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ASSOCIATIONS OF THE EFFECT OF LEVOTHYROXINE ON THE COURSE OF HEART FAILURE WITH POLYMORPHISMS OF B-ADRENERGIC RECEPTORS GENES

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Objective: *to study the associations of levothyroxine effect on the course of heart failure with polymorphisms of genes of the β-adrenoceptor system.*

Object and methods of the study. We included 218 patients with HF in the setting of post-infarction cardiosclerosis. Genotyping for 4 polymorphisms (Gly389Arg of the β_1-adrenoceptor gene (β_1-AR), Ser49Gly of the β_1-AR gene, Gln27Glu of the β_2-AR gene, and Ser275 of the β3-G protein subunit (GN β_3) was performed by polymerase chain reaction. 109 patients (28.61%) were taking levothyroxine in individually selected doses for at least a year at the time of enrolment in the study, with euthyroid status achieved, according to indications (clinical hypothyroidism in the setting of autoimmune thyroiditis).

Study results. *The use of LT reduces the risk of rehospitalisation (RH) in patients with HF (OR = 0.490 (0.281–0.857), p = 0.018). There was a trend towards a reduction in the risk of achieving the combined endpoint (by 27.9%, p = 0.074). The analysis did not reveal any significant associations of the effect of LT use on the incidence of PG with polymorphisms of the β-adrenoceptor system genes. The division of patients into groups by LT dose (according to ROC analysis) revealed that the use of the drug at a dose > 0.53 μg/kg in homozygous carriers of the C allele of the Gln27Glu (c.79C>G) polymorphism of the β_2-AR gene leads to a reduction in the risk of HG over two years (OR = 0.09 (0.02–0.48)). In the subgroup of patients with heterozygous (C/G) genotype, an increased risk of unfavourable HF course (increased frequency of HF, OR = 3.82 (1.29–11.31), p = 0.0087) was found in the absence of LT. No significant dependence of the effect of LT on the course of HF with other polymorphisms of the β -adrenoceptor system genes was found.*

Conclusions. *Congenital genetic differences in the β-adrenoceptor pathway may affect the effects of levothyroxine. Thus, the use of this drug at a dose of > 0.53 μg/kg in homozygous carriers of the C allele of the Gln27Glu (c.79C>G) polymorphism of the β_2-adrenoceptor gene leads to a decrease in the risk of rehospitalisation due to decompensation of heart failure within two years.*

Key words: *heart failure, gene, polymorphism, β-adrenoceptor, levothyroxine, disease course.*

Introduction. Heart failure (HF) is an important medical, social and economic problem (McDonagh T.A., et al., 2021). The morbidity, prevalence and mortality from this pathology remain high today, and the prognosis is still unfavourable (McDonagh T.A., et al., 2021). Optimisation of existing and development of new treatment strategies is important in HF.

Interest in the role of thyroid hormones (TH) in HF has increased over the past decade. Experimental and a number of clinical studies have demonstrated that thyroid hormones counteract the progression of HF, probably through genomic and non-genomic effects in the myocardium, cardiac vessels and the whole body (Pingitore A., et al., 2008). According to current standards for the treatment of HF, the use of thyroid hormones in the absence of hypothyroidism is not recommended (McDonagh T.A., et al., 2021). At the same time, in patients with primary hypothyroidism that occurred on the background of autoimmune thyroiditis, in the phase of long-term drug compensation, it is possible to assess the effect of levothyroxine (LT) on the course of HF.

Several decades ago, it was noticed that cardiovascular symptoms detected in thyrotoxicosis resemble those in hypercatecholemia. At the same time, it was found that the concentration of catecholamines

in the blood was usually normal or even reduced (Silva J.E., 2000). To explain these observations, it has been hypothesised that TH increases the sensitivity or number of β-adrenoceptors (β-AR) on myocardial cells (Dillmann W.H., 2002). The genes encoding β-ARs have several polymorphisms that affect both the activity of the receptors themselves and the cross-sectional area of the heart and the effectiveness of β-adrenergic blockers (β-ABs) (Hesse C., Eisenach J.H., 2008). It is possible to assume that genetic differences in β-ARs may influence the effects of LT in HF.

Objective: to study the associations of levothyroxine effect on the course of heart failure with polymorphisms of genes of the β -adrenoceptor system.

Object and methods of the study. The protocol of this prospective cohort study was approved by the local Ethics and Deontology Committee of the State Institution "L.T. Malaya National Institute of Therapy of the National Academy of Medical Sciences of Ukraine". All study procedures involving patients were performed in accordance with the ethical standards of the Declaration of Helsinki.

Patients were enrolled in the study at the time of hospitalisation in the cardiology department due to HF decompensation. A total of 218 patients with HF (60 women and 158 men) were included, with a median age of 58.0 [54.0:67.0] years. Inclusion criteria: signed informed consent; history of myocardial infarction (MI); verified diagnosis of HF – NYHA FC II-IV. Exclusion criteria: failure to sign an informed consent, haemodynamically significant valvular heart disease, HF other than post-infarction cardiosclerosis, inflammatory diseases, other serious pathologies (tumour, tuberculosis) that could complicate treatment or reduce life expectancy.

The control group consisted of 55 healthy individuals (without coronary heart disease, HF). Of these, 18 were women (32.7%) and 37 were men (67.3%). The average age was 57.00 [52.00–65.00] years. Statistical analysis revealed no significant difference in age and gender frequency distribution between the control group and patients with HF.

Diagnosis of HF and treatment of patients was performed in accordance with the recommendations of the European Society of Cardiology (McDonagh T.A., et al., 2021).

In 157 patients with HF, polymorphisms of the genes of the β -adrenoceptor system (β-AR) were determined. Three main criteria were used in the selection of gene polymorphisms: 1) localisation in the genes of the β -AR system; 2) frequency of the minor allele in the European population ≥ 5% according to HapMap; 3) a small number or absence of studies on the associations of LT effects.

The dbSNP, SNPinfo, and SNPnexus databases were used to select polymorphisms (Cooper D.S., et al., 2009; Covolo L., 2004). A total of 4 polymorphisms in 3 genes were selected. Table 1 shows the specific primers used for genotyping. The laboratory staff did not know which group the patients belonged to; 10% of all DNA samples were re-genotyped for quality control purposes. Blood samples for molecular genetic studies was drawn into VACUTEST vacutainers with K3EDTA. DNA was extracted from whole blood using a DNA-Sorb-B reagent kit (Amplisense, Russia). The extracted DNA was stored at minus 20°C for no more than 3 months before amplification.

Table 1

Characteristics of the studied polymorphisms

Gene	Polymorphism	Nucleotide substitution	Amino acid substitution	5'-3'(F) and 3'-5'(R) primers for polymerase chain reaction
β_1-AR	rs1801253	p.1165G>C	Gly389Arg	F: ccccgacttccgcaaggccttccag R: gactgctctgctgcgcgcgcagggc
β_1-AR	rs1801252	c.145A>G	p.Ser49Gly	F: ctcgttgctgcctcccgccagcgaa R: gccccgagccgctgtctcagcagtg
β_2-AR	rs1042714	c.79C>G	p.Gln27Glu	F: tgcgccggaccacgacgtcacgcag
GNβ_3	rs5443	c.825C>T	p.Ser275	F: agagcatcatctgcggcatcacgtc R: gtggccttctccctcagtggccgcc

Genotyping of polymorphic sites of β_1-adrenoceptor genes (β_1-AR) (rs1801253; p.1165G>C; p.Gly389Arg), β_2-adrenoceptor (β_2-AR) (rs1042714; c.79C>G; p.Gln27Glu) and β_3-gene of G-protein coupled receptor (GN β3)(rs5443; c.825C>T; p.Ser275) were performed by real-time polymerase chain reaction using Syntola reagent kits according to the manufacturer's instructions. To genotype the Ser49Gly polymorphism of the β1-AR gene (rs1801252; c.145A>G; p.Ser49Gly), TaqMan SNP Genotyping Assay (Assay ID C_8898508_10) and Universal PCR Master Mix (Ref. 4304437) (Thermo Fisher Scientific, USA) were used in accordance with the TaqMan® Universal PCR Master Mix USER GUIDE (Applied Biosystems by Life Technologies). Amplification was performed using the CFX96 Touch Real-Time PCR Product Detection

System (BioRad). CFX Manager Software was used for allelic discrimination. All the polymorphisms we studied were in Hardy-Weinberg equilibrium in the control and study groups, which excluded the possibility of genotyping error.

Doppler echocardiography and ultrasound examination of the thyroid gland were performed using the VIVID-3 system (General Electric, USA) according to standard protocols (Іванів Ю., Оришин Н., 2025).

109 patients (28.61%) were taking levothyroxine in individually selected doses for at least a year at the time of inclusion in the study with euthyroid status, according to indications (clinical hypothyroidism in the setting of autoimmune thyroiditis). They formed group I. Group II also included 109 patients without LT treatment. The median time of LT use before enrolment in the study was 12.0 [10.0; 16.5] months. After discharge from the hospital, patients were followed up for 2 years, the presence of rehospitalisation (RH) for HF decompensation and mortality were taken into account. These indicators were used to determine the combined end point (CEP).

The normality of the distribution of indicators was analysed using the Shapiro-Wilk test. The data are presented as median (Me) and interquartile range (in case of data distribution that differs from normal). Quantitative indicators were compared using the non-parametric Mann-Whitney test. The difference among the frequencies of traits in the groups was assessed by Pearson's χ2criterion (with Yates' correction when the number of traits was less than 10). The odds ratio (OR) with 95% confidence interval (CI) was calculated. ROC analysis was performed to determine the effect of LT dose on the course of HF. The difference between the values was considered statistically significant at the level of significance criterion $p < 0.05$. Statistical processing was performed using IBM software SPSS®® Statistics, 20.0. Genetic and epidemiological analysis was performed using the SNPStats on-line calculator (Sole X., et al, 2006).

Results of the study. Patients in both groups did not differ in age and gender (Table 2). Follow-up of patients for 2 years demonstrated that the use of LT reduces the risk of admission to the cardiology department (OR = 0.490 (0.281-0.857), p = 0.018). There was a tendency to reduce the risk of achieving CEP (by 27.9%, p = 0.074).

Table 2

Characteristics of patient groups (n = 218)

Indicator, units of measurement	Therapy		χ2; p
	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
RH, n (%)	32 (29.4)	50 (45.9)	6.334; 0.012
Death, n (%)	9 (8.3)	6 (5.5)	0.644; > 0.05
CEP, n (%)	39 (35.8)	52 (47.7)	3.188; 0.074

The analysis did not reveal any significant associations of the effect of LT use on the incidence of AP with polymorphisms of the β-AR system genes (Table 3).

The ROC analysis revealed that the risk of rehospitalization in patients with HF decreased with the use of LT at a dose of > 0.53 μg/kg (sensitivity – 56.62%, specificity – 60.98%, p = 0.016). According to these data, HF patients were divided into 3 groups. Group I included patients who did not use LT.

Group II included patients who continued to take LT after enrolment in the study at a dose of (0.1-0.53) mcg/kg. Group III included patients taking LT at a dose > 0.53 mcg/kg.

Patients taking LT at a dose of > 0.53 mcg/kg for 2 years had the lowest incidence of rehospitalisation (27.8%) compared with that of patients taking LT at a dose of 0.1-0.53 mcg/kg (32.4%) and no prescription of this drug (45.9%) (χ2 = 6.559, with p = 0.038).

Further analysis using the SNPStats on-line calculator demonstrated that the use of LT at a dose > 0.53 mcg/kg in homozygous carriers of the C allele (Gln27Gln) polymorphism (c.79C>G) of the β_2-AR gene leads to a reduction in the risk of rehospitalisation within two years (OR = 0.09 (0.02-0.48)) (Table 4). At the same time, in the subgroup of patients with heterozygous (C/G) genotype, an increased risk of unfavourable HF was found (increased frequency of HF, OR = 3.82 (1.29-11.31), p = 0.0087) in the absence of LT.

The analysis did not demonstrate any significant dependence of the effect of LT in different doses on the course of HF with other polymorphisms of the β-AR gene system.

Table 3

Dependence of the frequency of HF on β-AR gene polymorphisms and the use of LT

Gly389Arg (c.1165G>C) polymorphism of the β_1-AR gene (n= 153)						
Polymorphism	Without LT (n = 72)			With LT (n = 81)		
	Without RH	WITH RH	OR (95% CI)	Without RH	With HR	OR (95 % CI)
G / G	21	20	1.00	34	7	0.20 (0.07-0.57)
G/C	13	13	1.11 (0.41-3.00)	25	10	0.4 (0.15-1.07)
C / C	2	3	1.33 (0.19-9.17)	4	1	0.19 (0.02-2.06)
p = 0,67						
Ser49Gly (c.145A>G) polymorphism of $_{the}$b						
Polymorphism	Without LT (n = 74)			With LT (n = 76)		
	Without CEP	WITH CEP	OR (95 % CI)	Without CEP	With CEP	OR (95 % CI)
G / G	29	32	1.00	41	17	0.34 (0.16-0.74)
G/A	8	5	0.49 (0.14-1.75)	22	3	0.11 (0.03-0.41)
p = 0,66						
Gln27Glu (c.79C>G) polymorphism of $_{the}$b						
Polymorphism	Without LT (n = 74)			With LT (n = 83)		
	Without RH	With RH	OR (95 % CI)	Without RH	With RH	OR (95 % CI)
C/C	22	13	1.00	32	3	0.12 (0.03-0.50)
C / G	9	18	3.78 (1.28-11.15	24	10	0.69 (0.25-1.96)
G / G	6	6	1.58 (0.40-6.23)	7	7	1.86 (0.51-6.78)
p = 0,091						
Ser275 (c.825C>T) polymorphism of the GN geneb						
Polymorphism	Without LT (n = 74)			With LT (n = 83)		
	Without RH	With RH	OR (95 % CI)	Without RH	With RH	OR (95 % CI)
C/C	20	24	1.00	31	9	0.21 (0.08-0.55)
C/T	15	12	0.67 (0.25-1.77)	27	11	0.33 (0.13-0.84)
T/T	2	1	0.34 (0.03-4.29)	5	0	0.00
p = 0,32						

Discussion. The effect of TH on cardiovascular function is a complex "mixture" of beneficial adaptive and maladaptive effects. One of the many genomic and non-genomic effects of their action is the impact on the β-AR system of cardiomyocytes (Dillmann Wolfgang H., 2009).

β-ARs are paired transmembrane proteins found on cells throughout the body, including cardiomyocytes and vascular smooth muscle cells. There are three subclasses of ARs (β_1, β_2, β_3) (Naga Prasad SV., et al, 2001). β_1- and β_2-ARs implement catecholamine stimulation on intracellular processes through the cytosolic G-protein, a heterotrimer consisting of three subunits: α, β, and γ (Xiao R.P., 2001).

G-protein, in turn, affects the classical cAMP/protein kinase pathway [13]. The active form of G-protein (Gs), which binds to the allosteric centre of adenylate cyclase, activates the formation of cAMP. cAMP serves as a regulator of the activity of many enzymes.

According to the literature, most studies on the effect of TH on β -ARs focus on their effect on the number of receptors (Carvalho-Bianco K., Reed Larsen., 2004). While the lion's share of studies demonstrated that TH increased the number of β-ARs, some of them also reported an increase in adenylate cyclase activity (Bilezekian JP, Loeb JN., 1983; Pracyk J.B., Slotkin T.A.,1991). Another study found a temporary increase in the affinity of β-AR to epinephrine on the membrane of rat cardiomyocytes after LT treatment, followed by its normalisation after a month of treatment (Hoit B.D., 1997). Only a small number of studies did not demonstrate changes in the amount and sensitivity of β-AR with the use of TH (Novotny J., et al., 1999). T_3 increases the expression of β-ARs (Bahouth S.W., 1991) and the level of their gene transcription (Bahouth S.W., et al. (1997). While these and other classical studies, which are often cited, suggest adrenergic hyperreactivity of the myocardium in hyperthyroidism due to an increase in the amount of β-AR, other studies (Zolk O., et al., 1998; Heubach J.F., et al., 1999) with transgenic mice overexpressing β-AR showed that despite 400-fold overexpression of the receptors, there is no proportional increase in binding sites or receptor-stimulated increase in cAMP production. This suggests that changes in other components of the β-adrenoceptor cascade develop in hyperthyroidism (Carvalho-Bianco K., Reed Larsen., 2004).

The β_1-AR gene is localised on chromosome 10q24-26. Two clinically significant polymorphisms associated with single nucleotide substitutions are known: at position 49 (extracellular N-terminal site), associated with the replacement of the amino acid serine (Ser) with glycine (Gly) and at position 389 (intracellular carboxy-terminal site), associated with the replacement of arginine (Arg) with glycine. The frequency of the Gly allele in the European population is 0.23 (Covolo L., et al., 2004). These β_1-AR variants are thought to play an important role in the clinical course of HF. There is evidence of a longer hospital stay in patients carrying the Gly389 allele of the Arg389Gly polymorphism who underwent cardiac surgery. There were expectations that carriers of the Arg389Arg genotype (CC) would have a lower risk of cardiovascular disease (CVD) than people with the "wild" genotype (GG). Meanwhile, the assessment of its impact on the course of cardiac pathology yielded much more modest results.

We did not obtain reliable data on the association of the Gly389Arg polymorphism of the β_1-AR gene with the effect of LT on the course of HF.

Another frequent polymorphism of the β_1-AR gene is the replacement of the amino acid serine (A allele) with glycine (G allele) at position 49 (Ser49Gly). The frequency of the Gly allele is 0.14 in the European population (Aquilante C.L., 2008). In vitro studies have shown that Ser homozygotes (AA genotype) have lower functional adenylate cyclase activity compared to G allele carriers, but are more sensitive to adrenaline stimulation (Levin M., et al., 2002).

We were unable to obtain reliable data on the association of the Gly49Ser polymorphism of the β_1-AR gene with the effect of LT on the course of HF.

The β_2-AR gene is located on chromosome 5q31_32. While β_1-ARs only activate the G-protein (Gs), β_2-ARs can also inhibit it (Gi), reducing cAMP production (Xiao R.P., 2001). The consequences of the cross-interactions that occur between Gs and Gi proteins activated by β_2-ARs remain not fully understood (Xiao R.P., 2001). Their physiological significance is likely to lie in the tuning of β-adrenergic responsiveness (Carvalho-Bianco K., Reed Larsen., 2004). In addition, such simultaneous activation of these opposing pathways by β_2-adrenoceptors generates independent signals that increase receptor specificity. For example, in cultured cell models of "pure" β_1-AR or β_2-AR, activation of β_1-AR induces apoptosis, whereas stimulation of "pure" β_2-AR activates both pro-apoptotic and anti-apoptotic signals, leading to cellular survival rather than death, as in the β_1-AR model (Zhu W.Z., et al., 2001). This great complexity in the biology of the adrenergic signalling cascade of the β-AR system should be kept in mind when analysing the data on the effect of TH on β-adrenergic sensitivity in the heart (Carvalho-Bianco K., Reed Larsen., 2004). Significant mutations of the β_2-AR gene are Gly16Arg, Gln27Glu, Val34Met and Thr164Ile. Gly16Arg and Gln27Glu are located in the extracellular part of the receptor, while Thr164Ile is located in the transmembrane domain, and Val34Met is a rare mutation in the first transmembrane portal domain. The proportion of small β2-AR polymorphisms in the population is

Table 4

Dependence of PG frequency on β-AR gene polymorphisms and LT dose

Gly389Arg (c.1165G>C) polymorphism of the β1-AR gene (n = 153)									
Polymorphism	No LT (n = 72)			LT (0.1-0.53 μg/kg) (n = 23)			LT (> 0.53 μg/kg) (n = 58)		
	Without RH	WITH RH	OR (95% CI)	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)
G / G	21	20	1.00	8	3	0.38 (0.09-1.69)	26	4	0.15 (0.04-0.51)
G/C	13	13	1.11 (0.41-3.00)	8	3	0.40 (0.09-1.78)	17	7	0.40 (0.13-1.21)
C / C	2	3	1.33 (0.19-9.17)	1	0	0.00	3	1	0.24 (0.02-2.76
p = 0,77									
Ser49Gly (c.145A>G) polymorphism of the β_1-AR gene (n=158)									
Polymorphism	No LT (n = 74)			LT (0.1-0.53 μg/kg) (n = 23)			LT (> 0.53 μg/kg) (n = 60)		
	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)
G / G	29	32	1.00	12	6	0.46 (0.15-1.41)	29	11	0.29 (0.12-0.71)
G/A	8	5	0.48 (0.13-1.71)	5	0	0.00	17	3	0.14 (0.04-0.55)
p = 0,36									
Gln27Glu (c.79C>G) polymorphism of the β_2-AR gene (n = 157)									
Polymorphism	No LT (n = 72)			LT (0.1-0.53 μg/kg) (n = 23)			LT (> 0.53 μg/kg) (n = 58)		
	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)
C/C	22	13	1.00	5	1	0.26 (0.03-2.72)	27	2	0.09 (0.02-0.48)
C / G	9	18	3.82 (1.29-11.31)	12	2	0.27 (0.05-1.46)	12	8	1.12 (0.35-3.61)
G / G	6	6	1.54 (0.39-6.13)	0	3	---	7	4	0.99 (0.23-4.28)
p = 0,0087									
Ser275 (c.825C>T) polymorphism of the GN β_3 gene (n = 157)									
Polymorphism	No LT (n = 74)			LT (0.1-0.53 μg/kg) (n = 23)			LT (> 0.53 μg/kg) (n = 60)		
	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)	Without RH	With RH	OR (95% CI)
C/C	20	24	1,00	9	1	0.08 (0.01-0.71)	22	8	0.25 (0.09-0.72)
C/T	15	12	0,67 (0,25-1,77)	5	5	0.86 (0.21-3.47)	22	6	0.21 (0.07-0.64)
T/T	2	1	0,34 (0,03-4,25)	3	0	0.00	2	0	0.00
p = 0,18									

as follows: Arg16, Glu27, Ile164 – 39%, 43% and less than 5%, respectively, with a rare proportion of Met34 (Xiao R.P., 2001). For some polymorphisms, interethnic variability in allele frequency has been shown: Gln27Glu in Europeans occurs with a frequency of 35%, in African Americans – 21%, in Chinese – 7%. A single-nucleotide substitution of cytosine (C) for guanine (G) at position 79 of the β_2-AR gene leads to the replacement of glutamine (Gln) with glutamic acid (Glu) at codon 27 (rs1042714). The C allele is called the "wild type" because it is the most common in the population, and the glutamic acid allele is less common, so it is called the "mutant" allele. The allelic frequencies of C and G in the general population are 0.55/0.45, respectively. According to the literature, the association of the Gln27Glu β_2-AR polymorphism with the clinical course of HF is rather ambiguous. In 2002, exercise tolerance in patients with compensated HF was investigated and it was found that patients with Arg16/Glu27 had greater endurance compared to the group with Gli16/Gln27 polymorphism. The analysis revealed that the β_2-AR Arg16 and Gln27 polymorphisms may be associated with a lower risk of HF. At the same time, in 2004, other researchers studied 256 cases of HF, paying attention to the β_1AR Arg389Gly, β_2-AR Arg16Gly and Gln27Glu polymorphisms, but found no significant correlation with HF (Covolo L., et al., 2004). Two studies have investigated the effect of β_2-AR gene polymorphisms on the risk of developing and progressing HF. The Italian study included 236 patients with HF and 230 healthy volunteers. No associations were found between Arg16Gly, Gln27Glu polymorphisms and the course of HF (Covolo L., et al., 2004). Another group of researchers reported the results of a randomised trial involving a large number of patients with ischaemic and idiopathic cardiomyopathy. There was no effect of β_2-AR gene polymorphisms 16 and 27 on the risk of developing and the characteristics of HF (Matkovich S.J., et al., 2010).

We were able to establish a dose-dependent association of LT use with the Gln27Glu (c.79C>G) polymorphism of the β_2-AR gene with respect to the effect on the course of HF. Thus, the administration of LT at a dose of > 0.53 μg/kg in homozygous (C allele (Gln27Gln) polymorphism (c.79C>G) of the β_2-AR gene) patients leads to a reduction in the risk of HF over two years (OR = 0.09 (0.02-0.48)). At the same time, in a subgroup of patients with a heterozygous (C/G) genotype, an increased risk of unfavourable HF course was found (increased frequency of HF, OR = 3.82 (1.29-11.31), p = 0.0087) in the absence of LT. In our opinion, the explanation for this phenomenon may be that patients with HF who have the "wild-type" Gln27Gln genotype develop a more rapid decrease in sensitivity in the presence of hypercatecholemia inherent in heart failure (Dayem Ullah AZ, 2012), compared with patients with the Glu27 genotype. The use of LT is likely to block this effect of the polymorphism.

β-ARs implement catecholamine stimulation on intracellular processes through the cytosolic G-protein, a heterotrimer consisting of three subunits: alpha, beta, and gamma (Naga Prasad SV., et al., 2001). The active form of G-protein (Gs), which binds to the allosteric centre of adenylate cyclase, activates the formation of cAMP. cAMP serves as a regulator of the activity of many enzymes. G-proteins are expressed in all human cells. The most common is the C825T polymorphism of the β_3-subunit gene (GNB3) (Sheppard R., et al., 2016). Despite the fact that the T polymorphism is functionally inactive, it leads to alternative splicing of exon 9 (GNB3) and eventually to a “truncated” β3subunit of G-protein. Such an altered subunit increases α-adrenergic activation and is associated with increased activity of signalling pathways. This polymorphism primarily affects vascular reactivity and cardiomyocyte growth. There are few and rather contradictory results of studies of the effect of the GNB3 TT genotype on the course of HF in Europeans.

We were unable to obtain reliable data on the association of the C825T polymorphism of the GNB3 gene with the effect of LT on the course of HF.

Conclusion. Congenital genetic differences in the β-adrenoceptor pathway may influence the effects of levothyroxine. Thus, the use of this drug in a dose > 0.53 μg/kg in homozygous carriers of the C allele of the Gln27Glu (c.79C>G) polymorphism of the β_2-adrenoceptor gene leads to a decrease in the risk of rehospitalisation for decompensation of heart failure within two years (OR = 0.09 (0.02-0.48)).

Prospects for further research. Identification of factors modelling the response to drug prescription in patients with heart failure, taking into account comorbid pathology and their pharmacogenetic profile, is an urgent task of modern medical science. Achievement of this goal allows to increase the effectiveness of drug therapy.

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АСОЦІАЦІЇ ВПЛИВУ ЛЕВОТИРОКСИНУ НА ПЕРЕБІГ СЕРЦЕВОЇ НЕДОСТАТНОСТІ З ПОЛІМОРФІЗМАМИ ГЕНІВ СИСТЕМИ В-АДРЕНОРЕЦЕПЦІЇ

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Мета: *вивчити асоціації впливу левотироксину на перебіг серцевої недостатності з поліморфізмами генів системи β-адренорецепції.*

Об'єкт і методи дослідження. *Включено 218 хворих із СН на фоні післяінфарктного кардіосклерозу. Виконувалося генотипування за 4 поліморфізмами (Gly389Arg гена β_1-адренорецепторів (β_1-АР), Ser49Gly гена β_1-АР, Gln27Glu гена β_2-АР та Ser275 гена β_3-субодиниці G-протеїна (GN β3)) за допомогою полімеразно-ланцюгової реакції. 109 пацієнтів (28,61%) за показами (клінічний гіпотиреоз на фоні АІТ) на момент включення до дослідження приймали левотироксин в індивідуально дібраних дозах не менше року з досягненням еутиреоїдного стану.*

Результати дослідження. *Застосування ЛТ зменшує ризик повторної госпіталізації (далі – ПГ) хворих СН (ВШ = 0,490 (0,281-0,857), p = 0,018). Виявлено тенденційне зниження ризику досягнення комбінованої кінцевої точки (на 27,9%, p = 0,074). Аналіз не виявив вірогідних асоціацій впливу застосування ЛТ на частоту ПГ з поліморфізмами генів системи β-адренорецепції. Поділ пацієнтів на групи за дозою ЛТ (згідно до ROC-аналізу) дав змогу виявити, що застосування препарату в дозі > 0,53 мкг/кг у гомозиготних носіїв С алелля поліморфізму Gln27Glu (c.79C>G) гена β_2-АР веде до зниження ризику ПГ протягом двох років (ВШ = 0,09 (0,02-0,48)). У підгрупі хворих з гетерозиготним (C / G) генотипом виявлено підвищення ризику несприятливого перебігу СН (збільшення частоти ПГ, ВШ = 3,82 (1,29-11,31), p = 0,0087) за відсутності застосування ЛТ. Не виявлено вірогідних залежностей ефекту ЛТ на плин СН з іншими поліморфізмами генів системи β-адренорецепції.*

Висновки. *Вроджені генетичні відмінності в шляхах β-адренорецепції можуть впливати на ефекти левотироксину. Так, застосування цього препарату в дозі > 0,53 мкг/кг у гомозиготних носіїв С алелю поліморфізму Gln27Glu (c.79C>G) гена β_2-адренорецепторів веде до зниження ризику повторної госпіталізації у зв'язку з декомпенсацією серцевої недостатності протягом двох років.*

Ключові слова: *серцева недостатність, ген, поліморфізм, β-адренорецептор, левотироксин, перебіг захворювання.*