

# An Interventional Study of Carnitine in Patients with Congestive Heart Failure

F. Jalali MD\* and K. O. Hajian-Tilaki PhD\*\*

## Abstract

**Background-** Carnitine has a major role in utilization of fatty acids and glucose by the myocardium. Some patients with heart failure have carnitine deficiency. This study evaluates the effects of oral carnitine on heart failure.

**Methods-** This prospective interventional study was conducted on 41 patients with heart failure on the basis of the Framingham classification. Before and after intervention with 500mg of carnitine in 2 divided doses for six months, the general condition and functional class were evaluated and end-diastolic, end-systolic diameters, ejection fraction, left atrial diameter and severity of mitral regurgitation were measured by color Doppler, M-mode, and 2-D echocardiography. These data in addition to sex, age and etiology of heart failure were analyzed using SPSS software with paired t- test and Wilcoxon-matched pair test.

**Results-** The mean age of the patients under study was  $60.2 \pm 15.3$  years. Out of 41 patients, 27 subjects were males and 14 were female. The causes of heart failure were valvular heart disease, coronary artery disease and dilated cardiomyopathy in 10, 16 and 16 patients, respectively; and one patient had both valvular and coronary artery disease. Carnitine reduced end-diastolic, end-systolic and left atrial diameter, increased ejection fraction, improved function class and degree of mitral regurgitation. All the changes were statistically significant.

**Conclusion-** The results show that 500mg oral daily carnitine for six months has favorable clinical effects on heart failure and improves cardiac echocardiographic parameters (*Iranian Heart Journal 2006; 7 (3):9-15*).

**Key words:** carnitine ■ ejection fraction ■ heart failure ■ echocardiography

Refractory heart failure patients suffer serious problems. In spite of progress in medical and nursing care in hospitals and home and the high cost of their management, they are not able to return to their job with satisfaction.<sup>1-7</sup> Medical processes including modern drug and non-drug therapy such as PTCA, stent, enhanced external counter pulsation (EECP), coronary bypass surgery, heart transplantation, etc., are the modern methods of treating such patients.

However, in many cases these patients are not able to pay for their charges because of a lack of financial support and low income. In addition, age, co-morbidity, such as carotid artery, cerebral, kidney and liver diseases, diabetes mellitus and hypertension preclude applying these methods of therapy. In these high risk groups, conventional drug therapy may be preferable because of less expense and fewer side-effects but may have less efficacy on long-term survival.<sup>1</sup>

Received Nov 13, 2005; Accepted for publication Sep. 26, 2006.

From the \*Department of Cardiology, Shaheed Beheshti Hospital, Babol Faculty of Medicine, and \*\*Department of Social Medicine and Health Babol University of Medical Sciences, Babol, Iran. Fax: 0098-111-2229936 of Medical Sciences, Babol, Iran; Email:SFJalali42@yahoo.com

For severe heart failure patients, many drugs including positive inotropic agents such as digoxin, digitoxin, sympathomimetic amines, arterial vasodilators and phosphodiesterase inhibitors have been used. These conventional drugs have practically no significant effect on life expectancy and may only increase life satisfaction and relieve the clinical symptoms. All of these drugs have some side effects that can add to disability and mortality as well.<sup>2, 8-12</sup>

Carnitine (betahydroxy gamma-three methyl ammonium butyrate) is a necessary cofactor for entry of fatty acids, facilitating the aerobic metabolism of carbohydrates and increasing the rate of phosphorylation-oxidation and extraction of organic acids. This substance is made in the liver and kidney from the residuals of lysine; the red meats and chicken are the main sources of carnitine. The four microelements that are necessary for its production are vitamin C, B6, B12 and iron. The prescription of carnitine to normal subjects has no side effect, and it has been confirmed that the dose of carnitine up to 15g per day can be tolerated.<sup>12-17</sup> In fact, the cause of arrhythmias due to myocardial ischemia is lack of heart carnitine and accumulation of long chain fatty acids. The deficiency of carnitine blocks metabolism of long-chain fatty acids in the body and thus leads to blocked hepatic metabolism of ketones.<sup>12</sup> The appearance of lipid cytoplasmic inclusions in myocytes and hepatocytes are characteristic.

The deficiency of carnitine might be primary or secondary. The primary deficiency is due to the defect in absorption or synthesis or carnitine action. This carnitine deficiency leads to hypoglycemia, coma or CHF. The secondary deficiency is observed in RTA (renal tubular acidosis) cases because of increasing urinary excretion.<sup>12</sup> The symptoms of carnitine deficiency are classified into two groups of systematic and myopathic disorders. The systematic disorder originates from the deficiency of

carnitine concentration in plasma, muscle and kidney, which leads to muscle weakness, cardiomyopathy, hepatic failure, impairment in ketone production and fasting hypoglycemia, and myopathic disorder leads to muscle weakness originating from lipid infiltration in muscle fibers.<sup>12</sup>

Published studies have documented that prescription of carnitine in patients with heart failure improves cardiac indices.<sup>13-23</sup>

For example, Terranova et al.<sup>14</sup> found that 300 mg carnitine for 4.5 months had an effective response in treating lower limb arterial obstruction without any side effect. Matsomuto et al.<sup>16</sup> reported that prescription of 500 mg/day carnitine for 6 months relieved chest pain, increased left ventricle ejection fraction and eventually decreased complications and mortality. However, the optimal dose and duration of carnitine still is controversial and there is no definite therapeutic strategy for management of patients.

The aim of this study was to evaluate the effect of oral carnitine 500 mg/day (two doses of 250 mg/day) on cardiac outcomes in patients with congestive heart failure.

## Methods

We conducted an interventional study (before and after) in patients with diagnosis of congestive heart failure (coronary artery disease, cardiomyopathy, valvular disease). All these patients had contraindications for surgical therapy and/or they did not consent to surgical therapy. The patients were referred to the university heart clinic or private clinic between 2002 and 2004 with clinical and paraclinical criteria of heart failure based on Framingham standard classification and did not respond to conventional treatment. All the patients gave a written consent for recruitment of our carnitine therapy. At entry, all the patients underwent clinical and paraclinical exams like ECG, CXR, echocardiography (M-mode, 2-D, color Doppler), thallium scan

and if necessary, coronary angiography and catheterization.

The cardiac outcomes (end-diastolic diameter, end-systolic diameter, ejection fraction, size of left atrium, functional class and the degree of mitral regurgitation) were measured at the entry and end of the study. The cause of cardiac failure and the demographic data such as age and gender were collected. The patients were prescribed oral carnitine tablets of 250mg (Daro, Tehran). The dose of carnitine was 500 mg/day (two doses of 250 mg) with a duration of six months. Patients who were not compliant because of the expense of carnitine or lack of tolerance were excluded from our study. Compliance was confirmed by the patients' accompanying persons. In cases of hospitalization, the patients were excluded. Overall, 41 patients met the study criteria and were compliant and had a full description of data.

In the statistical analysis, we used SPSS software with paired t-test analysis and non-parametric Wilcoxon-matched pair tests to determine the effect of carnitine on cardiac indices. We also conducted subgroup analysis with respect to the gender and type of heart failure.

## Results

The results showed that the mean age ( $\pm$ SD) of the patients under study was  $60.2 \pm 5.3$  with a range of 15 to 83 years, and 27 subjects were male and 14 subjects were female. Out of 41 subjects, 10 cases had valvular disease, 16 cases had coronary artery disease and 16 subjects had cardiomyopathy (one subject had both coronary artery disease and valvular disease). Table I shows that 25 subjects were aged  $\geq 65$  years, 6 subjects were  $< 45$  years and 10 subjects were 45 - 64 years old.

Overall, Table II shows that the mean difference of end-diastolic diameter, end-systolic diameter, the size of left atrium, functional class and degree of mitral regurgitation decreased significantly (mean difference: -3.7, -4.7, -3.6, -0.66 and -0.74, respectively,  $P < 0.0001$ ). Ejection fraction increased from 0.38 to 0.43 significantly ( $P < 0.0001$ ). These results also show that the functional class became worse in 1 case, did not change in 16 cases, improved to class 1 in 20 cases and improved to class 2 in 4 cases. In Table III, the cardiac indices are presented with respect to the gender status. The effect of carnitine on all cardiac parameters was significant in both sexes except for left ventricle ejection fraction.

In Table IV, the effect of carnitine on cardiac indices is shown with respect to the cause of failure. Except for coronary artery disease, the effects on end-diastolic diameter and functional class were not statistically significant. In all three causes of failure, the effect of carnitine on cardiac indices was significant. In addition, after treating with carnitine, none of the cases were found with functional failure of kidney and liver, and none had changes on electrocardiogram.

**Table I. The age distribution of patients with refractory heart failure with respect to gender.**

| Age (year) | Male No | Female No | Total No |
|------------|---------|-----------|----------|
| < 45       | 4       | 2         | 6        |
| 45 – 60    | 10      | -         | 10       |
| > 60       | 13      | 12        | 25       |
| Total      | 27      | 14        | 41       |

**Table II. The mean ( $\pm$  SD) of cardiac parameters before and after treating with carnitine and the P-value.**

| Cardiac parameters             | Before treatment<br>Mean $\pm$ SD | After treatment<br>Mean $\pm$ SD | Mean<br>Difference | P-value of paired T-<br>test or Wilcoxon |
|--------------------------------|-----------------------------------|----------------------------------|--------------------|--|
| End-diastolic diameter (mm)    | 65.6 $\pm$ 7.7                    | 61.9 $\pm$ 7.4                   | 3.7                | 0.000                                    |
| End-systolic parameter (mm)    | 52.6 $\pm$ 7.7                    | 47.9 $\pm$ 7.9                   | 4.7                | 0.000                                    |
| Ejection fraction              | 0.38 $\pm$ 0.07                   | 0.43 $\pm$ 0.07                  | -0.05              | 0.000                                    |
| Left atrium diameter (mm)      | 48.1 $\pm$ 4.3                    | 44.5 $\pm$ 4.3                   | 3.6                | 0.000                                    |
| Functional class               | 2.48 $\pm$ 0.5                    | 1.82 $\pm$ 0.66                  | 0.66               | 0.000                                    |
| Degree of mitral regurgitation | 2.39 $\pm$ 0.82                   | 1.65 $\pm$ 0.79                  | 0.74               | 0.000                                    |

**Table III. Mean ( $\pm$  SD) of cardiac parameter in patients with refractory heart failure before and after treating with carnitine.**

| Cardiac parameters             | Sex    | No | Before treatment<br>Mean $\pm$ SD | After treatment<br>Mean $\pm$ SD | Mean<br>Difference | P-value Paired t<br>test or Wilcoxon |
|--------------------------------|--------|----|-----------------------------------|----------------------------------|--------------------|--------------------------------------|
| End-diastolic diameter (mm)    | Male   | 27 | 67.3 $\pm$ 8.3                    | 63.7 $\pm$ 6.8                   | 3.6                | 0.000                                |
|                                | Female | 14 | 62.2 $\pm$ 5.4                    | 58.4 $\pm$ 7.5                   | 3.8                | 0.019                                |
| End-systolic diameter (mm)     | Male   | 27 | 53.2 $\pm$ 8.4                    | 48.3 $\pm$ 8.1                   | 4.9                | 0.000                                |
|                                | Female | 14 | 51.2 $\pm$ 6.0                    | 47.0 $\pm$ 7.9                   | 4.2                | 0.006                                |
| Ejection fraction              | Male   | 27 | 0.4 $\pm$ 0.06                    | 0.45 $\pm$ 0.06                  | 4.2                | 0.006                                |
|                                | Female | 14 | 0.33 $\pm$ 0.07                   | 0.40 $\pm$ 0.09                  | -0.07              | 0.016                                |
| Left atrium diameter           | Male   | 27 | 48.8 $\pm$ 4.9                    | 45.1 $\pm$ 3.7                   | 3.7                | 0.000                                |
|                                | Female | 14 | 46.9 $\pm$ 2.5                    | 43.2 $\pm$ 5.2                   | 3.4                | 0.009                                |
| Functional class               | Male   | 27 | 2.55 $\pm$ 0.5                    | 1.88 $\pm$ 0.69                  | 0.67               | 0.000                                |
|                                | Female | 14 | 2.35 $\pm$ 0.49                   | 1.71 $\pm$ 0.61                  | 0.64               | 0.021                                |
| Degree of mitral regurgitation | Male   | 27 | 2.22 $\pm$ 0.84                   | 1.55 $\pm$ 0.8                   | 0.67               | 0.000                                |
|                                | Female | 14 | 2.71 $\pm$ 0.72                   | 1.82 $\pm$ 0.77                  | 0.86               | 0.003                                |

**Table IV. The mean ( $\pm$ SD) of cardiac parameter before and after treating with carnitine and p-value with respect to cause of heart failure.**

| Cardiac parameters             | Cause of heart failure  | No | Before treatment<br>Mean $\pm$ SD | After treatment<br>Mean $\pm$ SD | Mean<br>difference | P-value paired t<br>test or Wilcoxon |
|--------------------------------|-------------------------|----|-----------------------------------|----------------------------------|--------------------|--------------------------------------|
| End-diastolic diameter (mm)    | Valvular disease        | 10 | 66.9 $\pm$ 4.7                    | 63.7 $\pm$ 4.5                   | 3.2                | 0.015                                |
|                                | Cardiomyopathy          | 16 | 67.6 $\pm$ 10.6                   | 61.6 $\pm$ 9.5                   | 6.0                | 0.000                                |
|                                | Coronary artery disease | 16 | 62.6 $\pm$ 4.5                    | 61.0 $\pm$ 6.4                   | 1.5                | 0.185                                |
| End-systolic diameter (mm)     | Valvular disease        | 10 | 53.6 $\pm$ 4.5                    | 49.7 $\pm$ 5.1                   | 3.9                | 0.002                                |
|                                | Cardiomyopathy          | 16 | 54.7 $\pm$ 10.3                   | 47.9 $\pm$ 10.9                  | 6.81               | 0.000                                |
|                                | Coronary artery disease | 16 | 50.0 $\pm$ 5.2                    | 47.1 $\pm$ 5.9                   | 2.87               | 0.014                                |
| Ejection fraction              | Valvular disorder       | 10 | 0.40 $\pm$ 0.06                   | 0.45 $\pm$ 0.04                  | -0.04              | 0.009                                |
|                                | Cardiomyopathy          | 16 | 0.38 $\pm$ 0.07                   | 0.46 $\pm$ 0.08                  | -0.08              | 0.000                                |
|                                | Coronary artery disease | 16 | 0.36 $\pm$ 0.08                   | 0.45 $\pm$ 0.07                  | 3.8                | 0.002                                |
| Left atrium diameter (mm)      | Valvular disease        | 10 | 49.5 $\pm$ 3.9                    | 45.7 $\pm$ 4.3                   | 3.8                | 0.002                                |
|                                | Cardiomyopathy          | 16 | 46.8 $\pm$ 3.5                    | 42.8 $\pm$ 4.5                   | 4                  | 0.003                                |
|                                | Coronary artery disease | 16 | 48.8 $\pm$ 5.0                    | 45.6 $\pm$ 3.6                   | 3.1                | 0.002                                |
| Functional Class               | Valvular disease        | 10 | 2.7 $\pm$ 0.48                    | 2.0 $\pm$ 0.47                   | 0.7                | 0.002                                |
|                                | Cardiomyopathy          | 16 | 2.51 $\pm$ 0.51                   | 1.56 $\pm$ 0.72                  | 0.94               | 0.001                                |
|                                | Coronary artery disease | 16 | 2.3 $\pm$ 0.47                    | 2.0 $\pm$ 0.63                   | 0.3                | 0.059                                |
| Degree of mitral regurgitation | Valvular disease        | 10 | 2.7 $\pm$ 0.67                    | 1.9 $\pm$ 0.73                   | 0.8                | 0.011                                |
|                                | Cardiomyopathy          | 16 | 2.37 $\pm$ 1.14                   | 1.5 $\pm$ 1.03                   | 0.87               | 0.003                                |
|                                | Coronary artery disease | 16 | 2.31 $\pm$ 0.6                    | 1.75 $\pm$ 0.57                  | 0.56               | 0.003                                |

## Discussion

Our finding showed that consumption of carnitine 500 mg/day for 6 months improved the functional class and other cardiac indices under study significantly. Published studies also reported the efficacy of carnitine with different doses on cardiac patients.<sup>13-28</sup> In many studies, the prescribed dose was much higher than that in ours. Furthermore, there are not many studies on the effect of carnitine on functional class and patient satisfaction. Probably, this is because of the presence of error and lack of confidence of subjective data of patient compliance. Terranova et al. reported that carnitine is an effective treatment without any complications in coronary patients.<sup>14</sup> Matsumoto et al. also reported that prescription of carnitine with a dose of 500 mg/day at 6 months improved chest pain and increased ejection fraction and finally it decreased cardiac complications and mortality.<sup>15</sup> Witte et al. also found that carnitine improved the physical activity in patients with heart failure.<sup>16</sup> In a study by Rizos et al., the consumption of carnitine 2g/day significantly increased the duration of life compared with a control group.<sup>19</sup> In our study, carnitine is effective in decreasing end-diastolic, end-systolic diameters and the size of left atrium. A similar finding was also reported by Colonna et al.,<sup>18</sup> Romagnoli et al.<sup>26</sup> in Italy, Jeejeebhoy et al.<sup>27</sup> in Canada and El-Beshlaw<sup>24</sup> in Egypt. In addition, Pierpont et al.<sup>28</sup> reported that the prescription of oral carnitine leads to the elimination of severe cardiomyopathy and the prevention of the relapsing of heart failure in 5-years' follow up. However, in our study, the elimination of cardiomyopathy was not observed, and we were not able to attain 5 years' follow-up of our cases. In another situation, Gurlek et al.<sup>25</sup> in Turkey found that prescription of 2g/day carnitine for 1 month had a useful effect on the function of left ventricle in patients suffering ischemic cardiomyopathy. There dissimilarity of dose

and duration of consumption between this study and ours. While their dose of prescription was higher than that of ours, the duration of consumption was shorter. Overall, the said study used 60 grams carnitine and we prescribed 90 grams.

In terms of the difference in the effect of carnitine between males and females, although its effect on echocardiographic parameters and functional class tended to be greater in the males than females, the differences were not significant. This might be either due to a lack of a real difference in the effect of carnitine with respect to gender or a lack of sufficient sample size. In addition, the published data did not address gender difference for the effect of carnitine.

Based on our findings, the effect of carnitine was different with respect to causes of heart failure (coronary artery disease, valvular disease and cardiomyopathy). Our results showed that the magnitude of effect of carnitine on end-diastolic and end-systolic diameter of the left ventricle and ejection fraction was greater in patients with cardiomyopathy, followed by patients with coronary artery and valvular disease, respectively. With regard to the effect of this drug on the size of the left atrium, the difference between the three groups of patients was not significant. In addition, its effect on functional class was greater in patients with cardiomyopathy compared with other patients; and finally, its effect on the degree of mitral regurgitation was greater in patients with cardiomyopathy and coronary artery disease compared with valvular disease.

In conclusion, our findings show that the prescription of carnitine at a dose of 500 mg/day for 6 months improved cardiac parameters without any side effect and complications. Because of the absence of side effects, we recommend that this drug be prescribed to patients with heart failure who are resistant to conventional treatment, in particular to patients with cardiomyopathy. For more clarification, a multi-center

randomized clinical trial with an adequate sample size is necessary to evaluate the efficacy of this drug for definite clinical decision making.

### References

- Bristow MR, Lowes BD. Braunwald's Heart Disease. 7th edition, USA, Elsevier-Saunders, 2005; 24 : 603-625.
- Lejemtel TH, Sonneblick EH. Hurst's The Heart. 11th edition, USA, McGraw-Hill Co. Inc, 2004; 25: 723-750.
- Cowie MR, Mosterd A, Wood DA. The epidemiology of heart failure. *Eur Heart Journal* 1997; 18: 208-25.
- Vasan RS, Benjamin E, Levey D. Congestive heart failure with normal left ventricular systolic function. *Arch Intern Med* 1996; 156: 146-157.
- Vasan RS, Benjamin E, Levey D. Prevalence, clinical features and prognosis of diastolic heart failure. An epidemiologic perspective. *J Am Coll Cardiol* 1995; 26 (7): 1565-1574.
- Nishimura RA, Tajik AK. Evaluation of diastolic filling of left ventricle in heart disease: Doppler echocardiography. *J Am Coll Cardiol* 1997; 30: 8-18.
- MacDowell P, Karla PA, O'Donoghue DJ. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998; 352: 13-16.
- Mason JW, O'Connell JB, Herkowitz A. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995; 333: 269-275.
- Varg DL, Kramer WG, Black PK. Bioavailability pharmacology of toseamide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther* 1995; 56: 601-609.
- Van Veldhuisen DJ, De Graeff PA, Remme WJ, Lie KI. Value of digoxin in heart failure and sinus rhythm. New features of an old drug? *J Am Coll Cardiol* 1996; 28: 813-819.
- Lefkonitz RS, Hoffman BB, Taylor P. Digoxin for heart failure. *Prog Cardiology Dis* 1995; 37: 40-58.
- Marcus R, Coulston AM. Goodman & Gillman's The Pharmacological Basis of Therapeutics. 9th Edition, USA, McGraw-Hill Co., 1996; 14: 1569-1571.
- Sole MJ, Jeejeebhoy KN. Conditional nutritional requirements: therapeutic relevance to heart failure. *Herz* 2002; 27(20):174-8.
- Terranova R, Luca S. Treatment of chronic arterial occlusive disease of the lower limbs with propionyl-L-carnitine in elderly patients. *Minerva Med* 2001; 93(1): 61-6.
- Matsumoto Y, Sato M, Ohashi H, et al. Effects of L-carnitine supplementation on cardiac morbidity in hemodialyzed patients. *Am J Nephrol* 2000; 20(3): 201-7.
- Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. *J Am Coll Cardiol* 2001; 37(7): 1705-74.
- El Aroussy W, Rizk A, Mayjoub G, et al. Plasma carnitine levels as a marker of impaired left ventricular functions. *Mol Cell Biochem* 2000; 213(1-2): 37 - 41.
- Colonna P, Iliceto S. Myocardial infarction and left ventricular remodeling. *Am Heart J* 2000; 139 (2, pt. 3): S124 - 30.
- Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J* 2000; 139 (2, pt. 3): S120 - 3.
- Hong YM, Kim HS, Yoon HR. Serum lipid and fatty acid profiles in adriamycin-treated rats after administration of L-carnitine. *Pediatr Res* 2002; 52(20): 249-55.
- Vescovo G, Ravara B, Gobbo V, et al. L-carnitine a potential treatment for blocking apoptosis and preventing skeletal muscle myopathy in heart failure. *Am J Physiol Cell Physiol* 2002; 283 (3): C802 - 10.
- Mengi SA, Ohalla NS. Carnitine palmitoyl transferase-I a new target for treatment of heart failure. *Am J Cardiovasc Drugs* 2004; 4(4): 201 - 9.

23. Lionetti V, Linke A, Chandler MP, et al. Carnitine palmitoyl transferase – I inhibition prevents ventricular remodeling and delays decompensation in pacing induced heart failure. *Cardiovasc Res* 2005; 1: 454 – 62.
24. El Beshlawy A, Ragab L, Fattah, et al. Improvement of cardiac function in thalassemia major treated with L-carnitine. *Acta Haematol* 2004; 111(3): 143 – 8.
25. Gurlek A, Tuter E, Akcil E, et al. The effect of L-carnitine treatment on left ventricular function and erythrocyte superoxide dismutase activity in patients with ischemic cardiomyopathy. *Eur J Heart Fail* 2000; 2 (2): 189 – 93.
26. Romagnoli GF, Naso A, Carraro G, et al. Beneficial effects of L-carnitine in dialysis patients with impaired left ventricular function: an observational study. *Curr Med Res Opin* 2002; 18(3): 172 – 5.
27. Jeejeebhoy F, Keith M, Freeman M, et al. Nutritional supplementation with myovive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *Am Heart J* 2002; 143 (6): 1092 - 100.
28. Pierpont ME, Brenningstall GN, Stanley CA. Familial carnitine transporter defect: A treatable cause of cardiomyopathy in children. *Am Heart J* 2000; 136 (2, pt. 3): S96 - S106.