

Effects of inspiratory muscle training combined with aerobic exercise training on neurovascular control in chronic heart failure patients

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Abstract

Aims We tested the hypothesis that the effects of combined inspiratory muscle training and aerobic exercise training (IMT + AET) on muscle sympathetic nerve activity (MSNA) and forearm blood flow in patients with heart failure with reduced ejection fraction are more pronounced than the effects of AET alone.

Methods and results Patients aged 30–70 years, New York Heart Association Functional Class II–III, and left ventricular ejection fraction $\leq 40\%$ were randomly assigned to four groups: IMT ($n = 11$), AET ($n = 12$), IMT + AET ($n = 9$), and non-training (NT; $n = 10$). MSNA was recorded using microneurography. Forearm blood flow was measured by venous occlusion plethysmography and inspiratory muscle strength by maximal inspiratory pressure. IMT consisted of 30 min sessions, five times a week, for 4 months. Moderate AET consisted of 60 min sessions, three times a week for 4 months. AET (-10 ± 2 bursts/min, $P = 0.03$) and IMT + AET (-13 ± 4 bursts/min, $P = 0.007$) reduced MSNA. These responses in MSNA were not different between AET and IMT + AET groups. IMT (0.22 ± 0.08 mL/min/100 mL, $P = 0.03$), AET (0.27 ± 0.09 mL/min/100 mL, $P = 0.01$), and IMT + AET (0.35 ± 0.12 mL/min/100 mL, $P = 0.008$) increased forearm blood flow. No differences were found between groups. AET (3 ± 1 mL/kg/min, $P = 0.006$) and IMT + AET (4 ± 1 mL/kg/min, $P = 0.001$) increased peak oxygen consumption. These responses were similar between these groups. IMT (20 ± 3 cmH₂O, $P = 0.005$) and IMT + AET (18 ± 3 cmH₂O, $P = 0.01$) increased maximal inspiratory pressure. No significant changes were observed in the NT group.

Conclusions IMT + AET causes no additive effects on neurovascular control in patients with heart failure with reduced ejection fraction compared with AET alone. These findings may be, in part, because few patients had inspiratory muscle weakness.

Keywords Heart failure; Aerobic exercise training; Inspiratory muscle training; Muscle sympathetic nerve activity

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Introduction

Despite advances in the treatment of heart failure, the prognosis of patients suffering from this syndrome remains poor. Fifty per cent of patients with heart failure with reduced ejection fraction (HFrEF) die during the first 5 years after the diagnosis of this syndrome.¹ Heart failure is characterized by sympathetic hyperactivation, peripheral vasoconstriction,

and skeletal myopathy.^{2–4} These physiological alterations contribute to exercise intolerance and dyspnoea, which adversely influences the quality of life in patients with HFrEF.⁴

Exercise has been recommended for the treatment of patients with HFrEF.⁵ Aerobic exercise training (AET) provokes a remarkable improvement in neurovascular control in these patients. Previous studies show that exercise training decreases muscle sympathetic nerve activity (MSNA) and

peripheral vasoconstriction,⁶ which contributes to the amelioration of skeletal myopathy.² Moreover, this nonpharmacological therapy improves functional capacity, quality of life, and prognosis in patients with heart failure.^{7,8}

More recently, inspiratory muscle training (IMT) emerged as a strategy for training in heart failure patients. This exercise paradigm reduces MSNA and increases muscle blood flow in patients with HFrEF.^{9–11} Moreover, IMT seems to increase physical capacity in patients with cardiovascular disease.^{9,12} Some investigators propose additional benefits of combined IMT + AET on exercise capacity,^{13,14} but this training adaptation remains a controversial issue.¹⁵ In the present study, we investigated the changes in MSNA, muscle blood flow, and functional capacity provoked by IMT, AET, and IMT + AET in patients with HFrEF.

Our hypothesis is that IMT + AET causes a more pronounced improvement in MSNA and muscle blood flow in patients with HFrEF than AET alone.

Methods

Study design

In this prospective, controlled trial, the patients were randomly divided into four groups: non-training (NT, $n = 10$), IMT ($n = 11$), AET ($n = 12$), and combined IMT + AET ($n = 9$). Assessments were conducted at the beginning and after 4 months of interventions or clinical follow-up. The study was approved by the Human Subject Protection Committee of the Clinical Hospital, School of Medicine, University of São Paulo (CAPPesq; 814/10). The trial is registered at www.ClinicalTrials.gov (NCT01747395). The investigation conforms to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

It is noteworthy that eight patients in the NT, seven in the IMT, and seven in the AET groups were also involved in a previous study on skeletal muscle adaptation to IMT and AET.¹⁶ The sample size calculation was based on a previous study about the effects of aerobic training on MSNA in patients with HFrEF.⁶ The G-Power 3.1.9.4 statistical program with a power of 90% and confidence interval of 95% (alpha of 5%) indicated that the sample size was five patients in each group. Because of dropouts observed in our previous studies, we made the decision to include more patients in each group.

Heart failure patients aged 30 to 70 years, New York Heart Association (NYHA) Functional Class II–III, left ventricular ejection fraction (LVEF) $\leq 40\%$, peak oxygen uptake (VO_2 peak) ≤ 20 mL/kg/min, body mass index ≤ 35 kg/m², with optimized medication participated in the study. The exclusion criteria were myocardial infarction or heart surgery in the last 6 months, unstable angina, permanent pacemaker, cardiac

resynchronization therapy or implantable cardiac defibrillator, atrial fibrillation, smoking, pregnancy, severe pulmonary disease, neurologic and orthopaedic diseases, neoplasia, chronic kidney disease with dialysis support, insulin-dependent diabetes mellitus, and participation in a regular exercise programme. Changes in medication or hospitalization during the study were also exclusion criteria. The primary outcome was MSNA, and the secondary outcomes were muscle blood flow, physical capacity, respiratory muscle strength, and quality of life.

Measures and procedures

Physical capacity

Physical capacity was evaluated by a maximal incremental cardiopulmonary exercise test on a cycle ergometer (Via Sprint 150P; Ergoline, Bitz, Germany). A ramp protocol with work rate increments of 5–15 W every minute until exhaustion was conducted as previously described.¹⁶ Breath-by-breath analysis in a computerized system was used to assess the oxygen uptake (VO_2) and carbon dioxide production (Vmax Encore 29 System; VIASYS Healthcare Inc, Yorba Linda, CA). Peak VO_2 was defined as the maximum attained VO_2 at the end of the exercise period in which the patient could no longer maintain the cycle ergometer at 60 rpm. Anaerobic threshold, respiratory compensation point, and VE/VCO_2 slope were determined as previously described.^{16–18} The cardiopulmonary exercise test was performed in a blinded manner.

Muscle sympathetic nerve activity

Muscle sympathetic nerve activity was directly recorded from the peroneal nerve (multiunit postganglionic) using the microneurography technique.¹⁹ Signals were amplified by 50 000 to 100 000 and band-passed filtered (700–2000 Hz). For recordings and analysis, nerve activity was rectified and integrated (time constant: 0.1 s) to obtain a mean voltage display (662C-4 Nerve Traffic Analysis System; The University of Iowa, Iowa City, IA). MSNA was expressed as burst frequency (burst per min) and burst incidence (bursts per 100 heart beats). They were visually analysed by two investigators (C. E. N. and L. M. A. C.) in a blinded manner.

Forearm blood flow

Venous occlusion plethysmography was used to measure forearm blood flow (FBF) as previously described.²⁰ Briefly, the right arm was elevated above heart level to ensure adequate venous drainage. A mercury-filled silastic tube attached to a low-pressure transducer was placed around the forearm and connected to a plethysmograph (Hokanson-AI-6, USA). Sphygmomanometer cuffs were placed around the wrist and upper arm. At 20 s intervals, the upper arm cuff was inflated above venous pressure for 10 s. The increase in the tension in the silastic tube reflects the increase in the

forearm volume and, consequently, the vasodilation. Forearm vascular conductance (FVC) was calculated by dividing FBF by mean arterial pressure times 100.

Blood pressure and heart rate

Blood pressure was noninvasively evaluated on a beat-to-beat basis by using a finger photoplethysmograph (Finometer Pro; Finapres Medical Systems, Amsterdam, the Netherlands). Heart rate was also recorded by Finometer Pro.²¹

Respiratory muscle strength

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) was assessed using a pressure transducer (MVD-500 Globalmed, Porto Alegre, Brazil). Maximal static inspiratory and expiratory pressure was determined as previously described.²²

Quality of life

Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire.²³

Other measurements

Cardiac function was evaluated by left ventricular ejection fraction (LVEF) using two-dimensional echocardiography, Simpson method (IE33; Philips Medical Systems, Andover, MA).²⁴ Plasma B-type natriuretic peptide (BNP) levels were measured by venous blood sampling.

Inspiratory muscle training

Inspiratory muscle training consisted of 30 min session, five times a week, for 4 months. All patients exercised at 60% MIP using a resistive loading device (POWER breathe Plus®, POWER breathe International Limited, UK). Patients were instructed to maintain diaphragmatic breathing at 15 to 20 breaths/min. The intensity was assessed once a week. Four training sessions per week were performed at home, and one session was performed at the hospital under supervision.¹⁶

Aerobic exercise training

Moderate AET consisted of 60 min session, three times a week, for 4 months under supervision. It included 5 min stretching exercises, 40 min of cycling, 10 min of local strengthening exercises, and 5 min of cool down. The cycling exercise was performed at anaerobic threshold up to 10% below the respiratory compensation point.¹⁶

Combined inspiratory muscle training and aerobic exercise training

Combined inspiratory muscle training and aerobic exercise training was performed as previously described.¹⁶ Briefly, AET was performed three times per week and IMT five times per week for 4 months. When both AET and IMT were scheduled for the same day, IMT was conducted at an alternative time.

Evaluation protocol

The evaluation protocol consisted of three visits within 1 week of initiating the intervention or clinical follow-up and within 1 week of concluding the intervention or clinical follow-up.

First visit

In the morning, after a light meal with no caffeine, cardiac function and physical capacity were evaluated.

Second visit

At least 2 h after a light meal without caffeine, in a quiet and acclimatized room (21–22°C), in a supine position, the participant's leg was positioned for microneurography recordings. A microelectrode was inserted into the peroneal nerve. Cuffs were placed for FBF, blood pressure, and heart rate evaluations. Measurements were conducted throughout the protocol.

Third visit

Quality of life questionnaire was obtained, and respiratory muscle strength was evaluated. Thereafter, a blood sample was obtained for BNP measures.

Statistical analysis

The data are presented as means \pm SE. The Kolmogorov–Smirnov and Levene tests were used to assess normality of distribution and homogeneity. Baseline characteristics and absolute changes (Δ = post – pre) were tested by one-way analysis of variance (ANOVA). In the case of significance, Tukey *post hoc* multiple comparisons were conducted. Non-parametric tests (Kruskal–Wallis test, Mann–Whitney *U*-test, and Wilcoxon matched-pairs test) were used when needed. A χ^2 test was used to assess categorical data differences. Probability values of $P < 0.05$ were considered statistically significant.

Results

From January 2012 to July 2016, 135 patients were screened to participate in the study. Eighty-two patients did not meet the inclusion criteria. Fifty-three patients were included in the study. Eleven patients did not complete the study: one death in the NT group; one death, two acute heart failures, one myocardial infarction, and one drop out in the IMT group; one acute heart failure, one diagnosis of neoplasia, and one development of atrial fibrillation in the AET group; and one insufficient medication intake, and one drop out in the IMT + AET group. No event was related to IMT or AET. The minimum attendance in the AET, IMT, and IMT+AET

groups was 75%. Thus, 42 patients completed participation in the study: NT ($n = 10$), IMT ($n = 11$), AET ($n = 12$), and IMT + AET ($n = 09$) (Figure 1). MSNA recording was not possible in seven patients. Thus, the results of MSNA are representative of nine patients in NT; nine patients in IMT; nine patients in AET; and eight patients in IMT + AET.

Baseline measures

Physical, clinical, functional capacity, neurovascular, and hemodynamic characteristics are shown in Table 1. No differences in age, gender, weight, BMI, NYHA Functional Class, aetiology of heart failure, medication, co-morbidity, LVEF, blood BNP concentration, peak VO_2 , VE/VCO_2 slope, MIP, and incidence of inspiratory muscle weakness between groups were found. Baseline heart rate, blood pressure, MSNA, FBF, and FVC were also similar between groups. The quality of life was greater in the IMT + AET group compared with that in the NT, IMT, and AET groups.

Effects of training

The changes in peak VO_2 and peak workload obtained in the cardiopulmonary exercise test were greater in the AET and IMT + AET groups compared with those observed in the NT group (Figure 2A and 2B, respectively). The changes in peak ventilation obtained in the cardiopulmonary exercise test were also greater in the AET and IMT + AET groups than in the NT group (Table 2). The changes in peak ventilation were greater in the IMT + AET group compared with those found in the IMT group. VE/VCO_2 slope and oxygen consumption efficiency slope (OUES) were not different between groups (Table 2). Likewise, LVEF and BNP were not different between

groups (Table 2). Inspiratory muscle training increased MIP. IMT and IMT + AET elicited greater changes in MIP compared with that in AET (Figure 2C). The interventions did not change maximal expiratory pressure. IMT, AET, and IMT + AET elicited greater changes in quality of life than those observed in the NT controls (Figure 2D).

Aerobic exercise training and IMT + AET similarly reduced MSNA. The comparisons between groups showed that the changes in MSNA burst frequency and burst incidence after IMT + AET and AET alone were greater than those observed in the NT group (Figure 3A and 3B, respectively). All interventions improved FBF and FVC. The comparisons between groups showed that the changes in FBF and FVC after IMT, AET, and IMT + AET were greater than those observed in the NT group (Figure 4A and 4B). Heart rate, systolic, diastolic, and mean blood pressures did not change with IMT, AET, or IMT + AET (Table 2).

Discussion

In the present study, we found that the magnitude of reduction in MSNA after 4 months of IMT + AET was similar to that observed after 4 months of AET alone. In addition, the increase in muscle blood flow was similar in patients who participated in IMT + AET and in patients who participated in AET alone.

Effects of combined inspiratory muscle training and aerobic exercise training

Because AET reduces MSNA, we raised the hypothesis that IMT + AET would elicit a greater decrease in MSNA than AET alone. Surprisingly, the changes in MSNA after

Figure 1 Schematic patient flowchart. NT, non-training group; IMT, inspiratory muscle training group; AET, aerobic exercise training group; IMT + AET, combined inspiratory muscle training and aerobic exercise training group.

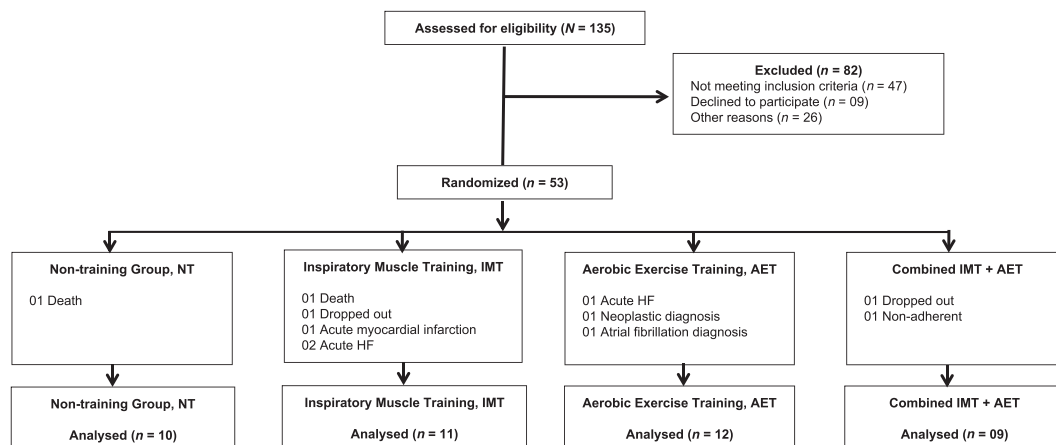


Table 1 Physical, clinical, and functional capacity in patients with heart failure with reduced ejection fraction assigned to inspiratory muscle training, aerobic exercise training, combined inspiratory muscle training and aerobic exercise training groups

	NT (n = 10)	IMT (n = 11)	AET (n = 12)	IMT + AET (n = 9)	P-value
Age, years	57 ± 3	55 ± 3	57 ± 2	56 ± 3	0.94
Gender, n					
Male	6	3	7	7	0.14
Female	4	8	5	2	
Weight, kg	72 ± 4	77 ± 6	76 ± 6	80 ± 6	0.80
BMI, kg/m ²	27 ± 1	29 ± 2	28 ± 1	28 ± 1	0.80
NYHA (II/III), n	9/1	8/3	9/3	7/2	0.78
Aetiology, n					
Ischemic	6	1	4	6	0.20
Hypertensive	2	4	2	0	
Idiopathic	1	5	3	2	
Chagasic	1	0	2	0	
Peripartum	0	0	1	1	
Alcoholic	0	1	0	0	
Medication, n					
Beta-blocker	10	11	12	9	1.00
ACEI/ARB	10	11	12	9	1.00
Spironolactone	10	10	12	8	0.50
Diuretic	9	11	12	7	0.17
Statins	5	6	5	6	0.72
Hypoglycaemic drugs	2	2	2	3	0.80
Co-morbidities, n					
Diabetes mellitus	2	2	2	3	0.80
Dyslipidaemia	6	6	6	6	0.88
Hypertension	8	7	9	6	0.83
LVEF, %	25 ± 1	31 ± 2	26 ± 2	27 ± 1	0.23
BNP, pg/mL	197 ± 45	212 ± 116	265 ± 89	275 ± 90	0.91
Peak VO ₂ , mL/kg/min	16 ± 1	16 ± 1	15 ± 1	17 ± 1	0.65
VE/VCO ₂ slope	37 ± 3	30 ± 2	34 ± 2	34 ± 2	0.10
MIP, cmH ₂ O	85 ± 8	86 ± 9	87 ± 10	81 ± 8	0.97
IMW, n	2	3	3	3	0.93
HR, b.p.m.	68 ± 3	61 ± 2	65 ± 2	65 ± 3	0.40
SBP, mmHg	121 ± 4	121 ± 4	124 ± 5	116 ± 8	0.78
DBP, mmHg	66 ± 2	68 ± 4	69 ± 3	64 ± 4	0.72
MBP, mmHg	87 ± 2	86 ± 3	85 ± 3	85 ± 4	0.98
MSNA, bursts/min	44 ± 5	43 ± 3	46 ± 3	48 ± 4	0.80
MSNA, HB	64 ± 7	71 ± 6	72 ± 5	75 ± 6	0.62
FBF, mL/min/100 mL	2.05 ± 0.25	1.55 ± 0.16	1.51 ± 0.16	1.51 ± 0.17	0.17
FVC, u.a.	2.43 ± 0.30	1.82 ± 0.22	1.74 ± 0.21	1.88 ± 0.20	0.17
Quality of life, u.a.	55 ± 6	50 ± 6	56 ± 2	32 ± 4 ^{abc}	0.01

ACEI, angiotensin converter enzyme inhibitor; ARB, angiotensin receptor blockade; AET, aerobic exercise training group; BMI, body mass index; BNP, brain natriuretic peptide; DPB, diastolic blood pressure; FBF, forearm blood flow; FVC, forearm vascular conductance; HR, heart rate; IMT, inspiratory muscle training group; IMT + AET, combined inspiratory muscle training and aerobic exercise training group; IMW, inspiratory muscle weakness; LVEF, left ventricular ejection fraction; MIP, maximal inspiratory pressure; MSNA, muscle sympathetic nerve activity; NT, non-training group; NYHA, New York Heart Association; SBP, systolic blood pressure; VE/VCO₂, ventilation over carbon dioxide; VO₂, oxygen uptake. Values are presented as mean ± standard error.

^aversus NT.

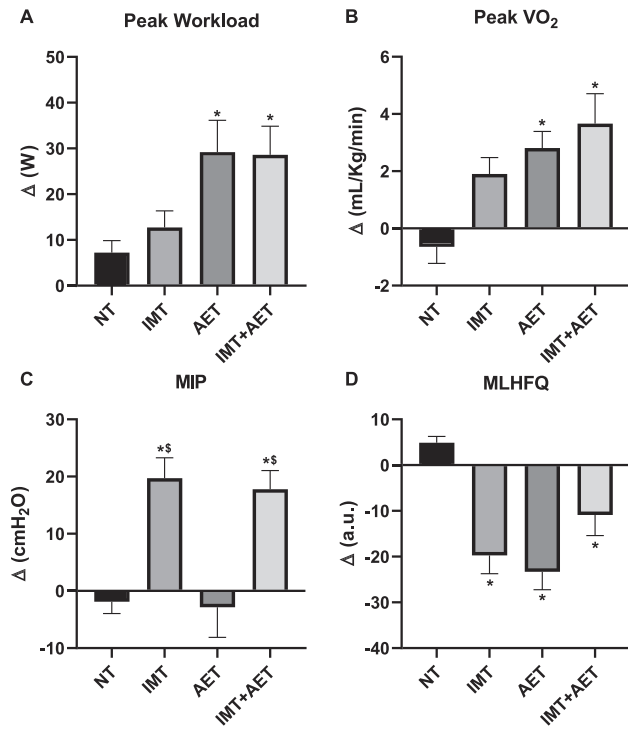
^bversus IMT.

^cversus AET.

IMT + AET were similar to those achieved by AET alone. There is no definitive explanation for these findings. One possibility is that the improvement in neurovascular control in exercise-trained patients with HFrEF is fully achieved through AET. This interpretation seems to be unlikely because in a recent study, we found that high-intensity interval training caused a more pronounced reduction in MSNA than moderate continuous aerobic exercise did.²⁵ IMT + AET is a very demanding exercise training protocol. Exercise sessions are scheduled every day and three times a week that include both AET and IMT sessions. This

exercise paradigm may reduce motivation and interest in exercise sessions. Alternatively, the distribution of heart failure aetiology across groups may have influenced our findings. The rationale for this thought is that patients with heart failure associated with hypertension are those that mostly benefit from exercise training.²⁶ However, the distribution of aetiology was not significantly different between groups.²⁶ In line with MSNA responses, IMT + AET does not elicit additive effects on muscle blood flow. The changes in FBF and FVC were not different between IMT + AET and AET alone. As previously reported

Figure 2 Effects of inspiratory muscle training (IMT), aerobic exercise training (AET), and combined inspiratory muscle training and aerobic exercise training (IMT+AET) on (A) peak workload, (B) peak oxygen consumption (VO₂), (C) maximal inspiratory pressure (MIP), and (D) Minnesota Living with Heart Failure Questionnaire (MLHFQ) in patients with heart failure with reduced ejection fraction. NT, non-trained. *vs. NT group, $P < 0.05$; [§]vs. AET group, $P < 0.05$.



in a multicentre trial,¹⁵ we found no additional improvement in physical capacity after IMT + AET compared with AET alone. Finally, IMT + AET did not change cardiac function (LVEF) and BNP levels.

Table 2 Changes provoked by inspiratory muscle training, aerobic exercise training, and combined inspiratory muscle training and aerobic exercise training in patients with heart failure with reduced ejection fraction

	NT (n = 10)	IMT (n = 11)	AET (n = 12)	IMT+AET (n = 09)	P-value
LVEF, %	1.60 ± 2.77	0.27 ± 1.86	2.75 ± 2.49	0.00 ± 1.60	0.80
BNP, pg/mL	58.80 ± 60.66	-20.82 ± 36.39	-2.92 ± 61.30	-6.11 ± 52.63	0.74
AT VO ₂ , mL/kg/min	0.04 ± 0.79	-0.07 ± 0.56	1.21 ± 0.55	1.03 ± 0.67	0.35
Peak VE, L/min	-4.69 ± 2.51	5.16 ± 2.13	7.95 ± 2.35 ^a	16.59 ± 4.26 ^{ab}	0.002
VE/VCO ₂ slope	-2.08 ± 2.43	0.80 ± 1.23	-2.25 ± 1.55	2.09 ± 1.20	0.19
OUES	-45.91 ± 66.60	46.87 ± 84.81	184.4 ± 76.33	21.87 ± 72.37	0.19
MEP, cmH ₂ O	-1.38 ± 4.72	3.00 ± 3.57	2.89 ± 4.25	2.66 ± 6.69	0.91
HR, b.p.m.	-3.55 ± 2.96	-1.77 ± 2.34	-3.87 ± 1.67	-2.60 ± 3.30	0.92
SBP, mmHg	2.56 ± 2.50	3.01 ± 3.89	-4.10 ± 7.36	6.83 ± 4.80	0.52
DPB, mmHg	1.57 ± 2.06	-1.57 ± 2.83	-4.38 ± 2.29	1.26 ± 2.60	0.28
MBP, mmHg	1.22 ± 2.40	-1.08 ± 3.50	-2.98 ± 2.40	3.84 ± 3.25	0.40

AET, aerobic exercise training group; AT, anaerobic threshold; BNP, brain natriuretic peptide; DPB, diastolic blood pressure; HR, heart rate; IMT, inspiratory muscle training group; IMT + AET, combined inspiratory muscle training and aerobic exercise training group; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; MEP, maximal expiratory pressure; NT, non-training group; OUES, oxygen uptake efficiency slope; SBP, systolic blood pressure; VE, ventilation; VE/VCO₂, ventilation over carbon dioxide; VO₂, oxygen uptake. Values are presented as mean ± standard error.

^aversus NT, $P < 0.05$.

^bversus IMT, $P < 0.05$.

Effects of aerobic exercise training

Accumulated evidence shows that AET decreases MSNA in patients with HFrEF. Since the first report in 2003,⁶ we know that moderate AET for 4 months provokes a remarkable reduction in MSNA. This response has been consistently replicated in different sets of heart failure patients. AET decreases MSNA regardless of age, gender, and aetiology.^{26–28} In addition, AET increases muscle blood flow at rest and during exercise in patients with heart failure.^{2,29} This neurovascular adaptation is confirmed in the present study. AET decreased MSNA and increased muscle blood flow. Skeletal muscle changes were not involved in our study. However, it is legitimate to suggest that the reduction in MSNA and the increase in muscle blood flow favour the amelioration in skeletal myopathy and, as a consequence, physical capacity.^{2,16} In the present study as in others,^{30,31} a 10% to 20% increase in peak VO₂ is achieved through AET in patients with HFrEF.

Effects of inspiratory muscle training

It has been suggested that respiratory myopathy plays a role in the exercise intolerance in patients with HFrEF.³² Despite the increased ventilatory work, the inspiratory muscle capacity may be decreased in patients with muscle inspiratory strength levels close to normal.³³ This pathophysiological characteristic is the rationale for prescribing IMT for patients with HFrEF. In a previous study, some investigators reported that home-based IMT provokes reduction in MSNA in patients with chronic heart failure.¹¹ In the present study, we found that IMT decreases MSNA, but this response was not significant. The differences in MSNA responses between studies may be due to inspiratory muscle weakness. In the

Figure 3 Effects of inspiratory muscle training (IMT), aerobic exercise training (AET), and combined inspiratory muscle training and aerobic exercise training (IMT + AET) on muscle sympathetic nerve activity (MSNA) burst frequency (A) and burst incidence (B) in patients with heart failure with reduced ejection fraction. NT, non-trained. *vs. NT group, $P < 0.05$.

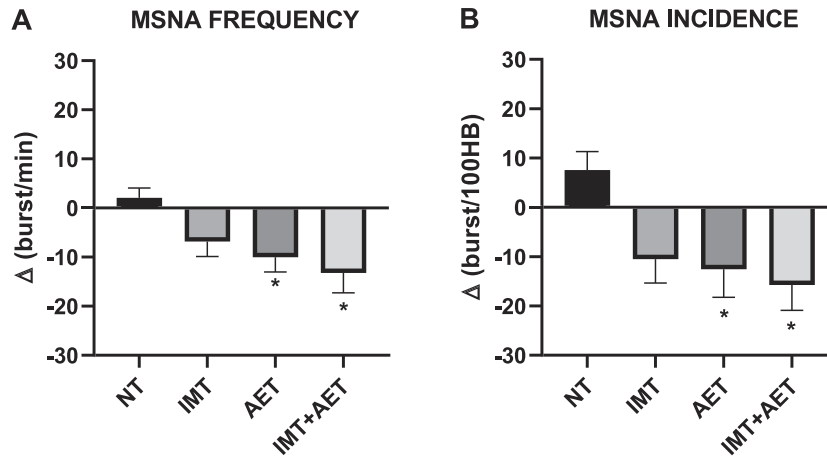
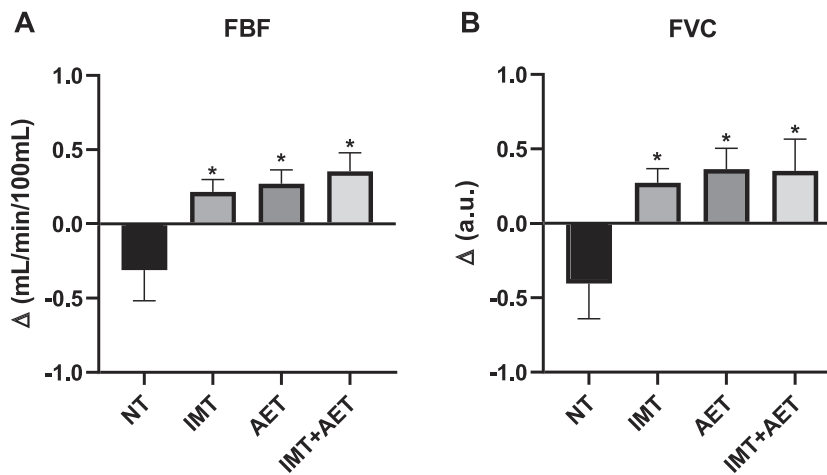


Figure 4 Effects of inspiratory muscle training (IMT), aerobic exercise training (AET), and combined inspiratory muscle training and aerobic exercise training (IMT + AET) on (A) forearm blood flow (FBF) and (B) forearm vascular conductance (FVC) in patients with heart failure with reduced ejection fraction. NT, non-trained. *vs. NT group, $P < 0.05$.



present study, inspiratory muscle weakness was not an inclusion criterion. Further analysis, in which the patients from the IMT group were divided according to inspiratory muscle strength, revealed that the patients with inspiratory muscle weakness had a 26% reduction in MSNA versus 10% reduction in patients with preserved inspiratory muscle strength (data not shown). These findings lead us to speculate that the magnitude of improvement in sympathetic outflow after IMT depends on the baseline inspiratory muscle strength. Of course, we cannot exclude the possibility that a longer period of IMT is necessary to reduce MSNA in patients with HFrEF.

Previous studies demonstrated that IMT increases resting and exercise muscle blood flow in patients with heart failure.¹⁰ The present study confirms this finding. IMT substantially increased forearm blood flow. However, it should be noted that this vascular response occurs regardless of the muscle involved in the exercise training, which confers to IMT a systemic training adaptation.

The effect of IMT on physical capacity in patients with HFrEF has been a matter of controversy. Some investigators report no changes in peak VO_2 after IMT.¹⁵ In contrast, others show that IMT increases peak VO_2 in patients with HFrEF.⁹ In

the present study, we found a 12% increase in peak VO_2 , which is clinically relevant.^{34,35} The amelioration in inspiratory muscle strength may have contributed to the increase in peak VO_2 in our patients. In fact, the patients with inspiratory muscle weakness had a 20% improvement in peak VO_2 versus 8% in the patients with preserved inspiratory muscle strength (data not shown).

Study limitations

We recognize limitations in our study. Because inspiratory muscle strength was not considered as an inclusion criterion, someone could argue that the lack of additional effect of IMT + AET on neurovascular control was due to the fact that few patients had inspiratory muscle weakness. In fact, further analysis showed that the changes in MSNA were more pronounced in patients with inspiratory muscle weakness than in patients without inspiratory muscle weakness. These findings strengthen the hypothesis that the effects of IMT + AET depend upon the baseline inspiratory muscle strength. Future studies should focus on this issue. The small number of patients who finished the study may lead to the interpretation that the sample size limited our study. However, it is important to note that this is a Herculean study. It involves complex measures and procedures. Supervised AET was conducted three times a week and IMT five times a week in very sick patients. As previously stated, from January 2012 to July 2016, 135 patients were screened. Fifty-three patients were included in the study. Eleven did not finish the study for different reasons. More importantly, the sample size calculation indicated five patients in each group. Ten patients in the NT, 11 in the IMT, 12 in the AET, and 9 in the IMT + AET group finished the study. Thus, it is unlikely that sample size limited our findings. We found that IMT + AET does not have additive effects on neurovascular control in patients with HFrEF.

Clinical perspectives

Aerobic exercise training is a unique strategy in the treatment of patients with HFrEF. This exercise paradigm remarkably reduces sympathetic nerve activity and increases muscle blood flow. This is important information in clinical practice. Both MSNA and forearm blood flow are independent predictors of mortality in patients with HFrEF.³⁶ The present findings suggest that IMT + AET has no additional benefit in the neurovascular control in patients with HFrEF. Increase in exercise intensity seems to be a more suitable strategy in the amelioration of neurovascular control in patients with HFrEF. A recent study provides evidence that high-intensity interval training provokes further improvement in MSNA and muscle blood flow in patients with HFrEF.²⁵

Conflict of interest

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