Effects of L-Carnitine on Exercise Tolerance in Patients with Stable Angina Pectoris

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SUMMARY

The effects of L-carnitine (900 mg, p.o. daily) on exercise performance were studied in 12 patients with stable effort angina using a multistage treadmill exercise test. Exercise tests were performed at the end of the placebo period and after 4 and 12 weeks of carnitine therapy. While 12 patients experienced angina during treadmill tests in the placebo period, 2 patients were free of angina after treatment with carnitine. The mean exercise time was 11.4±0.7 min (mean±SE) in the placebo period. This increased significantly to 12.2±0.5 min ($p<0.05$) after 4 weeks and 12.8±0.5 min ($p<0.01$) after 12 weeks of treatment with carnitine. The time required for 1 mm ST depression to occur was 6.4±0.9 min in the placebo period. This increased significantly to 7.6±0.9 min ($p<0.01$) after 4 weeks and 8.8±1.0 min after 12 weeks of treatment with carnitine. There was significantly less ST segment depression during the same exercise load after 12 weeks of treatment as compared with that in the placebo period ($p<0.05$). The heart rate and the pressure rate product at the same work load showed no significant difference among the 3 testing periods.

The results of this study suggest that L-carnitine may improve exercise tolerance in patients with effort angina.

Additional Indexing Words:

L-Carnitine Angina pectoris Exercise test

FREE fatty acids (FFA) at high concentrations have been shown to impair myocardial cellular function,[1)-5)] whereas they are a major metabolic fuel for the heart.[6),7)] The accumulation of intermediates subsequent to impaired

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oxidation of FFA has been suggested as a cause of the cellular damage in the ischemic myocardium,[8] and a decrease in the myocardial free carnitine concentration has been demonstrated in experimental myocardial ischemia.[9),10] Because carnitine is essential for the transport of long-chain fatty acids to the sites of oxidation in the mitochondria,[11),12] much attention has been focused on its role in impaired fatty acid metabolism in the ischemic myocardium. The protective effects of exogenous carnitine on metabolic derangement in the ischemic heart have been described in several reports,[10),13),14] but there have been few reports concerning the effectiveness of carnitine in the treatment of angina pectoris.

The purpose of this study was to evaluate the effect of L-carnitine on exercise tolerance in patients with effort angina using a multistage treadmill exercise test protocol.

Methods

Study patients:

Twelve patients were studied, 10 men and 2 women. Their mean age was 56.8±2.5 (mean±SE) and ranged from 43 to 70 years. The requirements for inclusion in this study were as follows:

1) definite electrocardiographic evidence of myocardial ischemia; 1 mm or more of horizontal or downsloping ST depression during the exercise test,
2) presence of a definable end-point of ischemia during the exercise test with typical anginal pain,

Table I. Study Patients

Case No.	Age (yr)	Sex	Old MI	Coronary angiogram
1	58	M	Anterior	LAD 100%, LCX 75%, RCA 75%
2	54	M		LCX 75%
3	43	M		
4	50	F		LAD 75%
5	46	M	Inferior	LCX 75%
6	63	M		LAD 99%, LCX 75%, RCA 90%
7	70	M		
8	68	M	Anterior	
9	62	F	Anterior	
10	58	M	Anterior	LAD 100%
11	61	M	Anterior	LAD 100%, LCX 75%
12	48	M	Anterior	LAD 90%, RCA 99%

Abbreviations: MI=myocardial infarction; RCA=right coronary artery; LCX=left circumflex coronary artery; LAD=left anterior descending coronary artery; %=luminal diameter narrowing.

3) no evidence of rest angina,
4) no evidence of valvular heart disease, cardiomyopathy, or significant non-cardiac disease,
5) absence of conduction disturbances such as bundle branch block,
6) no digitalis for at least 1 month prior to the study.

Patients with unstable angina or recent myocardial infarction (within 6 months) were excluded. The characteristics of the patients at entry into this study are shown in Table I.

Exercise testing:

Exercise tests were carried out using a treadmill. The exercise apparatus was a computer assisted system for exercise (CASE) (Marquette Electronics Inc., U.S.A.). Speed and elevation were increased every 3 min. The initial stage was 1.7 miles/hour at a 0 percent gradient (stage 0) and the next 1.7 miles/hour at a 5% gradient (stage 1/2). When the stage was 1/2 completed, the test was continued using the conventional Bruce protocol.[15]

Prior to this study, all patients underwent exercise testing on at least 3 different days. Each exercise test was performed at approximately the same time of day. Patients performed treadmill exercise until the onset of angina, at which time they stopped exercising. Neither ST depression nor target heart rate was used as an indication for stopping the test in the control and placebo periods. If the patients were free of angina until the target heart rate, the target heart rate was used as an indication for stopping the test during the period of treatment.

During exercise the electrocardiogram was monitored using leads ${}_aV_F$, V_1 and V_5. The heart rate and blood pressure were recorded at the end of each stage of the exercise test while the patient was standing at rest. The time from the start of exercise to the appearance of a 1 mm horizontal or downsloping ST depression was recorded.

Plasma carnitine and FFA:

Plasma carnitine and FFA were estimated at the time of each exercise test 15 min before the start of exercise. Free carnitine was determined enzymatically using carnitine acetyl transferase by the method of Marquis and Fritz.[16] FFA was determined by the method of Itaya and Ui.[17]

Drug protocol:

L-carnitine was supplied in 100 mg tablets. During the first 4 weeks of the study all patients received placebo. After 4 weeks patients received 900 mg of L-carnitine for 12 weeks. Patients received 3 tablets 3 times daily.

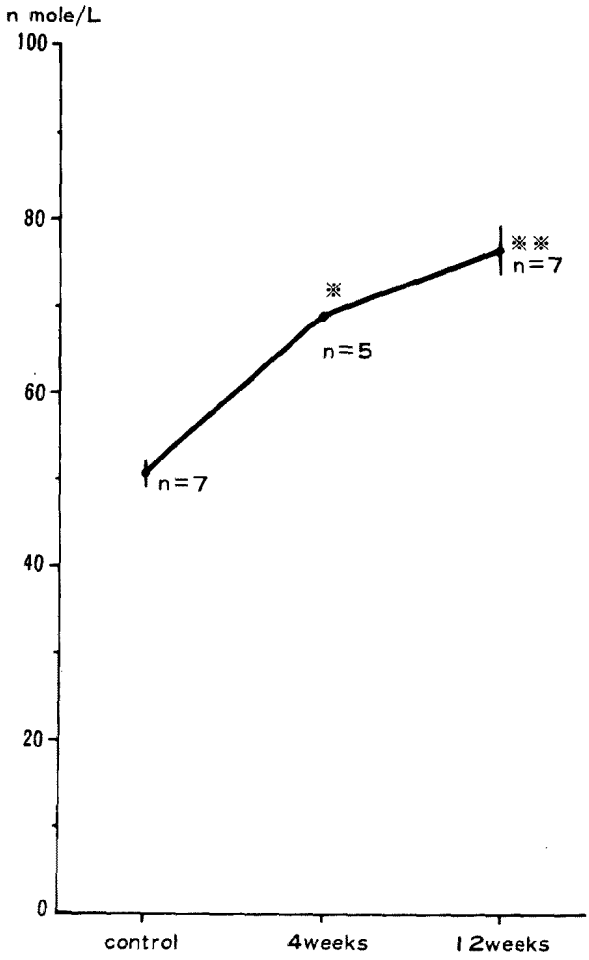

Fig. 1. Effect of L-carnitine on plasma levels of carnitine. Values are represented as mean±SE. Asterisks represent the significance of changes as compared with the levels before the administration of L-carnitine.
※$p<0.05$, ※※$p<0.01$.

During the study the patients were permitted to use sublingual nitroglycerin at the onset of angina, but all other cardioactive drugs were discontinued.

The exercise tests were performed before and after the placebo period and at 4 weeks and 12 weeks after the beginning of L-carnitine administration.

Statistical analysis:

Analysis of the statistical significance of differences observed in the exercise time, the time to onset of 1 mm ST depression, heart rate and pressure-rate product between values from before and after treatment with the placebo or between the placebo and treatment with carnitine were examined by

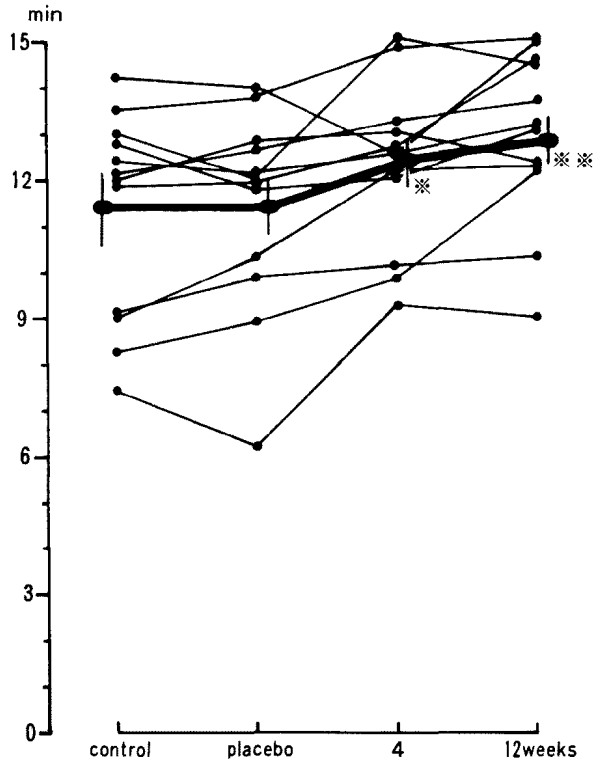

Fig. 2. Effect of L-carnitine on the duration of exercise. Asterisks represent the significance of changes as compared with the exercise duration during the placebo period.
※$p<0.05$, ※※$p<0.01$.

Student's t test.

Results

Plasma levels of carnitine:

The plasma levels of carnitine were 50.7±3.3 n mole/L (mean±SE) after 4 weeks on placebo. With L-carnitine, plasma levels of carnitine increased significantly to 69.1±0.5 after 4 weeks of treatment and 76.5±5.4 after 12 weeks of treatment ($p<0.05$, $p<0.01$ vs placebo (Fig. 1).

Treadmill exercise responses:

A) Exercise time

The mean exercise times were 11.4±0.6 min (mean±SE) during the control and 11.4±0.7 min after 4 weeks on placebo. With L-carnitine, the exercise time increased significantly to 12.2±0.5 min ($p<0.05$) after 4 weeks of

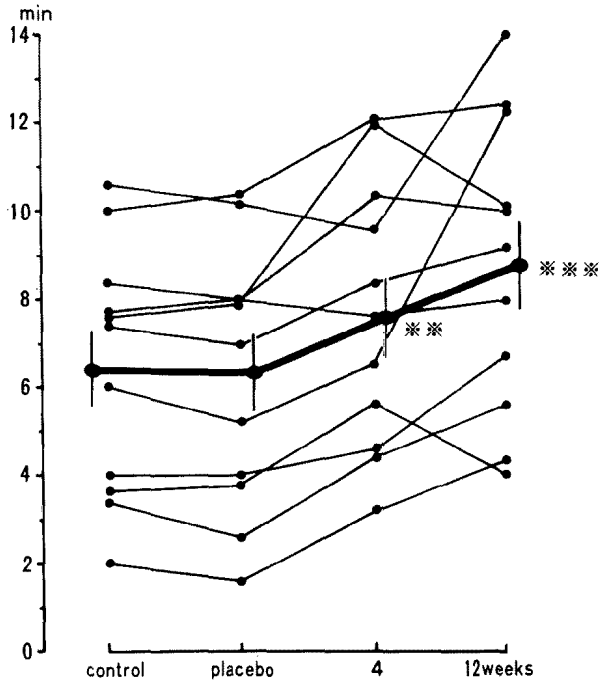

Fig. 3. Effect of L-carnitine on the times to onset of 1 mm ST depression. Asterisks represent the significance of changes as compared with the times during the placebo period.
※※p<0.01, ※※※p<0.001.

treatment and 12.8±0.5 min ($p<0.01$) after 12 weeks of treatment (Fig. 2). During the placebo period the exercise tests were stopped due to angina in all 12 patients. After 4 weeks of treatment with carnitine exercise tests were stopped because of angina in 10 patients, while 2 patients were free of angina during exercise testing.

B) Time to onset of 1 mm ST depression

The time required for the appearance of 1 mm ST depression was 6.3± 0.9 min during the control and 6.4±0.9 min after 4 weeks on placebo. With L-carnitine, the time increased to 7.6±0.9 min after 4 weeks ($p<0.01$) and 8.8±1.0 min after 12 weeks of treatment ($p<0.001$) (Fig. 3).

C) ST segment changes

The mean maximal ST depression was −2.4±0.5 mm (mean±SE) during the control and −2.3±0.4 mm after 4 weeks on placebo. With L-carnitine, ST segment changes showed no significant improvement after 4 and 12 weeks of treatment as compared with those of the placebo period. The ST segment changes at the same exercise load (Bruce I°, Bruce II°) showed no significant improvement after 4 and 12 weeks of treatment when compared

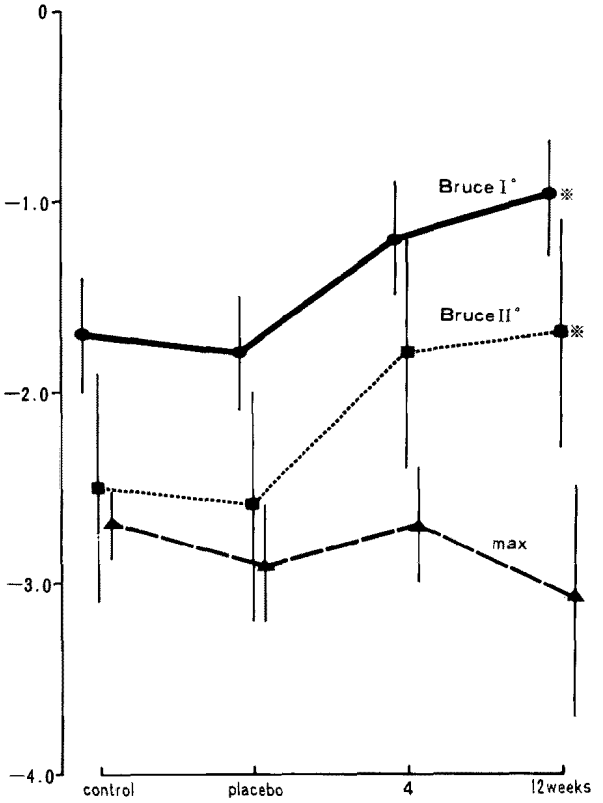

Fig. 4. Effect of L-carnitine on the ST index. Values are represented as mean±SE. Asterisks represent the significance of changes compared with the index during the placebo period.
※$p<0.05$.
●——●: Bruce I°, ■——■: Bruce II°, ▲——▲: maximum.

with those of the placebo period.

In this study we used the ST index, which was the calculated ST depression (mV) to which the ST slope (mV/sec) was added. The mean maximal ST index was -2.6 ± 0.2 during the control and -2.9 ± 0.3 after 4 weeks on placebo. With L-carnitine, the ST index was -2.7 ± 0.3 after 4 weeks and -3.1 ± 0.6 after 12 weeks of treatment. The ST index showed no significant improvement at maximal work load after 4 and 12 weeks of treatment, while the ST index at the same work load showed significant improvement after 12 weeks of treatment. In the Bruce I° stage, the mean ST index was -1.7 ± 0.3 during the control and -1.8 ± 0.3 during the placebo periods. With L-carnitine, the mean ST index was -1.2 ± 0.3 after 4 weeks and -1.0 ± 0.3 after 12 weeks of treatment ($p<0.05$). In the Bruce II° stage, the mean ST index was -2.5 ± 0.6 during the control and -2.6 ± 0.6 during the placebo

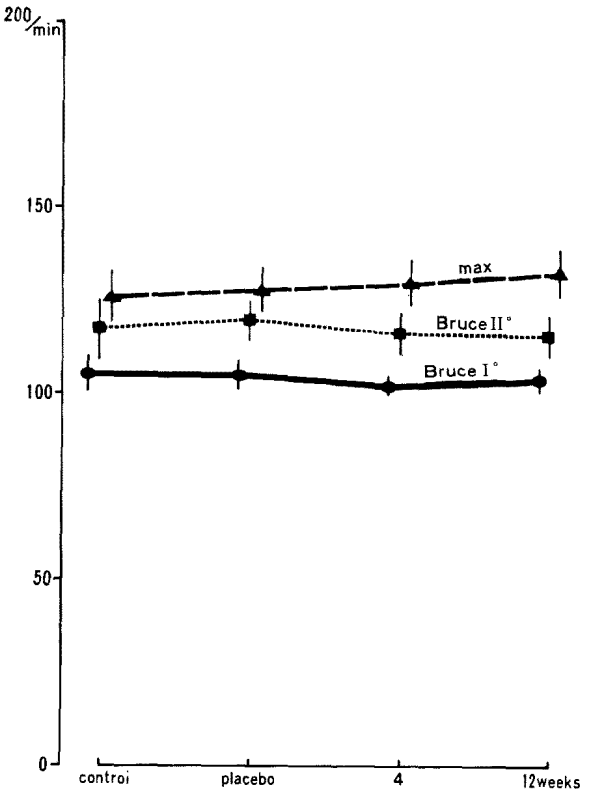

Fig. 5. Effect of L-carnitine on the heart rate. Values are represented as mean±SE.
●——●: Bruce I°, ■——■: Bruce II°, ▲——▲: maximum.

periods. With L-carnitine, the index was -1.8 ± 0.5 after 4 weeks and -1.7 ± 0.5 after 12 weeks of treatment ($p<0.05$) (Fig. 4).

D) Heart rate and pressure rate product

The maximal heart rate achieved at termination of the exercise test was 126.7 ± 5.8 beats/min during the placebo period and 130.0 ± 6.4 after 4 weeks and 132.9 ± 5.8 after 12 weeks of treatment with carnitine. There were no significant differences. The heart rate at the same work load was not significantly different at the 3 testing periods (Fig. 5).

The maximal pressure rate product achieved at termination of the exercise test was 17310 ± 2070 (mean±SE) during the placebo period and 18000 ± 1550 after 4 weeks and 17920 ± 2030 after 12 weeks of treatment. There were no significant differences. The pressure rate product at the same work load was not significantly different at the 3 testing periods (Fig. 6).

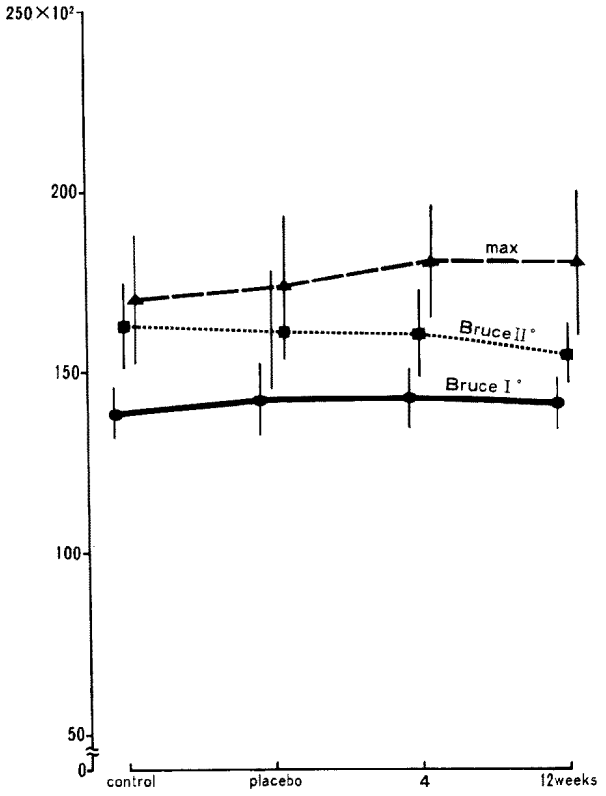

Fig. 6. Effect of L-carnitine on the pressure rate product. Values are represented as mean±SE.
●——●: Bruce I°, ■——■: Bruce II°, ▲——▲: maximum.

Discussion

Our results demonstrated that oral administration of 900 mg of L-carnitine daily for 4 weeks improved the exercise tolerance in patients with effort angina. One possible objection to these results might be that the placebo therapy itself might have resulted in a prolongation of exercise duration as a result of familiarization with the procedure. However, all patients underwent exercise testing on at least 3 different days before the study, and 4 weeks of placebo treatment did not change the duration of exercise or the time to the onset of ischemic ST changes. Therefore, the improvement observed after 4 and 12 weeks of carnitine therapy was not due to training or placebo effect.

The mechanisms of action of L-carnitine in effort angina are unclear. Thomsen et al[18] reported that the intravenous administration of L-carnitine improved the cardiac pacing tolerance associated with an increase in heart rate and pressure rate product in ischemic human hearts. They pro-

posed that carnitine might improve the metabolism of the ischemic myocardium because the increased tolerance was accompanied by improved myocardial lactate metabolism.

Carnitine, a water-soluble, naturally occurring amino acid, is essential for fatty acyl derivatives to penetrate across the inner mitochondrial membranes and to be transported to the sites of oxidation in the mitochondria.[11),12)] In the human heart, decreased tissue levels of carnitine in the myocardium have been reported in patients with heart failure[19)] and with myocardial infarction.[20)] We have also reported a decrease in myocardial free carnitine and an accumulation of long chain acyl carnitine and acyl CoA in the ischemic myocardium, while pretreatment with L-carnitine prevented the depletion of tissue levels of free carnitine and ATP and the accumulation of long chain acyl carnitine and acyl CoA in the ischemic myocardium.[10)]

Because the accumulation of long chain acyl CoA inhibits adenine nucleotide translocase,[8)] the decreased levels of long chain acyl CoA in the ischemic myocardium after the administration of carnitine may permit the ischemic myocardium to utilize its remaining limited oxygen supply more efficiently.

Our findings also suggest that L-carnitine may be an effective pharmacologic agent in the management of ischemic heart disease. Because carnitine's mode of action apparently differs from that of other antianginal agents such as β-blocking agents, Ca^{++} antagonists and nitrates, it might be used in combination with these agents.

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