.05 was considered statistically significant. The probit-regression analysis was performed. IBM®SPSS® Statistics, 20.0 and MedCalc, 18.9.1 (free version) software packages were used.

RESULTS AND THEIR DISCUSSION

It is known that the treatment of hamsters of the genetic line of cardiomyopathy (TO-2) with the subclinical hypothyreosis (SCH) with a combination of T_4 and T_3 at the age of 4 to 6 months prevented the progression of fibronecrosis and the subsequent loss of cardiac myocytes (apoptosis), and also led to a weakening of the progression of left ventricular dilatation and its dysfunctions [7, 8]. The authors found that the use of TH in hamsters of the TO-2 line leads to the normalization of blood flow in the coronary arteries both at rest and during exercise [7, 8]. This was the first study to demonstrate the potential benefits of TH treatment in subclinical hypothyroidism (SCH) in an animal model of HF [7]. It has been suggested that patients with HF may benefit from treatment with TH.

In studies on rats, it was established that the concentrations of TH in the serum can be normal, at the same time, the content of these hormones in the heart tissue is much lower [9]. The authors suggest that concentrations of TH in the myocardium are more reliable indicators of LV function than hormone levels in blood serum [9]. This raises an important question: to what extent is ventricular dysfunction in patients with cardiovascular disease (CVD) diagnosed with euthyroidism actually due to low tissue hormone levels? The lack of TH at the tissue level may increase as a result of a decrease in the activity of nuclear receptors for these hormones, which occurs in HF [10].

Although the majority of studies concerning the use of TH in HF have focused mainly on improving inotropic and lusotropic function of the myocardium without increasing the heart rate, there are data on the beneficial effect of hormones on myocardial remodeling, which is important [1]. In preclinical studies, it has been demonstrated that the induction of hyperthyroidism in rats without HF leads to a balanced increase in the length and width of myocytes [1], which is similar to physiological growth. Propylthiouracil-induced hypothyroidism in rats initially leads to myocyte atrophy [11]. However, under conditions of long-term hypothyroidism, myocyte elongation is induced as a result of the construction of new series of sarcomeres [11]. This is also observed in patients with HF [1].

The effect of the combination of T_3 and T_4 on LV dimensions and myocyte remodeling was investigated in aging rats with hypertension approaching LV dilatation and the development of HF [12]. A positive effect of the use of TH on the ratio of the diameter of the chamber to the thickness of the wall was established, despite the presence of persistent hypertension. This change in the structure of the chamber is explained by a specific modification of the shape of myocytes, namely, an increase in the diameter of the myocyte and a decrease in its length [12]. The results of another study on rats that received the drug T_3 after an MI also showed favorable changes in the shape of myocytes [13]. It is possible that the violation of transverse growth during the progression of LV dilatation is associated with a low tissue concentration of TH [1].

Cardiovascular symptoms found in thyrotoxicosis are similar to those in hypercatecholemia. At the same time, it was demonstrated that the concentration of catecholamines in the blood is usually normal, or even reduced [14]. To explain these observations, the hypothesis was proposed that TH increase the sensitivity or the amount of ß-adrenoreceptors (ß-AR) on myocardiocytes [27].

In the left part of the works, it was demonstrated that TH increase the number of ß-AR [15]. An increase in the activity of adenylate cyclase was also reported [16]. In another study, a temporary increase in the affinity of ß-AR for adrenaline on the membranes of cardiomyocytes of rats was detected when levothyroxine

was used, followed by its normalization after a month of using the drug [15].

At the same time, there are studies in which no changes in the amount and sensitivity of ß-AR were recorded when using TH [17]. T_3 increases the expression of $ß_1$-AR and the level of transcription of the corresponding gene [15].

In the often-cited classic profile works, the position regarding adrenergic hyperreactivity of the myocardium in hyperthyroidism, explained by an increase in the number of ß-AR, is developed as a scientific hypothesis [18, 19]. Although based on the results of studies with transgenic mice with overexpression of ß-AR, it was established that despite a 400-fold increase in receptor overexpression, there is no proportional increase in binding sites or receptor-stimulated increase in cAMP production. This suggests that hyperthyroidism develops changes in other components of the cascade of the ß-adrenoreceptor system [20].

The discussion about the possibility of using TH in patients with HF has been going on for several decades. Clinical data on this issue are limited to only a few studies [21-25]. A strong argument in favor of the use of TH in HF is that in the myocardium, when its function is impaired, gene expression changes similar to those in hypothyroidism are observed [26], with all deviations in the metabolism, which at the same time are reversed during replacement therapy. The effect of TH on peripheral target tissues, such as the heart, is poorly understood. The main limitation is the assessment of the level of TH in tissues based on the concentration of hormones in the blood. The issue of dosage, timing of starting and stopping the use of TH in patients with LT_3S still remains unclear. A biomarker of intracardiac TH signaling would be useful but has not yet been identified. In the absence of such a marker, a rational, cautious therapeutic approach may consist in restoring and maintaining biochemical euthyroidism for a long time, which is confirmed by normal levels of circulating TSH, T_4 and T_3.

There are several arguments in favor of the fact that new therapeutic strategies based on the effects of TH can be implemented not only in the early but also in the final stages of the course of HF [27]. In particular, it is known that treatment with physiological doses of T_3 is able to restore the expression of Ca^{+2} in the myocyte, as well as the contractile function of the heart. This was demonstrated in an animal model of HF [27]. The use of triiodothyronine can stimulate the self-organization of primary neonatal proteins of the myocardium, which leads to an increase in the rate of contraction and recovery of relaxation.

Analogues of levorotatory isomers of thyroxine and triiodothyronine were tested in a number of preclinical studies, and replacement therapy based on the use of diiodothyropropionic acid (DITPA) was performed in patients with HF [21, 22, 28–30]. Synthetic levothyroxine and levotriiodothyronine improved the function of the left ventricle at rest and during physical activity, and a decrease in total peripheral vascular resistance was also noted. At the same time, the protocols for the use of T_3 in patients with HF in such studies differed greatly. Regardless of the mode of use, levotriodothyronine, unlike DITPA, was well tolerated by patients, no undesirable side effects (arrhythmias, myocardial ischemia or hemodynamic instability) were registered. In one of these clinical studies, the improvement of cardiac activity caused by the use of T_3 did not lead to an increase in oxygen consumption by the myocardium [30]. In the aforementioned studies [30, 31] the effect of TH replacement therapy on cardiac function and myocardial morphology was evaluated using cardiac MRI, which is currently considered the gold standard for assessing LV size and regional and global function. The high image quality and 3-dimensional MRI algorithm allowed us to accurately assess the course of post-ischemic LV remodeling with high reproducibility, allowing smaller sample sizes to reach statistical significance.

Several clinical studies have proven the potential benefits of using TH in patients with acute HF. In patients who underwent heart surgery with or without LV myocardial dysfunction, administration of T_3 reduced the frequency of postoperative atrial fibrillation (AF) [32], improved hemodynamic indicators, ensured a decrease in troponin I. In the complex, it reduced the need for inotropic drugs [25]. Treatment with T_3 also reduced surgical mortality in patients with high perioperative risk

during open-heart surgery [33]. During heart transplantation, the use of T_3 induced faster attainment of hemodynamic stabilization, which allowed to significantly reduce inotropic support of the donor organ, provided excellent hemodynamic function in recipients after alloplasty [23]. Similar effects were obtained when using T_3 in addition to dobutamine in patients with acute myocarditis and hemodynamic instability [34]. At the same time, it should be noted that modern international and national standards for the treatment of patients with HF do not provide for the use of TH in the absence of hypothyroidism [35].

In 1972, the results of the Coronary Drug Project were published [36], where it was about the use of excessively high doses of the «inactive» dextrorotatory isomer of thyroxine (DT_4). Later it became clear that this leads to the accumulation of active levothyroxine in the body in toxic concentrations [37]. The use of large doses of DT_4 was motivated by a decrease in the level of cholesterol in blood serum [36]. The results of this study demonstrated a slight increase in the incidence of arrhythmia and mortality [36].

In another phase II clinical trial with the DITPA analogue of TH in HF, some improvements in hemodynamics were demonstrated, but there was no reliable improvement in exercise tolerance [28]. It is suggested that an excessive dose was also used in this case, as the treated patients had increased heart rate, weight loss, and diarrhea [28].

In two studies, synthetic levothyroxin (LT) was administered orally in a «physiological» dose of 100 μg/day for short periods (1 week) and 3 months in a row [22] in patients with non-ischemic cardiomyopathy. In both studies, LT was well tolerated and resulted in improvements in cardiac systolic function and exercise tolerance and a reduction in total peripheral vascular resistance. Interestingly, low-dose dobutamine (10 μg/kg per min) in the LT group led to a significantly higher increase in ejection fraction and heart rate than in patients who received placebo instead of LT [22]. This may indicate an increase in adrenergic sensitivity of the myocardium, according to experimental data on the effect of TH on the expression of $ß_1$-AR on the membrane of myocytes [1].

Beneficial hemodynamic effects of intravenous LT (20 μg/h) were recorded in 10 patients with cardiogenic shock who did not respond to the use of conventional pharmacological inotropic drugs and intra-aortic balloon counterpulsation [29]. In this study, most patients had LT_3S before the use of LT, but the levels of T_3 and T_4 after infusion of the drug were not reported [1]. The cardiovascular effects of continuous LT infusion persisted for a long time [29].

In conclusion, it should be noted that the therapy of TH under conditions of HF is currently still an «open book». Several unanswered questions remain: regimen, doses and schedule of drug use, consequences of such therapy. Large clinical studies will be able to provide information on the effect of TH on the long-term prognosis of patients with HF [5]. At the same time, the presence of comorbid thyroid pathology (TP), which requires the appointment of levothyroxine, allows a partial answer to this question.

Thus, HF can be characterized as the final stage of the development of many cardiovascular diseases, primarily coronary heart disease (CHD). Understanding the new pathophysiological mechanisms of the formation of heart failure will contribute to the development of more effective therapeutic strategies. Data from experimental and clinical studies confirm the significant role of thyroid hormones in ensuring cardiovascular homeostasis under both physiological and pathological conditions. Comorbid thyroid pathology is quite common among patients with heart failure. A large percentage of such patients have subclinical gland dysfunction or low triiodothyronine syndrome. Over the past decades, a lot of data has been accumulated that this syndrome is a strong and independent predictor of mortality in patients with heart failure. All of the above substantiates the relevance of conducting further research with the aim of in-depth study of the pathogenetic bases of heart failure, which was formed against the background of ischemic heart disease and concomitant thyroid pathology, as well as the influence of ß-adrenoblockers (ß-AB) for a separate prognosis in patients of this category.

Modern recommendations adhere to the avoidance of thyroid hormone therapy in HF. Probably, such a rule arose after the publica-

tion of the results of the Coronary Drug Project study in 1972 [36], in which an excessively high dose of the «inactive» dextrorotatory isomer of thyroxine (DT_4) was used. Later it became clear that it was transformed in the body into a toxic dose of active levothyroxine [36]. Thanks to a large dose of DT_4, the researchers aimed to significantly reduce the level of cholesterol in the blood serum [36]. The results of this study demonstrated an increase in the frequency of arrhythmia development and mortality [36]. In another phase II trial of the DITPA analogue of TH in HF, some improvements in hemodynamics were demonstrated, but there was no reliable improvement in exercise tolerance [28]. It has been suggested that this study may also have used an excessive dose of the drug, as the treated patients experienced an increase in heart rate, weight loss, and diarrhea [28].

In our study, the I group of patients, compared to II one, at the time of hospitalization had a higher serum levels of T_{3f} (by 19%, p = 0.01), T_{4f} (by 14.2%, p = 0.02) and lower TSH level (by 39.1%, p = 0.0001). The level of T_{3r} did not differ significantly between groups. Patients who received LT had a lower NT-proBNP level (by 26.3%, p = 0.009). Patients who used LT before hospitalization, compared to patients without this treatment, had smaller LV dimensions (EDD and ESD) and

Table 1

Characteristics of groups of patients with heart failure (n = 218)

Indicator, units	Therapy		c
	With LT (n = 109)	Without LT (n = 109)	
Age, years	58.0 [55.0; 67.0]	58.0 [54.0; 67.0]	> 0.05
Gender: women, n (%) men, n (%)	 31 (28.4) 78 (71.6)	 29 (26.6) 80 (73.4)	 0.092; > 0.05
NYHA FC: II, n (%) III, n (%) IV, n (%)	 48 (44.0) 45 (41.3) 16 (14.7)	 38 (34.9) 58 (53.2) 13 (11.9)	3.114; > 0.05
SBP mmHg	140.0 [130.0; 160.0]	145.0 [130.0; 160.0]	> 0.05
DBP, mm Hg	90.0 [80.0; 94.5]	90.0 [80.0; 95.0]	> 0.05
HR, min^{-1}	72.0 [68.0; 82.0]	77.0 [68.0; 84.0]	> 0.05
BMI, kg/m^2	27.7 [25.8; 31.2]	27.1 [25.0; 31.1]	> 0.05
T_{3f}, pmol/l	2.5 [1.9; 3.3]	2.1 [1.7; 3.1]	0.01
T_{4f}, pmol/l	16.9 [13.4; 19.4]	14.8 [11.4; 16.6]	0.02
TSH	1.4 [0.8; 1.9]	2.3 [1.1; 3.4]	0.0001
T_{3r}	276.4 [201.4; 325.4]	292.6 [205.6; 367.8]	> 0.05
NT-proBNP, pg/ml	408.0 [297.3; 681.8]	553.7 [339.0; 1110.9]	0.009
EDD, cm	5.4 [5.0; 5.8]	5.6 [5.2; 6.2]	0.009
EDV, ml	143.1 [119.9; 168.6]	155.6 [131.2; 196.3]	0.009
ESD, cm	4.1 [3.7; 4.4]	4.4 [4.0; 5.1]	0.0001
ESV, ml	74.1 [59.1; 89.0]	89.0 [71.1; 125.5]	0.0001
LVEF, %	48.1 [40.3; 55.8]	37.1 [30.1; 45.8]	0.0001
IMM, g/m^2	108.7 [93.5; 125.3]	116.5 [99.7; 132.9]	> 0.05
LA, cm	4.1 [3.9; 4.4]	4.2 [3.9; 4.5]	> 0.05
RV, cm	2.6 [2.5; 2.9]	2.8 [2.6; 3.0]	> 0.05
RA, cm	3.7 [3.4; 4.0]	3.7 [3.5; 4.0]	> 0.05

Note:
SBP — systolic blood pressure, DBP — diastolic blood pressure, HR — heart rate, BMI — body mass index.

Table 2

Dependence of the left ventricular ejection fraction on the dose of levothyroxine (one-way ANOVA)

Group	Dose LT (μg/kg))	Subset for α = 0.05 (M ± SD for LV EF (%))		
		1	2	3
I (n = 109)	0	38.5 ± 11.0		
II (n = 25)	0.1–0.33	38.8 ± 10.0		
III (n = 19)	0.34–0.59	45.1 ± 7.0	45.1 ± 7.0	
IV (n = 20)	0.6–0.69	46.0 ± 5.7	46.0 ± 5.7	
V (n = 22)	0.7–1.19		53.1 ± 7.0	53.1 ± 7.0
VI (n = 21)	≥ 1.20			58.2 ± 6.7

F = 22.4; p = 0.0001

Table 3

The effect of the use of levothyroxine on the course of heart failure (n = 218)

Indicator, units	Therapy		c
	With LT (n = 109)	Without LT (n = 109)	
RH, n (%)	32 (29.4)	50 (45.9)	6.334; 0.012
Death, n (%)	9 (8.3)	6 (5.5)	0.644; > 0.05
CE, n (%)	39 (35.8)	52 (47.7)	3.188; 0.074

Table 4

Relationship of levothyroxine dose with the risk of re-hospitalization of patients with heart failure and AIT (ROC analysis)

Indicator, units	Cut-off value	AUC	95 % CI	Sensitivity, %	Specificity, %	p
LT dose, μg/kg	> 0.53	0.589	0.521–0.655	56.62	60.98	0.016

volumes (ESV and EDV) (Table 1) and a larger LV EF by 22.9% (p=0.0001) [38, 39].

The median dose of LT was 0.63 [0.35; 1.11] μg/kg. To identify the association of LVEF with the dose of LT, patients with HF were divided into 6 subgroups by percentile of dose the drug (Table 2). In the subgroup of patients receiving LT at a dose of 0.1–0.69 μg/kg, LVEF was not different from that in patients without LT. At a dose of 0.7–1.19 μg/kg, LVEF is higher, compared to that in patients not receiving LT (by 37.9%) and compared to patients receiving LT at a dose of 0.1–0.33 μg/kg (36.9%).

LVEF was the highest in patients receiving LT at > 1.20 μg/kg (58.2 ± 6.7%). In this subgroup of patients, it was larger compared to that in patients who did not use LT, or took it at a dose of 0.1–0.69 μg/kg, but it was not significantly different from that in patients with LT dose 0.7–1.19 μg/kg (see Table 2).

Observation of patients during 2 years showed that further use of LT reduces the risk of RH in the cardiac department (OR = 0.490 (0.281–0.857), p = 0.018). A tendency for a reduction in the risk of CE achieving (by 27.9%, p = 0.074) was identified (Table 3).

During the ROC analysis, it was found out that the risk of RH in patients with HF decreases with the use of LT at a dose over 0.53 μg/kg (sensitivity — 56.62%, specificity — 60.98%, p=0.016) (Table 4).

According to the results of ROC analysis, patients with HF were divided for 3 groups. The I one included 109 (50.0%) patients who did not use LT. In the II group there were 37 (16.9%) patients who continued to take LT at a dose of 0.1-0.53 μg/kg after inclusion in the study.

In group III there were 72 patients (33.1%) taking LT at a dose > 0.53 μg/kg (Table 5).

Patients taking LT at dose > 0.53 μg/kg for 2 years had the lowest RH rate (27.8%), compared to dose 0.1–0.53 μg/kg (32.4%) and without prescription of this treatment (45.9%) (χ^2 = 6.559, at p = 0.038) (see Table 5).

Table 5

The effect of different doses of levothyroxine on the course of heart failure (n = 218)

Indicator, units	Without LT (n = 109)	Dose LT (μg/kg)		c
		0.1–0.53 (n = 37)	> 0.53 (n = 72)	
RH, n (%)	50 (45.9)	12 (32.4)	20 (27.8)	6.559; 0.038

Table 6

The data of probit-regression analysis of the dependence of the probability of re-gospitalisation on the dose of LT

Indicator, units	
Volume of grope, n	109
The coefficient of logarithmic plausibility is zero model of re-hospitalization	138,29
Coefficient of logarithmic plausibility of the complete model of re-hospitalization	134,41
χ^2	3,88
P	0,049
$R^2_{(Koks \& Snell)}$	0,035
$R^2_{(Nagelkerk)}$	0,049
ß-coefficient, M ± m	– 0,65 ± 0,33
Vald's coefficient	3,76

The probit-regression analysis showed a negative (ß = –0.65 ± 0.33) dependence of the reduction in the probability of re-hospitalization of patients on the dose of LT (μg/kg) (see Table 6 and Fig. 1).

A few decades ago, it was noticed that the cardiovascular symptoms found in thyrotoxicosis resemble those in hypercatecholemia. Along with this, it was found that the concentration of catecholamines in the blood was usually normal or even reduced [14]. To explain these observations, it was hypothesized that TH increases the sensitivity of ß-AR on myocardiocytes [41]. Genes encoding ß-AR have several polymorphisms, which are reflected both in the activity of the receptors themselves,

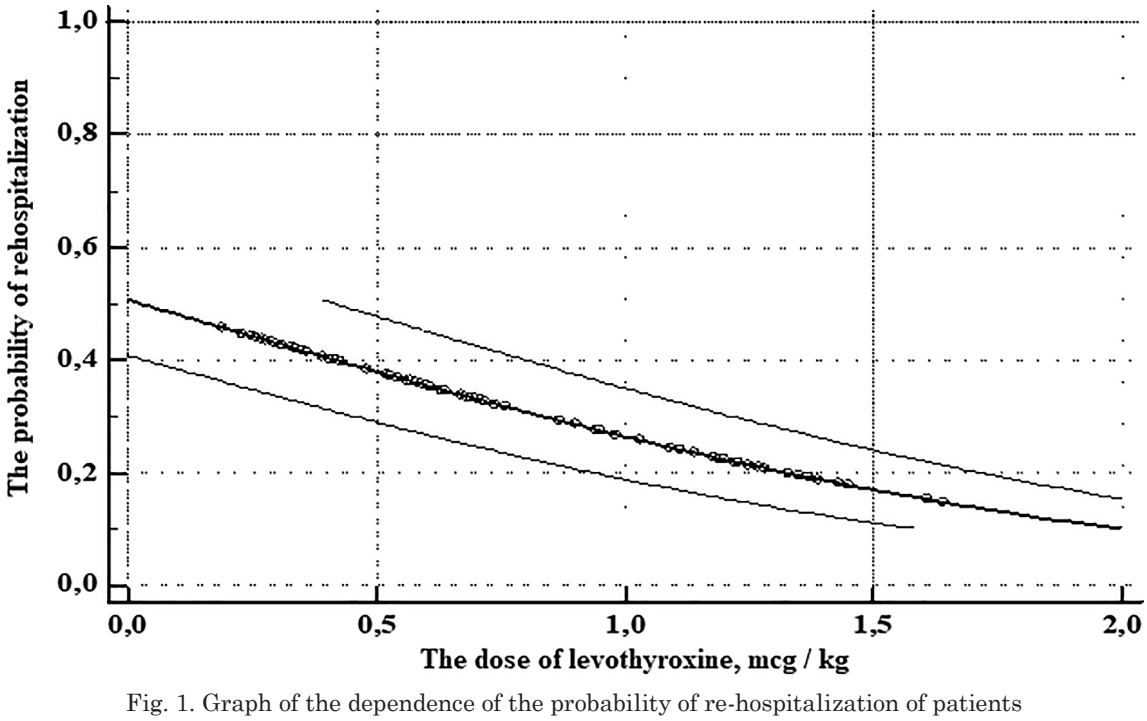

Fig. 1. Graph of the dependence of the probability of re-hospitalization of patients with heart failure from a dose of levothyroxine (χ^2 = 3,88; p = 0,049)

as well as in the course of HF and the effectiveness of ß-AB [42]. It is possible to assume that genetic differences in the structures of the ß-adrenoreceptor system can affect the effects of RT in HF.

According to the literature, most of the studies on the effect of TH on ß-AB focusing on the study of their effect on the number of receptors [20]. While in the lion's share of works it has been demonstrated that TH increase the number of ß-AR, some of them also reported an increase in the activity of adenylate cyclase [15]. In another study, a temporary increase in the affinity of ß-AR for adrenaline on the membrane of cardiomyocytes of rats was detected when using LT, with subsequent normalization after a month of using the drug [16]. Only a small number of studies did not show a change in the amount and sensitivity of ß-AR when using TH [17]. T_3 increases the expression of ß-AR and the level of transcription of their gene [15]. While these and other classic studies, often cited, suggest adrenergic hyperreactivity of the myocardium in hyperthyroidism due to an increase in the amount of ß-AR, other works [18, 19] with transgenic mice overexpressing ß-AR, showed that despite 400-fold receptor overexpression, there was no proportional increase in binding sites or receptor-stimulated increases in cAMP production. This suggests that hyperthyroidism develops changes in other components of the cascade of the ß-adrenoreceptor system [20].

We did not receive reliable data on the association of polymorphisms *Gly389Arg* and *Gly49Ser* of the $ß_1$-AR gene with the effect of LT on the course of HF. Along with this, we managed to establish a dose-dependent association of the use of LT with the polymorphism *Gln27Glu* (*c.79C > G*) of the $ß_2$-AR gene, regarding the effect on the course of HF. Thus, the appointment of LT in a dose > 0.53 µg/kg in homozygous (for the *C* allele (*Gln27Gln*) polymorphism (*c.79C > G*) of the $ß_2$-AR gene) patients leads to a reduction in the risk of PN within two years (OR = 0.09 (0.02–0.48)). At the same time, in the subgroup of patients with the heterozygous (*C/G*) genotype, an increase in the risk of an adverse course of HF was found (increased frequency of RH (OR = 3.82 (1.29–11.31), p = 0.0087) in the absence application of LT [43].

While $ß_1$-ARs only activate G-protein (Gs), $ß_2$-ARs can also inhibit it (Gi), reducing the production of cAMP. The consequences of cross-interactions arising between Gs and Gi proteins activated by $ß_2$-AR remain incompletely understood [44]. Their physiological significance probably lies in the adjustment of ß-adrenergic sensitivity [20]. In addition, such simultaneous $ß_2$-AR activation of these opposing pathways generates independent signals that increase receptor specificity. For example, in cultured cell models of «pure» $ß_1$- or $ß_2$-AR, activation of $ß_1$-AR induces apoptosis. While stimulation of «pure» $ß_2$-AR activates simultaneously pro-apoptotic and anti-apoptotic signals, leading to cell survival and not death, as in the $ß_1$-AR model [45]. This great complexity in the biology of the adrenergic signaling cascade of the ß-ARi system must be taken into account when analyzing data on the effect of TH on ß-adrenergic sensitivity in the heart [20].

This phenomenon can be explained by the fact that patients with HF who have the «wild» Gln27Gln genotype develop a faster decrease in sensitivity under conditions of hypercatecholemia inherent in heart failure, compared to patients with the Glu27 genotype. The use of LT probably leads to the blocking of this effect of polymorphism.

CONCLUSIONS

In conclusion, it should be said that the final chapter in the history of the possibility of using levothyroxine in patients with heart failure has not yet been written. Further studies, including pharmacogenetics, are needed.

Our study shows that the long-term administration of levothyroxine in patients with heart failure and accompanying hypothyroidism has a dose-dependent positive effect on the value of the left ventricular ejection fraction and on the course of heart pathology. The maximum ejection fraction of the left ventricle is observed in patients who took the drug in a dose > 1.2 µg/kg. The use of the drug in a dose > 0.53 µg/kg leads to a probable decrease in the frequency of re-hospitalization within 2 years due to decompensation of heart failure.

REFERENCES

1. Gerdes AM, Iervasi G. *Circulation* 2010;122(4): 385-393. https://doi.org/10.1161/CIRCULATIONAHA.109.917922
2. Pantos C, Malliopoulou V, Paizis I, et al. *Mol Cell Biochem* 2003;242: 173-180.
3. Pantos C, Mourouzis I, Cokkinos DV. *Heart Fail Rev* 2010;15: 143-154. https://doi.org/10.1007/s10741-008-9111-0
4. Pantos C, Mourouzis I, Markakis K, et al. *Eur J Cardiothorac Surg* 2007;32: 333-339. https://doi.org/10.1016/j.ejcts.2007.05.004
5. Pantos C, Mourouzis I, Markakis K, et al. *Basic Res Cardiol* 2008;103: 308-318. https://doi.org/10.1007/s00395-008-0697-0
6. Pantos CI, Malliopoulou VA, Mourouzis IS, et al. *Thyroid* 2002;12: 325-329. https://doi.org/10.1089/105072502252949469
7. Khalife WI, Tang YD, Kuzman JA, et al. *Am J Physiol Heart Circ Physiol* 2005;289: H2409-H2415. https://doi.org/10.1152/ajpheart.00483.2005
8. Kuzman JA, Tang Y, Vogelsang KA, Said S. *Can J Physiol Pharmacol* 2007;85: 311-318. https://doi.org/10.1139/y07-011
9. Liu Y, Redetzke RA, Said S, et al. *Am J Physiol Heart Circ Physiol* 2008;294: H2137-H2143. https://doi.org/10.1152/ajpheart.01379.2007
10. Kinugawa K, Yonekura K, Ribeiro RC, et al. *Circ Res* 2001;89: 591-598. https://doi.org/10.1161/hh1901.096706
11. Tang YD, Kuzman JA, Said S, et al. *Circulation* 2005; 112: 3122-3130. https://doi.org/10.1161/circulationaha.105.572883
12. Thomas TA, Kuzman JA, Anderson BE, et al. *Am J Physiol Heart Circ Physiol* 2005;288: H2118-H2122. https://doi.org/10.1152/ajpheart.01000.2004
13. Iervasi G, Nicolini G. *Intern Emerg Med* 2013;Suppl: 1-4. https://doi.org/10.1007/s11739-013-0911-4
14. Silva JE, Braverman LE, Utiger RD. *Philadelphia* 2000: 642-651.
15. Kim B, Carvalho-Bianco SD, Larsen PR. *Arq Bras Endocrinol Metab* 2004;1(48): 43-51. https://doi.org/10.1590/s0004-27302004000100019
16. Hoit BD, Khoury SF, Shao Y, et al. *Circulation* 1997;96: 592-598. https://doi.org/10.1161/01.CIR.96.2.592
17. Novotny J, Bourova L, Malkova O, et al. *J Mol Cell Cardiol* 1999;31: 761-772. https://doi.org/10.1006/jmcc.1998.0913
18. Heubach JF, Trebess I, Wettwer E, et al. *Cardiovasc Res* 1999;42: 173-182. https://doi.org/10.1016/S0008-6363(98)00262-4
19. Zolk O, Kilter H, Flesch M, et al. *Biochem Biophys Res Commun* 1998;248: 801-805. https://doi.org/10.1006/bbrc.1998.9030
20. Carvalho-Bianco K, Larsen R. *Arq Bras Endocrinol Metab* 2004;48(1): 171-175. https://doi.org/10.1590/S0004-27302004000100019
21. Iervasi G, Emdin M, Colzani RMP, et al. *New Trends in Research, Diagnosis and Treatment* : *Second International Congress on Heart Disease,* Englewood, 2001: 549-553
22. Moruzzi P, Doria E, Agostoni PG. *Am J Med* 1996;101: 461-467. https://doi.org/10.1016/s0002-9343(96)00281-1
23. Novitzky D. *Thyroid* 1996;6: 531-536. https://doi.org/10.1089/thy.1996.6.531
24. Portman MA, Fearneyhough C, Ning XH, et al. *J Thorac Cardiovasc Surg* 2000;120: 604-608. https://doi.org/10.1067/mtc.2000.108900
25. Ranasinghe AM, Quinn DW, Pagano D, et al. *Circulation* 2006;114(suppl): I-245-I-250. ttps://doi.org/10.1161/circulationaha.105.000786
26. Klein I, Danzi S. *Circulation* 2007;116(15): 1725-1735. https://doi.org/10.1161/circulationaha.106.678326
27. Ito K, Kagaya Y, Shimokawa H. *Vascul Pharmacol* 2010; 52: 138-141. https://doi.org/10.1016/j.vph.2009.10.004
28. Goldman S, McCarren M, Morkin E, et al. *Circulation* 2009; 119: 3093-3100. https://doi.org/10.1161/CIRCULATIONAHA.108.834424
29. Malik FS, Mehra MR, Uber PA, Park MH. *J Card Fail* 1999;5: 31-37. https://doi.org/10.1016/s1071-9164(99)90022-2
30. Pingitore A, Galli E, Barison A, et al. *J Clin Endocrinol Metab* 2008;93: 1351-1358. https://doi.org/10.1210/jc.2007-2210
31. Ripoli A, Pingitore A, Favilli B, et al. *J Am Coll Cardiol* 2005;45: 439-445. https://doi.org/10.1016/j.jacc.2004.10.044
32. Klemperer JD, Klein IL, Ojamaa K. *Ann Thorac Surg* 1996;61: 1323-1327. https://doi.org/10.1016/0003-4975(96)00102-6
33. Novitzky D, Fontanet H, Snyder M. *Cardiology* 1996;87: 509-555. https://doi.org/10.1159/000177147
34. Brokhin M, Klein I. *Clin Cornerstone* 2005;7: S28-S29. https://doi.org/10.1016/S1098-3597(05)80057-2
35. Ponikowski P, Voors AA, Anker SD, et al. *Eur Heart J* 2016;8: 123. https://doi.org/10.1093/eurheartj/ehw128
36. The coronary drug project research group. *JAMA* 1972; 220: 996-1008.
37. Zhang Y, Dedkov E, Lee B, et al. *J Card Fail* 2014;12: 1012-1019. https://doi.org/10.1016/j.cardfail.2014.10.003
38. Pyvovar SM. Optimisation of prognosis of the clinical outcome and effectiveness of heart failure treatment in patients with coronary artery disease with concomitant thyroid pathology : The qualifying thesis as a manuscript. Thesis for the Degree of Doctor of Medical Sciences, Kharkiv, 2021 : 383 p.
39. Pyvovar SM, Rudyk IS, Lozyk TV, et al. *Probl Endocrine Pathol* 2020;1(71): 58-64. https://doi.org/10.21856/j-PEP.2020.1.08

40. Brian DH, Saeb FK, Yanfu S, et al. *Circulation* 1997;96: 592-598. https://doi.org/10.1161/01.CIR.96.2.592

41. Dillmann WH. *Thyroid* 2002;12: 447-452. https://doi.org/10.1089/105072502760143809

42. Hesse C, Eisenach JH. *Curr Pharmacogenomics Person Med* 2008; 6(3): 160-170. http://dx.doi.org/10.2174/1875692110806030160

43. Pyvovar SM, Rudyk YS, Lozyk TV, et al. *Herald Probl Biol Med* 2020;4(2);(154): 181-188. https://doi.org/10.31718/mep.2019.23.5-6.05

44. Xiao RP. *Sci STKE* 2001;2001(104): re15. https://doi.org/10.1126/stke.2001.104.re15

45. Zhu WZ, Zheng M, Koch WJ, et al. *Proc Natl Acad Sci USA* 2001;98: 1607-1612. https://doi.org/10.1073/pnas.98.4.1607

THE DILEMMA OF USE OF THE LEVOTHYROXIN IN PATIENTS WITH HEART FAILURE (literature review and own data)

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Systematization of literature data on the use of thyroid hormones in patients with heart failure and the results of own research are given.

The therapy of levothyroxine in patients with heart failure, at the moment of time, remains still an «open book». Several questions remain unsolved: regimen, doses and schedule of levothyroxine use, consequences of this therapy. It is necessary to conduct large, multicenter, prospective, placebo-controlled studies, which should provide information on the safety and impact of levothyroxine on the long-term prognosis of these patients.

Our study shows that the long-term administration of levothyroxine in patients with heart failure and accompanying hypothyroidism has a dose-dependent positive effect on the value of the left ventricular ejection fraction and on the course of heart pathology. The maximum ejection fraction of the left ventricle is observed in patients who took the drug in a dose > 1.2 μg/kg. The use of the drug in a dose > 0.53 μg/kg leads to a probable decrease in the frequency of re-hospitalization within 2 years due to decompensation of heart failure.

Keywords: heart failure, levothyroxine, hypothyreosis, left ventricular engect fraction, course of desease.

ДИЛЕМА ЗАСТОСУВАННЯ ЛЕВОТИРОКСИНУ У ХВОРИХ ІЗ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ (огляд літератури та власні дані)

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Наведено систематизацію даних літератури щодо застосування гормонів щитовидної залози у хворих із серцевою недостатністю та результати власного дослідження.

Терапія левотироксином у хворих із серцевою недостатністю на даний момент залишається «відкритою книгою». Невирішеними є наступні питання: режим, дози та схема застосування препарату, наслідки цієї терапії. Необхідно провести великі, багатоцентрові, проспективні, плацебо-контрольовані дослідження, які повинні надати інформацію про безпеку та вплив левотироксину на довгостроковий прогноз цих пацієнтів.

Наше дослідження показує, що довготривале призначення левотироксину у хворих із серцевою недостатністю та супутнім гіпотиреозом має дозозалежний позитивний вплив на величину фракції викиду лівого шлуночка та на перебіг патології серця. Максимальна фракція викиду лівого шлуночка спостерігається у хворих, що приймали препарат у дозі > 1,2 мкг/кг. Застосування препарату у дозі > 0,53 мкг/кг призводить до вірогідного зниження частоти повторної шпиталізації протягом 2 років у зв'язку з декомпенсацією серцевої недостатності.

Ключові слова: серцева недостатність, гіпотиреоз, левотироксин, фракція викиду, перебіг захворювання.