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Physical capacity increase in patients with heart failure is associated with improvement in muscle sympathetic nerve activity

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ABSTRACT

Background: Exercise training improves physical capacity in patients with heart failure with reduced ejection fraction (HFrEF), but the mechanisms involved in this response is not fully understood. The aim of this study was to determine if physical capacity increase in patients HFrEF is associated with muscle sympathetic nerve activity (MSNA) reduction and muscle blood flow (MBF) increase.

Methods: The study included 124 patients from a 17-year database, divided according to exercise training status: 1) exercise-trained (ET, $n = 83$) and 2) untrained (UNT, $n = 41$). MSNA and MBF were obtained using microneurography and venous occlusion plethysmography, respectively. Physical capacity was evaluated by cardiopulmonary exercise test. Moderate aerobic exercise was performed 3 times/wk. for 4 months.

Results: Exercise training increased peak oxygen consumption (VO_2, 16.1 ± 0.4 vs 18.9 ± 0.5 mL·kg^{-1}·min^{-1}, $P < 0.001$), LVEF (28 ± 1 vs 30 ± 1%, $P = 0.027$), MBF (1.57 ± 0.06 vs 2.05 ± 0.09 mL.min^{-1}.100 ml^{-1}, $P < 0.001$) and muscle vascular conductance (MVC, 1.82 ± 0.07 vs 2.45 ± 0.11 units, $P < 0.001$). Exercise training significantly decreased MSNA (45 ± 1 vs 32 ± 1 bursts/min, $P < 0.001$). The logistic regression analyses showed that MSNA [(OR) 0.921, 95% CI 0.883–0.962, $P < 0.001$] was independently associated with peak VO_2.

Conclusions: The increase in physical capacity provoked by aerobic exercise in patients with HFrEF is associated with the improvement in MSNA.

1. Introduction

Heart failure is a common feature at the end stage of many cardiovascular diseases [1]. In the early 2000s until 2019, heart failure was the first cause of death in the world affecting 6.5 million adults in the United States alone [2]. Heart failure with reduced ejection fraction (HFrEF), a burdensome and costly disease for the healthcare system, represents approximately 50% of all cases of heart failure [2]. Exercise intolerance, fatigue, and dyspnea are cardinal features of this syndrome with considerable impact on quality of life in patients with HFrEF [2].

Neurohumoral exacerbation is a physiological marker of heart failure [3]. This compensatory response to decreased cardiac output and perfusion pressure [4] provokes intense peripheral vasoconstriction [5], which over time contributes to progression of heart failure [6]. In a previous study, we found that muscle sympathetic nerve activity (MSNA) is an independent predictor of mortality in patients with HFrEF

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[7]. Similarly, findings were observed in muscle blood flow (MBF). Low peak oxygen consumption (peak VO_2) obtained in cardiopulmonary exercise test is associated with low physical capacity and poor prognosis in patients with HFrEF [8]. Peak VO_2 is also very useful in the clinical practice for evaluation of progression of heart failure and the decision about cardiac transplantation [9]. Altogether, these findings suggest that there is a common feature between neurovascular control and physical capacity in patients with HFrEF.

Exercise training is a Class I recommendation and Level A of evidence in patients with HFrEF [10]. Exercise training reduces pro-inflammatory markers [11] and oxidative stress, [12] and increases capillarization and muscle fiber cross-sectional area [13]. A large body of evidence demonstrates that moderate aerobic exercise training decreases MSNA and increases MBF in patients with HFrEF [14–17]. In addition, exercise training increases physical capacity, which has an important impact on quality of life and prognosis in these patients [18].

Based on principles of exercise physiology in which exercise performance depends on pulmonary, circulatory, and skeletal muscle integrative response, we raised the question whether there is a link between increase in physical capacity and amelioration in neurovascular control and skeletal myopathy in exercise-trained patients with HFrEF. In this study, we report the association between the increase in peak VO_2 and the improvement in MSNA and MBF in exercise-trained patients with HFrEF obtained from a 17-year follow-up cohort in a single Center.

2. Methods

2.1. Study population

Patients with HFrEF, clinically stable and optimally medicated at least for the previous three months, aged between 30 and 70 years, left ventricular ejection fraction <40% (LVEF), New York Heart Association (NYHA) Functional Class I-III, were included in the study. Patients with chronic pulmonary disease, neurological complications, neoplasia, chronic kidney disease on hemodialysis, insulin-dependent diabetes mellitus and pacemaker carriers were excluded. This study was approved by the Institutional Review Board of the Instituto do Coração (InCor-HCFMUSP) (# SDC 5262/21/037) and by the Human Subject Protection Committee of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brazil (# CAAE 46432721.4.0000.0068). All experimental procedures and measurements were conducted according to the Declaration of Helsinki, and prior to participating in the study, each subject provided written informed consent.

2.2. Study protocol

This study includes 124 outpatients with reduced ejection fraction heart failure from accumulated database from previous studies dealing with the effects of exercise training in patients with heart failure [17,19–23], conducted between July 2002 and March 2019 in the Unidade de Reabilitação Cardiovascular e Fisiologia do Exercicio, Instituto do Coração (InCor-HCFMUSP), São Paulo, Brazil. Patients were divided into two groups according to their participation in the previous studies: Exercise-trained (ET, $n = 83$) and untrained (UNT, $n = 41$). The patients included in the study were randomized into ET and UNT groups [17,19,21,22], except in two studies [20,23]. All patients were evaluated before and after four months of moderate exercise training or clinical follow-up, except one study that the evaluations were conducted before and after three months of moderate exercise training or clinical follow-up [17].

2.3. Mesurements and procedures

2.3.1. Muscle sympathetic nerve activity

MSNA was assessed by microneurography [24]. Signals of the peroneal nerve were amplified by a factor of 50.000 to 100.000 and band passed filtered (700 to 2.000 Hz). The nerve activity was rectified and integrated (time constant 0.1 s) to obtain a mean voltage display of sympathetic nerve activity. The nerve signal was analyzed in burst frequency (bursts/min) by principal investigator and one experienced investigator. Nerve recording was not obtained in six ET patients and three UNT patients. All patients underwent MSNA assessment within seven days prior the beginning of the exercise training or clinical follow-up and within five days after the completion of experimental protocol.

2.3.2. Muscle blood flow

Venous occlusion plethysmography was used to assess MBF [5]. This technique consists of placing a silastic band filled with mercury around the forearm, connected to a plethysmograph device. Two cuffs were placed in nondominant arm, one in wrist and one in forearm. The wrist cuff was inflated at 200 mmHg and maintained throughout the measurements. The forearm cuff was inflated at 60 mmHg for 7 to 8 s and deflated for an equal time, completing 15–16 s. Muscle vascular resistance (MVR; units) measures were obtained by dividing mean arterial pressure (MAP) by MBF, and muscle vascular conductance (MVC) measures were obtained by dividing MBF by MAP [5,16]. MBF was analyzed by the principal investigator and one experienced investigator. The MBF was evaluated within seven days prior the beginning of the exercise training or clinical follow-up and within five days after the completion of experimental protocol.

2.3.3. Hemodynamic assessments

Arterial blood pressure and pulse rate was obtained noninvasively on a beat-to-beat basis by a finger photoplethysmography (Finapres 2300, Ohmeda, Englewood, CO or FinometerPro; Finapress Medical Systems, Amsterdam, The Netherlands) [21,25]. Left ventricular ejection fraction was determined by institutional echocardiogram using Simpson's method [26]. Echocardiography was conducted within seven days prior the beginning of the exercise training or clinical follow-up and within five days after the completion of experimental protocol.

2.3.4. Physical capacity

Cardiopulmonary exercise test (Vmax, Mod. 29 S series YL012278C, Sensor Medics Corporation) was performed while the patient was on a cycle ergometer (Medifit 400 L, Medical Fitness Equipment) using a ramp protocol with constant load increment between 5 and 15 watts every minute, depending on the patient's estimated maximal load. All patients maintained between 60 and 70 rotations per minute until exhaustion. The anaerobic threshold and respiratory compensation point were determined as previously described [27]. The maximal physical capacity was determined by peak VO_2. Completion of the test occurred when, despite verbal encouragement, the patient could no longer maintain the exercise intensity, and maximal respiratory exchange ratio reached was $\geq$1.10. Heart rate was continuously recorded at rest and during exercise testing using a 12-lead digital electrocardiogram (ERGO PC 13, MICROMED Biotechnology Ltd). All patients underwent cardiopulmonary exercise testing using the same protocol within seven days prior the beginning of the exercise training or clinical follow-up and within five days after the completion of experimental protocol.

2.3.5. Exercise training

Moderate exercise training was conducted three times a week, for four months, under supervision of an exercise physiologist at the Unidade de Reabilitação Cardiovascular e Fisiologia do Exercício, InCor-HCFMUSP. In one study, moderate exercise training was conducted for three months [17]. Each training session consisted of 5 min of warm-up,

25 min on ergometer bicycle in the first month and increased progressively to 40 min in the subsequent months, followed by 10–15 min of moderate strength exercise. The aerobic exercise intensity on ergometer bicycle was established by heart rate that corresponded to anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test [14,16].

2.4. Statistical analysis

This is an exploratory analysis of data obtained from 2002 until 2019 and the sample size was not determined for this propose. Data are shown as mean ± standard deviation or median with lower and upper quartile (95% CI). Kolmogorov-Smirnov test was used to test normality of the variables. The delta differences between groups were obtained using *t*-test. Two-way ANOVA with Bonferroni post hoc was used for comparing parametric variables between conditions. Chi-square (X^2) test was used for categorical variables. Pearson correlation and logistic regression were used when appropriate. Statistical significance was set with a $P <$ .05. Software Statistical Package for the Social Science (SPSS, version 23 for Windows) was used for all analyses.

3. Results

3.1. Baseline characteristics

The study enrolled 83 ET and 41 UNT control patients with HFrEF. Baseline characteristics of the ET and UNT are displayed in Table 1. There were no differences between groups, except in heart failure etiology. There were more idiopathic patients (19% vs 37%, $P = 0.024$) in UNT group than in ET group. Baseline physiological and clinical parameters were similar between groups (Table 2). Baseline analysis showed that only MSNA was different between groups [45 ± 1 (95% confidence internal (CI): 42–48) vs 40 ± 2 (95% CI: 36–44) bursts/min, $P = 0.029$, Fig. 1].

Table 1
Characteristics of exercise-trained and untrained patients with heart failure with reduced ejection fraction.

	Exercise-Trained ($n = 83$)	Untrained (n = 41)	*P* Value
Sex (f/m)	30/53	11/30	0.319
Age (year)	58 ± 8	55 ± 8	0.106
HF etiology, n (%)			
Chagasic	6 (8)	7 (17)	0.092
Idiopathic	16 (19)	15 (37)	0.024
Ischemic	30 (36)	10 (24)	0.188
Hypertensive	31 (37)	9 (22)	0.084
Comorbidity, n (%)			
Hypertension	31 (37)	9 (22)	0.084
Dyslipidemia	27 (33)	17 (41)	0.330
Diabetes	6 (7)	7 (17)	0.094
Obesity	12 (14)	6 (15)	0.979
Medication, n (%)			
β-blocker	82 (99)	41 (100)	1.000
ACE-I	63 (76)	26 (63)	0.148
ARB	17 (20)	15 (37)	0.080
MRA	61 (73)	34 (83)	0.245
Loop diuretics	65 (78)	35 (65)	0.352
Digitalis	25 (30)	9 (22)	0.399
Statin	29 (35)	16 (39)	0.658
Metformin	8 (9)	7 (17)	0.234

Data are presented as mean ± SD or %. *P* value referred to Student *t*-test and Chi-square test for etiology, comorbidity, and medication. ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

3.2. Effects of exercise training

Over the 17 years of the study, no harm or serious adverse effect associated with exercise training was observed. Exercise training significantly improved Functional Class (Class I/II/III; 3/45/35 vs 43/35/5, $P < 0.001$; Table 2). Exercise training significantly decreased MSNA [45 ± 1 (95% CI: 42–48) vs 32 ± 1 (95% CI: 30–34) bursts/min, $P < 0.001$; Fig. 1] and MVR [59.2 ± 2.4 (95% CI: 54.5–63.9) vs 47.7 ± 2.4 (95% CI: 42.9–52.4) units, $P < 0.001$; Table 2]. Exercise training significantly increased LVEF [28 ± 1 (95% CI: 27–30) vs 30 ± 1 (95% CI: 28–32) %, $P = 0.027$, Table 2], MVC [1.83 ± 0.07 (95% CI: 1.68–1.97) vs 2.45 ± 0.11 (95% CI: 2.23–2.66) units, $P < 0.001$; Table 2], MBF [1.57 ± 0.56 (95% CI: 1.46–1.68) vs 2.05 ± 0.09 (95% CI: 1.88–2.22) mL.min^{-1}.100 mL^{-1}, $P < 0.001$; Table 2], and peak VO_2 [16.1 ± 0.5 (95% CI: 15.2–17.0) vs 18.9 ± 0.5 (95% CI: 17.9–20.1) mL·kg $^{-1}$·min^{-1}, $P < 0.001$; Fig. 2]. The postintervention comparison between groups showed that MSNA [32 ± 1 (95% CI: 30–34) vs 41 ± 2 (95% CI: 38–45) bursts/min, $P < 0.001$; Fig. 1], MVR [47.7 ± 2.4 (95% CI: 42.9–52.4) vs 63.3 ± 3.3 (95% CI: 56.7–69.8) units, $P < 0.001$; Table 2) and MAP (86 ± 2 (95% CI: 83–89) vs 93 ± 2 (95% CI: 89–98) mmHg, $P = 0.013$; Table 2] were significantly lower in ET patients compared with UNT patients. In addition, MBF (2.05 ± 0.09 (95% CI: 1.88–2.22) vs 1.61 ± 0.12 (95% CI: 1.38–1.85) mL.min^{-1}.100 mL^{-1}, $P = 0.003$; Table 2), MVC (2.45 ± 0.11 (95% CI: 2.23–2.66) vs 1.76 ± 0.15 (95% CI: 1.46–2.06) units, $P <0.001$; Table 2) and peak VO_2 (18.9 ± 0.5 (95% CI: 17.9–20.1) vs 16.4 ± 0.7 (95% CI: 14.9–17.9) mL·kg^{-1}·min^{-1}, $P = 0.006$; Fig. 2) were significantly greater in ET patients compared with UNT patients. No differences in weight, BMI, LVEF, and HR were found between groups (Table 2).

The univariate logistic regression analysis (Table 3), in which the changes in peak VO_2 (effect size with median < 2.05 mL.kg^{-1} min^{-1}) were used as dependent variables, showed that only MSNA (OR 0.947, 95% CI: 0.913–0.983, $P = 0.004$) achieved significant levels. In the multivariate logistic regression analysis, MSNA (OR 0.946, 95% CI: 0.902–0.991, $P = 0.020$) remained independently associated with changes in peak VO_2 (Table 3) after adjustment for age, sex, BMI, LVEF, HR, beta-blocker usage, MBF, MVC, and MVR. Further analysis showed a negative correlation between changes in peak VO_2 and changes in MSNA ($r = -0.418$, $P < 0.001$; Fig. 3).

4. Discussion

The present study in a large sample size confirms the findings obtained in small clinical trials that moderate exercise training decreases MSNA and increases MBF in patients with HFrEF [17,19–23]. In addition, this study confirms that moderate exercise training increases physical capacity in this set of patients. The novelty in our study is the association between the reduction MSNA and the increase in physical capacity in a large cohort of ET patients with HFrEF.

4.1. Association between sympathetic nerve reduction and physical capacity increase

Accumulated evidence shows that skeletal myopathy secondary to cardiac dysfunction plays an important role in exercise intolerance in patients with HFrEF [28,29]. Thus, strategies to improve skeletal muscle alterations are of a lot of interest in the treatment of heart failure. Our study shows that moderate aerobic exercise decreases MSNA in patients with HFrEF. Moreover, this response favors the increase in physical capacity in patients with heart failure. This important finding, obtained by database from a single Center, in a large cohort of supervised exercise-trained heart failure patients who were submitted to direct evaluation of sympathetic nerve activity, suggests that the reduction in MSNA mediates the amelioration in skeletal muscle alterations. The mechanisms underlying the improvement in skeletal myopathy by reduction in sympathetic outflow are not available. However, someone

Table 2
Effects of exercise training in patients with heart failure with reduced ejection fraction.

	Exercise-Trained (n = 83)			Untrained (n = 41)			Between groups - Interaction
	Pre	Post	*P* Value	Pre	Post	*P* Value	*P* Value
NYHA (I/II/III)	(3/45/35)	(43/35/5)	<0.001	(0/29/12)	(3/27/11)	0.504	< 0.001
Weight (kg)	72.9 ± 1.9	73.2 ± 1.9	0.448	72.6 ± 2.6	73.5 ± 2.7	0.122	0.933
BMI (kg/m^2)	26.6 ± 0.5	26.7 ± 0.5	0.509	26.3 ± 0.7	26.5 ± 0.7	0.194	0.897
MBF (mL.min^{-1}.100 mL^{-1})	1.57 ± 0.06	2.05 ± 0.09	<0.001	1.67 ± 0.08	1.61 ± 0.12	0.550	0.003
MVC (units)	1.82 ± 0.07	2.45 ± 0.11	<0.001	1.89 ± 0.10	1.76 ± 0.15	0.324	<0.001
MVR (units)	59.2 ± 2.4	47.7 ± 2.4	<0.001	61.4 ± 3.3	63.3 ± 3.3	0.579	<0.001
LVEF (%)	28 ± 1	30 ± 1	0.027	26 ± 1	29 ± 1	0.013	0.575
HR (beats/min)	64 ± 1	63 ± 1	0.265	66 ± 2	64 ± 2	0.165	0.562
MAP (mmHg)	88 ± 2	86 ± 2	0.256	91 ± 2	93 ± 2	0.218	0.013

Data are presented as mean ± SD. *P* value referred to two-way ANOVA with Bonferroni post hoc. BMI, body mass index; HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MBF, muscle blood flow; MVC, muscle vascular conductance; MVR, muscle vascular resistance; NYHA, New York Heart Association.

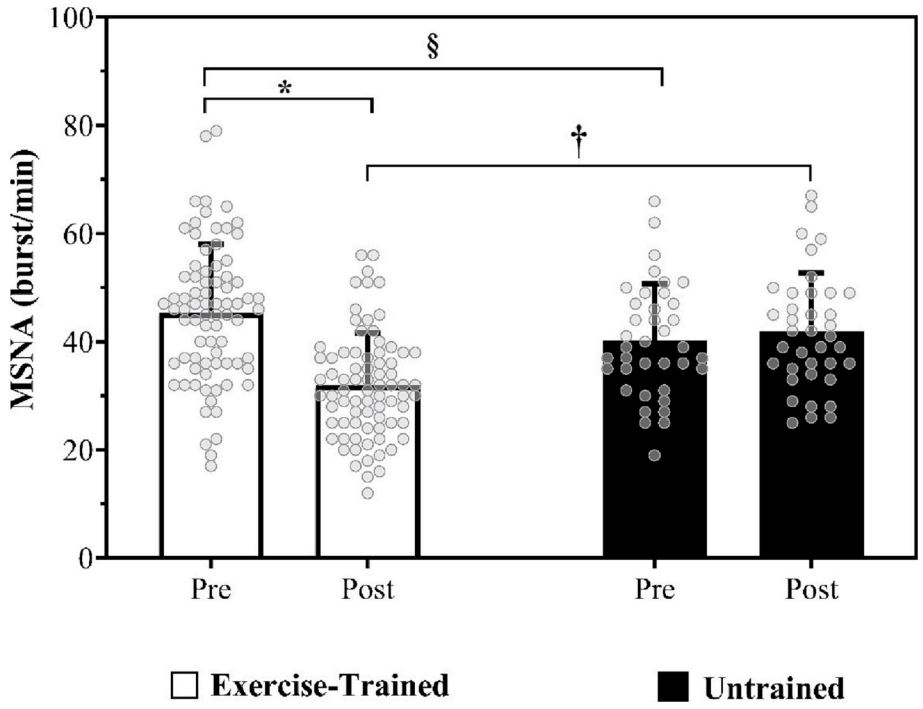

Fig. 1. Muscle Sympathetic Nerve Activity in exercise-trained ($n = 77$) and untrained patients ($n = 38$) with heart failure with reduced ejection fraction. Data are presented as mean ± SD. Muscle sympathetic nerve activity (MSNA); Preintervention (Pre); Postintervention (Post). * = $P < 0.001$; § = $P < 0.005$; † = $P < 0.001$. Nerve recording was not obtained in six exercise-trained patients and three untrained patients.

can raise the idea that the decrease in sympathetic outflow alleviates muscular and kidney vasoconstriction, which in turn decreases muscle inflammation and angiotensin II concentration [13]. In fact, Gielen and collaborators [11] elegantly described that exercise training decreases TNF-α, IL-1, and IL-6 levels (inflammatory markers) present in skeletal muscle in chronic HF patients. Endothelial function amelioration in these patients is associated with reduction in pro-inflammatory markers, oxidative stress, and angiotensin II concentrations [13–16]. Additionally, in a recent study, we found that the improvement in the molecular pathways related to protein synthesis and muscle regeneration is accompanied by a decrease in muscle vasoconstriction and an increase in physical capacity in patients with HFrEF [30].

4.2. Implications of the sympathetic nerve activity reduction

Sympathetic overdrive is the hallmark of heart failure [3,7,31]. This autonomic response compensates the low cardiac output in the first stage of heart failure [4–6]. However, in the later stages of heart failure, the exacerbated sympathetic nerve activity contributes to the worsening in prognosis in patients with HFrEF. In fact, in a previous study, we reported that MSNA is an independent predictor of mortality in patients with heart failure [7]. In the present study, in a large sample size, we found that exercise training provokes a remarkable reduction in MSNA. This finding strongly suggests that the reduction in MSNA provoked by exercise training contributes to the improvement in prognosis in patients with heart failure. The reduction in MSNA after exercise training cannot be attributed to changes in medications because changes in medications were criterion of exclusion in all previous studies involved in the present study. Another interesting observation in our study is the independent association of changes in MSNA and changes in peak VO_2, which is consistent with the idea of amelioration in skeletal myopathy in exercise-trained patients.

4.3. Possible mechanisms involved in the muscle sympathetic activity reduction

Mechanisms underlying the reduction of MSNA after exercise training in patients with HFrEF are complex and not fully understood.

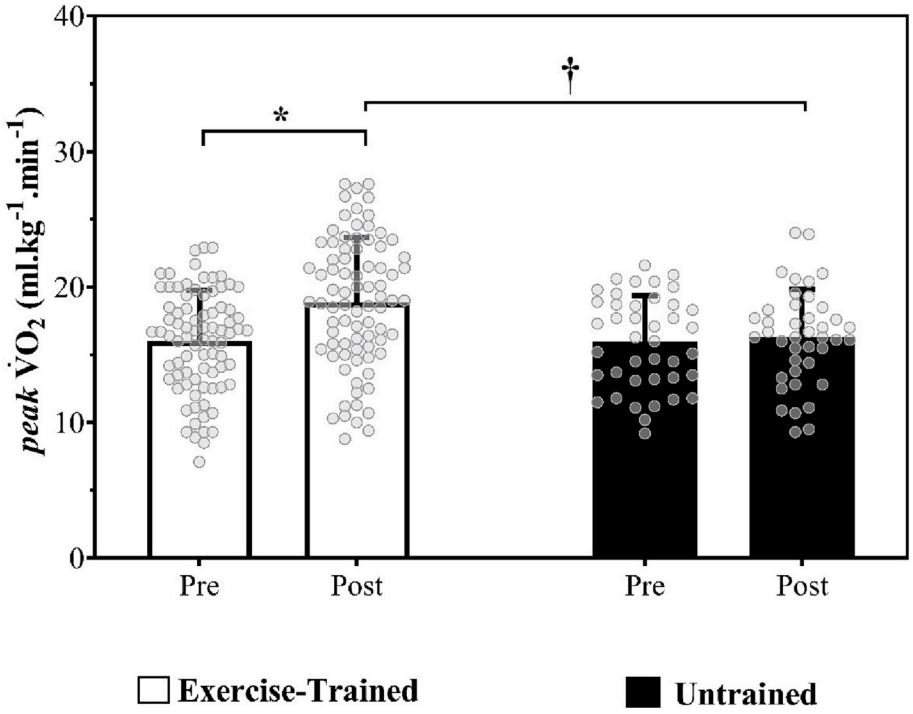

Fig. 2. Peak oxygen consumption in exercise-trained ($n = 82$) and untrained patients ($n = 41$) with HFrEF. Data are presented as mean ± SD. Peak oxygen consumption (VO_2); Preintervention (Pre); Postintervention (Post). * = $P < 0.001$; † = P =0.005. One exercise-trained patient did not do the cardiopulmonary exercise test after intervention.

Table 3
Logistic regression model using changes in peak VO_2 (median < 2.05 mL.kg^{-1}.min^{-1}) as the dependent variable.

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (per year increase)	0.992	0.951–1.035	0.722	–	–	–
Sex (f/m)	1.050	0.498–2.216	0.898	–	–	–
Etiology	1.179	0.461–3.014	0.731	–	–	–
BMI (per 1 kg/m^2 increase)	0.828	0.619–1.107	0.202	–	–	–
LVEF (per 1% increase)	0.985	0.930–1.043	0.600	–	–	–
HR (per 1 beat increase)	1.033	0.982–1.086	0.205	–	–	–
MAP (per 1 mmHg increase)	0.991	0.960–1.023	0.577	–	–	–
MVC (per 1 unit increase)	1.350	0.878–2.075	0.172	–	–	–
MSNA (per 1 burst/min increase)	**0.947**	**0.913–0.983**	**0.004**	**0.946**	**0.902–0.991**	**0.020**
MBF (per 1 mL.min^{-1}.100 ml^{-1} increase)	1.514	0.863–2.655	0.148	–	–	–
MVR (per 1 unit increase)	0.339	0.975–1.009	0.319	–	–	–

BMI, body mass index; CI, confidence interval; HR, heart rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MVC, muscle vascular conductance; MSNA, muscular sympathetic nerve activity; MBF, muscle blood flow; MVR, muscle vascular resistance; OR, odds ratio; peak VO_2, peak oxygen consumption.

However, studies in animals and humans suggest that changes in the peripheral reflex control and central neural integration play important roles. ET improves the baroreflex control [32,33] and the balance between muscle metaboreflex and mechanoreflex controls [21]. ET also reduces the chemoreflex hypersensitivity in chronic HF [34]. Evidence also suggests that the reduction in sympathetic outflow after ET in HF takes place in the central nervous system. ET decreases the expression of angiotensin I receptors in the nucleus tract solitarius, rostral ventral lateral medulla, and paraventricular nucleus [35]. This response contributes to the reduction in angiotensin II-mediated sympathetic outflow in the central nervous system.

4.4. Increase in physical capacity

Peak VO_2 is a marker of physical capacity and a predictor of prognosis in patients with HFrEF [9,36]. Improvement in physical capacity after an exercise training program is well documented. In a recent meta-analysis, Taylor and colleagues [37] report the beneficial effects of cardiac rehabilitation on physical capacity in HF patients. Our study confirms this response with the advantage of involving large number of patients from a single Center in which all patients underwent same cardiopulmonary exercise testing and exercise training protocol.

4.5. Methodologic strategy

In this study, we used a database obtained during a 17-year period in which patients with HFrEF underwent exercise training or clinical follow-up. All patients underwent direct measurement of MSNA by microneurography, measurement of MBF by venous occlusion plethysmography, and evaluation of peak VO_2 by maximal cardiopulmonary exercise testing on cycle ergometer using a ramp protocol. This set of evaluations was conducted before and after moderate exercise training or clinical follow-up. Exercise training was established by heart rate that corresponded to anaerobic threshold up to 10% below the respiratory

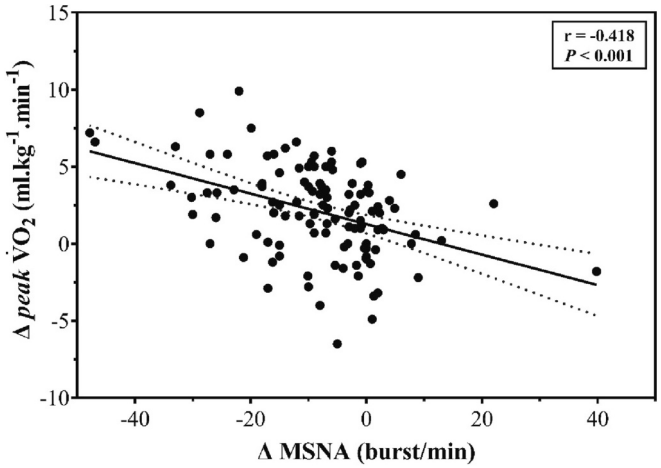

Fig. 3. Correlation coefficient between changes in peak oxygen consumption (VO_2) and changes in muscle sympathetic nerve activity (MSNA) in patients with heart failure with reduced ejection fraction (HFrEF).

compensation point obtained in the cardiopulmonary exercise test. Thus, all ET patients experienced the same exercise training protocol. This unique methodologic strategy allowed us to demonstrate in a large cohort of ET patients with HFrEF that the increase in peak VO_2 is associated with the improvement in MSNA.

5. Limitations

We recognize limitations in our study. We used registry data from a single Center. Although there is the advantage of maintaining the same methods and procedures during the entire period of 17 years (July 1, 2002 through March 13, 2019), we cannot exclude possible bias. In two of the studies contained in the database used in the present study, the patients were not randomized into ET and UNT groups. In contrast to the other studies, Sales' study [17] was conducted for three months. Nevertheless, this difference in experimental design did not influence our findings, because additional analysis, in which Sales' study was excluded, showed no change in our findings (Data not shown). The difference in etiology between groups may have influenced our findings. The improvement in neurovascular control caused by exercise training is more pronounced in hypertensive patients with HFrEF than in idiopathic and ischemic patients with HFrEF [38]. MSNA and MBF were examined at rest. Thus, these findings should not be extrapolated to exercise.

6. Conclusions

The present study shows that the increase in peak VO_2 provoked by supervised moderate exercise training in patients with HFrEF is associated with an improvement in MSNA. This finding suggests that the increase in physical capacity in this set of patients depends on the skeletal myopathy amelioration mediated by the reduction in sympathetic nerve activity.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

This article has never been published before and is not under consideration for publication in any other journal.

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Author contributions

BRGS and CEN conceived and designed the research. BRGS, ER, GWPF, ARKS, MRS, LMAC, LMUP, PO, PFT, FGMF, RF, MJNNA, MUPBR, LAH, RKF and CEN contributed to the acquisition, analysis, or interpretation of the data. BRGS, ER, GWPF, LMAC, MUPR, and CEN drafted the manuscript. All authors approved the manuscript submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

All authors have reported that there is no relationship with industry or financial associations, which might pose a conflict of interest in connection to this article.

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