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COMPARATIVE ANALYSIS OF ENDOCRINE PROFILE AND FIVE-YEAR SURVIVAL OF CARDIAC RESYNCHRONIZATION THERAPY MALE RESPONDERS RESIDING IN CONDITIONS OF THE FAR NORTH AND SOUTH OF TYUMEN REGION

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Aim. To evaluate endocrine profile, biomarkers of heart failure, 5-year survival of cardiac resynchronization therapy (CRT) male responders living in the Far North (FN) and the south of Tyumen region (sTr).

Methods. Fifty-six CRT male responders (with decrease of left ventricular end-systolic volume >15% in November 2020) under the age of 65 (55.0±7.8 years old) were divided into 2 groups: 1(n=23) - FN patients; 2 (n=33) - sTr. Echocardiography (Echo), thyroid-stimulating hormone (TSH), triiodothyronine (fT3), thyroxine (fT4), parathyroid hormone (PTH), cortisol (CORT), testosterone (TES), estradiol (E2), dihydroepiandrosterone sulfate (DHEAS), progesterone (PGN), adrenaline (Adr), norepinephrine (NAdr), interleukins (IL) 6, 10, tumor necrosis factor (TNF-α), C-reactive protein (CRP), NT-proBNP, myeloperoxidase (MPO), matrix metalloproteinase (MMP-9), tissue inhibitor of metalloproteinases (TIMP-1) were assessed. Relationship of hormones with Echo, biomarkers was evaluated by Spearman method, 5-year survival - by Kaplan-Meier method, and association of lastmentioned with studied factors - by Cox regression.

Results. Radiofrequency ablation of atrioventricular junction (RFA AVJ) were differed in groups (47.8 vs 21.2%; p=0.036). At the initial stage, in group 1, right ventricle, Adr, TNF-α, CRP, TIMP-1, CORT, TSH, fT4 were greater, fT3/fT4 was lower. In groups, reverse cardiac remodeling was revealed in dynamics; decrease of TIMP-1, PGN in Gr1; decrease of NT-proBNP, TIMP-1, MPO, PGN, increase of TES, E2, TNF-α in Gr2,. Positive associations of TSH, PTH and negative - DHEAS with Echo; positive connections between PGN, CORT and MMP-9; TES with NAdr; E2 with IL-10 were registered. Five-year survival rate was 80.7% vs 83.4% (Log Rank test=0.724), associated with IL-6 level in northerners.

Conclusion. Multihormonal imbalance, manifested by greater levels of CORT, TSH, fT4, lower values of fT3/fT4, accompanied by sympatho-adrenal, immune activation, fibroformation imbalance, higher power of RFA AVJ, indicates greater severity of heart failure, tension of adaptive mechanisms in CRT male responders of FN. CRT modulating effects in groups contributed to comparable 5-year survival associated with level of IL-6 in northerners.

Key words: chronic heart failure; cardiac resynchronization therapy; endocrine imbalance; survival; the Far North

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Chronic heart failure (CHF) is a global health challenge due to its high prevalence and continuous growth. The estimated global incidence of CHF is 64.3 million cases[1]. Epidemiological studies in the Russian Federation over 20 years indicate an increase in CHF prevalence from 6.1% to 8.2% for functional classes I-IV and from 1.8% to 3.1% for classes III-IV[2]. A critical factor in the complex pathogenesis of CHF is endocrine imbalance[3], which is associated with sympatho-adrenal[4] and immune activation[5], as well as increased fibroformation[6].

The expansion of economic activities in the Arctic has heightened scientific interest in the impact of Arctic climatic conditions on the development of various diseases. Previous studies have established that residing in the Far North (FN) for over four years contributes to the early onset of coronary atherosclerosis [7] and arterial hypertension[8]. CHF, as the culmination of the cardiovascular continuum, is currently managed using cardiac resynchronization therapy (CRT). We hypothesize that the adverse climatic conditions of the Far North influence changes in hormonal systems involved in cardiac homeostasis, leading to specific patterns of CHF development and progression. However, these patterns are not yet documented in the scientific literature, underlining the relevance of our study.

Aim: To perform a comparative analysis of the endocrine profile (thyroid and parathyroid hormones, cortisol, sex hormones), biomarkers of immune, sympatho-adrenal, and neurohumoral systems, fibroformation, and five-year survival of male CRT responders living in the Far North and the south of the Tyumen region (sTr).

METHODS

To eliminate the influence of gender and age on the analysis of the endocrine profile and to create a homogeneous group, the study included 56 male CRT responders (defined by a reduction in left ventricular end-systolic volume [LVESV] >15% from baseline at the endpoint in November 2020) under the age of 65 (55.0±7.8 years). These participants resided in the Far North (FN, n=23) in the Yamalo-Nenets Autonomous Okrug (YNAO) and in the south of the Tyumen region (sTr, n=33). They were recruited from the "Registry of Performed CRT Procedures" (State Database Registration Certificate No. 2010620077 dated February 1, 2010). Ischemic CHF was diagnosed in 26 men (46.4%), and CRT devices with a defibrillator function were implanted in 34 (60.7%) patients. Informed consent was obtained from all participants, and the study was approved by the ethics committee.

Patient evaluations were conducted at baseline, after 1, 3, and 6 months, and then every subsequent 6 months post-CRT implantation. For this analysis, data from the baseline and the final visit (November 2020) were included. For deceased patients, data collected prior to their death were used.

Echocardiography (Echo) was performed using a Philips IE-33 system (USA) to assess standard parameters. Left ventricular ejection fraction (LVEF) was measured using Simpson's method. Plasma levels of adrenaline (Adr), norepinephrine (NAdr), myeloperoxidase (MPO), matrix metalloproteinase 9 (MMP-9), and tissue inhibitor of metalloproteinase 1 (TIMP-1) were assessed via solid-phase enzyme-linked immunosorbent assay (ELISA), with optical density measured using a StatFax 4200 reader (USA). Plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), interleukins (IL) 6 and 10, tumor necrosis factor α (TNF-α), total testosterone (TES), progesterone (PGN), dehydroepiandrosterone sulfate (DHEAS), estradiol (E2), cortisol (CORT), intact parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) were analyzed using a solid-phase chemiluminescent immunoassay on an IMMULITE 1000 analyzer (Siemens Diagnostics, USA). High-sensitivity C-reactive protein (CRP) levels in serum were determined using analytical kits from Roche Diagnostics GmbH on a COBAS INTEGRA 400 Plus analyzer (Roche Diagnostics GmbH, Germany).

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 23 software package. For data with a normal distribution, assessed using the Kolmogorov-Smirnov test, results were presented as M±sd, where M is the mean and sd is the standard deviation. For data with a non-normal distribution, results were presented as the median (Me) with interquartile range (IQR) as the 25th and 75th percentiles. Qualitative variables were analyzed using the χ^2 test. For quantitative data in unrelated groups, Student's t-test was applied for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data.

Spearman's method was used to assess correlations between hormone levels and Echo parameters and biomarkers. Kaplan-Meier survival analysis was utilized to evaluate survival rates. Cox regression analysis (univariate and multivariate) was applied to identify factors associated

Table 1.

Clinical characteristics of the studied groups

Indicator	Group I FN (n=23)	Group II sTr (n=33)	p between groups
MSP, months	74.5 [34.3;107.0]	63.0 [42.0;100.0]	0.690
Age, years	55.9±5.4	54.4±9.1	0.668
CRT-D, n (%)	14 (60.9)	20 (60.6)	0.984
CAD, n (%)	9 (39.1)	17 (51.5)	0.361
PICS, n (%)	6 (26.1)	7 (21.2)	0.671
CABG, n (%)	1 (4.3)	0 (0)	0.227
PCI, n (%)	6 (26.1)	7 (21.2)	0.671
NYHA FC I, n (%)*	0 / 4 (17.4)	0 / 12 (36.4)	0.888 / 0.461
NYHA FC II, n (%)	15 (65.2) / 15 (65.2)	24 (72.7) / 17 (51.5)	
NYHA FC III, n (%)	7 (30.5) / 3(13.1)	7 (21.2) / 3(9.1)	
NYHA FC IV, n (%)	1 (4.3) / 1 (4.3)	2 (6.1) / 1 (3.0)	
p within the group	0.502	0.075	
HTN, n (%)	17 (73.9)	24 (72.7)	0.921
AF, n (%)	14 (60.9)	15 (45.5)	0.202
AVJ RFA, n (%)	11 (47.8)	7 (21.2)	0.036
DM, n (%)	3 (13.0)	3 (9.1)	0.639
Obesity, n (%)	10 (43.5)	17 (51.5)	0.551
BMI, kg/m^2	29.4±6.3	29.9±6.0	0.696
QRS duration, ms	132.1±40.8	148.0±40.2	0.325
LBBB, n (%)	8 (34.8)	20 (60.6)	0.057

Note: hereinafter, FS - Far North; sTr - southern Tyumen region; MSP - mean observation period; CRT-D - cardiac resynchronization therapy device with defibrillator function; CAD - coronary artery disease; PICS - post-infarction cardiosclerosis; CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; NYHA FC - New York Heart Association functional class of heart failure; * - data dynamics indicated with a slash; HTN - arterial hypertension; AF - atrial fibrillation; AVJ RFA - atrioventricular junction radiofrequency ablation; DM - diabetes mellitus; BMI - body mass index; LBBB - left bundle branch block.

with survival. A p-value of <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the studied patients are presented in Tables 1 and 2. Patients were comparable in terms of baseline clinical parameters, except for a higher frequency of atrioventricular junction radiofrequency ablation (RFA AVJ) in Group 1. In Group 1, there was no significant change in NYHA functional class dynamics, which might be attributed to the small sample size or clinical features of the patients. In contrast, Group 2 demonstrated a trend (p=0.075) towards improvement in NYHA functional class. Initially, there were no differences in the prescription frequency of major drug groups between the groups. However, during follow-up, Group 1 showed a higher frequency of calcium channel blockers (amlodipine, felodipine), likely due to a greater need for blood pressure control. Additionally, Group 1 showed an increased frequency of statin prescriptions, likely reflecting more diligent outpatient monitoring of patients with CRT devices. The frequency of statin use in Group 2 remained unchanged.

Changes in exercise tolerance based on the six-minute walk test and Echo parameters are shown in Table 3. Initially, Group 1 had larger right ventricle sizes. CRT therapy in both groups resulted in favorable and consistent Echo parameter dynamics. However, Group 1 exhibited smaller left ventricular (LV) end-diastolic diameter and end-systolic volume. Only Group 2 showed a significant improvement in exercise tolerance.

Biomarker dynamics are detailed in Table 4. Initially, Group 1 showed higher levels of adrenaline, TNF-α, and CRP. TIMP-1 and MMP-9 levels were elevated in both groups, reflecting the severity of the disease and fibroformation imbalance. There were no differences in MMP-9 levels between groups, but Group 1 exhibited higher TIMP-1 levels. MPO levels were within reference values in both groups. Over time, Group 1 showed a reduction in TIMP-1 levels, while Group 2 experienced increases in norepinephrine and TNF-α, alongside decreases in MPO, NT-proBNP, and TIMP-1.

Hormone dynamics are presented in Table 5. Average levels of testosterone, estradiol, and progesterone in both groups were within reference ranges. There were no differences in sex hormone levels between groups. Initially, DHEAS levels were below reference ranges in both groups. Despite no significant changes in DHEAS levels during follow-up, final values were within reference ranges. Only Group 2 showed increases in testosterone and estradiol over time. Both groups demonstrated reductions in progesterone levels, associated with heart remodeling during CRT therapy. Cortisol levels were within reference ranges across all time points, with higher initial levels in Group 1. No significant changes in cortisol levels were observed in either group. Baseline parathyroid hormone (PTH) levels in Group 1 and follow-up levels in Group 2 exceeded reference ranges, with a tendency for higher PTH levels in Group 2. No significant changes in PTH levels were observed during follow-up.

Thyroid hormone levels (TH) were within reference ranges across all time points in both groups. Group 1 had higher initial TSH and free T4 levels and lower T3/T4 ratios. Among three patients from YNAO, TSH levels were above normal in two patients and below normal in one. Thyroid abnormalities were managed appropriately. During follow-up, TSH levels in all YNAO patients normalized, reflecting the effectiveness of medical management. No significant changes in TH levels were observed in either group during CRT therapy. Correlations be-

Table 2.

Drug therapy in the study groups

Indicator	Group I FN (n=23)	Group II sTr (n=33)	p between groups
AAD, n (%)	6 (26.1) / 8 (34.8)	9 (27.3) / 11 (33.3)	1.000 / 0.910
p within group	0.625	0.625	
MRA, n (%)	16 (69.6) / 18 (78.3)	29 (87.9) / 27 (81.8)	0.154 / 0.742
p within group	1.000	0.625	
Diuretics, n (%)	11 (47.8) / 18 (78.3)	18 (54.5) / 31 (93.9)	0.741 / 0.081
CCA, n (%)	6 (26.1) / 10 (43.5)	8 (24.2) / 8 (24.2)	0.800 / 0.039
p within group	0.125	1.000	
BB, n (%)	19 (82.8) / 19 (82.8)	31 (93.9) / 27 (81.8)	0.338 / 0.939
p within group	1.000	0.125	
Digoxin, n (%)	9 (39.1) /6 (26.1)	9 (27.3) / 8 (24.2)	0.291 / 0.875
p within group	0.453	1.000	
Anticoagulants, n (%)	10 (43.5) / 12(52.2)	16 (48.5) / 15 (45.5)	0.825 / 0.621
p within group	1.000	1.000	
Antiplatelets, n (%)	9 (39.1) / 8 (34.8)	16 (48.5) /14 (42.4)	0.580 / 0.565
p within group	0.500	0.625	
ACEI, n (%)	20 (87.0) / 17 (73.9)	26 (78.8) / 23 (69.7)	1.000 / 0.731
p within group	0.125	0.375	
ARB, n (%)	2 (8.7) /5 (21.7)	7 (21.2) / 7 (21.2)	0.234 / 0.962
p within group	0.250	1.000	
Statins, n (%)	6 (26.1) / 19 (82.8)	16 (48.5) 21 (63.6)	0.116 / 0.122
p within group	<0.001	0.227	

Note: hereinafter, AAD - Antiarrhythmic drugs (amiodarone, sotalex); MRA - Mineralocorticoid receptor antagonists; CCA - Calcium channel antagonists (amlodipine, felodipine); BB - β-blockers; ACEI - Angiotensin-converting enzyme inhibitors; ARB - Angiotensin receptor blockers.

tween hormone levels, Echo parameters, and biomarkers at the study endpoint are detailed in Table 6.

Kaplan-Meier analysis revealed comparable five-year survival rates between the groups (80.7% vs. 83.4%; Log Rank test=0.724) (Figure 1). Multivariate analysis results are presented in Table 7. In Group 1, univariate analysis showed associations between five-year survival and levels of IL-6, TIMP-1, and NT-proBNP at the study endpoint. However, multivariate analysis identified only IL-6 levels at the study endpoint as being associated with five-year survival. In Group 2, univariate analysis linked survival with Echo parameters (LV end-diastolic and end-systolic volumes, LV ejection fraction) and MMP-9 levels. However, none of these factors were associated with survival in multivariate analysis.

DISCUSSION

The literature highlights the issue of multihormonal imbalance in patients with chronic heart failure (CHF), involving the somatotropic axis (growth hormone and its tissue effector, insulin-like growth factor-1 (IGF-1)) [9], anabolic steroids (testosterone (TES) and dehydroepiandrosterone sulfate (DHEAS)), glucocorticoids (cortisol), and thyroid and parathyroid hormones [3]. Each identified defect is associated with a deterioration in clinical status, functional capacity, and increased mortality [10]. Among the participants of the Italian T.O.S.CA registry (Trattamento Ormonale nello Scompenso CArdiaco; n=480 with LVEF <40%), 77% were diagnosed with multiple hormonal deficiencies, significantly increasing the relative risk of death [HR 2.2 (1.28-3.83), p = 0.01] [11]. In our study, hormonal profile abnormalities were identified in 29 patients (51.8%), including 13 (56.5%) from the Far North and 16 (48.5%) from the south of the Tyumen region. The lower percentage of endocrine changes in our cohort is likely due to the specific characteristics of the sample.

The high expression of androgen receptors in the myocardium underpins the role of sex hormones in cardiac structural remodeling and their influence on cardiac rhythm through modulation of ion channels. TES, the predominant circulating androgen with numerous genomic and non-genomic (rapid) effects, has a poorly understood and potentially contradictory impact on the cardiovascular system [12]. The oxidative-redox status of the cellular environment has been shown to modulate the cardioprotective or detrimental effects of TES [13].

Table 3.

Dynamics of the results of the 6-minute walk test and EchoCG parameters in the studied groups

Indicator		Group I FN (n=23)	Group II sTr (n=33)	p between groups
6MWT, m	baseline	330.5±85.1	347.6±101.3	0.389
	dynamics	369.2±80.3	383.0±89.1	0.408
p within the group		0.157	0.030	
LA, mm	baseline	50.2±5.0	50.8±5.3	0.481
	dynamics	48.2±11.04	45.6±5.4	0.768
p within the group		0.003	<0.001	
RA, ml	baseline	90.6±34.4	77.0±21.8	0.229
	dynamics	67.9±23.6	68.7±35.6	0.229
p within the group		0.053	0.118	
RV, mm	baseline	31.9±3.9	29.0±4.1	0.016
	dynamics	28.8±3.9	28.2±3.1	0.682
p within the group		0.080	0.088	
LVESD, mm	baseline	59.2±5.3	58.4±7.5	0.575
	dynamics	41.0±9.0	46.0±8.5	0.216
p within the group		0.045	<0.001	
LVEDD, mm	baseline	65.9±6.0	68.9±7.5	0.239
	dynamics	56.0±5.9	60.3±7.9	0.038
p within the group		<0.001	<0.001	
LVESV, ml	baseline	155.7±43.0	172.2±46.4	0.400
	dynamics	79.0±31.6	99.5±40.4	0.091
p within the group		<0.001	<0.001	
LVEDV, ml	baseline	225.7±48.1	250.0±63.3	0.443
	dynamics	156.4±38.6	185.3±57.5	0.042
p within the group		<0.001	<0.001	
IVS, mm		11.0±1.8	10.5±1.5	0.373
LVPW, mm		10.7±1.7	10.5±1.1	0.939
LVEF, %	baseline	31.8±5.3	31.4±4.4	0.956
	dynamics	50.8±8.8	46.4±8.5	0.223
p within the group		<0.001	<0.001	
sPAP, mmHg	baseline	44.4±8.3	42.3±10.3	0.579
	dynamics	27.8±5.7	31.7±9.4	0.123
p within the group		0.020	<0.001	

Note: hereinafter, 6MWT - 6-minute walk test; LA - left atrium; RA - right atrium; RV - right ventricle; LVESD - left ventricular end-systolic diameter; LVEDD - left ventricular end-diastolic diameter; LVESV - left ventricular end-systolic volume; LVEDV - left ventricular end-diastolic volume; IVS - interventricular septum; LVPW - left ventricular posterior wall; LVEF - left ventricular ejection fraction; sPAP - systolic pulmonary artery pressure.

Among its cardioprotective effects, TES exhibits antioxidant properties [14], promotes rapid increases in [Ca2+] i in cardiac myocytes [15], and induces vasodilation [16]. However, TES may also exert pro-oxidant effects [17]. Particularly notable is its adrenomodulatory action, as sympathoadrenal activation is recognized as a key mechanism in the pathogenesis and a mortality factor in CHF. In a rat model of CHF, TES therapy for 4 weeks induced β-2-adrenergic receptor expression, contributing to fibrosis [18]. The observed correlation between TES and norepinephrine (NAdr) in our study suggests a potential association with sympathetic regulation. Increased TES levels in the second group were linked to higher NAdr levels. However, the reduction in myeloperoxidase (MPO) levels in this group may have facilitated greater cardioprotective effects of TES. The absence of changes in TES and MPO in the first group likely indicates strained adaptive mechanisms.

In the second group, a dynamic increase in estradiol (E2) levels was observed, though its role in men remains unclear. Estrogens in men can exert physiological and pathophysiological effects depending on their absolute levels in plasma and cells. The literature discusses the immunomodulatory effects of E2 [19], which align with our findings of its correlation with interleukin-10 (IL-10), a potent anti-inflammatory cytokine that mitigates adverse cardiac remodeling [20].

The biological role of DHEAS remains unclear. During its metabolism, TES and dihydrotestosterone

Table 4.

Dynamics of biomarkers of the sympathoadrenal, immune, neurohumoral systems, and fibroformation in the study groups

Indicator		Reference values	Group I FN (n=23)	Group II sTr (n=33)	p between groups
Adr, ng/ml	baseline	0.018-6.667	2.1[1.2;2.9]	0.6[0.1;2.1]	0.033
	dynamics		0.9[0.3;3.0]	1.5[0.5;2.8]	0.703
p within the group			0.878	0.064	
NAdr, ng/ml	baseline	0.093-33.333	8.0[1.1;21.3]	0.6[0.3;5.6]	0.109
	dynamics		12.4[6.1;21.6]	12.1[3.8;20.2]	0.538
p within the group			0.328	0.028	
NT-proBNP, pg/ml	baseline	<125	1227.0 [764.3;4357.0]	1788.0 [1252.0;3191.0]	0.464
	dynamics		440.0 [249.0;826.0]	602.0 [265.0;1511.0]	0.373
p within the group			0.239	0.003	
IL-6, pg/ml	baseline	0-9.7	3.3[2.2;12.1]	2.5[2.3;3.2]	0.126
	dynamics		2.3[2.0;4.0]	2.3[2.2;3.6]	0.538
p within the group			0.347	0.679	
IL-10, pg/ml	baseline	0-9.1	4.3[2.6;5.0]	2.5[1.7;4.7]	0.194
	dynamics		4.1[3.1;5.0]	3.7[2.2;4.4]	0.074
p within the group			0.697	0.134	
TNF-α, pg/ml	baseline	<8.11	10.2[8.3;11.8]	6.0[4.0;9.3]	0.017
	dynamics		8.0[6.5;10.2]	8.7[7.3;10.5]	0.573
p within the group			0.146	0.043	
CRP, mg/ml	baseline	<3.0	6.9[1.6;11.4]	2.7[1.3;3.7]	0.007
	dynamics		6.8[3.6;11.7]	4.0[2.4;10.3]	0.200
p within the group			0.934	0.062	
MPO, pg/ml	baseline	1.45-72.67	35.3[20.8;76.1]	62.8[27.1;87.8]	0.274
	dynamics		34.9[20.3;76.6]	28.6[19.6;72.1]	0.608
p within the group			0.388	0.049	
MMP-9, ng/ml	baseline	2.0-139.4	172.1 [153.4;255.3]	154.5 [139.4;239.4]	0.551
	dynamics		182.7 [140.4;249.0]	197.5 [154.7;223.7]	0.871
p within the group			0.507	0.910	
TIMP-1, ng/ml	baseline	92-116	428.4 [207.7;628.1]	219.0 [161.1;298.4]	0.043
	dynamics		171.0 [131.0;214.6]	144.3 [111.5;193.0]	0.054
p within the group			0.001	0.002	

Note: hereinafter, Adr - adrenaline; NAdr - noradrenaline; IL - interleukin; TNF-α - tumour necrosis factor alpha; CRP - C-reactive protein; MPO - myeloperoxidase; NT-proBNP - N-terminal pro-brain natriuretic peptide; MMP-9 - matrix metalloproteinase 9; TIMP-1 - tissue inhibitor of matrix metalloproteinase 1.

are synthesized. Low levels of DHEAS have been associated with an increased risk of CHF and mortality [21]. In our study, negative correlations of DHEAS with echocardiographic (Echo) parameters highlight its significant role in cardiac remodeling during CRT. Similarly, the role of progesterone (PGN) in HF remains ambiguous, though it is traditionally considered a precursor hormone for all steroid hormones. A Swedish study in elderly men and women reported an association between PGN and increased HF prevalence [22]. Experimental studies have demonstrated immunosuppressive [23], antimineralocorticoid [24], anti-apoptotic [25], and antiarrhythmic [26] effects of PGN. Additionally, PGN has been shown to enhance myocardial regenerative processes by promoting cardiomyocyte proliferation [27]. In our study, PGN levels decreased dynamically in both groups, correlating with reverse cardiac remodeling under CRT and reduced need for regenerative processes. The identified correlation between PGN and MMP-9 indicates its influence on extracellular cardiac matrix remodeling.

In the first group, the higher prevalence of AF requiring RFA of the AVJ likely indicates more pronounced cardiac remodeling. Literature data on the association of sex hormones with AF remain contradictory. A meta-analysis by P. Hu et al. (2022), encompassing 3,979 studies, suggested that higher endogenous DHEAS levels are associated with a lower risk of AF in men, whereas no relationship was found between TES, estradiol (E2) concentrations, and AF risk [28]. The initially low DHEAS level in conjunction with other factors in the first group may have contributed to the onset of AF.

Table 5.

Dynamics of hormones in the study groups

Indicator		Reference values	Group I FN (n=23)	Group II sTr (n=33)	p between groups
TES, nmol/L	baseline	7.35-25.7	17.0 [12.5;19.9]	15.0 [11.1;19.2]	0.443
	dynamics		16.6 [13.0;24.9]	17.3 [12.8;23.3]	0.807
p within the group			0.875	0.019	
E2, ng/mL	baseline	0-56.0	44.3 [31.2;58.0]	34.4 [22.9;42.3]	0.210
	dynamics		51.4 [28.3;106.0]	47.8 [28.7;53.8]	0.202
p within the group			0.300	0.048	
PGN, nmol/L	baseline	0-2.39	2.0 [1.2;2.3]	1.2 [0.8;2.3]	0.223
	dynamics		0.7 [0.6;1.0]	0.8 [0.6;1.2]	0.274
p within the group			0.004	0.036	
DHEAS, µg/dL	baseline	80.0-560	67.1 [15.0;132.3]	67.7 [47.2;158.3]	0.528
	dynamics		83.9 [56.8;124.5]	130.5 [51.1;181.0]	0.256
p within the group			0.308	0.209	
CORT, nmol/L	baseline	138-690	505.0 [423.8;563.5]	341.0 [295.5;456.8]	0.014
	dynamics		425.0 [273.5;561.5]	306.5 [183.8;527.5]	0.558
p within the group			0.343	0.582	
PTH, pg/mL	baseline	11.0-67.0	81.6 [48.8;117.5]	59.3 [34.1;101.0]	0.274
	dynamics		57.7 [39.4;77.3]	72.6 [56.1;88.4]	0.053
p within the group			0.094	0.936	
TTH, ME/ml	baseline	0.4-4.0	2.7 [2.0;4.0]	2.0 [1.3;2.8]	0.049
	dynamics		1.8 [1.3;2.2]	1.6 [1.1;2.7]	0.981
p within the group			0.126	0.345	
fT3, pg/mL	baseline	1.5-4.1	3.1 [2.7;3.4]	3.5 [2.9;3.8]	0.333
	dynamics		3.2 [2.7;3.9]	2.7 [2.5;3.9]	0.565
p within the group			0.337	0.633	
fT4, pmol/l	baseline	10.3-24.5	18.5 [15.8;20.7]	15.9 [13.6;17.2]	0.023
	dynamics		14.9 [11.8;17.2]	15.6 [13.3;18.2]	0.509
p within the group			0.235	0.960	
cT3/cT4, units	baseline		0.115 [0.089;0.147]	0.142 [0.118;0.170]	0.045
	dynamics		0.128 [0.110;0.210]	0.120 [0.086;0.171]	0.389
p within the group			0.302	0.715	

Note: hereinafter, TES - total testosterone; E2 - estradiol; PGN - progesterone; DHEAS - dehydroepiandrosterone sulfate; CORT - cortisol; PTH - parathyroid hormone; fT3 - free triiodothyronine; fT4 - free thyroxine.

Thyroid dysfunction is a common comorbidity in CHF. According to K.W. Streng et al. (2018), thyroid dysfunction was identified in 10.9% of patients with reduced LVEF, 13.7% of those with mid-range LVEF, and 17.9% with preserved LVEF [29]. The low prevalence of thyroid pathology in our study is likely due to the specificity of the cohort, which included only CRT responders with preserved adaptive capacity. TH effects on the heart include genomic mechanisms promoting cardiac differentiation during the perinatal period and nongenomic actions maintaining cardiovascular homeostasis [30]. Free triiodothyronine (fT3) plays a central role in regulating metabolic activity and exerts negative feedback on the pituitary gland. It influences cardiac genes encoding contractile proteins, the α- and β-myosin heavy chains, sodium-calcium exchange, and sarcoplasmic reticulum calcium ATPase (SERCA2), and affects β-adrenergic receptors. By acting on these mechanisms, T3 increases myocardial contractility, reduces vascular resistance by dilating peripheral arterioles, regulates mitochondrial function and morphology, and mediates antifibrotic and proangiogenic effects, promoting regeneration and recovery processes [31].

In CHF, T4-to-T3 conversion in cardiac muscle decreases due to hypoxia, immune inflammation activation, oxidative stress, and glutathione peroxidase deficiency, reducing deiodinase activity in the ventricular myocardium. This, combined with reduced T3 plasma levels, may decrease intracellular T3 bioavailability [32]. A reduction in serum T3 without an increase in TSH levels is termed "Low-T3 syndrome," which affects 30% of CHF patients [33]. Even minor alterations in circulating TH concentrations within the normal range are associated with increased cardiovascular risk [34]. Both fT4 and the fT3/fT4 ratio are independent predictors of cardiovascular mortality [35], and a low fT3/fT4 ratio predicts all-cause mortality in HF patients [36].

Subclinical hypothyroidism has been linked to the ineffectiveness of CRT [37]. Low fT3 levels correlate with worsened cardiac function and an unfavourable prognosis following CRT implantation [38]. In our study, hypothyroidism was identified in 3 (13.0%) northerners, and subclinical hyperthyroidism in 1 (4.3%). Low fT3 levels were observed in 6 (26.1%) men in Group 1 and 4 (12.1%) in Group 2. Initially, higher mean TSH and fT4 levels, along with a lower fT3/fT4 ratio, were documented in Group 1. Deviations in TH levels, even within the normal reference range, can significantly impact health. Elevated fT4 levels in Group 1 likely reflect impaired conversion to fT3 due to hypoxia in FN conditions. Positive correlations of TSH with TNF-α and echocardiographic parameters, alongside a negative association with LVEF, underscore TSH's critical role in cardiac homeostasis and reverse remodeling processes in CRT patients.

Cortisol (CORT), the primary glucocorticoid hormone produced in the adrenal gland's zona fasciculata, is often termed the "stress hormone." It regulates diverse physiological functions, including energy metabolism, electrolyte balance, blood pressure, and cognitive functions. Stress triggers the release of GCs, such as CORT, and catecholamines, like adrenaline (Adr). In our study, significantly elevated CORT levels in Group 1 correlated with higher Adr levels compared to Group 2, indicating chronic stress and strained adaptive capacity among northern-

Table 6.

Correlations of hormone levels with echocardiography parameters and biomarkers

	PTH	TEC	PGN	DHEAS	E2	TSH	CORT
TSH	r=0.442 p=0.031						
fT4					r=-0.568 p=0.006		
PTH						r=0.442 p=0.031	
N T - proBNP	r=0.266 p=0.062						
MMP-9			r=0.320 p=0.021				r=0.665 p=0.026
NAdr		r=0.347 p=0.023					
IL-10					r=0.367 p=0.006		
TNF-α						r=0.352 p=0.072	
LA				r=-0.312 p=0.021		r=0.389 p=0.045	
RA	r=0.328 p=0.026			r=-0.397 p=0.004			
RV	r=0.304 p=0.033			r=-0.323 p=0.018			
LVEDD						r=0.348 p=0.076	
LVESD	r=0.427 p=0.015						
LVESV						r=0.340 p=0.082	
LVEF						r=-0.340 p=0.083	
SPAP	r=0.327 p=0.064			r=-0.334 p=0.046			

ers. GC signalling occurs via glucocorticoid receptors in cardiomyocytes, essential for maintaining normal cardiac morphology and function. However, GCs may also bind mineralocorticoid receptors, which are highly expressed in the myocardium of HF patients. Activation of these receptors can disrupt calcium, magnesium, and other ion regulation, induce mitochondrial calcium overload, and promote oxidative stress and immune inflammation, resulting in subsequent remodeling, interstitial fibrosis, and CHF [39].

In our study, the initially higher CORT levels in northerners were associated with heightened immune activation and fibrogenesis imbalance. Myeloperoxidase (MPO) levels, a marker of oxidative stress activity, were within the reference range across all study points in both groups. However, Group 2 demonstrated a significant reduction in MPO levels over time, whereas no dynamic changes were observed in Group 1 under chronic stress conditions. Moderate correlations between CORT and MMP-9 suggest its role in modulating the extracellular cardiac matrix. Associations of higher CORT levels with elevated Adr, cytokines, and CRP levels further support the concept of chronic stress and strained adaptive mechanisms in northerners.

PTH (parathyroid hormone) impacts cardiomyocyte physiology by activating G-protein signalling and subsequent calcium influx into cardiac cells, which does not directly induce contractility but causes several indirect effects on the myocardium. PTH promotes protein kinase C activation, potentially weakening contractility by inhibiting β-adrenergic receptor stimulation. Hypercalcaemia increases catecholamine (Adr and NAdr) release and arterial response to catecholamines [40]. Correlations between PTH levels and CHF severity have been reported [41], although its prognostic role remains controversial. PTH serves as a reliable biomarker of congestion in HF patients, associated with peripheral oedema and orthopnoea [42]. Literature also highlights a link between PTH levels and AF incidence [43].

In our study, baseline PTH levels in Group 1 exceeded reference values and were associated with higher initial Adr levels and arrhythmias in the form of tachycardic AF requiring RFA AVJ. Elevated PTH levels were observed in 18 (32.1%) patients, including 9 (39%) northerners and 9 (27.3%) patients from the sTr. Correlations between PTH and echocardiographic parameters, as well as NT-proBNP levels, support its involvement in cardiac remodeling and HF severity verification. It has been demonstrated that PTH adds prognostic value to NT-proBNP and serves as an independent predictor of cardiovascular events [44].

The greater severity of HF in Group 1 was further verified by elevated baseline levels of TIMP-1, TNF-α, CRP, Adr, and increased right ventricular dimensions. Fibrosis and inflammation are interlinked mechanisms driving HF progression [45]. The observed association of 5-year survival in northerners with IL-6 levels indicates the independent impact of immune inflammation on prognosis. The literature discusses the prognostic significance of the right ventricle [46]. Long-term (lifetime) hypoxia triggers adaptive responses, including sympathetic activation and hypoxic pulmonary vasoconstriction [47], which increases right heart strain, reduces right ventricular output, and eventually leads to its enlargement. This highlights the heart's ability to adapt successfully to hypoxia both in the short and long term.

Comparable 5-year survival rates across the groups may be attributed to the numerous effects of CRT, including immunosuppressive and adrenomodulating influences [48], effects on thyroid function [49], sex steroids [50], oxidative stress [51], and fibrosis [52].

Study limitations

The limitations of our study include its single-centre design and the inclusion of a small number of patients.

CONCLUSION

Thus, male CRT responders residing in the Far North exhibited a complex set of adaptive reactions, including elevated levels of cortisol and thyroid hormones (TSH, fT4), reduced fT3/fT4 ratio, increased parathyroid hormone levels, associated with heightened sympatho-adrenal and immune activation, fibroformation imbalance, larger right ventricular dimensions, and a higher incidence of tachysystolic atrial fibrillation requiring AVJ RFA. These findings likely reflect the complex pathophysiological nature of the Arctic strain syndrome, which contributes to the development of heart failure in Arctic conditions. Comparable 5-year survival rates between Far North residents and patients from the southern Tyumen region were attributed to the modulatory effects of CRT. The observed association of survival in Far North patients with IL-6 levels highlights the independent impact of immune inflammation on prognosis.

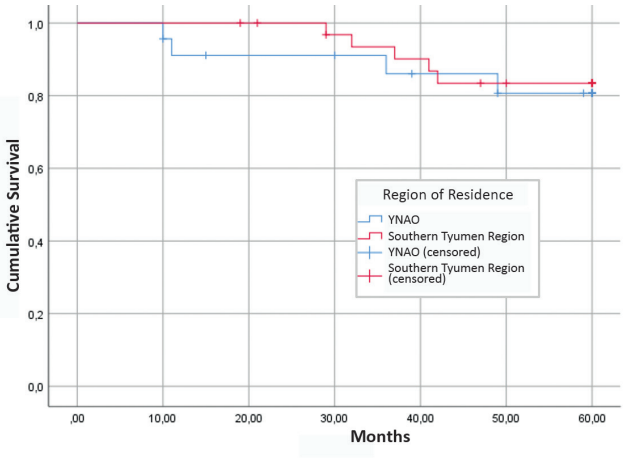

Fig. 1. Five-year survival of male responders to cardiac resynchronization therapy under the age of 65.

Table 7.

Results of Cox multivariate regression analysis

	Factors	HR (95% CI)	p
Group I - FN (n=23)	IL-6	4.013 (1.278-12.605)	0.017
	TIMP-1	0.986 (0.959-1.012)	0.290
	NT-proBNP	1.000 (1.000-1.001)	0.489
Group II - sTr (n=33)	LVEDV	1.032 (0.979-1.088)	0.237
	LVESV	0.969 (0.899-1.044)	0.408
	LVEF	0.887 (0.698-1.127)	0.327
	MMP-9	0.991 (0.964-1.020)	0.543

Note: hereinafter, HR - Hazard Ratio; CI - Confidence Interval.

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