**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


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 angiogenic 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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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).

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, alpha = 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
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 sostenutamente instabili. Inoltre, i risultati di questo studio permetteranno di valutare gli effetti dell’TA ad avvio precoce su signaling beta-recettoriale e livelli aderenti la 7-point Likert scale; livelli ematici di lymphocyte G protein-coupled receptor kinase-2, VEGF, angioipetina, TNF alfa, IL-1 e IL-6 e 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 and 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

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References

4. Mezzani A, Hamm LF, Jones AM, et al. European Association for Cardiovascular Prevention and Rehabilitation; American Association of Cardiovascular and Pulmonary Rehabilitation; Canadian Association of Cardiac Rehabilitation; European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. Eur J Prev Cardiol 2013; 20: 442-467.