Original Research

CARDIOLOGY

Cardiology 2010;116:178–182
DOI: 10.1159/000318810

Received: January 21, 2010
Accepted after revision: March 29, 2010
Published online: July 16, 2010

L-Carnitine Treatment in Patients with Mild Diastolic Heart Failure Is Associated with Improvement in Diastolic Function and Symptoms

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Key Words
Diastology · Antioxidant · Diastolic function · L-Carnitine · Echocardiography · Heart failure, diastolic · Carnitine

Abstract
Objectives: L-Carnitine is a crucial component of activated fatty acid transport. The aim of this study was to evaluate the effect of L-carnitine on patients with a history of mild heart failure and diastolic dysfunction. ***Methods:*** Twenty-nine patients with a history of NYHA functional class II symptoms and ejection fraction >45% with documented grade 1 diastolic dysfunction on echocardiogram were randomized in blinded fashion to receive 1,500 mg of L-carnitine daily for 3 months in comparison to a no treatment group (31 patients). Baseline echocardiographic and follow-up measurements of diastolic parameters were assessed after 3 months. ***Results:*** Important parameters of diastolic function improved in the L-carnitine group only: left atrial size (3.6 ± 0.4 cm before treatment vs. 3.4 ± 0.5 cm after treatment, p = 0.01); isovolemic relaxation time (127 ± 26 ms before vs. 113 ± 24 ms after treatment, p = 0.007); septal mitral E′ velocity (0.064 ± 0.01 m/s before vs. 0.074 ± 0.01 m/s after treatment, p = 0.01), and lateral mitral E velocity (0.082 ± 0.01 m/s before vs. 0.091 ± 0.02 m/s after treatment, p = 0.006). Dyspnea also significantly improved in L-carnitine-treated patients. ***Conclusion:*** In patients with a history of diastolic heart failure, important indices of diastolic function and symptoms appear to improve with L-carnitine treatment.

Introduction

Heart failure secondary to left ventricular diastolic dysfunction with preserved systolic function is not uncommon with associated morbidity and mortality. The presence of even mild diastolic dysfunction in asymptomatic patients is associated with a fivefold increase in mortality compared with asymptomatic individuals with normal diastolic function [1]. Unlike systolic function, diastolic dysfunction grading can be difficult and the classification of diastolic function using echocardiography can be challenging. In a large study, among 647 individuals aged 50–89 years randomly assigned from an urban population, 2.5% had a diagnosis of impaired relaxation [2]. Successful treatment of isolated diastolic dysfunction could reduce the burden of heart failure in the aging population with an increasing prevalence of diastolic dysfunction.

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L-Carnitine is required for release of energy from fatty acid. L-Carnitine transports fatty acids into mitochondria for ATP production. Heart muscle is a highly oxidative tissue that produces more than 90% of its energy through fatty acid oxidation. In heart failure patients, the main myocardial energy substrates change from fatty acids to glucose, with a downregulation of the enzymes involved in fatty acid oxidation [3]. L-Carnitine is essential for the utilization of pyruvate in the Krebs cycle which may improve muscle metabolism by L-carnitine supplementation. Oral propionyl-L-carnitine has been shown to improve exercise tolerance in heart failure patients in some studies [4] but not others [5]. It has been tested in patients requiring cardiac surgery [6], in patients with angina pectoris [7–9], acute myocardial infarction [10, 11], shock [12] and peripheral vascular disease [13]. In this study, we evaluated the effect of L-carnitine in patients with symptomatic isolated diastolic heart failure using echocardiographic indices and symptoms.

Table 1. Baseline characteristics of the patients enrolled in the study

Variables	L-Carnitine	Control	p value
Age, years	55 ± 10	58 ± 7	0.2
Gender, F/M	21/8	24/7	0.6
Left atrial size, cm	3.6 ± 0.4	3.3 ± 0.5	0.02
Deceleration time, ms	268 ± 74	272 ± 83	0.9
IVRT, ms	127 ± 26	125 ± 28	0.5
Mitral E velocity, m/s	0.73 ± 0.2	0.70 ± 0.2	0.6
Mitral A velocity, m/s	0.85 ± 0.21	0.88 ± 0.2	0.5
Mitral E/A	0.85 ± 0.15	0.83 ± 0.19	0.5
Mitral E′ septal velocity, m/s	0.06 ± 0.011	0.06 ± 0.008	0.5
Mitral A′ septal velocity, m/s	0.09 ± 0.017	0.09 ± 0.016	0.3
Mitral E′ lateral velocity, m/s	0.08 ± 0.017	0.08 ± 0.019	0.9
Mitral A′ lateral velocity, m/s	0.1 ± 0.020	0.1 ± 0.018	0.4
E/E′ in lateral annulus	9.2 ± 3.3	8.7 ± 3.3	0.4
E/E′ in medial annulus	11.5 ± 3.9	10.7 ± 3.8	0.4

Patients and Methods

Patients were recruited from adult cardiology clinics at Modarres Hospital. Patients were eligible if they had grade 1 diastolic dysfunction based on echocardiography, dyspnea on exertion (NYHA functional class II) and left ventricular ejection fraction of >45%. Exclusion criteria were diabetes, thyroid disease, elevated serum creatinine, uncontrolled hypertension (systolic blood pressure >140 and diastolic pressure >90), valvular heart disease (more than mild), wall motion abnormalities or previous history of documented ischemic heart disease.

Exercise stress test with the standard Bruce protocol after reaching 85% of the expected predicted maximal heart rate was performed in all patients in an attempt to exclude most patients with asymptomatic ischemic heart disease. None of the study subjects received any medication before starting the study. After obtaining informed consent, 60 eligible individuals with isolated diastolic dysfunction documented on echocardiogram were randomized into 2 groups. Twenty-nine patients received L-carnitine, 1.5 g/day. L-Carnitine dosing was independent of body surface area. Thirty-one patients did not receive any treatment and served as a control arm. The participants were evaluated monthly for a period of 3 months. Repeated echocardiographic measurements of diastolic indices were performed after 3 months. The interpreting cardiologists and echocardiographers were blinded to the study groups. Assessment of dyspnea improvement was made by direct questioning by the treating physician during a follow-up visit.

All of the measurements were conducted using an ultrasound machine with a 3.5-MHz transducer. Doppler measurements of diastolic function were averaged over 3 consecutive cardiac cycles. Transmitral pulsed-wave Doppler velocities were recorded at rest from an apical 4-chamber view with a Doppler sample of 2 mm placed at the tip of mitral leaflets. Tissue Doppler imaging of the interventricular septum and lateral wall were used to measure early diastolic myocardial peak velocity (E′) at the septal and lateral mitral annulus. These variables were: (1) left atrial (LA) diameter in parasternal long axis view (cm); (2) deceleration time (DT, ms); (3) isovolemic relaxation time (IVRT, ms); (4) mitral E = peak velocity of the early filling wave of the transmitral flow (m/s); (5) mitral A = peak velocity of the atrial filling wave of the transmitral flow (m/s); (6) mitral E/A; (7) mitral E′ = early diastolic mitral annular relaxation velocity (m/s); (8) mitral A′ = peak velocity of the atrial filling wave of the mitral annular flow (m/s); (9) E/E′ in lateral annulus, and (10) E/E′ in medial annulus.

Statistical Analysis

Data are expressed as mean ± SD. Because continuous variables were not normally distributed we used non-parametric tests for analysis of differences between the study groups using Mann-Whitney U and Wilcoxon signed rank tests for analysis of differences between the study groups. SPSS 10.0 (SPSS Institute Inc, Chicago, Ill., USA) was used as the statistical software package. All p values reported are 2-sided and p values of <0.05 considered statistically significant.

Results

There were 21 females and 8 males in the treatment group. Wall thicknesses were within the normal range. There were 24 females and 7 males in the control group (p = NS). The ages (mean ± SD) of the treated and non-treated groups were 55 ± 10 and 58 ± 7 years, respectively (p = 0.27). Baseline characteristics and measurements in all patients at the start of the study are shown in table 1. Except for LA size, all parameters were similar

Table 2. Echocardiographic data after 3 months comparing treatment with no treatment groups

Variables	L-Carnitine	Control	p value
Left atrial size, cm	3.4 ± 0.5	3.3 ± 0.6	0.4
Deceleration time, ms	267 ± 58	271 ± 81	0.8
IVRT, ms	113 ± 24	123 ± 25	0.091
Mitral E velocity, m/s	0.76 ± 0.12	0.69 ± 0.21	0.3
Mitral A velocity, m/s	0.85 ± 0.16	0.89 ± 0.18	0.3
Mitral E/A	0.92 ± 0.18	0.82 ± 0.10	0.023
Mitral E′ septal velocity, m/s	0.074 ± 0.018	0.069 ± 0.011	0.5
Mitral A′ septal velocity, m/s	0.092 ± 0.019	0.096 ± 0.018	0.3
Mitral E′ lateral velocity, m/s	0.091 ± 0.02	0.085 ± 0.02	0.3
Mitral A′ lateral velocity, m/s	0.1 ± 0.024	0.1 ± 0.019	0.026
E/E′ in lateral annulus	8.8 ± 2.2	8.4 ± 3.4	0.6
E/E′ in medial annulus	11 ± 3.1	10.2 ± 3.7	0.5

Table 3. Echocardiographic data before and after 3 months in non-treatment group

Variables	Baseline	3 months later without L-carnitine	p value
Left atrial size, cm	3.3 ± 0.5	3.3 ± 0.6	0.4
Deceleration time, ms	272 ± 83	271 ± 81	0.4
IVRT, ms	125 ± 28	123 ± 25	0.6
Mitral E velocity, m/s	0.7 ± 0.2	0.69 ± 0.21	0.6
Mitral A velocity, m/s	0.88 ± 0.2	0.89 ± 0.18	0.9
Mitral E/A	0.83 ± 0.19	0.82 ± 0.10	0.6
Mitral E′ septal velocity, m/s	0.066 ± 0.008	0.069 ± 0.011	0.1
Mitral A′ septal velocity, m/s	0.095 ± 0.016	0.096 ± 0.018	0.7
Mitral E′ lateral velocity, m/s	0.083 ± 0.019	0.085 ± 0.02	0.4
Mitral A′ lateral velocity, m/s	0.11 ± 0.018	0.11 ± 0.019	0.1
E/E′ in lateral annulus	8.7 ± 3.3	8.4 ± 3.4	0.5
E/E′ in medial annulus	10.7 ± 3.8	10.2 ± 3.7	0.2

between the 2 groups (in the treatment group LA size before L-carnitine treatment was 3.6 ± 0.4 cm and in the control group it was 3.3 ± 0.5 cm; p = 0.024). There were no changes in echocardiographic parameters of patients in the non-treatment group whereas important indices of diastolic parameters (LA size, mitral E/A ratio and annulus velocities) showed significant improvement after 3 months of L-carnitine therapy. Comparison between baseline and 3 months of treatment can be seen in tables 2–4. Furthermore, as mentioned, in individuals who received treatment, in comparison to the control group, L-carnitine was associated with a significant improvement in dyspnea symptoms during follow-up evaluation. Twenty-six patients in the treatment group had an improvement in their symptoms in comparison to 2 participants in the control arm ($p < 0.01$ by Fisher's exact test). After treatment, mitral E/A measurements were 0.82 ± 0.1 in the control vs. 0.92 ± 0.18 in the treatment arm (p = 0.023 by Mann-Whitney U test). Mitral A′ in lateral annulus was 0.11 ± 0.019 m/s in the controls vs. 0.10 ± 0.024 m/s in the treatment arm (p = 0.026 by Mann-Whitney U test). In patients treated with L-carnitine, important parameters of diastolic function improved as follows: LA size (3.6 ± 0.4 cm before treatment vs. 3.4 ± 0.5 cm after treatment, p = 0.01); IVRT (127 ± 26 ms before treatment vs. 113 ± 24 ms after treatment, p = 0.007); septal mitral E′ velocity (0.064 ± 0.011m/s before treatment vs. 0.074 ± 0.018 m/s after treatment, p = 0.01), and lateral mitral E velocity (0.082 ± 0.017 m/s before treatment vs. 0.091 ± 0.02 m/s after treatment, (p = 0.006; tables 3, 4).

Table 4. Echocardiographic data before and after 3 months in the treatment group

Variables	Baseline	3 month after L-carnitine	p value
Left atrial size, cm	3.6 ± 0.4	3.4 ± 0.5	0.01
Deceleration time, ms	268 ± 74	267 ± 58	0.96
IVRT, ms	127 ± 26	113 ± 24	0.007
Mitral E velocity, m/s	0.73 ± 0.2	0.7 ± 0.12	0.4
Mitral A velocity, m/s	0.85 ± 0.21	0.85 ± 0.16	0.6
Mitral E/A	0.85 ± 0.15	0.92 ± 0.18	0.1
Mitral E′ septal velocity, m/s	0.064 ± 0.011	0.074 ± 0.018	0.013
Mitral A′ septal velocity, m/s	0.093 ± 0.017	0.092 ± 0.019	0.7
Mitral E′ lateral velocity, m/s	0.082 ± 0.017	0.091 ± 0.02	0.006
Mitral A′ lateral velocity, m/s	0.1 ± 0.02	0.1 ± 0.024	0.1
E/E′ in lateral annulus	9.2 ± 3.3	8.8 ± 2.2	0.2
E/E′ in medial annulus	11.5 ± 3.9	11 ± 3.1	0.1

Discussion

The prevalence of diastolic heart failure differs considerably between countries [1, 14]. In terms of pathophysiology, a normal forward cardiac output in patients with diastolic heart failure can only be maintained by a compensatory elevation of ventricular filling pressure. L-Carnitine is a crucial component of the activated fatty acid transport mechanism into the mitochondria where β-oxidation occurs with release of energy in the ATP form. In 1973, L-carnitine deficiency was discovered in some pa-

tients with cardiomyopathy and reduced fatty acid oxidation [15]. The result was a decrease in ATP concentration in the myocardial tissue [16]. After longer periods (>20 weeks) of L-carnitine deficiency, alterations occured in the myocardium that might have resulted in impaired contractile performance, particularly at higher workloads [17]. In a rat model of L-carnitine deficiency, it was demonstrated that as led as 3–6 weeks of severe systemic L-carnitine deficiency led to abnormalities in myocardial function including systolic dysfunction, reduced contractile reserve, and a blunted frequency-force relationship [18]. In a model [19], L-carnitine supplementation had a positive and dose-dependent effect on preserving ventricle compliance and improving myocardial relaxation [20]. Furthermore, L-carnitine supplementation has been shown to improve diastolic and systolic function in diabetic rat hearts [21]. In our study, we found that L-carnitine improves LA size, IVRT, septal and lateral mitral E′ velocities. We administered it at a dose of 1.5 g/day based on a previous study by Bain et al. [22] showing nonlinearity in the pharmacokinetics of oral L-carnitine above a dose of 0.5 g 3 times/day. In our study, L-carnitine treatment for 3 months showed improvement in some important indices of diastolic parameters such as IVRT and mitral annular Doppler velocities together with improvement in symptoms. Isovolumic relaxation is energy-dependent, requiring ATP for calcium ion uptake by the sarcoplasmic reticulum. In diastolic dysfunction, a proposed metabolic explanation is thought to be impaired generation of energy, which diminishes the supply of ATP required for the early diastolic uptake of calcium by the sarcoplasmic reticulum and relaxation. Fatty acid oxidation for ATP production occurs when the cytoplasmic long-chain acyl-CoA is transported into the mitochondrial matrix. This transportation from the cytosol into the matrix is regulated by a L-carnitine-dependent transport system [23]. In agreement with our findings, a small clinical trial using trimetazidine (involved in the fatty acid metabolism) for 6 months has shown improved diastolic function as assessed by an increase in the peak E/A ratio on mitral flow (from 0.68 ± 0.1 to 0.89 ± 0.3) in comparison to a placebo [24]. In our study the L-carnitine-treated group experienced more symptom relief during exertion suggesting that improvement in the diastolic parameters of our treated patients translated into clinical benefit. Improvement in diastolic parameters in our population was significant but small. However, we only enrolled patients with mild diastolic dysfunction explaining the only modest changes in the diastolic parameters. Our results need to be validated in larger trials and in patients with more advanced diastolic heart failure. Our study is hypothesis-generating and should be used for future design of larger clinical trials with regard to the L-carnitine effect on diastolic heart failure. The clinical effect of L-carnitine treatment has been documented in patients with peripheral vascular disease. It has been shown to correct secondary muscle L-carnitine deficiency in patients with peripheral vascular disease, significantly improving walking capacity [25]. There have been several studies evaluating L-carnitine treatment in cardiovascular diseases and heart failure [26]. A multicenter trial CEDIM (L-carnitine Ecocardiografia Digitalizzata Infarto Miocardico) showed a positive effect of L-carnitine on cardiac remodeling after myocardial infarction [27]. The effect of L-carnitine treatment in patients with heart failure has shown significant increases in exercise capacity, maximum exercise time, peak heart rate, and peak oxygen consumption consistent with a positive effect of L-carnitine treatment as was found in our population after L-carnitine treatment [28–30]. Improvement in echocardiographic parameters similar to our findings has been documented which validates our data [28]. The effect of L-carnitine treatment on ejection fraction has been inconsistent [28, 29]. However, these studies lack a control group in contrast to our study showing a positive effect of L-carnitine treatment in comparison to a control group. Improvement in a 3-year survival observed after L-carnitine treatment in patients with dilated cardiomyopathy and class III–IV heart failure is promising warranting further investigation [30].

Limitation

We did not measure the L-carnitine level in our population. L-Carnitine deficiency can lead to myocardial abnormalities [18]. However, secondary L-carnitine deficiency is very rare. Furthermore, our study excluded patients with diabetes, chronic ischemia or hypertension limiting our findings to selected patients without these comorbidities. We enrolled only a small number of patients for this pilot study. Therefore, our results need to be confirmed in larger randomized trials.

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