Anais da Academia Brasileira de Ciências (2018) 90(3): 3099-3104
(Annals of the Brazilian Academy of Sciences)
Printed version ISSN 0001-3765 / Online version ISSN 1678-2690
http://dx.doi.org/10.1590/0001-3765201820170352
www.scielo.br/aabc | www.fb.com/aabcjournal

# L-carnitine supplementation in the recovery of plasma L-carnitine in patients with heart failure submitted to coronary artery bypass grafting

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*Manuscript received on May 17, 2017; accepted for publication on November 16, 2017*

**ABSTRACT**

Coronary artery bypass grafting reduces plasma L-carnitine and may impair the production of myocardial energy. L-carnitine supplementation may elevate plasma L-carnitine and increase cardiac mechanical efficiency. The objective of this study was to verify the recovery of preoperative plasma LC in patients with heart failure undergoing coronary artery bypass grafting supplemented with a daily oral dose of 50 mg / kg. Volunteers with ischemic heart failure who underwent surgery were randomized into a supplemented group (A-received 50 mg / kg L-carnitine) or placebo group (B) for 60 days. Supplementation was started on the third postoperative day. The spectrophotometric enzymatic method was used to quantify plasma L-carnitine. In the preoperative period, both groups had plasma L-carnitine adequate to the reference range (18.9-71.1 μM). On the second postoperative day, there was a reduction in plasma L-carnitine in groups A (17.4%) and B (14.4%). In the comparison between the groups, plasma L-carnitine was higher in group A than B in 10º ($p = 0.024$), 30º ($p = 0.001$), and 60º postoperative day ($p = 0.008$). Supplementation of L-carnitine at a daily oral dose of 50 mg / kg in patients with heart failure undergoing coronary artery bypass grafting may recover preoperative plasma L-carnitine within 10 days.

**Key words:** ischemic heart failure, myocardial revascularization surgery, oral L-carnitine supplementation, plasma L-carnitine.

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## INTRODUCTION

Of all the human organs, the heart has the greatest expenditure of energy at rest, and therefore has a high demand for energy to sustain its workload. Under physiological conditions, with an adequate supply of oxygen, the heart preferably uses beta-oxidation of fatty acids (FA) to generate energy. L-carnitine (LC) is a nutrient that plays an important role in the transport of FA to mitochondria and theirs consequent oxidation. In addition, LC acts in the removal of mitochondrial metabolism products (Silvério et al. 2009). In heart failure (HF), the heart becomes unable to provide oxygen and nutrients to meet the needs of the body. The available evidence suggests that a reduction of cardiac bioenergetics may be determinant in the development of HF (Wong et al. 2016). In ischemic HF, oxygen supply is decreased and myocardial revascularization is a treatment that aims to increase myocardial perfusion (Ziabakhsh-Tabary et al. 2014). In a single study published by Da Silva Guimarães et al. (2013), the authors showed that plasma LC was reduced after surgical revascularization. Low plasma LC can facilitate oxidative stress and, reduce energy production, compromising mechanical efficiency of the heart (Dantas et al. 2015). LC supplementation can be a strategy to recover and maintain adequate plasma LC. Despite the numerous clinical studies showing the benefit of supplementation in ischemic HF (Dinicolantonio et al. 2013, Soukoulis et al. 2009) there is still no recommendation of dosage and time of administration. Human studies used doses ranging from 2 to 6 g day for periods of days to weeks or months (Iliceto et al. 1995, Cruciani et al. 2006). We decided to test a daily oral dose of 50mg / kg. The objective of this study was to verify the recovery of preoperative plasma LC in patients with heart failure submitted to coronary artery bypass grafting supplemented with daily oral dose of 50 mg / kg.

## METHODS

This is a randomized, double blinded, placebo-controlled study. Volunteers with ischemic heart failure indicated for myocardial revascularization surgery were recruited at the National Institute of Cardiology / RJ between July 2012 and March 2014. Inclusion criteria were left ventricle ejection fraction (LVEF) ≤ 50%, myocardial viability and clinical and hemodynamic stability. Participants with liver or renal diseases or receiving L-carnitine supplement or with disabsorptive syndromes were excluded. Participants developing stroke, sepsis, prolonged hemodynamic shock and those who stopped using the supplement after surgery were also excluded. Participants were randomly placed in two groups using Excel® Microsoft®: LC supplemented group, which received daily oral dose of 50 mg/kg (Group A), or a control group (Group B), which received a placebo. The trial lasted for 60 days. The choice of daily oral dose was based on the results obtained by Iliceto et al. (1995), who administered a daily oral dose of 6 g for 12 months without observing any adverse effects. Today the United States Food and Drug Administration (FDA) consider that LC supplementation in many disorders is safe (El-Hattab and Scaglia 2015).

All patients were on the use of angiotensin converting enzyme inhibitors, beta blockers, angiotensin receptor blockers and diuretics during the study. Oral supplementation was started three days after surgery.

To determine the plasma LC, 10 mL of blood was withdrawn from each participant under fasted conditions and measured by the spectrophotometric enzyme method (Indyk and Woolard 1995) standardized by the Laboratory of Inborn Errors of Metabolism of the Federal University of Rio de Janeiro. The reference range was established between 18.9 to 71.1 µM. Blood samples were collected in the pre and postoperative periods (2$^{nd}$,

10th, 30th and 60th days) for comparison between the groups.

The study was approved by the Ethics Committee of the Federal University of Fluminense (CAAE: 00612812.0.0000.5243) and conducted according to the Declaration of Helsinki. All participants signed the Informed Consent Term. The study was registered in the Brazilian Registry of Clinical Trials (RBR-7376mq).

Data were analyzed using SPSS software V.10 (SPSS Inc.), PASW v.18 (IBM) and Microsoft Excel. The normality of the data was verified by the Shapiro-Wilk test. The groups were compared in the periods studied using Student's t-test and Mann-Whitney, if applicable. The differences were considered significant at $p < 0.05$.

## RESULTS

From July 2012 to March 2014, 46 patients were recruited and followed up. Six patients died, two had liver disease and one renal disease, three developed sepsis, two had hemodynamic shock and four were lost at follow-up. The remaining 28 participants completed the study. The demographic and clinical characteristics of the participants, prior to surgery, are presented in Table I.

The minimum and maximum total daily oral doses of LC supplemented were 3 and 4.8 g, respectively. Mean plasma LC of both groups, in the evaluated periods, are presented in Figure 1. Considering the reference range used (18.9 - 71.1 μM), adequate plasma LC were found in both groups in the preoperative period. In the comparison between the groups, on the second postoperative day of myocardial revascularization there was a reduction in plasma L-carnitine in groups A (17.4%) and B (14.4%), with no statistical difference ($p = 0.798$). Plasma L-carnitine was higher in group A than B in 10º ($p = 0.024$), 30º ($p = 0.001$), and 60º postoperative days ($p = 0.008$). It was observed

**TABLE I**
**Baseline characteristics.**

| | n (%) | Group A n=19 (%) | Group B n=9 (%) |
|---|---|---|---|
| Age[a] | 58.1 ± 10.5 | 60.9 ± 9.8 | 55.1 ± 10.9 |
| Male | 26 (92.9) | 17 (89.5) | 9 (100) |
| Body Mass Index (BMI)[ab] | 27.9 ± 4.1 | 28.4 ± 3.8 | 27.4 ± 4.6 |
| NYHA Class | | | |
| II | 16 (57.1) | 9 (56.3) | 7 (43.8) |
| III | 12 (42.9) | 5 (41.7) | 7 (58.3) |
| LVEF (%)[a] | 39.4 ± 12.0 | 38.8 ± 12.6 | 40.7 ± 10.6 |
| **Comorbidities** | | | |
| Hypertension[c] | 26 (92.9) | 18 (94.7) | 8 (88.9) |
| Type 2 Diabetes[d] | 13 (46.4) | 6 (31.6) | 7 (77.8) |
| Dyslipidemia[e] | 28 (100) | 19 (100) | 9 (100) |
| Previous myocardial infarction | 19 (67.9) | 12 (63.1) | 7 (77.8) |

[a] Mean ± standard deviation.
[b] BMI: Normal reference range 18.5 e 24.99 $Kg/m^2$ (de Onis and Habicht 1996).
[c] Resting blood pressure > 139/90 mmHg (Sociedade Brasileira de Cardiologia 2010).
[d] Fasting blood glucose >126 mg/dL (Sociedade Brasileira de Diabetes 2015).
[e] Total cholesterol > 239 mg/dL and Triglycerides < 150 mg/dL (Sposito et al. 2007).
LVEF – Left Ventricular Ejection Fraction > 50% Teichholz Method.
Group A = Supplemented Group B = Placebo.

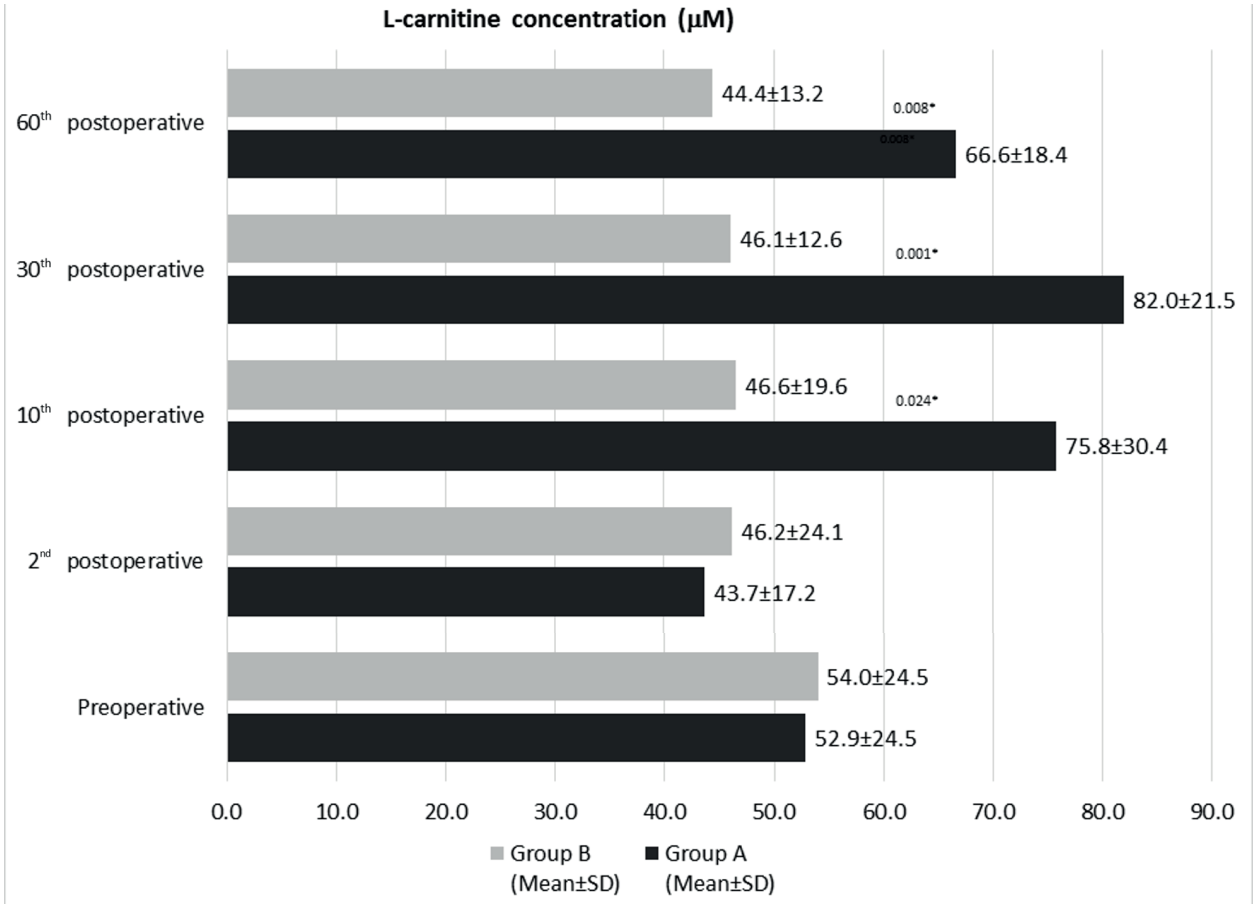


**Figure 1 -** Plasma concentrations of L-carnitine in all evaluated periods.
Results were presented as Mean and Standard Deviation (SD). Significance of differences: $p < 0.05$* compared A with B groups.

that group B did not recover the value found in the preoperative period.

## DISCUSSION

Plasma LC deficiency was not observed in the present study, although patients with HF may be deficient in nutrients important for cardiac metabolism, such as LC, coenzyme Q10, creatine, taurine and thiamine (Wong et al. 2016).

Surgical revascularization can improve myocardial perfusion but it may also cause increased production of free radicals and systemic inflammatory stimuli (Hatemi et al. 2016). These side effects may be responsible for the reduction of plasma LC observed after surgery. Similar results were found by Da Silva Guimarães et al. (2013) and Nemoto et al. (2004). L-carnitine is considered a conditionally essential nutrient because in certain critical metabolic situations its plasma concentrations are reduced (Bonafe et al. 2014).

In this study, LC supplementation at the daily oral dose of 50 mg / kg was initiated on the third postoperative day. An increase in plasma LC was observed in the supplemented group on the 10$^{th}$ day, 30$^{th}$ day and was maintained until the 60$^{th}$ postoperative day. This increase was expected due to supplementation with L-carnitine. The observed high plasma LC values may have been the result of continuous daily supplementation. This suggests that the metabolic requirement may have been exceeded. Physiologically, L-carnitine homeostasis is maintained by the balance between oral ingestion,

endogenous synthesis, tissue saturation and renal excretion (El-Hattab and Scaglia 2015). According to Evans and Fornasini (2003), the renal absorption threshold decreases when the plasma LC exceeds 60 μM. Vaz et al. (2002) demonstrated that in the presence of a high oral intake of LC and adequate saturation of tissues, there is a reduction in the efficiency of renal resorption.

There are some limitations of this study that should be mentioned. First, the high loss of follow-up, resulting in a small number of participants who completed the study. Second, this study did not evaluate the urinary L-carnitine required to confirm that the renal threshold was exceeded.

## CONCLUSIONS

The supplementation of L-carnitine at a daily oral dose of 50 mg / kg in patients with heart failure undergoing myocardial revascularization regains preoperative plasma LC in 10 days. Supplementation may be advantageous for patients with ischemic heart failure in removing toxic mitochondrial products and restoring cardiac energy metabolism, improving cardiac efficiency. This study opens up hypotheses for further studies of dose and time of supplementation.

## ACKNOWLEDGMENTS

The authors would like to thank the study volunteers.

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