

ORIGINAL ARTICLE

## CARNITINE IMPROVES EXERCISE TOLERANCE AND RESPIRATORY MUSCLE STRENGTH IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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### KEYWORDS:

COPD, L-Carnitine, Respiratory muscle strength, Exercise, Dietary supplements.

**Objective:** We evaluated the safety and effects of L-carnitine on exercise capacity and respiratory muscle strength in patients with chronic obstructive pulmonary disease (COPD).

**Methods:** Prospective double blind study. Thirty four patients were screened; however, only 8 completed the study. Elderly men with COPD (70±4 years) participated of incremental and submaximal exercise testing, maximal inspiratory (PI<sub>max</sub>) and expiratory pressures (PE<sub>max</sub>) and blood sample analysis to determine plasmatic free L-carnitine. Protocols consisted of placebo supplementation during the first 6 weeks (glucose solution in 2 daily doses) and L-carnitine supplementation (two times a day, i.e., 2 g daily in water solution) after more 6 weeks. Patients did not know if they were receiving glucose (placebo) or carnitine. Patients were evaluated before and after placebo and supplementation. Data were analyzed by repeated measures analysis (ANOVA). Delta of change was compared by Student t test. Correlations between deltas of walking distance, PI<sub>max</sub> with plasmatic free L-carnitine were performed by Pearson's test.

**Results:** Placebo did not change plasmatic free L-carnitine, exercise capacity and pulmonary function. However, after 6 weeks of L-carnitine supplementation, plasmatic free L-carnitine (from 56±9 to 87±16µMol/L), submaximal exercise (from 446±47 to 498±35m), PI<sub>max</sub> (from 56±13 to 74±10cmH<sub>2</sub>O) and PE<sub>max</sub> (from 65±12 to 85±12cmH<sub>2</sub>O) significantly improved. Significant correlation was found between PI<sub>max</sub> and plasmatic free L-carnitine (r=0.65 and p=0.04). In addition, during L-carnitine supplementation no signals of intolerance or collateral effects were observed.

**Conclusion:** L-carnitine supplementation appeared to be safe, well-tolerated and positively influenced exercise capacity and respiratory muscle strength in COPD patients.

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## INTRODUCTION

Intolerance to exercise is a common manifestation in patients with chronic obstructive pulmonary disease (COPD), a fact that has been attributed primarily to respiratory disturbance<sup>1</sup>. However, it has been verified that systemic effects of COPD can be linked to exercise intolerance, such as pulmonary oxidative stress, and a high profile of pro-inflammatory cytokines<sup>2</sup>. In addition, muscle wasting and muscle dysfunction are recognized as important problems in COPD, contributing to morbidity and mortality<sup>3</sup>. Skeletal muscle dysfunction and weakness of the respiratory muscles have been progressively recognized as important factors in reducing exercise capacity and impairing health-related quality of life in these patients<sup>4</sup>. These COPD changes have been attributed to several factors including increased energy expenditure, decreased dietary intake, imbalance between protein synthesis and breakdown and weight loss<sup>4,5</sup>.

Muscle dysfunction in COPD seems to represent a combination of muscle wasting and remodeling, as reflected by changes on fiber-type distribution and muscle metabolism<sup>6,7</sup>. Therefore, a proportional decline of muscle function and mass would suggest that atrophy was the sole mechanism for muscle weakness; conversely, a disproportionate functional reduction in relation to muscle mass supports the notion that mass-independent ("qualitative") characteristics are also involved<sup>8</sup>. In fact, patients with COPD present significant reduction of oxygen delivery to the tissues, redistribution of fiber type within the muscle, capillary rarefaction, and decreased mitochondrial function, alterations that are all capable of reducing aerobic muscle capacity<sup>9</sup>.

In this context, novel ergogenic supplementation has been suggested to improve muscular performance<sup>10</sup>. In particular, L-carnitine is an endogenous compound with well-established functions in the energy intermediary metabolism<sup>11</sup>. L-carnitine function has been related to lipid metabolism, sparing muscle glycogen, improving tolerance to physical activity and reducing muscle fatigue<sup>11</sup>. However, in healthy subjects, the effects of long-term treatment with L-carnitine on physical performance are inconsistent.

In contrast, some studies have shown exercise performance improvement in cardiovascular<sup>12</sup>, and hemodialysis patients<sup>14</sup>. Association of L-carnitine supplementation with physical exercise enhanced exercise performance in COPD patients<sup>10</sup>. However, to our knowledge, the effects of L-carnitine alone in COPD patients have not been tested. Thus, the purpose of the present study was to verify the safety and effects of oral L-carnitine supplementation on functional capacity and pulmonary function in patients with moderate-to-severe COPD.

## METHODS

### *Subjects*

Ambulatory elderly COPD patients (male gender) with moderate to severe, but stable, airway obstruction and mild hypoxemia were recruited. Inclusion criteria were: elderly, male gender, clinical evidence of COPD, exertional dyspnea, forced expiratory volume on first second (FEV<sub>1</sub>) <50%, FEV<sub>1</sub>/forced vital capacity <70% of predicted percentage, PaO<sub>2</sub> ≥ 55 ≤ 75 mmHg in room air and body mass index between 20 and 25 Kg/m<sup>2</sup>. Patients with evidence of *cor pulmonale*, metabolic disease, endocrine, orthopedic, asthma, renal, hepatic, neuromuscular or cardiac disorders were excluded from the study. In addition, there were no changes in medications, no oral corticoids and no disease exacerbation in the preceding 2 months. All patients were nonsmokers at the time of the study. However, they all had smoking history of 20 cigarettes/day for more than 20 years.

The study protocol was approved by the Ethics Committee for Human Research of the Federal University of São Carlos and all patients signed informed consent to participate of the study.

### *Study design*

This was a prospective, cross-sectional study. After a screening visit to evaluate eligibility, patients underwent 2 days visits to perform baseline tests, which consisted of 2 six-minute walking tests, pulmonary function, and treadmill performance (study protocol). After this, patients were assigned to receive, initially, the placebo in two doses a day (2g of glucose water solution) during 6 weeks. Before the study protocol patients were

physically and clinically examined by a physician that re-evaluated the patients during and after the study. Symptoms such as diarrhea, vomiting, nausea or any intolerance supplementation signs were questioned during and after the study. After this time, all patients were re-evaluated (R1) and assigned to receive L-carnitine supplementation for the following six weeks (2g a day in two doses, water solution) and were reevaluated (R2). L-carnitine or placebo supplementation was dispensed in 10mL glass bottles containing 1g each, taken in two doses/day. The placebo was similar in color and taste after a sensory test that was conducted before the use of L-carnitine and placebo by 3 independent researchers. Patients did not know if they were receiving carnitine supplementation or placebo. L-carnitine was obtained from Sintofarma Laboratory (São Paulo, SP, Brazil). The purity of L-carnitine was evaluated by enzymatic method using a spectrophotometer *UV U1 - Ultrospec C100* (Pharmacia, Cambridge, England) and was found to be consistent with the concentrations stated on the labeling (98% of purity).

#### *Study Protocol*

The study procedures listed below were performed on three occasions: baseline (B), post-placebo (R1) and post L-carnitine supplementation (R2). Successive tests involving incremental exercise test, six-minute walking test, respiratory muscle strength, body composition and testing for plasmatic free L-carnitine were performed.

#### *Lung function test*

Vital capacity (VC) and forced vital capacity (FVC) maneuvers were performed with a spirometer according to recommendations for pulmonary function (Hand Held 2021; Vitalograph, Buckingham, England)<sup>10</sup>. At least three measurements of each maneuver were considered acceptable and determined the values of FEV<sub>1</sub>, VC, FVC, according to the standardization of lung function testing. Respiratory muscle strength was assessed by maximal inspiratory (P<sub>I<sub>max</sub></sub>) and expiratory (P<sub>E<sub>max</sub></sub>) pressure according Neder et al<sup>15</sup>. P<sub>I<sub>max</sub></sub> and P<sub>E<sub>max</sub></sub> were assessed with subject breathing at the level of residual volume (RV) and total lung capacity (TLC), respectively, using a manovacuometer (Ger-Ar Med, São Paulo, Brazil) with scale of  $\pm 300$  cmH<sub>2</sub>O. The subjects were verbally encouraged to give maximal effort. Patients were asked to

perform maximal inspiratory and expiratory efforts against an obstructed mouthpiece with a small leak to prevent patients from closing their glottis during the maneuver. The determinations were repeated until three measurements show variability < 5.

#### *Incremental exercise testing*

Subjects exercised on an Imbramed Milenium® ATL treadmill (Porto Alegre, RS, Brazil). After a 10-minute resting period, the exercise test was begun with a 2-minute warm-up (2 Km/h) with a constant 3% grade, followed by an increase in speed rate of 0.5 km/h every 2 minutes until exhaustion. The test was interrupted if dyspnea, leg fatigue, and disabling symptoms occurred, or by the investigator, for safety reasons. If SpO<sub>2</sub> dropped below 80% or if threatening signs and symptoms occurred, such as electrocardiography alterations, or if HR reached the predicted age maximum, the test could also be interrupted. Heart rate by electrocardiogram lead 1 (TC500, Ecafix, São Paulo, SP, Brazil) and arterial oxygen saturation (portable pulse oximetry Nonin® 8400, Plymouth, MS, USA) were continuously monitored throughout the test. In addition, arterial blood pressure was measured with a manual sphygmomanometer and stethoscope by indirect method<sup>10</sup>. At the beginning and at the end of the test patients were evaluated for breathing difficulty (dyspnea) using Borg's CR10 scale<sup>16</sup>. HR reserve was calculated as  $100\% - (100 \times \text{peak HR}) / (220 - \text{age})$ <sup>17</sup>. During the test, blood samples were withdrawn from each ear lobe at rest, every 2 minutes during the test and 2 minutes after the end of incremental exercise testing. Each blood sample was collected with a capillary tube that had been previously covered with 25µL heparin. After collection, the blood samples were transferred to 2-mL tubes containing 50 µL of 1% sodium fluoride in order to prevent glycolysis. Blood was stored at 10°C for further analysis. Blood lactate concentration was determined by an electroenzymatic method (YSI 1500® - Sport Lactate Analyzer, Yellow Springs, OH, USA) as previously described<sup>10</sup>.

#### *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<sup>18</sup>. To avoid learning effects, the best of two reproducible walks was used on

the occasion of the first visit. SpO<sub>2</sub>, 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 pre-test. The predicted values of distance walked were compared with those obtained by the patients, according to the American Thoracic Society Statement<sup>18</sup>.

#### *Body composition*

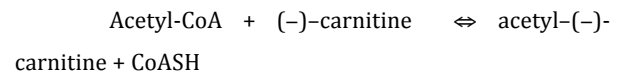
All body composition measurements were taken at 8 am when the patients arrived at the laboratory. Weight and height were measured and body mass index was calculated ( $Kg/m^2$ ). Lean body mass and fat mass were assessed using leg-to-leg bioelectrical impedance (Tanita Body Fat Analyser, TBF 300 M, Tokyo, Japan). Measurement of body composition was standardized. All measurements were taken on the same equipment by the same investigator each time. In the study visit mornings, patients were questioned about their liquid and food intake that morning. The validity and usefulness of bioelectrical impedance in the measurement of body composition in COPD patients has been documented<sup>19</sup>.

In addition, three consecutive measurements of triceps skinfold (TSF) thickness and three measurements of mid-arm circumference (MAC) were performed in the nondominant arm with a nondistensible measuring tape around the midpoint of arm tissue, halfway between the tip of the shoulder (acromium) and the tip of the elbow (olecranon). Mid-arm muscle area (MAMA) was calculated by the following equation:  $(MAC \text{ [in centimeters]} - (\pi \times \text{tricipital skinfold thickness, in millimeters})^2)^{20}$ .

#### *L-carnitine determination*

For the determination of the plasmatic free L-carnitine concentration, a 10-ml blood sample was obtained at baseline, and after 24 hours of placebo or L-carnitine supplementation, post-prandially. Blood was collected from an antecubital vein and was mixed with lithium heparin. Following centrifugation (10min. at 2500rpm), plasma was stored at -80°C until analysis. All measurements were performed in duplicate. Plasmatic free L-carnitine was determined by enzymatic method as described<sup>21</sup> in a spectrophotometer UV U1 - *Ultrospec C100* (Pharmacia, Cambridge, England).

The addition of carnitine to a system containing carnitine acetyltransferase and an excess of acetyl-CoA gives rise to the formation of CoASH:



Coupling of this system to any irreversible assay for CoASH then gives a measure of the (-)-carnitine added. The procedure uses the general thiol reagent 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to follow CoASH release<sup>21</sup>.

#### *Statistical analysis*

Values are reported as mean  $\pm$  SD. Due to Gaussian distribution and/or homogeneity of variable values, parametric tests were selected for statistical analysis. Comparisons between baseline, after 6 weeks of placebo (R1) and after 6 weeks of L-carnitine supplementation (R2) were compared first with one way ANOVA. In addition, delta of variation between both interventions (R1-baseline and R2-R1) was analyzed by Student's t test. Correlations between deltas of walking distance,  $PI_{max}$  with plasmatic free L-carnitine were analyzed by Person's Correlation. SPSS version 13.0 statistical software was used for data analysis (SPSS, Chicago, IL, USA). The level of statistical significance was set at  $p < 0.05$  for all tests.

## **RESULTS**

#### *Baseline evaluation*

A total of twenty patients were evaluated, however twelve patients were not eligible for the study. During the study two patients showed clinical instability and were excluded and 2 declined to participate in the study. In this context, only eight patients completed the study.

Baseline patient characteristics are presented in Table 1. All eight patients had moderate-to-severe airflow obstruction and 2 were classified as GOLD stage II, with the remaining patients being considered as GOLD stages III-IV<sup>1</sup>. All procedures were well tolerated by all patients, and no intolerance symptoms or signs were reported during the study period.

**Table 1: Baseline characteristics and pulmonary function.**

<b>Anthropometric Characteristics</b>	
Age (years)	70±3.2
Height (m)	1.62 ± 0.07
Body Mass (kg)	62 ± 10
Body Mass Index (kg/m <sup>2</sup> )	23 ± 4.2
<b>Pulmonary Function</b>	
FEV <sub>1</sub> , L	0.86 ± 0.27
FEV <sub>1</sub> (% predicted)	37 ± 11
FVC (% predicted)	41 ± 10
FEV <sub>1</sub> /FCV	46 ± 0.8
SVC (% predicted)	64 ± 10
MVV (% predicted)	37 ± 12
PI <sub>max</sub> (cmH <sub>2</sub> O)	66 ± 12
PI <sub>max</sub> (% predicted)	67 ± 18
PE <sub>max</sub> (cmH <sub>2</sub> O)	70 ± 6
PE <sub>max</sub> (% predicted)	70 ± 19
PaO <sub>2</sub> (mmHg)	64.4±8.4
PaCO <sub>2</sub> (mmHg)	40.7±4.0
SaO <sub>2</sub> (%)	92±3.6

Data are mean±SD. Definition of abbreviations: FEV<sub>1</sub>= forced expiratory volume in one second; FVC= forced vital capacity; MVV: maximal voluntary ventilation; SVC: slow vital capacity; lung PI<sub>max</sub>= maximal inspiratory pressure; PE<sub>max</sub>= maximal expiratory pressure. PaO<sub>2</sub>= arterial partial pressure of oxygen; PaCO<sub>2</sub>= arterial partial pressure of dioxide carbon; SaO<sub>2</sub>= arterial oxygen saturation (n=8).

*Lack of effect of performance during incremental exercise testing*

No significant changes were observed in maximal exercise tolerance after 6 weeks of L-carnitine supplementation. In addition, blood lactate, HR, SpO<sub>2</sub>, systolic and diastolic blood pressure did not change after L-carnitine supplementation (Table 2).

*Effects of Free L-carnitine supplementation on body composition and plasmatic free L-carnitine.*

There were no significant differences in baseline characteristics between placebo and L-carnitine supplementation, including body weight, MAC, MAMA, lean body mass or fat mass (p>0.05). In contrast, after 6 weeks of L-carnitine supplementation there was a

significant improvement of plasmatic free L-carnitine (Table 2 and Figure 1).

*Effects of L-carnitine supplementation on walking distance (SMWT) and respiratory muscle strength*

L-carnitine supplementation significantly improved walking distance when compared baseline to six weeks of placebo (Table 2, p<0.05). Delta comparisons between treatments (placebo versus L-carnitine) showed a significant increase of walking distance on L-carnitine group (Table 2, Figure 1).

PI<sub>max</sub> and PE<sub>max</sub> significantly improved after L-carnitine supplementation (Table 2, Figure 1C and 1D). In contrast, placebo did not modify PI<sub>max</sub> and PE<sub>max</sub> after 6 weeks. Significant correlation was found between plasmatic free L-carnitine and PI<sub>max</sub> deltas (r=0.65 and p=0.04).

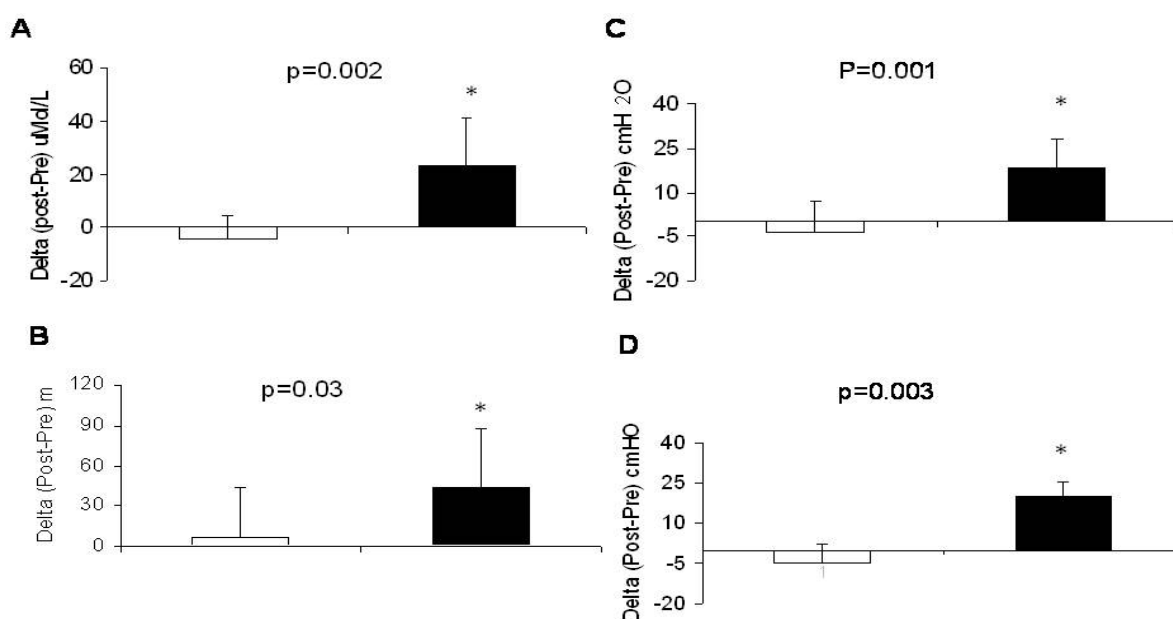
**Table 2. Effect of L-carnitine supplementation on body composition, maximal, submaximal performance, respiratory muscle strength and plasmatic free L-carnitine.**

	<b>Baseline (n=8)</b>	<b>R1 (n=8)</b>	<b>R2 (n=8)</b>
<b>Body Composition</b>			
BMI (kg/m <sup>2</sup> )	23±4.2	22±3.9	22±3.9
FFM (kg)	49.8±6.1	50±6.2	49.9±6.2
Fat mass (kg)	11.2±5.2	10.9±5.0	10.6±5.2
Triceps skinfold (mm)	10±5	10±5	11±5
MAC (cm)	26±4	27±4	27±4
MAMA	23±3	24±3	24±3
<b>Maximal exercise testing</b>			
Peak speed (Km/h)	5.0±0.6	5.1±0.9	5.3±1.1
Walking distance (m)	855±205	906±455	966±370
Heart rate Absolute (bpm)	121±16	123±14	127±12
Heart rate reserve (%)	81±12	82±10	85±9
SBP (mmHg)	159±32	166±39	164±28
SpO <sub>2</sub> (%)	84±6	84±5	85±6
Lactate (mM/L)	1.9±0.5	1.7±0.6	2.3±0.6
Borg Scale (0-10)	5±1.2	5.2±1.2	4.1±2.1
<b>Distance on SMWT, meters</b>			
	447±41	446±47*	498±35†
% predicted	77±8	78±8*	85±7 †
<b>PI<sub>max</sub>, cmH<sub>2</sub>O</b>			
	60±14	56±13*	74±10 †
% predicted	64±17	64±15*	84±13 †
<b>PE<sub>max</sub>, cmH<sub>2</sub>O</b>			
	70±14	65±12*	85±12 †
% predicted	72±20	67±18*	87±18 †
<b>Free L-carnitine, μMol/l</b>			
	63.4±8.0	55.9±9.5	87.1±15.8†

Data are showed as mean±SD. R1= reevaluation after 6 weeks of placebo; R2= reevaluation after 6 weeks of L-carnitine supplementation; BMI= body mass index; FFM= free fat mass; MA= mid-arm circumference; MAMA= mid-arm muscle area; SBP= systolic blood pressure; SpO<sub>2</sub>= peripheral oxygen saturation; SMWT= six-minute walking test; PI<sub>max</sub>=maximal inspiratory pressure; PE<sub>max</sub>= maximal expiratory pressure (n=8)

\*Significant differences between baseline and L-carnitine, ANOVA one way (p<0.05).

† Significant differences between placebo and L-carnitine, ANOVA one way (p<0.05).



**Figure 1.** Differences found between delta of variation between R1 (baseline – re-evaluation 1) and R2 (re-evaluation 1 - re-evaluation 2). L-carnitine supplementation is showed in black (■) and placebo is showed in white (□) to plasmatic free L-carnitine (A), walking distance (B) maximal inspiratory (C) and expiratory pressures (D). Paired T test \* Data are shown as mean±SD.

## DISCUSSION

Major findings of the study were that L-carnitine supplementation significantly improved plasmatic free L-carnitine concentration. Secondly, L-carnitine supplementation had an additive effect of performance on the six minute walking test and improved the respiratory muscle strength in moderate to severe COPD patients. However, L-carnitine supplementation did not modify body composition and maximal exercise capacity in patients with COPD.

### *Effects of L-carnitine supplementation on body composition and plasmatic L-carnitine*

Patients who have COPD typically present physical exercise intolerance. In addition, reduction of weight is associated with decreased exercise performance due to reduced muscle aerobic capacity and increased mortality, independent of lung function in patients with advanced COPD<sup>7,22</sup>. In this context, the supplementation with

bioactive nutrients that positively affect muscle energy and substrate metabolism can be an attractive therapy<sup>23</sup>. In the present study, L-carnitine supplementation did not change body composition. However, significant increase of plasmatic free L-carnitine was found after supplementation. Although the majority of individuals are capable of endogenous synthesis of carnitine<sup>11</sup> with a healthy nutrition, many metabolic disorders lead to decreased biosynthetic capacity and are at risk of developing carnitine deficiency. However, our patients presented an stable condition and parameters of body composition were in the 50% percentiles. Inconsistent results of weight gain have been reported by many authors in patients with COPD<sup>23</sup>. On the other hand, L-carnitine supplementation has been tested as a “fat

burner” due to its enhancement of lipid metabolism, but the real effects are still a matter of controversy<sup>11</sup>.

Moreover, our patients were older than other populations of COPD patients studied and the aging process has been described as leading to a reduction of L-carnitine stores<sup>24</sup>. In this context, L-carnitine supplementation has been effective in mitochondrial-supported bioenergetics improvement and also improves general antioxidant status, thereby attenuating any putative increase in oxidative stress<sup>25</sup>.

#### *Effects of L-carnitine supplementation on exercise performance*

It is well established that COPD has systemic consequences such as peripheral and respiratory muscle dysfunction<sup>1,3-5,7</sup>. Interestingly, in the present study, improvement of walking distance was promoted with L-carnitine supplementation ( $p < 0.05$ ). However, 6 weeks of L-carnitine was not enough to improve maximal exercise performance in these patients. Additionally, none of the physiologic parameters at exercise peak were enhanced after supplementation (Table 2). It is suggested that L-carnitine supplementation, solely due to potential effects on the oxidative metabolism, would enhance muscle endurance; however, the benefit to exercise tolerance was more effective at submaximal capacity than maximal performance. Our results are consistent with the findings described previously in experimental studies<sup>26</sup> and in humans<sup>27</sup>.

Other researchers have demonstrated that L-carnitine oral supplementation reduced oxidative stress<sup>24</sup>, the fatigue<sup>14,25</sup> and improved the muscle strength<sup>14</sup>. These results are relevant, since COPD may produce marked state pro-inflammatory and abnormality on muscle metabolism<sup>1,3</sup>. In addition, a lower percentage of type-I fibers and a corresponding higher percentage of type-II fibers has been reported in lower limb muscles of COPD patients and alterations are also enhanced by the aging process<sup>25</sup>. Thus, our results appear to be co-substantiated, since the ability at submaximal performance was significantly increased in our patients.

However, in our study, hemodynamic variables and blood lactate was not modified with L-carnitine loading at peak of exercise. In this way, the evaluation of these variables during submaximal performance would be more precise than during maximal performance. In fact, pulmonary

rehabilitation programs have demonstrated significant improvement of dyspnea and lactate reduction in submaximal rather than maximal intensities<sup>1</sup>.

#### *Effects of L-carnitine supplementation on respiratory muscle strength*

Diaphragmatic and peripheral muscle dysfunction have been assigned to marked alterations in the morphology and metabolism of respiratory muscles in COPD patients, due to hypoxia, oxidative stress, nutritional depletion, systemic inflammation, medication and disuse<sup>6</sup>. It is not surprising that the exercise-limiting symptoms in these patients are a sense of leg effort (exertional discomfort) or breathlessness (exertional dyspnea). There is a hypothesis to explain the increased respiratory muscle strength in our study: the potential alterations in the metabolism of respiratory muscles that could be enhanced by the L-carnitine supplementation. The diaphragm muscle of COPD patients undergoes a fiber-type shift toward more fatigue-resistant fiber. Additionally, changes in sarcomere length, mitochondrial density and enzyme activity occur within the diaphragm muscle fibers of these patients<sup>1,7,28</sup>. Consequently, pathophysiology of the failure of this muscle to generate force is reduced.

L-carnitine loading, in the present study, significantly improved in 24% and 23% of the inspiratory and expiratory muscle strength of our patients, respectively (see Table 2). In addition, significant and positive correlation ( $r = 0.65$ ,  $p < 0.01$ ) were found between  $PI_{max}$  and plasmatic free L-carnitine deltas after supplementation. However, no previous studies have reported the effects of L-carnitine supplementation on respiratory muscle strength alone. We postulated in a previous study that L-carnitine supplementation associated with respiratory muscle training significantly improved respiratory muscle strength<sup>11</sup>. These results are consistent with other investigators that found significant reductions of muscle fatigue in the elderly<sup>29</sup>, during hypoxic conditions<sup>31,32</sup>, and improvement in muscle strength in patients with peripheral arterial disease<sup>13</sup>. On the other hand, low carnitine levels may be associated with lower  $PI_{max}$  in type 2 diabetes<sup>34</sup>.



### Study limitations and strength

The main limitation of our study was the small number of participants, a fact possibly due to the strict criteria for patient inclusion, age (elderly), sex (only men) and the severity of the disease of the patients evaluated (FEV<sub>1</sub><50% of predicted and without corticoids medication). Thus, a study with larger number of patients would be useful to confirm the findings of this population. Another limitation of this study was the impossibility of obtaining ventilatory and metabolic measurements.

Moreover, in this study only one group of the recruited patients was followed throughout study period (baseline-placebo-L-carnitine supplementation); the other groups, used each patient was their own control. Therefore, the results were not influenced by inter-individual variations. This was considered the strength of this protocol (each subject was its own control). However, larger double-blind and controlled trials are need to confirm these preliminary findings.

### CONCLUSION

We concluded that 2g daily of oral L-carnitine supplementation during 6 weeks improved submaximal exercise tolerance and respiratory muscle strength in older men with moderate-to-severe COPD. In addition, L-carnitine supplementation did not have any collateral effects, demonstrating good tolerability and safety.

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