Inspiratory Muscle Training and Functional Electrical Stimulation for Treatment of Heart Failure With Preserved Ejection Fraction: Rationale and Study Design of a Prospective Randomized Controlled Trial

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) has become the most prevalent form of heart failure in developed countries. Regrettably, there is no evidence-based effective therapy for HFpEF. We seek to evaluate whether inspiratory muscle training, functional electrical stimulation, or a combination of both can improve exercise capacity as well as left ventricular diastolic function, biomarker profile, quality of life (QoL), and prognosis in patients with HFpEF. A total of 60 stable symptomatic patients with HFpEF (New York Heart Association class II–III/IV) will be randomized (1:1:1:1) to receive a 12-week program of inspiratory muscle training, functional electrical stimulation, a combination of both, or standard care alone. The primary endpoint of the study is change in peak exercise oxygen uptake; secondary endpoints are changes in QoL, echocardiogram parameters, and prognostic biomarkers. As of March 21, 2016, thirty patients have been enrolled. Searching for novel therapies that improve QoL and autonomy in the elderly with HFpEF has become a health care priority. We believe that this study will add important knowledge about the potential utility of 2 simple and feasible physical interventions for the treatment of advanced HFpEF.

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Additional Supporting Information may be found in the online version of this article.

Introduction

Heart failure (HF) constitutes a major cause of morbidity and mortality worldwide.¹ More than 50% of patients with HF have preserved left ventricular ejection fraction (HFpEF), which is especially common in the elderly, women, and highly comorbid patients.^{2,3} Although the associated morbidity and mortality seems to be equal to or even greater than that associated with HF with reduced ejection fraction (HFrEF),^{4–6} contemporary evidence-based therapy has failed to demonstrate a substantial improvement in prognosis and symptoms in HFpEF.^{7–13}

Along this line, current evidence in HFrEF supports the beneficial effect of physical therapies on soft endpoints, such as exercise capacity and quality of life (QoL), as well as major clinical outcomes, including HF-related readmissions and the composite of cardiovascular death and HF hospitalization.^{14–16} Regrettably, the evidence endorsing the feasibility and clinical utility of physical therapies in HFpEF is small or even absent, particularly in patients with advanced disease.¹⁷ The purpose of this randomized controlled trial is to evaluate the effect of inspiratory muscle

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Previous history of symptomatic HF of NYHA functional class $\geq$ II	Could not perform a valid baseline exercise test
Normal LVEF: (1) LVEF >0.50 by Simpson method; (2) end-diastolic diameter <60 mm or end-diastolic volume <97 mL/m ²	Significant primary moderate to severe valvular disease
Structural heart disease according to ESC criteria ¹⁸ : (1) LVH/LA enlargement and/or (2) diastolic dysfunction estimated by 2D echocardiography	ACS or cardiac surgery within the previous 3 months; signs or symptoms of ischemia, ventricular or uncontrolled arrhythmias, or uncontrolled BP during cardiopulmonary exercise testing
Previous admission for acute HF	Significant primary pulmonary disease, including PAH, chronic thromboembolic pulmonary disease, or COPD
Clinical stability, without hospital admissions in past 3 months	Any other comorbidity with life expectancy <1 year
Abbreviations: ACS, acute coronary syndrome; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ESC, European Society of Cardiology; HF, heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.	

training (IMT) and functional muscular electrical stimulation (FES) on functional capacity and other surrogates of severity in patients with moderate to severe HFpEF.

The primary endpoint of the study is 3-month and 6-month absolute change in peak oxygen uptake (peak VO₂). The secondary endpoints are (1) 3-month and 6-month absolute changes in echocardiographic parameters (E/E' ratio and left atrial volume index); (2) 3-month and 6-month absolute change in QoL, assessed by the Minnesota Living With Heart Failure Questionnaire (MLHF); and (3) 3-month and 6-month absolute changes in prognostic biomarkers (N-terminal pro-B-type natriuretic peptide [NT-proBNP] and serum carbohydrate antigen 125 [CA125]).

Safety endpoints include number of episodes of hospitalization for acute HF, number of episodes of worsening HF not requiring hospitalization, and mortality rate at 6 months.

Methods

Study Design

This study is designed as a prospective, randomized, controlled, 4-arm efficacy trial. The population includes patients with the diagnosis of HFpEF according to criteria of the European Society of Cardiology (ESC)¹⁸ and New York Heart Association (NYHA) functional class II–III/IV. A computer-generated randomization sequence previously designed will be used to allocate participants (in a 1:1:1:1 ratio) to receive either (1) a home-based 12-week program of IMT; (2) a 12-week program of FES of the lower-limb muscles; (3) a combination of IMT and FES (IMT + FES); or (4) standard treatment (ST) alone. The study will be conducted in a single center in Spain. Discounting the time due to staggered entry, the total duration of a patient's follow-up will be 6 months from first to last visit. All patients will provide signed informed consent before randomization. The protocol already has been approved by the research ethics committee of our center, in accordance with the principles of the Declaration of Helsinki and national regulations. No specific substudies are planned.

Population Sampling

Candidate patients will be selected from the HF outpatient clinics of the Hospital Clínico Universitario de Valencia. All

patients will be given standard medical treatment, advice on the general recommendation of regular aerobic exercise according to current guidelines,¹⁸ and a HF educational program. All patients will be instructed to self-report regular physical activity on a diary card. Inclusion and exclusion criteria are summarized in Table 1.

Patient enrollment began in September 2015. As of March 21, 2016, thirty patients had been enrolled in the study. Baseline characteristics of enrolled patients are summarized in Table 2.

Interventions

After reviewing the inclusion/exclusion criteria and signing the informed-consent form, participants will undergo a comprehensive medical history, physical examination, anthropometry, and examination tests performed by 2 cardiologists blinded to the patients' allocation groups. The examination tests will include electrocardiography (ECG), echocardiography, cardiopulmonary exercise testing, 6-minute walking distance (6MWD), inspiratory muscle function testing, QoL assessment by the MLHF, and blood samples for a panel of baseline biomarkers. Finally, patients will be randomized in a 1:1:1:1 ratio to one of the study interventions for a period of 12 weeks: the home-based IMT program, the FES program, the IMT + FES combination, or ST alone.

Inspiratory Muscle Training Arm: Patients allocated to the IMT arm will be instructed to train at home twice daily, for 20 minutes each session, using a Threshold inspiratory muscle trainer (Respironics Inc., Parsippany, NJ). They will be instructed by a physiotherapist responsible for training intervention and educated to maintain diaphragmatic breathing during the training period. The subjects will start breathing at a resistance equal to 25% to 30% of their maximal inspiratory mouth pressure (MIP) for 1 week. The respiratory therapist will examine the patients at weekly intervals by checking the diary card and measuring the MIP each time. The resistance will be modified each session according to the 25% to 30% of their MIP measured.

Functional Muscular Electrical Stimulation Arm: Patients allocated to the FES arm will be trained in a FES program of both legs by a physiotherapist responsible for the training

Table 2. Baseline Characteristics of Enrolled Patients

Characteristic	Enrolled Patients, N = 30
Demographic and medical history	
Age, y	77 (68 ± 80)
Female sex	18 (60)
Body weight, kg	81 (70 ± 87)
Body surface area, m ²	1.87 (1.71 ± 2.0)
HTN	26 (87)
Dyslipidemia	22 (73.3)
DM	9 (30)
Insulin-dependent DM	5 (16.5)
Ischemic heart disease	12 (40)
Baseline NYHA class III/IV	15 (50)
Past smoker	7 (23.3)
AF	11 (39.3)
Pacemaker	2 (7.4)
Vital signs	
HR, bpm	71 (60 ± 80)
SBP, mm Hg	131 (122 ± 142)
DBP, mm Hg	71 (65 ± 76)
Laboratory	
Hgb, g/dL	13 (11.8 ± 14)
eGFR, mL/min/m ²	56.9 (41.7 ± 77.6)
NT-proBNP, pg/mL	697 (282 ± 1712)
CA125, U/mL	13 (8 ± 19)
Echocardiography	
Sodium, mEq/L	141 (140 ± 141)
LVEF, %	67 (63 ± 76)
LAVI, mm/m ²	46 (38 ± 59)
LVEDD, mm	50 (46 ± 55)
LVMI, g/m ²	128 (114 ± 157)
e', septal, cm/s	5.4 (4.5 ± 6.5)
E/e' ratio	15.5 (12 ± 23.6)
PASP, mm Hg ^a	43 (35 ± 49)
Medication	
β-Blockers	24 (80)
Furosemide	23 (77)
Thiazide	4 (13)
Spironolactone	5 (17)

Table 2. Continued

Characteristic	Enrolled Patients, N = 30
ACEI	4 (13)
ARB	13 (43)
Statins	20 (67)
OAC	14 (46)
Nitrates	6 (20)
Digoxin	2 (7)
Exercise performance, MIP, and QoL	
Peak VO ₂ , mL/min/kg	9.5 (8 ± 12)
VE/VCO ₂ slope	36 (33 ± 42)
6MWD, m	262 (220 ± 358)
MIP, cm H ₂ O	55 (41 ± 67)
MLHF score	34 (23 ± 52)

Abbreviations: 6MWD, 6-minute walking distance; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CA125, carbohydrate antigen 125; DBP, diastolic blood pressure; DM, diabetes mellitus; e', early diastolic velocity of mitral annulus; E, mitral inflow velocity; eGFR, estimated glomerular filtration rate using MDRD formula; Hgb, hemoglobin; HR, heart rate; HTN, hypertension; IQR, interquartile range; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MDRD, Modification of Diet in Renal Disease; mEq, metabolic equivalents; MIP, maximal inspiratory mouth pressure; MLHF, Minnesota Living With Heart Failure questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulants; PASP, pulmonary artery systolic pressure; peak VO₂, peak exercise pulmonary oxygen uptake; QoL, quality of life; SBP, systolic blood pressure; VE/VCO₂ slope, relationship between minute ventilation and the rate of CO₂ elimination.

Data are presented as n (%) or median ± IQR.

^aData available in 25 patients.

intervention for 45 minutes a day, 2 days per week, for the total of 12 weeks. Eight adhesive electrodes will be positioned on the skin over the quadriceps muscles (5 cm below the inguinal fold and 3 cm above the upper patella border) and gastrocnemius muscles (2 cm below the knee joint and just over the proximal end of the Achilles tendon) of both legs. The stimulator (Rehab 400; CefarCompex, Barcelona, Spain) will be configured to deliver a biphasic current of low frequency (10–50 Hz) for 5 seconds, followed by a 5-second rest. The intensity of the stimulation will be adjusted to achieve a visible muscle contraction without discomfort.

Inspiratory Muscle Training + Functional Electrical Stimulation Arm: Patients allocated to the IMT + FES arm will receive concurrent IMT and FES training provided by a physiotherapist responsible for the training intervention during the 12 weeks.

Standard Treatment Arm: Patients allocated to the ST arm will not receive IMT or FES. They will be checked each week by a physiotherapist responsible for training intervention who will measure their MIP.

Figure 1. Flowchart for patient inclusion and follow-up. Abbreviations: AHF, acute heart failure; CPX, cardiopulmonary exercise testing; ECG, electrocardiogram; FES, functional electrical stimulation; HF, heart failure; IMT, inspiratory muscle training; IMT + FES, combination of inspiratory muscle training and functional electrical stimulation; MIP, maximal inspiratory pressure; QoL, quality of life.

All patients will be clinically evaluated by 2 cardiologists blinded to the patients' allocation groups in an HF unit at 12 weeks and 6 months after randomization. Additional visits will be permitted according to patient clinical status. Each visit's evaluation includes medical history, physical examination, anthropometry, and functional and QoL assessment tests (ECG, cardiopulmonary exercise testing, 6MWD, inspiratory muscle function test, MLHF questionnaire, and blood tests). The study flowchart is summarized in the Figure 1.

Procedures

Cardiopulmonary Exercise Testing: Maximal functional capacity will be evaluated with incremental and symptom-limited cardiopulmonary exercise testing (MetaMax 3B; Cortex, Leipzig, Germany) on a bicycle ergometer, beginning with a workload of 10 W and increasing stepwise at 10-W increments every 1 minute. During exercise, patients will be continuously monitored with 12-lead ECG and blood pressure measurements every 2 minutes. Gas-exchange data and cardiopulmonary variables will be averaged every 10 seconds. Peak VO_2 will be considered the highest value of VO_2 during the last 20 seconds of exercise. The VE/VCO_2 slope will be determined by measuring the slope across the entire course of exercise.¹⁹ Each subject will undergo 3 tests, at baseline, 12 weeks, and 6 months (Figure 1).

Six-Minute Walking Distance: Patients will be instructed to cover the maximum distance possible in 6 minutes, at a self-graded walking speed, pausing to rest when needed.²⁰ Each subject will undergo 4 tests (2 at baseline, 1 at 12 weeks, and 1 at 6 months; Figure 1). The goal of the first will be to allow the patient to become familiar with the test.

Inspiratory Muscle Training: Inspiratory muscle training will be obtained using a handheld respiratory mouth

pressure meter (PM-15 electronic manometer; ELKA-Elektronik GmbH, Lüdenschied, Germany). With a nose clip on, patients will be instructed to breathe through the mouthpiece during inspiration.²¹ The MIP values will be obtained in standing position by inspiration from residual volume. At each visit (Figure 1), the MIP will be repeated within 1-minute intervals until 3 technically satisfactory and reproducible measurements are obtained (variation of -10%). The MIP will be calculated as the median of the 3 reproducible measurements.

Quadriceps and Gastrocnemius Muscle Strength Test: Maximum voluntary force of the quadriceps and gastrocnemius muscles will be measured using the Lafayette MMT dynamometer (Lafayette Instrument Co., Lafayette, IN). Each subject will undergo 3 tests (at baseline, 12 weeks, and 6 months; Figure 1).

Echocardiography: Doppler echocardiogram examinations will be performed under resting conditions using 2D echocardiography (iE33 ultrasound system; Philips, Amsterdam, Netherlands). Each subject will undergo 3 examinations (at baseline, 12 weeks, and 6 months; Figure 1). All parameters, including tissue Doppler parameters, will be measured according to current guidelines of the European Society of Echocardiography.²²

Health-Related Quality of Life: The MLHF questionnaire²³ will be used to assess the impact of the intervention on QoL. Each subject will undergo 3 examinations (at baseline, 12 weeks, and 6 months; Figure 1). Overall scores will be analyzed.

Serum Biomarkers: Three blood samples will be collected under standardized conditions (at baseline, 12 weeks, and 6 months) for biomarker profiling. Prognostic biomarkers in HF (NT-proBNP and CA125) will be analyzed.²⁴ The NT-proBNP will be measured by electrochemiluminescence

immunoassay; CA125 will be measured by the Elecsys CA 125 II assay (Roche Diagnostics, Pleasanton, CA).

Sample-Size Calculation

The null hypothesis of the study is that, among the 4 intervention arms, the mean peak VO_2 absolute differences from baseline are similar at 3 and 6 months. Sample-size determination for this study assumes 2-sided testing at the 0.05 significance α level. Because this is a randomized clinical trial, we assume no differences in peak VO_2 at baseline among the 4 groups. The effect size in peak VO_2 associated with IMT was based on a pilot study conducted by our group; in this study, IMT was associated with a significant increase of mean of peak VO_2 of 3 mL/kg/min (from 9 ± 2.5 mL/kg/min to 12 ± 2.5 mL/kg/min) at 12 weeks.²¹ In addition, the correlation coefficient between pre and post measures was 0.80 ($P < 0.001$). With these data in mind, we assume a mean change of 3.0 mL/kg/min and a common SD of 3.0. The effect size in FES was based on a recent study of HFpEF where FES was associated with a significant increase of mean of peak VO_2 of 2 mL/kg/min (from 9.6 ± 3.5 mL/kg/min to 11.6 ± 2.8 mL/kg/min) at 10 weeks.²⁵ Due to lack of any source on the effect of FES in HFpEF, we speculate a similar increase in peak VO_2 for patients with HFpEF. Therefore, we assume a mean change of 2.0 mL/kg/min and a common SD of 3.0. For patients allocated to both interventions (IMT + FES), and assuming a synergistic effect of both therapies, we postulate an effect size for both interventions of about 4.0 mL/kg/min (± 3.0). Assuming an allocation ratio of 1:1:1:1, a total of 48 patients (12 patients per group) would provide 80% power at an α significance level < 0.05 . Assuming 20% in withdrawals and/or losses to follow-up, a total of 15 patients per arm (60 patients) will be enrolled. The software used for the sample-size calculation was GLIMPSE (<http://samplesizeshop.org>).

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD or median (interquartile range) as appropriate; categorical variables are given as numbers and percentages. All statistical comparisons will be made under the intention-to-treat principle. A repeated-measures analysis of variance (ANOVA) will be used for the comparisons of continuous outcomes among the 4 intervention arms. The interaction group $\times$ time points will be tested to unveil any effect of time (3 and 6 months) on the magnitude of the intervention. Only in the event of imbalance in baseline characteristics will repeated-measures ANCOVA be used. A 2-sided P value < 0.05 will be considered statistically significant for all analyses. All analyses will be performed with Stata version 14.1 (StataCorp LP, College Station, TX).

Discussion

Background and Rationale

Heart failure with preserved ejection fraction is a complex clinical syndrome characterized by exercise intolerance, markedly reduced functional capacity,²⁶ normal left ventricular ejection fraction ($> 50\%$) and, in most

cases, some evidence of diastolic dysfunction.¹⁸ Despite being a contemporary challenge, the pathophysiological mechanisms of impaired exercise capacity in these patients are not yet entirely clarified.²⁷

From a theoretical point of view, the mechanisms underlying exercise intolerance are divided into cardiac and noncardiac conditions. Among cardiac mechanisms, recent studies have mainly focused on diastolic dysfunction, right ventricular failure, and chronotropic incompetence, among others.²⁸ Regarding peripheral conditions in advanced HF, some studies have reported abnormalities in endothelial function²⁹ and changes in skeletal muscle structure and function,³⁰ such as abnormal skeletal muscle oxidative capacity and mitochondrial content.^{31,32} These peripheral muscle abnormalities would lead to a dysregulation of the cardiovascular and respiratory function during exercise due to an exaggerated exercise pressor reflex originated in skeletal muscle.³³ Along this same line, contemporary evidence has shown that weakness and fatigue of the diaphragm muscle may impact the ability of HF patients to sustain increased ventilation seen at rest or during exercise, affecting the sensation of dyspnea.³⁴

From an epidemiological perspective, patients with HFpEF are usually older, predominantly female, and have a high prevalence of comorbid conditions such as atrial fibrillation, obesity, hypertension, and renal failure,^{2,3} which in the end contribute to reduced exercise tolerance and promote inactivity deconditioning and poor self-sufficiency. In this regard, patients with advanced HFpEF do not adapt easily to conventional exercise training programs because they are unable to perform low to moderate levels of physical exertion. Moreover, data from current HF registries revealed that this profile of patient is less likely to receive referral to cardiac rehabilitation programs after HF admission.³⁵

Physical therapies such as IMT and FES appear to be suitable alternatives to conventional exercise training programs^{35,36} in patients with advanced HFpEF for several reasons: (1) they could be easily administered by the patients themselves as a home-based treatment,³⁶ (2) they could enhance patient adherence to treatment recommendations,³⁷ and (3) they could improve functional capacity and QoL in HFpEF patients. In fact, previous small studies have reported a positive effect of IMT and FES in improving functional capacity and QoL in patients with advanced HFpEF.^{21,38}

Biological Plausibility

Among the potential physiological mechanisms underlying the effects of IMT and FES on HF, the following particularly stand out: (1) delay in the development of diaphragmatic fatigue, which leads to a reduction in the recruitment of accessory respiratory muscles and, ultimately, to an improvement in ventilatory efficiency^{21,39}; (2) attenuation of the exercise pressor reflex originating in skeletal muscle³³; (3) augmentation in muscle strength and endurance^{36,40}; (4) improvement in the oxidative capacity²⁵; and (5) amelioration of endothelial function.³⁸ Likewise, similar mechanisms have been proposed on improvement of exercise performance after IMT or FES training in healthy people.³⁹

Feasibility and Future Implications

Both IMT and FES seem to be safe and feasible approaches that could be implemented as a nonpharmacological therapy for management of HFpEF patients.^{21,38} Both are simple, low-cost, and harmless interventions that do not require special logistics or infrastructure to be implemented. Worth noting is the fact that patients could follow home-based exercise training after short and simple instruction. Thus, IMT and FES could represent an alternative form of exercise for advanced HFpEF patients who are unable or unwilling to participate in conventional exercise sessions or cardiac rehabilitation programs.

Conclusion

To date, evidence about the benefit of different exercise training modalities in HFpEF is scarce. In this 4-arm randomized controlled trial, we aim to evaluate the role of 2 simple physical therapies, IMT and FES, for the treatment of advanced HFpEF.

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