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ASSOCIATION OF TESTOSTERONE LEVELS AND OXIDATIVE STRESS ACTIVITY WITH 10-YEAR SURVIVAL IN MEN WITH CARDIAC RESYNCHRONIZATION THERAPY

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Aim. To investigate the association of testosterone levels (TES) and oxidative stress activity with 10-year survival in men with cardiac resynchronization therapy (CRT).

Methods. 86 men with CRT (59.0±9.8 years; 66.3% ischemic cardiomyopathy) were divided into 4 groups: Gr.1 (n=19) TES<median level (16.4nmol/l) + myeloperoxidase (MPO) < median level (32.5 ng/mL); Gr.2 (n=18) TES<median level + MPO>median level; Gr.3 (n=23) TES> medians + MPO < median level; Gr.4 (n=26) TES > median level + MPO > median level. Echocardiography parameters, incidence of ventricular extrasystole, TES in plasma, estradiol, progesterone, dehydroepiandrosterone sulfate, norepinephrine, MPO, NT-proBNP, matrix metalloproteinase, tissue inhibitor of metalloproteinase were assessed. Prognostic level of NT-proBNP was assessed by ROC analysis; 10-year survival was measured by Kaplan-Meier method, factors associated with it were evaluated using Cox regression.

Results. The majority of patients were NYHA II and NYHA III for Gr. 3 and Gr.4 respectively (p3-4=0,010). At baseline: there was no difference in echocardiography parameters, levels of NT-proBNP, MPO, steroids, matrix metalloproteinase between groups; tissue inhibitor of metalloproteinase was higher in Gr.2 and Gr.4; the highest norepinephrine levels was in Gr.4. Follow-up: reverse cardiac remodeling was associated with NT-proBNP decreasing and was registered in Gr.4 and Gr. 3. The level of MPO was decreased in Gr.3, Gr.4., and was the highest in Gr.4. The level of estradiol was increased in Gr.1; There were no difference in hormone levels in Gr.2. TES, dehydroepiandrosterone sulfate was increased, but progesterone was decreased in Gr.3 and in Gr.4. The norepinephrine`s levels were increased in all groups. The number of ventricular extrastimuli was increased in Gr.4. Predictive level of NT-proBNP was 756.0 pg/ml (AUC=0.685; p=0.003; sensitivity: 64%, specificity: 68%). The 10-year survival rate was 15.4%; 33.5%; 76.3%; 24.4% for Gr. 1-4 respectively (Log Rank test: Gr.1-2=0.378; Gr.1-3<0.001; Gr.1-4=0.070; Gr.2-3=0.009; Gr.2-4=0.772; Gr.3-4=0.010). The survivance was higher in patients with the best CRT response time (p=0.004), the level of NT-proBNP>756.0 pg/ml (p=0.001) in Gr.1, Gr.2; the best CRT response time (p=0.001), left ventricular ejection fraction (p=0.046), MPO>median (p=0.041), amiodarone administration (0.008) in Gr. 3, Gr. 4.

Conclusion. CRT modulates steroidogenesis. Increase of TES and dehydroepiandrosterone sulfate with lower oxidative stress activity is associated with greater reverse cardiac remodeling and better 10-year survival rate. The higher level of TES and simultaneously MPO more than 32.5 pg/ml were related to less reverse cardiac remodeling, higher rate of amiodarone administration by 5.2 times, increasment of ventricular arrhythmias rate and higher relative risk of death by 4.2 times. Relationship between 10-year survival rate and period of best CRT response indicates less physiological nature of forceful modulating effects of CRT.

Key words: cardiac resynchronization therapy; sex hormones; testosterone; steroidogenesis; heart failure; oxidative stress; NT-proBNP; survival

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Previous studies have established the prognostic significance of testosterone (TES) in men [1] and women [2] with chronic heart failure (CHF). There are positive [3] and negative [4-7] experiences with short courses of TES drugs for the treatment of CHF not only in men but also in women [8]. However, the issue of safety of TES therapy for CHF still remains controversial and open due to the not fully understood mechanisms of TES action on the cardiovascular system.

The role of oxidative stress, manifested in the form of imbalance between prooxidants and antioxidant defense components, in the pathogenesis of cardiovascular pathology [9], including CHF [10], has been established. The experiment revealed the ability of TES to increase the pro-

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duction of reactive oxygen species. The influence of redox status of the cell on the effects of TES was shown - at high activity of oxidative stress the change of cardioprotective effects of TES to cardionegative ones was noted. The pro-oxidant effect of TES under conditions of high oxidative stress activity leads to cardiomyocyte damage, inflammation, cell death, and aggravation of heart failure [11].

Currently, the predictor and prognostic significance of TES and other sex hormones in patients with cardiac resynchronization therapy (CRT), which is the current standard of care for the treatment of patients with CHF with a wide QRS complex and can modulate steroidogenesis, has not been studied [12].

We hypothesized that an increase in TES levels in men on the background of CRT with increasing oxidative stress activity in the dynamics, verified by myeloperoxidase (MPO) levels, is associated with worse survival due to a possible change from cardioprotective to cardionegative effects of TES.

Table 1.

Clinical characteristics of the studied groups

Indicator	TESend < medians		TESend > medians		Reliability of differences
	Group 1 (n=19)	Group 2 (n=18)	Group 3 (n=23)	Group 4 (n=26)	
MFP, months	43.0[32.0;76.0]	53.0[16.8;103.8]	92.0[35.0;146.0]	58.0[33.3;90.3]	p_{1-3}=0.006, p_{3-4}=0.042
Age, years	61.7±8.1	58.6±8.9	55.0±12.6	60.7±8.0	p_{1-3}=0.057, p_{3-4}=0.064
CHD, n (%)	16 (84.2)	13 (72.2)	12 (52.2)	16 (61.5)	p_{1-3}=0.028, p_{1-4}=0.097
PS, n (%)	6 (31.6)	9 (50.0)	10 (43.5)	16 (61.5)	p_{1-4}=0.047
CABG, n (%)	1 (5.3)	0 (0)	5 (21.7)	2 (7.7)	p_{2-3}=0.035
PCI, n (%)	7 (36.8)	6 (33.3)	6 (26.1)	9 (34.6)	n/a
CHF FC II, n (%)	11 (57.9)	6 (33.4)	18 (78.3)	12 (46.2)	p_{1-3}=0.069, p_{2-3}=0.012, p_{3-4}=0.010
CHF FC III, n (%)	5 (26.3)	8 (44.4)	5 (21.7)	13 (50.0)	
CHF FC IV, n (%)	3 (15.8)	4 (22.2)	0 (0)	1 (3.8)	
AH, n (%)	16 (84.2)	13 (72.2)	16 (69.6)	19 (73.1)	n/a
AF, n (%)	12 (63.2)	9 (50.0)	5 (21.7)	6 (23.1)	p_{1-3}=0.020, p_{1-4}=0.016, p_{2-3}=0.066, p_{2-4}=0.041
DM, n (%)	6 (31.6)	2 (11.1)	3 (13.0)	3 (11.5)	n/a
Obesity, n (%)	13 (68.4)	9 (50.0)	7 (30.4)	10 (38.5)	p_{1-3}=0.014, p_{1-4}=0.047
BMI, kg/m^2	31.6±6.0	29.9±5.8	28.4±5.6	28.2±5.6	p_{1-3}=0.081, p_{1-4}=0.057
QRS, ms	160[143;184]	130[101;175]	158[113;176]	167[143;182]	p_{1-2}=0.046, p_{2-4}=0.042
CBBB, n (%)	15 (78.9)	7 (38.9)	13 (56.5)	16 (61.5)	p_{1-2}=0.013,
AAD n (%)	6 (31.6)	10 (55.6)	7 (30.4)	7 (26.9)	n/a
Amiodarone, n (%)	4 (21.1)	10 (55.6)	6 (26.1)	5 (19.2)	
Sotagexal, n (%)	2 (10.5)	0 (0)	1 (4.3)	2 (7.7)	
ACEi, n (%)	17 (89.5)	15 (83.3)	20 (87.0)	22 (84.6)	n/a
Diuretics, n (%)	15 (78.9)	7 (38.9)	13 (56.5)	14 (53.8)	p_{1-2}=0.010
CCB, n (%)	3 (15.8)	5 (27.8)	2 (8.7)	3 (11.5)	n/a
BAB, n (%)	19 (100.0)	17 (94.4)	23 (100.0)	24 (92.3)	n/a
Digoxin, n (%)	4 (21.1)	1 (5.6)	1 (4.3)	4 (15.4)	n/a
OAC, n (%)	9 (47.4)	5 (27.8)	8 (34.8)	6 (23.1)	n/a
Antiplateles, n (%)	9 (47.4)	11 (61.1)	12 (52.2)	16 (61.5)	n/a
ACEi or ARB, n (%)	19 (100.0)	17 (94.4)	23 (100.0)	26 (100.0)	n/a
Statins, n (%)	14 (73.7)	3 (16.7)	8 (34.8)	13 (50.0)	p_{1-2}<0.001, p_{1-3}=0.013, p_{2-4}=0.013
Non-respondents, n (%)	10 (52.6)	14 (77.8)	10 (43.5)	15 (57.7)	p_{2-3}=0.027
Respondents, n (%)	9 (47.4)	4 (22.2)	13 (56.5)	11 (42.3)	

Notes: MFP - mean follow-up period; CHD - coronary heart disease; PS - postinfarction scar; CAB - aorto-coronary bypass grafting; PCI - percutaneous coronary intervention; CHF - functional class of chronic heart failure according to the New York classification; AH - arterial hypertension; AF - atrial fibrillation; DM - diabetes mellitus; BMI - body mass index; CBBB - complete left bundle branch blockade; AAD - antiarrhythmic drugs; MCRA - mineralocorticoid receptor antagonists; CCB - Ca-channel blockers (amlodipine, felodipine); BAB - β-adrenoblockers; OAC - oral anticoagulant therapy; ACEi - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blockers.

The aim of this study was to investigate the association of TES level and oxidative stress activity, verified by MPO level, with 10-year survival of men with CRT.

METHODS

Eighty-six men with CRT from the «Registry of CRT surgeries performed» were included in the study. The mean age of the patients was 59.0±9.8 years. CHF of ischemic genesis was diagnosed in 57 men (66.3%). CRT devices with cardioverter-defibrillator function were implanted in 64 (74.4%) patients. Patients with atrioventricular junction radiofrequency ablation surgery were not included in the study. The indications for CRT implantation were: left ventricular ejection fraction (LVEF) <35%, New York Heart Association (NYHA) functional class II-IV, QRS complex duration> 130 ms. The presence of evidence of intra- and/or interventricular dyssynchrony by echocardiography (Echo) was considered. Patients signed informed consent to participate in the study approved by the ethical committee. Registry patients were examined at baseline, 1, 3, 6, and then every 6 months after CRT implantation. The study presented retrospectively included the results of the baseline and last visit (through November 2020), or in the case of a patient's death, examination data prior to the date of death were included. According to the dynamics of left ventricular (LV) end-systolic volume (ESV), patients were classified into nonresponders (decrease in LV ESV <15%) and responders (decrease in LV ESV >15%). The duration of best response to CRT was retrospectively assessed by the maximum reduction in LV ESV during dynamic follow-up.

Echo was performed on Philips IE-33 (USA) with evaluation of standard parameters: left atrial size and right atrial volume, LV end-systolic and end-diastolic dimensions, LV end-systolic and end-diastolic volumes, LVEF, pulmonary artery systolic pressure. Daily ECG monitoring was performed on the INKART device (St. Petersburg), which was used to estimate the total number of ventricular extrasystoles (VEs) and the number of VEs in 1 hour of the study. LVEF was measured by the Simpson method. Plasma levels of adrenaline, noradrenaline (Nadr), N-terminal fragment of natriuretic peptide (NT-proBNP), MPO, matrix metalloproteinase 9 (MMP-9), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) were analyzed by solid-phase chemiluminescent immunoassay (sandwich method) on the analyzer IMMULITE 1000 (SiemensDiagnostics, USA). The MMP-9/TIMP-1 index was calculated. Determination of highly sensitive fraction of C-reactive protein (hsCRP) in blood serum was performed by immunoturbidimetric method using analytical kits C-REACTIVE PROTEIN hs (BioSystems, Spain) on analyzer Clima MC-15 (Spain). Plasma levels of total TES, progesterone (PGN), dehydroepiandrosterone sulfate, and estradiol were examined by competitive solid-phase chemiluminescent immunoassay.

Statistical analysis

IBM SPSS Statistics 23 application program package was used for statistical analysis. In the case of normal distribution of data estimated by the Kolmogorov-Smirnov method, the results were presented as M±sd, where M is the mean, sd is the standard deviation; in the case of distribution other than normal, the results were presented as Me (median) with interquartile range as the 25th and 75th percentiles. The χ^2 value was used to analyze the qualitative indicators. The Student's t-test was used to compare the quantitative data in unrelated groups if they were normally distributed, and the Mann-Whitney test was used if they were not normally distributed. The Kaplan-Meier method was used to analyze survival. ROC analysis was applied to determine the prognostic level of NT-proBNP. Factors associated with 10-year survival were identified using Cox regression. The level of $p < 0.05$ was taken as reliability of differences between the studied parameters. Bonferroni correction was used for multiple comparisons, significant level of difference $p < 0.013$.

RESULTS

According to the TES and MPO levels at the study endpoint, 4 groups were distinguished: 1 (n=19) - TES < median (16.4 nmol/L) + MPO < median (32.5 ng/mL); 2 (n=18) - TES < median + MPO > median; 3 (n=23) -TES > median + MPO < median; 4 (n=26) - TES > median + MPO > median.

The clinical characteristics of the studied groups are presented in Table 1. Patients with ischemic CHF predominated in all groups. With Bonferroni correction (p=0.013), the groups were comparable in terms of age, frequency of comorbidities. In group 1 compared to group 2, there was a higher incidence of complete blockade of the left bundle branch and the use of diuretics in treatment, which may be an indication of the severity of patients in group 1. There was a higher frequency of prescription of statins in group 1 compared to groups 2 and 3. Group 3 showed significantly lower FC (NYHA) compared with groups 2 and 4, significantly longer follow-up period compared with group 1. At the study endpoint, fewer responders were observed in group 2 compared to group 3.

Initially, there were no significant differences in Echo parameters in the studied groups (Table 2). At the end point, there was no significant change in echocardiographic parameters in groups 1 and 2 with TES levels less than the median. By the end of the study, significant reverse cardiac remodeling was observed only in groups 3 and 4 with TES levels above the median, more pronounced in group 3 with lower oxidative stress activity, in which left atrial reduction was detected in dynamics, LV end-systolic dimension, LV end-diastolic dimension, LV ESV, LV EDV, and increased LVEF, with the degree of decrease (Δ) in LV ESV being highly significant greater compared with group 2, and ΔLVEF being highly significant greater compared with groups 2 and 4. That is, the most favorable reverse cardiac remodeling on the background of CRT at the end point of the study was registered in men of group 3. In group 4, despite the high level of TES, reverse cardiac remodeling was less pronounced - in contrast to group 3, there was no dynamics of the left atrium and LV end-systolic size, and ΔLVEF was significantly smaller.

Initially, the mean TES levels did not differ significantly between the groups (Table 3); however, in group 1, its mean values were close to the deficit, which is a level of less than 12.1 nmol/L according to the recommendations of the Russian Association of Endocrinologists [13] and the

European Association of Urologists [14]. In groups 1 and 2 there was no significant dynamics of TES level on the background of CRT. The degree of change (Δ) of TES was with a negative sign. The mean values of TES at the end of the study in groups 1 and 2 are consistent with its deficiency. In group 3, there was a significant increase in the TES

Table 2.

Dynamics of echocardiography parameters

Indicator		TESend < medians		TESend > medians		Reliability of differences
		Group 1 (n=19)	Group 2 (n=18)	Group 3 (n=23)	Group 4 (n=26)	
LA, mm	initially	51.0[46.0;55.0]	49.0[46.0;52.8]	50.0[46.8;53.3]	48.0[43.5;53.8]	n/a
	at the end	48.5[44.8;54.5]2	45.0[43.0;56.5]	47.0[40.0;52.0]	45.5[40.0;53.0]	n/a
p in group		0.407	0.621	0.031	0.203	-
ΔLA, mm		-1.0[-7.3;3.0]	-3.0[0.0;4.0]	-5.0[-6.5;0.3]	-3.0[-5.5;2.5]	p_{2-3}=0.083
RA, ml	initially	70.0[60.0;101.8]	62.5[51.3;83.8]	67.0[57.8;89.0]	68.0[53.0;98.5]	n/a
	at the end	80.0[48.8;97.5]	65.0[49.0;80.0]	57.5[45.0;83.5]	64.0[54.5;88.0]	n/a
p in group		0.609	0.642	0.409	0.706	-
ΔRA, ml		-2.0[-31.0;28.0]	0.0[-11.8;21.3]	-10.0[-17.0;8.0]	-3.0[-15.0;8.0]	n/a
RV, mm	initially	29.0[27.0;31.0]	28.0[25.0;31.0]	28.5[25.0;32.8]	32.5[27.0;34.0]	n/a
	at the end	30.0[28.0;34.0]	29.0[26.5;33.5]	28.0[26.0;32.0]	30.0[26.0;32.0]	n/a
p in group		0.361	0.173	1.000	0.353	-
ΔRV, mm		2.0[-1.0;4.0]	0.5[-1.0;2.8]	0.5[-4.0;3.0]4	0.0[-3.0;2.0]	n/a
LV ESD, mm	initially	58.0[55.5;66.0]	55.0[46.0;62.5]	59.0[55.3;66.0]	57.5[53.5;60.0]	n/a
	at the end	60.0[42.5;64.0]	55.0[49.3;63.3]	44.0[38.0;64.0]	54.0[46.3;60.5]	n/a
p in group		0.854	0.854	0.006	0.505	-
ΔLVESD, ,		-7.0[-13.0;0.0]	-0.5[-2.5;2.3]	-15.0[-21.3-2.5]	-2.0[-5.3;4.0]	p_{2-3}=0.056, p_{3-4}=0.019
LV EDD, mm	initially	68.0[65.0;78.0]	68.0[62.5;74.5]	68.0[63.8;74.0]	68.5[64.0;71.8]	n/a
	at the end	69.0[56.0;74.0]	65.0[59.5;74.5]	65.0[54.0;74.0]	64.5[57.8;70.3]	n/a
p in group		0.061	0.955	0.018	0.008	-
ΔLV EDD, mm		-3.0[-10.0;3.0]	0.0[-2.0;2.8]	-3.5[-10.5;2.3]	-3.0[-7.0;0.0]	p_{2-4}=0.034
LV ESV, ml	initially	160[140;231]	177[125;202]	173[145;203]	161[138;175]	n/a
	at the end	167[81;205]	141[104;212]	118[76.8;200]	136[87;179]	n/a
p in group		0.920	0.920	0.001	0.014	-
ΔLV ESV, ml		-30.8[-76.2;14.9]	-0.5[-14.8;15.3]	-49.1[-90.5;-13.9]	-19.5[-51.2;-2.0]	p_{1-2}=0.080, p_{2-3}=0.004, p_{2-4}=0.060
LV EDV, ml	initially	239[216;326]	239[198;294]	240[207;280]	235[205;264]	n/a
	at the end	247[154;298]	216[177;294]	216[141;281]	209[165;255]	n/a
p in group		0.812	0.812	0.021	0.012	
ΔLV EDV, ml		-15.0[-70.0;29.0]	0.0[-14.5;21.5]	-33.0[-73.8;18.5]	-17.0[-52.0;5.0]	p_{2-3}=0.041, p_{2-4}=0.059
IVS, mm		11.0[10.0;12.0]	11.0[10.0;14.0]	10.0[9.0;12.0]	10.0[10.0;11.0]	p_{2-3}=00.96
LV PW, mm		11.0[10.0;12.0]	10.0[9.0;12.5]	10.0[9.0;12.0]	10.0[10.0;11.0]	p_{1-4}=0.030
LVEF, %	initially	32.0[29.0;34.0]	31.0[28.5;35.0]	31.0[25.0;33.0]	32.0[27.5;34.0]	n/a
	at the end	38.0[31.0;48.0]	35.0[29.0;40.0]	44.0[31.0;54.0]	36.0[29.8;45.0]	n/a
p in group		0.169	0.169	<0.001	0.003	-
ΔEFLV, %		6.0[1.0;14.0]	1.0[-1.0;4.0]	14.0[3.3;20.8]	4.0[-1.0;10.0]	p_{1-2}=0.075, p_{1-3}=0.055, p_{2-3}<0.001, p_{3-4}=0.007
PASP, mm Hg	initially	42.5[34.5;56.3]	44.0[28.0;52.0]	36.0[35.0;43.8]	45.0[35.3;50.0]	n/a
	at the end	45.0[31.0;62.5]	35.0[28.0;54.0]	29.5[26.8;44.5]4	34.0[29.0;47.8]	p_{1-3}=0.096
p in group		0.716	0.716	0.596	0.270	-
ΔPASP, mm Hg		18.0[-8.0;24.5]	-9.0[-16.0;14.0]	-6.0[-11.0;1.5]	-2.0[-13.0;2.0]	p_{1-4}=0.073

Notes: hereafter LA - left atrium; RA - right atrium; RV - right ventricle; LV ESD - left ventricular (LV) end-systolic dimension; LV EDD - LV end-diastolic dimension; LV ESV - LV end-systolic volume; LV EDV - LV end-diastolic volume; IVS - interventricular septum; LVPW - posterior wall of the LV; LVEF - LV ejection fraction; PASP - pulmonary artery systolic pressure.

level in dynamics by an average of 3.1%, while in group 4 - almost 2-fold (by 82.8%). Only group 3 showed a significant increase in DHEAS levels along with an increase in TES levels. In groups 3 and 4, a significant decrease in PGN level on the background of CRT was revealed. A highly significant increase in E2 level as well as the highest value of estradiol/TES index was observed in group 1.

Table 4 shows the dynamics of the studied biomarkers in the groups. NAdr levels in the groups were within reference values at all study sites. Men in group 4 had significantly higher levels of NAdr at baseline compared to the other groups. The dynamics of NAdr level in the groups was unidirectional - in all groups there was an increase in NAdr level by the end of the study.

The initial mean MPO level in the groups was within the reference values and had no differences between the groups. At the end of the study, there was a significant decrease in MPO levels in groups 1 and 3. In groups 2 and 4 no dynamics of MPO level was revealed, however, in men of group 4 average MPO levels were higher than reference values and greater in comparison with other groups. Δ MPO in group 4 was greater compared to group 1.

At all study points, NT-proBNP levels exceeded reference values, indicating the severity of the patients included in the study. A meaningful decrease in NT-proBNP levels by the end of the study was seen only in group 3 and was associated with the greatest reverse cardiac remodeling in this group.

Average hsCRP levels were higher than reference values initially in groups 2 and 4 with higher activity of oxidative stress, at the end of the study - in all groups hsCRP levels exceeded reference values.

The mean values of MMP-9 in all groups and at all points of the study exceeded the reference values, indicating high activity of collagenolytic processes, the highest in group 4 at the end of the study. Mean TIMP-1 levels were also above reference levels at all study sites, confirming the severity of the men studied. TIMP-1 levels decreased over time in all groups. With the highest initial value and no dynamics of the MMP-9/TIMP-1 index in group 3, its values in the other groups significantly increased.

According to the data of daily ECG monitor, only in group 4, a significant increase in the total number of VEs and VEs at 1 hour of the study was detected in the dynamics. The dynamics of the frequency of VEs is presented in Table 5.

The 10-year survival rates in the groups were estimated by the Kaplan-Meier method: 15.4%; 25.1%; 76.3%; 12.2%, respectively (Log Rank test 1-2=0.378; 1-3<0.001;

Table 3.

Dynamics of sex hormones in groups

		TESend < medians		TESend > medians		Reliability of differences
		Group 1 (n=19)	Group 2 (n=18)	Group 3 (n=23)	Group 4 (n=26)	
TES, nmol/L	initially	12.3[10.4;16.4]	13.3[11.3;15.8]	19.7[9.6;21.7]	12.8[10.5;16.3]	n/a
	at the end	10.7[7.5;14.9]	11.6[8.8;15.0]	20.5[17.3;28.8]	23.4[20.3;26.7]	p_{1-3}<0.001, p_{1-4}<0.001, p_{2-3}<0.001, p_{2-4}<0.001
p in group		0.380	0.208	0.010	0.002	-
ΔTES, nmol/L		-1.8[-5.4;3.6]	-1.7[-8.0;2.7]	7.7[2.1;15.1]	12.8[5.8;16.6]	p_{1-3}=0.002, p_{1-4}<0.001, p_{2-3}=0.006, p_{2-4}=0.001
PGN, ng/ml	initially	30.4[21.6;38.7]	27.9[19.5;45.4]	34.0[20.5;42.6]	29.5[24.9;40.0]	n/a
	at the end	62.0[28.1;135]	50.1[37.1;73.4]	51.3[36.4;103]	45.9[29.1;84.4]	n/a
p in group		0.003	0.191	0.209	0.112	-
ΔE2, ng/mL		26.0[-2.6;102]	17.1[-15.1;37.4]	12.4[-27.2;41.5]	16.5[-15.3;38.3]	n/a
E2/TES, units	initially	2.2[1.9;3.8]	2.1[1.6;3.2]	1.8[1.2;5.4]	2.4[2.1;4.9]	n/a
	at the end	6.2[3.6;13.5]	4.6[3.2;6.7]	2.7[1.6;4.3]	1.9[1.3;4.4]	p_{1-2}=0.063, p_{1-3}=0.001, p_{1-4}<0.001, p_{2-3}=0.008, p_{2-4}=0.001
p in group		0.005	0.068	0.859	0.300	-
PGN, nmol/L	initially	0.8[0.6;1.5]	1.4[0.7;1.7]	1.1[0.7;2.0]	1.2[0.8;2.1]	n/a
	dynamics	0.9[0.6;1.2]	0.6[0.6;0.9]	0.7[0.6;0.9]	0.8[0.6;1.1]	n/a
p in group		0.875	0.091	0.037	0.048	-
ΔPGN, nmol/L		0.0[-0.4;0.3]	-0.6[-1.1;0.0]	-0.4[-0.8;0.0]	-0.4[-1.4;0.2]	n/a
DHEAS, mcg/dL	initially	63.8[39.3;119]	90.4[52.4;192]	52.0[23.7;130]	59.1[23.7;145]	n/a
	dynamics	48.4[25.2;74.7]	58.9[36.8;106]	123[49.1;171]	61.8[37.8;121]	p_{1-3}=0.004, p_{2-4}=0.039, p_{3-4}=0.052
p in group		0.923	0.158	0.041	0.501	-
ΔDHEAS, μg/dL		-5.3[-44.3;43.0]	-14.8[-30.4;-4.3]	34.9[-2.8;81.1]	3.5[-12.1;36.5]	p_{1-3}=0.059, p_{2-3}=0.006

Note: hereafter TES - testosterone (reference values 7.35-25.7 nmol/L); E2 estradiol; PGN - progesterone (reference values 0-56.0 ng/mL, 0-2.39 nmol/L); DHEAS - dehydroepiandrosterone sulfate (reference values 80.0-560.0 μg/dL).

Table 4.

Dynamics of catecholamines, biomarkers of neurohumoral and immune activation, fibro-formation

Indicator	RV	DT	TESend < medians		TESend > medians		Reliability of differences
			Group 1 (n=19)	Group 2 (n=18)	Group 3 (n=23)	Group 4 (n=26)	
NAdr, ng/mL	0,093-33,3	initially	1.1[0.2;4.3]	2.1[1.1;3.7]	0.6[0.4;7.0]	8.0[5.9;13.9]	p_{1-4}=0.005, p_{2-4}=0.004, p_{3-4}=0.033
		at the end	12.9[6.4;16.5]	11.6[6.2;38.8]	13.6[6.5;31.9]	13.8[12.2;19.7]	n/a
p in group			0.055	0.043	0.028	0.050	
Δ NADr, ng/mL			10.7[0.9;17.0]	7.9[3.1;16.6]	10.5[3.4;22.8]	5.2[-1.7;13.7]	n/a
MPO, ng/mL	1,45-72,7	initially	38.4[19.4;84.0]	42.0[24.1;62.2]	48.8[26.9;82.5]	50.2[31.7;86.1]	n/a
		at the end	25.0[16.6;29.1]	54.4[42.7;85.8]	21.5[12.6;28.2]	73.0[42.8;92.3]	p_{1-2}, p_{1-4}, p_{2-3}, p_{3-4}<0.001
p in group			0.014	0.889	0.002	0.460	
Δ MPO, ng/mL			-11.6[-62.6;1.5]	-1.0[-22.6;116.0]	-27.1[-68.5;-8.2]	6.4[-14.2;37.8]	p_{1-4}=0.033, p_{2-3}=0.094, p_{3-4}=0.004
NT-proBNP, pg/mL	Up to 125	initially	2275.5[729.0;5699.0]	2399.5[800.8;8013.3]	1788.0[1258.5;6636.5]	2887.0[862.0;5789.0]	n/a
		at the end	1120.0[388.0;6304.0]	695.5[411.8;4044.0]	386.0[183.0;2319.0]	980.6[436.3;2463.8]	p_{1-3}=0.037
p in group			0.638	0.345	0.015	0.075	
Δ NT-proBNP, pg/mL			276.5[-1059.8;1044.8]	344.5[-1003.5;3925.3]	-982.7[-1850.5;301.3]	-852.5[-1891.3;-16.0]	p_{2-3}=0.071
hsCRP, mg/mL	<3,0	initially	2.5[1.5;4.2]	3.1[0.9;11.4]	2.7[0.4;6.7]	4.2[2.6;8.3]	n/a
		at the end	4.8[2.3;10.0]	6.0[4.0;11.7]	6.3[3.8;8.4]	6.0[2.6;11.8]	n/a
p in group			0.041	0.983	0.412	0.363	
Δ hsCRP, mg/mL			1.8[-0.3;6.9]	-0.9[-3.6;3.9]	2.2[-1.4;5.7]	1.9[-3.6;7.2]	n/a
MMP-9, ng/mL	2,0-139	initially	148.4[127.0;208.5]	126.9[108.6;206.1]	239.4[174.9;250.9]	168.6[123.5;252.6]	p_{1-3}=0.080, p_{2-3}=0.059
		at the end	163.6[136.9;223.7]	220.9[161.8;265.1]	175.0[98.7;190.0]	211.2[153.7;258.9]	p_{2-3}=0.033, p_{3-4}=0.012
p in group			0.307	0.119	0.234	0.480	
Δ MMP-9, ng/mL			-28.3[-73.4;101.2]	81.7[-52.6;131.2]	-51.7[-146.3;3.5]	39.4[-85.5;120.3]	p_{1-3}=0.090, p_{2-3}=0.045, p_{3-4}=0.065
TIMP-1, ng/mL	92-116	initially	242.1[210.5;408.9]	485.2[150.0;692.9]	187.2[156.4;242.2]	374.6[191.2;492.9]	p_{1-3}=0.076, p_{2-3}=0.006, p_{3-4}=0.019
		at the end	142.9[117.5;193.4]	162.4[123.3;204.9]	115.4[102.7;164.3]	145.5[115.5;198.9]	p_{1-3}=0.071, p_{2-3}=0.057
p in group			0.001	0.035	0.074	0.003	
Δ TIMP-1,ng/mL			-116.9[-215.9;-44.1]	-312.2[-588.1;-20.3]	-68.0[-113.5;14.6]	-270.4[-366.7;113.4]	p_{2-3}=0.039, p_{3-4}=0.008
MMP-9/TIMP-1, units		initially	0.6[0.3;0.8]	0.2[0.2;0.7]	1.2[0.9;1.4]	0.5[0.3;1.0]	p_{1-3}=0.022, p_{2-3}=0.007, p_{3-4}=0.037
		at the end	1.1[0.8;1.8]	1.3[0.9;2.0]	1.4[0.9;1.7]	1.4[1.1;2.1]	n/a
p in group			0.010	0.046	0.800	0.001	

Note: hereinafter RV - reference values; TD - time of determination; NADP - norepinephrine; hsCRP - C-reactive protein; NT-proBNP - N-terminal fragment of natriuretic peptide; MMP-9 - matrix metalloproteinase 9; TIMP-1 - tissue inhibitor of matrix metalloproteinase 1; MPO - myeloperoxidase.

1-4=0.070; 2-3=0.004; 2-4=0.889; 3-4=0.004). The best 10-year survival was observed in group 3 with high TES and low MPO. In the 4 high TES and MPO groups, survival was comparable to the low TES groups. Using ROC analysis, a prognostic NT-proBNP level > 756.0 pg/mL was assessed in the overall group (AUC=0.685; p=0.003; sensitivity 64%, specificity 68%).

Factors associated with 10-year survival in subgroups with different levels of TES were identified using Cox regression (Table 6). According to single-factor analysis in the subgroup with TES level < median (groups 1 and 2), the following factors were significant: time to best response to CRT, presence of left bundle branch block, end-point Echo parameters (right atrium, LV end-diastolic volume, LV ESV), NT-proBNR > 756.0 pg/mL, and MMP-9 level at the end of the study. When these factors were included in the multivariate analysis, the following were associated with 10-year survival: time to best response to CRT and NT-proBNR > 756.0 pg/mL.

In the subgroup with TES level > median (groups 3 and 4), the following were significant in single-factor analysis: duration of best response to CRT, echocardiogram parameters at the end of the study (LV ESV, LVEF), hsCRP level at end point, MPO > median (32.5 ng/mL), and antiarrhythmic drug intake. In multivariate analysis, the following were associated with 10-year survival: duration of best response to CRT, LVEF at endpoint, MPO > median, and antiarrhythmic drug use. The fact that MPO levels exceeded the median (32.5 pg/mL) in an endpoint with high TES increased the relative risk of death by 4.2-fold, and taking an antiarrhythmic drug by 5.2-fold (Fig. 1). In all groups, the predominant antiarrhythmic drug was amiodarone.

DISCUSSION

According to the literature in men with CHF, the prevalence of low TES ranges from 30 to 50% and correlates with the severity of CHF, FC (NYHA) [1]. However, the information on the prognostic value of TES level is rather contradictory. In our study, baseline mean TES values were close to its deficiency (12.1 nmol/L) in men in group 1, and at the end of the study in groups 1 and 2. In men in group 4, baseline and trend mean TES levels were within reference values; however, 10-year survival was comparable to groups 1 and 2. Clearly, it is not appropriate to consider the prognostic value of TES in isolation.

As the predominant circulating androgen in males, TES is known to have genomic and non-genomic (fast) effects that act in concert on multiple cellular functions. The genomic actions of TES induce gene transcription and protein synthesis. Non-genomic (fast) effects are related to interactions with protein/receptor/ion channels of the plasma membrane, are still not fully understood and require clarification. The action of TES at the cellular level is mediated through androgen receptors (ARs) highly expressed in atrial and ventricular myocardial cells. Depending on the redox status of the cellular environment, cardioprotective or cardionegative effects of TES on the cardiovascular system are possible [11]. The ability of TES to increase the production of reactive oxygen species (ROS) by increasing the phosphorylation of c-Src, which is a regulator of NADPH-oxidase expression and activity, has been shown experimentally [15]. The prooxidant effect of TES is possible due to its conversion by cytochrome P-4501B1 into 6β-hydroxytestosterone and increased NADPH-oxidase activity with the formation of ROC, which is accompanied by cardiomyocyte damage, inflammation, cell death, and aggravation of heart failure [16]. The results we obtained do not contradict the experimental data. In men of group 4, normal TES level initially and its increase on the background of CRT (by 82.8%) in conditions of increased activity of oxidative stress is associated with less reverse cardiac remodeling, shorter follow-up period, worse 10-year survival compared to group 3. Despite the high TES rate over time, the survival of men in group 4 was comparable to groups 1 and 2 with low TES.

The cardioprotective antioxidant effect of TES may be based on its conversion to 17β-estradiol by aromatization, which increases the levels of antioxidant enzymes SOD and GSH-Px and reduces lipid peroxidation in cardiomyocytes [17]. TES via AR attenuates the effect of hydrogen peroxide (H_2O_2) initiating cell death through activation of NF-kB [18]; affects calcium metabolism by causing a rapid increase in [Ca^{2+}] in cardiomyocytes through activation of plasma membrane AR associated with PTX-sensitive G-protein-PLC/IP3 signaling pathway; increases the activity of Na/K-ATPase, Ca^{2+}-ATPase [19]; has a vasodilating effect by activation of eNOS, modulation of K^+ and Ca^{2+}channels [20]. In group 3, the cardioprotective effect of TES under conditions of low oxidative stress activity may have contributed to greater reverse cardiac remodeling,

Table 5.

Dynamics of the frequency of ventricular extrasystole in the studied groups

		TESend < medians		TESend > medians		Reliability of differences
		Group 1 (n=19)	Group 2 (n=18)	Group 3 (n=23)	Group 4 (n=26)	
Number of VEs	initially	457[130;2451]	157[0;825]	108[26.5;808]	5570[28;1521]	p_{1-2}=0.089, p_{1-3}=0.069,
	at the end	519[44;2663]	1419[137;3717]	577[150;2085]	1191[42;6767]	n/a
p in group		0.507	0.225	0.735	0.028	-
VE per 1 hour	initially	34.4[6.2;107.0]	6.5[0;38.4]	4.5[1.2;34.7]	22.8[2.1;71.5]	p_{1-2}=0.073, p_{1-3}=0.089
	at the end	24.6[2.0;120.9]	61.2[7.4;156.1]	32.3[6.7;85.9]	52.6[3.0;286.0]	n/a
p in group		0.463	0.225	0.735	0.023	-

Note: VE - ventricular extrasystole

verified by a significant decrease in NT-proBNP levels. In men of group 4, the increase in oxidative stress activity, despite a significant increase in TES level in dynamics, probably contributed to the pro-oxidative effect of TES, which was accompanied by less reverse cardiac remodeling and no significant dynamics of NT-proBNP level.

Of particular interest are the works indicating the adrenomodulatory effect of TES therapy because sympathetic hyperactivation is recognized as a key link in the pathogenesis and lethality factor in CHF. It is known that chronic adrenergic stimulation is accompanied by a decrease in cardiac inotropic reserve due to altered beta-adrenoreception (beta-AR). The development of CHF is accompanied by desensitization and a decrease in beta-1-AR density and an increase in beta-2-AR density [21], overexpression of which leads to interstitial fibrosis, considered as the main proarrhythmic substrate.

In a rat model of heart failure, TES therapy for 4 weeks had a modulatory effect on the cardiac beta-adrenergic system in castrated rats by inducing the expression of beta-2-AR levels [22]. Probably, in patients with CHF with initial overexpression of beta-2-AR, TES therapy, as well as the increase in TES level on the background of CRT, due to additional beta-2-adrenergic stimulation, may be accompanied by an increase in the process of myocardial fibro-formation, affecting the development of ventricular arrhythmias. Among the effects of TES therapy in patients with CHF, effects on ventricular repolarization and QT interval duration have been discussed [23, 24], indicating a possible role of TES as an antiarrhythmic agent. In two groups of our study - 3 and 4 - in dynamics there was noted an increase in the level of TES, associated in conditions of increased activity of oxidative stress in patients of group 4 with a significant increase in the number of VEs, which suggests leveling of cardioprotective antiarrhythmic effect of TES on the background of greater activity of oxidative stress.

It has been found that sympathetic hyperactivation in CHF is verified by increased levels of circulating catecholamines [25]. In a study by Ying Han et al. [26] 8 weeks after castration of rats with isoproterenol-induced heart failure, there was noted aggravation of sympathetic dysfunction in the form of increased plasma norepinephrine level, decreased content of norepinephrine and protein tyrosine hydroxylase in myocardium. TES therapy caused a decrease in plasma norepinephrine levels, an increase in its levels in the myocardium and TH-labeled nerve fiber density, and an increase in myocardial tyrosine hydroxylase protein expression. The identified neuroprotective effects of TES indicate an important modulating ability of androgens and suggest potential beneficial effects of TES in the treatment of patients with CHF. However, it is necessary to note a pronounced heterogeneity of sympathetic regulation in patients with systolic CHF, confirmed in the study of G.Vergaro et al [27]. Different effects of TES therapy on sympathetic activity depending on the initial degree of its dysfunction can be hypothesized. In this regard, TES therapy poses a potential safety issue for patients with CHF. In our work, in men of group 4, at all study points, NAdr levels were significantly greater in comparison with the other groups, indicating greater sympathetic hyperactivation, possibly due to the adrenomodulatory effect of TES under conditions of greater oxidative stress activity. The dynamics of NADr level in all groups was unidirectional - at the end of the study in three groups out of four studied there was a tendency to increase the level of NADr, in group 3 the increase of NADr reached statistical significance. The increase of NAdr level in the groups at the end of the study looks quite natural due to the progression of CHD.

While there were no significant differences in baseline DHEAS levels between groups, only men in group 2 had mean values within the normal range. In the remaining groups, mean DHEAS levels were below reference levels, confirming the severity of the men included in the study. At the endpoint of the study, only men in group 3 had its values within the normal range. The association between low DHEAS levels and risk of overall mortality was reported in the Swedish Registry [28]. A cohort study involving 8143 participants also found a negative association between DHEAS levels and risk of CH and mortality in men and women [29]. However, in our study, sex steroid levels by Cox regression were not associated with 10-year survival, which is probably due to the severity of the patients included in the study. According to the literature, patients with CHF, regardless of LVEF, often have a deficiency of anabolic hormones, including DHEAS, which have an important role in the regulation of antioxidant systems. Studies have found correlations of DHEAS with total antioxidant capacity [30, 31]. In our study, despite the absence of correlations between DHEAS and MPO levels, a reliable and significant (almost 2.5-fold) increase in DHEAS on the background of CRT in men of group 3 was associated with a highly significant decrease in MPO levels and the greatest degree of MPO level reduction (ΔMPO), confirming the high activity of antioxidant systems in the group and possible participation of DHEAS in their modulation.

Only in men of group 1 there was a highly significant (p=0.003) increase in the dynamics of E2 level, the role of which in men is not completely clear. A meta-analysis by G.Corona et al. (2011), which

Table 6.

Results of multivariate Cox regression analysis

Groups	Factors	HR(95% CI)	Log-rank P value
TES < medians	Deadline for the best response to the CRT	0.961(0.935-0.987)	0.004
	NT-proBNPend > 756.0 pg/mL	8.066(2.297-28.322)	0.001
TES > medians	Deadline for the best response to the CRT	0.950(0.920-0.980)	0.001
	MPO > median (32.5 ng/mL)	4.153(1.061-16.263)	0.041
	FWLJand	0.933(0.872-0.999)	0.046
	AAD intake	5.174(1.538-17.411)	0.008

Note: end - study endpoint; AAD - antiarrhythmic drug.

included 70 articles, showed a clear association between low TES/high E2 levels and increased risk of cardiovascular disease and cardiovascular mortality [32].

High level of hsCRP in dynamics in all studied groups, as well as its association with 10-year survival in single-factor Cox regression analysis indicate an important role of immune activation in the progression of CHF and coincide with the data of scientific literature.

The levels of MMP-9 and TIMP-1 exceeding the reference values at all study points indicate an imbalance of the fibro-formation process in the studied groups. Despite the absence of significant MMP-9 dynamics in all groups, the end point showed significantly lower levels in group 3 compared with groups 2 and 4, which was associated with less oxidative stress activity and greater reverse cardiac remodeling in the absence of anabolic steroid deficiency. According to the study of A.Mancini et al. (2018) oxidative stress contributes to the increase of MMP-9 levels [33].

The pathogenesis of CCN includes oxidative (oxidative) stress, which is based on the imbalance of prooxidants and antioxidant defense components. In 1985. H.Zis was the first to introduce the term «oxidative stress», considered as «disturbance of the balance between oxidants and antioxidants in favor of the former» [34]. The enzyme MPO, having peroxidase activity, promotes the formation of reactive oxygen species and is secreted by inflammatory cells - neutrophils, monocytes, macrophages. The main function of MPOs is antimicrobial actions realized by phagocytosis. However, due to the synthesis of extremely reactive substances (perchloric acid, formaldehyde, acrolein), MPO can damage the body by modifying key ion channels and impairing myocardial contractile function, activating matrix metalloproteinases (MMPS) and inhibiting tissue inhibitors of metalloproteinases (TIMPs), promoting reorganization of the extracellular matrix and enhancing collagen formation, which, in turn, is a substrate of heart rhythm disorders [35].

The data of scientific literature on the prognostic significance of MPO in patients with CHF are rather contradictory [36]. In some studies, MPO has been recognized as an independent predictor of mortality in patients with heart failure, with prognostic power increased in combination with BNP [37]. A correlation of MPO with clinical severity of CHF, regardless of its etiology (ischemic, non-ischemic), has been reported [38]. Other studies have failed to prove the diagnostic or prognostic value of MPO in patients with CHF [39]. In our study, when patients were divided into subgroups based on only one factor, MPO level (greater than or less than the median), no significant difference in male survival was found. It was the combination of the two factors, elevated TES and MPO levels, that was associated with decreased life expectancy and worse 10-year survival in men with CRT. Cox regression results indicate a 4.2-fold increase in the relative risk of death when MPO levels are greater than 32.5 ng/mL in men with TES levels greater than 16.4 nmol/L. Earlier studies revealed a threshold MPO level of 33.9 ng/mL contributing in combination with hsCRP and BNP (brain sodium uretic peptide) to the development of CHF with systolic dysfunction (specificity 94.3%, negative predictive value >99%) [40]. In our study, the MPO level at the end of the study in group 4 men was more than 2-fold higher at 73.0 [42.8;92.3] ng/mL, which may have contributed to disease progression. In a study by H.Sunman et al (2018), a decrease in MPO levels after CRT implantation was observed [41]. A.Sultan et al. (2020) showed that the study of MPO level is important for assessing the severity of CHF and predicting the response to CRT - MPO value 242 ng/mL and higher is a predictor of negative response to CRT (sensitivity 93.5%, specificity 71.4%) [42].

Our results suggest the prognostic significance of increased MPO and TES in men with CRT. Increasing endogenous TES levels in men with severe CHF is safe under conditions of low oxidative stress activity with long-term (up to 10 years) follow-up. The world scientific literature presents only 4 studies demonstrating negative experience with TES drugs in men with severe CHF [4-7], which have been heavily criticized by interested pharmaceutical companies involved in the production of TES drugs. Our results support the legitimacy of the existence of these works, as we can assume a high activity of oxidative stress in the severe patients included in these studies. Further studies are needed on the feasibility of using TES drugs in the treatment of men with CHF, taking into account their oxidative stress activity.

It is necessary to note in the studied subgroups the association of survival with the time of the best response to CRT, verified retrospectively by the maximum reduction of LV ESV in the dynamics. The prognostic significance of the response time to CRT has been discussed in the literature [43]. It was shown that the best functional

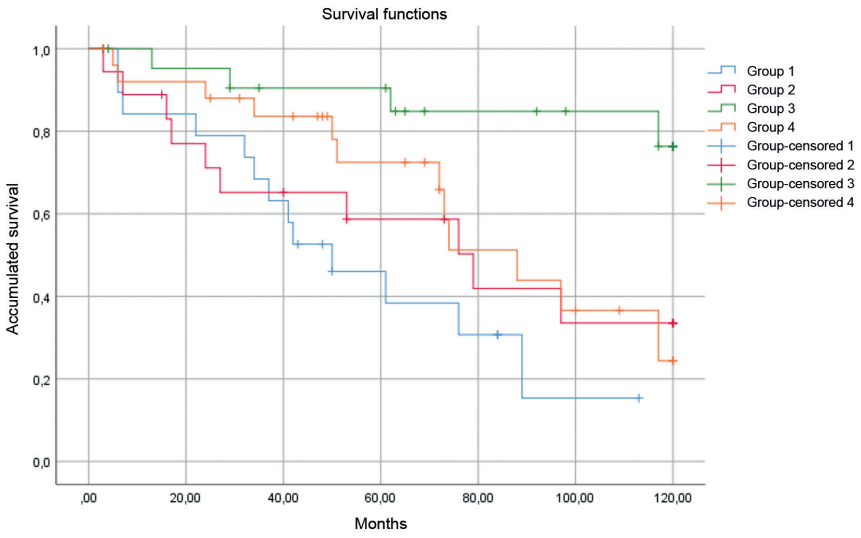

Fig. 1. 10-year survival rates in groups of men with different levels of TES and MPO, where group 1, 15.4%; group 2, 33.5%; group 3, 76.3%; group 4, 24.4%; Log Rank test 1-2=0.378; 1-3<0.001; 1-4=0.070; 2-3=0.009; 2-4=0.772; 3-4=0.010.

response to CRT at a time period longer than 24 months was associated with better 5-year survival and was accompanied by greater reverse cardiac remodeling, decreased activity of fibrosis development, immune, neuro-humoral and sympatho-adrenal activation compared to patients with an early response to CRT (up to 24 months) [44]. Probably, high intensity of modulating effects of CRT in the presence of severe organic changes in the heart is accompanied by rapid depletion of adaptive capabilities, transformation of compensatory mechanisms into damaging ones.

In the subgroup with TES> median (groups 3 and 4), administration of amiodarone was associated with 10-year survival, which was the predominant antiarrhythmic drug in all study groups. The prognostic significance of amiodarone is equivocal. In the study of C.Torp-Pedersen et al. (2007) against the background of amiodarone administration, the risk of death increased 1.5 times ($p < 0.001$), and the differences were mainly due to the risk of death due to CHF (hazard ratio=2.4; $p < 0.001$), while the risk of sudden death had no differences (hazard ratio=1.07; p=0.7) [45]. In the Sudden Cardiac Death in Heart Failure Trial, it was shown that amiodarone had the same effect as placebo in FC II, but in FC III amiodarone increased the risk of death by 44% [46]. E.C.Adelstein et al. (2019) demonstrated in patients with CRT on the background of amiodarone administration a lower increase in LVEF and a higher risk of death [47]. In a German device registry (DEVICE) in patients with ICDs and CRT-D (4499 patients), a one-year increase in all-cause mortality was found with therapy with amiodarone and in combination with β-adrenoblockers, especially in subgroups of patients with sinus rhythm or severely reduced left ventricular function. It is discussed that long-term use of amiodarone, which is a multichannel blocker in all phases of cardiac action potential, is accompanied by numerous side effects, including slowing of atrioventricular and intraventricular conduction, prolongation of QTc interval with development of life-threatening torsades de pointes tachycardia. Amiodarone can directly affect cardioverter-defibrillator function by altering the defibrillation or cardiac pacing threshold or reducing the amplitude of the right ventricular signal, leading to a risk of insensitive ventricular tachycardia or ventricular fibrillation [48]. Being an iodine-containing drug, amiodarone can alter thyroid function, the role of which in the genesis of CHF [49] and reverse cardiac remodeling on the background of CRT [50] is actively discussed in the literature. Due to its prognostic significance, the administration of amiodarone should be judicious and under close patient monitoring. In group 4 of our study, the percentage of men with grade III FC (NYHA) was the highest at 50%, in 19.2% of whom amiodarone was prescribed. There was less reverse cardiac remodeling in group 4 compared to group 3 with a smaller increase in LVEF (ΔLVEF, p=0.007). Only in group 4 there was a significant increase in the number of VEs, which could be a consequence of a significant increase in the level of TES (by 82.8%) against the background of CRT and manifestation of its cardionegative effects, among which there is a possible proarrhythmogenic one due to adrenostimulating effect and enhancement of myocardial fibroforming under conditions of oxidative stress activity growth.

Limitations of the study

The limitation of our study is the small number of patients, single-center study. Taking into account the creation of the Register in 2003 in the absence of modern recommendations for implantation of CRT devices, the study included patients with signs of intra- and/or interventricular dyssynchrony detected by echocardiography, which, in our opinion, increases the effectiveness of CRT.

CONCLUSION

Thus, CRT has a modulating effect on steroidogenesis, which can be compared with hormone replacement therapy with TES in men with CHF over a long follow-up period. Increase in TES and DHEAS levels on the background of CRT with low activity of oxidative stress is associated with greater reverse cardiac remodeling, increase in LVEF, and better 10-year survival. Increase in TES level in combination with increase in oxidative stress activity on the background of CRT is associated with sympathetic activation, less reverse cardiac remodeling, increased ventricular arrhythmias and worse 10-year survival, which supports the hypothesis about possible change of cardiopositive effects of TES to cardionegative ones. At high TES, the fact that MPO levels exceeded 32.5 pg/mL at the endpoint increased the relative risk of death by 4.2-fold, and administration of amiodarone increased it by 5.2-fold. The association of 10-year survival with the time to best response to CRT suggests a less physiologic nature of the intense modulating effects of CRT.

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