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Effects of oral administration of orodispersible levo-carnosine on quality of life and exercise performance in patients with chronic heart failure

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ABSTRACT

Objective: Chronic heart failure (CHF) is characterized by several micronutrient deficits. Amino acid supplementation may have a positive effect on nutritional and metabolic status in patients with CHF. Levo-carnosine (β-alanyl-L-histidine) is expressed at a high concentration in myocardium and muscle. Preliminary studies with L-carnosine in healthy individuals have suggested a potential role in improving exercise performance. To our knowledge, no study has been conducted in patients with heart failure. The aim of this study was to test the oral supplementation of L-carnosine and its effects on quality of life and exercise performance in patients with stable CHF.

Methods: Fifty patients with stable CHF and severe left-ventricular systolic dysfunction on optimal medical therapy were randomized 1:1 to receive oral orodispersible L-carnosine (500 mg OD) or standard treatment. Left-ventricular ejection fraction (LVEF) was measured by echocardiography. Cardiopulmonary stress test, 6-minute walking test (6MWT) and quality-of-life (visual analog scale score and the EuroQOL five dimensions questionnaire [EQ-5D]) were performed at baseline and after 6 mo.

Results: Patients receiving orodispersible L-carnosine had an improvement in 6MWT distance ($P = 0.014$) and in quality-of-life (VAS score) ($P = 0.039$) between baseline and follow-up. Compared with controls, diet supplementation with orodispersible L-carnosine was associated with an improvement in peakVO_2 ($P < 0.0001$), VO_2 at anaerobic threshold, peak exercise workload, 6MWT and quality-of-life assessed by the EQ-5D test and the VAS score.

Conclusion: This study suggests that L-carnosine, added to conventional therapy, has beneficial effects on exercise performance and quality of life in stable CHF. More data are necessary to evaluate its effects on left-ventricular ejection fraction and prognosis in CHF.

Introduction

Heart failure (HF) is characterized by a poor quality of life (QoL), adverse prognosis, and high medical costs. [1] Despite advances in drug therapy and development of new devices to improve patient prognosis, individuals with chronic heart failure (CHF) continue to have an unsatisfactory QoL and reduced exercise tolerance. A hallmark of HF is the reduced ability to perform aerobic exercise. This reduction in functional capacity and exercise tolerance is mediated by several factors including alterations of endothelial and vasodilatory function, abnormalities in skeletal muscle metabolism, and reduction in muscle blood flow during exercise [2]. Improving these parameters remains a major unmet need of HF treatment. Recently, the role of the nutritional status and cachexia in HF has been extensively shown [3–5]. Supplementation of essential amino acids (AAs) has demonstrated promising results with regard to improvement of functional capacity and, in some cases, in left ventricular ejection fraction (LVEF) [6–8]. Although these studies were small in size and heterogeneous with regard to the analyzed molecules, they highlight the need for a deeper knowledge of the

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effects of nutritional support and the correction of macro- and micronutrient deficiencies in patients with HF. The failing heart is exposed to several mechanisms (hemodynamic, neurohormonal, and inflammatory) that contribute to left-ventricular remodeling and to progressive decrease in cardiac function [9]. Recently, it has been proposed that one mechanism of action of these stressors may involve myocytes metabolism (metabolic remodeling) in the failing heart, where AAs become essential for energy production through the Krebs cycle [10,11]. AAs also regulate protein turnover and synthesis, and contribute to the maintenance of hormonal balance by increasing the activity of anabolic hormones. An adequate intake of AAs, therefore, may be of primary importance in patients with HF and AA supplementation may represent a proper treatment, by reverting the alterations of cardiac and systemic metabolism [12].

Carnosine and Levo-carnosine: a potential aid in heart failure patients

Levo-carnosine (L-carnosine) is a cytoplasmic dipeptide (β-alanyl-L-histidine) found in high concentrations in the tissues of longeval mammals, especially in muscles, heart, and brain [13–15]. In vitro studies have shown the ability of carnosine to slow the aging of human fibroblasts [16,17]. Other studies also have demonstrated that the levels of carnosine decrease with age, with a loss of 63%, from 10 to 70 y and carnosine levels in mammals also seem to be directly correlated with life expectancy [18]. Carnosine is considered a multifunctional molecule with antioxidant and antiaging action, and operates as a selective inhibitor of protein glycosylation and protein–protein cross-linking [19–22]. In humans, the carnosinase enzyme degrades circulating carnosine. Recent studies have shown that the diabetic nephropathy is associated with a (CTG)*n* polymorphism in the carnosine dipeptidase-1 gene (*CNDP1*), and patients homozygous for (CTG)5 have a lower risk for developing diabetic nephropathy and also have lower plasma levels of carnosinase [23]. Studies included small groups of patients have demonstrated that oral supplementation of carnosine in subjects with deficient carnosinase enzyme activity increases carnosinemia and could have a protective effect on the kidneys of patients with diabetes by reducing glycation end products and oxidative stress [24,25]. Recently, the administration of carnosine has been associated with a nephroprotective effect in patients with diabetic nephropathy, and nephropathy induced by contrast medium. This favorable effect seems to be related to the reduction of plasma levels of proinflammatory cytokines and the synthesis of fibronectin and type IV collagen [26]. In preliminary studies, carnosine has been shown to induce Na,K-ATPase activation and to prevent membrane depolarization with a potential role in the management of HF and myocardial infarction [27]. In a rabbit model in which HF was induced by infusing doxorubicin, the administration of carnosine reduced cardiotoxic effects compared with rabbits treated with doxorubucine alone [28]. Carnosine plays a key role against the oxidative damage that occurs during exercise under anaerobic conditions. During exercise, there is an increase of lactic acid with a subsequent dissociation into lactate and H+, which reduce pH levels. These protons are usually buffered by the bicarbonate system, which has an acid dissociation constant (pKa) of 6.1, whereas L-carnosine has a pKa value of 6.83, closer to the physiological pH (7.38–7.42) [29]. Carnosine plays an effective buffering action through the imidazole group of histidine, which binds a proton reducing the pH value. The pKa of carnosine is closer to the physiological pH and could be used sooner as a buffer during exercise [30,31]. An increase in muscle L-carnosine levels may improve contractility and reduce fatigue [32]. Other mechanisms include regulatory effects on myocardial calcium levels, an increase in sensitivity of calcium-release channels and of the contractile apparatus, with favorable effects on cardiac contractility and function [33–35]. Thus, carnosine is potentially useful as an addition to the standard treatment of patients with HF. The aim of this study was to test the oral supplementation of L-carnosine and its effects on QoL and exercise performance in patients with stable CHF.

Materials and methods

Study patients

We studied patients with HF of ≥6-mo duration, with New York Heart Association (NYHA) class II or III symptoms, an LVEF ≤45% by echocardiography and the ability to perform a cardiopulmonary exercise test. Patients had to be on optimal medical therapy, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-blockers, if not contraindicated, at stable dose for at least 4 wk before entering the study. Patients were excluded if they had symptoms of myocardial ischemia, acute coronary syndrome, or had a coronary revascularization procedure in the previous 3 mo; implantation of a cardiac resynchronization therapy device in the previous 6 mo or likely to receive implantation in the next 3 mo; history of severe valvular disease; congenital heart disease, acute myocarditis, hypertrophic or restrictive cardiomyopathy; cerebrovascular events or major surgery in previous 6 mo, or any concomitant disease that might adversely impair their exercise performance or their prognosis. The study was conducted in the cardiology unit of University and Civil Hospital of Brescia, Italy. Fifty consecutive patients evaluated in the outpatient unit were included.

We certified that the study complied with the ethical standards of the responsible committee and with the Declaration of Helsinki [36]. The study received ethical approval from the ethics review board of Cardiovascular Department, University of Brescia, and all patients gave their written, informed consent to participate.

Study protocol

This was a prospective, open-label, randomized controlled, parallel group study to assess the effects of administration of 500 mg/d of orodispersible L-carnosine. The 500 mg dose has been tested in a randomized trial and its safety has been proven [37].

Patients eligible for the study were randomized 1:1 to oral orodispersible L-carnosine (500 mg/d, treatment group) or standard treatment (control group). Patients in the treatment group were asked to consume oral L-carnosine every morning before breakfast for 6 mo. All patients were evaluated at baseline and after 6 mo of follow-up.

Patients underwent clinical assessment, transthoracic echocardiography, maximal cardiopulmonary exercise test, 6-minute walk test (6MWT), the EuroQOL five dimensions questionnaire (EQ-5D) and EuroQol-visual analog scale (VAS), and standard hematologic and biochemical assays including N-terminal pro-brain natriuretic peptide before initiation of L-carnosine administration and after 6 mo [38,39].

Transthoracic echocardiography was performed using a Vivid 7 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway). All patients underwent a comprehensive examination including M-mode, two-dimensional echocardiography, continuous wave, pulsed, and color Doppler in accordance with the American Society of Echocardiography, by experienced echocardiographers [40]. For each measurement, three cardiac cycles were averaged. In all patients the left ventricular (LV) end-diastolic, end-systolic volumes and LVEF were measured using the biplane Simpson's rule method. Cardiopulmonary bicycle exercise testing was performed with the patients in the sitting position with simultaneous expiratory gas exchange. Exercise was started at workload of 0 watts with further increments of 10 watts/min at an average rate of 65 rpm up to the appearance of limiting dyspnoea or fatigue (CPXD Medical Graphics System, St Paul, MN, USA). Peak oxygen uptake (pVO_2) and slope of ventilatory requirement versus carbon dioxide production (VE/VCO_2 slope) were measured on breath-by-breath basis. The VE/VCO_2 slope was calculated using data from the onset of exercise to the ventilatory threshold. A maximal exercise was defined by reaching a respiratory exchange ratio ≥1.10. The anaerobic threshold was determined by standard criteria [41,42]. pVO_2 was obtained averaging the final 30 sec of exercise. Electrocardiographic and respiratory variables were continuously monitored.

6MWTs were conducted in an enclosed corridor on a 50-m course. Heart rate, blood pressure, and peripheral oxygen saturation were measured at the beginning and at the end of the exercise [43].