ORIGINAL ARTICLE

THE EFFECT OF BETA-BLOCKERS ON A COURSE OF CHRONIC HEART FAILURE IN PATIENTS WITH A LOW TRIIODOTHYRONINE SYNDROME

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ABSTRACT

The aim: The aim is to study the effect of β-ABs in patients with LT_3S on the course of HF.

Materials and methods: 354 patients with HF on a background of post-infarction cardiosclerosis were included in the 2-yeared follow-up study. LT_3S was diagnosed at 89 (25.1%) patients. The levels of thyroid-stimulating hormone, free T_{3f} and T_{4f}, and reversible T_3 were determined. The echocardioscopy was performed.

Results: Patients with HF in combination with LT_3S have a heavier functional class by NYHA, greater dilatation of the left heart cavities, less myocardial contractility, a higher frequency of atrial fibrillation and re-hospitalization. The use of β-ABs in patients with HF without LT_3S leads to a likely decrease in hospitalization frequency, while in patients with LT_3S it has an opposite effect. The frequency of rehospitalization increases with an excess of β-ABs dose > 5 mg (equivalent to bisoprolol). At these patients a decrease in serum T_3 level and negative dynamics of parameters of intracardiac hemodynamics are observed.

Conclusions: The use of β-ABs in patients with LT_3S leads to an increase in re-hospitalization at a dose over 5.0 mg (equivalent to bisoprolol). In these patients there is a decrease in serum T_3, an increase in T_4 level; and the ejection fraction decrease; and heart cavities size increase.

KEY WORDS: low triiodothyronine syndrome, β-blockers, thyroid-stimulating hormone, ROC curve, risk, ventricular dilatation, reversible triiodothyronine, heart failure

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INTRODUCTION

The progression of heart failure (HF) is a complex process affecting many organs and systems that leads to hormonal and immune alterations, including low triiodothyronine syndrome (low T_3 syndrome, LT_3S). The LT_3S is characterized by low levels of triiodothyronine (T_3), increased or normal reversible triiodothyronine (T_{3r}), normal or slightly altered levels of thyroid-stimulating hormone (TSH), and normal thyroxine (T_4) content, [1-3]. The occurrence of LT_3S in HF patients may reach 30% [3]. The LT_3S is associated with impaired peripheral conversion of inactive T_4 to active T_3 by deiodinases by increasing proinflammatory potential, hypoxia [4-8]. The LT_3S that accompanies HF can lead to a number of disorders, including the reduction of systolic heart function, the development of arrhythmias, increased vasoconstriction [1, 9-11]. The β-blockers (β-AB) reduce mortality (up to 30%) and morbidity in symptomatic patients with HF [12]. In addition, this group of medications did not show a significant effect on survival in decompensated patients. It is also known that β-ABs lead to blockade of deiodinases, which leads to a decrease in T_3 to T_4 conversion [13], thus they are prescribed to patients with hyperthyroidism. It may be supposed that the use of β-ABs in patients with HF in combination with LT_3S may increase its severity.

THE AIM

The aim is to study the effect of β-ABs in patients with LT_3S on the course of HF.

MATERIALS AND METHODS

The protocol of this prospective cohort study was approved by the local Ethics and Deontology Committee of Government Institution "L.T.Malaya Therapy National Institute" (Ukraine). All study procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. From January 2015 to June 2019, we included patients in the study and conducted prospective follow-up (for 2 years). Patients were involved in the study on admission with the HF decompensation at the cardiology department. 354 patients with HF (110 women and 244 men) of the Caucasian race were included into the study. The inclusion criteria were: signed of the Patient Informed Consent, history of myocardial infarction (MI), verified diagnosis of HF II – IV functional classes (FC) by NYHA. The exclusion criteria: no informed consent, hemodynamically significant valvular heart defects, HF of other aetiology than cardiac infarction, hormone replacement therapy

Table I. Characteristics of groups of patients with HF according to presence /absence of the l LT_3S (T_{3f} criterion ≤ 2.07 pmol / l)

Parameters	Groups of patients with HF (n = 354)		P
	Without LT_3S (n = 265)	With LT_3S (n = 89)	
1	2	3	4
Age, years	58,00 [54,00 – 68,00]	58,00 [54,00 – 66,00]	0,657
Male sex, n (%)	179 (67,5)	65 (73)	χ^2 = 0,936 p = 0,333
IBM, kg/m²	27,65 [25,71 – 31,15]	27,63 [25,52 – 31,74]	0,945
NYHA FC, n (%): II III IV	 124 (46,8) 123 (46,4) 18 (6,8)	 18 (20,2) 54 (60,7) 17 (19,1)	 χ^2 = 24,642 p = 0,0001
Angina pectoris FC, n (%): I II III	 4 (1,5) 29 (10,9) 84 (31,7)	 0 10 (11,2) 33 (37,1)	 χ^2 = 2,143 p = 0,543
Type 2 diabetes mellitus, n (%)	62 (23,8)	28 (31,8)	χ^2 = 2,236 p = 0,135
Coronary intervention, n (%)	19 (7,2)	9 (10,1)	χ^2 = 0,792 p = 0,374
Non-toxic goiter, n (%)	43 (16,2)	28 (31,5)	χ^2 = 9,644 p =0,002
Atrial fibrillation, n (%)	16 (6,0)	12 (13,5)	χ^2 = 5,070 p = 0,024
β-AB, n (%)	208 (78,8)	74 (86,0)	χ^2 = 2,183 p = 0,140
- Carvedilol, n (%)	22 (10,6)	16 (21,6)	χ^2 = 5,711
- Bisoprolol, n (%)	186 (89,4)	58 (78,4)	p = 0,017
ACEI, n (%)	225 (84,9)	81 (91,0)	χ^2 = 2,119 p = 0,146
ARB, n (%)	37 (14,0)	6 (6,7)	χ^2 = 3,255 p = 0,072
MRA, n (%)	125 (47,2)	40 (44,9)	χ^2 = 0,133 p = 0,716
Diuretics, n (%)	223 (84,2)	70 (78,7)	χ^2 = 1,413 p = 0,235
Ivabradine, n (%)	4 (1,5)	1 (1,1)	χ^2 = 0,071 p = 0,790
Digoxin, n (%)	60 (22,6)	19 (21,3)	χ^2 = 0,064 p = 0,800
SBP, mm Hg	147,00 [130,00 – 160,00]	145,00 [130,00 – 160,00]	0,854
DBP, mm Hg	90,00 [80,00 - 100,00]	90,00[80,00 – 100,00]	0,944
HR, min^{-1}	74,00 [66,50 - 82,00]	75,00 [66,00 – 84,00]	0,613
RBC, 10^{12} /l	4,50 [4,10 – 4,82]	4,60 [4,30 - 4,86]	0,194
Hb, g/l	140,00 [128,00 – 150,00]	141,00 [134,00 – 150,00]	0,194
WBC, 10^9 / l	6,30 [5,50 – 7,42]	6,60 [5,40 – 7,40]	0,717
Granulocytes,%	60,30 [54,78 – 66,70]	60,15 [55,65 – 64,43]	0,923
Lymphocytes,%	30,00 [24,60 – 36,70]	31,40 [26,55 – 35,05]	0,367
Monocytes,%	6,70 [5,10 – 8,00]	6,70 [5,10 – 8,25]	0,912
Platelets, 10^9 / l	201,00 [172,25 – 239,00]	207,00 [178,50 – 239,75]	0,408
Creatinine, µmol / l	90,40 [77,00 – 105,80]	92,50 [78,50 – 103,75]	0,899
Glucose, mmol / l	5,47 [4,80 – 6,51]	5,72 [4,93 – 6,73]	0,377
Total cholesterol, mmol/ l	4,71 [3,77 – 5,70]	54,88 [3,77 – 5,91]	0,753
LDL, mmol /l	2,56 [1,87 – 3,48]	2,90 [1,80 – 3,75]	0,208
HDL, mmol /l	1,10 [0,95 – 1,37]	1,00 [0,88 – 1,25]	0,030
VLDL, mmol/l	0,69 [0,46 – 1,07]	0,77 [0,52 – 1,06]	0,326
TG, mmol / l	1,49 [1,03 – 2,26]	1,63 [1,08 – 2,21]	0,635
TSH, mIU/l	1,60 [1,05 – 2,50]	1,36 [0,91 – 2,05]	0,035
T_{3f}, pmol/l	2,87 [2,44 – 3,53]	1,72 [1,51 – 1,87]	0,0001
T_{4f}, pmol/l	14,24 [11,11 - 16,52]	14,89 [12,46 – 16,32]	0,308
T_{3f}, pg/ml	289,54 [214,53 - 367,77]	252,26 [205,55 – 309,75]	0,041
T_{3f} / T_{4f} ratio	0,20 [0,16 – 0,29]	0,12 [0,09 – 0,14]	0,0001
LV EDD, cm	5,40 [5,00 – 5,80]	5,60 [5,20 – 6,00]	0,020
LV EDV, ml	143,15 [119,86 – 168,62]	155,61 [131,23 – 182,17]	0,059
LV ESD, cm	4,07 [3,70 – 4,61]	4,40 [4,00 – 4,93]	0,0001
LV ESV, ml	74,09 [59,10 – 99,23]	89,00 [71,11 – 115,743]	0,0001
IVS, cm	1,20 [1,10 - 1,22]	1,20 [1,10 - 1,21]	0,792
LVPW, cm	1,20 [1,10 - 1,20]	1,15 [1,10 - 1,20]	0,925
LV EF, %	45,97 [37,22 – 55,17]	38,19 [32,18 – 48,05]	0,0001
LV MM, g	317,30 [280,83 – 367,51]	336,07 [302,03 – 378,31]	0,037
LV IMM, g/m²	109,48 [96,20 – 125,32]	114,77 [99,37 – 129,80]	0,307
LA, cm	4,20 [3,90 - 4,50]	4,10 [3,80 – 4,40]	0,255
ILA, cm/m²	0,46 [0,41 – 0,50]	0,48 [0,44 – 0,54]	0,006
RV, cm	2,70 [2,58 - 3,00]	2,80 [2,60 – 3,00]	0,302
RA, cm	3,70 [3,50 – 4,00]	3,60 [3,50 – 3,98]	0,523

Notes: SBP – Systolic blood pressure; DBP –diastolic blood pressure, HR – heart rate, TG – triacylglycerides, ACEI – angiotensin-converting-enzyme inhibitors, ARB – angiotensin II receptor blockers, MRA – Mineralocorticoid receptor antagonists.

with L-thyroxine, thyro-suppressive treatment, clinical or subclinical hypothyroidism, pathothyroidism, inflammatory diseases, other serious pathologies (neoplasm, tuberculosis), which could complicate treatment or reduce life expectancy. Diagnosis of HF and treatment of patients were performed according to the recommendations of the European Society of Cardiologists [14].

For pateintes doppler echocardioscopy was performed using the VIVID-3 ultrasonic 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) , the LV posterior wall (LVPW), the diameter of the left atrium (LA), right ventricle (RV), other options were determined. The left ventricle end-diastolic volume (LV EDV) and the end-systolic volume (LV ESV), the ejection fraction (LVEF) of the left ventricle, the left atrium index (ILA), the mass of the LV myocardium (MM LV) and its index (IMM LV) were calculated.

To determine blood 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})) (normal range – 10–25 pmol / l) reagent kits (ELISA "TSH", "T_{4f}" and "T_{3f}" by Hema, Ukraine) were used. The level of reversible triiodothyronine (T_{3r}) (normal range – 90–350 pg / ml) was determined using an ELISA kit reagent (Elabscience®, China). Immunoferment studies were performed on a semi-automatic enzyme-linked immunosorbent analyser "Immunochem-2100" (High technology, USA). Durin the biennial follow-up period the course of HF was evaluated, the frequency of repeated hospitalizations for decompensation of the disease, mortality, the dynamics of thyroid hormones levels and parameters of intracardiac hemodynamics were studied.

The analysis of the normality of the distribution of indicators was performed using the Shapiro – Wilk test. Continuous variables are given as the median (Me) and the interquantile range (for non-normally distributed variables) or as the mean (M) and the standard deviation (± SD) (in the case of the normal distribution). The quantitative indicators were compared using a non-parametric criterion – Mann – Whitney and a paired T-test (in the study of parameter dynamics). The categorical variables were compared using the Pearson's chi-squared test (χ^2) (Yates correction for traits less than 10). The receiver operating characteristic (ROC) curves were analysed to determine the prognostic level of T_{3f}. The relative risk (RR) of re-hospitalization and mortality was calculated with a 95% confidence interval (CI). P-value less than 0.05 was considered as statistically significant. Statistical processing was performed using IBM® SPSS® Statistics, 20.0 (free-download full Version) and MedCalc, 18.9.1 (free version) software packages.

RESULTS

Previously we reported that the threshold level of T_{3f} for the low T3 syndrome below the lower threshold of its normal range (2.5 pmol / l) did not demonstrate a relationship of this state with peculiarities of the HF course. The threshold value was reduced to ≤ 2.07 pmol / l and the effect of LT_3S on HF course was studied [15].

At the initial stage of the statistical analysis, all patients with HF were divided into 2 groups: the first group included 265 (74.9%) patients who had normal levels of T_{3f}, T_{4f}, and TSH (Table I); in the second – 89 (25.1%) patients with T_{3f} level ≤ 2.07 pmol / l at normal T_{4f} and TSH levels. These patients were diagnosed with LT_3S.

In the group of patients with HF in combination with LT_3S II FC by NYHA was in 20.2% of patients, compared to 46.8% in the group without this syndrome, III FC by NYHA was in 60.7% of patients, versus 46.4% in another group and IV FC was in 19.1% of patients, versus 6.8% in the group without this syndrome ($\chi^2 = 24.642$; p = 0.0001); these patients more often had non-toxic goiter (31.5% versus 16.2%, ($\chi^2 = 9.644$; p <0.002) and atrial fibrillation (13.5% vs. 6.0%, ($\chi^2 = 5.070$; p <0.024) (Table I).

The patients with LT_3S compared with patients without it, had lower HDL (by 9.1%, p = 0.030); TSH (by 15.0%, p = 0.035), T_{3f} (by 36.6%, p = 0.0001), T_{3r} (by 12.9%, p = 0.041) levels, and T_{3f} / T_{4f} ratio (by 40.0%, p = 0.0001); higher LV EDD (by 3.7%, p = 0.020), LV ESD (by 7.2%, p = 0.0001), LV ESV (by 20.1%, p = 0.0001), MM (by 5.9%, p = 0.037) and ILA (by 4.3%, p = 0.006); lower LV EF value (by 7.9%, p = 0.0001) (see Table I).

The patients in both groups did not differ in HF therapy. However, patients with LT_3S were more likely to take carvedilol (21.6% vs. 10.6%, p = 0.017), comparing to patients of another group.

The hospitalization frequency due to HF decompensation within 2 years, among patients with LT_3S, was higher (55.1%, vs. 20.4%, p = 0.0001).

The relative risk of re-hospitalization of HF patients with LT_3S within 2 years was 2.098 [1.506 – 2.921] (p = 0.0001). The relative risk of death of these patients during the specified period, was 1.642 [0.711 – 3.797] (p = 0.245). Thus, the presence of LT_3S significantly increased the relative risk of re-hospitalization within 2 years from 20,4 to 55,1% (see Table II).

The effect of the β-ABs use on the frequency of rehospitalization due to HF decompensation was analyzed (Table III).

In the group of patients with HF without LT_3S, the frequency of re-hospitalization was lower when using beta-blockers, compared to that in patients who could not take this group of medication due to side effects (16.3% vs. 35.1%, respectively, p = 0.002). The relative risk of re-hospitalization in this group when using β-blockers is 0.466 [0.291 – 0.744] (p = 0.0014). Thus, the use of β-blockers in the group of patients with HF without LT_3S leads to a 53.6% reduction in the relative risk of re-hospitalization within 2 years.

In the group of patients with HF, flowing on the background of LT_3S, taking β-AB, there is a tendency to increase the frequency of re-hospitalization, compared with that in patients who were unable to take this group

Table II. The Biennial rehospitalisation and mortality.

Parameters	Groups of patients with HF (n = 354)		χ^2 (p)
	Without LT_3S (n = 265)	With LT_3S (n = 89)	
Rehospitalisation, n (%)	54 (20,4)	49 (55,1)	38,838 (0,0001)
Mortality, n (%)	14 (5,3)	8 (9,0)	1,570 (0,210)

Table III. β-Abs effect on biennial rehospitalization and mortality

Parameters	All patients with HF (n = 354)		χ^2 (p)
	Without β-ABs (n = 72)	With β-ABs (n = 282)	
Rehospitalization, n (%)	25 (34,7)	78 (27,7)	1,387 (0,239)
Mortality, n (%)	6 (8,3)	16 (5,7)	0,694 (0,405)
	Patientes with HF without LT_3S (n = 265)		
	Without β-ABs (n = 57)	With β-ABs (n = 208)	
Rehospitalization, n (%)	20 (35,1)	34 (16,3)	9,685 (0,002)
Mortality, n (%)	3 (5,3)	11 (5,3)`	0,107* (0,744)
	Patientes with HF with LT_3S (n = 89)		
	Without β-ABs (n = 15)	With β-ABs (n = 74)	
Rehospitalization, n (%)	5 (33,3)	44 (59,5)	3,440 (0,064)
Mortality, n (%)	3 (20,0)	5 (6,8)	1,300* (0,255)

Note *χ2Yates

Table IV. Dependence of frequency of hospitalization and mortality on type of β-AB

Parameters	Patients with HF without LT_3S (n = 265)		χ^2 (p)
	Carvedilol (n = 22)	Bisoprolol (n = 186)	
Rehospitalization, n (%)	8 (36,4)	26 (14,0)	7,201 (0,007)
Mortality, n (%)	0	11 (5,9)	1,374 (0,241)
	Patients with HF and LT_3S (n = 89)		
	Carvedilol (n = 16)	Bisoprolol (n = 58)	
Rehospitalization, n (%)	11 (68,8)	33 (56,9)	0,731 (0,393)
Mortality, n (%)	2 (12,5)	3 (5,2)	1,069 (0,301)

of drugs (59.5%, vs. 33.3 %, respectively, p = 0,064) (see Table. 3). The relative risk of re-hospitalization in the LT_3S group when using β-ABs was 2.378 [1,088 – 5,199] (p = 0.029). Thus, the use of β-blockers in patients with HF in combination with LT_3S significantly increases the risk of re-hospitalization from 33.3% to 59.5%.

In the group of patients with HF without LT_3S, 22 patients received carvedilol and 186 – bisoprolol. The incidence of re-hospitalization in the bisoprolol subgroup (14.0%) was significantly lower, compared to that with carvedilol (36.4) (p = 0.007). No significant difference in mortality was found.

In the LT_3S group, 16 patients were treated with carvedilol and 58 with bisoprolol. No significant difference was found in the effect of carvedilol, compared with bisoprolol, on the frequency of hospitalization and mortality in patients with LT_3S (see Table IV).

Taking into account small subgroups of patients with LT_3S taking bisoprolol or carvedilol, for further analysis a unifying dose of these drugs was performed according to the scheme presented in [16].

A ROC analysis was performed to stratify the dose of β-ABs affecting the risk of re-hospitalization in patients with HF. The incidence of hospitalization in the group of patients with HF without LT_3S was found to be higher at a dose of ≤ 5.0 mg (equivalent to bisoprolol), comparing to a higher dose (sensitivity – 85.00% and specificity –47.41%, p = 0,0001).

At the same time, ROC analysis showed the opposite effect of β-ABs in the group of patients with LT_3S. The re-hospitalization incidence of patients with HF in combination with LT_3S increases when the optimal cut-off value for the β-ABs dose exceeds 5 mg (equivalent to bisoprolol) (sensitivity – 67.35% and specificity –57.50%, p = 0.025) (see Table V).

Among all patients, the biennial hospitalization frequency when using β-ABs at a dose less or equal to 5 mg was 33.5%, compared with 23.7% when receiving over 5 mg

Table V. Relationship of β-ABs dose (equivalent to bisoprolol) with rehospitalization (ROC analysis)

Group	Cut-off value	Area under the curve (AUC)	95% CI	Sensitivity, %	Specificity, %	p
All patients with HF (n = 354)	≤ 2,5 mg	0,549	0,498 - 0,600	35,78	73,90	0,131
HF without LT_3S (n = 265)	≤ 5,0 mg	0,686	0,630 – 0,739	85,00	47,41	0,0001
HF with LT_3S (n = 89)	> 5,0 mg	0,634	0,525 – 0,733	67,35	57,50	0,025

Table VI. Dependence of re-hospitalization incidence on dose of β-ABs (n (%))

All patients with HF (n = 354)		χ^2 (p)
≤ 5 mg (n = 194)	> 5 mg (n = 160)	
65 (33,5)	38 (23,7)	4,033 (0,045)
Patients with HF without LT_3S (n = 265)		
≤ 5 mg (n = 155)	> 5 mg (n = 110)	
49 (31,6)	5 (4,5)	29,053 (0,0001)
Patients with HF and LT_3S (n = 89)		
≤ 5 mg (n = 39)	> 5 mg (n = 50)	
16 (41,0)	33 (60,0)	5,523 (0,019)

(p = 0.045) (Table IV). The relative risk of re-hospitalization with β-ABs dose exceeding 5 mg was 0.709 [0.504 – 0.977] (p = 0.048). It can be concluded that the use of β-ABs in such dose at HF (without LT_3S) reduces the relative risk of re-hospitalization by 29.3 %.

Among patients with HF without LT_3S, the biennial re-hospitalization incidence when using β-ABs at a dose less or equal to 5 mg was 31.6%, compared with 4.5% when receiving over 5 mg (p = 0.0001).

The relative risk of re-hospitalization of these patients using dose of β-blockers over 5 mg was 0.144 [0.059 – 0.349] (p = 0.0001). Thus, the use of β-ABs > 5 mg in the group of patients with HF without LT_3S reduces the relative risk of re-hospitalization.

In the group of patients with HF in combination with LT_3S, the biennal re-hospitalization incidence when using β-ABs at a dose of less or equal to 5 mg was 41.0%, compared to 60.0% when receiving over 5 mg (p = 0.019) (see Table VI). The relative risk of re-hospitalization in patients with LT_3S taken β-ABs > 5 mg was 1.609 [1,051 – 2,462] (p = 0.029). Thus, the use of β-ABs > 5 mg in the group of patients with HF in combination with LT_3S increases the relative risk of re-hospitalization by 46.3%.

In order to study the effect of different doses of β-ABs on the dynamics of parameters of intra-cardiac hemodynamics and thyroid hormones levels for 2 years, patients with HF and LT_3S were divided into 2 groups. The first group included 39 (43.8%) patients who failed to increase the dose of β-ABs over 5 mg due to side effect. The second group included 50 (56.2%) patients taking β-blockers at a dose over 5 mg. In the group of patients with LT_3S with a dose of β-ABs below and equal to 5 mg for 2 years, there was an increase in T_{3f} level (by 0.185 ± 0.413 pmol / l, p = 0.011), a decrease in ESD (by 0.480 ± 1.079 cm, p = 0.008) and ESV (20.734 ± 6.984 ml, p = 0.029), an increase in LV EF value (by 10.053 ± 13.370%, p = 0.0001); decrease in LA (0.262 ± 0.719 cm, p = 0.035) and RV size (0.208 ± 0.372 cm, p = 0.010).

In addition, in the subgroup of patients with LT_3S receiving β-ABs at a dose exceeding 5 mg / day during 2 years a decrease in serum T_{3f} level (by 0.107 ± 0.275 pmol / l, p = 0.014), an increase of the T_{4f} level (by 1,148 ± 2,245 pmol / l, p = 0.002), the decrease in the value of the T_{3f} / T_{4f} ratio (by 0.018 ± 0.035, p = 0.002); increase in LV EDD (by 0.350 ± 0.813 cm, p = 0.004), LV EDV (by 24.800 ± 5.14 ml, p = 0.003), LV ESD (by 0.342 ± 1.045 cm, p = 0.003), LV ESV (by 21.325 ± 48.750 ml, p = 0.004), ILA (0.947 ± 0.221 cm, p = 0.0001), and RV (0.419 ± 0.586 cm, p = 0.0001) were observed.

DISCUSSION

The thyroid secretes several hormones, including T_4, T_3, and T_{3r}, and it is the sole source of T_4. Unlike the latter, T_3 (biologically more active hormone) is secreted by the thyroid gland not more than 20% of the total level. The remaining T_3 is synthesized by other tissues (outside the thyroid gland) by enzymaticly removing the iodine atom from the T_4 molecule by deiodinases, which exist in several forms. Type I deiodinase (D_1) is primarily found in the liver and kidneys and is responsible for the synthesis of 80% of T_3. Type II deiodinase (D_2) is mostly located in the brain and muscles, including the human heart, and regulates T_3 tissue concentration. Type III (D_3) deiodinase, converting T_4 to reversible T_3 (inactive), decreases serum T_{3f} level [17]. T_{3f} penetrates the membrane into the cell and is responsible

Table VII. Dependence of thyroid hormone dynamics and intracardiac haemodynamic parameters on dose of β-ABs in patients with HF in combination with LT_3S (n = 89).

Parameters	Dose of β-ABs	
	≤ 5 mg (n = 39)	> 5 mg (n = 50)
1	2	3
TSH, mIU/l	+ 0,027 ± 0,809 (p = 0,833)	+ 0,155 ± 0,895 (p = 0,259)
T_{3f}, pmol/l	+ 0,185 ± 0,413 (p = 0,011)	- 0,107 ± 0,275 (p = 0,014)
T_{4f}, pmol/l	+ 0,539 ± 2,926 (p = 0,276)	+ 1,148 ± 2,245 (p = 0,002)
T_{3f} / T_{4f} ratio	- 0,0002 ± 0,0607 (p = 0,980)	- 0,018 ± 0,035 (p = 0,002)
LV EDD, cm	- 0,221 ± 1,045 (p = 0,194)	+ 0,350 ± 0,813 (p = 0,004)
LV EDV, ml	-13,249 ± 73,454 (p = 0,267)	+ 24,800 ± 5,140 (p = 0,003)
LV ESD, cm	- 0,480 ± 1,079 (p = 0,008)	+ 0,342 ± 1,045 (p = 0,026)
LV ESV, ml	- 20,734 ± 6,984 (p = 0,029)	+ 21,325 ± 48,750 (p = 0,004)
LV EF, %	+ 10,053 ± 13,370 (p = 0,0001)	- 3,245 ± 17,367 (p = 0,197)
LA, cm	- 0,262 ± 0,719 (p = 0,035)	+ 0,060 ± 0,657 (p = 0,526)
ILA, cm/m^2	+ 0,911 ± 0,183 (p = 0,0001)	+ 0,947 ± 0,221 (p = 0,0001)
RV, cm	- 0,208 ± 0,372 (p = 0,010)	+ 0,419 ± 0,586 (p = 0,0001)
RA, cm	- 0,165 ± 0,619 (p = 0,214)	+ 0,067 ± 0,649 (p = 0,515)

for genomic and non-genomic effects. T_3 has a positive inotropic and chronotropic effect on the myocardium, regulating the transcription of myocyte-specific genes [17]. T_3 directly affects vascular unstriated muscles, contributing to dilatation of arterioles and reduced peripheral vascular resistance. For normal functioning of the cardiovascular system, optimal concentrations of thyroid hormones are necessary; their excess or deficiency have a disintegrating effect. A decrease in serum T_3 concentration and a parallel increase in T_{3r} are a common result of many diseases, such as injuries, starvation and post-surgery conditions. [18] Such changes in function of "Hypothalamic-pituitary-thyroid " axis , are generally called as LT_3S. In the fasting state, this transition from the production of the metabolically potent hormone T_3 to the synthesis of the metabolic-inactive inverse (reversible) T_{3r} plays a compensatory role. However, in chronic conditions, such as HF and depression, low T_3 concentration can cause adverse effects [18]. The main mechanism of low serum T_3 concentration in patients with nontyroid disease is reduced D_1 activity in the liver. Increased concentrations of cytokines, such as interleukin-6 and tumor necrosis factor α, cause violation of hepatic D_1 expression. Other mechanisms involved in the pathogenesis of low T_3 syndrome include a decrease in the concentration of thyroid hormone binding proteins and a decrease in the secretion of thyroid hormone and TSH. Dopamine secretion and prolonged hypercortisolemia may play a role in this process [18]. There is no consensus in the literature regarding the criteria for defining low T_3 syndrome. So in [19, 20] a lower value of the range of the norm T_{3f}, which ranged from 4.0 to 2.5 pmol / l, at normal levels of T_{4f} and TSH are used. In the Articles of the Italian researchers [21, 22] new ones in addition to the above mentioned parameters, an additional criterion – an increased T_{3r} level is introduced. In the previous work, we were unable to form a representative group of patients with HF with decreased T_{3f} levels, normal TSH and T_{4f} concentrations, and increased T_{3r} levels [15]. It has also been demonstrated that the risk of re-hospitalization of patients with HF with regard to decompensation of the disease increases when reaching the cut-off value for serum T_{3f} concentration below or equal to 2.07 pmol / l [15]. In our study, the incidence of LT_3S (T_{3f} ≤ 2.07 pmol / l) in patients with HF is 25.1%.

According to Japanese researchers, even patients with HF of I FC by NYHA and in the stage of compensation have some early manifestations of LT_3S [19]. In patients with HF, this syndrome is associated with poor LV function, tachyarrhythmia and increased mortality [23]. A low T_3 concentration in HF is a stronger prognostic predictor than dyslipidemia, age, or LV EF [23]. We revealed that in the group HF in combination with the LT_3S patients have a more severe NYHA functional class, they have more often atrial fibrillation, more severe dilatation of cavities of the left parts of the heart and less contractile capacity of myocardium, higher incidence of rehospitalization due to HF decompensation during two years.

Clinical trial results showed that β-ABs has a positive effect on the clinical course of HF and reduces the risk of five-year mortality by 30% [12, 24, 25]. In Recommendations of the European Society of Cardiologists (ESC) [14] and the American College of Cardiologists and the American Association of Cardiologists (ACC / ANA) [26] it is emphasized that β-ABs are a first-line drug for the treatment of patients with HF. In addition, β-ABs has also long been used in the treatment of symptomatic patients with thyrotoxicosis. This drugs block metabolism of thyroid hormones by inhibiting D_1 outside the glandula [13]. This effect is inherent in the

non-selective β-ABs [27], but it is also characteristic of selective medication [28, 29]. In patients a decrease in serum T_3 concentration [30, 31] and an increase in T_{3r} levels by inhibiting its breakdown are observed. Usually, patients remain euthyroid and have stable serum TSH values [29]. But in patients with low thyroid hormones levels (including LT_3S) at the start of β-ABs treatment, this phenomenon may have clinical implications in the long term [32]. Clinical manifestations of β-ABs withdrawal are also associated with sharp fluctuations in thyroid levels [33, 34].

During the statistical analysis, we revealed that the use of β-ABs in patients with HF without LT_3S leads to a likely reduction in re-hospitalization within 2 years. At the same time, in the presence of LT_3S β-blockers led to an increase in the frequency of re-hospitalization of patients due to HF decompensation. Using ROC analysis, it was found out that the incidence of re-hospitalization in the group of patients with HF without LT_3S was higher at a dose of β-ABs below and equal to 5.0 mg (equivalent to bisoprolol), compared to a higher dose. The reverse effect of β-ABs was detected in the group of patients with LT_3S. The risk of re-hospitalization of patients with HF in combination with low T_3 syndrome increases with an excess of β-blockers dose over 5 mg. In the subgroup of patients receiving β-ABs at a dose over 5 mg / day, within 2 years a decrease in serum T_{3f} level and the T_{3f} / T_{4f} ratio, an increase in T_{4f} level,; further enlargement of the heart cavities and reduction of LV EF were observed. This may indicate further growth affect of low triiodothyronine syndrome.

Thus, it is likely that at the beginning of the treatment by β-ABs in patients with HF it is necessary to exclude the presence of LT_3S. It is not advisable to titrate a dose of β-ABs higher than 5 mg (equivalent to bisoprolol) in patients with HF in combination with LT_3S.

Our research has strengths and weaknesses. The advantage is the study protocol and very strict inclusion criteria. Unlike other studies, this approach has allowed the creation of a very homogeneous group with the exclusion of patients with sub- and clinical thyroid dysfunction, with concomitant pathology that may affect hormone levels. On the other hand, such criteria did not allow the formation of a large group of patients with LT_3S who received β-ABs with different selectivity to receptors. Also, our study is limited to 2 years of follow-up period.

CONCLUSIONS

The incidence of low triiodothyronine syndrome in patients with heart failure is 25.1%. Patients in this category have more severe NYHA functional class, more frequent atrial fibrillation, greater dilatation of the left heart cavities and less myocardial contractility, a higher frequency of re-hospitalization for HF decompensation over two years. The use of β-blockers in patients with heart failure without low triiodothyronine syndrome leads to a likely reduction in hospitalization. At the same time, the use of β-blockers in patients with low triiodothyronine syndrome results in an increased incidence of re-hospitalization. The re-hospitalization incidence in the group of patients with heart failure without low T_3 syndrome is higher at a dose of ≤ 5.0 mg (equivalent to bisoprolol), compared to a higher dose. The effect of β-blockers is reversed in low triiodothyronine syndrome: for this patients the risk of re-hospitalization for HF decompensation when the dose of β-blockers is over 5 mg; a decrease in serum triiodothyronine level and in T_{3f}/ T_{4f} ratio, an increase in thyroxin; further enlargement of the heart cavities and reduction of the ejection fraction are observed.

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