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ORIGINAL ARTICLE

EaRly-start ExerciSe training afTer acute hemodynAmic decompensation in patients with chRonic hearT failure (RE-START)

A multicenter, randomized, controlled trial on short-term feasibility and impact on functional capacity, symptoms and neurohumoral activation

Allenamento fisico ad avvio precoce dopo instabilizzazione emodinamica nei pazienti con scompenso cardiaco cronico

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ABSTRACT: ***eaRly-start ExerciSe training afTer acute hemodynAmic decompensation in patients with chRonic hearT failure (RE-START). A. Mezzani, F. Cacciatore, R. Catanzaro, A. Gualco, D. Guzzetti, D. Leosco, M. Monelli, F. Tarro Genta, P. Totaro, E. Traversi, E. Zanelli, P. Giannuzzi.***

RE-START is a multicenter, randomized, prospective, open, controlled trial aiming to evaluate the feasibility and the short- and medium-term effects of an early-start AET program on functional capacity, symptoms and neurohormonal activation in chronic heart failure (CHF) patients with recent acute hemodynamic decompensation. Study endpoints will be: 1) safety of and compliance to AET; 2) effects of AET on i) functional capacity, ii) patient-reported symptoms and iii) AET-induced changes in beta-adrenergic receptor signaling and circulating angiogenetic and inflammatory markers. Two-hundred patients, randomized 1:1 to training (TR) or control (C), will be enrolled. Inclusion criteria: 1) history of systolic CHF for at least 6 months, with ongoing acute decompensation with need of intravenous diuretic and/or vasodilator therapy; 2) proBNP >1000 pg/ml at admission. Exclusion criteria: 1) ongoing cardiogenic shock; 2) need of intravenous inotropic therapy; 3) creatinine >2.5 mg/dl at admission. After a 72-hour run-in period, TR will undergo the following 12-day early-start AET protocol: days 1-2: active/passive mobilization (2 sessions/day, each 30 minutes duration); days 3-4: as days 1-2 + unloaded bedside cycle ergometer (3 sessions/day, each 5-10 minutes duration); days 5-8: as days 1-2 + unloaded bedside cycle ergometer (3 sessions/day, each 15-20 minutes duration); days 9-12: as days 1-2 + bedside cycle ergometer at 10-20 W (3 sessions/day, each 15-20 minutes duration). During the same period, C will undergo the same activity protocol as in days 1-2 for TR. All patients will undergo a 6-minWT at day 1, 6, 12 and 30 and echocardiogram, patient-reported symptoms on 7-point Likert scale and measurement of lymphocyte G protein coupled receptor kinase, VEGF, angiopoietin, TNF alfa, IL-1, IL-6 and eNOS levels at day 1, 12 and 30.

Key words: chronic heart failure, hemodynamic decompensation, physical training, functional capacity, neurohumoral activation.

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Introduction

Chronic heart failure (CHF) is a disabling syndrome that affects close to 7 million Europeans and 5 million North Americans. Hospitalization rates have progressively increased over time, and the annual incidence reaches 2% to 3% in patients older than 85 years. In Italy, there were nearly 185000 hospital admissions for decompensated CHF in 2001, and CHF costs represent 1.4% of yearly health care expenditures. An ideal agent for treating acutely decompensated CHF patients should reduce left ventricular filling pressures, improve symptoms and renal function, preserve myocardial tissue, reduce neurohormonal levels, and not be arrhythmic or induce symptomatic hypotension (1). Interestingly, aerobic exercise training (AET) does have several such characteristics. AET is a well-established non-pharmacologic treatment of stable CHF patients, which has been shown to determine favorable central and peripheral adaptations, reducing the neurohormonal activation typical of the CHF pathophysiological picture and hence improving functional capacity and quality of life (2-4). The efficacy of AET in CHF has been evaluated in patients in stable New York Heart Association class I to III, but no data at all are available in patients with recent acute decompensation, i.e. a severely symptomatic population with poor functional capacity, maximal neurohormonal activation and bad prognosis. In this regard, preliminary data in normal subjects show an early increase of flow-mediated vasodilation (i.e. one of the main determinants of total peripheral resistance and left ventricular afterload) to AET, which becomes evident and statistically significant after three days of training (5). Similarly, a favorable adaptation of sympatho-vagal balance (i.e. an increased parasympathetic tone) as early as one day after AET start has been demonstrated (6).

Objective

RE-START aims at evaluating the feasibility and the short- and medium-term effects of an early-start AET program on functional capacity, neurohormonal activation and quality of life in CHF patients with recent acute decompensation, a population usually excluded by formal training programs. Our working hypothesis is that AET should impact the pathophysiology of recently decompensated CHF, by favorably modulating the increase of total peripheral resistance and the sympathetic overactivation typical of this syndrome. In addition, AET should induce a more rapid functional recovery of patients after a period of obligatory bed rest due to hemodynamic instability. Overall, these effects are expected to exert a favorable clinical effect, possibly reducing the short- and medium-term rate of rehospitalizations of trained patients.

Methods

Study type and endpoints

RE-START is a multicenter, randomized, prospective, open and controlled trial. All Cardiac Rehabilitation Divisions of the Salvatore Maugeri Foundation, IRCCS, will participate in the trial. The primary endpoints evaluated in the study will be: 1) safety of and compliance to AET; 2) effects of AET on i) functional capacity, evaluated as distance walked at 6-min walking test (6-minWT) and ii) patient-reported symptoms, evaluated by the 7-point Likert scale. Secondary outcome will be evaluation of AET-induced changes in beta-adrenergic receptor signaling and circulating angiogenetic and inflammatory markers.

Study population

Statistical power calculation for repeated-measures ANOVA indicates that, assuming a 40% increase of distance walked at 6-minWT in the training group after early-start AET, 200 patients, randomized 1:1 to training or control, will have to be enrolled in the study to detect a significant time x group interaction (power = 0.80, alfa = 0.05).

Inclusion criteria will be as follows: 1) history of CHF for at least 6 months, with ongoing acute decompensation defined as onset or worsening of heart failure signs and/or symptoms during the previous 15 days with need of intravenous diuretic and/or vasodilator therapy; 2) age >18 years; 3) left ventricular ejection fraction <40%; 4) proBNP >1000 pg/ml at admission. Exclusion criteria will be: 1) ongoing cardiogenic shock; 2) need of intravenous inotropic therapy; 3) acute coronary syndrome during the preceding 3 months; 4) clinical and/or instrumental evidence of myocardial ischemia and/or life-threatening arrhythmias; 5) previous cardiac valve surgery; 6) creatinine >2.5 mg/dl at admission; 7) severe comorbidities limiting functional capacity.

Intervention

All patients with CHF admitted in the participating Centers for acute hemodynamic decompensation will be screened for recruitment in the study. After 72-hour of pharmacologic treatment, eligible patients will be randomized 1:1 to training (TR) or control (C). TR will undergo the following 12-day early-start AET protocol: days 1-2: active/passive mobilization (2 sessions/day, each 30 minutes duration); days 3-4: as days 1-2 + unloaded bedside cycle ergometer (3 sessions/day, each 5-10 minutes duration); days 5-8: as days 1-2 + unloaded bedside cycle ergometer (3 sessions/day, each 15-20 minutes duration); days 9-12: as days 1-2 + bedside cycle ergometer at 10-20 W (3 sessions/day, each 15-20 minutes duration). During the same period, C will undergo only the same activity protocol as in days 1-2 for TR. In addition, when possible according to their clinical conditions, both TR and C will undergo one assisted ambulation session of 15-20 minutes per day.

As AET has never been tested to date in recently decompensated CHF patients, assessment of treatment feasibility (with a special attention to safety) is a primary outcome of the study. In any case, as the functional capacity of recruited patients is expected to be severely reduced, a low-intensity training stimulus should be sufficient to obtain a training effect, which should reduce to the minimum possible exercise-related risks. Short-term safety of and compliance to the early-start AET

program will be evaluated by monitoring adverse events, number of training sessions performed, total training time and percent of prescribed sessions time carried out. All patients will undergo a 6-minWT at day 1, 6, 12 and 30. A standardized procedure will be followed, with walks taking place at approximately the same time of the day, at least 2 hours after a meal. Patients will be asked to walk from one end to the other of a 20 m walking track, covering as much ground as possible in 6 minutes. Patients will be allowed to rest whenever required and to stop if angina, dyspnea, or musculoskeletal pain occur or in case of attainment of hemoglobin oxygen saturation levels <85%. If a patient will not be able to walk, a distance equal to 0 meters will be recorded. In addition, the following evaluations will be carried out at day 1, 12 and 30: 1) echocardiogram; 2) patient-reported symptoms on 7-point Likert scale; 3) measurement of lymphocyte G protein coupled receptor kinase, VEGF, angiopoietin, TNF alfa, IL-1, IL-6 and eNOS levels. A telephonic follow-up aiming at recording clinical events possibly occurred after the 30-day evaluation will be carried out at 3 and 6 months after randomization.

Significance and innovation

This study can provide information about both feasibility and efficacy of AET as a new and low-cost tool for the management of recently decompensated CHF patients. If proven feasible end efficient early after acute decompensation of CHF, i.e. during a period never taken into consideration to date for formal exercise training in this patient population, AET may enter the therapeutic armamentarium of recently decompensated CHF beside traditional pharmacologic treatments.

Riassunto

RE-START è uno studio multicentrico, randomizzato, prospettico, in aperto e controllato, che mira a valutare la fattibilità e gli effetti a breve e medio termine di un programma di training aerobico (TA) ad avvio precoce su capacità funzionale, sintomi e attivazione neuro-ormonale nei pazienti con scompenso cardiaco cronico (SCC) e recente instabilizzazione emodinamica. Gli endpoint primari dello studio saranno: 1) sicurezza del TA e compliance ad esso da parte dei pazienti; 2) effetti del TA su capacità funzionale, valutata come distanza percorsa al walking test di 6 minuti e sintomi, valutati mediante 7-point Likert scale. Endpoint secondario sarà la valutazione delle modificazioni indotte dal TA sul signaling beta-recettoriale e sui livelli di marker angiogenetici e infiammatori circolanti. Saranno arruolati 200 pazienti, con storia di scompenso sistolico da almeno 6 mesi e instabilizzazione acuta in atto (definita come esordio o peggioramento di segni e/o sintomi di scompenso cardiaco durante i 15 giorni precedenti), con necessità di terapia diuretica e/o vasodilatatrice e.v. Principali criteri d'esclusione saranno: 1) shock cardiogeno in atto; 2) necessità di terapia con inotropi e.v.; 3) creatinina >2.5 mg/dl; 4) presenza di severa/e comorbidità limitante/i la capacità funzionale del paziente. Dopo 72 ore di trattamento farmacologico, i pazienti eleggibili saranno randomizzati 1:1 a TA o controllo (C). Il gruppo TA sarà sottoposto a un protocollo di training della durata di 12 giorni, che prevede sedute di cicloergometro da camera a carichi crescenti e di mobilizzazione assistita. Il gruppo C eseguirà solo mobilizzazione assistita. Tutti i pazienti saranno sottoposti a walking test di 6 minuti al giorno 1, 6, 12 e 30. Inoltre, le seguenti valutazioni saranno eseguite ai giorni 1, 12 e 30: ecocardiogramma; sintomi riportati dal paziente secondo la 7-point Likert scale; livelli ematici di lymphocyte G protein-coupled receptor kinase-2, VEGF, angiopoietina, TNF-alfa, IL-1 e IL-6.

Lo studio fornirà informazioni utili per valutare adeguatamente la sicurezza del TA ad avvio precoce e i suoi effetti a breve e medio termine su capacità lavorativa e sintomi nei pazienti con SCC recentemente instabilizzato. Inoltre, i risultati di questo studio permetteranno di valutare gli effetti del TA ad avvio precoce su signaling beta-recettoriale e livelli di marker angiogenetici e infiammatori circolanti, ponendo le basi razionali per futuri studi sull'argomento dotati di adeguata potenza statistica.

Parole chiave: scompenso cardiaco, scompenso emodinamico, training fisico, attivazione neuroumorale

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