Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness

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Background This small clinical trial tested the hypothesis that the addition of inspiratory muscle training (IMT) to aerobic exercise training (AE) results in further improvement in cardiorespiratory responses to exercise than those obtained with AE in patients with chronic heart failure (CHF) and inspiratory muscle weakness (IMW).

Methods Twenty-four patients with CHF and IMW (maximal inspiratory pressure <70% of predicted) were randomly assigned to a 12-week program of AE plus IMT (AE + IMT, n = 12) or to AE alone (AE, n = 12). Before and after intervention, the following measures were obtained: maximal inspiratory muscle pressure (PI_{max}), peak oxygen uptake ($\dot{V}O_2$peak), peak circulatory power, oxygen uptake efficiency slope, ventilatory efficiency, ventilatory oscillation, oxygen uptake kinetics during recovery ($T_{1/2}\dot{V}O_2$), 6-minute walk test distance, and quality of life scores.

Results Compared to AE, AE + IMT resulted in additional significant improvement in PI_{max} (110% vs 72%), $\dot{V}O_2$peak (40% vs 21%), circulatory power, oxygen uptake efficiency slope, ventilatory efficiency, ventilatory oscillation, and $T_{1/2}\dot{V}O_2$. Six-minute walk distance and quality of life scores improved similarly in the 2 groups.

Conclusion This randomized trial demonstrates that the addition of IMT to AE results in improvement in cardiorespiratory responses to exercise in selected patients with CHF and IMW. The clinical significance of these findings should be addressed by larger randomized trials. (Am Heart J 2009;158:768.e1-768.e7.)

An important clinical manifestation of chronic heart failure (CHF) is impaired exercise capacity because of dyspnea or fatigue. Some patients with CHF present with reduced strength and endurance of the inspiratory muscles, which are currently recognized as additional factors implicated in the limited exercise response, as well as in poor prognosis.[1] We have recently shown that inspiratory muscle training (IMT) improves exercise capacity and ventilatory responses to exercise in CHF patients with inspiratory muscle weakness (IMW)[2,3] and that this effect is associated with the attenuation of the inspiratory muscle metaboreflex.[4]

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Whole-body aerobic exercise training (AE) is currently recommended for all stable outpatients with CHF.[5] Aerobic exercise improves cardiovascular[6] and ventilatory responses to exercise in CHF, resulting in significant changes in peak oxygen uptake ($\dot{V}O_2$peak), ventilatory efficiency,[7] oxygen uptake efficiency slope,[8] oscillatory ventilation,[9] and oxygen uptake kinetics during recovery.[10] There is little information on the effects of AE on inspiratory muscle strength, but Beniaminovitz et al[11] and Vibrarel et al[12] found no significant increase in maximal inspiratory pressure (PI_{max}) after 8 to 12 weeks of AE in patients with CHF. Because IMT improves exercise capacity in CHF by mechanisms that are probably different from those of AE,[1,4,13,14] it is conceivable that IMT could have additional effects to AE. Therefore, the present clinical trial was conducted to test the hypothesis that the addition of IMT to AE could result in further improvement in the primary outcome measures PI_{max} and $\dot{V}O_2$peak in patients with CHF and IMW. As secondary outcome measures, we also evaluated the effects of the addition of IMT to AE on cardiorespiratory responses to exercise, quality of life scores, and 6-minute walk test distance in these patients.

Methods

Patients

A prospective, randomized, controlled trial was conducted in patients with the diagnosis of stable CHF attributable to left ventricular systolic dysfunction (left ventricular ejection fraction <45%), with IMW (PI_{max} <70% of the predicted[15]). All patients had diagnosis of CHF for >6 months and had no admission to the hospital or change in medications over the previous 3 months. Exclusion criteria were history of pulmonary disease, current smoking, angina, recent myocardial infarction or cardiac surgery (<6 months), orthopedic or neurologic disease, treatment with steroids, or cancer chemotherapy. The protocol was approved by the committees for ethics in research of both institutions and all subjects signed an informed consent form. The trial has been registered at ClinicalTrials.gov under the number NCT00634296 and was supported by grants from the Brazilian Research Council (CNPq), the Research Incentive Fund from Hospital de Clínicas De Porto Alege, and Research Incentive Fund from UNIJUI. The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper, and its final contents.

Protocol

Eligible patients were initially evaluated by medical history, physical examination, and inspiratory muscle function. Patients were randomly assigned to AE or to AE plus inspiratory muscle exercise training program (AE + IMT) for 12 weeks. Before and after the intervention, respiratory muscle function tests, cardiopulmonary exercise testing, 6-minute walk test, and quality of life assessment were obtained by investigators who were unaware of the allocation of patients to different interventions.

Aerobic exercise training

All patients were enrolled in a supervised exercise program performed 3 times per week, for 12 weeks, to complete a total of 36 sessions. Patients exercised on a mechanically braked cycle ergometer (Embreex, Joinville, Brazil), at a cadence of 60 rpm, and exercise intensity was monitored by heart rate using a pulse oximeter (Onix 9500, Nonin, SIMS BCI Inc, Waukesha, WI). Each session included a 5-minute period of warm-up with no resistance, followed by a period exercising at the target heart rate that corresponded to the first ventilatory threshold on the cardiopulmonary exercise test. Patients who had atrial fibrillation or for whom the first ventilatory threshold could not be determined (1 patient in the AE group and 2 patients in the AE + IMT group) exercised at an intensity corresponding to 5 points in the 10-point Borg scale.[16] During the first 2 weeks, the duration of the exercise at the target intensity was 20 minutes, and 5 minutes were added every 2 weeks until the exercise reached 45 minutes. The exercise sessions ended with a 5-minute cool-down period without resistance.

Inspiratory muscle training

Patients randomized to AE + IMT used the Threshold Inspiratory Muscle Training device (Threshold Inspiratory Muscle Trainer, Healthscan Products Inc, Cedar Grove, NJ) for 30 minutes, 7 times per week, with an inspiratory load at 30% of PI_{max}, as previously described.[2] Every week, training loads were adjusted to maintain 30% of the PI_{max}, and patients performed 6 training sessions at home and 1 training session was supervised at the hospital.

Respiratory muscle function

Inspiratory and expiratory muscle function testing was performed using a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil). PI_{max}, maximal static expiratory pressure (PE_{max}), as well as inspiratory muscle endurance using an incremental test (Pth_{max}) and constant load test (endurance time) were measured as previously described.[2]

Cardiopulmonary exercise testing

The maximal incremental exercise test was performed on an electrically braked cycle ergometer (ER-900, Ergoline, Jaeger, Würzburg, Germany) and gas exchange variables were measured breath-by-breath by a validated system (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany) and calculated as previously described.[2-4] The quantification of ventilatory oscillations was performed as originally proposed by Francis et al[17] and modified by Dall'Ago et al.[2] For every 2 adjacent 20-second period of V_E, the amplitude of oscillation was calculated as difference between the 2 points divided by their mean. This value was again divided by the mean to obtain the relative amplitude, and the values of the entire cardiopulmonary test were averaged to convey in a single ratio. The first ventilatory threshold (also referred to as the anaerobic threshold) was determined by review of the gas exchange curves as the V_{O_2} and heart rate at which the ventilatory equivalent for oxygen increased systematically without an increment in the ventilatory equivalent for carbon dioxide.[18]

Submaximal functional capacity

The maximum distance covered during the 6-minute walk test was used to assess submaximal functional capacity.[19]

Quality of life

Quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire.[20]

Statistical analysis

Based on previous trials of AE[7-10] and IMT,[2] we estimated a mean 20% increase in V_{O_2}peak in the AE group and judged that an increment of >30% in V_{O_2}peak would be consistent with an additional effect. Therefore, a sample size of 12 individuals in each group would have a power of 80% to detect a 10% difference in the change in V_{O_2}peak, for an $\alpha = .05$, but with the expectation that we would have >30% dropouts, 38 patients were initially randomized. 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 effects of interventions on continuous variables were compared by 2-way analysis of variance (ANOVA) repeated measures, and post hoc analysis was conducted by the

Table I. Clinical characteristics and baseline values for patients randomized to aerobic training or aerobic plus IMT

	AE (n = 12)	AE + IMT (n = 12)	P*
Age (y)	59 ± 9	54 ± 12	.25*
Gender (male/female)	4/8	7/5	.55†
Body mass index (kg/m^{-2})	25 ± 4	28 ± 5	.18*
Atrial fibrillation	3	5	.69†
Etiology of CHF (n)			
Ischemic cardiomyopathy	1	3	.65†
Dilated cardiomyopathy	11	9	.98†
Ejection fraction (%)	34 ± 11	39 ± 12	.24*
PI_{max} (cm H_2O)	56 ± 13	57 ± 12	.84*
PI_{max} (% predicted)	61 ± 2.5	61 ± 2	.89*
PE_{max} (cm H_2O)	74 ± 236	79 ± 31	.60*
PE_{max} (% predicted)	3 ± 22	65 ± 23	.88*
V_{O_2}peak (mL kg^{-1} min^{-1})	16.1 ± 4.6	15.1 ± 4.2	.85*
Drugs (%)			
Diuretics	80	80	.82†
Digoxin	67	40	.79†
Angiotensin-converting inhibitor	82	80	.86†
β-Blocker	45	50	.95†

Values are expressed as mean ± SD.
* Student *t* test.
† Fisher exact test.

Tukey test. The Pearson correlation coefficient was used to evaluate associations.

Results

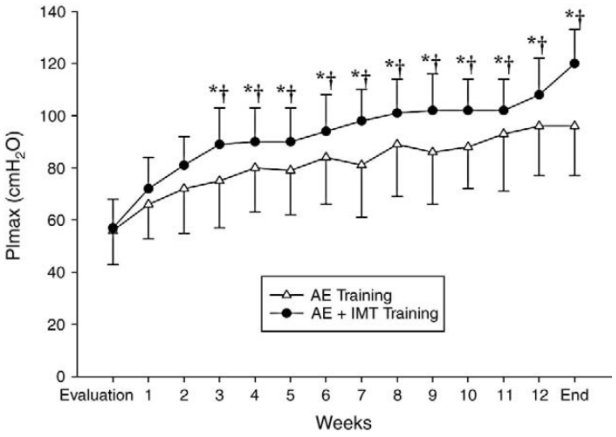
Patients

A total of 209 patients with CHF were screened, but 105 patients did not have IMW and another 66 had exclusion criteria or logistic problems that precluded their participation in the supervised AE intervention. Therefore, a total of 38 individuals were randomized. Of these patients, 14 (7 in the AE and 7 in the A + IMT group) did not complete the program because of the following reasons: logistic problems (9 patients), orthopedic problems (2 patients), death (1 stroke in the AE, and 1 myocardial infarction in the A + IMT group), and hospital admission (1 patient in the A + IMT group). In the opinion of the attending physicians, these problems were not directly associated with the training programs. Therefore, 12 patients completed the protocol in each group. As shown in Table I, clinical characteristics and baseline values for both groups were similar after randomization. There were no changes in the medical regimen throughout the experiments. The mean heart rate attained during each of the 36 aerobic exercise sessions for the AE group was 68% ± 3% of peak heart rate, whereas the A + IMT group exercised at a mean heart rate of 70% ± 3% of peak heart rate. Heart rates at each exercise sessions were not significantly different between the groups.

Inspiratory muscle function

Figure 1 shows that the AE and the A + IMT presented significant improvements in PI_{max}, which were apparent after the third week of intervention. However, the 110% mean increment in PI_{max} at 12 weeks in the A + IMT was significantly larger than the 72% mean increment observed in the AE group. Table II demonstrates that the A + IMT also resulted in significantly larger increments in PE_{max} as well as in the measures of inspiratory muscle endurance, Pth_{max}, Pth_{max}/PI_{max}, and endurance time, when compared to the AE.

Figure 1



Weekly values of PI_{max} (mean ± SD) for the AE and for the AE + IMT. *Two-way ANOVA for repeated measures: $P < .01$ for group, training, and interaction effects. †Significantly ($P < .05$) different from baseline evaluation by the Tukey test.

Table II. Respiratory muscle function tests before and after intervention for patients randomized to aerobic training or aerobic plus IMT

	AE (n = 12)		A + IMT (n = 12)	
	Before	After	Before	After
PE_{max} (cmH_2O)	74 ± 23	108 ± 27	79 ± 31	123 ± 31†
Pth_{max}	29 ± 6	36 ± 3	28 ± 6	41 ± 2*
Pth_{max}/PI_{max}	52 ± 4	73 ± 12	51 ± 4	80 ± 14*
Endurance time, sec	153 ± 45	199 ± 43	110 ± 44	254 ± 68*,†

Values are expressed as mean ± SD. Two-way ANOVA for repeated measures.
* $P < .001$ for training and interaction effects.
† $P < .001$ for group effect.

Cardiopulmonary exercise testing

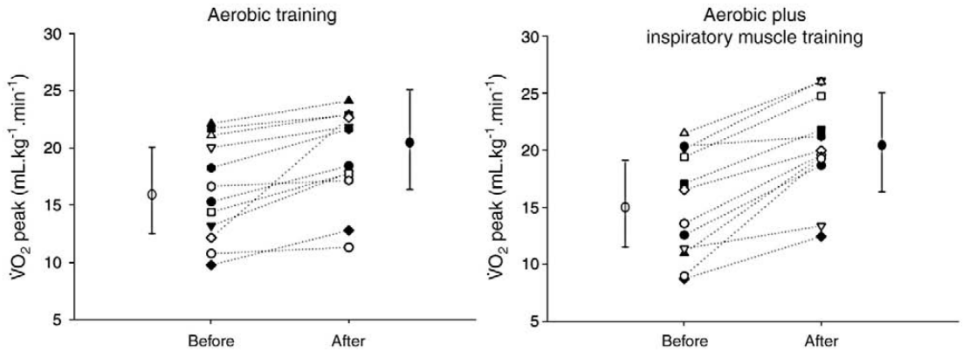
Table III presents the results of the maximal cardiopulmonary exercise tests before and after intervention. Both interventions resulted in improvement in peak performance, submaximal ventilatory responses, and recovery gas exchange kinetics (repeated-measures ANOVA time effect $P < .001$); however, the adaptations were more marked in the A + IMT group (repeated-

Table III. Results obtained in the maximal cardiopulmonary exercise test before and after intervention for patients randomized to aerobic training or aerobic plus IMT

	AE (n = 12)		AE + IMT (n = 12)	
	Before	**After**	**Before**	**After**
Peak exercise				
Peak heart rate (beat/min)	144 ± 26	142 ± 24	136 ± 24	135 ± 33
Peak systolic pressure (mm Hg)	156 ± 32	157 ± 26	157 ± 25	165 ± 15
$\dot{V}O_2$peak (mL kg^{-1} min^{-1})	16.1 ± 4.6	19.2 ± 4.2	15.1 ± 4.2	19.7 ± 4.1*
$\dot{V}CO_2$peak (L/min)	1.213 ± 0.252	1.378 ± 0.302	1.422 ± 0.221	1.513 ± 0.339
$\dot{V}E$peak (L/min)	48 ± 17	52 ± 13	48 ± 21	56 ± 30*
R_{peak}	1.13 ± 0.15	1.11 ± 0.08	1.12 ± 0.07	1.05 ± 0.14
Peak circulatory power (mm Hg mL O_2 Kg^{-1} min^{-1})	2,569 ± 880	3,065 ± 869	2,250 ± 815	3,276 ± 857*,†
Ventilatory responses				
$\dot{V}E/\dot{V}CO_2$ slope	37 ± 7	33 ± 6	44 ± 5	30 ± 7*,†
OUES (mL min^{-1} O_2/L min^{-1} $\dot{V}E$)	1,398 ± 567	1,880 ± 617	1,323 ± 766	2,040 ± 545*,†
First ventilatory threshold (mL kg^{-1} min^{-1})	11.9 ± 3.8	13.7 ± 2.9	10.6 ± 2.6	15.2 ± 4.1*
Oscillation in $\dot{V}e$	0.08 ± 0.002	0.06 ± 0.003	0.08 ± 0.003	0.02 ± 0.001*,†
Recovery gas exchange				
$T_{1/2}\dot{V}o_2$ (min)	2.22 ± 1.25	1.90 ± 1.23	2.96 ± 1.63	1.68 ± 0.54*,†

The values are expressed as mean ± SD. Two-way ANOVA for repeated measures. *$\dot{V}CO_2$peak*, Peak carbon dioxide output; *E_{peak}*, peak minute ventilation; *R_{peak}*, peak respiratory exchange ratio; *$\dot{V}E/\dot{V}CO_2$ slope*, slope of the regression line of the change in $\dot{V}E$ and $\dot{V}CO_2$ during exercise; *$T_{1/2}$*, time required for 50% from peak.
* $P < .001$ for training and interaction effects.
† $P < .001$ for group effect.

Figure 2



Individual and mean (±SD) values for peak oxygen uptake ($\dot{V}O_2$peak) before and after intervention for patients randomized to aerobic training (left panel) or aerobic plus IMT (right panel). Both groups increased significantly $\dot{V}O_2$peak (2-way ANOVA for repeated measures, $P < .001$ for time effect), but the aerobic plus IMT group presented a significantly larger increment (2-way ANOVA for repeated measures, $P < .001$ for interaction effect).

measures ANOVA interaction effect, $P < .001$). As shown in Figure 2, the 40% mean increment in $\dot{V}O_2$peak in the A + IMT was significantly larger than the 21% mean increment observed in the AE group. There was a significant negative correlation between the improvement in $\dot{V}O_2$peak and the initial PI_{max} expressed as percentage of predicted ($r = -0.41$, $P = .04$). AE + IMT also induced a significantly larger increase in peak circulatory power and oxygen uptake efficiency slope (OUES) when compared to AE. Likewise, $\dot{V}E/\dot{V}CO_2$ slope and the relative size of ventilatory oscillations during exercise decreased significantly more with A + IMT. There was a significant negative correlation between the improvement in PI_{max} and the changes in $\dot{V}E/\dot{V}CO_2$ slope ($r = -0.63$; $P = .01$) and ventilatory oscillations ($r = -0.51$; $P = .02$). Recovery oxygen uptake kinetics was also reduced by a significantly larger magnitude after A + IMT when compared to AE.

Six-minute walk test

Both groups presented similar improvement in the distance covered in the 6-minute walk test (AE + IMT 420 ± 90 m before and 500 ± 72 m after; AE 433 ±

108 m before and 489 ± 81 m after; ANOVA: $P < .001$ only for training).

Quality of life

The Minnesota Living with Heart Failure Questionnaire scores also improved similarly after both training programs (A + IMT 45 ± 21 before and 20 ± 15 after; AE 45 ± 18 before and 18 ± 15 after; ANOVA: $P < .001$ only for training).

Discussion

In this randomized trial, we have shown that the addition of IMT to AE results in significant increases in V_{O_2}peak, peak circulatory power, the first ventilatory threshold, and OUES, as well as in improvement of V_E/V_{CO_2} slope, the relative size of ventilatory oscillations during exercise, and recovery oxygen uptake kinetics in patients with CHF and IMW. The mean additional increment in the main outcome measure V_{O_2}peak (about 19%) is not trivial, considering the fact that IMT was added to an effective intervention to improve peak exercise capacity, that is, AE. To our knowledge, this is the first evidence that IMT may have additional effects to AE in the cardiorespiratory responses to exercise in this patient population.

There is growing evidence that IMT improves functional capacity of patients with CHF and IMW.[1-4] However, in contrast to our previous observations,[2-4] 2 small randomized trials failed to demonstrate improvement in some measures of exercise capacity with IMT using the threshold device.[21,22] In the present study, the AE + IMT resulted in a mean 110% increment in PI_{max} while AE increased PI_{max} by a mean of 72%, in contrast with previous studies that had not shown improvement in PI_{max} after AE in patients with CHF.[11,12] Compared to other studies, the present trial, as well as previous studies from our laboratory,[2-4] selected only patients with IMW, whereas in the other studies, a small percentage of patients had IMW. Therefore, a unifying explanation for these conflicting results could be that, in patients with CHF and IMW, any training stimulus, being AE, IMT, or both, may result in significant improvement in inspiratory muscle strength, with consequences in functional capacity. For patients with CHF but without IMW, such as most of those studied by Laoutaris et al,[14] higher-intensity IMT may be required to improve functional capacity and the responses may not be consistent. This interpretation is supported by our finding of an inverse correlation between the improvement in V_{O_2}peak and initial PI_{max} expressed as percentage of predicted.

Confirming our hypothesis, OUES, ventilatory efficiency, the first ventilatory threshold, and oscillatory breathing, as well as oxygen uptake kinetics in the recovery, measures that are independent of patients' motivation, were improved more with A + IMT than with AE alone. The isolated effects of AE and IMT in these variables had been previously demonstrated.[2-4,7-9] Peripheral chemoreflex response is a major determinant of ventilatory efficiency as well as in oscillatory gas exchange kinetics during exercise in CHF,[23] and preliminary data from our laboratory have shown that IMW is associated with augmented peripheral chemoreflex response.[24] As suggested by the correlations between changes in PI_{max} and changes in V_E/V_{CO_2} slope and in ventilatory oscillations, the improvement of inspiratory muscle strength might have resulted in attenuation of the peripheral chemoreflex with impact on ventilatory efficiency and oscillatory breathing, but this hypothesis should be tested in future studies.

Our results are compatible with the notion that AE and IMT have complementary effects on pathophysiologic mechanisms associated with CHF. Laoutaris et al[13,14] have recently shown that, contrary to AE,[25-28] IMT has no significant impact on heart rate variability and endothelium-dependent vasodilatation or in the circulating levels of N-terminal pro-brain natriuretic peptide, tumor necrosis factor α, interkeukin 6, C-reactive protein, and soluble apoptosis mediators. We have previously shown that IMT may affect exercise capacity in patients with CHF by improving blood flow to the exercising limbs through the attenuation of the inspiratory muscle metaboreflex,[4] and these findings are now supported by Borghi-Silva et al[29] who demonstrated that unloading ventilation improves exercise capacity and skeletal muscle perfusion in this patient population. Moreover, preliminary animal data indicate differential catabolic effects of CHF on skeletal muscle and diaphragm, therefore supporting the rationale of combined (AE + IMT) training interventions as an anticatabolic stimulus in CHF.[30]

Study limitations

This is a small randomized trial and, therefore, the possibility of a type I error cannot be ruled out. Our sample size was calculated with the assumption that there would be no change in PI_{max} with AE, but it did occur. Despite this unexpected finding, the addition of IMT to AE still resulted in significant improvement in cardiorespiratory responses to exercise. This larger improvement was observed in V_{O_2}peak, which depends on patient effort, and also on submaximal measures that do not depend on patient effort. However, these additional effects of IMT were not detected on the 6-minute walk test or on the Minnesota Living with Heart Failure Questionnaire. The 6-minute walk test is known to be less sensitive to interventions, particularly in patients with higher exercise capacities,[19] but we have previously shown that IMT improves performance in the 6-minute walk test and also improves quality of life scores in

patients with CHF and IMW.[2] Therefore, the addition of IMT to AE may not have implications for the daily activities of patients with CHF because submaximal exercise capacity and quality of life showed similar responses. On the other hand, all the cardiopulmonary exercise testing–derived variables have important prognostic implications,[31] and our results may raise the hypothesis that the addition of IMT to AE could improve survival in this patient population. This may be particularly important after the publication of the AF-ACTION trial, which failed to show improved survival with AE in patients with CHF.[32] Finally, in this efficacy trial, we used a very rigorous AE + IMT in a highly selected and closely monitored cohort of patients. Therefore, the generalization of our approach to real-world cardiac rehabilitation programs should be evaluated by effectiveness studies with larger sample sizes.

Clinical implications

The accumulated evidence strongly supports the concept that CHF patients with IMW improve functional capacity with IMT,[2-4] and the present study also indicates that these patients may benefit from the combination of AE and IMT. Because of the small sample size of our study, the clinical significance of these findings is not apparent. However, if confirmed by larger randomized trials, these findings suggest that routine screening for IMW may be performed in all patients with CHF and that both kinds of training programs may be considered for those with IMW.

Conclusions

This randomized clinical trial demonstrates that the addition of IMT to AE results in improvement in cardiorespiratory responses to exercise in selected patients with CHF and IMW. The complementary effects of these training modalities were demonstrated in cardiopulmonary exercise testing–derived variables, which are known to have impact in prognosis. Therefore, large-scale clinical trials are warranted to evaluate the long-term effects of these interventions on clinical outcomes.

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Disclosures

None of the authors have potential conflict of interests related to the content of this article.

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