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Research Article

Lactate Threshold-Based Training Programs Associated with Reduced Ergoreflex Activation and Better Functional Improvement in Heart Failure Patients with Reduced Left Ventricular Ejection Fraction

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Abstract

Objective: This study aimed to assess changes in ergoreflex activity in patients with Heart Failure with Reduced Ejection Fraction (HFrEF) after two different aerobic exercise programs.

Methods: This single-center prospective observational study with a control group included 297 patients with HFrEF. The study group comprised 237 patients who underwent a physical exercise training program based on the individual Lactate Threshold (LTH). The control (CON, n = 60) group underwent standard physical training. Ergoreflex activity and exercisecapacityaccordingtoVO2peak values were determined in all patients. Ergoreflex activity and exercise capacity dynamics were assessed at 3 and 9 months of follow-up; additionally, serum inflammatory marker levels and heart failure functional class were compared between the groups.

Results: At 9 months of follow-up, the LTH-based personalized training program resulted in a better improvement of HFrEF patients: a greater percentage of patients with NYHA class II post-treatment (75% and 44% in the CON and LTH groups, respectively, P=0.003) and a greater gain in VO2 peak (by 45% and 17% in the CON and LTH groups, respectively, P=0.0017). The VO2 peak increased by ≥ 10% after completion of training in70% and 94% of patients in the CON and LTH groups, respectively. The ergoreflex activity decreased by ≥15% in 63% and 97% of patients in the CON and LTH groups, respectively. The extent of ergoreflex activity decline correlated with a decrease in the monocyte count, which was used as a surrogate marker of systemic inflammation (r = 0.63, P=0.01).

Conclusion: Aerobic exercise training in patients with HFrEF resulted in a decreased ergoreflex activity, which was associated with the improvement in heart failure functional class and exercise tolerance. A personalized exercise training program based on the LTH demonstrated superior effectiveness in reducing ergoreflex activity and heart failure compensation compared with the standard protocol.

Keywords: Heart failure with educed ejection fraction; Ergoreflex activity; Aerobic exercise; Exercise training; Lactate threshold; Exercise capacity.

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Introduction

The concept of neurohormonal activation in Heart Failure (HF) has provided a rationale for the use of vβ-blockers and angiotens in-converting enzyme inhibitors (ACEis) in preventing the deleterious effects of increased sympathetic tone and Renin-Angiotensin-Aldosterone System (RAAS) over activation on the survival of patients with Heart Failure (HF) with Reduced Ejection Fraction (HFrEF) [1]. Nevertheless, mortality rates in patients with HFrEF remain unacceptably high, averaging 65% over a 10-year period [2,3]. One of the promising approaches to the treatment of this category of patients is the reversal of overtsympath ovagal imbalance, generally aimed at stimulating the parasympathetic system and/or inhibiting sympathetic tone. Although several drug- and device-based therapies are currently in development, the results of large-scale, randomized clinical trials of their effectiveness are still unavailable.

Currently, enhanced Ergoreflex (ER) responsiveness is considered one of the main mechanisms of autonomic imbalance in patients with HFrEF, providing a pathogenetic link between skeletal muscle myopathy and disease progression. ER is initiated by the activation of mechano- and metaboreceptors of contracting muscles, which are connected to the autonomic centers of the brainstem by type III and IV muscle afferent fibers, respectively [4]. Increased sensory input to the respiratory center and pressorsites of the brainstem results in sympathetic activation, which elicits increased respiratory and heart rates, constriction of resistant arteries, and catecholamine release from the adrenal medulla. HFrEF has been shown to be associated with augmented ER, potentially by increasing the sensitivity of ergoreceptors in patients with skeletal muscle myopathy [5]. Therefore, persistent ER activation in patients with HFrEF may contribute to sustained neurohormonal activation, which is not fully controlled even in patients receiving recommended doses of β-blockers and anti-RAAS medications. Therefore, there is an unmet medical need for new non-drug therapies to normalize the enhanced activity of ER in HFrEF. For example, physical training is a valuable therapeutic option for HFrEF, effectively improving exercise capacity, restoring sympathovagal imbalance, and reducing ergoreceptor sensitivity [6]. It is unknown, however, whether ER activity in patients with HFrEF is influenced by the prescribed physical training regimen.

In this single-center prospective observational study, we aimed to evaluate changes in ER activity in patients with HFrEF after a prescription of either a standard physical training program or an individualized program designed according to individual Lactate Threshold (LTH) values. The relationship between ER activity and exercise capacity, serum levels of inflammatory markers, and New York Heart Association (NYHA) functional class before and after training were also assessed.

Methods

The study was performed in accordance with the principles of the Declaration of Helsinki. Study results are presented according to the STROBE statement for reporting observational studies. This single-center prospective observational study comprised 297 consecutive patients referred to the HF competence center of the Almazov National Medical Research Center between January 2018 and December 2020 (85 women and 212 men; mean age, 55.0 [44; 61] years) who were eligible according to the inclusion criteria and signed informed consent. The inclusion criteria were as follows: 1) HFNYHA class III, diagnosed>6 months prior to study enrollment; 2) history of ischemic heart disease or dilated cardiomyopathy; 3) aged 18–65 years; 4) Body Mass Index (BMI) between 19–28 kg/m^2; 5) stable clinical course >2 weeks; 6) left ventricular ejection fraction (LVEF) <45%; 7) maximally tolerated disease-modifying therapy for HF according to guidelines actual at enrollment; 8) observed in the HF competence center; and 9) ability to perform Cardiopulmonary Exercise Testing (CPET). Exclusion criteria were as follows: 1) history of recent (<6 weeks) myocardial infarction or pulmonary embolism; 2) history of recent (<6 months) coronary artery bypass grafting or Cardiac Resynchronization Therapy (CRT) device implantation; 3) acute ischemic stroke; 4) stages 3–4 of chronic obstructive pulmonary disease according to Global Initiative for Chronic Obstructive Lung Disease classification, 5) diabetes mellitus; 6) non-HF skeletal muscle disease; 7) advanced cognitive dysfunction; 8) hemoglobin level <121 g/L in women and <131 g/L in men; 9) acute inflammation or infection; 10) recent surgical operations; and 11) diseases affecting joints or connective tissue. The sample size of this observational study was determined by the timeframe of inclusion.

Study Design

Two patient groups were included in this study. In the experimental group (LTH, n = 237), the prescribed physical exercise program was based on the individual lactate threshold. In the control group (CON, n = 60), the patients were prescribed standard physical training according to the consensus of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation [7]. The CON group comprised patients who refused to undergo personalized training based on the lactate threshold. The parameters of CPET were registered at baseline and at 3 and 9 months after enrollment. In all patients, the following data were available for analysis at baseline and 9 months later: peak oxygen consumption (VO_{2peak}), oxygen consumption at lactate threshold ($VO_{2\,LT}$), Diastolic Blood Pressure (DBP), Ventilation Volume (V_E), the volume of carbon dioxide (V_{CO2}), total leukocyte count, and monocyte count in the blood. All patients were stable at baseline and received the maximum tolerated doses of standard therapy. Compliance was assessed by consulting physicians. If the patient was regarded as non-compliant, he or she was advised to terminate study participation.

The primary end-point of the study was ER activity, determined as the difference between baseline V_E and V_E at 9 months and expressed in % (ΔV_E).

The secondary endpoints were HF NYHA functional class and exercise capacity (VO_{2peak}). The following criteria for a positive response to physical training were established: decrease in ER activity by ≥15% and increase in VO_{2peak} by ≥10% from a baseline value. The relationship between ER activity and exercise capacity, the monocyte count, and the NYHA functional class were also studied.

Cardio Pulmonary Exercise Testing and ER Assessment

CPET was performed using a treadmill (T-2100, GE Medical Systems Information Technologies, Milwaukee, WI, USA), stress testing unit (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany),and ramp protocol consisting of 49 15-s steps adapted for lactate threshold determination. We measured the $VO_{2\,peak}$, $VO_{2\,LT}$, V_E, VCO_2, and V_E/VCO_2 using breath-to-breath gas analysis with automated averaging of values for 10 s each [8]. ER activity was determined using the post-exercise regional circulatory occlusion technique, accompanied by the measure-

ment of DBP, VCO_2, and V_E [9]. The parameters characterizing ER activity at baseline are presented as a percentage relative to the baseline value and designated as Δ. The changes in the parameters of ER activity after completion of the 9-month training were expressed as the difference between the baseline value and the value achieved at the end of the study. The corresponding designations in the text are as follows: ($\Delta DBP_{at\ baseline}$-$\Delta DBP_{9months}$), ($\Delta VCO_{2at\ baseline}$-$\Delta VCO_{29months}$), and ($\Delta V_{E\ at\ baseline}$-$\Delta V_{E9months}$). The physiological stages of compensation during exercise were determined using a previously described technique based on the changes in lactate levels, blood pH, $VO_{2\ peak}$, VCO_2, VCO_2/VO_2, V_E, and V_E/VCO_2 [10].

Measurement of Lactate Levels and Lactate Threshold

Prior to CPET, a catheter was inserted in the cubital vein in all participants. Blood samples were obtained at baseline and at each minute during physical exercise. The lactate level (mmol/L) in the venous blood was measured using a blood gas analyzer (i-STAT, Abbott Laboratories, Abbott Park, IL, USA). The lactate threshold was identified when lactate concentration started to increase.

Calculation and Design of the Exercise Training Program

In the LTH group, walking was performed daily for 60 min at a speed corresponding to 95% of the speed registered at the moment of lactate threshold onset during initial CPET [11].

Patients in the CON group were assigned physical training according to the recommend at ions of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation [7]. Briefly, walking was performed 3 times per week at a speed corresponding to a 50% $VO_{2\ peak}$.

In both groups, patients were trained initial 2 weeks on a treadmill under the supervision of a cardiologist. Subsequently, the patients were trained at home. After 3 months of training, the lactate threshold was reevaluated in the LTH group, and $VO_{2\ peak}$ was reevaluated in the CON group, the speed of walking was corrected according to the new values.

Evaluation of Blood Cell Counts

Complete blood cell counts were determined in all patients (Sysmex-XT1800iV, Sysmex, Kobe, Japan). The blood was sampled in a fasted condition between 7:00–9:00 a.m. The absolute counts of leukocytes and monocytes were considered and evaluated as non-specific markers of systemic inflammation [12,13].

Statistical Analysis

Statistical analysis was performed using SPSS (version 12.0; IBM Corporation, Armonk, NY, USA).Statistical significance was set at P<0.05. Categorical data are presented as frequencies (percentages) and were analyzed using χ^2 or, in case of small samples, Fisher's exact test. Numerical data samples were initially tested for normal distribution using the Kolmogorov-Smirnov criterion. Quantitative parameters with normal distribution are presented as mean ± standard error of mean. Non-normally distributed data are presented as medians [25 quartile; 75 quartile].Theeffectsofcategoricalvariablesonnormallydistributeddatawere analyzed using *t*-tests and analysis of variance with post-hoc analysis. Non-normally distributed data were analyzed using the non-parametric Mann–Whitney *U* test. The relationship between parameters was assessed by calculating the Spearman correlation coefficient and by multiple linear regression analysis.

Results

Baseline demographic and clinical characteristics of study participants are shown in (Table 1). There were no significant differences in age, BMI, LVEF, history of ischemic heart disease, dilated cardiomyopathy, and arterial hypertension among the groups. The number of patients treated with ACE is or angiotens in receptor blockers, β-blockers, mineralocorticoid receptor antagonists, and diuretics was also similar among the groups. The LTH group comprised more women, more CRT-treated patients, and more patients with a history of a trial fibrillation than the CON group. The N-terminal pro-brain natriuretic peptide (NT-proBNP) values were higher in the LTH group than in the CON group.

Table 1: Baseline demographic and clinical characteristics of the patients.

Characteristic	Control group (n = 60)	Lactate threshold group (n = 237)	*P* value
Gender (male/female)	36/24	176/61	0.03
Age (years)	54.5 [43; 60]	55.0 [47; 60]	0.99
BMI (kg/m^2)	26.2±2.8	27.5 ± 0.5	0.50
LVEF (%)	26.0 [18; 30]	25.0 [20; 31]	0.07
NT-proBNP (pg/mL)	2428.1 [1039; 4485]	2835.0 [1235; 4634]	0.04
IHD	35 (58%)	158 (67%)	0.31
DCMP	25 (42%)	79 (33%)	0.12
HTN	30 (50%)	130 (55%)	0.31
AF	6 (10%)	29 (12%)	0.04
ACEI/ARB	60 (100%)	237 (100%)	0.25
BB	60 (100%)	237 (100%)	0.19
MRA	54 (91%)	212 (90%)	0.61
Diuretics	60 (100%)	237 (100%)	0.37
CRT	9 (15%)	52 (22%)	0.01
CABG	19 (28%)	73 (30%)	0.10

Data are presented as n (%), except for BMI data, which are presented as mean ± standard deviation, and age, LVEF, and NT-proBNP values, which are presented as median [25 quartile; 75 quartile]. ACEI/ARB: Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers; AF: A Trial Fibrillation; BB: Beta-Blocker; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CRT: Cardiac Resynchronization Therapy; DCMP: Dilated Cardiomyopathy; HTN: Arterial Hypertension; IHD: Ischemic Heart Disease; LVEF: Left Ventricular Ejection Fraction; MRA: Mineralocorticoid Receptor Antagonists; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide.

Twenty-three patients were excluded from the study (LTH, 13 patients, 5%; CON, 10 patients, 17%). The reasons for drop out were as follows: unwillingness to continue physical training (non-compliance, n = 10), heart transplantation (n = 5), hospital admission for reasons unrelated to HF (n = 6), and hospital admission due to HF decompensation associated with an acute respiratory infection (n = 2). Therefore, 274 patients completed the study, with 50 (83%) and 224 (95%) in the CON and LTH groups, respectively (Figure 1).

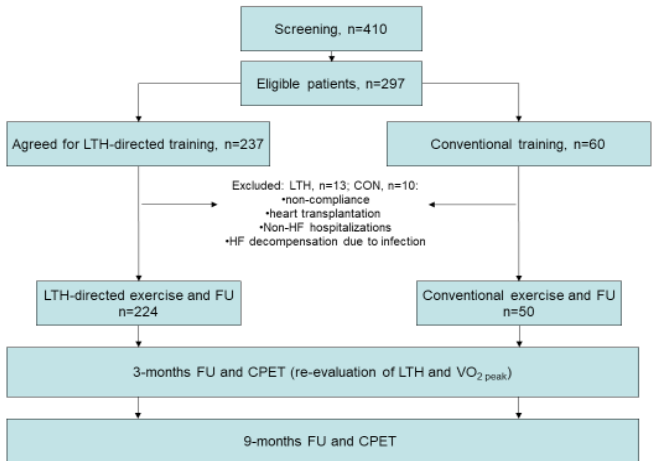

Figure 1: Study flowchart.
CPET – Cardiorespiratory Test; FU – Follow-Up; LTH – Lactate Threshold

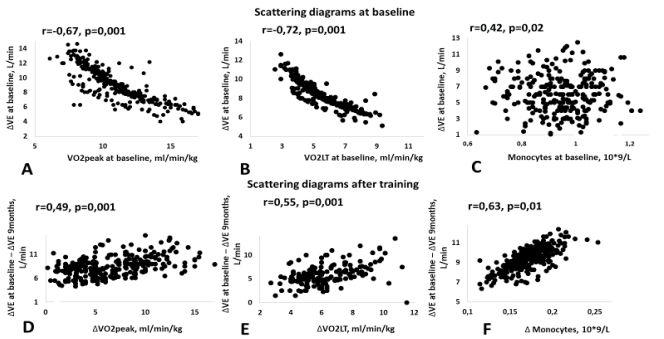

Figure 2: The correlations among ergoreflex (ER) activity, exercise tolerance, and blood monocyte count at baseline **(A-C)** and after 9 months of training **(D-F)**. The data are grouped for all patients included in the analysis (n = 274). **A** – correlation between ER activity (as per ΔV_E) and VO_{2peak} at baseline; **B** – correlation between ER activity and VO_{2LT} at baseline; **C** – correlation between ER activity and monocyte count at baseline; **D** – correlation between the extent of change in ER activity (baseline – post-treatment) and difference in VO_{2peak} between baseline and post-treatment values; **E** –correlation between the extent of change in ER activity (baseline – post-treatment) and difference in $VO_{2\,LT}$ between baseline and post-treatment values; **F** – correlation between the extent of change in ER activity (baseline – post-treatment) and difference in monocyte count between baseline and post-treatment values.

At baseline, we observed an inverse relationship between ER activity and $VO_{2\,peak}$ (r= – 0.67, *P*=0.001), as well as $VO_{2\,LT}$ (r= – 0.72, *P*=0.001, Figure 2). Additionally, a positive correlation was found between ER activity and monocyte count (r=0.42, *P*=0.021, Figure 2).

After 3 months of training, increased walking speed was registered in 210 (94%) and 35 (70%) participants in the LTH and CON groups, respectively (*P*<0.01). The prescription of a personalized training program based on LTH resulted in better HFrEF compensation, as evidenced by a greater percentage of patients with NYHA class II post-treatment (75% and 44% in the CON and LTH groups, respectively, *P*=0.003).

After completion of treatment at 9 months, exercise capacity increased in both groups. However, the net gain in exercise capacity was significantly greater in the LTH group than in the CON group. In particular, at the end of the study, the $VO_{2\,peak}$ increased by 45% and 17% in the LTH and CON groups, respectively (Table 2, *P*=0.0017). The gain in $VO_{2\,LT}$ was also found to be greater in the LTH group than in the CON group (24% vs. 15%, *P*=0.005, Table 2). The $VO_{2\,peak}$ was increased by ≥10% after training completion in210 (94%) and 35 (70%) patients in the CON and LTH groups, respectively (*P*<0.01). Notably, a greaterincreaseinVO$_{2\,LT}$ after physical training in both groups was associated with decreased monocyte counts (r= – 0.75, *P*=0.01).

Table 2: Changes in exercise capacity, ergoreflex activity, and systemic inflammation parameters over the study period in two groups of patients.

Parameter	Me				Q1				Q3			
	LTH group		CON group		LTH group		CON group		LTH group		CON group	
	BL	9 mo	BL	9mo	BL	9 mo	BL	9 mo	BL	9 mo	BL	9 mo
Exercise capacity												
$VO_{2\,LT}$, L/min	8.40	10.40*	8.50	9.70*	6.50	8.90*	6.60	7.60*	9.90	12.50*	10.10	10.70*
$VO_{2\,peak}$, L/min	13.40	19.40*	13.80	16.10*	11.10	15.90*	11.60	12.30*	17.10	24.70*	16.00	16.50
Ergoreflex activity												
ΔDBP_{BL}-ΔDBP_{9mo}, %	18.00	10.00*	18.00	16.00	12.00	7.00*	12.00	11.00	36.00	16.00*	35.00	32.00
ΔV_{EBL}- ΔV_{E9mo}, %	7.00	3.40*	6.70	5.10*	4.30	2.0*	4.50	4.40	12.70	6.00*	12.50	12.00
ΔVCO_{2BL}-ΔVCO_{29mo}, %	163.00	101.00*	170.10	143.00*	99.00	75.00*	107.00	95.00	313.00	178.00*	302.00	284.00*
Intensity of systemic inflammation												
Leukocytes, 10^9/L	8.31	6.35*	8.15	8.25	6.10	4.32*	6.55	4.55*	9.67	6.98*	9.53	9.68
Monocytes, 10^9/L	0.81	0.64*	0.80	0.77	0.75	0.58*	0.75	0.73	0.93	0.76*	0.92	0.87

BL: Baseline; CON – Control; LTH: Lactatethreshold; mo: Months; DBP: Diastolic Blood Pressure; Me: Median; Q1: Lowerquartile; Q3: Upperquartile; VO2 LT; Oxygenconsumptionatlactatethreshold; VO2 peak: Oxygenconsumptionatpeakexercise; VE: Ventilationvolume; VCO2: Volumeofcarbondioxide *P< 0.05, vs. baseline.

Exercise training resulted in decreased ER activity (by ≥15%) in 230 (97%) and 31 (63%) patients in the LTH and CON groups, respectively (*P*<0.01). No relationship was found between ER activity and HF cause, LVEF, sex, age, and NT-proBNP levels (P>0.05).

The extent of ER activity decrease was significantly greater in the LTH group than in the control group. In particular, ΔDBP, ΔV_E, and ΔVCO_2 were decreased post-training by 40%, 53%, and 38% in the LTH group and by 21%, 23%, and 15% in the CON group, respectively (Table 2, *P*=0.007, 0.0015, and 0.002, respectively). After completion of training and improvement in NYHA class in some patients, a positive correlation between ER activity and NYHA functional class was identified (r=0.57, *P* = 0.01). Moreover, decreased ER activity, determined as ($\Delta V_{Eat\ baseline}$-$\Delta V_{E9months}$), was strongly associated with an increased VO_2

$_{LT}$(r=0.55, *P*=0.001)and $VO_{2\ peak}$(r=0.49, *P*=0.001), and was correlated with a decreased monocyte count (r=0.63, *P*=0.01, Figure 2).

Discussion

The main finding of the present study is that the lactate threshold-based approach for the calculation of physical training intensity in patients with HFrEF leads to superior outcomes in comparison with the standard training protocol. In particular, lactate threshold-based training results in greater ER reduction, better exercise capacity, and lower systemic inflammation. It has been found that more patients improved their NYHA functional class after the completion of a 9-month personalized lactate threshold-based training.

In our cohort of symptomatic stable HF patients with NYHA class III receiving optimal guideline-directed therapy, baseline relationships between ER activity (determined as ΔV_E), HF functional class and oxygen consumption at peak exercise intensity have been revealed. A trend towards greater values of ER activity in older patients with HF has also been noted.

Along with other reflexes, ER is currently considered an essential mechanism of sympathetic activation and sympathovagal imbalance in HF. In contrast to other sympathoexcitatory reflexes, such as arterial and cardiopulmonary baroreflex and chemoreflex, ER is undetectable in healthy individuals and is activated only in patients with HF [6,14]. It has previously been shown in patients with chronic HF that ER activity is related to peak oxygen uptake and V_E/VCO_2 [9]. Pardaensetal have investigated ER activity in 24 patients with HFrEF and reported an increased ER only in patients with decompensated HF [15]. However, other investigators have observed increased ER activity in both clinically stable patients and those with HF decompensation [16]. Several studies with small populations have demonstrated that ER activity can be decreased in optimally treated patients with HF through physical training [17,18], which has been confirmed by our findings in a much larger cohort of patients with HFrEF. Moreover, we have raised the question of whether the extent of decrease in ER activity is dependent on the training regimen. It should be noted that the selection of a training regimen for HF is not strictly regulated and depends on the preference of the attending cardiologist. In this study, we have compared the results obtained using two different approaches to design the training protocol. Our data indicate that the application of a lactate threshold-based algorithm for training intensity calculation is associated with better clinical outcomes, greater post-treatment exercise capacity, and more pronounced ER activity suppression. Lactic acid is traditionally viewed as a byproduct of anaerobic glycolysis that has important regulatory effects on metabolism [21]. In particular, lactate accumulation in the muscle plays a role as an exercise-limiting factor due to the development of fatigue. Therefore, we have selected the $VO_{2\ LT}$ value as a basis for the calculation of "no-tiredness" exercise intensity. Of note, this training regimen provides an opportunity for ramped exercise build-up and is additionally associated with fairly good patient adherence. Recent studies have corroborated the importance of determining VO_{2LT} as a sensitive marker of the physiological reserve [17]. Previously, the studies by our group have demonstrated that personalized training based on the determination of VO_{2LT} results in the decreased thickness of both muscle fibers and endomysium, indicating the stabilization of the muscular mechanotransduction system [22]. Additionally, personalized training has been associated with better muscle regeneration, improved metabolism, and enhanced expression of genes responsible for the establishment of a proton gradient across the membrane of the synaptic vesicles [23]. Hypothetically, the latter effect might contribute to decreased muscle fatigue and improved exercise tolerance by decreasing the proton load of the sarcoplasm. Training-induced attenuation of ER activity might be considered as a complementary mechanism underlying the improvement of HF symptoms associated with the reversal of skeletal muscle myopathy. It appears that the synergistic effect of maximum tolerated dosages of disease-modifying drugs and aerobic physical training resulted in appreciable clinical improvement in patients with HFrEF, which is further supported by the significant increase in maximal oxygen consumption after completion of the training protocol. A better understanding of the pathophysiological basis of ER modulation in physical exercise may reveal new methods of controlling residual neurohormonal activation and chronic low-grade systemic inflammation, both of which persist in the majority of patients with advanced HF despite optimal drug therapy.

A significant body of evidence exists on the relationship between the severity of heart failure myopathy and the intensity of systemic inflammation [19,20]. Our data confirm the presence of this association in patients with HFrEF stabilized at NYHA functional class III. Specifically, we have demonstrated a direct correlation between ER activity and blood monocyte count and an inverse correlation between ER activity and $VO_{2\ peak}$. Taken together, these data provide strong evidence for close pathogenetic interaction between these two patterns of HF progression. Not with standing, prolonged physical training has resulted in partial reduction of excessive ER activity by 15%–53% in both groups and of severe chronic inflammation by >20% in the LTH group. It is likely that a reduced ER activity and an associated blunted sympathetic tone might contribute to the limitation of RAAS activity and, consequently, attenuate chronic inflammation.

The main clinical contribution of this study is the introduction of a personalized algorithm that calculates physical exercise intensity based on oxygen consumption at the lactate threshold. The practical application of this algorithm showed that it is well tolerated by patients due to minimal muscle fatigue, which enables the prescription of a more prolonged exercise. The latter might contribute to enhanced aerobic oxidation of substrates in the muscle fibers, eventually improving exercise capacity. Overall, this study suggests that ER activity has to be considered not only as an additional diagnostic marker of HF severity, but also as a viable therapeutic target.

Study Limitations

The present study has certain methodological limitations. First, this was an observational study without patient randomization, which might affect the clinical impact of the results. However, recent analytical work underlines the usefulness of observational studies, which provide evidence for the effectiveness of new therapies in patient cohorts that better reflect "real clinical practice" [24]. Second, patients with comorbidities such as diabetes mellitus, cachexia, and obesity were not included in the present study, as were patients receiving angiotens in receptor-neprilysin inhibitors and selective renal sodium glucose-cotransporter 2 inhibitors. Third, systemic inflammation was evaluated using surrogate markers such as total leukocyte count and monocyte count, which are readily available during routine examinations. Determining plasma levels of high-sensitivity C-reactive protein, interleukin-1β, interleukin-6, and tumor necrosis factor-α would strengthen the conclusion about

the relationship between ER activity and the severity of systemic inflammation. Future studies should address these important issues.

Conclusions

Augmented ER activity is detected in clinically stable patients with HFrEF (NYHA class III) who receive optimal guideline-directed therapy both at baseline and during physical exercise training. The ER activity is associated with NYHA functional class and monocyte count, whereas it is inversely proportional to exercise capacity. A personalized exercise program design based on the LTH is associated with superior effectiveness in reducing ER activity and HF compensation compared with the standard protocol.

Data Availability

All data generated or used during the study are available from the corresponding author by request.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this article.

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