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High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial

Ester Marco[1,2,3,4]*, Alba L. Ramírez-Sarmiento[3,4,5,6], Ana Coloma[7], Monique Sartor[1,3,4], Josep Comin-Colet[8,9], Joan Vila[10,11], Cristina Enjuanes[8,9], Jordi Bruguera[8], Ferran Escalada[1,2], Joaquim Gea[4,5,12], and Mauricio Orozco-Levi[3,4,5,6,12]

[1]Physical Medicine and Rehabilitation Department, Hospital del Mar, Barcelona, Catalonia, Spain; [2]Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain; [3]Research Group on Injury, Immunitary Response and Lung Function, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Catalonia, Spain; [4]Biomedical Research Network for Respiratory Diseases (CIBERES), ISCIII, Ministerio de Ciencia y Tecnología, Spain; [5]Respiratory Department, Hospital del Mar, Barcelona, Catalonia, Spain; [6]Respiratory Department, Centro de Investigaciones, Fundación Cardiovascular de Colombia; [7]Physical Medicine and Rehabilitation Department Hospital, Universitari i Politècnic La Fe, Valencia, Spain; [8]Heart Failure Program, Cardiology Department, Hospital del Mar, Barcelona, Catalonia, Spain; [9]Heart Diseases Biomedical Research Group, IMIM, Barcelona, Catalonia, Spain; [10]Department of Biostatiscs, IMIM, Barcelona, Catalonia, Spain; [11]Biomedical Research Network for Epidemiology and Public Health (CIBERESP), Spain; and [12]Departament de Ciències Experimentals i de la Salut (CEXS), Universitat Pompeu Fabra Barcelona, Catalonia, Spain

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Aims The purpose of this study was to evaluate the effectiveness, feasibility, and safety of a 4-week high-intensity inspiratory muscle training (hi-IMT) in patients with chronic heart failure (CHF).

Methods and results A double-blind randomized clinical trial was carried out in 22 patients with CHF. Participants were assigned to the hi-IMT or sham-IMT group. The trainer device was a prototype of the Orygen-Dual Valve®. The training workloads were adjusted weekly at the inspiratory pressure which allowed the performance of 10 consecutive maximal repetitions (10RM). Main outcomes were strength and endurance of the respiratory muscles assessed by maximal respiratory pressures (PI_{max} and PE_{max}) and a 10RM manoeuvre, respectively. Twenty-one patients presented impairment in respiratory muscle strength and endurance. Patients in the hi-IMT group showed a significant improvement in both strength and endurance: inspiratory muscle strength in the intervention group increased 57.2% compared with 25.9% in the control group ($P = 0.001$). The percentage change in endurance was 72.7% for the hi-IMT group compared with 18.2% in the sham-IMT group ($P < 0.001$). No adverse effects occurred during the intervention.

Conclusion A 4-week hi-IMT with the use of the Orygen-Dual Valve® is shown to be an effective, feasible, and safe tool to improve weakness and fatigue of the inspiratory muscles. The key point of this study is to discuss immediate practical implications in terms of respiratory muscle dysfunction postulated as a potential prognostic factor and as an additional therapeutic target.

Trials registration NCT01606553.

Keywords Inspiratory muscle training • Muscle strength • Muscle endurance • Heart failure • Cardiopulmonary rehabilitation

* Corresponding author. Tel: +34 93 367 42 14, Fax: +34 93 367 42 76, Email: emarco@parcdesalutmar.cat

Introduction

The current guidelines of the European Cardiology Society and the American College of Cardiology FoundationAmerican Heart Association recommend exercise training as an adjunctive approach to improve clinical status in stable adult patients with current or prior symptoms of heart failure and reduced LVEF.[1–4]

Chronic heart failure (CHF) is known to alter the structure and/or function of muscles. Strength and endurance are the two main functional properties of both respiratory and peripheral muscles. When the strength and/or endurance is reduced, this is called muscle dysfunction. Strength mainly depends on muscle mass, and endurance is related to its aerobic properties. Muscle weakness is a relatively stable condition related to the loss of muscle strength which requires long-term therapeutic measures (training and/or nutritional interventions). In contrast, muscle fatigue is a temporary dysfunction related to endurance.[5]

Respiratory muscles (RespMs) are the contractile elements that establish airflow between the lungs and the ambient air. A wide variety of studies have focused on RespM abnormalities in CHF patients.[6,7] The impairment of RespM strength in CHF is related to the severity of the disease.[8] Furthermore, reduced strength and endurance of RespMs are currently recognized as additional factors involved in limited exercise response and health-related quality of life (HRQOL), as well as poor prognosis.[9] Furthermore, inspiratory muscle training (IMT) has been shown to result in improvements in inspiratory strength, functional capacity, ventilatory response to exercise, and HRQOL of patients with CHF and RespM weakness.[10,11]

Despite the variety of studies, the optimal training scheme is still to be defined. The specifications of the loads to be imposed during training is the main factor determining the outcome. Thus, high-intensity and not too frequent stimuli will bring about an increase in the strength derived from improving fibre and muscle size. In contrast, moderate repetitive efforts result in increased muscle strength, by enlarging the elements involved in aerobic muscle activity. Previous clinical trials supported the effectiveness of low to moderate intensity IMT (maximum 38 cmH_2O) alone and in combination with aerobic exercise.[12–14] To date, only one randomized study has demonstrated that the addition of high-intensity IMT (hi-IMT) to aerobic exercise resulted in incremental benefits in muscle weakness, cardiopulmonary function, and HRQOL.[15] The same authors also reported effects on dyspnoea, functional status, immune response (plasma cytokines, C-reactive protein, and apoptosis mediators), autonomic activity, endothelial vasodilator function, and NT-proBNP levels in case–control studies.[16–18]

Our research group has demonstrated the good functional results of a 4-week supervised high-intensity respiratory training in patients with COPD.[19,20] This intervention makes the rehabilitation programme more efficient than usual training as it requires fewer resources in terms of time and staff, and allows patients to acquire skills for further training outside the hospital.

On the basis of these considerations, the primary endpoint of this study was to evaluate the effectiveness, feasibility, and safety of a 4-week hi-IMT in CHF patients and, secondly, to discuss immediate practical implications in terms of RespM dysfunction postulated as a potential prognostic factor and as an additional therapeutic target.

Methods

Trial design and participants

A prospective, double-blind, randomized controlled clinical trial was established according to the Consolidated Standards of Reporting Trials Statement[21] to determine the efficacy of the hi-IMT in rehabilitation of patients with CHF. The setting was a cardiopulmonary rehabilitation unit integrated into a multidisciplinary Heart Failure Programme in an acute-care university hospital in Barcelona, Catalonia, Spain.

Patients were eligible for inclusion if they met the following criteria: (i) age >18 years; (ii) CHF of any aetiology; (iii) NYHA functional class II–III; (iv) clinically stable condition, with no worsening of heart failure or changes in cardiac medication in the previous 3 months and during the study; and (v) ability to understand and accept the trial procedures and to sign an informed consent in accordance with national legislation. Exclusion criteria included: (i) previous history of any chronic respiratory disease; and (ii) absence of general and/or RespM training in the previous 3 months. Prior to randomization, all patients underwent clinical and echocardiographic assessment, were under optimal medical treatment (beta-blockers, ACE inhibitors, diuretics, and digoxin), and attended regular review visits with their cardiologists.

The clinical trial was approved by the local Clinical Research Ethics Committee and performed in accordance with the Declaration of Helsinki. An informed consent was obtained from all patients. The trial was included on the Clinical Trials Register (NCT01606553).

Intervention

Patients were distributed between two groups: (i) Group I received hi-IMT; and (ii) Group II received sham-IMT.

Patients were informed about the trial and its risks and gave their written consent. After having been randomly allocated to one of the two groups, all patients were instructed to maintain adequate inspiration and expiration while using the Orygen-Dual valve® (*Figure 1*) at a rate of 15–20 breaths/min. Training loads in Group I were adjusted weekly to the inspiratory pressure which allowed patients to perform 10 consecutive maximal repetitions (10RM), so that training intensity was 100% of their 10RM. Group II received sham-IMT at an initial workload of 10 cmH_2O which was increased 2.5 cmH_2O every

Figure 1 The Orygen Dual valve, a respiratory trainer device comprised of two separate chambers: inspiratory (right) and expiratory (left).

week. Both groups performed five sets of 10 repetitions followed by 1–2 min of unloaded recovery breathing off the device, twice a day, 7 days per week, for 4 weeks. Once a week, the IMT was performed under supervision of a physiotherapist. On the same day, a different doctor researcher adjusted the workload according to 10RM.

Randomization and blinding

Treatment blinding and randomization were carried out in the complementary examinations department using a programme to generate random numbers. Neither patients nor doctors assessing respiratory pressures were aware of which group they had been allocated to. Clinical assessment was conducted exclusively by the same rehabilitation specialist who had no knowledge of the procedure, in order to ensure the blind status of the trial.

Primary endpoints

Table 1 summarizes the primary endpoints of the trial (effectiveness, feasibility, and safety) and the parameters used to evaluate them.

Effectiveness

The main effectiveness parameters were maximal RespM strength (ability to develop a brief maximal effort) and endurance (ability to maintain a submaximal contraction over time). RespM strength was assessed through maximal inspiratory and expiratory pressures (PI_{max} and PE_{max}, respectively). The PI_{max} was measured at the mouth during a maximum effort from residual volume against an occluded airway.[22] To determine the PE_{max}, patients performed a maximum expiratory effort from total lung capacity in the face of the occluded airway. The mouthpiece used in the maneouvres had a small orifice to minimize the participation of face and mouth muscles and was connected to a pressure transducer (Sibelmed, Sibel, Barcelona) attached to a digital recorder (Biopac Systems, Goleta, CA, USA). The highest value of three reproducible maneouvres (<10% variability between values) was used for analysis. Reference values were those previously published for a Mediterranean population.[23] Values >80% were considered normal. For the purposes of the study, strength training responders included patients with an increase >25% in PI_{max}. The method used to measure inspiratory endurance was a 10RM maneouvre consisting of a progressive inspiratory threshold by the use of the Orygen-Dual valve®. Inspiratory load was increased each minute by 10 cmH_2O until the subject was no longer able to sustain the task despite strong encouragement. According to our own data, healthy subjects appear capable of performing 10RM at a workload of ~ 80% of their PI_{max}. Endurance was considered reduced when patients did not manage to perform the 10RM maneouvre at 50% PI_{max} workload. Endurance training responders were patients with an increase of ≥ 25% in inspiratory muscle endurance.

Table 1 Primary endpoints of the trial and parameters used to evaluate them

Primary endpoints	Measures
Effectiveness	Inspiratory muscle strength Inspiratory muscle endurance Dyspnoea (MMRC) Quality of life (MLHFQ) Change in NT-proBNP and other blood biomarkers
Feasibility	The acronym TELOS refers to the five areas of feasibility: Technical: 'Are staff trained to implement the new training scheme?' Economic: 'Is the cost of training acceptable?' Legal: 'Does the treatment conflict with legal requirements?' Operation: 'Does the treatment solve a clinical problem?' Scheduling: 'It is reasonable time to achieve effectiveness?'
Safety	Adverse effects Patient acceptance Changes in chronic disease biomarkers

MMRC, Modified Medical Research Council; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

Other measurements

Peripheral muscle strength was estimated by the handgrip strength: patients had to perform a maximum voluntary isometric contraction of finger flexor muscles, using a hand-held dynamometer (Jamar®, Nottinghamshire, UK), comparing the reading observed with reference values.[24]

Dyspnoea severity was assessed using the Modified Medical Research Council (MMRC) dyspnoea scale. Levels of dyspnoea were graded from 0 (dyspnoea only with strenuous exercise) to 4 (too breathless to leave the house or dyspnoea when dressing).[25]

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is the most commonly used instrument for evaluating effects of symptoms, functional limitations, and HRQOL in patients with heart failure.[26] It comprises 21 items, an overall total score, and two dimensions: physical and emotional. Patients were asked to answer, using a 6-point Likert scale (0–5), how much each of 21 facets prevented them from living as they desired. Overall score (0–105) is the sum of responses for each item. The MLHFQ has been validated for the Spanish population.[27]

The Short Form 36 Health-related Quality of Life Questionnaire (SF-36) is a self-administered questionnaire containing 36 items. It measures health on eight multi-item dimensions: physical functioning, role limitations (physical problems), bodily pain, general health, vitality, social functioning, role limitations (emotional problems), and mental health. For each dimension, item scores are coded, summed, and transformed on to a subscale ranging from 0 (worst possible health) to 100 (best possible health).[28] The SF-36 has also been validated for the Spanish population.[29]

The NT-proBNP levels and other blood biomarkers for chronic disease including high-sensitivity C-reactive protein, serum iron, transferrin, transferrin saturation percentage, soluble transferrin receptor, reticulocyte haemoglobin, mean corpuscular haemoglobin (MCH), corpuscular mean haemoglobin concentration, creatinine, glomerular filtration rate (GFR), lactate dehydrogenase, creatine kinase, aspartate aminotransferase, γ-glutamyltransferase, total proteins, and albumin were measured.

Feasibility

The acronym TELOS (technical, economic, legal, operation and scheduling) refers to the five feasibility areas (*Table 1*). Five yes/no questions were formulated to assess these areas. The intervention was considered feasible if the answer was 'yes', except for the legal area that should be 'no'.

Safety outcomes

Safety was estimated by the absence of adverse effects, patient acceptance, and/or little change in chronic disease biomarkers.

Sample size

The sample size was calculated so that at least 10 patients were necessary in each group by accepting a mean difference between treatments of 15 cmH_2O and a standard deviation (SD) of 12 cmH_2O in the PI_{max}, with an alpha-risk of 0.05 and a beta-risk of 20% on a bilateral contrast. The sample size was overestimated to allow potential loss of 10%.

Procedure

Data collected at first evaluation (before training) included: age, sex, heart failure aetiology, NYHA functional class, respiratory and metabolic diseases, pharmacological treatments, and previous hospital admission because of heart failure. Respiratory functional tests (forced spirometry, static lung volumes, airway resistance, diffusing capacity for carbon monoxide, and oxygen saturation) were determined using standard procedures.[30–32]

Statistical analysis

Categorical variables are given in absolute and percentage values. Quantitative variables are given together with the mean and SD, or else with the median and 25th and 75th percentiles (P25–75) when they did not meet normality criteria. In the case of quantitative variables, the assumption of normality was analysed through normal probability graphs and using the Kolmogorov–Smirnov test corrected by the Lilliefors test. Univariate analysis was performed using χ^2, Fisher's exact, Student's *t*- or Mann–Whitney U-tests depending on the variables analysed. Changes in the follow-up were studied performing analysis of variance using a repeated-measures mixed design (intrasubject) and a one-factor (intersubject) design for the analysis of values over time. When the sphericity criteria were not complied with, the degrees of freedom were corrected using Greenhouse–Geisser's method. A *P*-value ≤ 0.05 was considered as statistically significant. Data were analysed using the IBM SPSS Statistics 21 program.

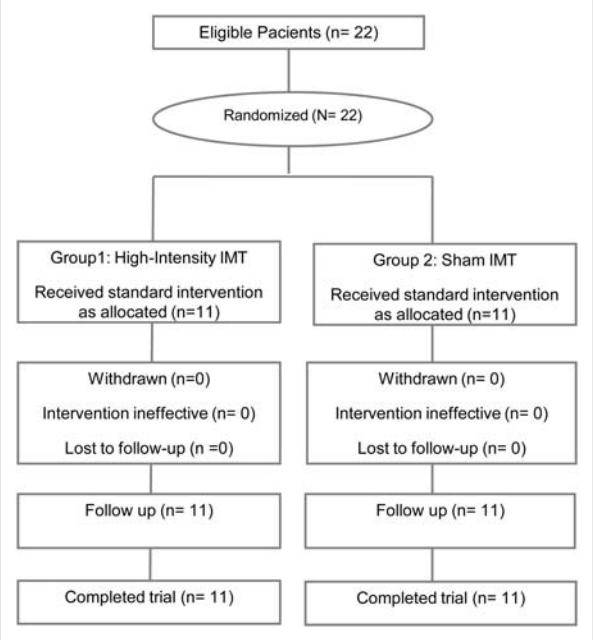

Figure 2 Trial profile (CONSORT flow diagram).

Results

The trial procedure is described in *Figure 2*. Twenty-two patients were enrolled in the trial and divided into the two groups. None of the patients was excluded upon completion. The baseline demographic and clinical characteristics are shown in *Table 2*. No differences were observed between groups regarding any of these clinical and demographic characteristics. The mean age was 69.3 (SD 9.65) years and the gender distribution was 17 (77.3%) men and 5 (22.7%) women. The heart failure aetiology was predominantly ischaemic and patients had mild to moderate LV dysfunction, as well as mild to moderate impairment of functional capacity in all cases. Although participants did not have previous history of chronic respiratory diseases, mean values for most lung function variables were within the range of moderate impairment.

The main measure outcomes under study were analysed by intention-to-treat and showed the following results over the follow-up period.

Respiratory muscle function

All participants presented reduced respiratory strength and/or endurance. The baseline distribution according to RespM function is summarized in *Table 3*. Twenty-one subjects (95.5%) presented impairment in inspiratory muscle strength and, in one-third of them, PI_{max} was $< 50\%$ of predicted values. The hi-IMT resulted in a marked improvement of PI_{max} (57.2% vs. 25.9% in Group II), $P = 0.005$ (*Table 4*). A direct relationship was found between PI_{max} and forced vital capacity (FVC; Pearson's correlation coefficient 0.787, $P = 0.020$). However, we did not detect any significant correlation between RespM function and the EF. *Figure 3* shows the progression of PI_{max} and endurance during follow-up. A significant correlation was found between inspiratory muscle endurance and the PI_{max} (Pearson's coefficient 0.745, $P < 0.001$). The percentage change in endurance was 72.7% for the hi-IMT group vs. 18.2% in the sham-IMT group, $P < 0.001$. Endurance was estimated by the load at which patients could perform 10 maximal inspirations and it did not correlate significantly with any of the lung function measurements.

The distribution of patients according to training response is described in *Table 5*. A marginally significant difference in the proportion of responders was observed: nine patients in the hi-IMT group showedimproved $PI_{max} > 25\%$ vs. four patients in the sham-IMT group. There were nine endurance training responders in the hi-IMT group and only one patient in the sham-IMT group, $P = 0.002$.

Upper limb muscle function

The strength of the upper limb muscles was preserved in almost all patients (*Table 2*). No significant changes were observed in either group at the end of the IMT. The strength of handgrip did not correlate with PI_{max} or PE_{max}.

Table 2 Baseline characteristics of the sample

	Total sample (n = 22)	High-intensity IMT (n = 11)	Sham-IMT (n = 11)	P-value
Age (years)	69.3 (SD 9.66)	68.5 (SD 8.88)	70.1 (SD 10.75)	0.701
Sex (men/women)	17 (77.3%) 5 (22.7%)	7 (63.6%)/4 (36.4%)	10 (90.9%)/1 (9.1%)	0.136
Body mass index	27.3 (SD 3.21)	28.4 (SD 3.64)	26.3 (SD 2.4)	0.113
LVEF	36.9 (SD 16.43)	38.31 (SD16.02)	35.5 (SD 17.49)	0.694
NYHA functional classification				0.619
II	17 (77.3%)	8 (72.7%)	9 (72.7%)	
III	5 (22.7%)	3 (27.3%)	2 (18.2%)	
Heart failure aetiology				0.672
Ischaemic	13 (59.1%)	6 (54.5%)	7 (63.6%)	
Other	9 (40.9%)	5 (45.5%)	4 (36.4%)	
Hospital admissions due to acute exacerbations				0.655
Yes	7 (31.8%)	4 (36.4%)	3 (27.3%)	
No	15 (63.3%)	15 (68.2%)	8 (72.7%)	
Smoking status				0.068
No	6 (27.3%)	4 (36.4%)	2 (18.2%)	
Yes	5 (22.7%)	4 (36.4%)	1 (9.1%)	
Ex-smoker	11 (50%)	3 (27.3%)	8 (72.7%)	
Respiratory function tests				
FEV1 (%)	63.1 (SD 14.0)	62.9 (SD 14.3)	63.3 (SD 14.4)	0.953
FVC (%)	68.3 (SD 10.2)	66.5 (SD 6.8)	69.6 (SD 12.2)	0.499
FEV1/FVC (%)	64.7 (SD 9.6)	66.4 (SD 10.6)	63.4 (SD 9.0)	0.503
TLC (%)	97.2 (SD 15.4)	100 (SD 16.6)	94.9 (SD 14.9)	0.503
RV (%)	127.6 (SD 37.0)	127.9 (SD 36.0)	127.0 (SD 47.8)	0.976
RV/TLC (%)	52.5 (SD 10.6)	53.1 (SD 7.3)	52.0 (SD 13.1)	0.828
DL_{CO} (%)	65.4 (SD 20.3)	66 (SD 21.1)	65 0 (SD 20.79)	0.924
Airway resistance (%)	227 (SD 131.1)	245 (SD 100.3)	213.9 (SD 153.2)	0.624
Spirometric patterns[a]				0.280
Normal	2 (9.1%)	1 (9.1%)	1 (9.1%)	
Obstructive	14 (63.6%)	5 (45.5%)	9 (81.8%)	
Restrictive	1 (4.5%)	0 (0%)	1 (9.1%)	
Mixed	3 (13.6%)	3 (27.3%)	0 (0%)	
Unknown	2 (9.1%)	2 (18.2%)	0 (0%)	
Respiratory muscle strength				
PI_{max} (cmH_2O)	56.6 (SD 23.4)	55.1 (SD 23.6)	58.1 (SD 24.3)	0.773
PI_{max} (%)	56.2 (SD 17.5)	56.2 (SD 20.0)	56.2 (SD 15.7)	1.0
PE_{max} (cmH_2O)	100.3 (SD 35.4)	96.5 (SD 28.2)	103.7 (SD 42.1)	0.654
PE_{max} (%)	61.4 (SD 24.0)	58.3 (SD 30.8)	64.6 (SD 15.5)	0.553
Respiratory muscle endurance				
10RM load	33.8 (SD 12.2)	34.5 (SD 12.8)	33.1 (SD 12.2)	0.801
Limb muscle function				
Handgrip dominant (%)	91.6 (SD 22.8)	91.9 (SD 29.8)	99.7 (SD 33.2)	0.950
Handgrip non-dominant (%)	98.8 (SD 25.1)	99.7 (SD 33.2)	98.0 (SD 14.8)	0.875
MMRC dyspnoea scale	1.9 (SD 1.0)	2.1 (SD 1.0)	1.6 (SD 1.03)	0.316
Minnesota Living with Heart Failure Questionnaire	32.3 (SD 28.9)	39 (SD 33.6)	25.6 (SD 23.0)	0.288
Short-form 36				
Physical functioning	52.9 (SD 26.4)	46.8 (SD 22.9)	59.1 (SD 29.1)	0.285
Role physical	45.5 (SD 42.7)	38.6 (SD 40.1)	52.3 (SD 45.4)	0.467
Bodily pain	69.1 (SD 26.1)	61.5 (SD 25.8)	76.8 (SD 25.1)	0.173
General health	41.1 (SD 22.8)	35.4 (SD 19.5)	46.9 (SD 25.2)	0.244
Vitality	50.2 (SD 26.6)	43.6 (SD 24.8)	56.8 (SD 27.9)	0.255
Social functioning	70.5 (SD 32.4)	59.1 (SD 31.7)	81.8 (SD 30.3)	0.101

Continued

Table 2 *Continued*

	Total sample (n = 22)	High-intensity IMT (n = 11)	Sham-IMT (n = 11)	P-value
Role emotional	60.6 (SD 45.6)	48.5 (SD 50.3)	72.7 (SD 38.9)	0.221
Mental health	67.8 (SD 28.8)	57.5 (SD 21.2)	78.2 (SD 26.6)	**0.057**
Standardized physical component	38.7 (SD 9.7)	37.3 (SD 7.7)	40.1 (SD 11.5)	0.505
Standardized mental component	45.1 (SD 13.1)	39.8 (SD 14.9)	50.5 (SD 8.6)	**0.056**

Variables are presented as mean [standard deviation (SD)] or number (proportion) as appropriate.
DL_{CO}, carbon monoxide lung diffusion; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; IMT, inspiratory muscle training; M MRC, Modifued Medical Research Council; PE_{max}, maximal expiratory pressure; PI_{max}, maximal inspiratory pressure; RM, maximal repetitions; RV, residual volume; TLC, total lung capacity.
[a]The obstructive ventilatory pattern was defined as FEV1/FVC ratio <70%; restrictive ventilatory pattern as FVC and TLC <80%, and FEV1/FVC >70%; and mixed ventilatory pattern as similar abnormal percentages but without previous criteria for obstructive or restrictive abnormalities.

Table 3 Distribution of patients according to respiratory muscle function (strength and resistance)

	Total sample (n = 22)	High-intensity IMT (n = 11)	Sham-IMT (n = 11)	P-value
Muscle strength				
Inspiratory muscle weakness				
Normal (PI_{max} ≥80%)	1 (4.5%)	1 (9.1%)	0	0.455
Reduced (PI_{max} <80%)	21 (95.5%)	10 (90.9%)	11 (100%)	
Expiratory muscle weakness				0.754
Normal (PE_{max} ≥80%)	3 (14.3%)	1 (10%)	2 (18.2%)	
Reduced (PE_{max} <80%)	18 (85.7%)	9 (90%)	9 (81.8%)	
Muscle endurance				
Inspiratory muscle fatigue				0.135
Normal (10RM ≥50% PI_{max})	4 (18.2%)	2 (18.2%)	2 (18.2%)	
Reduced (10RM 30–50% P_{Imax})	18 (81.8%)	9 (81.8%)	9 (81.8%)	

Variables are presented as number and proportion.
IMT, inspiratory muscle training; PE_{ma}, maximal expiratory pressure; PI_{max}, maximal inspiratory pressure; RM, maximal repetitions.

Dyspnoea

At the end of training, the scores of the MMRC dyspnoea scale improved in the hi-IMT group: -0.8 ± 1.39 vs. -0.3 ± 0.46, $P = 0.04$ (*Table 4*).

Quality of life

There were no significant intergroup differences in the baseline measures of quality of life on either the MLHFQ or SF-36. When comparing the SF-36 dimensions with those of the Spanish general population, a significant decrease in all the dimensions except for Bodily Pain and Mental Health was observed. During the 4-week intervention, no significant differences were detected between or within groups.

Biomarkers for chronic disease

The blood values for chronic disease biomarkers are shown in *Table 6*. No statistically significant differences were found at baseline. It should be noted that no significant changes were found in NT-proBNP levels either between or within groups. After completing the procedure, the only significant mild improvement was in the renal function (creatinine and GFR) for the sham-IMT group.

Feasibility

The physiotherapists responsible for conducting the testing received 2 h of specific training. The inclusion of IMT in the rehabilitation programme fulfilled legal requirements and did not involve any significant increase in costs. The treatment was effective in most participants (*Table 5*) in a relatively short time.

Safety

Patient acceptance was good in all cases and none of them complained of any discomfort or poor tolerance. No adverse effects occurred during the trial.

Discussion

To our knowledge, this is the first study showing that IMT in the face of maximal 10RM is feasible, well tolerated, effective, and safe in CHF patients. In terms of effectiveness, the benefits of

Table 4 Two-factor analysis of variance of main effectiveness outcomes prior to starting inspiratory muscle training and during the follow-up period

	Before IMT		1 week training		2 week training		3 week training		4 week training		Time–status interaction *P*-value
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
PI_{max} (%)	56.1 ± 19.9	56.1 ± 15.6	64.7 ± 19.3	60.6 ± 17.2	77.7 ± 19.3	60.2 ± 15.6	85.4 ± 21.5	67.7 ± 16.4	88.2 ± 21.3	70.8 ± 16.4	**0.001**
10RM load	34.4 ± 12.8	33.0 ± 12.1	46.8 ± 17.2	35.1 ± 11.3	52.7 ± 18.8	36.8 ± 10.4	58.6 ± 18.8	38.5 ± 10.3	59.4 ± 17.5	39.0 ± 10.1	**< 0.001**
Dom HG	26.9 ± 10.4	31.3 ± 9.9	30.8 ± 11.8	27.0 ± 10.2	28.9 ± 11.4	29.6 ± 9.1	27.8 ± 10.2	29.7 ± 9.7	29.8 ± 10.9	31.2 ± 11.1	0.889
No dom HG	26.6 ± 11.4	30.4 ± 9.5	29.2 ± 10.2	27.4 ± 7.9	26.9 ± 7.4	28.6 ± 9.2	25.7 ± 7.1	30.2 ± 10.1	27.3 ± 8.1	30.5 ± 10.2	0.460
MMRC dyspnoea	2.1 ± 1.04	1.6 ± 1.03	–	–	–	–	–	–	1.3 ± 0.65	1.3 ± 0.79	**0.4**

Quantitative variables are presented as mean and standard deviation.
Dom HG, dominant handgrip; MMRC dyspnoea, Modified Medical Research Council dysponea scale; No dom HG, non-dominant handgrip; PI_{max}, maximal inspiratory pressure; RM, maximal repetitions.

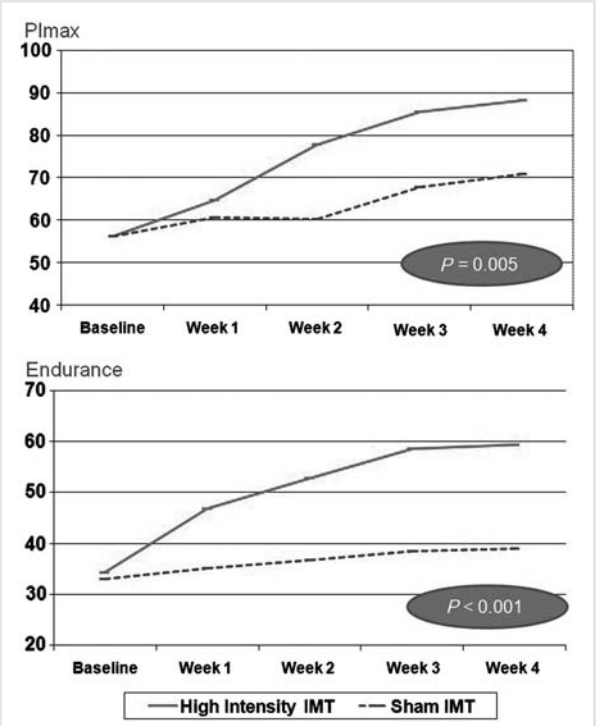

Figure 3 Progression of strength [maximal inspiratory pressure (PI_{max})] and endurance [10 maximal repetitions (RM)] during follow-up. IMT, inspiratory muscle training.

hi-IMT on the strength and endurance of inspiratory muscles were statistically significant as of the second week of training.

The system used to test inspiratory muscle endurance and determine the training intensity (10RM) is a strong point of this study. The main advantage of using 10RM is that it enables establishment of the degree of training without any kind of respiratory pressure manometer. Therefore, it can be used in any setting (regardless of its technological complexity) and can also be easily modified during training without having to request further examinations. Since this is the first study using the Orygen-Dual®, further information is required on the device mechanism and the progression of training intensity. The Orygen-Dual Valve® is a respiratory training device designed and patented by researchers of the Institut d'Investigacions Mèdiques-Hospital del Mar, Barcelona, Catalonia. It is comprised of two separate chambers connected to a central element. The inspiratory chamber includes a diaphragm coated with a silicone sheet, fixed perpendicularly to the vertical axis of the central chamber. The diaphragm is coupled to a C-shaped-steel lamina which is retracted by a screw. The pressure is proportional to the turns given to the screw. This allows a linear increase of the opening pressure of the valve depending on the tension (retraction) of the C-lamina. During the inspiratory effort, the diaphragm is opened to a known threshold pressure, enabling the inspiratory flow. The flow shows a curve with quadratic morphology (plateau) causing the system to behave as a threshold-opening mechanism. The silicone membrane allows identification of a resonant sound when the valve is opened (flux

Table 5 Distribution of patients according to strength and endurance training response (improvement >25%)

	Total sample ($n = 22$)	High-intensity IMT ($n = 11$)	Sham-IMT ($n = 11$)	*P*-value
Inspiratory weakness				**0.08**
Responders	13	9 (81.8%)	4 (36.4%)	
Non-responders	9	2 (18.2%)	7 (63.6%)	
Inspiratory fatigue				**0.002**
Responders	10	9 (81.8%)	1 (9.1%)	
Non-responders	12	2 (18.2%)	10 (90.9%)	

Variables are presented as number and proportion.
IMT, inspiratory muscle training.

Table 6 Two-factor analysis of variance of the N-terminal pro brain natriuretic peptide levels and other blood biomarkers of chronic disease before and after inspiratory muscle training

	Before IMT		Post-IMT		*P*-value
	Heavy duty IMT	Sham-IMT	Heavy duty IMT	Sham-IMT	
NT-proBNP	1677.4 (SD 1658.4)	2212.9 (SD 3155.5)	1593.7 (SD 1308.6)	2294.8 (SD 3567.6)	0.864
Haemoglobin	13.8 (SD 1.8)	12.5 (SD 1.5)	13.6 (SD 2.0)	12.89 (SD 1.4)	**0.082**
Mean corpuscular haemoglobin	29.7 (SD 2.9)	30.0 (SD 1.7)	29.76 (SD 2.5)	30.0 (SD 1.8)	0.109
CMHC	32.3 (SD 1.2)	31.7 (SD 0.9)	37.7 (SD 1.3)	31.9 (SD 0.7)	0.012
Sideraemia	74.2 (SD 18.5)	65.5 (SD 32.5)	79.9 (SD 30.4)	65.36 (SD 31.4)	0.626
Ferritin	183.3 (SD 202.8)	189.4 (SD 183.4)	150.4 (SD 165.6)	307.70 (SD 430.9)	0.403
Transferrin	282.2 (SD 46.1)	247.7 (SD 37.4)	288.6 (SD 52.4)	237.9 (SD 18.9)	0.369
Transferrin saturation	21.7 (SD 7.0)	21.2 (SD 10.2)	22.7 (SD 8.2)	21.2 (SD 7.8)	0.965
Soluble transferrin receptor	1.6 (SD 0.4)	1.6 (SD 0.4)	1.41 (SD 0.7)	1.33 (SD 0.9)	0.234
Reticulocyte haemoglobin	32.4 (SD 4.0)	33.7 (SD 3.8)	33.5 (SD 2.9)	35.08 (SD 2.9)	0.684
Creatinine	1.3 (SD 0.3)	1.4 (SD 0.2)	1.3 (SD 0.3)	1.28 (SD 0.2)	**0.03**
Glomerular filtration rate	49.1 (SD 9.4)	45.7 (SD 8.9)	49.3 (SD 9.0)	51.66 (SD 7.9)	**0.007**
Lactate dehydrogenase	395.2 (SD 90.2)	363.0 (SD 65.5)	384.9 (SD 85.0)	380.0 (SD 92.7)	0.128
Creatinine kinase	65.6 (SD 21.9)	74.2 (SD 45.5)	73.7 (SD 23.7)	57.0 (SD 27.5)	**0.079**
Aspartate aminotransferase	20.8 (SD 9.3)	19.9 (SD 3.4)	20.5 (SD 7.6)	20.18 (SD 5.8)	0.680
γ-Glutamyltransferase	34.1 (SD 24.3)	38.6 (SD 33.4)	31.2 (SD 20.5)	45.36 (SD 37.0)	0.264
Total protein	7.5 (SD 0.4)	7. 68 (SD 0.8)	7.5 (SD 0.5)	7.6 (SD 0.8)	0.687
Albumin	4.3 (SD 0.4)	4.2 (SD 0.5)	4.41 (SD 0.4)	4.13 (SD 0.6)	**0.089**
hs-CRP	0.6 (SD 0.6)	1.5 (SD 1.5)	0.4 (SD 0.4)	3.3 (SD 3.9)	0.241

Variables are presented as mean and standard deviation (SD).
CMHC, corpuscular mean haemoglobin concentration; hs-CRP, high-sensitivity C-reactive protein; IMT, inspiratory muscle training.

established). The diaphragm occludes the inspiratory circuit during expiration. The expiratory chamber is located at the opposite end of the central chamber and has a C-steel element coupled to a compression screw to establish resistance to expiratory flow, and is kept closed during inspiration. The system calibration shows that both inspiratory and expiratory pressures increase linearly with a function of: $y = 9.31x + 25.9$ cmH_2O (inspiratory) and $y = 11.89x + 4.98$ cmH_2O (expiratory), where 'x' is the number of full turns of the compression or retraction screws, respectively. These coupled mechanisms in two chambers in a single device allow both simultaneous and sequential realization of dual training (inspiratory and expiratory), which has given its name to the valve itself. The Orygen-Dual valve® is a relatively cheap, portable, and easy to use piece of equipment that provides workloads up to 70 cmH_2O.

Regarding other available devices, most studies use the Threshold-IMT® to obtain loads of 7–41 cmH_2O. High-intensity devices include the Power Breathe® (Southam, UK) and the Trainair® (Project Electronics Ltd, London, UK) which consists of an electronic pressure manometer interfaced with a computer running purpose-designed software. Scientific evidence has shown that both high- and low-intensity training are effective in achieving improvements in RespM strength.[10,11] The hi-IMT achieves this result in a shorter time, which is an advantage for

improving the efficiency of rehabilitation programmes within the public health system. Secondly, the training scheme proposed by our group allows hi-IMT supervised by a therapist once a week during the first month, with further self-administered training, so that it does not require a large investment in equipment or staff. However, individual patient evaluation must be conducted to determine, in each case, the most appropriate and better tolerated type of training. Further studies should be carried out to better define the optimal training schedule in CHF patients.

Some limitations of this study should be noted. It is well known that rehabilitation samples tend to be pre-selected for the patients' potential to follow a rehabilitation programme. Therefore, there is an initial bias due to the fact that not all CHF patients are referred to an outpatient cardiopulmonary rehabilitation programme. Although participants did not mention previous history of chronic respiratory diseases, 14 subjects (63.6%) presented a mild impairment in their spirometry, but none of them presented respiratory symptoms nor followed any specific treatment. COPD is a prevalent co-morbidity frequently observed in cardiopulmonary rehabilitation settings, and this is why we decided not to exclude patients with this condition.

In a recent meta-analysis,[11] dyspnoea was measured using the Borg Rating of Perceived Exertion or the MMRC dyspnoea scale. The effect size for the reduction of dyspnoea after IMT was large, ranging from −0.68 to −3.28, but not all studies reported this outcome. Although patients in our study reported overall improvement in dyspnoea perception, changes were fewer than expected in the intervention group. In our opinion, the relative insensitivity to change over short periods of the MMRC dyspnoea scale is responsible for this.

In this sample, no changes in the scores of the MLHFQ and SF-36 were observed. This finding might suggest that this 4-week hi-IMT training has no impact on symptoms and/or quality of life since it was not associated with any kind of discomfort. Nevertheless, the possibility that these questionnaires are not sensitive enough to detect changes resulting from training must be considered. Moreover, this is a small sample of 22 selected patients with relatively good baseline MLHFQ scores; therefore, it would be interesting to repeat this analysis in a group of more symptomatic patients as well as studying the impact on daily activities.

In summary, this trial concludes that a 4-week hi-IMT with the Orygen-Dual Valve® proves to be an effective, feasible, and safe tool to improve weakness (strength) and fatigue (endurance) of the inspiratory muscles in mild to moderate CHF. The hi-IMT manages to achieve results in a very short period, which make it an interesting and efficient therapeutic strategy.

Conflict of interest: J.G. and M.O.-L. are the inventors of the trainer device used in this clinical trial. E.M., A.-L.R.-S., and M.O.-L. are co-funders of LungOn SL, distributors of the Orygen Dual Valve. All other authors have no conflict of interest to declare.

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