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Original article

Functional outcome in chronic heart failure after exercise training: Possible predictive value of heart rate variability

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ABSTRACT

Background: Controlled exercise training (ET) is a valuable therapeutic addition to pharmacological treatment in most patients with chronic heart failure (CHF), reducing long-term mortality, preventing cardiac remodelling and improving functional capacity. Despite the fact that the mechanism underlying its benefits might be multifactorial, a sustained improvement in autonomic balance is usually attributed as a major effect. Nevertheless, not all eligible subjects show the same response to ET, probably due to several differences in the subpopulations enrolled. We hypothesize that some heart rate variability (HRV) indexes could be valid tools to optimize the selection and follow-up of CHF patients receiving ET intervention.
Methods: Forty patients with CHF and left ventricular ejection fraction (LVEF) $\leq$ 40% under complete evidence-based pharmacological treatment were included; 20 were assigned to a program of controlled ET on a 3-times/week basis during 24 weeks, training group (TG) and 20 received a standard follow-up program, control group (CG). In each patient, full clinical assessments, echocardiography, HRV analysis and 6-minute-walk test were performed at the beginning and the end of the study.
Results: After 24 weeks, patients in the TG showed a significant improvement in LVEF, 6-minute walk test, functional class of symptoms and HRV parasympathetic related indices (HF and rMSSD). Patients in the CG did not exhibit any improvement in the aforementioned indices and experienced more adverse events. Moreover, an initial value of HF $<$ 150 ms^2/Hz or rMSSD $<$ 20 ms predicted better outcomes of the ET program, including improvements in systolic function, the distance walked in 6 minutes, and the functional class of symptoms, along with a reduction in clinical events.
Conclusions: In CHF patients, HRV indexes related to parasympathetic function are valid and clinically useful tools to select and follow-up those candidates that could experience superior functional improvement after ET.

1. Background

Chronic heart failure (CHF) is an important cause of mortality and morbidity worldwide, representing the final pathophysiological stage of several heart diseases [1]. This complex syndrome is characterized by progressive neurohormonal [2] and endothelial dysfunction [3], exercise intolerance [4], poor prognosis and impaired quality of life (QOL) [1].

Exercise training (ET) has demonstrated the following diverse clinical, structural and physiological benefits in patients with CHF: reduction in long-term morbidity and mortality [5], prevention of cardiac remodelling [6], improvement in neurovascular control and functional capacity regardless of age [7], relieving of cardiac symptoms, minimization of re-hospitalizations and improvement in quality of life (QOL) [1,8]. In light of these benefits, all patients with confirmed CHF should be transitioned to a cardiac rehabilitation program consisting of a supervised, multidisciplinary aerobic ET protocol, thereby reinforcing the pharmacological treatment. This intervention remains crucial for the development of life-long preventive healthy habits [9] and all of these

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theoretical and practical benefits [10–12] have been fully recognized by the currently available guidelines [1,13].

The multifactorial mechanisms by which ET might exert its effects in CHF are usually attributed to potential improvements in endothelial function [14], the reduction in inflammation [15], and/or improvements in neuro-hormonal and autonomic imbalance [16,17]. At least theoretically, the improvement of autonomic modulation could play a central role in preventing the chronic progression of heart failure. Unfortunately, not all patients with CHF have been found to experience similar outcomes after ET [5,6,9,12,14] and the differences in response may be attributable to the variable severity of autonomic dysfunction in each subject.

Heart rate variability (HRV) analysis has been established as a noninvasive method for the assessment of autonomic nervous system balance in both healthy and diseased subjects [18]. Moreover, a reduced HRV has a strong prognostic value and has been related to increased mortality in the CHF patient population [19].

We hypothesize that HRV analysis could be a clinically useful tool to facilitate the selection of those CHF patients that will show optimal responses to ET.

2. Methods

2.1. Design and study population

Forty subjects participating in a University Heart Failure Management Program were prospectively included. We performed a detailed anamnesis and complete physical examination in all patients at allocation and during regular follow-up. This cohort met the following criteria: aged 18–80 years, sinus rhythm, New York Heart Association Functional Class (NYHA) I to III, and LVEF $\leq$ 40% as documented by echocardiogram. Exclusion criteria were as follows: a history of stroke; extended anterior myocardial scar; revascularization procedures or recurrent angina within the previous 3 months; orthopaedic impairment; alcohol or drug abuse; implant of pacemaker or cardioverter-defibrillator (AICD); frequently ventricular dysrhythmias, atrial flutter or fibrillation; insulin-dependent diabetes mellitus; severe chronic obstructive pulmonary disease; severe renal dysfunction; comorbid non-cardiac disease limiting short term survival; previous enrolment in an ET program and an increased propensity for noncompliance. Some patients refused participation in the study. Others were dropped because they lived at great distance from the hospital (see Fig. 1). Finally, 40 patients were randomized either to a training group (TG) that performed a supervised Clinical Rehabilitation (CR) program ($n = 20$) or a control group (CG) that received usual care with no changes to their previous physical activity ($n = 20$). All patients received an optimal pharmacologic treatment including diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and beta-adrenergic blocking agents, and all had been stable on medications for at least 2 months before recruitment. During the study, medication regimens were unchanged, except potentially necessary adjustments in diuretic dosages and other temporary medication changes during hospitalization or emergency room visits.

2.2. Individual clinical assessment

We evaluated all patients before randomization and at 24 weeks after enrolment. The following adverse clinical events were recorded: hospitalization; temporary or permanent withdrawal from the study protocol due to persistent atrial or ventricular arrhythmias; worsening of CHF symptoms; myocardial infarction; unstable angina; need for cardiac interventions such as pacemaker, AICD, coronary revascularization or cardiac transplantation; stroke or transient ischemic attack and severe peripheral intermittent claudication or death observed during training or follow-up sessions. Finally, we obtained laboratory analytics both before enrolment and whenever clinically necessary during follow-up (haemoglobin, serum ionic, basic metabolic panel, kidney function [eGFR], liver function testing, lipid and thyroid profiles and Chagas serology).

2.3. Bi-dimensional Doppler echocardiography

The area-length method was measured to obtain biplane left ventricle volumes. LVEF was derived from the standard equation. A single experienced operator performed the measurements in a blinded manner (ATL Apogee CX 200, Advanced Technology Laboratories; Bothell, Wash).

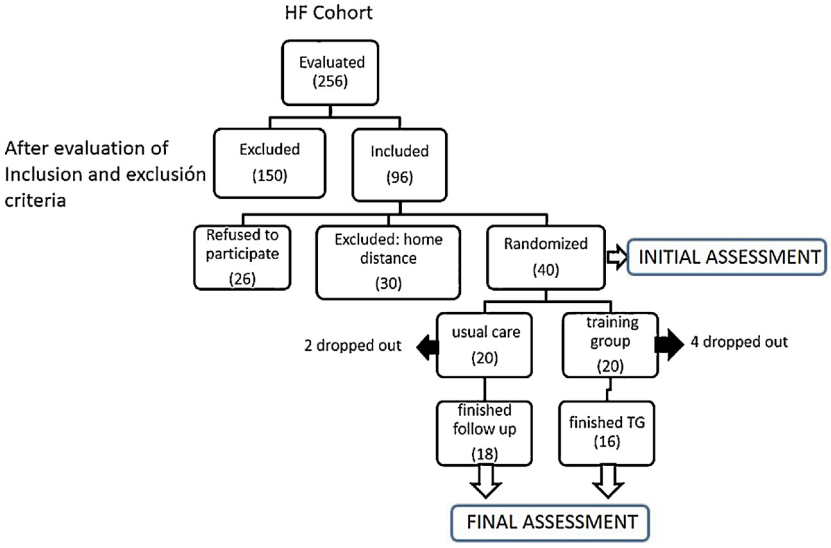

Fig. 1. Diagram of inclusions. In brackets number of patients.

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