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L-carnitine as an ergogenic aid for patients with chronic obstructive pulmonary disease submitted to whole-body and respiratory muscle training programs

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Abstract

The effects of adding L-carnitine to a whole-body and respiratory training program were determined in moderate-to-severe chronic obstructive pulmonary disease (COPD) patients. Sixteen COPD patients (66 ± 7 years) were randomly assigned to L-carnitine (CG) or placebo group (PG) that received either L-carnitine or saline solution (2 g/day, orally) for 6 weeks (forced expiratory volume on first second was 38 ± 16 and 36 ± 12%, respectively). Both groups participated in three weekly 30-min treadmill and threshold inspiratory muscle training sessions, with 3 sets of 10 loaded inspirations (40%) at maximal inspiratory pressure. Nutritional status, exercise tolerance on a treadmill and six-minute walking test, blood lactate, heart rate, blood pressure, and respiratory muscle strength were determined as baseline and on day 42. Maximal capacity in the incremental exercise test was significantly improved in both groups ($P < 0.05$). Blood lactate, blood pressure, oxygen saturation, and heart rate at identical exercise levels were lower in CG after training ($P < 0.05$). Inspiratory muscle strength and walking test tolerance were significantly improved in both groups, but the gains of CG were significantly higher than those of PG (40 ± 14 *vs* 14 ± 5 cmH_2O, and 87 ± 30 *vs* 34 ± 29 m, respectively; $P < 0.05$). Blood lactate concentration was significantly lower in CG than in PG (1.6 ± 0.7 *vs* 2.3 ± 0.7 mM, $P < 0.05$). The present data suggest that carnitine can improve exercise tolerance and inspiratory muscle strength in COPD patients, as well as reduce lactate production.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) are intolerant to exercise mainly due to limited ventilatory capacity (1). This leads to deconditioning, early lactic acidosis, and reduced capillarity and muscle strength (2). An exercise training (ET) program is the main component of pulmonary rehabilitation for COPD patients (3), increasing exercise capacity and reducing dyspnea. Therefore, ET can result in beneficial changes in exercise capacity and has been shown to consistently improve the quality of life of COPD patients (4).

Although training has been shown to be an essential component of the rehabilitation program, patients do not benefit from it to the same extent (5). Indeed, conflictive results concerning lactate reduction and improved physical exercise capacity or muscle strength after training have been reported (6). Patients with reduced exercise capacity who experience less ventilatory limitation for exercise and more reduced respiratory and peripheral muscle strength are more likely to improve their exercise tolerance with a physical training program (5).

In addition to exercise, nutritional factors such as L-carnitine supplementation (7) have been used to improve physical performance. L-carnitine is a quaternary amine whose function has been related to lipid metabolism, sparing muscle glycogen, improving tolerance to physical activity, and reducing muscle fatigue (7). It has also been demonstrated in skeletal and cardiac muscle, in plasma, kidney, liver, and brain.

The importance of the biochemical functions of carnitine in the altered muscle physiology associated with clinical carnitine deficiency supports the critical role of carnitine in muscle bioenergetics (8). In an experimental study, L-carnitine directly improved the fatigue characteristics of muscles enriched in type I fibers when evaluated by the kinetics of contraction and relaxation during a stimulation protocol (9).

In healthy persons, the beneficial effects of long-term treatment with L-carnitine on physical performance cannot be explained by an increase in muscle carnitine stores (10). The effects of supplementation on pathologic conditions that affect exercise performance are less clear. Some studies have shown improvement of exercise performance in patients with cardiovascular (11) and peripheral vascular disease (12). However, to our knowledge, the present study is the first to have been conducted on COPD patients. Thus, the purpose of the present study was to determine whether carnitine supplementation could improve the exercise tolerance, pulmonary function, nutrition, dyspnea, and respiratory muscle strength of COPD patients submitted to a whole-body and respiratory training program.

Patients and Methods

Subjects

Volunteers for this study were recruited from COPD outpatients evaluated in the Respiratory Clinic Therapy Unit of UFSCar (São Carlos Federal University) from April 2000 to November 2001. The total number of patients evaluated was 36, but only 16 satisfied the criteria for the experimental protocol. Patients with primary heart, endocrine, orthopedic, or asthma disorders and those living ten miles or more from the Laboratory were excluded from the study. Stable COPD patients (10 men and 6 women) agreed to participate in the study. All patients were nonsmokers at the time of the study, although all had a cigarette smoking history. Patients had chronic airflow obstruction, defined as measured forced expiratory volume on first second (FEV_1) <50%, FEV_1/forced vital capacity <70% of percent predicted and a clinical history consistent with COPD. The patients who were taking long-term medication continued to take all

drugs with no dosage changes. The study protocol was approved by the Ethics Committee for Human Research of the Federal University of São Carlos and all patients gave institutionally reviewed written informed consent to participate in the study.

Experimental design

Patients were randomly allocated to two groups by drawing lots. The L-carnitine group (N = 8) received a 2 g/day oral L-carnitine supplementation in two daily doses for 6 weeks, dispensed in 10-mL glass bottles containing 1 g each, and the control group (N = 8) received placebo (saline solution, similar in presentation to the L-carnitine preparation) for the same period of time. The supplementation and placebo were similar in color, shape and taste. The patients in each group did not know if they were receiving carnitine supplementation or placebo (single-blind controlled trial). Both groups took part in an exercise and respiratory training program which consisted of medical follow-up by a physician and individual training supervised by physical therapists. L-carnitine was obtained from Sintofarma Laboratory (São Paulo, SP, Brazil). The purity of L-carnitine was evaluated by enzymatic method, and was found to be consistent with the concentrations stated on the labeling (87-90%).

Lung function tests. All patients underwent spirometry with the determination of FEV_1, forced vital capacity and maximal voluntary ventilation according to American Thoracic Society recommendations (13). The values obtained were compared to the predicted normal values of Knudson et al. (14). Spirometry was performed using a Vitalograph® Hand-Held 2120 instrument (Ennis, Ireland), which was calibrated before each test according to manufacturer recommendations using a 1-L syringe.

The maximal respiratory pressures were assessed by maximal inspiratory (PI_{max}) and expiratory pressure (PE_{max}) at residual volume and at total lung capacity, respectively, with an analog pressure gauge according to the method of Black and Hyatt (15). Patients were asked to make maximal inspiratory and expiratory efforts against an obstructed mouthpiece with a small leak to prevent patients from closing their glottis during the maneuver. Patients sustained their maximal effort for one second and the best of three consecutive attempts was used. The predicted values for the Brazilian population reported by Neder et al. (16) were compared with those obtained for patients with COPD.

Body composition. After the patient arrived at the laboratory at 8 am before breakfast, weight and height were measured using a mechanical scale (Welmy, São Paulo, SP, Brazil) and body mass index was calculated. Three consecutive measurements of triceps skinfold (TSF) thickness were used as an indirect estimate of body fat (17). Three measurements of midarm circumference (MAC) were performed in the nondominant arm, positioned parallel to the trunk. A nondistensible tape was placed around the midpoint of the arm without compressing the arm tissue, halfway between the tip of the shoulder (acromial process) and the tip of the elbow (olecranon process). Arm muscle circumference (AMC) was derived from the following formula (18): AMC (cm) = MAC - π x TSF (cm).

Caloric intake. A dietitian interviewed each patient and obtained information regarding dietary habits. An estimate of mean daily kilocalorie intake was obtained for each patient by the three-day dietary record. Written instructions for reporting intake, estimating portion sizes and describing mixed dishes were mailed to the patients. Patients were instructed to record all food and beverage consumption for three consecutive days. During the visit, the record was reviewed with the patient and often with the spouse to insure completeness. The diet records were coded for computer nutrient analysis, and mean daily carbohydrate, protein and fat

intake were estimated using the Nutri® Program (Federal University of São Paulo, UNIFESP-EPM, São Paulo, SP, Brazil) to determine if both groups presented a similar pattern of calorie intake. All patients were instructed to maintain their usual diet during the study.

Exercise capacity. The maximal incremental exercise test was performed on a treadmill (Imbrasport, Milennium® - ATL, Porto Alegre, RS, Brazil). During the test, arterial oxygen saturation was measured by pulse oximetry (SpO_2; Nonim 8500A®, Plymouth, MN, USA), and arterial blood pressure and heart rate (HR) were measured at 2-min intervals. HR was measured from the R-to-R interval on the electrocardiogram (TC 500, ECAFIX, São Paulo, SP, Brazil), and arterial blood pressure was measured with a manual sphygmomanometer. At the beginning and at the end of the test the patients were evaluated for possible breathing difficulty (dyspnea) using Borg's CR10 scale (19).

Patients first performed an incremental exercise test that included a 2-min rest period in the sitting position. They began walking at 2.0 km/h with a constant 3% grade, followed by an increase in speed rate of 0.5 km/h every 2 min until exhaustion. The test could be interrupted either by the patients, because of dyspnea, leg fatigue or disabling symptoms, or by the investigator, for safety reasons. If SpO_2 dropped below 80% or if threatening signs and symptoms occurred such as electrocardiography alterations and if HR reached the age-predicted maximum, the test could be interrupted. HR reserve was calculated (20) as 100% - (100 x peak HR)/(220 - age). The metabolic equivalent (MET) was estimated at peak oxygen consumption (VO_2) from the following formula (21): VO_2 (mL kg^{-1} min^{-1}) = (S x 0.1) + (S x G x 1.8) + 3.5, within a range of intensities from 3.2 to 6.4 km/h, where: S = speed in m/min, G = grade in % (3% = 0.03) and 1 MET = 3.5 mLO_2 kg^{-1} min^{-1}.

Blood lactate concentration. Blood samples were drawn from each ear lobe. The first drop of blood was discarded to avoid contamination with lactate eliminated through sweat. Blood lactate concentration was measured at rest, every 2 min during the test and 2 min after the end of the maximal exercise test. Each blood sample was collected with a capillary tube previously calibrated with 25 µL heparin. After collection, the blood samples were transferred to 2-mL tubes containing 50 µL 1% sodium fluoride in order to prevent glycolysis. Blood was stored at -10ºC for later analysis. Blood lactate concentration was determined by an electroenzymatic method (YSI 1500® - Sport Lactate Analyzer, Yellow Springs, OH, USA).

Six-minute walking test (*SMWT*). Functional exercise performance was measured by the SMWT. This test was performed in a 30-m corridor, and encouragement was standardized (22). To avoid learning effects, the better of two reproducible walks was used on the occasion of the first visit. SpO_2, HR and Borg's scale were also measured during the test. The test could be interrupted by the patient because of dyspnea and/or leg fatigue. On the occasion of the second visit, the SMWT was performed under the same conditions as used for the pretest. The predicted values of distances walked were compared with those obtained by the patients, according to the 2002 ATS Statement (22).

Exercise training program

The 6-week ET program was conducted on an outpatient basis. Patients attended 1-h training sessions three times a week. The training intensity was set at walking on a treadmill at 80% of the maximal speed of the maximal test. Each ET session consisted of 30-min walking exercises on the treadmill and inspiratory muscle training (IMT). During the treadmill walking test, the patient's HR and SpO_2 were continuously monitored.

Blood pressure was measured before and after each training session. The IMT was performed with a pressure threshold resistive training device. During training, an attempt was made to apply a load corresponding to 40% of the patient's baseline PI_{max} (23). Nose clips were used to occlude nasal airflow. During each session, the patients breathed through an IMT mouthpiece device, with 3 sets of 10 loaded inspirations.

Statistical analysis

Values are reported as means ± SD. Due to non-Gaussian distribution and/or inhomogeneity of variance of variable values, nonparametric tests were selected for statistical analysis (24). Thus, the Mann-Whitney and Wilcoxon nonparametric tests were used for intergroup and intragroup comparisons, respectively, with the level of significance set at $P < 0.05$. The gain obtained by the groups was derived from absolute delta comparisons (post-treatment minus pretreatment values).

Results

Baseline patient characteristics are presented in Table 1. There were no significant differences in age, anthropometry, lung function, protein, fat, or total energy intake between groups. The results of the pulmonary function tests were characterized, on average, by moderate-to-severe airflow obstruction (FEV_1 around 40% of the predicted value in both groups). The various procedures were well tolerated by all patients, and no untoward effects of carnitine were reported.

Effects on body composition and dietary intake

No significant changes were observed in body composition after the exercise training program in either group, as shown in Table 2. There were no significant differences in energy intake of carbohydrates, lipids, protein, or total energy in either group.

Physiological parameters and performance during the incremental test

Table 3 shows the distance walked in the incremental test on a treadmill, as well as the time and the maximal speed reached. Peak metabolic equivalent obtained before the physical and respiratory program was around 5 METs for both groups. Six weeks of training produced a significant increase in time and speed compared to pretreatment in both groups, and the HR reserve significantly increased ($P < 0.05$) only in the carnitine group. No significant differences in systolic blood pressure, SpO_2, Borg scale, or blood lactate were observed between the two groups when compared at peak speed. A significant increase in HR peak was shown only in the placebo group from absolute delta comparison ($P < 0.05$). In the incremental exercise test, comparison of responses to identical exercise levels showed that HR, systolic blood pressure and blood lactate concentration were significantly lower, and that SpO_2 significantly increased only in the L-car-

Table 1. Characteristics of the patients in the L-carnitine and placebo groups.

	L-carnitine group	Placebo group
Age (years)	69 ± 9	65 ± 7
Weight (kg)	56 ± 11	61 ± 12
Height (cm)	160 ± 1	162 ± 1
BMI (kg/m^2)	22 ± 5	23 ± 5
FEV_1 (L)	0.85 ± 0.3	0.87 ± 0.3
FVC (L)	1.69 ± 0.6	1.63 ± 0.3
FEV_1 (% predicted)	38 ± 16	36 ± 12
Carbohydrate intake (%)*	52 ± 10	46 ± 6
Protein intake (%)*	15 ± 3	15 ± 4
Fat intake (%)*	33 ± 8	38 ± 6
Energy intake (kcal/day)*	1832 ± 452	2077 ± 401

Data are reported as mean ± SD for 8 patients in each group. There were no significant differences between the L-carnitine and placebo groups. BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity. *Estimated from information provided by the patients.

nitine group (Table 3). In addition, the reduction in blood lactate concentration was significantly greater for the L-carnitine group ($P < 0.05$).

Table 2. Effects of L-carnitine supplementation associated with exercise training on body composition and dietary intake.

	L-carnitine group			Placebo group		
	Pre	Post	Δ	Pre	Post	Δ
BMI (kg/m^2)	22 ± 5	21 ± 4	-1 ± 1	23 ± 5	23 ± 5	0 ± 1
TSF (mm)	13 ± 9	12 ± 6	-1 ± 3	13 ± 7	13 ± 7	1 ± 2
MAC (cm)	25 ± 4	26 ± 4	0 ± 1	27 ± 4	28 ± 4	0 ± 1
AMC (cm)	21 ± 2	22 ± 3	1 ± 1	24 ± 2	24 ± 2	1 ± 4
Carbohydrate intake (%)*	52 ± 10	52 ± 7	1 ± 10	46 ± 6	48 ± 6	2 ± 5
Protein intake (%)*	15 ± 3	16 ± 6	1 ± 6	15 ± 4	16 ± 2	1 ± 3
Fat intake (%)*	33 ± 8	32 ± 7	-1 ± 6	38 ± 6	36 ± 5	-3 ± 5
Energy intake (kcal/day)*	1832 ± 452	1885 ± 421	88 ± 317	2077 ± 401	2066 ± 337	-29 ± 168

Data are reported as mean ± SD for 8 patients in each group. There were no significant differences between the L-carnitine and placebo groups. BMI = body mass index; TSF = triceps skinfold; MAC = midarm circumference; AMC = arm muscle circumference; Δ = absolute delta comparison (post-treatment minus pretreatment values). *Estimated from information provided by the patients.

Table 3. Effect of L-carnitine supplementation associated with exercise training on peak exercise and physiological responses at identical levels of exercise.

	L-carnitine group			Placebo group		
	Pre	Post	Δ	Pre	Post	Δ
Peak speed (km/h)	5 ± 1	5.7 ± 1**	0.7 ± 0.4	5 ± 1	5.6 ± 0.7*	0.6 ± 0.5
Walking distance (m)	830 ± 295	1082 ± 372**	253 ± 141	831 ± 328	1027 ± 290*	196 ± 186
Time (min)	14 ± 4	16.7 ± 4**	2.8 ± 1.5	14 ± 4	16 ± 3*	2.4 ± 2.1
MET	4.8 ± 0.7	5.4 ± 1**	0.6 ± 0.3	4.8 ± 0.7	5.2 ± 0.6*	0.4 ± 0.4
HR (bpm)	123 ± 16	122 ± 20	-1 ± 6.6	127 ± 9	138 ± 8	11 ± 8^{++}
HR reserve (%)	28 ± 18	37 ± 18*	10 ± 11	27 ± 13	28 ± 10	1 ± 15
SBP (mmHg)	164 ± 20	157 ± 12	-7 ± 13	170 ± 24	168 ± 29	-2 ± 24
SpO_2 (%)	86 ± 5	87 ± 4	1 ± 4	87 ± 7	88 ± 5	1 ± 4
Lactate (mM/L)	2.7 ± 0.9	2.6 ± 1.6	-0.1 ± 1	2.6 ± 1	3.0 ± 1.3	0.5 ± 1
Borg's scale (0-10)	4 ± 1	5 ± 2	0.8 ± 3	3.8 ± 1	4.5 ± 2	0.1 ± 2
Same speed (km/h)	5 ± 1	5 ± 1	-	5 ± 1	5 ± 1	-
HR (bpm)	123 ± 16	114 ± 16*	-9.5 ± 8	127 ± 9	128 ± 11^{+}	0.2 ± 13
SBP (mmHg)	164 ± 20	147 ± 14*	-17 ± 18	170 ± 24	156 ± 29	-14 ± 32
SpO_2 (%)	86 ± 5	91 ± 4**	1 ± 4	87 ± 7	90 ± 5	1.5 ± 4
Lactate (mM/L)	2.7 ± 0.9	1.6 ± 0.7**	-1.1 ± 0.6	2.6 ± 1	2.3 ± 0.7^{+}	-0.3 ± 0.7^{++}
Distance on SMWT (m)	440 ± 71	527 ± 77**	87 ± 30	467 ± 80	501 ± 74*	34 ± 29^{++}

Data are reported as means ± SD for 8 patients in each group. Physiological values were compared at peak speed and at identical levels of exercise. MET = metabolic equivalent (3.5 mL O_2 kg^{-1} min^{-1}); HR = heart rate; SBP = systolic blood pressure; SpO_2 = arterial oxygen saturation estimated by pulse oximetry; SMWT = six-minute walking test; Δ = absolute delta comparison (post-treatment minus pretreatment values). There were no significant pre-training differences between groups.

*$P < 0.05$ compared to pre-training response in placebo and L-carnitine groups (Wilcoxon test). **$P < 0.01$ compared to pre-training response in L-carnitine group (Wilcoxon test). $^{+}$Significantly different from post-training response in L-carnitine group (Mann-Whitney test). $^{++}$Significantly different from absolute delta in L-carnitine group (Mann-Whitney test).

Performance in the six-minute walking test

No significant differences were observed between groups before training. The L-carnitine group showed a significant improvement in walking distance performance after treatment ($P < 0.01$), as did the placebo group ($P < 0.05$). However, the absolute delta in walking distance obtained by the L-carnitine group was significantly greater ($P < 0.05$), as illustrated in Table 3.

When the predicted values for distance walked were compared with those obtained by our patients, significant reductions ($P < 0.05$) were observed (497 ± 53 *vs* 453 ± 54 m, respectively).

Maximal respiratory pressure

No significant differences in maximal respiratory pressure were observed between groups before training. After training, PI_{max} increased significantly not only in the L-carnitine group (from 49 ± 12 to 89 ± 22 cmH_2O) but also in the placebo group (from 54 ± 19 to 68 ± 21 cmH_2O) with $P < 0.01$. Similar results were obtained for PE_{max} in the L-carnitine group (from 66 ± 18 to 90 ± 32 cmH_2O, $P < 0.01$) and the placebo group (from 69 ± 26 to 81 ± 25 cmH_2O, $P < 0.05$). However, the increase in inspiratory muscle strength (PI_{max}) was significantly greater for the L-carnitine group than the placebo group (40 ± 14 *vs* 14 ± 5 cmH_2O, respectively, $P < 0.05$).

When the predicted values were compared to the PI_{max} and PE_{max} values obtained by patients with COPD (92 ± 12 *vs* 51 ± 16 cmH_2O for PI_{max}, and 97 ± 18 *vs* 68 ± 22 cmH_2O for PE_{max}, respectively), we observed that both values were lower in comparison to healthy subjects of the Brazilian population.

Discussion

The main results of the present study show the beneficial effects of L-carnitine supplementation in enhancing physiological responses at identical levels of exercise, reducing lactate concentration, improving exercise tolerance and inspiratory muscle strength in COPD.

On the other hand, the supplementation was not associated with modification of the degree of airflow obstruction, improvement of nutritional status or increase in muscle mass. Although TSF and upper arm circumference measurements are extensively used to evaluate body composition, they are not sensitive, especially over short time periods, to detect changes in muscle mass after therapeutic interventions.

In the present study, both groups increased their maximal exercise tolerance. Therefore, the physical training program was efficient in improving the performance of these patients. Our results agree with those obtained by other investigators who reported the importance of physical training in COPD patients (25-27). Previous studies have observed positive effects on maximal exercise capacity with L-carnitine supplementation alone in patients with cardiac insufficiency (11) and peripheral arterial disease (12).

However, patients receiving L-carnitine supplementation demonstrated a greater increment of lactate removal rate. Casaburi et al. (25) showed that ET (without a nutrient supplement) results in significant increases of peak blood lactate concentration and no significant responses to identical exercise levels in the incremental test in COPD patients. Our results showed an expressive reduction in blood lactate concentration at identical exercise levels only in the L-carnitine-supplemented patients.

The literature reports that COPD patients present cardiovascular limitations associated with ventilatory limitation (28). Carnitine has multiple effects on the intermediate metabolism and therefore may be an important factor in cardiac muscle bioenergetics. Some studies have shown the L-carnitine supplementation produces central cardiovascular

modifications, which contribute to improving exercise performance. L-carnitine supplementation reduced left ventricular size and pulmonary arterial pressure in patients with congestive heart failure (29) and systolic and diastolic blood pressure and ST changes in patients with severe ischemia-induced cardiac insufficiency (11).

In the present study, the L-carnitine-supplemented group showed a significant reduction in HR and systolic blood pressure at submaximal intensities, as well as an increase in HR reserve. These changes are probably explained by the reduction of muscular lactate values (not measured, but lactate was only evaluated in plasma), which permitted a greater utilization of muscle oxygen during physical exercise, delaying the metaboreflex and cardiovascular adjustments. Premature lactic acidosis has been associated with reduced oxidative enzyme concentrations in lower limb muscles, and utilization of the bioactive nutrients involved in muscle energy and substrate metabolism can be of therapeutic importance.

Furthermore, Gosker et al. (30) observed that COPD and chronic heart failure can lead to wasting and weakness of skeletal muscle. These authors showed that patients with severe COPD or chronic heart failure were physically inactive, a fact assumed to have a negative or "detraining" effect on exercise capacity. In our study, we observed lower blood lactate levels, reduced maximal exercise capacity and high HR reserve compared to baseline values in patients with COPD, similar to other authors (25,30). Moreover, the higher HR reserve values demonstrated that patients with COPD were primarily limited by their ventilatory limitation and not by cardiac dysfunction, showing that a possible cardiac impairment was subordinate to pulmonary impairment in the present study.

The subjective sensation of dyspnea was not modified in our patients by L-carnitine supplementation and/or physical training. Similar results have been reported in the literature (31), although some investigators have observed a reduction in dyspnea (32). In our study, the Borg scale was applied only at the beginning and at the high point of exercise both before and after treatment, although it was not applied to the same workload.

Both groups significantly increased their walking distance in the SMWT, indicating increased tolerance to exercise after the program. In a previous study (33), we observed a significant increase of exercise tolerance in the SMWT in patients with mild to moderate COPD receiving L-carnitine supplementation associated with physical exercise. The increased performance of these patients was not associated with an increase of plasma free L-carnitine levels.

Redelmeier et al. (34) reported that an increase of 54 m in the walking distance in SMWT was thought to be clinically relevant. Thus, we may suggest that physical exercise associated with L-carnitine supplementation was more effective, considering that a mean of 87 m was obtained compared to physical exercise alone, corresponding to a 34 m increase. According to some investigators, L-carnitine supplementation (without physical training) can improve the exercise tolerance of patients with peripheral vascular (12) and cardiovascular (11) diseases and of patients submitted to hemodialysis (35).

Respiratory muscle training alone increased the respiratory muscle training of these patients, as also reported by others (36-38). Additionally, L-carnitine supplementation associated with respiratory muscle training significantly increased the inspiratory muscle strength of our patients compared to the placebo group. Our results suggest that IMT associated with L-carnitine supplementation was more effective in increasing respiratory muscle strength than IMT alone. However, no information is currently available on respiratory muscle training associated with L-carnitine. Previous

studies have observed the effects of L-carnitine supplementation on muscle performance, delayed muscle fatigue *in vitro* (9), increased workload during an incremental test in healthy subjects (39) and athletes (40), reduced muscle fatigue in hemodialysis patients (35), or improved myocardial performance in congestive heart failure patients (29).

The main limitation of our study was the small number of participants, a fact possibly due to the strict criteria for patient inclusion and the severity of the disease of the patients evaluated. Thus, a study with a larger number of patients would be useful to confirm the present findings. Another limitation of this study was the impossibility of obtaining ventilatory and metabolic measurements due to the high cost of the methodology. Moreover, this study was of the single-blind type, with only the patients being unaware of which medication they were taking since the same researcher controlled the treatment plan, training and administration of L-carnitine or placebo.

The present study demonstrated that L-carnitine administration adds benefit to exercise and respiratory strength training in outpatients with stable, moderate-to-severe COPD. Larger double-blind and controlled trials are now warranted to confirm these preliminary findings.

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