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Original research article

Exercise training program in patients with NYHA III class systolic heart failure - Parallel comparison to the effects of resynchronization therapy

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ABSTRACT

Purpose: The aim of this study was to assess exercise capacity and echocardiographic parameters in patients with heart failure with reduced ejection fraction (HFrEF) in NYHA III functional class, after cardiac resynchronization therapy (CRT) or implantable cardioverter-defibrillator (ICD) implantation followed by 6 months of supervised rehabilitation in ICD patients.

Materials and methods: The study included patients with HFrEF and impaired left ventricle systolic function (LVEF ≤ 35%), divided into two groups: CRT group - patients after CRT-D implantation > six weeks, and ICD-rehab group - patients after ICD implantation > six weeks, followed by 6 months of supervised aerobic interval training and the conditioning exercises. At baseline and after 6 months in all the patients cardiopulmonary exercise tests (CPX) and standard echocardiographic examinations were performed.

Results: The study included 61 patients (49–77 years) with HFrEF. At baseline, the values of CPX parameters were similar in both groups. After completing training almost all CPX parameters in the ICD-rehab group significantly improved, except for anaerobic threshold (AT). In the CRT group significant improvements were found in 2 parameters: peak oxygen uptake (VO_2) and exercise tolerance (metabolic equivalents, METs). Significant reductions in left and right ventricle diameters and an increase in LVEF were observed in both groups after 6 months.

Conclusions: Significant improvement in exercise tolerance capacity and increase of LVEF were observed in similar extent both in heart failure patients with CRT and with ICD undergoing the rehabilitation program. Regular, controlled exercise trainings provided additional, safe and easy to conduct therapeutic option for heart failure patients with no indications for CRT.

1. Introduction

Cardiac resynchronization therapy (CRT) is an additional, complimentary option in patients with heart failure with reduced ejection fraction (HFrEF). Its role has been strongly emphasized in the prevention of all-cause deaths and hospitalizations in the current European and American guidelines for heart failure management [1,2]. Multicenter clinical trials showed that CRT implementation in HFrEF patients with wide QRS complex and signs of dyssynchrony resulted in moderate improvement in NYHA functional class, quality of life, exercise capacity (peak oxygen uptake), left ventricular ejection fraction (LVEF) and reduction of mitral insufficiency volume [3,4]. Implantable cardioverter-defibrillator (ICD) decreases the risk of sudden cardiac death in patients with implanted CRT-D. ICD prevents arrhythmic deaths in secondary and also in primary prevention, but does not directly improve exercise capacity or prognosis resulting from progression of HFrEF [5]. Randomized clinical trials proved the survival benefit in patients with reduced LVEF and ICD. MADIT II trial (Multicenter Automatic Defibrillator Trial II) results showed, that patients after myocardial infarction and LVEF < 30% had significant survival benefit after ICD implantation [6]. SCD-HeFT study further expanded the criteria for ICD for all patients with cardiomyopathy (ischemic and non-ischemic) and LVEF < 35% [7]. Exercise training remains an important option in the treatment of patients with HFrEF, also with cardiovascular implantable electronic devices (CIED) [2]. Studies of regular training in patients with HFrEF including CRT-D or ICD confirm safety of exercise and improvement in exercise parameters [8–15].

The aim of the present study was to assess exercise capacity and echocardiographic parameters in patients with advanced HFrEF (NYHA III) after CRT and no rehabilitation programme (CRT group) or ICD

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implantation followed by 6 months supervised rehabilitation (ICD-rehab group).

2. Material and methods

2.1. Material

The enrolment of patients for this single center, prospective cohort study lasted from 2008 to 2012 and then patients were followed for six months from the study entry. The study included consecutive patients with HFrEF, LVEF ≤ 35% of ischemic and non-ischemic aetiology, in NYHA III class. They had been earlier admitted to hospital with the exacerbation of heart failure. The decision of the treatment option was made during hospitalization. Patients were divided into two groups: CRT group and ICD-rehab group (minimum six weeks after device implantation). Patients with implanted CRT had no exercise trainings in the past, at the moment of entering the study and during a 6-month follow-up. The decision of CRT implantation was based on the European Society of Cardiology Guidelines at that time: QRS width > 120 ms in patients with HFrEF in NYHA III or IV class, (recommendation class: IB) [16,17]. The ratio of responders to CRT was 70%, which was controlled during the study.

The ICD-rehab group consisted of patients after ICD implantation > 6 weeks before entering the study, followed by six months of supervised rehabilitation program.

Exclusion criteria comprised: acute or uncontrolled noncardiac diseases, severe musculoskeletal conditions which preclude physical rehabilitation (orthopedic, neurological), acute coronary syndromes, transient ischemic attacks (TIA) or stroke within the last 6 months, cardiac surgery or coronary intervention within last 3 months, history of venous thrombosis or pulmonary embolism, severe, uncontrolled hypertensive and valve diseases.

2.2. Methods

Outpatient ICD group performed loaded cycling on ergometer divided into intervals and the conditioning exercises with elements of resistance training three times a week. Intensity of endurance training was based on the maximum heart rate achieved by the patient during an exercise test. Maximal training heart rate was calculated according to the Karvonen formula. The training program consisted of 3 min of warm-up (10 W), 2 min of loaded cycling up to 120 W, 2 min of low intensity exercise (10 W load), and 2 min of rest. Every patient had individual values of maximum workload.

Cycloergometer sessions lasted 30 min during which patients were cycling with the cadence of 55 to 64 rpm. Resistance trainings lasted from 5 to 10 min. Exercises involving a single muscle group of one limb alternately with a load of up to 50% of muscle strength were performed. There were 10–12 repetitions in one cycle during 1 min working phase. Patients exercised until their fatigue level reached 11–12 points, according to the original 20-point Borg scale.

At the baseline and after 6 months all the patients performed cardiopulmonary exercise tests (CPX) on the cycloergometer according to the Ramp protocol: workload was increased by 10 W every minute [18,19]. The analysis included: exercise tolerance (METs), peak oxygen consumption (peak VO_2), peak carbon dioxide excretion (peak VCO_2), ventilatory anaerobic threshold (VAT) and minute ventilation (VE). Ventilatory efficiency and peak end tidal CO_2 (P_{ET} CO_2) were analyzed, but the values of these parameters did not differ between the study groups. All the patients had standard echocardiographic examinations (2D plus Doppler) at baseline and after 6 months. LVEF was measured by biplane Simpson method.

2.3. Ethical issues

The study was supported by the State Committee for Scientific Research grant and carried out between January 2008 and December 2011. The design and protocol of the study was approved by Institutional Review Board at the Institute of Cardiology, Warsaw (registration number IK-NP-0021-5/996/07, IK-NP-0021-73/1100/08). The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments.

Table 1
Demographic and clinical characteristics of patients.

N	CRT group, n = 28	ICD-rehab group, n = 33	P
Age, years	66.7 ± 7.9	62.1 ± 8.6	0.0993
Male, n(%)	24 (85.7)	29 (87.9)	0.8029
Body mass (kg)	80.0 ± 17.0	84.4 ± 17.7	0.3320
Height (m)	1.71 ± 0.08	1.74 ± 0.09	0.1973
BMI (kg/m^2)	27.2 ± 4.4	27.9 ± 4.9	0.6037
Hypertension, n(%)	11 (39.3%)	18 (54.5%)	0.2343
Prior infarction, n(%)	14 (50%)	25 (75.8%)	**0.0368**
Prior CABG, n(%)	3 (10.7%)	7 (21.2%)	0.3189
Diabetes, n(%)	11 (39.3%)	9 (27.3%)	0.3193
Atrial fibrillation, n (%)	10 (35.7%)	10 (30.3%)	0.6537
Beta-blockers, n (%)	28 (100%)	32 (97%)	1.000
ACE-Inhibitors, n (%)	22 (78.6%)	26 (78.8%)	0.9836
ARB, n (%)	7 (25.0%)	8 (24.2%)	0.9454
Calcium antagonists, n (%)	2 (7.1%)	6 (18.8%)	0.2694
Loop diuretics, n (%)	21 (75.0%)	26 (78.8%)	0.7259
Thiazide diuretics, n (%)	4 (14.3%)	6 (18.2%)	0.7413
Spironolactione, n (%)	22 (78.6%)	20 (60.6%)	0.1311
Eplerenone, n (%)	1 (3.5%)	11 (30.3%)	**0.0036**
Statins, n (%)	17 (60.7%)	26 (78.8%)	0.1230
Fibrates, n (%)	2 (7.1%)	3 (9.1%)	1.0000
Digoxin, n (%)	6 (21.4%)	10 (30.3%)	0.4323
Oral anticoagulants, n (%)	10 (35.7%)	9 (27.3%)	0.4780
Oral antidiabetic agents, n (%)	11 (39.3%)	9 (27.3%)	0.3193
Insulin, n (%)	1 (3.5%)	1 (3.0%)	1.000
ASA, n (%)	22 (78.6%)	26 (78.8%)	0.9836
Ticlopidin, n (%)	1 (3.5%)	1 (3.0%)	1.0000
Clopidogrel, n (%)	3 (10.7%)	9 (27.3%)	0.1050

BMI: body mass index, CABG: coronary artery bypass grafting, ARB: angiotensin receptor blockers, ASA: aspirin.

2.4. Statistical analysis

Results of patients who had all study visits were analyzed. As continuous variables were normally distributed, the results were presented as the arithmetic mean ± SD. After checking the homogeneity of variance by F-Fisher test, differences between means of the two study groups were assessed by two-sample *t*-test (Student's *t*-test). Comparison of pre- and post-rehabilitation parameters measurements was performed using the Student's ttest for paired samples. Categorical variables were presented as counts and percentage frequencies. Proportions were compared by Pearson's Chi-square test with continuity correction or Fisher's exact test when appropriate. Statistical conclusions were based on two-tailed test with the significance level set at alpha = 0.05. Statistical calculations were performed using the SAS package, version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

The study included 61 patients (53 male; aged 49–77 years) in NYHA III class, with impaired LV systolic function (LVEF ≤ 35%) of ischemic (60%) and non-ischemic (40%) etiology. Patients were divided into two groups: CRT group after CRT-D implantation > 6 weeks (28 pts; 24 male; mean age 66.7 ± 7.9 years) with mean QRS width 156 ± 12 ms, without any exercise trainings in the past, at the moment of entering the study, and during 6 months follow-up. ICD-rehab group consisted of 33 patients, 29 male, mean age 62.1 ± 8.6 years, QRS width < 120 ms, after ICD implantation > 6 weeks followed by 6

Table 2
Comparison of CPX parameters between study groups at baseline and after 6 months.

		CRT group, n = 28	ICD-rehab group, n = 33	P
HR rest (/min)	At baseline	81.0 ± 19.9	72.0 ± 12.2	0.0690
	After 6 months	75.0 ± 11.0	72.0 ± 12.4	0.3830
	P	0.1595	0.9887	
HR peak (/min)	At baseline	109.3 ± 26.2	106.1 ± 21.7	0.6527
	After 6 months	112.8 ± 22.8	115.6 ± 28.4	0.7112
	P	0.3054	**0.0141**	
VO_2 peak (ml/kg/min)	At baseline	11.5 ± 3.9	12.6 ± 3.9	0.3110
	After 6 months	13.4 ± 4.4	14.8 ± 5.6	0.3091
	P	**0.0208**	**0.0028**	
VO_2 peak (%)	At baseline	49.6 ± 18.2	50.3 ± 14.5	0.8799
	After 6 months	58.6 ± 17.8	59.8 ± 21.8	0.8368
	P	**0.0094**	**0.0029**	
VCO_2 peak (l/min)	At baseline	0.95 ± 0.39	1.11 ± 0.38	0.8377
	After 6 months	1.10 ± 0.45	1.37 ± 0.55	0.0505
	P	0.0592	**0.0007**	
VE max (l/min)	At baseline	44.4 ± 10.0	47.0 ± 11.8	0.4150
	After 6 months	45.0 ± 15.0	54.1 ± 15.3	**0.0396**
	P	0.7978	**0.0027**	
VE max (%)	At baseline	52.5 ± 12.4	54.7 ± 10.2	0.4767
	After 6 months	52.1 ± 13.2	61.5 ± 12.6	**0.0113**
	P	0.8854	**0.0147**	
VE/VCO_2 slope	At baseline	35.9 ± 7.1	34.5 ± 8.1	0.5529
	After 6 months	30.4 ± 8.8	33.8 ± 10.4	0.2338
	P	**0.0064**	0.7108	
AT – achieved, n (%)	At baseline	10 (41.7%)	17 (54.8%)	0.3329
	After 6 months	12 (50%)	24 (77.4%)	**0.0339**
	P	0.4142	**0.0196**	
AT	At baseline	12.2 ± 2.6	12.1 ± 3.3	0.9273
	After 6 months	11.3 ± 4.2	13.5 ± 5.6	0.3413
	P	0.6206	0.3317	
AT $\%VO_2$	At baseline	73.1 ± 24.6	74.7 ± 22.1	0.8777
	After 6 months	64.7 ± 26.5	72.0 ± 21.1	0.4878
	P	0.4851	0.6647	
METs	At baseline	3.5 ± 2.0	3.6 ± 1.8	0.8672
	After 6 months	4.5 ± 2.3	4.0 ± 1.4	0.4928
	P	**0.0263**	**0.0376**	
RER	At baseline	1.01 ± 0.07	1.07 ± 0.19	0.2023
	After 6 months	0.97 ± 0.10	1.07 ± 0.11	**0.0010**
	P	0.0301	0.8587	

HR: heart rate; VO_2 peak: peak oxygen uptake, VCO_2 peak: peak carbon dioxide elimination; VE: ventilation equivalent for carbon dioxide; AT: anaerobic threshold; METs: metabolic equivalents; HR = heart rate, RER – Respiratory Exchange Ratio.

months of supervised rehabilitation program. The study groups did not differ in terms of demographic data, with the exception of higher incidence of myocardial infarction history in the ICD-rehab group (Table 1).

The QRS mean widths were different in both study groups, but the study groups did not differ in exercise capacity at baseline: peak VO_2 was 11.5 ml/kg/min in the CRT group vs. 12.6 ml/kg/min, ns, in the ICD-rehab group, ns. The groups did not differ also in LVEF baseline values: 25.12% vs. 24.27% in the CRT and ICD-rehab groups, respectively. At baseline CPX parameters were similar in both groups.

VE/VCO_2 slope values for the CRT group were: 38.2 ± 9.2 at baseline vs. 32.8 ± 10.2 after completion of the program ($p < 0.05$) and for the ICD-rehab group: 35.9 ± 8.9 vs. 35.7 ± 11.9, ns, respectively (Table 2).

After completing exercise training almost all CPX parameters in the ICD-rehab group improved. Statistically significantly more patients in the ICD-rehab group achieved anaerobic threshold (AT) than in the CRT group. Also, the level of ventilation equivalent for carbon dioxide (VE/VCO_2) improved after training in the ICD-rehab group. In the CRT group statistically significant improvement was found only in 2 parameters: peak VO_2 and exercise tolerance, measured in metabolic equivalents (METs). Statistically significant differences between the study groups in favor of the ICD-rehab group were also observed in ventilation equivalents for carbon dioxide (VE/VCO_2 max) and VE max % (Table 2).

In the baseline echocardiographic examinations we observed differences in the left ventricular end-systolic dimension between the groups: CRT: 5.73 ± 1.22 cm and ICD-rehab: 5.0 ± 1.05 cm ($p = 0.0250$). Other echocardiographic parameters were comparable. Average pulmonary artery systolic pressure (PASP) was < 40 mmHg in both groups. Tricuspid annular plane systolic excursion (TAPSE) values were also similar (18.3 cm vs. 19.2 cm, ns). The majority of patients were on loop diuretics: CRT group: n = 21 (75%), ICD-rehab group n = 26 (78.8%).

Statistically significant reductions in systolic and diastolic left ventricle diameters, decrease in diastolic right ventricle diameter and increase in ejection fraction were observed in both groups after 6 months, but there were no differences between the groups (Table 3).

In the course of the study there were only 3 patients in NYHA III/IV class: 2 in the CRT-group and 1 in the ICD-rehab group. They were excluded from exercise trainings continuation.

4. Discussion

Despite the improvement in survival, morbidity and symptoms due to constant progress in the medical treatment of patients with HFrEF, a substantial part of them require device therapy: cardiac resynchronization therapy (CRT-P or CRT-D), or ICD implantation. Guidelines published at the time of study conduction recommended CRT primarily in patients with HFrEF in NYHA class III and IV to reduce symptoms, mortality and morbidity if QRS duration exceeded 120 ms and LVEF was below 35%, despite optimal medical therapy

Table 3
Echocardiographic parameters at baseline and after 6 months.

		CRT group, n = 28	ICD-rehab group, n = 33	P
LVEDD, cm	At baseline	6.94 ± 1.12	6.62 ± 1.02	0.2622
	After 6 months	6.49 ± 1.06	6.27 ± 0.76	0.3496
	P	**0.0122**	**0.0085**	
LVESD, cm	At baseline	5.73 ± 1.22	5.0 ± 1.05	**0.0250**
	After 6 months	4.88 ± 1.20	4.38 ± 0.84	0.0835
	P	**0.0007**	**0.0007**	
RVEDD, cm	At baseline	3.21 ± 0.43	2.71 ± 0.65	0.3130
	After 6 months	2.96 ± 0.89	2.50 ± 0.82	0.2015
	P	**0.0149**	**0.0006**	
LA, cm	At baseline	4.58 ± 0.98	4.65 ± 0.60	0.7257
	After 6 months	4.70 ± 1.11	4.58 ± 0.68	0.6395
	P	0.4078	0.5728	
Aorta, cm	At baseline	3.58 ± 0.46	3.61 ± 0.64	0.3071
	After 6 months	3.44 ± 0.38	3.47 ± 0.39	0.2418
	P	0.7562	0.6906	
EF, %	At baseline	25.12 ± 7.02	24.27 ± 6.16	0.7110
	After 6 months	31.80 ± 11.61	31.28 ± 8.87	0.8489
	P	**0.0007**	< **0.0001**	

LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; RVEDD: right ventricular end-diastolic dimension; LA: left atrial end-systolic diameter; Aorta: ascending aorta diameter; EF: left ventricular ejection fraction.

(recommendation class IB) [16]. ICD implantation is recommended in primary and secondary prevention to reduce the risk of sudden cardiac death and all-cause mortality in patients. The issue if ICD implantation in non-ischemic cardiomyopathy is more complicated in the light of recent studies results [7,20]. However, despite the neutral results of the DANISH trial, meta-analysis of randomized clinical trials demonstrated significant benefit on all-cause mortality in favor of ICD use for primary prevention [21]. ICDs prevent sudden arrhythmic cardiac deaths in HFrEF patients, but they do not improve exercise capacity and prognosis resulting from progression of heart failure. Another therapeutic option for these patients are individually tailored regular exercise training sessions. The results of studies in patients with HFrEF after ICD implantation (EF < 35%) confirm an increase in oxygen uptake, maximum workload and training safety: relatively low risk of arrhythmia worsening or ICD shocks [10–13].

CRT improves NYHA functional class, quality of life, exercise capacity measured by peak VO_2 and LVEF. CRT also decreases mortality and hospitalization risk, left ventricular dimensions and mitral insufficiency volume [22–26]. On the basis of existing evidence, overall clinical condition of patients with HFrEF after CRT implantation is improving.

The idea of the present study was to compare two treatment options in patients with HFrEF, NYHA III class, and low ejection fraction: regular exercise training in patients with no CRT (ICD-rehab group) vs. CRT only. The only differences between the groups were: higher rate of patients after myocardial infarction and treatment with eplerenone in the ICD-rehab group. The ICD group was relatively younger (62.1 vs. 66.7 years), but possibly due to small sizes of study groups the difference was not statistically significant (p = 0.0993). To our knowledge it is the first attempt to show the results of exercise training in comparison to CRT effects in the heart failure patients.

The LVEF at the beginning of the study was similar in both groups (25.1 vs. 24.2%, ns). There had been constant reductions of left and right ventricular remodeling in echocardiographic evaluations after 6 months in both groups.

The improvement in the CPX parameters had been observed in both groups after 6 months, but it was more evident in the ICD-rehab group. Statistically significantly more patients in the ICD-rehab group achieved AT than in the CRT group and had higher level of VE/VCO_2 after exercise training, which showed their better physical capacity. Benefits of CRT might be limited by no adequate response in approximately 30% of treated patients. Low biventricular pacing rate was due to arrhythmia occurrence (including atrial fibrillation) and higher heart rate because of possible poor medical treatment compliance. None of the patients in the study groups had atrioventricular node ablation. On the other hand, VO_2/VCO_2 slope values were statistically significantly reduced after 6 months only in the CRT group, which indicated better prognosis.

The beneficial results of regular exercise training are confirmed in systematic reviews, meta-analyses and single studies showing that physical conditioning by exercise training significantly improves exercise tolerance in HFrEF [3,4,10–13]. Health-related quality of life is better and heart failure hospitalization rates are lower in patients with reduced and preserved LVEF treated with regular exercise trainings. Supervision of exercise may be undertaken by the patients themselves and in community or hospital clinics by remote monitoring [1,2].

The present study reveals a unique situation of prospective clinical comparison between direct clinical effects of CRT and exercise trainings in patients with systolic heart failure and low ejection fraction (mean LVEF: 25%). The results and safety of these two treatment modalities in terms of patients' performance were satisfactory. Another issue interesting to consider would be a rehabilitation program in patients with HFrEF, LBBB and QRS > 120 ms before CRT implantation, but this may be the subject of a future study.

4.1. Limitations of the study

The study was conducted in one cardiology center, in relatively small-sized groups of HFrEF patients. The study heart failure patients proved difficult to work with, so the number of the patients was not high. Effective motivation of patients to take up regular long-term exercise was the challenge that required careful consideration. Availability of rehabilitation programs in our area for this specific patients' group was sufficient.

5. Conclusions

Significant improvement in exercise tolerance capacity and increase of left ventricle ejection fraction were observed in similar extent in both heart failure patients with CRT and with ICD undergoing rehabilitation program. Regular, controlled exercise trainings provided additional, safe and easy to conduct therapeutic option for heart failure patients with no indications for CRT.

Conflict of interests

The authors declare no conflict of interests

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