Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration

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We examined the efficacy of long-term L-carnitine administration for the treatment of heart failure caused by dilated cardiomyopathy in adult patients. To accomplish this, we studied 80 patients with moderate to severe heart failure (New York Heart Association classification III to IV) caused by dilated cardiomyopathy. This article reports on the nearly 3 years of follow-up data on patient mortality. Primary results will be published in the future. After a period of stable cardiac function up to 3 months, patients were randomly assigned to receive either L-carnitine (2 g/d orally) or placebo. There were no statistical differences between the 2 groups at baseline examination in clinical and hemodynamic parameters, such as ejection fraction, Weber classification, maximal time of cardiopulmonary exercise test, peak VO_2 consumption, arterial and pulmonary blood pressure, and cardiac output. After a mean of 33.7 ± 11.8 months of follow-up (range 10 to 54 months), 70 patients were in the study: 33 in the placebo group and 37 in the L–carnitine group. At the time of analysis, 63 patients were alive. There were 6 deaths in the placebo group and 1 death in the L-carnitine group. Survival analysis with the Kaplan-Meier method showed that patients' survival was statistically significant ($P < .04$) in favor of the L-carnitine group. L-carnitine appears to possess considerable potential for the long-term treatment of patients with heart failure attributable to dilated cardiomyopathy. (Am Heart J 2000;139:S120-S123.)

The usefulness of carnitine for the treatment of pediatric cardiomyopathy is well established. However, relatively few studies have examined the efficacy and safety of carnitine treatment for cardiomyopathy in adults. The natural history and prognosis of dilated cardiomyopathy in adults are considerably different from those observed in children, and clinical trial results obtained in pediatric populations may not be directly applicable to cardiomyopathy in older patients.

In adults, the course of dilated cardiomyopathy is usually characterized by progressive disability, and death commonly ensues within 6 months to a few years from the onset of symptoms.[1,2] The prognosis is related to the severity of left ventricular function impairment.[2-4]

In patients with idiopathic dilated cardiomyopathy, hemodynamic, electrophysiologic, and histologic measures of cardiac dysfunction are significantly correlated with impaired fatty acid metabolism within heart muscle.[4] Thus it may be anticipated that an agent stimulating myocardial fatty acid metabolism may improve cardiac function and reduce the severity of symptoms associated with dilated cardiomyopathy.

Experimental studies have demonstrated a severe depletion of tissue carnitine in animal models of heart failure, and numerous investigators have reported that L-carnitine improves measures of cardiac performance in animal models of cardiomyopathy.[5-7] Increased plasma carnitine and decreased myocardial carnitine have also been described in patients with cardiomyopathy.[8,9] Case reports have noted clinical improvements after carnitine treatment.[8,9] However, relatively few controlled studies have examined the effects of carnitine administration on clinical symptoms or death, and most published reports of the effects of carnitine in cardiomyopathy have included only a small number of patients.[10]

Regitz et al[9] reported reduced myocardial carnitine in patients undergoing cardiac transplantation for heart failure. Both free and total carnitine levels were decreased compared with controls, but free myocardial L-carnitine was decreased to a greater extent.

Long-term therapy with L-carnitine in patients with heart failure showed significant hemodynamic and functional improvement.[10,11] During the last few years, only a few studies have suggested the role of L-carnitine in the treatment of heart failure.[12,13] However, in all the studies L-carnitine was administered only up to 3 months with no long-term follow-up period.

Therefore, based on the literature from animal models and clinical reports and wishing to substantiate these findings in an adult population, we undertook this 3-year study to determine the effect on mortality rate and other efficacy parameters of long-term L-carnitine administration for the treatment of heart failure in adults attributable to dilated cardiomyopathy. This report is primarily devoted to long-term follow-up mortality data because short-term data will be reported in another publication.

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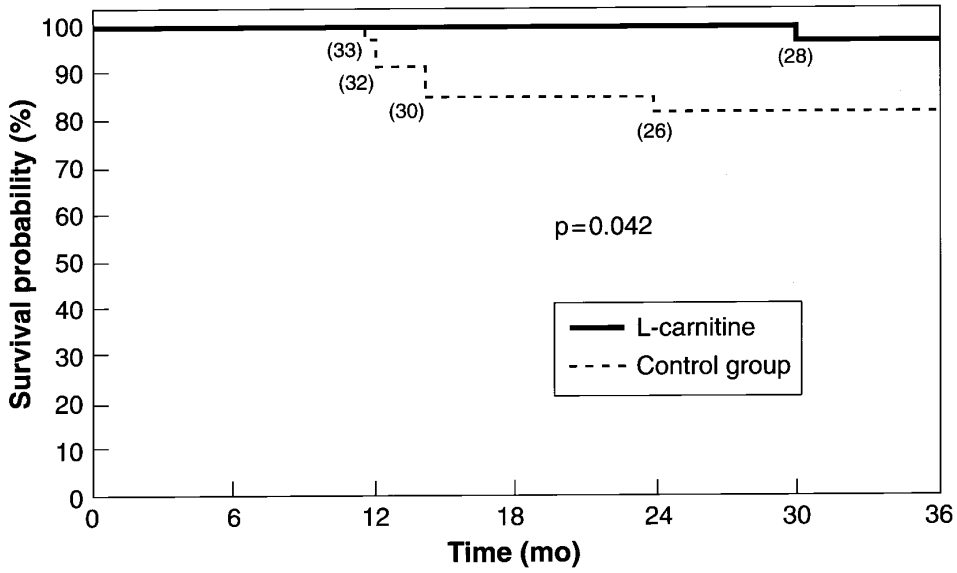
Figure 1



Three-year Kaplan-Meier survival analysis of patients with cardiomyopathy. The figures in parentheses represent the number of patients entering this time interval. Five patients in each group dropped out of the study before analysis was performed. One patient in the control group dropped out of the study after 13 months, following a cardiomyoplasty.

Methods

Study protocol

This was a double-blind, placebo-controlled study for an initial 3-month period and was unblinded for the remainder of the 3-year study. A total of 80 patients were randomly assigned to treatment with L-carnitine or placebo after a baseline hemodynamic study.

Patients

Patients were eligible for enrollment in this study if they had been diagnosed with dilated cardiomyopathy, were classified as stable (sinus rhythm) according to the New York Heart Association (NYHA) function class III to IV, and were able to perform treadmill exercise. Patient baseline characteristics are included in Table I. Exclusion criteria included ischemic heart disease (defined as occlusion more than 50%), significant valvular heart disease, atrial fibrillation, and alcohol abuse.

Hemodynamic and clinical parameters were also measured. Hemodynamics were performed during the stabilization phase before patients were entered into the study, at baseline (study entry), 1 month, 3 months, and approximately 6-month intervals thereafter throughout the study period. These studies included coronary angiography with left ventriculography (only at study entry), right catheterization and cardiopulmonary exercise tests according to the Weber protocol. Measured parameters included ejection fraction, Weber classification, maximal time of cardiopulmonary exercise test, peak VO_2 consumption, arterial and pulmonary blood pressure, and cardiac output.

Table I. Clinical characteristics of patients receiving L-carnitine or placebo

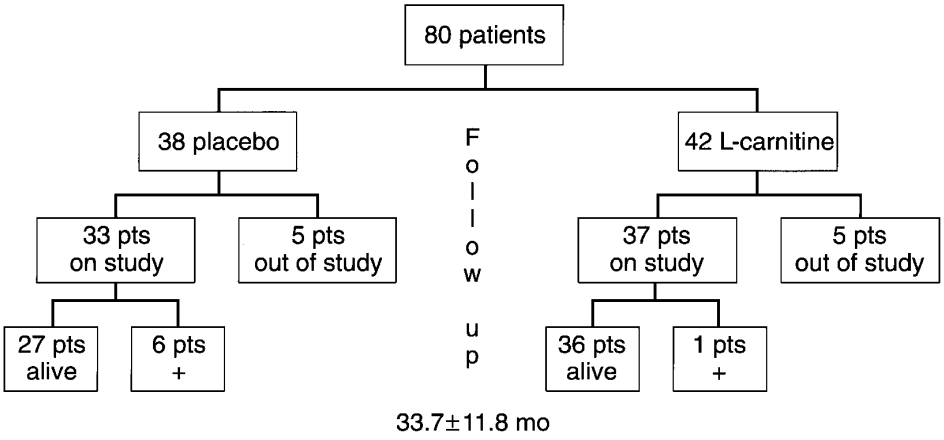
	L-carnitine (n = 42)	Placebo (n = 38)
Age	50 ± 14	48 ± 12
Sex	19 M, 23 F	20 M, 18 F
Ejection fraction (%)	27 ± 10	29 ± 11
Left ventricular end diastolic pressure (mm Hg)	14 ± 7	12 ± 10
NYHA III	30	29
NYHA IV	12	9

Values are n or mean ± SD.

Drug administration

For 1 to 3 months all patients received conventional therapy for heart failure that included diuretics, digoxin, and angiotensin-converting enzyme inhibitors. No antiarrhythmic drugs were administered. After entering the study, patients were randomly assigned to receive either oral L-carnitine at a dosage of 2 g/d or placebo for a 3-month period. After the study was unblinded, the patients in the L-carnitine group contin-

Figure 2



Disposition of patients at 3-year follow-up; +, death.

ued on 2 g/d orally, and the placebo group continued receiving standard therapy (no L-carnitine).

Trial end points

The primary end point of the study was death at 3 years, comparing the L-carnitine group and the placebo group. As a clinical end point, the hemodynamic study was repeated after 1- and 3-month administration of L-carnitine or placebo (and throughout the 3-year study period), but only the 3-month results are reported in this article.

Statistics

A Kaplan-Meier survival analysis, presented as a cumulative mortality curve, was used to describe patient death (Figure 1). The log-rank test was used to compare mortality between the 2 groups.

Results

Baseline characteristics

There were no statistically significant differences in baseline characteristics between the 2 groups in terms of clinical and hemodynamic parameters, such as ejection fraction, Weber classification, maximal time of cardiopulmonary exercise test, peak VO_2 consumption, arterial and pulmonary blood pressure, and cardiac output (Table I).

Death

After a mean of 33.7 ± 11.8 months of follow-up (range 10 to 54 months), 70 patients remained in the study: 33 patients in the placebo group and 37 patients in the L-carnitine group. At the end of nearly 3 years (mean), 5 patients had left the study from each group, including 1 patient in the placebo group who had undergone cardiomyoplasty. Six patients died in the placebo group:
5 from pump failure and 1 from sudden cardiac death. The 1 death in the L-carnitine group was from documented sustained ventricular tachycardia despite resuscitation (Figure 2).

The Kaplan-Meier 3-year survival analysis showed that patients' survival was statistically significant ($P < .04$) in favor of L-carnitine (Figure 1). At 12 months the survival rates began to diverge, which continued through the end of the 3-year analysis. The 3-year mortality rate for the placebo group was 18% vs 3% in the L-carnitine group.

Clinical findings and hemodynamics

After a 3-month period of administration of L-carnitine or placebo, the hemodynamic studies performed at baseline were repeated. After 3-month administration of study drugs, there was a statistically significant difference in favor of the L-carnitine patients in terms of Weber classification, maximal time of cardiopulmonary exercise test, peak oxygen consumption, arterial and pulmonary blood pressure, and cardiac output.

One patient in the L-carnitine group did not maintain sinus rhythm and had atrial flutter requiring cardioversion. Seven (21%) of the 33 patients in the placebo group had atrial fibrillation. Atrial fibrillation persisted in 5 of these patients, and 2 patients maintained a stable sinus rhythm after cardioversion and amiodarone treatment.

Adverse effects

All patients in the study tolerated L-carnitine. Of the 37 patients receiving L-carnitine who completed the study, 3 had minor gastrointestinal problems but were not withdrawn from the study.

Discussion

The results of this study suggest that the benefits of L-carnitine therapy may include improvement in long-term mortality rate in the adult population. Previous trials have not tested the effect of L-carnitine on mortality rate in adult patients with moderate to severe heart failure. However, this study showed an improvement in the mortality rate for the L-carnitine patients that was statistically significant at 3 years (18% placebo group vs 3% L-carnitine group). Although the sample size of our study was small, the clear differences maintained between the L-carnitine and placebo groups over a 3-year period are certainly encouraging.

A rather impressive finding was that only 1 patient in the L-carnitine group was unable to maintain sinus rhythm for the entire follow-up period, in contrast to 7 patients in the placebo group in whom atrial fibrillation developed. We know from Dries et al[14] that the presence of atrial fibrillation in patients with asymptomatic and symptomatic left ventricular systolic dysfunction is associated with an increased risk for all-cause mortality. Pozzoli et al[15] further support the finding that the onset of atrial fibrillation in patients with heart failure is associated with clinical and hemodynamic deterioration and may predispose patients to systemic thromboembolism and poor prognosis.

The electrical stability of the L-carnitine group might provide an explanation for the observed mortality risk reduction in favor of L-carnitine patients, as evidenced by the sinus rhythm scores. Perhaps greater stability may be caused by the salutary effect of L-carnitine.

Results from this trial therefore suggest that L-carnitine may improve the functional status of patients with moderate to severe heart failure attributable to dilated cardiomyopathy. A large, randomized, placebo-controlled trial is required to fully assess the usefulness of L-carnitine administration in this setting.

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