

Effect of L-carnitine on exercise performance in patients with mitochondrial myopathy

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Abstract

Exercise intolerance due to impaired oxidative metabolism is a prominent symptom in patients with mitochondrial myopathy (MM), but it is still uncertain whether L-carnitine supplementation is beneficial for patients with MM. The aim of our study was to investigate the effects of L-carnitine on exercise performance in MM. Twelve MM subjects (mean age \pm SD = 35.4 \pm 10.8 years) with chronic progressive external ophthalmoplegia (CPEO) were first compared to 10 healthy controls (mean age \pm SD = 29 \pm 7.8 years) before they were randomly assigned to receive L-carnitine supplementation (3 g/daily) or placebo in a double-blind crossover design. Clinical status, body composition, respiratory function tests, peripheral muscle strength (isokinetic and isometric torque) and cardiopulmonary exercise tests (incremental to peak exercise and at 70% of maximal), constant work rate (CWR) exercise test, to the limit of tolerance [Tlim]) were assessed after 2 months of L-carnitine/placebo administration. Patients with MM presented with lower mean height, total body weight, fat-free mass, and peripheral muscle strength compared to controls in the pre-test evaluation. After L-carnitine supplementation, the patients with MM significantly improved their Tlim (14 \pm 1.9 vs 11 \pm 1.4 min) and oxygen consumption ($\dot{V}O_2$) at CWR exercise, both at isotime (1151 \pm 115 vs 1049 \pm 104 mL/min) and at Tlim (1223 \pm 114 vs 1060 \pm 108 mL/min). These results indicate that L-carnitine supplementation may improve aerobic capacity and exercise tolerance during high-intensity CWRs in MM patients with CPEO.

摘要参考译文：

氧化代谢受损导致的运动耐受不良是线粒体肌病(MM)患者的一个主要症状,但仍然不确定补充左卡尼汀是否对线粒体肌病患者有利。我们的研究目的在于探讨左卡尼汀对线粒体肌病患者运动表现的影响。12例线粒体肌病伴有慢性进行性眼外肌麻痹(CPEO)的患者(平均年龄 \pm SD=35.4 \pm 10.8岁)与10例健康对照组(平均年龄 \pm SD=29 \pm 7.8岁)随机分配接受L-肉碱的补充(3g/每天)或安慰剂,一个双盲交叉试验。补充2个月左卡尼汀/安慰剂后对临床状态、身体成分、呼吸功能测试、周围肌肉力量(等速和等距转矩)和心肺运动试验(增量运动峰值和最大的70%),持续工作效率(CWR)运动测试,到耐受限度[Tlim])进行评估。与试验前评估的对照组相比,MM患者的平均身高、总体重、无脂体重和周围肌肉力量均较低。补充L-肉碱后,MM患者在持续运动时的Tlim(14 \pm 1.9 vs 11 \pm 1.4 min)和耗氧量($\dot{V}O_2$)均有明显改善, isotime(1151 \pm 115 vs 1049 \pm 104 mL/min)和Tlim(1223 \pm 114 vs 1060 \pm 108 mL/min)也得到改善。这些结果表明, L-肉碱的补充可以提高伴有慢性进行性眼外肌麻痹的线粒体肌病患者在高强度持续工作期间的有氧代谢能力和运动耐受性

diseases. These genetic defects in oxidative phosphorylation lead to specific abnormalities in exercise performance, such as a reduced maximal whole-body oxygen consumption and elevated lactate levels during exercise (1,2).

Exercise intolerance, particularly in the form of chronic progressive external ophthalmoplegia (CPEO), is a very common symptom in individuals with mitochondrial myopathy (MM) and is typically associated with undue fatigue at relatively low exertion levels (3). The most prominent symptoms come from skeletal muscle, due to their lower oxidative capacity and significant levels of mutant mtDNA compared with other tissues. Impaired oxidative phosphorylation may result in exercise intolerance breathlessness, exaggerated lactic acidosis, and low exercise capacity (4). This effect may augment the patient's

carnitine, an amine administered as a dietary supplement, has been reported to increase the influx of fatty acids into the mitochondria, facilitating pyruvate oxidation and reducing lactate synthesis (7). There is currently no available disease-modifying therapy for MM. Several agents, mostly nutritional supplements, including L-carnitine, have been investigated with double-blind, placebo-controlled studies, but none has demonstrated effects in clinical disease end-points, although numerous non-blind studies and case reports have suggested that it is beneficial (8).

Thus, the purpose of the present study was to determine whether L-carnitine can improve exercise tolerance in MM subjects. The central hypothesis was that the supplement would induce physiological changes by increasing oxidative metabolism, resulting in beneficial

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effects on skeletal muscle performance and exercise tolerance in these patients.

Material and Methods

Twelve patients with biopsy-proven MM followed at the Neuromuscular Division of the Escola Paulista de Medicina at the Universidade Federal de São Paulo (Unifesp) agreed to participate in the study. Patients were diagnosed after clinical and biopsy evaluation. The muscle biopsy was obtained from the right vastus lateralis at least 3 months before the beginning of the study protocol. Samples were frozen in isopentane cooled by liquid nitrogen for histological and histochemical analysis. All muscle biopsies exhibited abnormal mitochondrial proliferation as ragged red fibers under modified Gomori trichrome stain and succinate dehydrogenase staining, and as cytochrome c oxidase-deficient or negative fibers, as well as mosaic patterns dominated by type 1 fibers (8,9).

The inclusion criteria for the trial were: i) MM with CPEO; ii) age >14 years; and iii) complaint of exercise intolerance, mild fixed limb weakness, or myalgias. The exclusion criteria were: i) cardiac pacemaker; ii) severe limb weakness; iii) concomitant ergogenic supplementation treatment; iv) renal, cardiac, or pulmonary dysfunction; or v) participation in regular physical activity in the preceding year.

Written informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of the Universidade Federal de São Paulo (#0943/03).

Ten age- and gender-matched healthy volunteers constituted the control group. To match the habitual physical activities of the patients, controls were required to have very low daily physical activity scores as determined by the Baecke questionnaire (a total score of <6) (10).

Study protocol

The study protocol for MM patients followed a double-blind placebo/L-carnitine controlled crossover design. Before entering the study, all patients were evaluated for compliance of the proposed tests (pre-test evaluation). Control subjects did not receive any supplementary intervention and were only evaluated at the beginning of the study with the same tests, excluding the constant work rate (CWR) exercise test (Figure 1). For the double-blind trial, enrolled patients were randomly assigned to receive either 3 g L-carnitine or 3 g placebo in one daily dose (with breakfast or lunch) for 8 weeks. They took identical-looking capsules (DrogaDerma, Brazil). The second evaluation was performed 8 weeks after the patients had received either L-carnitine or placebo. After that, a 4-week washout period was carried out to minimize the drug effect and the third evaluation was performed after L-carnitine/placebo

crossover (Figure 1). Most studies that administered L-carnitine to patients with chronic diseases utilized daily doses between 2 and 4 g (11,12). The 3-g dose given in this study has been used empirically in the Neuromuscular Division of the Escola Paulista de Medicina, Unifesp.

Treatment adherence was confirmed by the patient during weekly phone calls and monthly appointments at the outpatient respiratory clinic. In these consultations, patients were asked to bring their empty bottles of L-carnitine and receive a new monthly supplement supply. They also reported possible side effects attributed to the supplement or placebo. The patients had 100% compliance with the protocol, and no patient dropped out during the study.

Measurements

Body composition. The patient's mid-arm circumference was measured, and the skin fold thicknesses at the bicipital and tricipital levels were obtained using a skin-fold caliper. The arm muscle circumference (cm) was derived from these readings. Bioelectrical impedance (Quantum BIA-101Q, RJL-101™, USA) was used to estimate the total body fat-free mass (FFM, kg). The FFM index (FFMI) was calculated as the ratio of the patient's FFM to his or her height (m²).

Pulmonary function testing. Spirometry lung volumes and maximal voluntary ventilation (MVV) were obtained in all subjects (Elite series, Medical Graphics Co. [MGC], USA). Data are reported as a percentage of the predicted values obtained in healthy Brazilian subjects (13-15).

Cardiopulmonary exercise testing (CPET). Incremental cardiopulmonary exercise tests (ICPET) were performed using an electromagnetically braked cycle ergometer (CPE 2000, MGC). The gas exchange, ventilator and cardiovascular variables were analyzed breath-by-breath (CardiO₂ System, MGC) during an ICPET following a linear "ramp" pattern of increase (16): 5-15 W/min and 15-25 W/min in patients and healthy subjects, respectively. This protocol was designed such that the test time was more than 8 min and less than 12 min, based on "symptom-limited interruption" for all the participants. The following variables were reported as 15-s means: oxygen uptake ($\dot{V}O_2$ in mL/min), carbon dioxide output ($\dot{V}CO_2$ in mL/min), minute ventilation ($\dot{V}E$ in L/min), and the end-tidal partial pressures of oxygen and carbon dioxide (PETO₂ and PETCO₂, mmHg). Subject heart rate (HR, bpm) was automatically calculated from the R-R distance obtained with 12-lead electrocardiogram tracing (CardiO₂ System, MGC). The $\dot{V}O_2$ at the estimated lactate threshold was evaluated using the gas-exchange threshold (GET) (17). The average $\dot{V}O_2$ in the last 15 s of exercise was considered representative of the subject's peak $\dot{V}O_2$ (18). On a different day, patients also underwent a CWR exercise test on a cycle ergometer with a load corresponding to 70% of that obtained in the peak

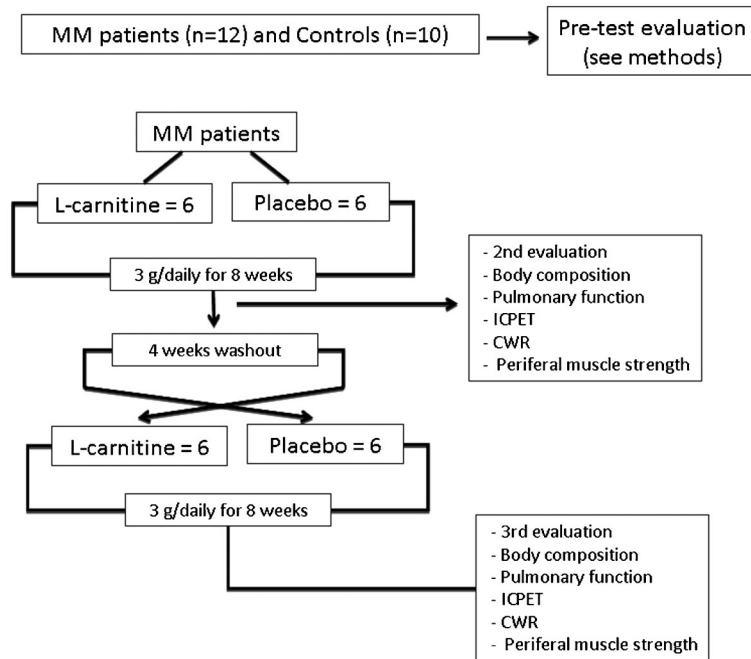


Figure 1. Design of study protocol. MM: mitochondrial myopathy; ICPET: incremental cardiopulmonary exercise test; CWR: constant work rate.

exercise to their limit of tolerance (Tlim).

Blood lactate. Blood samples from the earlobe were collected at peak of the ICPET and in the 5th min of the recovery period after L-carnitine or placebo treatment. These samples were analyzed on a lactimeter YSI model 1500 Sport (Yellow Springs Inc., USA) using an electro-enzymatic method.

Peripheral muscle testing. The isokinetic muscle endurance of the dominant knee extensor (quadriceps) was measured using a computer-based dynamometer (Contrex CE, Switzerland). The subject was seated upright on the dynamometer chair, with his or her back fully supported. The lever arm's mechanical axis of rotation was aligned with the knee's axis of rotation. Muscle strength (a concentric evaluation of the knee's flexion and extension movements) was determined from the peak torque (PT) measured during five consecutive maximal repetitions at an angular velocity at 60°/s. Isometric torque (IT) was evaluated from the maximal knee strength sustained for 5 s at 60°. The endurance of the quadriceps was determined as the total work (TW) achieved during 20 consecutive maximal repetitions at an angular velocity of 300°/s (19).

Statistical analysis

Statistical analysis was performed using SPSS 15.0 for Windows (USA). To compare data from controls with the placebo data of patients, we utilized *t*-tests for independent samples, and the results are reported as means and standard deviations. For comparison of the effect of placebo and L-carnitine in the patient group, a

crossover trial was performed using a generalized linear mixed model (GLM) design based on repeated measures to account for treatment and carry-over effects (placebo→L-carnitine vs L-carnitine→placebo) (Figure 1). For this analysis, we performed Mauchly's test of sphericity, and when this was not met, we applied the Huynh correction (20). In case of no influence of the intervention sequence, the randomized patients were analyzed as a single group (n = 12).

Results

During pre-test assessment, patients with MM were found to have lower weight, height, body mass index and FFMI, compared to normal subjects ($P < 0.05$, Table 1). The residual volume (RV; % predicted) was significantly increased, and the MVV (% predicted) was significantly lower in patients compared to controls. Patients also presented significantly lower peak torque, isometric torque, and total work (Table 2).

We also observed that peak $\dot{V}O_2$ (in mL/min and as a % predicted), peak work rate, and GET were significantly lower in patients compared to controls (Table 3). At peak exercise, patients with MM predominantly reported leg fatigue as evaluated by the Borg scale for lower limbs (Table 3).

No anthropometric or peripheral muscle test differences were observed after L-carnitine supplementation, compared to patients who received placebo (Table 4). Furthermore, MM subjects maintained the same body mass index, FFM, FFMI, and arm muscle circumference.

However, we did find a significant improvement in inspiratory capacity, both in absolute and % predicted, after L-carnitine supplementation.

With regard to the ICPET, no significant differences of metabolic, ventilator, or cardiovascular variables were detected comparing the studied interventions in the patient group (Table 5). In contrast, during CWR symptom-limited exercise testing (Table 6), we observed a significantly longer Tlim, higher $\dot{V}O_2$ at the 6th min of exercise (isotime) and at Tlim after L-carnitine supplementation compared to the placebo. We also observed a significantly higher oxygen pulse ($\dot{V}O_2/HR$, mL/beat) value at Tlim after L-carnitine compared to placebo. Importantly, at isotime, the gas-exchange ratio was lower after L-carnitine compared to placebo.

Discussion

In the evaluation of the physiological responses after a double-blind placebo/L-carnitine crossover design in patients with MM, we observed that L-carnitine (3 g/day) improved aerobic capacity and exercise tolerance during a high-intensity constant-work exercise in a select group of MM patients with CPEO.

Clinical characteristics and resting pulmonary function of patients with MM

As previously reported (21), our patients had lower weight, height, and muscle mass compared to controls and a significantly higher mean RV, RV to total lung capacity ratio, and reduced MVV compared to controls.

These findings might be related to a restrictive ventilatory pattern that is commonly observed in patients with neuromuscular diseases (22).

In the peripheral muscle evaluation, our patients exhibited significantly less muscle strength than controls, suggesting that the reduction in peripheral muscle strength might be related to alterations in oxidative phosphorylation, which is the hallmark characteristic of these patients (4,21,22). Our patients also showed significantly lower maximum exercise capacity and peak $\dot{V}O_2$ compared to controls. Several studies evaluating exercise tolerance in MM have demonstrated markedly low $\dot{V}O_2$ peak (23-27), reflecting impaired muscle mitochondrial oxidative phosphorylation. The maximal exercise capacity of MM subjects has been shown to directly correlate with the degree of O_2 extraction in the impaired muscle, which enables the use of the systemic arterial to venous O_2 difference as a surrogate marker for mitochondrial oxidative capacity (3,4).

Effect of L-carnitine supplementation on exercise performance in patients with MM

After oral supplementation of 3 g of L-carnitine over a 2-month period, we observed a statistically significant change in the patients' body composition as evaluated by their body mass index, FFM, and FFMI. To our knowledge, no studies have correlated changes in body composition with L-carnitine supplementation in patients with MM. Chazot et al. administered L-carnitine to chronic renal failure patients on dialysis and also found no changes in the body composition after this period of

Table 1. Characteristics of patients with mitochondrial myopathy (MM) and healthy controls.

	MM (n = 12)	Controls (n = 10)
Age (years)	34.5 ± 11.2	29 ± 7.8
Gender (M/F)	8/4	6/4
Weight (kg)	53.1 ± 13.5*	71.4 ± 9.8
Height (m)	1.61 ± 0.83*	1.70 ± 0.64
FFM (kg)	42.0 ± 9.3*	52.5 ± 7.9
BMI (kg/m ²)	20.6 ± 4.3*	24.5 ± 2.8
AMC (cm)	19.4 ± 4.4*	24.8 ± 4.7
FFMI (kg/m ²)	15.6 ± 2.4*	18 ± 2.0
FVC (% pred)	89 ± 13*	96.2 ± 9.8
FEV ₁ (% pred)	87 ± 16	93 ± 10
FEV ₁ /FVC (%)	80 ± 0.1	80 ± 0.8
RV (% pred)	120 ± 27*	91 ± 29
TLC (% pred)	90 ± 10	88 ± 8.0
RV/TLC (%)	33.5 ± 5.5*	24.7 ± 6.9
MVV (% pred)	89 ± 25.3	120 ± 47.6

Data are reported as means ± SD. BMI: body mass index; AMC: arm muscle circumference; FFM: fat-free mass; FFMI: fat-free mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; RV: residual volume; TLC: total lung capacity; MVV: maximal voluntary ventilation; % pred: percent of predicted. *P<0.05, compared to control (unpaired *t*-test).

Table 2. Peripheral muscle evaluation of patients with mitochondrial myopathy (MM) and healthy controls.

	MM (n = 12)	Controls (n = 10)
Peripheral muscle strength		
PT (60°/s; N/m)	93.4 ± 35.5*	150.2 ± 43.9
PT (% pred)	57.3 ± 15.9*	78.6 ± 16.8
IT (60°/s)	113.6 ± 42.8*	157.6 ± 51.9
TW (300°/s; J)	720.1 ± 336.0 ⁺	1577.5 ± 450.0

Data are reported as means ± SD. PT: peak torque; N/m: Newton/meter; IT: isometric torque; TW: total work; J: Joule; % pred: percent predicted. *P<0.05, ⁺P<0.001, compared to control (unpaired *t*-test).

supplementation, suggesting that L-carnitine did not influence body weight by decreasing fat mass (28).

No differences in peripheral muscle strength after L-carnitine or placebo administration were observed, a

finding that is in accordance with the results of a study in uremic patients with muscular atrophy. After 24-week treatment with L-carnitine (2 g at the end of hemodialysis or twice daily in the dialysis solution), other studies

Table 3. Exercise responses of the patients with mitochondrial myopathy (MM) and the healthy controls during peak cycling exercise.

	MM (n = 12)	Controls (n = 10)
Metabolic		
Work rate (Watts)	88 ± 28 ⁺	177 ± 38
$\dot{V}O_2$ (mL/min)	1193 ± 371 ⁺	2155 ± 480
$\dot{V}O_2$ (% pred)	64 ⁺	95
$\dot{V}O_{2AT}$ (mL/min)	704 ± 273*	1013 ± 261
GER	1.19 ± 0.1	1.20 ± 0.08
Ventilatory		
$\dot{V}E$ (% pred)	47.4 ± 14.3 ⁺	81.6 ± 20.9
f (ipm)	28.8 ± 8.5	42.2 ± 11.7
Vt (mL)	1372 ± 357 ⁺	1991 ± 404.2
$\dot{V}E/\dot{V}CO_2$	30 ± 4.85	31 ± 5.18
$\dot{V}E/\dot{V}O_2$	35.7 ± 7.5	38.1 ± 6.0
$\dot{V}E/MVV$	0.38 ± 0.1*	0.57 ± 0.15
PETCO ₂ (mmHg)	36.4 ± 5.5	37 ± 5.73
PETO ₂ (mmHg)	101.1 ± 6.7	103.7 ± 4.27
Cardiovascular		
HRmax (bpm)	159 ± 18*	177 ± 8
HR (% pred)	86 ± 8*	95 ± 4
$\dot{V}O_2/HR$ (mL/beat)	7.5 ± 2.8*	11.4 ± 3.2
$\dot{V}O_2/HR$ (% pred)	77*	97
Symptoms		
Borg dyspnea	5	3
Borg dyspnea/VE	0.111*	0.045
Borg LL	7	8
Borg LL/WR	0.096*	0.044

Data are reported as means ± SD. $\dot{V}O_2$: oxygen consumption; AT: anaerobic threshold; GER: gas-exchange ratio; $\dot{V}E$: minute ventilation; f: respiratory frequency; Vt: tidal volume; $\dot{V}CO_2$: CO₂ output; MVV: maximal voluntary ventilation; PETCO₂: end-tidal PCO₂; PETO₂: end-tidal PO₂; HR: heart rate; LL: lower limbs; WR: work rate; % pred: percent predicted. *P<0.05, ⁺P<0.001, compared to control (unpaired *t*-test).

Table 4. Anthropometry, lung function and peripheral muscle performance of mitochondrial myopathy patients, after L-carnitine or placebo supplementation.

	L-carnitine	Placebo
Anthropometry and lung volumes		
BMI (kg/m ²)	20.4 ± 1.1	20.6 ± 4.3
FFM (kg)	41.5 ± 2.8	42 ± 9.3
FFMI (kg/m ²)	15.4 ± 0.7	15.6 ± 2.4
AMC (cm)	20.3 ± 0.9	19.4 ± 4.4
IC (L)	2.45 ± 0.23*	2.26 ± 0.22
IC (% pred)	87 ± 6.92*	83.5 ± 6.40
Peripheral muscle tests		
PT (60°/s; N/m)	95.4 ± 12.1	93.4 ± 35.5
IT (60°/s)	115.5 ± 11.5	113.6 ± 42.8
TW (300°/s; J)	685.8 ± 367.4	720.1 ± 336

Data are reported as means ± SD. BMI: body mass index; FFM: fat-free mass; FFMI: fat-free mass index; AMC: arm muscle circumference; IC: inspiratory capacity; PT: peak torque; N/m: Newton/meter; IT: isometric torque; s: second; TW: total work; J: Joule; % pred: % predicted. *P<0.05, compared to placebo (unpaired *t*-test).

reported an approximately 7% increase in the diameters of type I and type IIa fibers, but no marked changes in type IIb fibers (29-31). These findings suggest a specific effect of L-carnitine on oxidative metabolism without causing muscle hypertrophy (31,32).

In our study, we observed a higher $\dot{V}O_2$ at Tlim and isotime during constant work exercise, and these findings were associated with significantly lower gas-exchange ratio values. This result supports our hypothesis that L-carnitine supplementation increases muscle oxidative activity in patients with MM. Similarly, Gorostiaga et al.

(33) demonstrated that endurance athletes supplemented with a daily dose of 2 g of L-carnitine for 28 days had significantly lower values for gas-exchange ratio during a 66% of maximal CWR exercise, on a cycloergometer. They suggested that the lower gas-exchange ratio values after L-carnitine were related to increased lipid utilization by peripheral muscles during exercise (33). Our hypothesis for the increase in the CWR at Tlim and the increase of $\dot{V}O_2$ at both isotime and Tlim is that L-carnitine optimizes glucose utilization during high-intensity exercise. Under these conditions, carnitine could remove the

Table 5. Exercise responses of the patients with mitochondrial myopathy during the incremental cardiopulmonary exercise test, after L-carnitine or placebo supplementation at peak exercise.

Peak	L-carnitine	Placebo
Metabolic		
Work rate (watts)	90.5 ± 9.4	88.0 ± 28.1
$\dot{V}O_2$ (mL/min)	1216.7 ± 402	1193 ± 371
Lactate (peak) (mM)	6.4 ± 3.0	5.7 ± 1.5
Lactate (recovery) (mM)	7.8 ± 3.3	8.7 ± 3.5
Ventilatory		
$\dot{V}E$ (% pred)	50.4 ± 15.0	47.4 ± 14.3
Cardiovascular		
HR (bpm)	160 ± 19	159 ± 18
$\dot{V}O_2$ /HR (mL/beat)	7.5 ± 2.6	7.5 ± 2.8
Symptoms		
Borg dyspnea	4	5
Borg lower limbs	7	7

Data are reported as means ± SD. $\dot{V}O_2$: oxygen consumption; $\dot{V}E$: minute ventilation; HR: heart rate; ICPE: incremental cardiopulmonary exercise test; peak: peak exercise in the ICPE; % pred: % predicted. There were no significant differences between groups (P>0.05, unpaired *t*-test).

Table 6. Metabolic, ventilatory and cardiovascular exercise variables at constant work rate (CWR) exercise at isotime and limit of tolerance (Tlim) in mitochondrial myopathy patients after L-carnitine or placebo supplementation.

CWR	L-carnitine	Placebo
Isotime		
$\dot{V}O_2$ (mL/min)	1151 ± 115*	1049 ± 104
GER	1.03 ± 0.04*	1.11 ± 0.04
$\dot{V}E$ (L/min)	45 ± 4	45 ± 4
HR (bpm)	157 ± 5	161 ± 4
$\dot{V}O_2/HR$ (mL/beat)	7.4 ± 0.7	6.8 ± 0.6
Limit of tolerance		
Tlim (min)	14 ± 1.9*	11 ± 1.4
$\dot{V}O_2$ at Tlim (mL/min)	1223 ± 114*	1060 ± 108
GER	1.4 ± 0.01	1.17 ± 0.03
$\dot{V}E$ (L/min)	48.4 ± 13	47.8 ± 14
HR (bpm)	159 ± 18	163 ± 17
$\dot{V}O_2/HR$ (mL/beat)	7.7 ± 2.4*	7 ± 2.2

Data are reported as means ± SD. $\dot{V}O_2$: oxygen consumption; isotime: 6th min of exercise; Tlim: time limit of tolerance in the CWR exercise; GER: gas-exchange ratio; $\dot{V}E$: minute ventilation; HR: heart rate. *P<0.05, compared to placebo (unpaired *t*-test)

excess acetyl groups that are formed during increased pyruvate oxidation, which predominantly occurs in type I muscle fibers. These effects maintain tricarboxylic acid cycle reactions and increase oxidative metabolism (34-36), which translated into an increased Tlim in our patients. In addition, high-intensity exercise, both in normal and MM subjects, has been found to reduce muscle carnitine concentration by two mechanisms: i) the high rate of acylcarnitine formation (7,36) and ii) increased metabolic oxidation of fatty acids (7). Indeed, up to an 85% reduction in muscle carnitine levels has been reported in patients with MM (7,37). Other studies have shown that in diseases with a primary or secondary carnitine deficiency, fatty acid oxidation occurs normally at rest but dramatically declines during prolonged exercise (cycloergometry) (34).

In conclusion, our findings suggest that at a higher rate of fatty acid utilization, L-carnitine supplementation was associated with a reduction in glucose metabolism, thus preserving glycogen content and ensuring maximum adenosine triphosphate oxidation rates. This was associated with fatigue reduction and improved exercise performance (7,37).

Study limitations

The results of this study should only be applied to patients with MM and with CPEO who are without evidence of cardiovascular manifestations or a more severe form of the disease. In this regard, our patients were selected on the basis of a histopathological and

clinical evaluation; their genotypic changes were not considered. We did not measure their plasma or muscle levels of carnitine, so we do not know whether these patients actually had a carnitine deficiency and/or how carnitine was retained in their muscles after supplementation. Another limitation was the small number of studied patients. However, they had all presented exclusively with CPEO at the Neuromuscular Diseases Clinic, Unifesp. However, in a *post hoc* analysis, this sample size resulted in significant power (>80%) for the principal variable (Tlim) considered in this study (38).

Our results indicated that in patients with MM (CPEO form), a 2-month program of L-carnitine supplementation (3 g/day) led to an improvement in aerobic performance characterized by: i) longer Tlim during a high-intensity constant-work exercise and ii) increased O_2 consumption measured at Tlim and isotime.

The influence of L-carnitine on oxidative metabolism in selected patients with MM provides insight into the regulation of skeletal muscle fat and carbohydrate oxidation during exercise. We suggest that these effects should be tested in future studies of patients with chronic and slowly-progressive muscle diseases such as MM.

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