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PRELIMINARY REPORT

Decompensated Chronic Heart Failure Reduces Plasma L-carnitine☆

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The heart has an intense aerobic metabolism and is among the most metabolically active organs in the body. Its tissue stores fatty acid, the main energetic substrate, and requires high concentrations of plasma L-carnitine. This nutrient is essential in the transport of fatty acids to the mitochondria to generate energy and maintain the proper concentration of coenzyme A free. In decompensated chronic heart failure metabolic changes, associated with inflammation, alter the metabolism of L-carnitine and compromise cardiac energy metabolism. The aim of this study was to evaluate plasma L-carnitine in chronic heart failure patients during cardiac decompensation. A cross-sectional study was conducted with 109 volunteers with chronic heart failure. Participants were stratified in the compensated (HF compensated) and decompensated (decompensated HF) groups. Plasma L-carnitine was evaluated by the spectrophotometric enzymatic method. Low plasma L-carnitine was found in the decompensated HF group ($p = 0.0001$). In this group it was also observed that 29.1% of the participants presented plasma L-carnitine below the reference range ($<$ 20 mmol). Reduced plasma L-carnitine in patients with decompensated chronic systolic heart failure was founded. These findings suggest that plasma L-carnitine assessment may be helpful in clinical practice for the treatment of patients with cardiac decompensation.

Key Words: Chronic heart failure, Plasma L-carnitine, Decompensated heart failure, L-carnitine deficiency.

Introduction

The Heart Failure (HF) represents a serious public health problem the world over due to its high rate of morbidity, mortality and economic overload. During HF, the heart is unable to supply adequate amounts of blood to meet metabolic needs (1). HF is characterized by dyspnea on efforts, water retention and decreased life expectancy. In cardiac decompensation, there is an exacerbation of signs and symptoms of HF at rest, requiring immediate and additional therapeutic intervention (2). Metabolic changes due to cardiac decompensation require greater production of cardiac energy. At the same time, the cardiomyocyte is now unable to meet this demand (3).

L-carnitine (LC) is a necessary nutrient for the transport of fatty acids (FA) through mitochondrial membranes, for generating energy and maintains the proper concentration of free coenzyme A (4). In humans, its homeostasis is maintained by intestinal absorption of dietary LC, biosynthesis, transport to the tissues and renal resorption (5). Plasma LC deficiency does not present a characteristic clinical picture, resulting in less energy production by the tissues (6).

Brazilian Registry of Clinical Trials: RBR-7376mq.

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The heart has an intense aerobic metabolism and it is among the most metabolically active organs in the body (7). Its tissue stores FA, the main energetic substrate, and requires high concentrations of LC, provided through plasma uptake, since the heart does not perform its biosynthesis (8). In HF, the LC metabolism is reported to be disturbed (9), and as the heart begins to fail, impairment in energy metabolism plays an important role in the pathogenesis and progression of HF (10). LC deficiency has been noted in critically ill patients (11). Its deficiency causes large changes in mitochondrial energy metabolism, resulting in deleterious clinical consequences (9). The aim of this study was to evaluate plasma LC in chronic HF patients during cardiac decompensation.

Materials and Methods

A cross-sectional study was conducted with 109 volunteers diagnosed with systolic HF recruited from April−October 2015 in a referral hospital, Rio de Janeiro, Brazil. The study was approved by the Ethics Committee of the University Hospital of the Federal Fluminense University (CAAE: 00612812.0.0000.5243) and conducted according to the Declaration of Helsinki. All participants signed the informed consent form. The study was registered in the Brazilian Registry of Clinical Trials (RBR-7376mq).

Participants diagnosed with compensated and decompensated chronic systolic HF were recruited. Left ventricular ejection fraction (LVEF) $<50\%$, evaluated by the Doppler echocardiogram, was used for the diagnosis of FH. The NYHA class was determined by the symptoms presented, according to the classification of the New York Heart Association. Clinical and demographic characteristics were collected from participants' charts. Those with hepatic and renal disease and supplement use containing L-carnitine were excluded from the study.

Participants were stratified in the compensated HF and decompensated HF groups. The participants of the decompensated HF group were selected at the emergency unit and presented Profile B, described as "warm and wet", based on clinical assessment of congestion and perfusion (congestion with adequate perfusion-wet-warm) (12). Participants in the compensated group were recruited during outpatient care.

To determine plasma L-carnitine, blood samples were collected during fasting. Subsequently, plasma was separated and stored at $-80°C$ until use. The spectrophotometric enzymatic method was used (13). Plasma L-carnitine values ≥ 20 mmol were considered adequate (14).

Statistical analyses were carried out using the software SPSS V.10 (SPSS Inc.). The normality of the data was verified by the Kolmogorov-Smirnov test. The groups were compared using anunpaired t-test for independent samples. The results are presented as a mean value and its standard deviation. Differences were considered significant at p-value <0.05.

Results

The demographic and clinical characteristics of the groups are presented in Table 1. We included 109 volunteers. Of these, 30 participants had compensated HF (80% male) and 79 decompensated HF (55.7% male).

Reduced plasma LC was observed in the decompensated HF Group (Figure 1). In this group were also found 23 (29.1%) participants with plasma LC below <20 mmol. Reduced plasma LC was not observed in participants in the compensated HF group.

Discussion

The heart muscle is dependent on the constant production of energy allowing it to maintain adequate electrical and mechanical activities (15).

FA is an important source of energy for the heart and LC is a cofactor of the carnitine palmitoyl transferase complex, which plays a crucial role in the transport of FA from the cytoplasm to the mitochondria, allowing the generation of energy (15). LC also participates in the elimination of toxic products from the cardiac mitochondrial metabolism and modulates the amount of free coenzyme A, favoring the oxidation of glucose reducing lactate production (16).

In addition, LC has been shown to inhibit apoptosis and to reduce cardiac arrhythmias due to the accumulation of FA and acylcarnitins (3).

Table 1. Demographic and clinical characteristics of the Groups

Characteristics[a]	Groups	
	Compensated HF (n = 30) n (%)	**Decompensated HF (n = 79) n (%)**
Age (years)[b]	63.0 ± 7.4	69.0 ± 13.9
Male	24 (80)	44 (55.7)
Smokers	27 (90)	61 (77.2)
Hypertesion	29 (96.7)	74 (93.7)
Dyslipidemia	30 (100)	75 (94.9)
Type 2 Diabetes	17 (56.7)	42 (53.2)
Overweight 25 a <30	20 (66.7)	55 (69.6)
Obesity, BMI> 30	5 (16.7)	14 (17.7)
NYHA class		
NYHA II	18 (60.0)	-
NYHA III	12 (40.0)	49 (62,0)
NYHA IV	-	30 (38.0)
Drugs in use		
Antidiabetic drugs	17 (56.7)	24 (30.4)
Lipid-lowering drugs	30 (100)	60 (75.9)
Antihypertensive drugs	29 (96.7)	69 (87.3)
Diuretics	15 (50.0)	79 (100)
Beta-blockers	26 (86.7)	54 (68.4)
Vasodilators	0 (0)	73 (92.4)
Digoxin	0 (0)	5 (6.32)

BMI, body mass index.
[a]Other than age, all data are expressed in terms of number of patients, with % of patients in parentheses.
[b]Results were presented as mean and standard deviation.

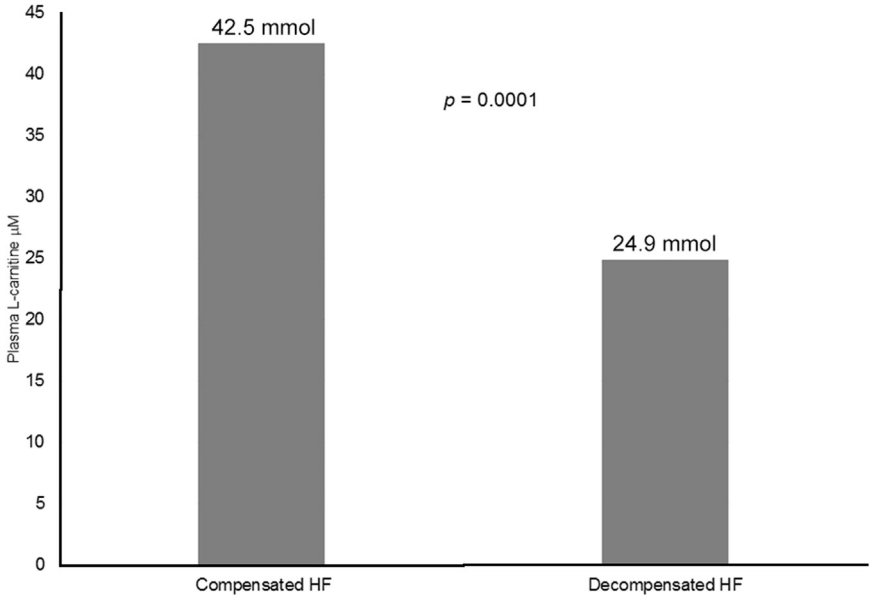

Figure 1. Plasma L-carnitine in compensated and decompensated HF groups. Compensated HF, Compensated Heart Failure; Decompensated HF, Decompensated Heart Failure.

The deficiency or anomalies in the carnitine-acyltransferase system results in the reduction of the oxidation of the FA and decrease energy production, besides accumulating free FA in the cytoplasm (17), provoking oxidative stress and inflammatory processes. The decrease in bioenergetics, due to the low plasma LC, plays an important role in the progression of HF (18).

Nickel et al. (2013) reported that the heart muscle of patients with HF presents disturbed energy metabolism due to mitochondrial dysfunction with dysregulation in FA oxidation (15). In addition a lower efficiency of energy use leads to accumulation of metabolic products are not effectively cleaned, leading to changes in cardiac metabolism (14). Secondary L-carnitine deficiency is described in some critical situations where there is a greater requirement L-carnitine to withdraw the accumulated products (11), which could justify the plasma LC deficiency found in decompensated HF patients.

Hunter WG, et al. (2016) reported that cardiac decompensation imposes metabolic changes that reflect alterations in the metabolism of FA and difficulty in cardiac energy generation. These authors observed alterations in the acylcarnitine profile of patients diagnosed with systolic HF and showed an oxidation of dysregulated FA (19). When FA oxidation is impaired, acyl-CoAs accumulate and reduce the intramitochondrial pool of LC because it is used to remove metabolites from metabolic block. This could explain the lower plasma LC found in patients with cardiac decompensation (15).

In vitro and in vivo studies have shown that LC modulates inflammatory processes by stimulating the reduction of inflammatory cytokines (16). Inflammation is important in clinical practice for patients with FH due to oxidative stress (20), which may contribute to the decompensation and progression of the disease.

The impact of these findings suggests that the assessment of plasma LC may be used in the clinical practice of patients with decompensated chronic HF. The method is simple and can identify low concentrations of plasma LC, easily treated by oral supplementation.

Conclusion

In summary, we found reduced plasma LC levels in patients with decompensated chronic systolic heart failure. These findings suggest that plasma LC assessment may be helpful in clinical practice for the treatment of patients with cardiac decompensation.

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