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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 Department of Cardiology, University of Brescia, and all patients gave their written, informed consent to participate. The study received ethical approval from the ethics review board of Cardiovascular Department, University of Brescia.

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].

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Self-made QoL tests (EQ-5D) consisted of five questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had three levels of answer: *no problems*, *some problems*, *severe problems*. Patients were asked to indicate the state of their health by ticking (or placing a cross) in the box next to the most appropriate statement for each of the five questions. This decision resulted in a one-digit number expressing the level selected for that dimension. The digits for five dimensions were combined in a five-digit number describing the respondent's state of health. The VAS recorded the patient's self-rated health on a vertical, VAS where the end points were classified as *best imaginable health state* and *worst imaginable health state*. This information was used as a quantitative measure of health outcome as judged by the individual respondents [44,45].

The primary end points of this study were the changes from baseline in exercise parameters (distance at 6MWT and cardiopulmonary exercise test) and the effects on QoL (EQ-5D and VAS) in the L-carnosine group compared with the control group. The secondary end points of this study were the effects of L-carnosine on echocardiographic parameters, LVEF, and hematologic and biochemical assays.

Statistical analysis

The variables were expressed as mean ± SD unless otherwise specified.

Paired Student's *t* test assessed the differences for continuous variables, whereas χ^2 analysis assessed differences for categorical variables. A two-tailed value of $P < 0.05$ was considered significant.

All analyses were performed using SPSS, version 19.0.1 software (Chicago, IL, USA).

Results

The study group included 50 consecutive ambulatory patients (mean age, 62.01 ± 9.55 y) with CHF due to left-ventricular systolic dysfunction (mean LVEF, 33.21 ± 7.57), who were referred to our institute between June and November 2012 and randomized to receive L-carnosine (500 mg OD) on top of standard therapy or standard treatment.

At study entry, the two groups were balanced with respect to demographic, clinical, and biochemical variables, as well as medical therapy (Table 1).

All patients were treated with angiotensin-converting enzyme inhibitors and/or renin-angiotensin system inhibitors and β-blockers; treatment did not change significantly during follow-up. At baseline, no differences were found in echocardiographic parameters, functional capacity, and QoL evaluations (Table 2). All patients had systolic dysfunction assessed by echocardiographic evaluation (LVEF, 32.4% ± 6.3% in the L-carnosine group; 32.4% ± 7.3% in the control). No significant differences were detected between groups in medical history or laboratory values (Table 1).

The functional capacity, assessed by cardiopulmonary stress test, was similarly reduced at baseline with a pVO2 of 14.5 ± 3.9 mL·kg·min in the L-carnosine group and 15.2 ± 3.7 mL·kg·min in the control group. Patients in the control group experienced no change from baseline in the parameters related to exercise capacity and QoL (pVo2, 15.2 ± 3.7 to 13.8 ± 4.0 mL·kg·min; $P = 0.209$), 6MWT (445.5 ± 69.5 to 435.0 ± 92.0 m; $P = 0.649$), VAS (70 ± 17.7 to 64.2 ± 17.9; $P = 0.256$), EQ-5D (8.8 ± 3.9 to 8.8 ± 3.8; $P = 0.964$). After 6 mo of treatment, orodispersible L-carnosine was associated with an improvement in 6MWT distance (419 ± 85 to 478 ± 80 m; $P = 0.014$) and in QoL calculated by VAS score (66.6 ± 19 to 77.6 ± 17.6; $P = 0.039$) (Table 2).

Comparing the two groups (Table 3; Fig. 1), pVO_2 increased in the L-carnosine group but not in the control group (1.1 ± 2.1 mL·kg·min versus −1.4 ± 2.4 in the control group; $P < 0.0001$), with similar positive changes in $\%pVO_2$ (4.5 ± 9.4 in the L-carnosine group versus −3.8 ± 9.8 in the control arm; $P = 0.004$), VO_2 at anaerobic threshold (0.7 ± 1.9 in the L-carnosine group versus −1.2 ± 2.3 in the control group; $P = 0.003$), and peak exercise workload (5.4 ± 21.0 in the L-carnosine group versus −6.6 ± 17.3 in the control group; $P = 0.033$). The treatment group also showed an improvement in the variation of 6MWT compared with the control group (59.4 ± 128.1 m in L-carnosine group versus −10.56 ± 62.3 m in the control arm; $P = 0.018$) (Table 3; Fig. 2).

Quality of life significantly improved in the treatment group compared with the control group, as shown by EQ-5D test (−0.56 ± 1.00 in the L-carnosine group versus 0.40 ± 1.7 in the control group; $P = 0.018$) and VAS score (11 ± 17.7 in the L-carnosine group versus −5.8 ± 12.3 in the control group; $P < 0.0001$) (Table 3; Fig. 2). No differences were observed for the other measurements. During the treatment period, no adverse effects were found in the treatment group and no patient died and/or was hospitalized for HF.

Table 1
Baseline demographic and clinical characteristics of study patients

Variables*	L-carnosine group (n = 25)	Control group (n = 25)	*P*-value†
Age (y)	61.2 ± 9.3	62.3 ± 9.9	0.682
Men	22 (88)	22 (88)	1.000
Weight (kg)	82.2 ± 14.8	75.6 ± 11.1	0.080
CAD	12 (48)	10 (40)	0.569
Hypertension	12 (48)	12 (56)	0.571
Diabetes	7 (28)	8 (32)	0.758
Smoker	3 (12)	4 (16)	0.684
Dyslipidemia	20 (80)	17 (68)	0.333
COPD	0 (0)	1 (4)	0.312
AF	9 (36)	7 (28)	0.569
CRT	9 (36)	10 (40)	0.979
NYHA class			
I	7 (28)	6 (32)	0.758
II	17 (68)	17 (68)	1.000
III	1 (4.3)	0 (0)	0.312
SBP (mm Hg)	118 ± 14	116 ± 15	0.559
DBP (mm Hg)	74 ± 10	73 ± 8	0.698
HR (bpm)	67 ± 11	66 ± 12	0.699
Hemoglobin (mg/dL)	14.4 ± 1.2	14.1 ± 1.6	0.456
Hematocrit (%)	42.0 ± 3.3	42.0 ± 5.1	0.870
Glucose (mg/dL)	116.2 ± 25.3	117.0 ± 33.1	0.919
Cholesterol (mg/dL)	190.0 ± 40.5	179.6 ± 37.4	0.329
Triglyceride (mg/dL)	145.1 ± 72.1	116.4 ± 69.8	0.159
Serum creatinine (mg/dL)	1.0 (0.8–1.0)	1.1 (0.8–1.2)	0.075
NT-proBNP (pg/mL)	603 (252.2–1026.5)	962 (126.5–1354.0)	0.846
C-reactive protein (mg/L)	1.2 (0.7–3.5)	1.0 (0.7–3.3)	0.444
Medical treatment n (%)			
β-blockers	25 (100)	25 (100)	1.000
ACE-I	19 (76)	20 (80)	0.475
RAS-I	7 (28)	6 (24)	0.502
Aldost-Ant	18 (72)	11 (48)	0.070
Diuretic	20 (80)	18 (72)	1.000
Statins	20 (80)	19 (76)	0.710
	18 (72)	19 (76)	0.812

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; Aldost-Ant, aldosterone antagonist; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; HR, heart rate; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; RAS-I, renin angiotensin system inhibitors; SBP, systolic blood pressure

* Unless otherwise specified, continuous variables are expressed as mean ± SD, dichotomous variables are expressed as n (%).

† *P*-values refer to differences between L-carnosine group and control group.

Discussion

To our knowledge, this study is the first to analyze the effects of oral supplementation in a 500 mg/d dose of L-carnosine in ambulatory patients with HF and severe left-ventricular systolic

Table 2
Echocardiographic parameters, exercise capacity data, and quality of life at baseline and at 6 M follow-up*

	L-carnosine group			Control group		
	Baseline	Follow-up	*P*-value†	Baseline	Follow-up	*P*-value†
NYHA class			0.584			0.200
I	7 (28)	8 (32)	0.730	8 (32)	7 (28)	0.730
II	17 (68)	17 (68)	1.000	17 (68)	15 (60)	0.522
III	1 (4)	0 (0)	0.312	0 (0)	3 (12)	0.073
Echocardiographic data						
DTD (mm)	70.4 ± 6.3	69.9 ± 5.8	0.814	67.3 ± 8.4	67.1 ± 8.4	0.827
DTS (mm)	57.5 ± 9.2	59.0 ± 7.6	0.920	54.3 ± 14.9	56.1 ± 10.1	0.668
LVEF (%)	32.4 ± 6.3	33.6 ± 6.6	0.517	32.4 ± 7.3	34.1 ± 10.1	0.521
PAPs (mm Hg)	26.8 ± 4.3	26.6 ± 4.4	0.822	30.1 ± 7.7	30.0 ± 7.2	0.955
MV mean-moderate	2 (8)	2 (8)	1.000	2 (8)	5 (20)	0.218
EDV (mL)	200.5 ± 57.6	201.3 ± 54.4	0.846	170.5 ± 56	174.8 ± 57	0.881
Cardiopulmonary stress test						
pVO_2 (mL·kg·min)	14.5 ± 3.9	15.5 ± 3.8	0.318	15.2 ± 3.7	13.8 ± 4.0	0.209
% p VO_2	57.8 ± 15.2	62.3 ± 15.3	0.304	60.0 ± 15.2	56.2 ± 15.9	0.397
VE/VCO_2 slope	33.1 ± 4.7	34.6 ± 4.7	0.263	35.8 ± 6.6	34.9 ± 6.9	0.612
VO_2 anaerobic threshold (mL·kg·min)	9.4 ± 2.0	10.1 ± 2.3	0.288	10.7 ± 3.4	9.5 ± 3.1	0.189
RER	1.17 ± 0.09	1.2 ± 0.09	0.287	1.12 ± 0.24	1.13 ± 0.09	0.838
Workload max (watts)	106.4 ± 32.9	111.8 ± 31.3	0.558	103.6 ± 29.1	97.0 ± 30.0	0.433
6MWT (m)	419.1 ± 85.2	478.4 ± 79.8	0.014	445.5 ± 69.5	435.0 ± 92.0	0.649
Quality of life						
EQ-5D	9.1 ± 3.9	8.5 ± 4.3	0.633	8.8 ± 3.9	8.8 ± 3.8	0.964
VAS (%)	66.6 ± 19.0	77.6 ± 17	0.039	70.0 ± 17.7	64.2 ± 17.9	0.256

DTD, telediastolic diameter; DTS, telesystolic diameter; EDV, end-diastolic volume; LVEF, left-ventricular ejection fraction; MV, mitral valve insufficiency; PAPs, systolic pulmonary arterial pressure; pVO_2, peak oxygen uptake; RER, respiratory exchange ratio; VAS, visual analog scale; VE/VCO_2 slope, slope of ventilatory requirement versus carbon dioxide production; VO_2, oxygen uptake; 6MWT, 6-minute walk test

* Unless otherwise specified, continuous variables are expressed as mean ± SD, dichotomous variables are expressed as n (%).

† *P*-values refer to differences between baseline and follow up in L-carnosine group and control group.

dysfunction, focusing on the effect on exercise tolerance and QoL. The administration of L-carnosine was performed in patients on optimized therapy for HF and who were clinically stable. L-carnosine is a dietary supplement in the formulation of orodispersible tablet. Carnosine is a molecule composed of two AAs, β-alanine and histidine.

This study demonstrated that the administration of the dypeptide L-carnosine to patients with CHF is associated with a significant improvement in exercise capacity, assessed both by cardiopulmonary exercise testing and the 6MWTD, and QoL without changes in LVEF.

Table 3
Changes in echocardiographic parameters, functional capacity, and quality of life in both groups

Variables*	L-carnosine	Control group	*P*-value†
Echocardiographic parameters			
Δ DTD (mm)	−0.4 ± 2.8	−0.5 ± 5.0	0.917
Δ DTS (mm)	−0.24 ± 3.9	1.5 ± 9.8	0.419
Δ LVEF	1.2 ± 4.7	1.6 ± 7.7	0.826
Δ EDV (mL)	−4.5 ± 13.6	3.5 ± 17.0	0.072
Δ PAPs (mm Hg)	−0.28 ± 4.95	−0.12 ± 5.33	0.913
Cardiopulmonary stress test			
Δ pVO_2 (mL·kg·min)	1.1 ± 2.1	−1.4 ± 2.4	<0.0001
Δ %pVO_2	4.5 ± 9.4	−3.8 ± 9.8	0.004
Δ VE/VCO_2 slope	1.5 ± 2.4	−1.0 ± 5.9	0.061
Δ VO2 anaerobic threshold (mL·kg·min)	0.7 ± 1.9	−1.2 ± 2.3	0.003
Δ RER	0.03 ± 0.2	0.01 ± 0.25	0.770
Δ Workload max (watts)	5.4 ± 21.0	−6.6 ± 17.3	0.033
6-Minute walk test			
Δ 6MWT (m)	59.4 ± 128.1	−10.56 ± 62.3	0.018
Quality of life			
Δ EQ-5D	−0.56 ± 1.00	0.40 ± 1.7	0.018
Δ VAS	11.0 ± 17.7	−5.8 ± 12.3	<0.0001

DTD, telediastolic diameter; DTS, telesystolic diameter; EDV, end-diastolic volume; LVEF, left-ventricular ejection fraction; PAPs, systolic pulmonary arterial pressure; pVO_2, peak oxygen uptake; RER, respiratory exchange ratio; VAS, visual analog scale; VE/VCO_2 slope, slope of ventilatory requirement versus carbon dioxide production; VO_2, oxygen uptake; 6MWT, 6-minute walk test

* Unless otherwise specified, continuous variables are expressed as mean ± standard deviation, dichotomous variables are expressed as n (%).

† *P*-values refer to differences between L-carnosine group and control group.

Advanced HF is characterized by a hypercatabolic state that involves all the organs, causes muscle wasting, and finally included cardiac cachexia, a strong independent risk factor for mortality [3,46]. Several macro- and micronutrient deficiencies have been associated with abnormalities of the muscle metabolism and may occur before reduction in exercise capacity and cachexia [16,47]. Among micronutrients, AAs act as a substrate for protein synthesis or intermediary metabolism. Recently, several studies have demonstrated a favorable effect of AA supplementation in the treatment of CHF [48,49]. One group of researchers [6] tested a mixture of AAs added to optimal medical therapies in older patients with CHF. They showed that supplementation with oral AAs, in addition to standard pharmacologic therapy, increased exercise capacity by improving circulatory function, muscle oxygen consumption, and aerobic production of energy in this CHF population [7,50]. The benefits of micronutrient supplementation in CHF with severe left-ventricular dysfunction was confirmed by another study that showed a significant improvement in left ventricular function and QoL and a reduction of proinflammatory cytokine level [8]. In patients with stable CHF and severe left-ventricular dysfunction, the addition of AA citrulline for 4 mo improved functional class and LVEF at rest and during effort [51].

L-carnosine is a cytoplasmic dipeptide synthesized from β-alanine and histidine, which is present at highest concentrations in the skeletal muscle [15]. Muscle carnosine is a major contributor to H+ buffering during high-intensity exercise [32]. To the best of our knowledge, no study with supplementation of L-carnosine has been conducted previously in patients with HF. However, preliminary studies discovered that power athletes have higher carnosine levels than untrained individuals and endurance athletes [52]. Carnosine concentration can be increased in muscle cells by L-carnosine supplementation or

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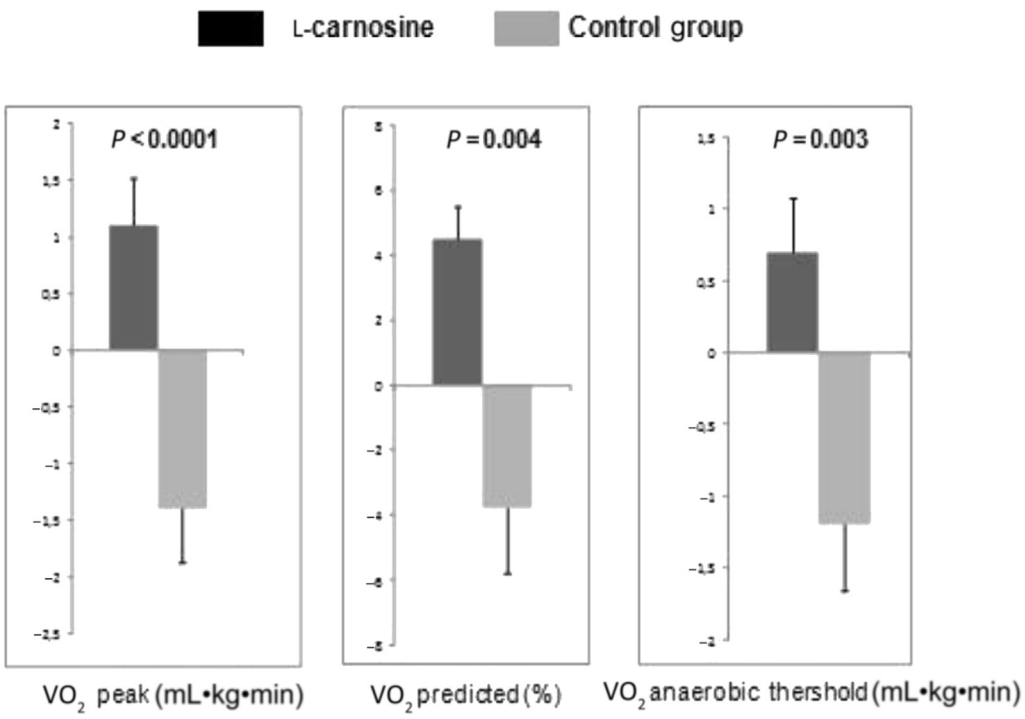

Fig. 1. Changes in cardiopulmonary parameters between the two groups. VO_2 peak, peak oxygen uptake; VO_2 predicted, $\%VO_2$ peak.

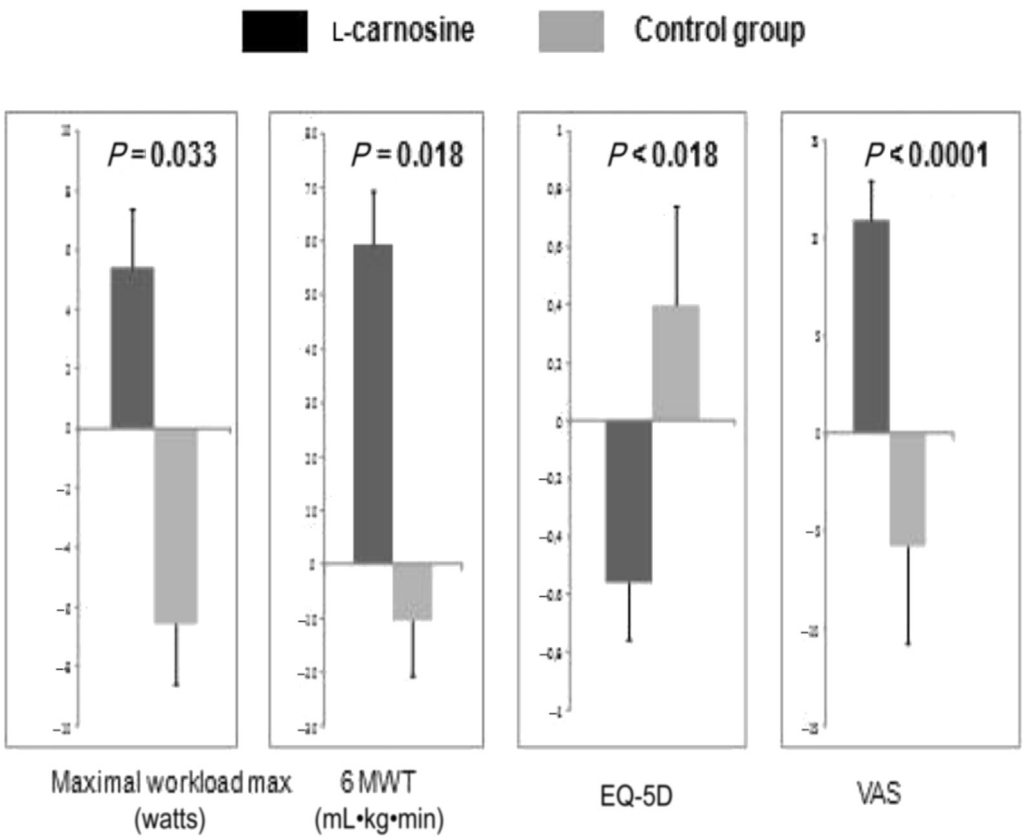

Fig. 2. Changes in cardiopulmonary parameters, 6MWT, and quality of life between the two groups. EQ-5D, EuroQOL five dimensions questionnaire; VAS, visual analog scale; 6MWT, 6-minute walk test.

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indirectly by oral administration of β-alanine, whereby carnosine synthetase rapidly converts β-alanine to carnosine inside muscle fibers [30]. The interest in carnosine mainly derives from the evidence that oral supplementation of β-alanine significantly increases the concentration of carnosine in the muscle with an improvement in exercise performance and capacity [53–55].

The buffering effect of L-carnosine delays the muscular acidosis, which may explain the improvement in exercise tolerance evidenced by the fact that the anaerobic threshold is reached later (0.7 ± 1.9 in L-carnosine group versus -1.2 ± 2.3 in the control group; $P = 0.003$); this positive effect also improved functional capacity expressed by peak exercise workload (5.4 ± 21.0 in the L-carnosine group versus -6.6 ± 17.3 in the control group; $P = 0.033$).

The favorable effects of carnosine on QoL can be partially explained by a reduction of lactic acid, which reduces fatigue and muscle pain.

Another mechanism of action of L-carnosine may involve an increase in Ca^{2+} sensitivity of the contractile apparatus in both types I and II fibers that directly increase muscle force [56].

Patients treated with L-carnosine compared with those in the control group did not show any differences in LVEF as assessed by echocardiography. However, the number of patients studied may have been too limited to detect significant changes in this parameter. L-carnosine has also shown favorable effects on calcium homeostasis, which may allow an improvement in cardiac function. Limitations of this study include the open-label design, and the small sample size.

Conclusion

This investigation demonstrated that once-daily oral supplementation of 500 mg L-carnosine, added to conventional therapy, may improve exercise performance and QoL in ambulatory patients with stable CHF. This study did not test L-carnosine against placebo and enrolled a relatively small number of patients. More data are necessary to confirm these promising results and placebo-controlled studies enrolling a larger number of patients are needed to evaluate potential effects of L-carnosine on left-ventricular function and prognosis.

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