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ASSOCIATION OF SEX HORMONE DYNAMICS WITH 10-YEAR SURVIVAL IN MEN WITH IMPLANTED CARDIAC RESYNCHRONIZATION THERAPY DEVICES

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Aim. To assess association of different dynamics of sex hormones with 10-year survival in men with congestive heart failure (CHF) and implanted cardiac resynchronization therapy (CRT) devices.

Methods. Based on tercile of testosterone at the end of the study (TESend), 157 men with CRT (mean age 58.7±9.7 years old; 95 men (60.5%) w/ ischemic CHF) were divided into 3 groups: gr. I (n=52) - TESend<13.3 nmol/l; gr. II (n=53) - TESend>13.3<19.2 nmol/l; gr. III (n=52) - TESend>19.2 nmol/l. Parameters of echocardiography (Echo) were investigated in dynamics, N-terminal fragment of probrain natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), total and free testosterone (TES), estradiol (E2), sex hormone-binding globulin (SHBG), progesterone (PGN), dehydroepiandrosterone sulfate (DHEAS), E2/TES ratio were tested in plasma. Survival in groups was assessed using Kaplan-Meier method.

Results. Groups were comparable in age, presence of ischemic CHF, arterial hypertension and surgeries on myocardial revascularization. Higher incidence of atrial fibrillation, obesity, complete left bundle branch block, tendency to higher incidence of diabetes mellitus and higher body mass index was revealed in gr. I compared to gr. III. At baseline, groups didn't differ in Echo parameters; the highest TES levels were found in gr. III. After CRT, there was less reverse cardiac remodeling, decrease of TES level (p<0.001) in gr. I vs increase of TES level in gr. II (p=0.041) and gr. III (<0.001); E2 level increased (p=0.008), levels of NT-proBNP and IL-6 decreased only in gr. III. In absence of dynamics of E2/TES index and DHEAS level in groups, E2/TES index was the highest and DHEAS level was the lowest in gr. I after CRT. 10-year survival of groups was 17.6%, 42.8%, 46.2% (Log Rank test I-II=0.016; Log Rank test I-III=0.004; Log Rank test II-III=0.528).

Conclusion. Obtained results indicated different dynamics of sex steroids after CRT. Sex hormones variation pattern, interrelated with increase in levels of testosterone, estradiol, dehydroepiandrosterone sulfate and decrease in testosterone to estradiol ratio, was associated with better 10-year survival in men with implantable CRT devices with greater reverse cardiac remodeling and reduction in activity of systemic immune inflammation.

Key words: cardiac resynchronization therapy; sex hormones; testosterone; biomarkers; heart failure; survival

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Chronic heart failure (CHF) is a disease with numerous hormonal abnormalities, among which testosterone (TES) deficiency has been discussed [1]. Low TES in men with CHF is a predictor of 90-day rehospitalisation and all-cause mortality [2]. We have previously shown the influence of TES levels on the efficacy of cardiac resynchronisation therapy (CRT) [3], which is the modern standard of care for patients with heart failure and a broad QRS complex. The relationship between hormonal dynamics and survival in men with implanted CRT devices has not been investigated, making our study urgent.

The aim of the study was to investigate the association between the dynamics of different sex hormones and 10-year survival in men with heart failure and implanted HRT devices.

MATERIAL AND METHODS

The study consecutively included 157 men with implanted CRT devices from 2006 to 2017 from the "Registry of performed cardiac resynchronisation therapy operations" (Certificate of state registration of database No. 2010620077 dated 1 February 2010), who were examined at baseline and in dynamics 1, 3, 6 months after CRT device implantation, then every 6 months. Data from the first and last examinations were retrospectively included in our analysis, a cross-sectional study was performed in November 2020. If the patient died before November 2020, the results of the last visit before death were analysed. To assess the maximum dynamics of the clinical, instrumental and laboratory parameters studied, the data furthest from

baseline were included. According to the dynamics of left ventricular end-systolic volume (LVESV) at the endpoint of the study, patients were divided into non-responders (reduced LVESV of less than 15% of baseline), responders (reduced LVESV of more than 15% but less than 30%) and super-responders (reduced LVESV of more than 30%). The mean age of the men was 58.7±9.7 years.

The diagnosis of CHF was based on the clinical guidelines for the diagnosis and treatment of heart failure [4]. Cardiomyopathy of ischemic origin was diagnosed in 95 (60.5%) men. CRT devices with cardioverter defibrillator function were implanted in 110 (70.1%) patients. The St Mary's Hospital (London) protocol [5] was used to refer patients for CRT implantation, which, together with left ventricular ejection fraction (LVESV) ≤ 35% according to Simpson, signs of intra- and/or interventricular dyssynchrony, functional class (FC) II-IV (NYHA) and duration of the QRS complex > 130 ms were considered. FC was determined using the 6-minute walk test and the clinical criteria of the NYHA classification. Echocardiography (Echo) was performed with a Philips IE -33 (USA), with parameters assessed according to standard criteria: left atrial size, right atrial volume, left ventricular end-systolic and left ventricular (LV) end-diastolic size (LVESS, LVEDS), LVESV and left ventricular end-diastolic volume (LVEDV), left ventricular (LV) ejection fraction (EF), systolic pulmonary artery pressure (SPAP). Plasma levels of N-terminal fragment of natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), total and free TES, progesterone (PGN), dehydroepiandrosterone sulphate (DHEAS), oestradiol (E2), sex hormone binding globulin (SHBG) were analysed by solid phase chemiluminescence immunoassay (sandwich method) on an IMMULITE 1000 analyser (Siemens Diagnostics, USA).

Statistical analysis was performed using the application software package IBM SPSS Statistics 23. The normality of the distribution was assessed using the Kolmogorov-Smirnov method. In case of normal distribution, results were presented as M±sd, where M is the mean and sd is the standard deviation; in case of non-normal distribution, results were presented as Me (median) with interquartile range as 25th and 75th. Pearson's χ^2 was used for qualitative analysis. For comparison of quantitative data in unrelated groups, Student's t-test was used in case of normal distribution and Mann-Whitney test in case of non-normal distribution.

Table 1.

Clinical characteristics of the study groups

Parameter	Group I (n=52)	Group II (n=53)	Group III (n=52)	p
Average observation period, months	51.0 [22.5;93.5]	72,0 [36.5;111.0]	67,0 [35.3;105.8]	un.
Average age, years	59.5±9.2	58.7±10.2	57.4±10.1	un.
CHD, n (%)	33 (63.5)	30 (56.6)	32 (61.5)	un.
PICS, n (%)	18 (34.6)	20 (37.7)	20 (38.5)	un.
CABG, n (%)	4 (7.7)	3 (5.7)	3 (5.8)	un.
PCI, n (%)	14 (26,9)	15 (28.3)	14 (26.9)	un.
II FC CHF, n (%)	26 (50.0)	32 (60.4)	31 (59.6)	un.
III FC CHF, n (%)	22 (42.3)	17 (32.1)	19 (36.5)	
IV FC CHF, n (%)	4 (7.7)	4 (7.5)	2 (3.9)	
AH, n (%)	38 (73.1)	38 (71.7)	34 (65.4)	un.
AF, n (%)	37 (75.0)	31 (60.4)	26 (50.0)	I-III=0,011
RFAVA, n (%)	19 (36.5)	19 (35.8)	16 (30.8)	un.
DM, n (%)	12 (23.1)	6 (11.3)	4 (7.7)	I-III=0,062
Obesity, n (%)	31 (59.6)	24 (45.3)	19 (36.5)	I-III=0,026
Body mass index, kg/m^2	31.6±5.5	29.5±5.6	29.5±6.8	I-II=0,054 I-III=0,096
QRS duration, ms	136.5±36.0	145.1±41.7	139.9±36.4	un.
LBBB, n (%)	29 (55.8)	28 (52.8)	18 (34.6)	I-III=0,042
AAD, %	22 (42.3)	16 (30.2)	15 (28.8)	un.
MRA, n (%)	46 (88.5)	41 (77.4)	42 (80.8)	un.
Diuretics, n (%)	24 (46.2)	30 (56.6)	28 (53.8)	un.
CCB, n (%)	7 (13.5)	13 (24.5)	6 (11.5)	un.
BAB, n (%)	49 (94.2)	49 (92.5)	44 (84.6)	un.
Digoxin, n (%)	10 (19.5)	16 (30.2)	11 (21.2)	un.
Anticoagulants, n (%)	23 (44.2)	30 (56.6)	21 (40.4)	un.
Antiplatelets, n (%)	24 (46.2)	22 (41.5)	24 (46.2)	un.
ACEI and ARB, n (%)	50 (96.2)	51 (96.2)	47 (90.4)	un.
Statins, n (%)	15 (28.8)	23 (43.4)	18 (34.6)	un.
Non-responder, n (%)	32 (61.5)	26 (49.1)	25 (48.1)	
Responder, n (%)	6 (11.5)	6 (11.3)	7 (13.5)	
Super-responder, n (%)	14 (26.9)	21 (39.6)	20 (38.5)	un.

Note: CHD - coronary heart disease; PICS - postinfarction cardiosclerosis; CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; FC CHD - functional class of chronic heart failure according to NYHA classification; AH - arterial hypertension; AF - atrial fibrillation; RFAVA - radiofrequency atrioventricular ablation; DM - diabetes mellitus; LBBB - left bundle branch block; AAD - antiarrhythmic drugs (amiodarone, sotagexal); MRA - mineralocorticoid receptor antagonists; CCB - Ca-channel blockers (amlodipine, feldipine); BAB - β-adrenoblockers; ACEI - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; un. - underestimated (p>0.05).

The relationships between the parameters studied were investigated using Spearman's correlation analysis. Survival analysis was performed by the Kaplan-Meier method. The significance of differences in the studied parameters was taken as $p<0.05$. For multiple comparisons, Bonferroni correction was used, the significant level of difference was $p<0.017$.

RESULTS

Three groups were distinguished according to the tertile of total TES at the CRT endpoint of the study (TESend): group I (n=52) - TESend tertile I (< 13.3 nmol/L); group II (n=53) - TESend tertile II (> 13.3 < 19.2 nmol/L); group III (n=52) - TESend tertile III (> 19.2 nmol/L). The clinical

Table 2.

Dynamics of echocardiography parameters in the study groups

Parameter		Group I (n=52)	Group II (n=53)	Group III (n=52)	P between groups
LA, mm	baseline	52.4±6.3	50.8±4.9	50.5±6.5	
	dynamically	52.1±8.9	49.0±8.6	48.9±8.2	I-II=0.071, I-III=0.060
	Δ	-0.4±7.2	-1.9±8.7	-0.9±5.1	un.
	p in the group	0.720	0.151	0.249	
RA, ml	baseline	87.7±38.0	83.0±24.3	85.1±38.0	
	in dynamics	99.2±47.5	73.0±23.8	84.1±38.5	I-II=0.001, I-III=0,.92, II-III=0.094
	Δ	6.1±44.9	-9.8±27.6	0.6±31.2	I-II=0.073
	p at the group	0.418	0.039	0.908	
LV, mm	baseline	31.4±4.9	29.9±4.8	30.9±4.2	un.
	in dynamics	31.2±5.1	29.8±3.6	31.2±5.2	un.
	Δ	-0.1±5.7	-0.1±4.3	0.2±4.5	un.
	p at the group	0.894	0.920	0.716	
LVESS, mm	baseline	59.1±8.3	58.8±7.1	55.0±9.3	I-III=0.084, II-III=0.078
	in dynamics	52.6±11.1	50.4±10.9	50.1±11.8	un.
	Δ	-5.9±8.2	-6.6±8.5	-4.2±10.5	un.
	p at the group	0,011	0.013	0.081	
LVEDS, mm	baseline	68.4±8.3	67.6±7.1	65.7±7.4	un.
	in dynamics	67.0±10.0	62.8±8.9	63.0±9.5	I-II=0.028, I-III=0.041
	Δ	-1.1±5.9	-5.1±8.1	-2.6±6.4	I-II=0.008, II-III=0.095
	p at the group	0.233	<0.001	0.009	
LVESV, ml	baseline	171.9±54.6	165.0±48.1	152.7±47.1	I-III=0.075
	in dynamics	154.3±66.7	124.5±58.3	126.7±65.8	I-II=0.019, I-III=0.039
	Δ	-18.1±41.4	-43.2±52.2	-27.1±47.8	
	p at the group	0.006	<0.001	<0,001	
LVEDV, ml	baseline	247.1±69.7	239.2±56.0	224.6±56.0	I-III=0.093
	in dynamics	237.9±77.9	204.6±64.9	206.9±71.2	I-II=0.023
	Δ	-8.1±46.3	-36.5±60.0	-16.8±47.7	I-II=0.013, II-III=0.083
	p at the group	0.255	<0.001	0.022	
LV EF, %	baseline	31.1±5.6	31.9±6.8	33.0±7.9	
	in dynamics	37.6±10.5		41.4±12.6	I-II=0.043
	Δ	6.4±9.3	10.8±9.9	8.9±11.2	I-II=0.031
	p at the group	<0.001		<0.001	
SPAP, mm Hg	baseline	45.2±13.3	44.1±11.7	44.1±11.8	
	in dynamics	46.0±13.4	35.4±11.2	37.3±13.4	I-II=0.001 I-III=0.005
	Δ	-2.0±16.6	-10.1±13.6	-5.1±14.7	I-II=0.051
	p in group	0.523	0.001	0.066	

Note: hereafter LA - left atrium; RA - right atrium; RV - right ventricle; LVESS - left ventricular end-systolic size; LVEDS - left ventricular end-dystolic size; LVESV - left ventricular end-systolic volume; LVEDV - left ventricular end-dystolic volume; LV EF - left ventricular ejection fraction; SPAP- systolic pulmonary artery pressure; un. - underestimated (p>0.05)..

characteristics of the groups studied are shown in Table 1. The groups were comparable in terms of age, mean follow-up time, presence of coronary artery disease, arterial hypertension, myocardial revascularization surgery.

The incidence of atrial fibrillation, obesity and complete left bundle branch block was significantly higher in group I than in group III, as was the tendency towards a higher incidence of diabetes mellitus and a higher body mass index.

The groups studied did not differ in terms of baseline Echo parameters. In all groups, a positive dynamic of Echo parameters was observed against the background of CRT.

Table 3.

Dynamics of sex hormones, NT-proBNP, and IL-6 in the study groups

Parameter		RV	Group I (n=52)	Group II (n=53)	Group III (n=52)	P between groups
TES, nmol/L	baseline	7.35-25.7	14.7 [11.3;17.0]	12.3 [10.4;16.2]	17.0 [12.3;21.5]	I-III<0.001, II-III=0.050
	dynamics		9.8 [7.2;11.5]	16.4 [15.2;17.4]	23.8 [21.8;29.5]	I-II<0.001, I-III<0.001, II-III<0.001
	Δ		-5.1 [-7.3;-2.3]	3.6 [-0.3;6.1]	7.8 [2.1;16.0]	I-II<0.001, I-III<0.001, II-III=0.016
	p in the group		<0.001	0.041	<0.001	
TES free index, %	dynamics	19.3-118.4	34.2 [20.2;45.5]	38.8 [31.1;57.4]	64.2	I-II=0.005, I-III<0.001, II-III<0.001
SHBG, nmol/L	dynamics	13-71	28.0 [19.7;46.3]	43.0 [28.4;53.3]	[42.0;100.9]	I-II=0.048
E2, ng/ml	baseline	0-56.0	34.6 [24.4;51.6]	32.6 [22.2;42.1]	38.7 [23.6;61.4]	Un.
	dynamics		30.1 [23.4;41.0]	25.0 [20.0;38.5]	38.3 [28.9;50.3]	I-III=0.002, II-III=0.007
	P in the group		0.692	0.497	57.2 [46.7;64.9]	
PGN, nmol/L	baseline	0-2.39	1.5 [0.8;2.4]	1.0 [0.6;1.7]	0.008	Un.
	dynamics		0.8 [0.6;1.2]	0.7 [0.6;1.0]	1.3 [1.0;2.1]	II-III=0.031
	P in the group		0.011	0.055	0.8 [0.7;1.2]	
DHEAS, μg/dL	baseline	80.0-560	72.4	70.8	0.001	Un.
	dynamics		[36.0;126.3]	[48.2;117.0]	39.3	I-II<0.001, I-III=0.022
	Δ		49.9 [25.9;79.9]	90.8	[23.2;127.0]	I-II=0.076, I-III=0.042
	P in the group		-11.6 [-48.6;10.1]	[50.6;138.8]	65.9	
E2/TES	baseline		0.066	-3, [-19.1;40.0]	[32.6;134.5]	Un.
	dynamics		2.6 [1.9;3.5]	0.475	3.5 [23.8;54.1]	I-II=0.005, I-III=0.004
	P at the group		3.8 [2.4;5.1]	3.0 [1.6;3.8]	0.295	
NT-proBNP, pg/ml	baseline	Up to 125	0.110	1.8 [1.3;2.6]	2.2 [1.5;4.2]	I-II=0.034, II-III=0.058
	dynamics		3292.5 [880.5;	0.351	2.1 [1.8;2.9]	I-II=0.011, I-III=0.012
	Δ		6929.8]	1751.0	0.180	I-III=0.067 II-III=0.034
	p in the group		2082.0	[1020.8;3518.8]	2521.0	
IL-6, pg/ml	baseline	0-9.7	[654.8;5289.8]	863.0	[1140.5;5461.8]	II-III=0.081
	dynamics		313.8	[355.5;2155.0]	934.1 [324.5;	I-III=0,067, II-III=0,016
	Δ		[-492.0;1716.3]	-75.4	2361.8]	I-III=0,053, II-III=0,067
	p in the group		0.145	[-1396.8;898.8]	-985.0	

Note: hereafter RV, reference values (for men over 50 years of age); TES, testosterone; SHBG, sex hormone binding globulin; E2, estradiol; PGN, progesterone; DHEAS, dehydroepiandrosterone sulphate; NT-proBNP, N-terminal fragment of natriuretic peptide; IL-6, interleukin 6.

However, group I showed less inverse cardiac remodelling compared to groups II and III, and there were no significant dynamics of LVEDS, LVEDV and SPAP. During CRT, left atrial size and right atrial volume, LVEDS, LVESV, LVEDV and SPAP were significantly larger in group I compared with groups II and III, and LV EF was smaller. The degree of change (Δ) of LV EF, LVEDS, LVEDV, SPAP was significantly smaller in group I. The dynamics of the Echo parameters are shown in Table 2.

Table 3 shows the dynamics of sex hormones in the groups. At baseline, mean TES levels were within reference values in all groups. Against the background of CRT, the total TES level in group I was correspondingly deficient - the mean TES level was below the norm (12.1 nmol/L) according to the recommendations of the Russian Association of Endocrinologists [6] and the European Association of Urologists [7], and was 9.8 [7.2;11.5] nmol/L. A highly significant decrease in total TES level was observed in group I, while groups II and III showed a significant increase in TES level. The level of free TES in the dynamics was within the reference values in group I, but at a significantly lower concentration than in the groups II and III. The degree of change in total TES in group I was reversed compared to groups II and III. Both at base-

Table 4.

Correlations of sex hormone levels with EchoCG, NT-prpBNP, and IL-6 parameters at study endpoint (start)

	TES	PGN	DHEAS	E2	E2/TES	IL-6	
Common group	LA	r=-0.159; p=0.049		r=-0.242; p=0.003			r=0.207; p=0.009
	RA			r=-0.444; p<0.001			r=0.227; p=0.006
	PV			r=-0.373; p<0.001			
	LVEDS	r=-0.233; p=0.003		r=-0.200; p=0.013		r=0,413; p=0,007	
	LVESS			r=-0.189; p=0.058			
	LVEDV	r=-0.251; p=0.002				r=0,413; p=0,007	
	LVESV	r=-0.243; p=0.002		r=-0.244; p=0.002		r=0,389; p=0,012	
	LV EF	r=0.169; p=0.035		r=0.257; p=0.001			
	SPP	r=-0.260; p=0.004		r=-0.391; p<0.001			r=0.329; p<0.001
	IL-6	r=-0.151; p=0.059			r=-0,154; p=0,056		
	NT-proBNP	r=-0.192; p=0.016		r=-0.462; p<0.001			r=0.190; p=0.017
Group I	LA						r=0.324; p=0.020
	RA			r=0.365; p=0.011			r=0.454; p=0.001
	PV			r=0.358; p=0.009			r=0.321; p=0.020
	LVEDS	r=-0.333; p=0.016		r=-0.270; p=0.053		r=0,456; p=0,022	
	LVESS			r=-0.389; p=0.025	r=0,413; p=0,017		r=0.312; p=0.077
	LVEDV	r=-0.327; p=0.018		r=-0.255; p=0.068		r=0,456; p=0,022	r=0.207; p=0.009
	LVESV	r=-0.291; p=0.036		r=-0.261; p=0.062		r=0,444; p=0,026	r=0.227; p=0.006
	LV EF			r=-0.564; p<0.001			
	SPP			r=-0.391; p=0.004			

line and over time, higher levels of total TES and free TES were found in the III group.

Only in the III group was a highly significant increase in E2 level observed along with an increase in total TES. The E2 level against the background of CRT was significantly higher in the group III than in groups I and II.

In the absence of initial differences in the E2/TES index, its values were significantly higher in group I against the background of CRT.

There were no differences in the initial level of DHEAS and its reliable dynamics against the background of CRT in the groups. However, the values in the dynamics were lowest in group I. Moreover, the degree of change in DHEAS level in groups I and III was significantly opposite, decreasing in group I and increasing in group III. PGN dynamics in the groups were unidirectional - PGN levels decreased against the background of CRT. The levels of NT-proBNP and IL-6 decreased significantly against the background of CRT only in the III group. The concentration of NT-proBNP and IL-6 in dynamics was highest in group I.

The results of the correlation analysis are shown in Table 4. There were statistically significant but weak and medium correlations of sex hormones with Echo parameters both in the total group and in the TESend tertile groups. The highest number of negative correlations with the DHEAS value is remarkable. Of the sex hormones studied, only DHEAS was highly significantly negatively correlated with NT -proBNP level. There was only one positive correlation of E2 with LVESS in the total group. Only positive correlations of E2/TES with Echo levels were observed in all groups. Positive correlations of PGN with LVEDS, LVESS, LVEDV, LVESV were observed in the group with the TES tertile III.

The Kaplan-Meier method was used to assess 10-year survival in the study groups (see figure 1). Group I had the lowest male survival rate, 17.6%, compared to groups II (42.8%) and III (46.2%) (Log Rank test I- II =0.016; Log Rank test I- III =0.004; Log Rank test II-III =0.528). The 10-year survival rates of the men in the groups II and III were comparable.

DISCUSSION

According to the literature, TES deficiency occurs in about 25% of men with heart failure [8]. A study by E.A. Jankowska et al. (2014) found no clear association between TES deficiency and age in men with heart failure: Low TES was found in 62% aged 45 years or younger, 22% aged 46-55 years, and 36% aged 66 years or older. TES deficiency was found in all FC (NYHA). A decrease

Table 4.

Correlations of sex hormone levels with EchoCG, NT-prpBNP, and IL-6 parameters at study endpoint (end)

		TES	PGN	DHEAS	E2	E2/TES	ИЛ-6
Group II	RA			r=-0.421; p=0.003			
	RV			r=-0.318; p=0.024			
	LV EF			r=0.280; p=0.046			
	SPP			r=-0.348; p=0.038			
	NT-proBNP			r=-0.351; p=0.011			
	IL-6	r=-0.320; p=0.019			r=-0.292; p=0.037		
Group III	LA					r=0.900; p=0.037	
	RA			r=-0.420; p=0.002			
	PV			r=-0.418; p=0.002			
	LVEDS	r=-0.300; p=0.031	r=0.395; p=0.004				
	LVESS		r=0.434; p=0.005				
	LVEDV	r=-0.328; p=0.018	r=0.435; p=0.001				
	LVESV	r=-0.322; p=0.020	r=0.359; p=0.009				
	LV EF			r=-0.533; p<0.001			

in TES level was found to be related to the severity of heart failure [9].

In our work, a higher incidence of atrial fibrillation exacerbating the course of heart failure was observed in men in group I compared to group III. The highest levels of NT-proBNP, a recognized marker of heart failure severity, were seen in group I before the background of CRT. Previously, the Freminegem study [10] and the FINRISK study [11] found an association between low TES and the incidence of AF. A higher incidence of obesity, diabetes mellitus and a higher body mass index in group I men may have contributed to the decline in TES over time. The association between TES deficiency and obesity [12] and diabetes mellitus [13] has been discussed extensively in the scientific literature. In an in vitro study, insulin was shown to increase TES synthesis [14] without resistance to it [15]. The different incidence of diabetes implies different insulin levels in the groups and possibly the presence of insulin resistance in Ig, which may lead to an inability of insulin to stimulate TES synthesis and contribute to its deficiency.

A decrease in free TES in heart failure may be due to congestion in the great circulation (liver), which may be associated with an increase in SHBG synthesis and consequent deficiency of free TES. We measured the levels of free TES and SHBG only during the CRT and found that they were also lower in the group I men. A possible reason for the lower level of sex steroids in group I could be the higher activity of systemic immune inflammation, as shown by the dynamics of IL-6 level: the IL-6 level was significantly higher in group I against the background of CRT, while the magnitude of its change was opposite compared to group III, reaching almost significance (p=0.053). Our data confirm the results of experimental in vitro studies with Leydig cells [14]. -Exposure of Leydig cell culture to IL-6 resulted in a highly significant (p<0.001) decrease of TES and PGN concentrations, which proves the negative effect of inflammatory cytokines on the steroidogenesis cascade through direct modulation of Leydig cell viability and function. Our correlations of IL-6 with Echo parameters and NT-proBNP levels indicate its negative effect not only on steroidogenesis but also on reverse cardiac remodeling. The association of low TES with poor prognosis in patients with CHF has been noted in a number of studies [16, 17]. In the HIMS (The Health In Men Study) men aged 70-89 years had the highest overall mortality and coronary heart disease mortality at the lowest (0.25-9.82 nmol/L) and highest (15,79-46.5 nmol/L) TES levels. The lowest risk of death was observed at TES levels of 12.56-15.75 nmol/L [18]. In our study, group I patients had the lowest mean total TES level (9.8[7.2;11.5] nmol/L) and was associated with a worse 10-year survival rate.

Although there is a lively debate in the scientific literature about the role of TES deficiency in the development and progression of heart failure, the evidence on the mechanisms of its effects on the cardiovascular system is quite controversial and remains incompletely understood. TES is a predominant circulating androgen with multiple genomic and non-genomic (rapid) effects that have a complex coordinated pattern of interactions and effects on various cellular functions. The genomic effects of TES are due to its ability to cross the plasma membrane of target cells unimpeded and bind to nuclear androgen receptors, inducing gene transcription and protein synthesis. The non-genomic effects are more rapid in onset and are due to interaction with protein/receptor/ion channels at the plasma membrane.

The complex mechanisms of non-genomic effects remain to be clarified and further investigated. Androgen receptors (AR) were found to be highly expressed in atrial and ventricular cardiac myocytes, so that TES acts directly at the cellular level, indicating a possible active involvement of TES in reverse cardiac remodelling in the setting of CRT. The cardioprotective antioxidant effect of TES is well known and is probably due to its conversion to 17β-oestradiol by aromatisation, which increases the levels of the antioxidant enzymes SOD and GSH-Px and reduces lipid peroxidation (a marker of oxidative damage) in cardiomyocytes [19]. TES attenuates the effects of H2O2, which causes cell death by activating NF-kB, via AR [20]; causes a rapid increase in [Ca2+] in cardiac myocytes due to activation of the plasma membrane AR, which is associated with the PTX-sensitive G-protein PLC/IP3 pathway; increases Na/K-ATPase and Ca2+-ATPase activity [21]; via nuclear and non-nuclear mechanisms, it has a vasodilatory effect through activation of eNOS, modulation of K+ and Ca2+ channels [22]. Low endogenous TES levels are known to be associated with a 3.3-fold increased risk of premature coronary heart disease compared to individuals with normal TES levels [23], likely due to the ability of TES to affect high-density lipoprotein cholesterol levels [24]. The cellular environment, particularly oxidative stress status, has been found to influence the cardiovascular effects of TES.

High levels of oxidative stress are associated with negative effects of TES, whereas low

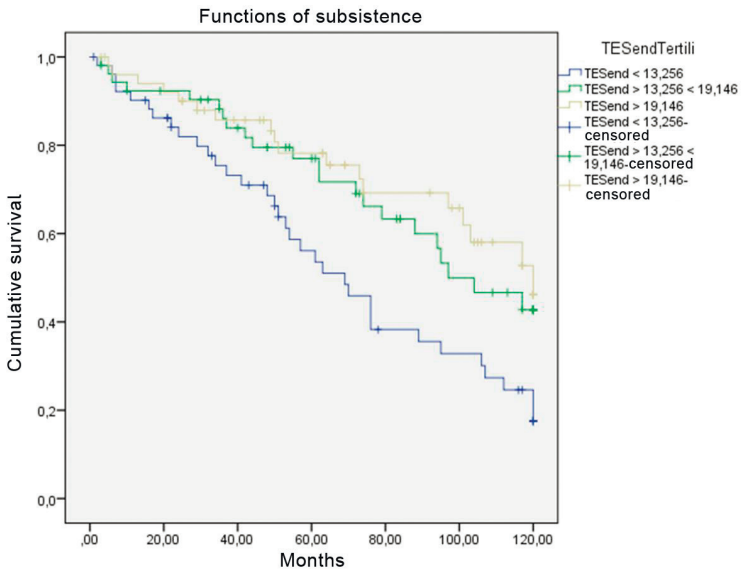

Fig. 1. 10-year survival rate of men with different TES levels on SRT background (Log Rank test I-II=0.016; Log Rank test I-III=0.004; Log Rank test II-III=0.528).

oxidative stress correlates with the cardioprotective effects of TES [25]. One experiment demonstrated that TES can increase the production of reactive oxygen species (ROS) by increasing phosphorylation of c-Src, an upstream regulator of NADPH oxidase expression and activity [26]. TES exacerbated cardiac injury through a mechanism involving conversion of TES to 6β-hydroxytestosterone via cytochrome P-4501B1 and increased NADPH oxidase activity to form ROS [27]. The prooxidant effect of TES under conditions of high oxidative stress due to an increase in ROS levels leads to cardiomyocyte damage, inflammation, cell death and heart failure.

We have found no data in the literature on sex hormone dynamics against a background of CRT. Only sporadic studies of TES levels in a cohort of men with end-stage heart failure (mean age 58 years) who required implantation of a left ventricular assist device are described. TES deficiency was found in 86% of cases in this group of men [28]. However, another study found no reduction in TES levels in patients with dilated cardiomyopathy (age 24-45 years) despite the severity of the disease [29]. It is likely that prognosis is determined by the combination of TES and other sex steroids. Evidence for this is the low mortality from coronary heart disease in patients with reduced TES levels and high DHEAS levels [30]. In our study, DHEAS levels were significantly lower in group I against a background of CRT, and the magnitude of its change decreased significantly compared to groups II and III. Our results confirm the importance of single moment analysis for the dynamics of TES and DHEAS.

The biological role of DHEAS is still unclear. It is metabolised to TES and dihydrotestosterone. It is thought to be a natural cortisol antagonist and to have several protective effects [31]. The negative associations we found of DHEAS with the parameters NT -proBNP and Echo may indicate a decrease in its level in relation to the severity of heart failure. However, its role in reversing cardiac remodelling in the setting of CRT cannot be ruled out. Further studies are needed.

The role of PGN in the development of heart failure is also unclear. In the scientific literature, it is traditionally considered an irrelevant precursor hormone for all steroid hormones, including TES. In a Swedish study of elderly men and women, PGN was found to be associated with an increased prevalence of heart failure [32]. Experimental studies showed cardioprotective effects of PGN: immunosuppressive [33], anti-mineralocorticoid, anti-inflammatory [34], anti-apoptotic [35] and antiarrhythmogenic [36]. One of the proven important physiological properties of PGN is its ability to promote regenerative processes in the myocardium through the proliferation of cardiomyocytes, thus contributing to the restoration of cardiac function [37]. In our study, there was a decrease in PGN levels in the dynamics in all groups, which can be explained by a reduced need for regenerative processes against the background of reverse cardiac remodelling by CRT. Positive correlations of PGN with Echo parameters in the III group seem logical - the larger the cardiac cavity, the greater the need for myocardial regeneration.

Greater inverse cardiac remodelling on the background of CRT is associated with reduced imunntance inflammation activity. It was the III group that showed a significant decrease in IL-6 concentration, the lowest levels of IL-6 were found in dynamics, and the magnitude of IL-6 change was opposite compared to groups I and II.

The importance of oestrogen in the male body has also not been fully explored. Up to 80% of oestrogen in men is formed by aromatisation from TES, the activity of which increases with age, so that older men may have oestradiol levels comparable to those of postmenopausal women [38]. Oestrogens can have physiological and pathophysiological effects in men that depend on their absolute plasma and cellular levels, as well as their ratio to TES (oestradiol/testosterone), which is an important hormonal constant in men [39]. The immunosuppressive effect of E2 has been extensively discussed in the scientific literature [40]. In our work, a significant increase in E2 and its higher concentration against the background of CRT were observed only in the III group. The immunosuppressive properties of E2 may have contributed to a greater decrease in the activity of immune inflammation in the III group. The ratio of E2/TES was lower in the III group than in the I group. In the experiment, a certain ratio of E2/TES=5:1 had an anti-apoptotic effect, which was beneficial in reducing lipid lesions, reducing foam cell formation and endothelial damage, modulating coagulation system function and inhibiting inflammation [41]. How high this ratio should be in men with heart failure has not been studied. The prognostic value of E2 is controversial in the literature [42].

Since in our study the changes in sex hormone levels in the III group were associated with better survival, they probably had a positive physiological meaning.

In this analysis, all patients received optimal drug therapy for at least 3 months before CRT implantation. Due to drug ineffectiveness, patients were implanted with CRT devices. TES levels are known to decrease with age, especially in the setting of chronic disease. The mean age of our patients was 58.7±9.7 years, and the mean follow-up time was 69.8±45.5 months. It is reasonable to assume that TES levels should decrease over 5 years in patients with severe chronic diseases. However, an increase in TES levels was observed in 2/3 of our patients.

Our results suggest a modulating effect of CRT on steroidogenesis, similar to hormone replacement therapy used to prevent the progression of heart failure not only in men but also in women [43]. The effect of HRT on sex steroid synthesis may be mediated via the immune system, neurohormonal regulation and oxidative stress activity. In the scientific literature, there are mainly positive experiences with the use of TES preparations in low doses over a short period of time (½-1 year). There are only 4 studies showing negative experiences with the use of TES preparations in patients with heart failure with severe concomitant diseases [44-47]. All of these studies have been heavily criticised due to financial interests of pharmaceutical companies producing TES drugs. The question of the feasibility of TES therapy in patients with heart failure remains open and uncertain. Our results indicate the safety and prognostic significance of endogenous TES elevation in patients with severe heart failure for more than 5 years. Howev-

er, evidence suggests that the effect of endogenous and exogenous TES may be different [47]. Further studies are needed.

CONCLUSION

Thus, the results of our study indicate different dynamics of sex steroids in the patients with CRT CRT. The pattern of sex hormone changes associated with an increase in testosterone, oestradiol, dehydroepiandrosterone sulphate and a decrease in the oestradiol/testosterone ratio is associated with better 10-year survival in men with implanted CRT devices against a background of greater reverse heart remodelling and lower systemic immune inflammation activity.

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