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Inspiratory Muscle Training in Patients With Heart Failure and Inspiratory Muscle Weakness

A Randomized Trial

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OBJECTIVES This study sought to evaluate the effects of inspiratory muscle training in inspiratory muscle strength, as well as in functional capacity, ventilatory responses to exercise, recovery oxygen uptake kinetics, and quality of life in patients with chronic heart failure (CHF) and inspiratory muscle weakness.

BACKGROUND Patients with CHF may have reduced strength and endurance in inspiratory muscles, which may contribute to exercise intolerance and is associated with a poor prognosis.

METHODS Thirty-two patients with CHF and weakness of inspiratory muscles (maximal inspiratory pressure [PI_{max}] <70% of predicted) were randomly assigned to a 12-week program of inspiratory muscle training (IMT, 16 patients) or to a placebo-inspiratory muscle training (P-IMT, 16 patients). The following measures were obtained before and after the program: PI_{max} at rest and 10 min after maximal exercise; peak oxygen uptake, circulatory power, ventilatory oscillations, and oxygen kinetics during early recovery ($\dot{V}O_2$/t−slope); 6-min walk test; and quality of life scores.

RESULTS The IMT resulted in a 115% increment PI_{max}, 17% increase in peak oxygen uptake, and 19% increase in the 6-min walk distance. Likewise, circulatory power increased and ventilatory oscillations were reduced. The $\dot{V}O_2$/t−slope was improved during the recovery period, and quality of life scores improved.

CONCLUSIONS In patients with CHF and inspiratory muscle weakness, IMT results in marked improvement in inspiratory muscle strength, as well as improvement in functional capacity, ventilatory response to exercise, recovery oxygen uptake kinetics, and quality of life. (J Am Coll Cardiol 2006;47:757–63) © 2006 by the American College of Cardiology Foundation

Most patients with chronic heart failure (CHF) are limited in their physical activity by fatigue and dyspnea, and it has been suggested that respiratory muscle weakness and deconditioning may be involved in the increased work of breathing during hyperpnea (1). Some of these patients show reduced maximal inspiratory pressure (PI_{max}) and endurance of inspiratory muscles, which are currently recognized as additional factors implicated in the limited exercise response and quality of life, as well as in their poor prognosis (2). Abnormal ventilatory response to exercise (3), periodic breathing (4), and delayed oxygen uptake kinetics during recovery of maximal effort (5) have also been associated with severity of and poor prognosis in CHF. The precise cause of this respiratory muscle dysfunction remains speculative, but diaphragm biopsies have shown a variety of histological abnormalities in CHF, including fiber type I atrophy (6), which have been implicated in a generalized skeletal muscle disorder in CHF (7).

Few studies have evaluated the effects of inspiratory muscle training in patients with CHF, and their results are contradictory (8–11). Nonrandomized trials (8,11) have shown improvement in maximal functional capacity after inspiratory muscle training, but these beneficial effects have not been confirmed by randomized studies (9,10). Moreover, the effects of inspiratory muscle training on several markers of prognosis obtained from cardiopulmonary exercise testing (CPET) have not been previously reported. Therefore, we conducted this randomized trial to test the hypothesis that a 12-week program of inspiratory muscle training could be associated with improvement in functional capacity, circulatory power, oscillatory ventilation, kinetics of oxygen consumption in the recovery period, and quality of life in patients with CHF and inspiratory muscle weakness.

METHODS

Patients and design. A prospective, randomized, controlled trial was conducted in patients with the diagnosis of CHF attributable to left ventricular systolic dysfunction (left ventricular ejection fraction <45%) who were recruited from the Heart Failure Clinic at the Hospital de Clínicas de Porto Alegre. Entry criteria for the study were a previous history of symptomatic heart failure caused by left ventricular systolic dysfunction, inspiratory muscle weakness (PI_{max} <70% of the predicted), and clinical stability, including no change in medications for the past three months. Exclusion criteria were unstable angina, myocardial infarction, or cardiac

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Abbreviations and Acronyms

α	= relative amplitude of oscillations
CHF	= chronic heart failure
CPET	= cardiopulmonary exercise testing
IMT	= inspiratory muscle training
P-IMT	= placebo inspiratory muscle training
PI_{max}	= maximal static inspiratory pressure
Pth_{max}	= maximal inspiratory pressure sustained for 1 min during incremental test
R	= respiratory exchange ratio
/t slope	= kinetics during recovery
$T_{1/2}$	= time required for 50% from peak
$\dot{V}CO_2$	= carbon dioxide output
$\dot{V}E$	= minute ventilation
$\dot{V}E/\dot{V}CO_2$ slope	= relationship between change in $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise
$\dot{V}O_2$	= oxygen uptake

surgery within the previous three months; chronic metabolic, orthopedic, or infectious disease; treatment with steroids, hormones, or cancer chemotherapy. Patients with previous pulmonary disease (forced vital capacity <80% of predicted and/or forced expiratory volume in 1 s <70% of predicted) (12), history of exercise-induced asthma, and smokers were not recruited. The protocol was approved by the Committee for Ethics in Research of the Hospital de Clínicas de Porto Alegre, and all subjects signed an informed consent form.

Eligible patients were initially evaluated by medical history, physical examination, resting electrocardiogram, two-dimensional echocardiogram, pulmonary function, and inspiratory muscle function. Patients were randomly assigned to inspiratory muscle training (IMT) or to placebo-inspiratory muscle training (P-IMT) for 12 weeks. Before and after the intervention, pulmonary function tests, inspiratory muscle function tests, cardiopulmonary exercise testing (CPET), 6-min walk test, and quality of life assessment were obtained. After finishing the intervention, none of the patients continued with inspiratory muscle training or with any formal exercise program. One year after entering the study, 11 patients in each group were re-evaluated for inspiratory muscle strength and quality of life. All evaluations were performed by investigators who were unaware of the allocation of patients to different interventions.

Inspiratory muscle training. Patients received either IMT or P-IMT for 30 min 7 times per week, for 12 weeks using the Threshold Inspiratory Muscle Training device (Threshold Inspiratory Muscle Trainer, Healthscan Products Inc., Cedar Grove, New Jersey). During training, patients were instructed to maintain diaphragmatic breathing, with a breathing rate at 15 to 20 breaths/min. For the IMT group, inspiratory load was set at 30% of maximal static inspiratory pressure, and weekly training loads were adjusted to maintain 30% of the PI_{max}. The P-IMT followed the same schedule, but with no inspiratory load. Each week, six training sessions were performed at home and one training session was supervised at the hospital.

Pulmonary function. Measurements of forced vital capacity and forced expiratory volume in 1 s were obtained with a computerized spirometer (Eric Jaeger, GmbH, Würzburg, Germany) as recommended by the American Thoracic Society (12), and results were expressed as percentage of predicted (13).

Inspiratory muscle function testing was performed using a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil), connected to a system with two unidirectional valves (DHD Inspiratory Muscle Trainer, Chicago, Illinois). Maximal static inspiratory pressure was determined in deep inspiration from residual volume against an occluded airway with a minor air leak (2 mm). The highest pressure of six measurements was used for analysis. The PI_{max} measurement was performed at rest, and on the 5th and 10th minute after CPET. Predicted values were corrected for age, gender, and weight (14). Additionally, for the determination of inspiratory muscle endurance, an incremental test was used in which patients breathed continuously through a mouthpiece connected to a Threshold Inspiratory Muscle Trainer with an initial load of 50% of PI_{max}, and increments of 10% of PI_{max} were added every 3 min until the patient was unable to continue breathing. The greatest inspiratory pressure that the subject was able to sustain for at least 1 min (Pth_{max}) was taken as the measure for inspiratory muscle endurance, and was expressed as a percentage of maximal inspiratory pressure (Pth_{max}/PI_{max}). In the second part of the protocol, subjects breathed against a constant inspiratory submaximal load equivalent to 80% Pth_{max}, and the time elapsed to task failure was defined as the inspiratory endurance time.

6-min walk test. The maximum distance covered during the walk test was used to assess submaximal functional capacity (15). Patients self-graded their degree of dyspnea during the test using the Borg scale (16).

Cardiopulmonary exercise testing. Maximal functional capacity was evaluated with an incremental exercise test, with expired gas analysis, on a treadmill (INBRAMED 10200, Porto Alegre, Brazil), using a ramp protocol, starting at a speed of 2.4 $km \cdot h^{-1}$ and 2% slope, with 20-s increments of speed (0.1 to 0.2 $km \cdot h^{-1}$) and 60-s increments in slope (0.5% to 1.0%), to reach volitional fatigue at approximately 10 min. Twelve-lead electrocardiographic tracings were obtained every minute (Nihon Khoden Corp., Tokyo, Japan). Blood pressure was measured every 2 min with a standard cuff sphygmomanometer. Metabolic and ventilatory variables were measured during and after exercise by 20-s mean aliquots, by a computer-aided gas analyzer (Total Metabolic Analysis System, TEEM 100, Aero Sport, Ann Arbor, Michigan), previously validated (17). Peak oxygen uptake ($\dot{V}O_2$peak) was considered the highest value of $\dot{V}O_2$ calculated in a period of 20 s of exercise. Maximal circulatory power was calculated as the product of $\dot{V}O_2$peak and peak systolic pressure (18).

Table 1. Baseline Characteristics of Patients Randomized to P-IMT or IMT

Characteristic	P-IMT Group (n = 16)	IMT Group (n = 16)	p Value*
Gender, male/female	10/6	11/5	0.60†
Age, yrs	58 ± 2	54 ± 3	0.21
Body mass index, $kg \cdot m^{-2}$	27 ± 5	27 ± 4	0.86
Etiology of heart failure, n			
Ischemic	7	6	0.90†
Non-ischemic	9	10	0.60†
Ejection fraction, %	38 ± 3	39 ± 3	0.79*
Forced expiratory volume in 1 s, % predicted	90.1 ± 12.6	83.7 ± 14.5	0.20*
Forced vital capacity, % predicted	84.7 ± 8.8	85.3 ± 13.4	0.96*
PI_{max}, kPa	5.7 ± 0.1	5.9 ± 0.9	0.29*
PI_{max}, % predicted	59.8 ± 2	59.5 ± 2.2	0.89*
$\dot{V}O_2$peak, $ml \cdot kg^{-1} \cdot min^{-1}$	17 ± 0.7	17.2 ± 0.5	0.75*
Drugs, %			
Diuretics	80	86	0.82†
Digoxin	50	57	0.79†
Angiotensin-converting enzyme inhibitors	78	85	0.86†
Beta-blocker	50	42	0.10†

Values are expressed as mean ± standard deviation. *Student *t* test. †Fisher exact test.
IMT = inspiratory muscle training; P-IMT = placebo-inspiratory muscle training; PI_{max} = maximal static inspiratory pressure; $\dot{V}O_2$peak = peak oxygen uptake.

Ventilatory efficiency was estimated using the relationship between minute ventilation ($\dot{V}E$) and carbon dioxide output ($\dot{V}CO_2$), i.e., $\dot{V}E/\dot{V}CO_2$−slope, by linear regression model using all data points obtained during CPET (3). The relative amplitudes of oscillations (α) in $\dot{V}E$, $\dot{V}O_2$, and $\dot{V}CO_2$ were calculated for every 20-s period as the ratio between amplitude and its respective mean throughout the test. The ratio between metabolic ($\alpha\dot{V}O_2$, $\alpha\dot{V}CO_2$) and ventilatory oscillations ($\alpha\dot{V}O_2/\alpha\dot{V}E$, $\alpha\dot{V}CO_2/\alpha\dot{V}E$) were also calculated (19). The $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ kinetics during the first 3 min of the recovery period were calculated by a linear regression model adjusted to a simple exponential curve ($\dot{V}O_2/t$, $\dot{V}CO_2/t$, $\dot{V}E/t$ − slope) (1). The time required for a 50% decrease from the $\dot{V}O_2$peak ($T_{1/2}\dot{V}O_2$), $\dot{V}CO_2$peak ($T_{1/2}\dot{V}CO_2$) and $\dot{V}E$ peak ($T_{1/2}\dot{V}E$) was calculated using the mathematical model of the minimum squares through the equation $y = a^{e(-kt)}$, where y corresponds to $\dot{V}O_2$, $\dot{V}CO_2$, or $\dot{V}E$ in time, a corresponds to the slope, k is a constant, and t stands for the time.

Quality of life. Quality of life was assessed with the Minnesota Living With Heart Failure Questionnaire (20). We analyzed overall scores as well as the separate effects of physical and psychological perceptions of quality of life.

Statistical analysis. Data were analyzed on the Statistical Package for Social Sciences (version 10.0, SPSS, Chicago, Illinois). Based on the results of previous studies (8), we estimated that a sample size of 15 individuals in each group would have a power of 80% to detect a 10% difference in peak oxygen uptake, for an $\alpha = 0.05$. Descriptive data are presented as mean ± SD. Baseline data were compared by the Student *t* test for continuous variables or by the Fisher exact test for categorical variables. The Pearson correlation coefficient was used to evaluate associations. The effects of interventions on continuous variables were compared by two-way analysis of variance for repeated measures (ANOVA), and post-hoc analysis was conducted by the Tukey test. Categorical data were analyzed by the chi-square statistic.

RESULTS

Patients. Between August 2001 and November 2003, 144 patients with CHF were screened for the study. Ninety-six patients did not meet the inclusion or met the exclusion criteria, and therefore, 44 patients were randomized. For the 22 patients randomized to IMT, 1 had a myocardial infarction, 1 developed atrial fibrillation, and 4 were not able complete the training protocol. For the 22 patients allocated to P-IMT, 2 had to be excluded because of indication of coronary artery bypass graft surgery, 3 for the development of symptoms at rest, and 1 because of bleeding secondary to oral anticoagulation. Therefore, 16 patients completed the protocol in each group. Table 1 describes the clinical characteristics for both groups. Etiology of CHF was predominantly non-ischemic, and patients had mild to moderate left ventricular dysfunction as well as mild to moderate impairment in functional capacity. Pa-

Table 2. Pulmonary Function and Inspiratory Muscle Function Tests Before and After Intervention for Patients Randomized to P-IMT or IMT

	P-IMT (n = 16)		IMT (n = 16)	
	Before	After	Before	After
FVC % pred	84.7 ± 8.8	83.2 ± 9.5	85.3 ± 13.4	84.8 ± 15.2
FEV_1 % pred	90.1 ± 12.6	90.1 ± 12.6	83.7 ± 14.5	82.4 ± 15.1
Pth_{max}, kPa	3.1 ± 0.5	3.2 ± 0.6	3.2 ± 0.5	3.8 ± 0.5*
Pth_{max}/PI_{max}, %	55 ± 14	56 ± 15	57 ± 9	66 ± 7*
Endurance time, s	256 ± 132	246 ± 121	298 ± 154	924 ± 503*†

Values are expressed as mean ± standard deviation. Two-way ANOVA for repeated measures. *$p < 0.001$ for training and interaction effects. †$p < 0.001$ for group effect.
FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; IMT = inspiratory muscle training; PI_{max} = maximal static inspiratory pressure; P-IMT = placebo inspiratory muscle training; Pth_{max} = maximal inspiratory pressure sustained for 1 min during incremental test.

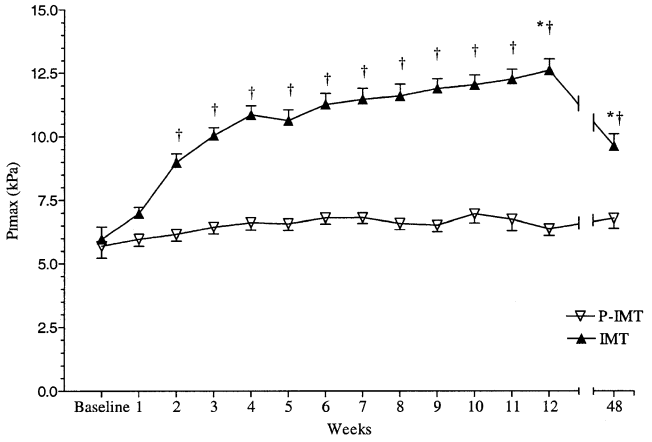

Figure 1. Weekly values of maximal inspiratory pressure (PI_{max}, mean ± SD) for the placebo-inspiratory muscle training group (P-IMT) and for the inspiratory muscle training group (IMT). After 12 weeks in the program, all training was stopped, and 11 patients from each group were re-evaluated at 48 weeks. *Two-way ANOVA for repeated measures: $p < 0.01$ for group, training, and interaction effects. †Significantly ($p < 0.05$) different from baseline evaluation by the Tukey test.

tients received similar medications and maintained the same medical regimen throughout the study period. At one-year follow-up, three patients from the IMT group had died and five patients from the P-IMT group had died.

Pulmonary function and inspiratory muscle function tests. After 12 weeks, spirometric evaluation did not show change in any of the groups (Table 2). The IMT induced marked improvement in PI_{max}, which was apparent after the second week of training and reached an increment of 115% after 12 weeks (Fig. 1). Despite the fact that training was stopped after 12 weeks of intervention, patients in the IMT group maintained part of the effect one year after starting the program. Inspiratory muscle endurance, evaluated by the Pth_{max}, Pth_{max}/PI_{max}, and time sustained in the inspiratory muscle function test, increased after IMT (Table 2). The IMT resulted in improvement in the recovery of PI_{max} at 10 min after maximal exercise (Fig. 2).

Six-minute walk test. The IMT resulted in a longer distance covered during the 6-min walk test (IMT, 449 ± 17 m before and 550 ± 17 m after; P-IMT, 432 ± 41 m before and 411 ± 60 m after [ANOVA <0.002 for group, training, and interaction effects]). Perception of dyspnea rated by the Borg scale during the 6-min walk test also improved after IMT (IMT, 3.7 ± 2.0 before and 1.5 ± 1.4 after; P-IMT, 3.1 ± 1.3 before and 3.0 ± 1.4 after [ANOVA <0.002 for group, training, and interaction effects]).

Cardiopulmonary exercise testing. Before intervention, $\dot{V}O_2$peak did not correlate with PI_{max} ($r = 0.08$; $p = 0.32$; $n = 32$). The IMT resulted in improvements in $\dot{V}O_2$peak and $\dot{V}E$ peak, whereas the peak respiratory exchange ratio (R) was not changed by intervention in either group (Table 3). The change in $\dot{V}O_2$ peak after intervention correlated with the change in PI_{max} ($r = 0.62$; $p < 0.001$; $n = 32$). Maximal circulatory power also increased only in the IMT group (Table 3).

Consistent with improvement in ventilatory efficiency, the $\dot{V}E/\dot{V}CO_2$ slope was reduced after IMT. The relative size of the oscillations in $\dot{V}E$ ($\alpha\dot{V}E$) was reduced after IMT. The relative size of the oscillations in $\dot{V}O_2$ ($\alpha\dot{V}O_2$) and $\dot{V}CO_2$ ($\alpha\dot{V}CO_2$) was not changed by either intervention. However, the ratio between the relative oscillations of $\dot{V}E$ and $\dot{V}CO_2$ increased after IMT.

Before the intervention, $\dot{V}O_2$/t−slope at the first minute in the recovery did not correlate with PI_{max} at 5 min after maximal exercise ($r = 0.18$; $p = 0.15$; $n = 32$). During recovery, $T_{1/2}$ of $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ were faster after IMT (Table 3). Likewise, $\dot{V}O_2$/t−slope in the first minute of recovery was higher after IMT (Table 3, Fig. 3). The change in $\dot{V}O_2$/t−slope at the first minute in the recovery after intervention correlated with the change PI_{max} at 5 min after maximal exercise ($r = 0.70$; $p < 0.001$; $n = 32$).

Quality of life. The Minnesota Living With Heart Failure Questionnaire scores improved after IMT (IMT, 27 ± 4 before and 6 ± 2 after; P-IMT, 30 ± 13 before and 30 ±

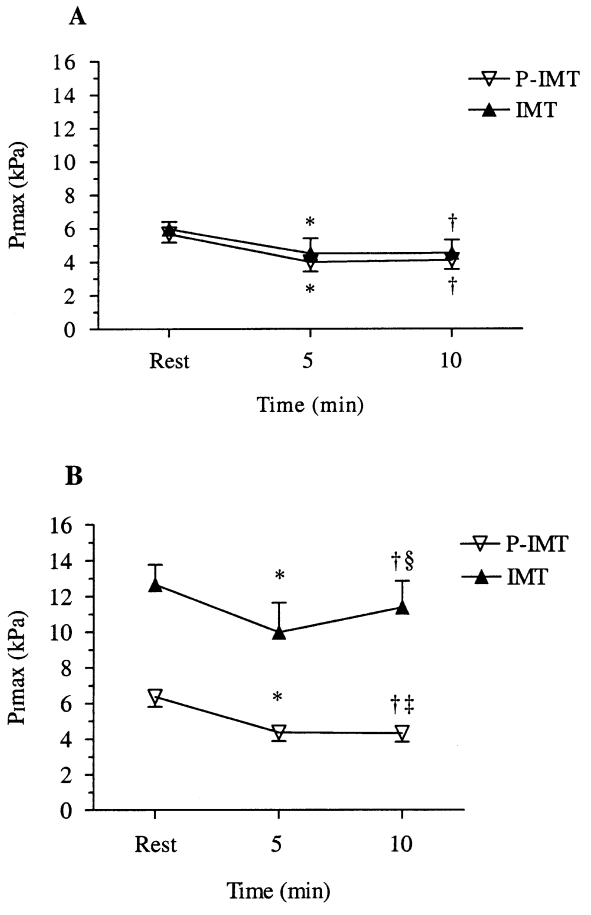

Figure 2. The PI_{max} values (mean ± SD) at rest and on the 5th and the 10th min of recovery after maximal cardiopulmonary exercise test. **(A)** Values before and **(B)** after intervention for the placebo inspiratory muscle training group (P-IMT) and the inspiratory muscle training group (IMT). Two-way ANOVA for repeated measurements: §IMT versus P-IMT ($p < 0.01$ for group, training, and interaction effects). Multiple comparisons by the Tukey test: *5th minute versus rest ($p < 0.05$); †10th minute versus rest ($p < 0.05$); ‡10th minute versus 5th min ($p < 0.05$).

Table 3. Results Obtained in the Maximal Cardiopulmonary Exercise Test for the P-IMT and the IMT Group

	P-IMT (n = 16)		IMT (n = 16)	
	Before	After	Before	After
Peak exercise				
$\dot{V}_E$ peak, l·min^{-1}	47 ± 3	49 ± 4	48 ± 2.7	62 ± 4*†
$\dot{V}O_2$ peak, ml·kg^{-1}·min^{-1}	17 ± 0.6	17 ± 0.8	17 ± 0.6	21 ± 0.7*†
$\dot{V}CO_2$ peak, l·min^{-1}	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.4	1.5 ± 0.4*†
R peak	1.0 ± 0.02	1.0 ± 0.02	1.0 ± 0.01	1.1 ± 0.02
Peak circulatory power, mm Hg·ml O_2·kg^{-2}·min^{-1}	2,714 ± 505	2,592 ± 421	2,829 ± 409	3,696 ± 524*†
Ventilatory efficiency				
$\dot{V}E/\dot{V}CO_2$ – slope	37 ± 4	37 ± 4	35 ± 3.5	30 ± 3*†
Oscillations in gas exchange				
$\alpha\dot{V}E$	0.06 ± 0.005	0.06 ± 0.006	0.07 ± 0.005	0.03 ± 0.006*†
$\alpha\dot{V}O_2$	0.01 ± 0.03	0.01 ± 0.004	0.05 ± 0.035	0.04 ± 0.004
$\alpha\dot{V}CO_2$	0.06 ± 0.005	0.07 ± 0.006	0.07 ± 0.004	0.07 ± 0.006
$\alpha\dot{V}O_2/\alpha\dot{V}E$	1.52 ± 0.27	1.08 ± 0.37	1.8 ± 0.26	2.12 ± 0.35
$\alpha\dot{V}CO_2/\alpha\dot{V}E$	1.02 ± 0.05	1 ± 0.02	1 ± 0.06	1.18 ± 0.02*†
Recovery gas exchange				
$\dot{V}O_2$/t – slope 1st min^{-1}	0.48 ± 0.12	0.48 ± 0.10	0.48 ± 0.12	0.81 ± 0.27*†
$T_{1/2}\dot{V}O_2$ (min)	1.55 ± 0.22	1.47 ± 0.35	1.56 ± 0.29	1.04 ± 0.16*†
$T_{1/2}\dot{V}CO_2$ (min)	1.60 ± 0.3	1.59 ± 0.2	1.60 ± 0.3	1.31 ± 0.2*†
$T_{1/2}\dot{V}E$ (min)	1.63 ± 0.1	1.63 ± 0.2	1.62 ± 0.2	1.33 ± 0.2*†

The values are expressed as mean ± SD. Two-way ANOVA for repeated measures. *$p < 0.001$ for training and interaction effects. †$p < 0.001$ for group effect. *[1]expressed in l · min^{-1} · min^{-1}.

α = relative amplitude of oscillations; IMT = inspiratory muscle training; PI_{max} = maximal static inspiratory pressure; P-IMT = placebo inspiratory muscle training; R = respiratory exchange ratio; $T_{1/2}$ = time required for 50% from peak; /t – slope = kinetics during recovery; $\dot{V}E$ = minute ventilation; $\dot{V}E/\dot{V}CO_2$ – slope = relationship between change in $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise; $\dot{V}E/\dot{V}O_2$ = ventilatory equivalent for oxygen uptake; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}O_2$ = oxygen uptake; other abbreviations as in Table 1.

13 after [ANOVA <0.001 for group, training, and interaction effects]). The global improvement was attributed to a change in physical dimension from 6 ± 3 to 3 ± 5 because no changes were observed in the psychological dimension of the score. Despite the fact that IMT was stopped after 12 weeks of intervention, patients who participated in the IMT program maintained part of the effect on quality of life scores one year after starting the program, from 27 ± 8 to 14 ± 3 (ANOVA <0.05 for group, training, and interaction effects).

DISCUSSION

In this randomized trial, a home-based, three-month IMT program improved inspiratory muscle strength and endurance as well as quality of life and functional capacity in patients with CHF and weakness in inspiratory muscles. Moreover, IMT improved peak circulatory power, ventilatory efficiency, and oscillations during incremental exercise, as well as oxygen uptake kinetics during recovery, which are all markers of poor prognosis in CHF. The efficacy of IMT was tested against a similar program with no inspiratory load, which served as a placebo intervention, and outcomes were blindly evaluated. Interestingly, part of the effect on PI_{max} and quality of life was sustained after one year, even though the patients did not continue training after four months. These data provide the first evidence showing that the effects of IMT are consistent and are partially maintained after one year of follow-up in patients with CHF and weakness of inspiratory muscles.

Inspiratory muscle strength and endurance. In accordance with previous studies (8–11), IMT did not affect resting pulmonary function test results but had a major impact on all measures of inspiratory muscle strength and endurance. The magnitude of improvement in PI_{max} (115%) in our patients is larger than described in previous studies (8–11), a finding that may be related to the fact that we used a linear pressure resistance device with weekly adjustments in load, resulting in possible training of other inspiratory muscles in addition to the diaphragm. Moreover, daily exercises and the presence of inspiratory muscle weakness in all patients may also have contributed to this increment. The improvement in PI_{max} after maximal exercise is consistent with delayed development in diaphragmatic fatigue (1).

Functional capacity and quality of life. Patients who participated in the IMT presented improvement in functional capacity as shown by a 19% increase in 6-min walk distance, which was also accompanied by a reduction in the perception of dyspnea. Likewise, there was a 17% increase in $\dot{V}O_2$peak and a 24% increase in circulatory power, consistent with clinically significant improvement in cardiovascular and respiratory response to maximal exercise. The improvement in functional capacity and the reduction in perception of dyspnea were probably responsible for the changes in the physical dimension of quality

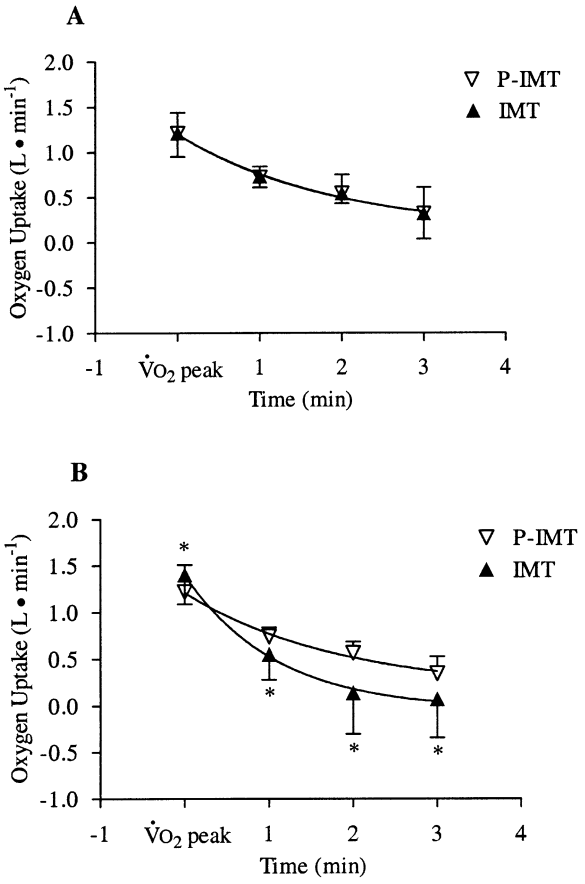

Figure 3. Values of the oxygen uptake kinetics during the first 3 min of recovery (mean ± SD) after maximal cardiopulmonary exercise test before **(A)** and after **(B)** intervention for the placebo inspiratory muscle training group (P-IMT) and the inspiratory muscle training group (IMT). Overall two-way ANOVA for repeated measures: $p < 0.001$ for group, training, and interaction effects. *Significantly different between groups ($p < 0.05$) by the Tukey test.

of life scores, which was partially maintained at the 12-month evaluation, several months after IMT had been stopped.

The IMT can delay the development of diaphragmatic fatigue in patients with CHF, leading to a reduction in the recruitment of accessory respiratory muscles, increasing ventilatory efficiency, and/or reducing the blood flow required by the respiratory muscles during exercise (21). In CHF, there is enhanced ventilatory sensitivity to both central and peripheral chemoreceptor stimulation (22), which can reflexively induce sympathetic vasoconstriction and reduce blood flow to skeletal muscles during exercise. Therefore, diaphragm fatigue may elicit sympathetically mediated vasoconstriction in limb muscles, a reflex that can be attenuated by whole-body aerobic exercise training (23). By improving ventilatory muscle strength and endurance, IMT may also delay the development of fatigue of the diaphragm, consequently reducing sympathetic activation, improving the perfusion of the peripheral muscles, and increasing functional capacity.

Ventilatory response to exercise. The present study confirms that three months of IMT causes substantial improvement in the ventilatory efficiency, as shown by a reduction in the $\dot{V}E/\dot{V}CO_2$–slope. Patients with CHF present hyperventilation during exercise, with increased breathing rate and decreased tidal volume, resulting in larger pulmonary dead space (3). Recent studies have indicated a putative role of an exaggerated chemoreceptor reflex originating from the exercising muscle and explaining the hyperventilatory response in CHF (23). Indexes reflecting the chemoreceptor stimulation correlate with $\dot{V}E/\dot{V}CO_2$–slope and ventilatory oscillations during exercise, variables with prognostic value in CHF patients (4,24). To our knowledge, this is the first study to show attenuation in ventilatory oscillation during exercise by IMT. Therefore, improvement in ventilatory muscle strength and endurance may also attenuate the exaggerated chemoreflex and improve ventilatory control during exercise.

Oxygen uptake kinetics during recovery. The effects of an IMT program on oxygen kinetics during the recovery from CPET have not been previously studied. Results of the present study show a faster $T_{1/2}\dot{V}O_2$ and an increase in the $\dot{V}O_2$/t–slope after IMT. Nanas et al. (1) have shown a relationship between inspiratory muscles weakness 10 min after maximal CPET and the reduced magnitude or prolonged $\dot{V}O_2$ recovery time. Therefore, the delay in the recovery of blood flow to the fatigued diaphragm could contribute to prolonged kinetics of recovery of $\dot{V}O_2$. In contrast to our findings, Myers et al. (25) showed that two months of high-intensity whole-body aerobic training improved $\dot{V}O_2$peak but had no significant effect on $\dot{V}O_2$ kinetics in the recovery period in patients with reduced ventricular function. Therefore, our findings underscore the role of strength and endurance of inspiratory muscles as determinants of oxygen uptake kinetics in the recovery period.

Study limitations. In this small clinical trial, we showed that a 12-week program of IMT has a consistent effect on several prognostic markers in CHF. However, this study was designed only to evaluate the efficacy of IMT on functional variables and not on survival. Our findings are limited to patients with mild CHF caused by left ventricular systolic dysfunction and weakness in inspiratory muscle, but a recent trial of IMT, including patients with more advanced CHF and with a higher baseline PI_{max}, found similar results (11). The training period was maintained for only 12 weeks, which does not allow us to conclude that the effect on functional capacity and quality of life is long-term. However, one-year follow-up showed that the effects on quality of life are partially maintained. We have suggested that part of the beneficial effects of IMT could be mediated by a reduction in sympathetic vasoconstrictor activity to peripheral muscle, but no assessment of sympathetic nerve activity was made, and mechanistic studies should be conducted to test this hypothesis.

Because whole-body aerobic exercise training is currently indicated for patients with CHF for improvement in functional capacity and possibly for reduction in mortality (26), it is not known whether the beneficial effects of IMT would further improve the functional capacity of patients with

CHF who perform aerobic exercise regularly. However, Vibarel et al. (27) showed that aerobic exercise training has no significant effect on the strength of inspiratory muscles, suggesting that the two programs may result in complementary effects, a hypothesis that should be addressed by a controlled trial isolating the effects of both interventions.

Clinical implications. Our findings indicate that a simple and inexpensive home-based IMT program results in clinically relevant increments of improvement in submaximal and maximal functional capacity, with reduction of perception of dyspnea and improvement in quality of life. Although the sample size is not appropriate to assess survival, these results, together with the observations of other small trials (8–11), suggest that IMT is a safe intervention that can be considered for the management of patients with CHF, particularly those with weakness in inspiratory muscles. Our results also raise the question of whether routine screening for weakness of inspiratory muscle should be performed in patients with CHF.

CONCLUSIONS

This randomized, placebo-controlled trial shows that a short-term, home-based program of IMT results in marked improvement in inspiratory muscle strength and endurance, which results in clinically relevant increments of improvement in submaximal and maximal functional capacity, as well as in quality of life in CHF patients with inspiratory muscle weakness. Moreover, IMT also improves ventilatory efficiency and oscillations during exercise, peak circulatory power, and oxygen uptake kinetics during recovery in this patient population.

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