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THE EFFECT OF LEVOTYROXINE ON THE COURSE OF HEART FAILURE IN PATIENTS WITH NON-TOXIC GOITER*

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Heart failure (HF) is one of the main causes of hospitalization and mortality in many countries in the world [1]. Last decades, the occurance of the HF has been increasing, indicating that our understanding of the disease pathogenesis is insufficient and new and affordable treatment are needed [2]. Currently HF is considered as a unique scenario of change in systemic homeostasis, in which myocardium, peripheral organs, neuroendocrine and immune systems dysfunctions are chronic cross-links between stress stimul with continual activation of the stress response [2]. Interest in the role of thyroid hormones (TH) in the HF has increased over the last decade. Previous small studies have shown that TH replacement therapy in patients with HF improves cardiac function, increases exercise tolerance [3]. In current international and national standards of HF treatment, in the absence of hypothyroidism, the use of thyroid hormones is not recommended. At the same time, at non-toxic goiter (NG), which is the most common thyroid pathology, levothyroxine (LT) is a recognized treatment strategy, even in the absence of tyroid gland hypofunction [1]. This makes it possible to study the effect of LT on the course of HF.

The aim is to study the effect of the LT use in patients with NG on the course of HF.

MATERIALS AND METHODS

The study protocol was approved by the local Ethics and Deontology Committee of Government Institution «L. T. Malaya Therapy National Institute». The study procedures were

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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 218 patients with HF with NG were included (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, non-toxic goiter (NG). Exclusion criteria: no informed consent, severe valvular heart defects, HF of other etiology than myocardial infarction, thyro-suppressive treatment, clinical hypothyroidism, pathothyroidism, inflammatory diseases, 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 [1].

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», «T_{4f}» and «T_{3f}» by Hema, Ukraine). Levels of reversible triiodothyronine (T_{3r}) (normal range: 90–350 pg/ml), and of the N-terminal fragment of the prohormon of the Brain natriuretic peptide (NT-proBNP) (norm < 125 pg/ml) were determined using an ELISA kit reagent (Elabscience®, China). Immuno-enzymatic studies were performed on a semi-automatic 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 (LV EDV, LV ESV, respectively) of the LV, 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. NG was diagnosed by ultrasound criteria [4] in the absence of signs of thyroid hyperfunction [5].

109 (50 %) patients (group I) with non-toxic goiter received LT at the time of inclusion in the study (of them 23 (21,1 %) had subclinical hypothyreosis, the remaining patients had laboratory evidence of autoimmune thyroiditis). Group II included 109 patients 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 — 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. IBM®SPSS® Statistics, 20.0 and MedCalc, 18.9.1 (free version) software packages were used.

RESULTS AND THEIR DISCUSSION

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

Table 1

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

Indicator, units	Therapy		X
	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

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

(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 for NG before hospitalization, compared to patients without this treatment, had smaller LV dimensions (EDD and ESD) and volumes (ESV and EDV) (Table 1) and a larger LV EF by 22.9 % (p = 0.0001).

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 for NG 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).

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 in non-toxic goiter on the course of heart failure (n = 218)

Indicator, units	Therapy		X
	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 non-toxic goiter (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

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)		X
		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

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 with NG 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%) ($\chi 2 = 6.559$, at p = 0.038) (see table 5).

Experimental studies have shown that TH counteracts the progression of HF, possibly due to genomic and non-genomic effects in the myocardium and heart vessels and the whole body [6].

Several clinical studies have demonstrated the potential benefits of using thyroid hormones in patients with acute HF [7], the TH treatment reduced the postoperative atrial fi-

brillation, improved hemodynamic parameters, reducing the need for inotropic drugs and reducing troponin I level [8, 9]. The treatment by thyroid hormones reduced the mortality of patients with open-heart intervention [10]. In heart transplantation, TH led to faster hemodynamic stabilization [11]. Similar effects were also obtained with the use of TH in addition to dobutamine in patients with acute myocarditis and hemodynamic instability [12].

Current medical practice adheres to avoiding thyroid hormones replacement therapy for HF. This rule probably arose after the publication of the results of the Coronary Drug Project study (1972) [13], where an excessively high dose of the "inactive" right-rotating thyroxine isomer (D-T_4) was used. Later it became clear that it was converted into a toxic dose of active levothyroxine in the body [3]. Researchers, due to a large dose of D-T_4, sought a significant reduction in serum cholesterol. The results of this study showed a slight increase in the incidence of arrhythmia and mortality [13]. In another Phase II trial on using of DITPA analogue of TH in HF, some improvements in hemodynamics were demonstrated, but there was no credible improvement in exercise tolerance. It is worth noting that the DITPA study also likely used an overdose because the patients treated had an increase in heart rate, decreased body weight, and diarrhea [14]. In our study, patients who took LT before hospitalization due to HF did not differ from patients who did not use this drug in terms of systolic and diastolic blood pressure, heart rate, body mass index, probably because of the low dose of LT (0.63 [0.35; 1.11] μg/kg).

There is an information on two studies in which patients with non-ischemic cardiomyopathy were treated by synthetic LT (L-T4) used orally at a physiological dose of 100 μg/day for a short period (1 week) and for 3 consecutive months [15, 16]. LT was well tolerated and led to an improvement in systolic cardiac function and exercise tolerance and decreased systemic vascular resistance. Low dosage of dobutamine (10 μg/kg per min) in the LT group resulted in a significantly higher increase in heart ejection fraction and heart rate than in patients receiving placebo [15, 16]. This may indicate an increase in myocardial adrenergic sensitivity, according to experimental data on the effect of thyroid hormones on the expression of $ß_1$-adrenoreceptors on the myocyte membrane [17].

The beneficial hemodynamic effects of intravenous LT (20 μg/h) have been reported in 10 patients with cardiogenic shock who did not respond to conventional pharmacological inotropic drugs and intra-aortic balloon counterpulsation [18].

In conclusion, the treatment by thyroid hormones at HF remains, at this point in time, still an «open book». There are several unanswered questions: the regimen, dose, and schedule of TH receiving, the effects of this therapy. Large, multicenter, prospective, placebo-controlled studies are needed to provide information on the efficiency, safety, and impact of thyroid hormones on long-term prognosis.

CONCLUSIONS

The use of levothyroxine in patients with nontoxic goiter in heart failure has a dose-dependent positive effect on the left ventricular ejection fraction. The highest ejection fraction is observed in patients receiving the medicine at a dose over 1.2 μg/kg. Receiving of levothyroxine at a dose of > 0.53 μg/kg results in a significant decrease in the rate of repeated hospitalization during 2 years due to heart failure decompensation.

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ВПЛИВ ЛЕВОТИРОКСИНУ НА ПЕРЕБІГ СЕРЦЕВОЇ НЕДОСТАТНОСТІ У ХВОРИХ З НЕТОКСИЧНИМ ЗОБОМ

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До дослідження включено 218 хворих з серцевою недостатністю (СН) на фоні післяінфарктного кардіосклерозу, що мали нетоксичний зоб (НЗ). 109 (50,0 %) хворих отримували левотироксин (ЛТ) у звязку з НЗ. Визначали рівні ТТГ, $T_{3в}$, $T_{4в}$, $T_{3г}$. Проводили ехокардіоскопію та ультразвукове дослідження щитоподібної залози. Вивчали перебіг СН протягом 2 років. Хворі, що застосовували ЛТ з приводу НЗ, порівнюючи до пацієнтів без даного препарату, мали менші розміри (КДР та КСР) та об'еми (КДО та КСО) лівого шліночка (ЛШ) та більшу на 22,9 % величину фракцію викиду (ФВ) ЛШ ($p = 0,0001$). Хворі, що приймали ЛТ мали нижчий сироватковий рівень NT-proBNP (на 26,3%, $p = 0,009$). У підгрупі хворих, котрі приймали ЛТ у дозі від 0,1 до 0,69 мкг/кг, ФВ ЛШ не відрізнялася від пацієнтів, що не застосовували даний препарат. При дозі 0,7–1,19 мкг/кг, ФВ ЛШ є більшою, порівнюючи до такої у пацієнтів, що не приймали ЛТ (на 37,9 %) та в порівнянні до хворих, що приймали ЛТ в дозі 0,1–0,33 мкг/кг (на 36,9 %). ФВ ЛШ була найвищою у пацієнтів, що приймали ЛТ у дозі > 1,20 мкг/кг. Застосування ЛТ з приводу НЗ протягом 2 років зменшує ризик повторної госпіталізації (ПГ) з приводу декомпенсації СН (відношення шансів = 0,490 (0,281–0,857), $p = 0,018$) та тенденційне зниження ризику досягнення комбінованої кінцевої точки (на 27,9 %, $p = 0,074$). За допомогою ROC-аналізу встановлено, що ризик ПГ хворих на СН з приводу декомпенсації захворювання, зменшується при застосуванні ЛТ в дозі > 0,53 мкг/кг (чутливість — 56,62 %, специфічність — 60,98 %, $p = 0,016$). Застосування левотироксину у хворих з нетоксичним зобом при серцевій недостатності має дозозалежний позитивний вплив на фракцію викиду лівого шлуночка. Найвища фракція викиду лівого шлуночка спостерігається у хворих, що приймали препарат в дозі > 1,2 мкг/кг. Застосування левотироксину в дозі > 0,53 мкг/кг при нетоксичному зобі призводить до вірогідного зниження частоти повторної госпіталізації у зв'язку з декомпенсацією серцевої недостатності протягом 2 років.

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

ВЛИЯНИЕ ЛЕВОТИРОКСИНА НА ТЕЧЕНИЕ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У БОЛЬНЫХ С НЕТОКСИЧЕСКИМ ЗОБОМ

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В исследование включено 218 больных с сердечной недостаточностью (СН) на фоне постинфарктного кардиосклероза, которые имели нетоксический зоб (НЗ). 109 (50,0 %) больных получали левотироксин в связи с НЗ. Определяли уровни ТТГ, $T_{3св}$, $T_{4св}$, $T_{3г}$. Проводили эхокардиоскопию и ультразвуковое исследование щитовидной железы (ЩЖ). Изучали течение СН на протяжении 2 лет. Больные, которые применяли ЛТ, сравнивая с пациентами без данного препарата, имели меньшие размеры (КДР и КСР) и объемы (КДО и КСО) Левого желудочка (ЛЖ) и большую на 22,9 % величину фракции выброса (ФВ) ЛЖ (p = 0,0001), а также более низкий сывороточный уровень NT-proBNP (на 26,3 %, p = 0,009). В подгруппе больных, принимавших ЛТ в дозе от 0,1 до 0,69 мкг/кг, ФВ ЛЖ не отличалась от пациентов, не применявших этот препарат. При дозе 0,7–1,19 мкг/кг, ФВ ЛЖ была большей, по сравнению с таковой у пациентов, не принимавших ЛТ (на 37,9%) и в сравнении с больными, принимавших ЛТ в дозе 0,1–0,33 мкг/кг (на 36,9%). ФВ ЛЖ была наибольшей у пациентов, принимавших ЛТ в дозе > 1,20 мкг/кг. Применение ЛТ на протяжении 2 лет уменьшает риск повторной госпитализации (ПГ) по поводу декомпенсации СН (отношение шансов = 0,490 (0,281–0,857), p = 0,018) и тенденциозное снижение риска достижения кобинированной конечной точки (на 27,9%, p = 0,074). С помощью ROC-анализа установлено, что риск ПГ больных с СН по поводу декомпенсации заболевания, уменьшается при применении ЛТ в дозе > 0,53 мкг / кг (чувствительность — 56,62%, специфичность — 60,98%, p = 0,016). Применение ЛТ у больных имеет дозозависимое положительное влияние на ФВ ЛЖ. Наибольшая ФВ ЛЖ наблюдается у больных, принимавших препарат в дозе > 1,2 мкг/кг. Применение ЛТ дозе > 0,53 мкг/кг приводит к достоверному снижению частоты повторной госпитализации в связи с декомпенсацией сердечной недостаточности на протяжении 2-х лет.

Ключевые слова: сердечная недостаточность, нетоксический зоб, левотироксин, фракция выброса, течение заболевания.

THE EFFECT OF LEVOTYROXINE ON THE COURSE OF HEART FAILURE IN PATIENTS WITH NON-TOXIC GOITER

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The study included 218 patients with heart failure (HF) on the background of post-infarction cardiosclerosis who had non-toxic goiter (NG). 109 (50.0 %) patients received levothyroxine (LT) in connection with NG. Whether the levels of TSH, T_{3f}, T_{4f}, T_{3r} were determined. Echocardioscopy and ultrasound examination of the thyroid gland were conducted. We studied the course of heart failure for 2 years. Patients who used LT, comparing with patients without this drug, had smaller dimensions (EDD and ESD) and volumes (ESV and EDV) of left ventricle (LV) and 22.9 % greater LV ejection fraction (EF) (p = 0.0001), as well as higher low serum NT-proBNP level (26.3 %, p = 0.009). In the subgroup of patients taking LT at a dose of 0.1 to 0.69 μg/kg, LVEF did not differ from patients without this tritment. At a dose of 0.7-1.19 μg/kg, LVEF is higher compared with that of patients who did not take LT (by 37.9%) and patients who took LT at a dose 0.1–0.33 mcg/kg (36.9 %). LVEF was the highest in patients taking LT at a dose of > 1.20 mcg/kg. The use of LT for 2 years reduces the risk of re-hospitalization (RH) due to decompensation of heart failure (Odds ratio = 0.490 (0.281–0.857), p = 0.018) and a tendentious decrease in the risk of combined endpiont achieving (by 27.9 %, p = 0.074). The ROC analysis showed that the risk of RH in patients with heart failure due to decompensation of the disease decreases with the use of LT at a dose of > 0.53 μg/kg (sensitivity – 56.62 %, specificity – 60.98 %, p = 0.016). The use of LT in patients has a dose-dependent positive effect on LVEF. The largest LVEF is observed in patients taking the drug at a dose of> 1.2 mcg/kg. The use of an LT dose of > 0.53 mcg/kg leads to a significant decrease in the frequency of re-hospitalization due to decompensation of heart failure during 2 years.

Key words: heart failure, non-toxic goiter, levothyroxine, ejection fraction, course of the disease.