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Effect of intravenous L-carnitine in Chinese patients with chronic heart failure

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6-min walk distance

Chronic heart failure (CHF) may be associated with an energy deficit in cardiac muscle. As levo-carnitine (LC) is involved in the production of myocardial energy, it is hypothesized that LC supplementation may ameliorate CHF symptoms. This multicentre, randomized, double-blind, and placebo-controlled study included 265 patients with CHF. Patients were randomized to receive either LC or placebo, twice a day. Endpoints were measured after 7 days of treatment. Primary endpoint was a reduction of at least one NYHA class. Secondary endpoints were changes in 6-min walk distance (6-MWD) compared with baseline, either alone or in combination with NYHA class decrease, left ventricular ejection fraction, and NT-proBNP level, together with adverse events. The primary endpoint was reached in 60.9% of patients treated with LC, compared with only 44.7% of the placebo group ($P = 0.012$). Among the secondary endpoints, 6-MWD, alone or in combination with NYHA class, improved significantly in the LC group compared with placebo ($P = 0.0497$ and $P = 0.003$, respectively). L-Carnitine was well tolerated. The lowest baseline

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values of plasma-free carnitine were observed in patients with NYHA classes III and IV where the effect of LC supplementation was greatest ($P = 0.002$). Treatment with LC significantly improved CHF symptoms in Chinese patients, probably by correcting a status of carnitine insufficiency.

Introduction

Chronic heart failure (CHF) is defined as the inability of the ventricles to fill with or eject blood.[1,2] The administration of neuroendocrine antagonists such as β-blockers, angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists, and aldosterone antagonists has improved the survival and quality of life of patients with CHF.[3] However, CHF remains a major health issue with a prevalence of 1–2%.[4–6] The development of new treatment strategies is crucial to improving the prognosis of this disease.

Impairment of myocardial energy metabolism,[7,8] together with the observation that inotropic stimulation can increase myocardial energy consumption and cause myocardial injury, has stimulated interventions aimed at reducing cardiac energy consumption and improving myocardial energy metabolism in CHF.[9,10] These interventions, if introduced early in the disease, may also affect subsequent myocardial remodelling.[11] The major energy source for myocardial metabolism comes from fatty acid metabolism and fatty acid oxidation disorders may lead to myocardial systolic and diastolic dysfunction.[11] Carnitine is a natural and essential vitamin-like substance that plays an essential role in myocardial energy production at the mitochondrial level.[12] It transfers long chain fatty acids across the inner mitochondrial membrane for β-oxidation and abnormalities in carnitine metabolism are thought to contribute to cardiac dysfunction.[13,14]

Many studies have demonstrated a beneficial effect of levo-carnitine (LC) supplementation in various types of cardiomyopathy.[15–17] L-Carnitine supplementation has given promising results in CHF, but warrants further study.[12,18] This study was carried out to investigate the efficacy of LC as treatment for CHF.

Methods

Study design

This randomized, double-blind, and placebo-controlled trial was carried out in 12 hospitals in China. The study complied with ICH-GCP principles in clinical pharmacology institutions certified by the China Food and Drug Administration. The trial is registered as clinicaltrials.gov registration number NCT01580553.

Study population

Adult patients, ≥18 years of age, with CHF and hospitalized because of a deterioration in symptoms were recruited. Inclusion criteria include NYHA class II to IV, left ventricular ejection fraction (LVEF) ≤45% (left heart failure), and cardiac output <4 L/min (right heart failure). Exclusion criteria include heart failure resulting from valve disease, mechanical obstruction, pericardial disease, or cardiac amyloidosis. Patients were also excluded if they had suffered a severe stroke or acute myocardial infarction within 3 months prior to randomization, severe anaemia, chronic obstructive pulmonary disease, or epilepsy, and participation in another clinical investigation within 3 months prior to randomization.

Throughout the study, administration of digitalis, diuretics, vasodilators, ACEi, and β-blockers was permitted and the following drugs were prohibited: myocardial energy metabolism improvement agents such as trimetazidine dihydrochloride tablets (vasorel), 1,6-fructose diphosphate, polarized solution (glucose–insulin–potassium solution), mildronate (trimethyl hydrazine-propionate, carnitine analogues), vitamins (C and B), and any drugs that could impair cardiac function.

Study conduct and endpoints

Patients were randomly assigned to receive either placebo (saline solution) or LC (3 g dissolved in 100 mL physiological saline) intravenously, twice a day, for 7 days. Efficacy endpoints were measured on Day-7 compared with baseline.

The primary endpoint was a decrease of at least one NYHA class, with efficacy rated as excellent (decrease of two classes), effective (decrease of one class), or ineffective (no class change). Secondary endpoints included a change in 6-min walk distance (6-MWD), either alone or in combination with a reduction of at least one NYHA class, on Day 7, and a decrease in incidence of major cardiovascular events (myocardial infarction, non-fatal stroke, cardiovascular death, re-admission due to congestive heart failure) measured on Day 30.

LVEF, N-terminal pro b-type natriuretic peptide (NT-proBNP) level and plasma LC level were assessed at baseline and after 7 days of treatment. Total (acyl + free) LC and free LC was detected in plasma by liquid chromatography–tandem mass spectrometry[19] (Anhui Medical University, Anhui, China). NT-proBNP plasma levels (pg/mL) were measured using commercially available kits (Roche Diagnostic).

Safety analysis

Laboratory tests (blood tests, blood biochemistry, blood clotting, and urine assays) and vital signs were measured prior to treatment and on Day 7. Subjects also underwent an electrocardiogram and Holter examination. All adverse events (AEs) during treatment, including serious AEs (SAEs), were recorded on a clinical report form.

Statistical analysis

Continuous variables are recorded as number, mean and standard deviation (SD). Between-group comparison of continuous variables was performed using one-way analysis of variance (ANOVA) or the Wilcoxon test. When ANOVA showed significant differences, *post hoc* analysis was performed using the Bonferroni test. Categorical data were compared between groups using the χ^2 test, Fisher's exact test or logistic regression.

The efficacy of LC and placebo treatments was measured in the per protocol (PP) population. The safety results were analysed in

the full analysis set (FAS) population [set of subjects that is as close as possible to the ideal implied by the Intention-to-Treat principle (ICH E9)].

Unless otherwise stated, all statistical analyses used double-sided tests and significance was set at $P < 0.05$. All statistical analyses were carried out using SAS 9.3 software.

Results

Study population

A total of 265 patients were enrolled in the study. Four patients dropped out of the trial and were excluded from the analysis. The FAS therefore consisted of 261 patients (LC = 133, placebo = 128). The PP population consisted of 242 patients (LC = 128, placebo = 114). The characteristics of the patients in the two groups are summarized in *Table 1*.

Primary endpoint

In the LC group ($n = 128$), the improvement in cardiac function (decreased NYHA class) was rated as excellent in six patients (4.69%) and effective in 72 (56.3%), with an overall efficacy of 60.9%. In the placebo group ($n = 114$), the improvement in cardiac function was rated as excellent in three patients (2.63%) and effective in 48 (42.1%), with an overall efficacy of 44.7%. The difference between the two groups was statistically significant ($P = 0.012$; *Table 2*).

Secondary endpoints

6-Min walk distance

A significant difference in 6-MWD was present at baseline, with a significantly longer 6-MWD in the placebo group ($P = 0.036$) (*Table 3*). On Day 7, the 6-MWD was longer in both groups than at baseline (LC group: 350.4 vs. 293.4 m; placebo group: 360.4 vs. 321.2 m, respectively). Both differences were statistically significant ($P < 0.0001$). The change from baseline was significantly greater in the LC group than with placebo (61.4 vs. 46.4 m, respectively; $P = 0.0497$) (*Table 3*).

NYHA class and 6-min walk distance

To evaluate efficacy using a more robust clinical endpoint, we measured the number of patients with both a reduction

Table 1 Characteristics of the study population

Characteristics	LC group	Placebo group	*P*
Age, mean ± SD (*n*)	51.9 ± 16.2 (133)	52.4 ± 16.5 (128)	0.85
Male (%)	63.1	54.3	0.15
Physical examination and laboratory findings			
Height (cm), mean ± SD (*n*)	164.8 ± 8.1 (131)	165.4 ± 7.7 (128)	0.53
Weight (kg), mean ± SD (*n*)	62.8 ± 12.2 (132)	63.9 ± 14.0 (128)	0.52
Body temp (°C), mean ± SD (*n*)	36.5 ± 0.35 (133)	36.5 ± 0.29 (128)	0.97
Heart rate, mean ± SD	84.2 ± 16.5	82.8 ± 14.6	0.47
Respiratory rate, mean ± SD	19.2 ± 2.39	18.9 ± 2.22	0.36
SBP (mmHg), mean ± SD (*n*)	122.4 ± 19.8 (133)	123.9 ± 23.1 (128)	0.58
DBP (mmHg), mean ± SD (*n*)	79.4 ± 14.3 (133)	81.3 ± 14.9 (128)	0.29
Creatinine (μmol/L), mean ± SD (*n*)	89.77 ± 38.5 (128)	90.42 ± 36.2 (114)	0.89
Sodium (mEq/dL), mean ± SD (*n*)	140.9 ± 3.28 (128)	139.41 ± 13.2 (114)	0.22
proBNP (pg/mL), mean ± SD (*n*)	2780.0 ± 4254.9 (124)	3366.1 ± 3842.7 (110)	0.27
cTnT (ng/L), mean ± SD (*n*)	1.04 ± 6.28 (118)	0.88 ± 4.33 (107)	0.83
Cardiac findings (PP population)			
NYHA class, *n*/%			0.33
II	17 (13.2)	10 (8.7)	
III	73 (57.0)	75 (65.7)	
IV	38 (29.7)	29 (25.4)	
LVEF (%), mean ± SD (*n*)	41.12 ± 17.5 (125)	40.39 ± 16.9 (113)	0.74
Cardiac output	3.17 ± 0.43	3.16 ± 0.57	0.91
Concomitant medications (*n*/%)			
Aspirin	24 (18.0)	21 (16.4)	0.92
β-Blockers	42 (31.5)	30 (23.4)	0.23
Angiotensin II receptor antagonists	11 (8.2)	11 (8.5)	0.79
ACEi	29 (21.8)	22 (17.1)	0.49
Ca^{2+} antagonists	2 (1.5)	10 (7.8)	0.01
Spironolactone	48 (36.0)	48 (37.5)	0.46
Torasemide	10 (7.5)	11 (8.5)	0.62
Furosemide	41 (30.8)	40 (31.2)	0.63
Hydrochlothiazide	0 (0)	5 (3.9)	0.02
Digoxin	26 (19.5)	25 (19.5)	0.78
Amiodarone	7 (5.2)	4 (3.1)	0.54
Vasodilators	30 (22.5)	32 (25.0)	0.41

Table 2 Efficacy[a] according to change in NYHA classification in the per protocol population

Group	Excellent	Effective	Ineffective	Efficacy rate (%)
LC ($n = 128$)	6 (4.7)	72 (56.2)	50 (39.1)	60.9
Placebo ($n = 114$)	3 (2.6)	48 (42.1)	63 (55.3)	44.7
LC placebo	(Excellent + effective) $P = 0.012$			

All values are shown as *n* (%).
[a]The efficacy rate is calculated as the sum of patients with excellent and effective NYHA delta responses over the total population. *P*-value calculated using the χ^2 test.

Table 3 Efficacy by evaluation with the 6-min walk distance (m) in the per protocol population

Time	LC group	Placebo group	Difference LC-placebo
Baseline	278.7 ± 136.2 ($n = 120$)	315.2 ± 124.0 ($n = 107$)	$P = 0.0367$
Day 7	339.9 ± 129.0 ($n = 120$)	361.5 ± 116.4 (=107)	$P = 0.1886$
Day 7 baseline	61.2 ± 61.2 ($n = 120$)	46.4 ± 51.2 ($n = 107$)	$P = 0.0497$

All values shown are mean $\pm$ SD (number of patients). *P*-value calculated using analysis of variance.

of at least one NYHA class and an increase in 6-MWD of at least 20% on Day 7 compared with baseline. Thirty-five patients (29%) in the LC group and 14 (13%) in the placebo group showed this combined improvement ($P = 0.003$; odds ratio = 2.74).

Left ventricular ejection fraction

At baseline, LVEF was similar in the two groups (*Table 1*). On Day 7, LVEF was higher than at baseline in both groups (LC group: 44.1 vs. 41.1%, placebo group: 44.9 vs. 40.4%) and the differences were statistically significant ($P < 0.0001$). Left ventricular ejection fraction increased by 3.4 ± 8.3% in the LC group compared with baseline and by 4.5 ± 8.3% in the placebo group. This difference was not statistically significant ($P = 0.5603$).

NT-proBNP levels

At baseline, there was no significant difference in NT-proBNP levels between the two groups (*Table 1*). On Day 7, NT-ProBNP levels were lower than at baseline in both the LC (-950.5 ± 2554.5 ng/L) and placebo (-1093.6 ± 2536.4 ng/L) groups. The difference between the two groups was not statistically significant.

Plasma-free L-carnitine levels

At baseline, plasma-free LC levels were much lower in CHF patients (16.3 ± 6.9, 12.5 ± 6.1, 11.6 ± 5.5 μmol/L in patients with NYHA classes II, III, and IV, respectively; *Table 4*) than in a similar group of healthy control subjects (44.5 ± 12.1 μmol/L). *Figure 1* shows the relation between plasma-free LC at baseline and at Day 7 according to NYHA classification in the two groups of patients (*Figure 1A*) and the corresponding efficacy according to NYHA class on Day 7 (*Figure 1B*). In patients with NYHA class II at baseline, no change in free LC was detected in the placebo group and no efficacy (measured as a decrease in NYHA class or increase in 6-MWD) was detected in either the placebo or LC group. Conversely, in patients with NYHA classes III and IV at baseline, plasma-free LC increased slightly in the placebo group on Day 7 and significant efficacy was detected in both groups. Efficacy was greater in the LC group ($P = 0.002$; *Figure 1B*), which had a much greater increase in plasma-free LC.

In order to better assess the influence of plasma-free LC on the efficacy of LC compared with placebo, we compared two subgroups of patients with a plasma LC level < or > the median plasma-free LC level of 11.8 μmol/L. As shown in *Figure 2*, the difference in ability to reduce the NYHA class between placebo and LC was statistically significant in the low plasma-free LC subgroup but not in the high plasma-free LC subgroup. Conversely, this analysis showed no influence of level of free LC on efficacy measured as 6-MWD (data not shown).

The same analysis was carried out on the plasma acyl/free LC ratio divided into two subgroups: < or > the median level of 0.73, considering that values above this ratio may indicate a status of carnitine insufficiency. In the subgroup with a high plasma acyl/free LC ratio, LC supplementation was significantly more effective than placebo, when measured as a decrease in NYHA class (*Figure 3A*) or increase in 6-MWD (*Figure 3B*). This difference disappeared in patients with a plasma acyl/free LC ratio below the median value. Therefore, the greater efficacy of LC over placebo is mainly restricted to patients with a high acyl/free LC ratio or with low free carnitine

Cardiovascular events

The incidence of cardiovascular events was measured in the FAS population ($n = 261$) on Day 30. There was no significant difference in incidence of major cardiovascular events between the LC and placebo groups (6.9 vs. 6.6%, respectively; $P = 0.922$). There was also no significant difference in incidence of major cardiovascular events in the PP population (6.2 vs. 2.7%, respectively; $P = 0.1873$).

Table 4 Plasma-free carnitine levels (μmol/L) in patients with the different NYHA classes at baseline (per protocol population)

Sample	Time	Plasma-free carnitine (μmol/L)				Difference between classes	Classes III–IV
		All patients	Class II	Class III	Class IV	*P*	
Total	Baseline	12.6 ± 6.1 ($n = 224$)	16.3 ± 6.9 ($n = 24$)	12.5 ± 6.1 ($n = 140$)	11.6 ± 5.5 ($n = 60$)	0.0056 II vs. III $P = 0.0064$ II vs. IV $P = 0.0017$ III vs. IV $P = 0.3388$	
	Day 7	26.6 ± 29.4 ($n = 224$)	34.8 ± 7.8 ($n = 24$)	23.4 ± 21.5 ($n = 140$)	31.0 ± 9.2 ($n = 60$)	0.0835	
	Day 7 baseline	14.0 ± 28.9 ($n = 224$)	18.5 ± 9.0 ($n = 24$)	10.9 ± 20.9 ($n = 140$)	19.5 ± 8.5 ($n = 60$)	0.1136	
LC group	Baseline	13.0 ± 6.4 ($n = 115$)	15.8 ± 6.1 ($n = 15$)	12.7 ± 6.6 ($n = 67$)	12.4 ± 5.8 ($n = 33$)	0.1847	
	Day 7	36.8 ± 32.9 ($n = 115$)	45.9 ± 44.3 ($n = 15$)	30.7 ± 15.2 ($n = 67$)	44.9 ± 48.3 ($n = 33$)	0.0638	
	Day 7 baseline	23.8 ± 33.4 ($n = 115$)	30.1 ± 45.4 ($n = 15$)	18.0 ± 17.2 ($n = 67$)	32.5 ± 47.8 ($n = 33$)	0.0900	
Placebo group	Baseline	12.2 ± 5.9 ($n = 109$)	17.0 ± 8.5 ($n = 9$)	12.3 ± 5.6 ($n = 73$)	10.6 ± 5.2 ($n = 27$)	0.0169	11.8 ± 5.5 ($n = 100$)
	Day 7	16.0 ± 20.3 ($n = 109$)	16.1 ± 7.0 ($n = 9$)	16.6 ± 24.2 ($n = 73$)	14.1 ± 7.9 ($n = 27$)	$P = 0.8646$	16.0 ± 21.1 ($n = 100$)
	Day 7 baseline	3.7 ± 18.6 ($n = 109$)	−0.9 ± 9.2 ($n = 9$)	4.4 ± 21.9 ($n = 73$)	3.6 ± 8.6 ($n = 27$)	$P = 0.7296$	4.1 ± 19.2 ($n = 100$)
	Baseline Day 7 difference						0.052
Difference LC placebo	Baseline	$P = 0.3594$	$P = 0.6820$	$P = 0.6975$	$P = 0.2108$		
	Day 7	$P < 0.0001$	$P = 0.0599$	$P = 0.0001$	$P = 0.0018$		
	Day 7 baseline	$P < 0.0001$	$P = 0.0573$	$P = 0.0001$	$P = 0.0030$		

Free carnitine values are reported as mean ± SD (number of patients).

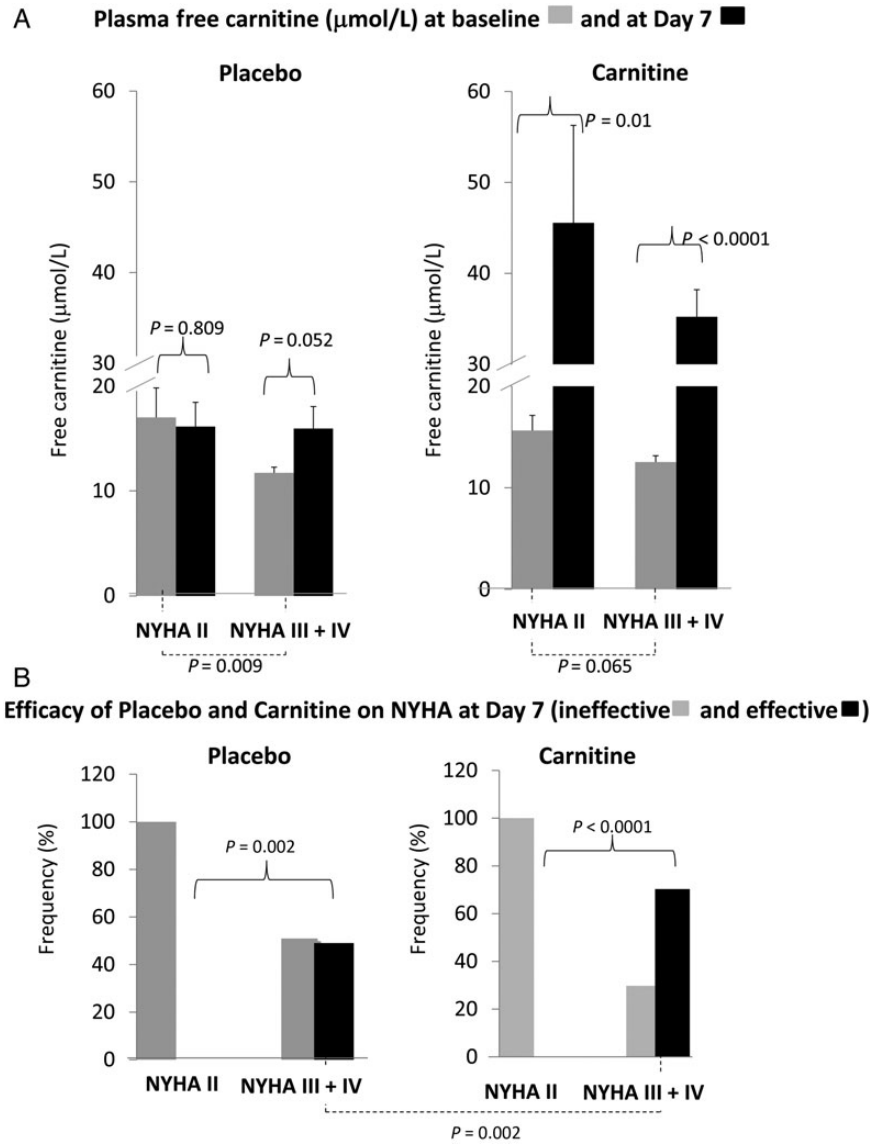

Figure 1 (*A*) Plasma free carnitine levels (μmol/L) according to NYHA classification at baseline (mean + SE). *P*-values calculated by analysis of variance comparing baseline and Day 7 plasma free carnitine levels among NYHA groups. (*B*) Efficacy according to NYHA classification. Values shown are *n* (%). *P*-values calculated by Fisher's exact test.

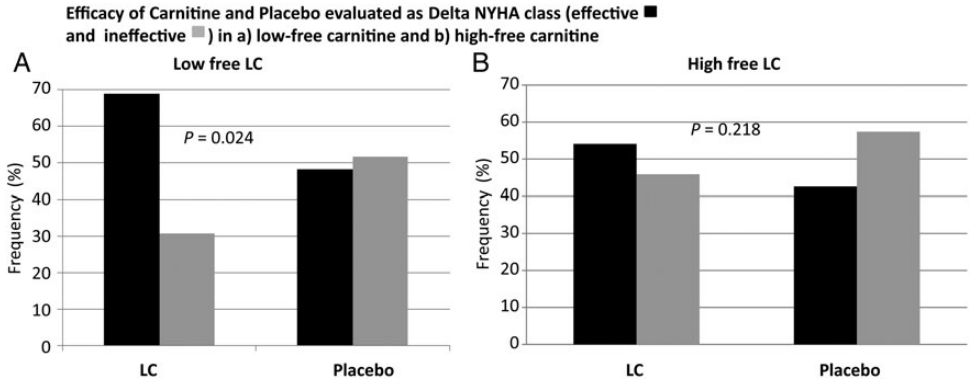

Figure 2 Efficacy evaluated as change in NYHA class in low free carnitine patients (left) and high free carnitine patients (right). Data are shown as *n* (%). *P*-values calculated by logistic regression.

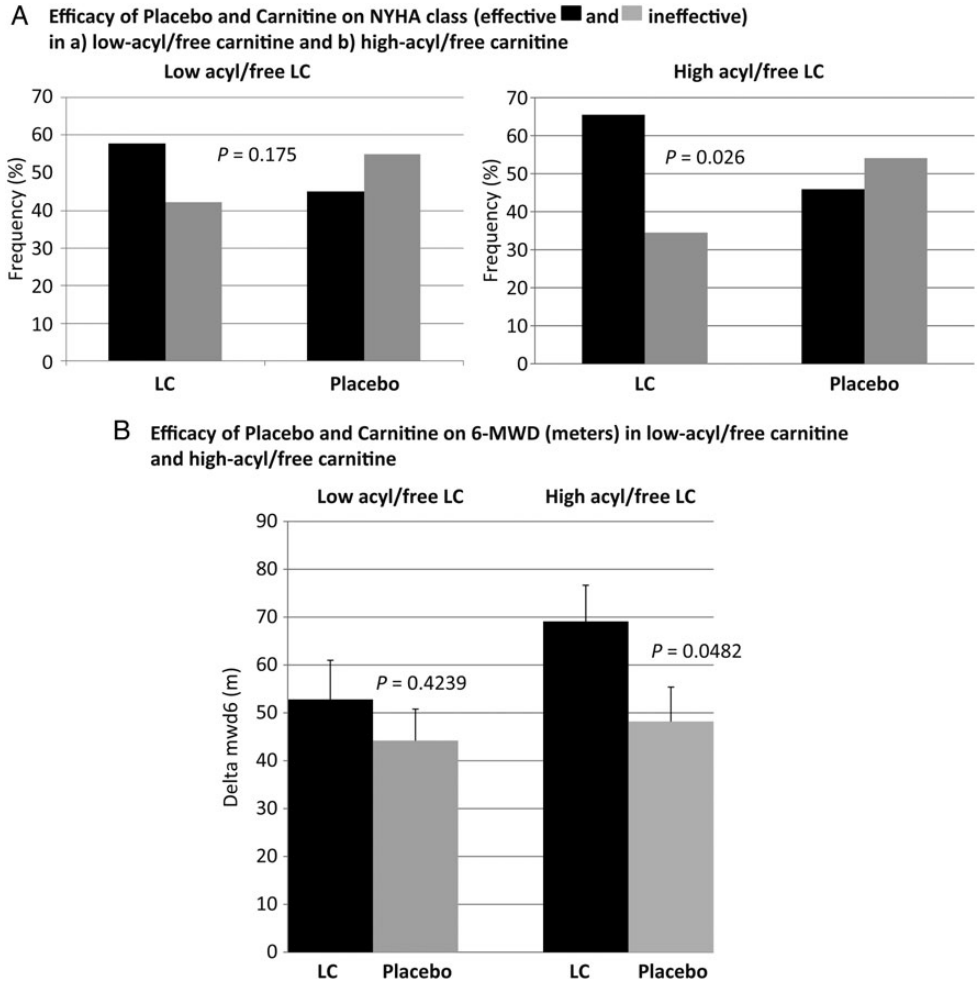

Figure 3 (*A*) Efficacy evaluated as change in NYHA class in low acyl/free carnitine patients (left) and high acyl/free carnitine patients (right). Median values were measured at baseline for the whole study cohort. Data are shown as *n* (%). (*B*) Efficacy evaluated as 6-min walk distance (m) in low acyl/free carnitine patients and high acyl/free carnitine patients. 6-min walk distance changes are shown as mean ± SE. *P*-values calculated by logistic regression.

Safety analysis

There were no significant differences in laboratory data, vital signs, or physical examinations between the two groups on Day 7. The incidence of AEs was 17.3 vs. 14.1% in the LC and placebo groups, respectively. This difference was not statistically significant ($P = 0.473$). Nine patients withdrew from the study due to an AE: one (0.8%) in the LC group and eight (6.3%) in the placebo group. This difference was not statistically significant ($P = 0.135$). The incidence of treatment-related AEs was 4.5 vs. 6.2%, respectively ($P = 0.533$).

There were two (1.5%) SAEs in the LC group and two (1.6%) in the placebo group ($P = 1.000$). According the investigator's judgment, no SAE was related to study treatment.

Discussion

This study demonstrates the clinical efficacy of LC supplementation in patients with CHF where the primary endpoint of a decrease of least one NYHA class and the secondary endpoint of an increase in 6-MWD, taken as an index of 'exercise tolerance', were achieved. These parameters are widely used to assess efficacy in heart failure trials.[20–22] Seven days of LC supplementation resulted in a significantly greater improvement in NYHA class (60.9 vs. 44.7%; $P = 0.012$), 6-MWD (+61 vs. +46 m; $P = 0.0497$) and combined improvement in NYHA class and 6-MWD (29 vs. 13%, $P = 0.002$) in the LC group compared with placebo. Conversely, no significant difference in LVEF, NT-proBNP plasma levels, and incidence of cardiovascular events was observed between the two groups. L-Carnitine was well tolerated.

Previous studies on the benefits of LC in various types of cardiomyopathy have given conflicting results.[15–17,23,24] Our study was conducted in a larger study cohort and the result provide more robust support for LC supplementation in patients with CHF. However, although significant, the effect of LC over placebo was not impressive.

More than 30 years have elapsed since the first suggestion[25] of possible carnitine insufficiency in humans with CHF. However, no consensus has been reached on

the target populations of CHF patients that may benefit from carnitine supplementation. Two alternative LC supplementation strategies can be adopted: (i) supplementation to replenish the cardiac depleted store (i.e. carnitine is given only in the presence of carnitine deficiency) or (ii) carnitine is administered as a pharmacological agent able to exert a beneficial effect in patients with normal carnitine status.[26] This second approach may increase cardiovascular risk through two mechanisms: (i) an increase in cytosolic carnitine above critical levels enhances the formation of intracellular acyl-carnitines which then exit the cells into the plasma.[27,28] This process may override the beneficial effects of correcting carnitine insufficiency since the increase in some acyl-carnitine derivatives in plasma may have a detrimental effect on cardiovascular function.[29,30] The paradoxical dose–effect relationship of carnitine on plasma triglycerides, showing a beneficial effect at low doses that disappears at high doses,[31] may be due to a similar mechanism; (ii) an increase in oral dose of carnitine above a critical level is associated with an increase in plasma trimethylamine[32] which may promote atherosclerosis.[33] Our results are not relevant to the first treatment approach based on carnitine insufficiency since the increased risk of developing major cardiac AEs has only been detected in humans with carnitine plasma concentrations >45.1 μmol/L. For these reasons, the first approach is much safer than the second. The definition of plasma and tissue levels of carnitine that might trigger functional and clinically significant carnitine insufficiency is central to the rational of using carnitine supplementation in the therapy of cardiovascular diseases.

A series of studies clearly demonstrates that during the development of experimental[34] and clinical[35] cardiac damage there is a release of free[36] and acyl-carnitines from the heart that increase plasma concentrations[29,37] and urinary excretion.[37] Conflicting results on the relationship between plasma levels and heart failure severity measured by the NYHA classification[29] have been obtained. The normal tissue carnitine concentration, mainly in heart and skeletal muscle, is ~1–2 mmol/kg. Carnitine release from these tissues and the consequent increase in urinary excretion, not adequately corrected by supplementation, may lead to cardiac and skeletal muscle carnitine depletion. Therefore, the duration and degree of release/excretion/intake processes should be taken into account when using plasma levels to define 'carnitine insufficiency'. Furthermore, variations within genes encoding the different proteins involved in the synthesis, storage, transport, and excretion of carnitine[38] may also influence the status of 'carnitine insufficiency'.[39]

Baseline plasma-free carnitine was much lower in our CHF patients than in healthy Chinese subjects, measured by us and by Niu *et al.*[40] and in healthy Caucasians.[41] The carnitine decrease in our CHF patients has never been recorded in Caucasian patients. In addition, our CHF patients had free LC levels similar to those found in dialyzed patients considered to require carnitine supplementation (~16 μmol/L).[42] Plasma carnitine is further decreased in NYHA classes III and IV patients compared with NYHA class II patients. Indeed, the effect of carnitine is relevant only to classes III and IV (see *Figure 1*). The improvement in NYHA class by carnitine was also statistically significant in the small subsets of patients with baseline plasma-free carnitine levels below the median value or with an acyl/free ratio above the median level. Taken together, these data support the notion that carnitine efficacy is particularly evident in patients with some degree of carnitine insufficiency.

We also detected a clear improvement in NYHA class and 6-MWD in the placebo group. This may be due to changes in food intake and physical exercise associated with hospitalization which may produce a small increase in plasma-free carnitine. Even though these changes were small (from 11.8 to 15.9 μM), the increase may be clinically relevant since it occurred within the kilometre range of the high-affinity carnitine transporter.[26] This small increase in plasma concentration may be enough to partially correct the depletion of cellular carnitine responsible for the loss of function. In genetically determined carnitine deficiency, even a small increase in cellular carnitine is sufficient to produce clinically significant improvement.[43] Future studies aimed at assessing the effect of carnitine supplementation must avoid any other changes that may reduce the magnitude of the difference in efficacy between LC and placebo.

Chronic heart failure is a multifactorial disease that requires a multi-targeted and phase-dependent treatment approach. Replenishment of carnitine depleted stores in patients with 'carnitine insufficiency' may represent a safe and effective adjuvant therapy which, by increasing high energy phosphate for contraction and relaxation, may have a synergistic effect with other drugs.

Our study has a number of limitations. Although we demonstrated a previously unreported marked reduction in plasma-free carnitine in Chinese patients with CHF, this does not provide information on the mechanisms underlying carnitine insufficiency. Furthermore, carnitine insufficiency may also affect skeletal muscle, which is the largest body tissue store. As skeletal muscle function may also be involved in the improvement in NYHA class and 6-MWD, it is likely that it also contributes to the efficacy of LC in CHF.

In summary, NYHA classification and 6-MWD, both clinically important indices for evaluating treatment efficacy in patients with CHF, are improved significantly by LC supplementation. This efficacy is particularly evident in patients with low plasma carnitine levels. L-Carnitine supplementation was well tolerated. Further studies are warranted to better define target groups of patients with 'carnitine insufficiency' where the beneficial effects of carnitine supplementation may be maximized.

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