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THE THERAPEUTIC EFFECT OF L-CARNITINE IN PATIENTS WITH EXERCISE-INDUCED STABLE ANGINA: A CONTROLLED STUDY

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Summary: *An investigation on the therapeutic effect of L-carnitine was performed at three different centres and included two hundred patients, 40 to 65 years of age, with exercise-induced stable angina. In one hundred randomly selected patients the drug was administered orally in daily doses of 2 g in addition to the already instituted therapy, and the effect studied over a 6-month period. Compared with the control group, these patients showed a significant reduction in the number of premature ventricular contractions (PVC) at rest, as well as an increased tolerance during ergometric cycle exercise as demonstrated by an increased maximal cardiac frequency, increased maximal systolic arterial blood pressure and therefore also increased double cardiac product and reduced ST-segment depression during maximal effort. This was accompanied by improvement in cardiac function and resultant performance, as shown by an increase in the number of patients belonging to class I of the NYHA classification and a reduction in the consumption of cardioactive drugs. Laboratory analysis showed an improvement in plasma lipid levels. The authors conclude, after having discussed the particular metabolic mechanisms, that L-carnitine undoubtedly represents an interesting therapeutic drug for patients with exercise-induced stable angina.*

Introduction

L-carnitine is a quaternary ammonium compound synthesized in the liver and kidneys, and is present in high concentrations in skeletal as well as myocardial muscle, where it plays an important role in the metabolism of fatty acids as a specific carrier of acyl radicals from the cytoplasm of muscle fibre cells to the intramitochondrial sites of β-oxidation (1–8).

Ischaemic conditions are responsible for a reduction in myocardial tissue levels of free L-carnitine and a rapid inhibition of the oxidative processes,

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resulting in an accumulation of intracytoplasmatic free fatty acids and their intermediate metabolites, primarily acetylene-CoA in long chains (9–13). Free fatty acids, and more importantly acetylene-CoA with its elevated detergent action, exercise a degrading effect on cellular membranes and inhibit enzymatic activities essential to mitochondrial energy metabolism. Amongst these essential enzymes is adenine nucleotide translocase, which is responsible for catalysing the transfer of ADP from the cytoplasm to the mitochondria, and ATP from the mitochondria to the cytoplasm where it serves in the contractile processes of the myocardium. The inhibition of above-mentioned enzymes is responsible for the accumulation of ATP and ADP inside mitochondria and cytoplasm respectively, with a resultant inhibition of ATP production due to a decrease in the availability of ADP in the mitochondrial oxidative phosphorylation processes (14, 15).

Several investigations have demonstrated that L-carnitine through various mechanisms protects ischaemic myocardium (16–20). Clinical studies concerning heart failure patients with atrial pacing have shown that L-carnitine improves myocardial energy metabolism by increasing the use of free fatty acids and by reducing the coronary lactate outflow (21, 22) and is able to increase the ischaemic threshold of angina and pacing tolerance by reducing left ventricular diastolic pressure as well as ST-segment and T-wave alterations (23).

A controlled multicentre double-blind crossover study concerning patients with exercise-induced stable angina has demonstrated that treatment with L-carnitine results in an increased tolerance to physical exercise, increased maximal physical effort and ischaemic threshold of angina, and a reduction in the electrocardiographic signs of ischaemia (24, 25). In patients with acute myocardial infarction, therapy with L-carnitine has been proved to reduce the necrotic area (3, 26, 27). It is also responsible for improving general conditions and range in the NYHA classification, a rapid regression in the number of atrial and ventricular ectopic contractions and a reduction in mortality during the first 6 months of treatment (28). In addition, in patients with previous infarction or stable angina associated with symptomatic premature ventricular contractions, a reduction in the number of ectopic beats and their clinical morbidity was observed with a progressive increase in the intervals between attacks (29, 30).

In patients with congestive heart failure, L-carnitine has been shown to improve haemody-

Table I *Ergometric testing.*

Variable	Periodic	L-carnitine	Control
Maximal cardiac frequency (mcf)	basal	105.60 ± 11.18	107.31 ± 9.30
	following treatment	110.67 ± 8.64	107.31 ± 9.33
Maximal arterial systolic blood pressure (mmHg)	basal	181.04 ± 18.53	176.31 ± 17.54
	following treatment	187.28 ± 13.57	176.41 ± 17.81
Maximal double cardiac product (mmHg × mcf)	basal	19219.7 ± 3488.2	19001.1 ± 3059.2
	following treatment	20790.1 ± 2590.2	19035.9 ± 3150.0
ST-segment depression (mm)	basal	0.515 ± 0.750	0.562 ± 0.824
	following treatment	0.149 ± 0.364	0.557 ± 0.826

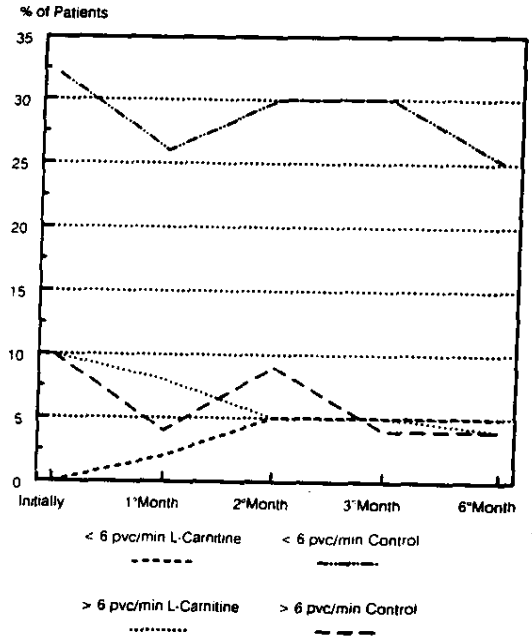

Fig. 1 Premature ventricular contractions.

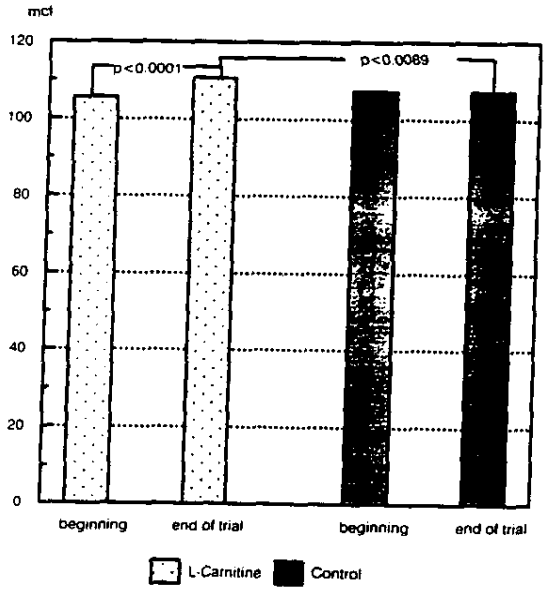

Fig. 2 Maximum cardiac frequency.

namic and cardiac parameters, therefore resulting in a reduction of the required daily dosage of cardiac glycosides and diuretics (31).

Recently a clinical phase IV study, concerning 3500 patients with various types of cardiopathies treated for one year with L-carnitine in addition to their normal therapy, has demonstrated L-carnitine to be cardioprotective, essentially because it is responsible for an improvement in functional status and a reduction in the consumption of other cardioactive drugs (32, 33). As a result of these observations, the authors found it interesting to investigate the cardioprotective and metabolic effects of L-carnitine in a group of patients suffering from exercise-induced stable angina.

Patients and methods

The present investigation included a group of 200 patients, 125 (62.5%) male and 75 (37.5%) female, 40 to 65 years of age, suffering from exercise-induced stable angina for at least one year and having ischaemic attacks characterised by classical onset and complete regression following rest or the administration of sublingual nitroglycerine. 144 (72%) belonged to functional class I of the NYHA classification and 56 (28%) to class II; 72 (36%) were smokers whereas 128 (64%) were nonsmokers.

Patients were excluded from the study according to the following criteria: below 40 or above 65 years of age; unstable or spontaneous angina, and if the ischaemic attacks primarily were exercise-

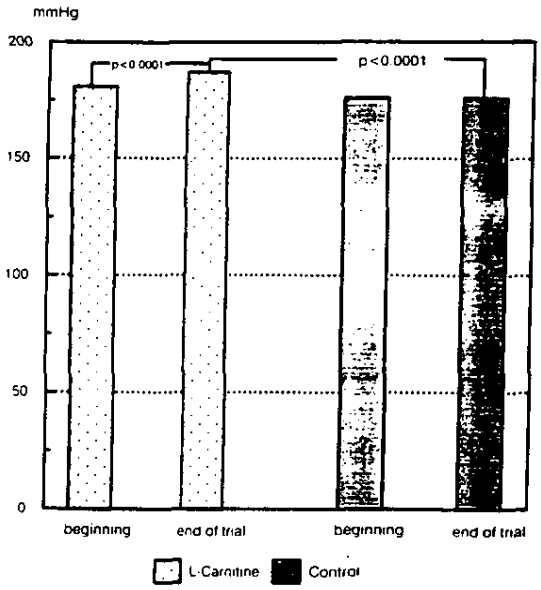

Fig. 3 Maximum systolic arterial blood pressure.

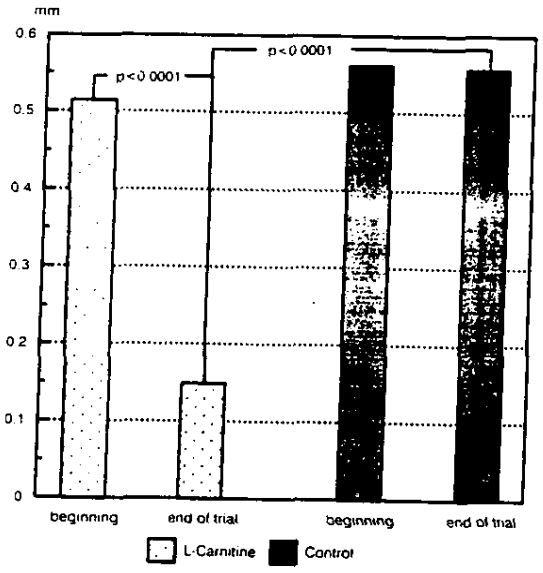

Fig. 5 ST-segment depression.

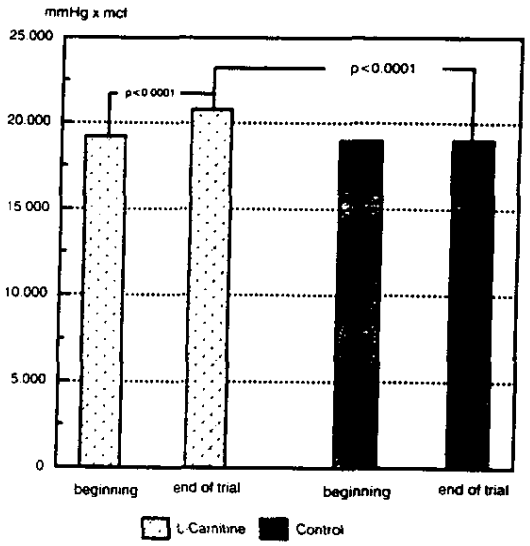

Fig. 4 Double cardiac frequency.

induced; previous myocardial infarction; ventricular arrhythmias of Lown's class III or IV; Wolfen–Parkinsonen–White syndrome; atrio-ventricular or intraventricular conduction disorders; uncontrolled arterial hypertension; valve disorders; central or peripheral vasculopathies; myocardial insufficiency (NYHA classes III and IV); severe systemic diseases (*i.e.* grave anaemia, liver and kidney insufficiency, diabetes mellitus, chronic lung disease and neoplasms).

One hundred of these randomly selected patients were treated with 2 g of L-carnitine orally for six months. All patients signed the informed consent form (Helsinki 1964-Tokyo 1975). No wash-out was performed, but all patients included in the study had the investigated product added to their normal pharmacological therapy, which included nitro derivatives, calcium channel blockers, β-blockers, antihypertensives, diuretics, cardiac

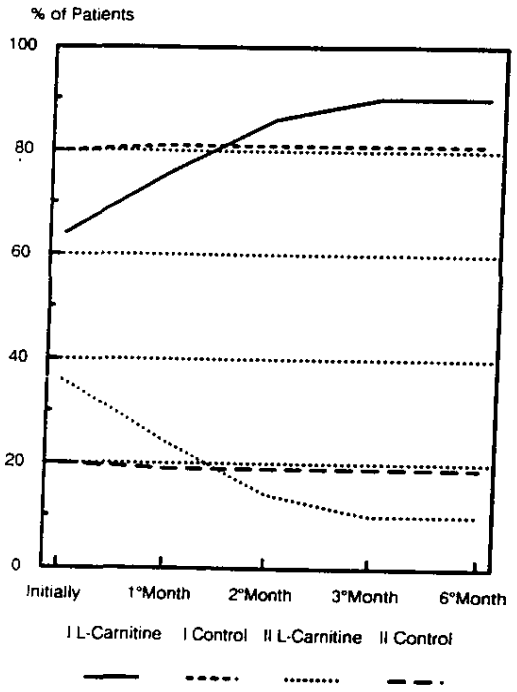

Fig. 6 NYHA functional capacity classification.

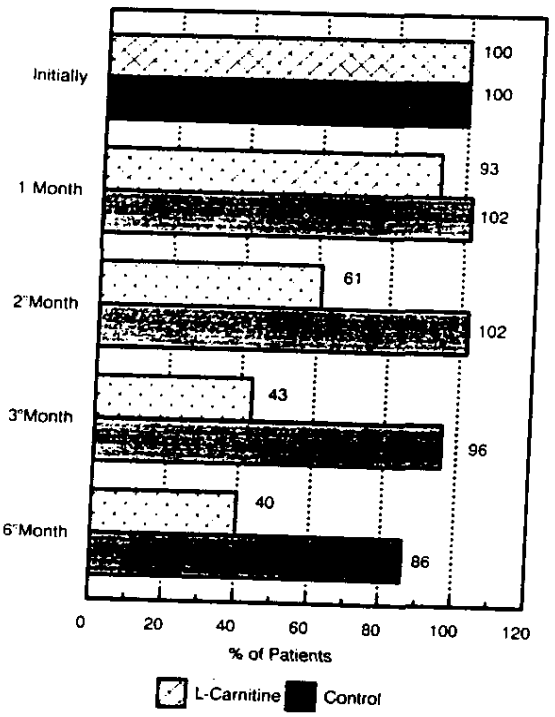

Fig. 7 Current therapy: nitroglycerine.

glycosides, antiarrhythmics, anticoagulants and hypolipidaemics.

Initially and 1, 2, 3 and 6 months afterwards, both groups of patients had their blood glucose, triglyceride, total cholesterol and HDL levels measured, an ECG performed at rest, functional status evaluated and the consumption of nitro derivatives and other cardiovascular-active drugs controlled. Ergometric cycle exercise testing was performed initially and at the end of the investigation in a sitting position following a multi-stage method, with an initial load of 25 watts which was increased by another 25 watts every 2 min. The "endpoints" were typical moderate angina; ST-segment depression ≥ 2.0 mm; marked dyspnea; absence of increased blood pressure following two consecutive increments in work load; excessive increase in arterial blood pressure (>200/100 mmHg); subjective symptoms of cerebral hypoxia; life-threatening arrhythmias and physical exhaustion.

Activity parameters during testing were obtained from haemodynamic evaluations (heart rate, systolic arterial blood pressure and double cardiac product) and tolerance to exercise (*i.e.* ST-segment depression during maximal effort). Twelve-channel ECG was registered at rest, every minute during exercise and for 6 min during the period of recovery. A continuous three-channel ECG recording

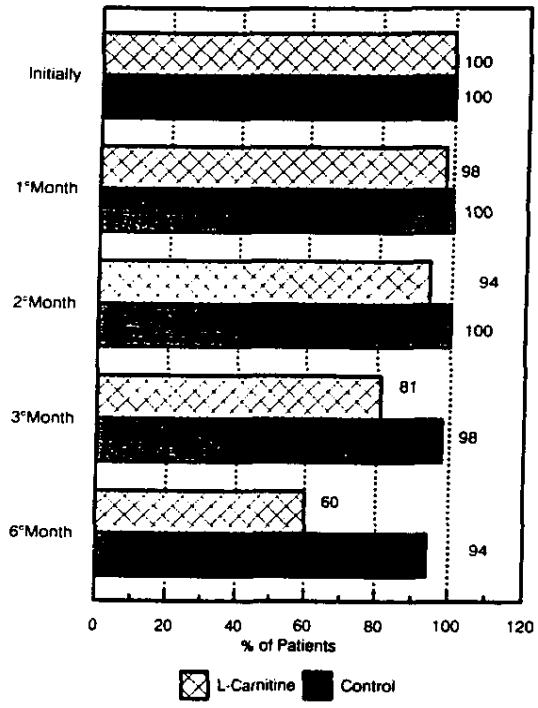

Fig. 8 Current therapy: nitro derivatives.

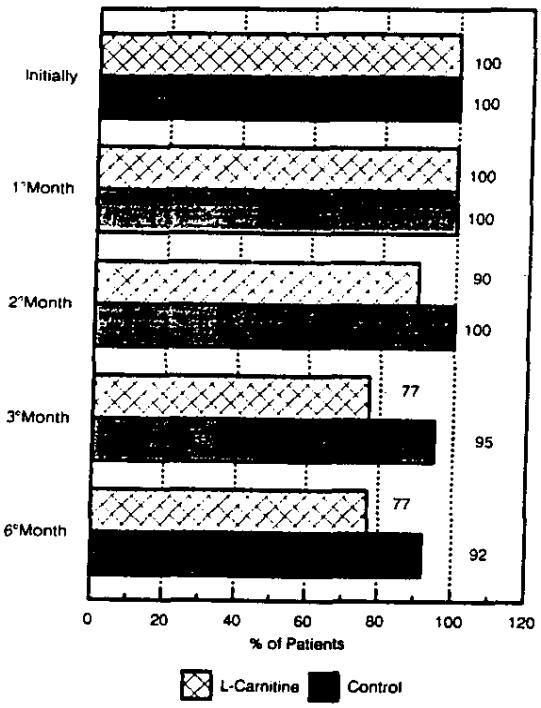

Fig. 9 Current therapy: nifedipin.

was made during the entire test, including the period of recovery. Arterial blood pressure was measured with a sphygmomanometer every minute during the testing and recovery periods; heart rate was obtained from the electrocardiogram. Parametric data were analysed by paired and unpaired Student's "t" test and two-way analysis of variance for repeated measures; $p<0.05$ was considered significant.

Results

During the entire period of therapy none of the two groups showed ST-segment or T-wave alterations in basal conditions, nor were any changes in the sinus rhythm or regressions in previously existent arrhythmias (premature atrial contractions or atrial tachycardia, flutter or fibrillation) observed, except for a number of PVCs which in patients treated with L-carnitine gradually decreased with a consequent increase in the number of patients with less than six PVCs per minute and a proportional reduction in the number of patients with more than six PVCs per minute (Fig. 1).

During exercise testing (Table I), patients treated with L-carnitine as opposed to those in the control group showed a significant increase in maximal

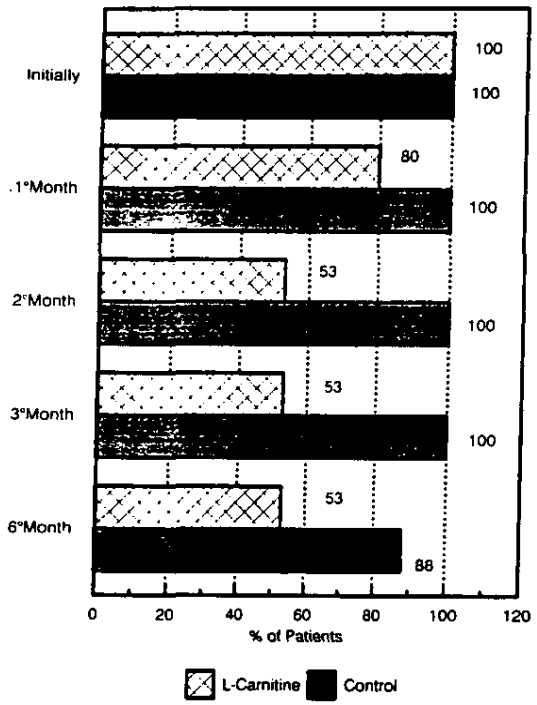

Fig. 10 Current therapy: diltiazem.

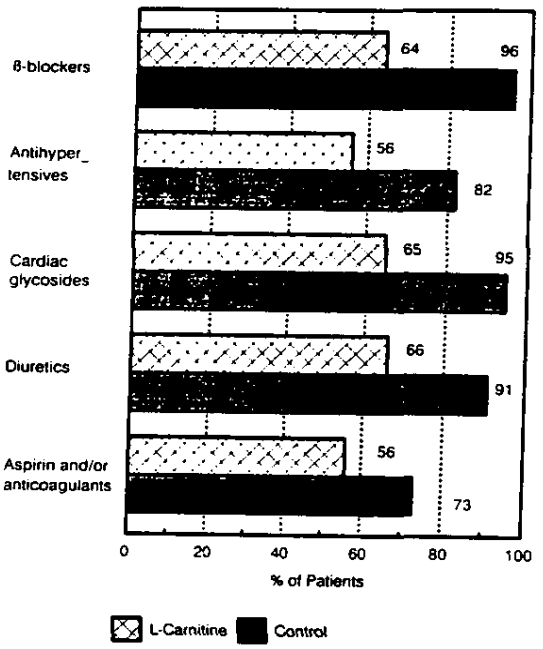

Fig. 11 Consumption of β-blockers, antihypertensives, cardiac glycosides, diuretics, aspirin and/or anticoagulants at the end of trial in the two treated groups. At the beginning of trial, all patients (100%) were concomitantly treated with these drugs.

cardiac frequency (mcf) ($p < 0.0001$) (Fig.2), maximal arterial systolic blood pressure (Fig. 3), the corresponding double cardiac product (Fig. 4) and increased tolerance to exercise as evidenced by a significant reduction in ST-segment depression at maximal effort (Fig. 5).

With respect to function, patients treated with L-carnitine showed almost immediate improvement in cardiac performance starting from their first control, with a gradual increase in the number of patients belonging to NYHA class I and a proportional reduction in those belonging to class II, whereas no such changes were observed in the control group (Fig. 6).

A significant reduction in drug consumption was observed only in the group of patients treated with L-carnitine. At the end of the investigation, the reduced consumption of nitroglycerides and other nitro derivatives was 60% (Fig. 7) and 40% (Fig. 8) respectively. Nifedipin and diltiazem consumption was reduced by 33% (Fig. 9) and 47% (Fig. 10) respectively. β-blockers were reduced by 36%, antihypertensives by 44%, cardiac glycosides by 35%, diuretics by 34%, anticoagulants by 44% (Fig. 11), antiarrhythmics by 70% (Fig. 12), haemokinetics and vasodilators by 60% (Fig. 13) and hypolipidaemics by 61% (Fig. 14).

The percentage of suspensions for the majority

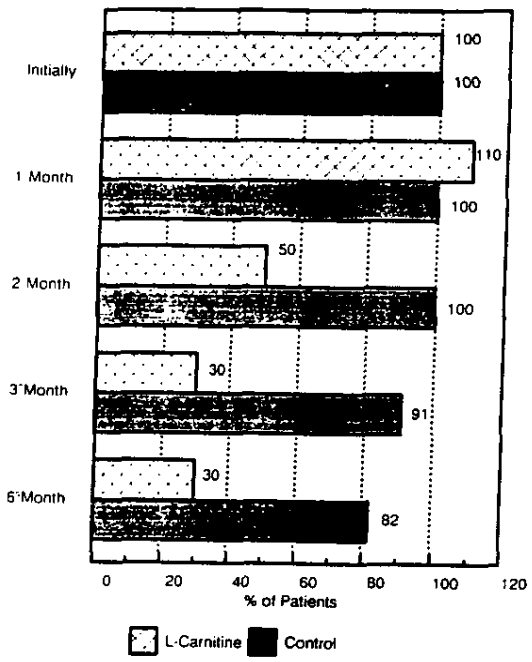

Fig. 12 Current therapy: anti-arrhythmics.

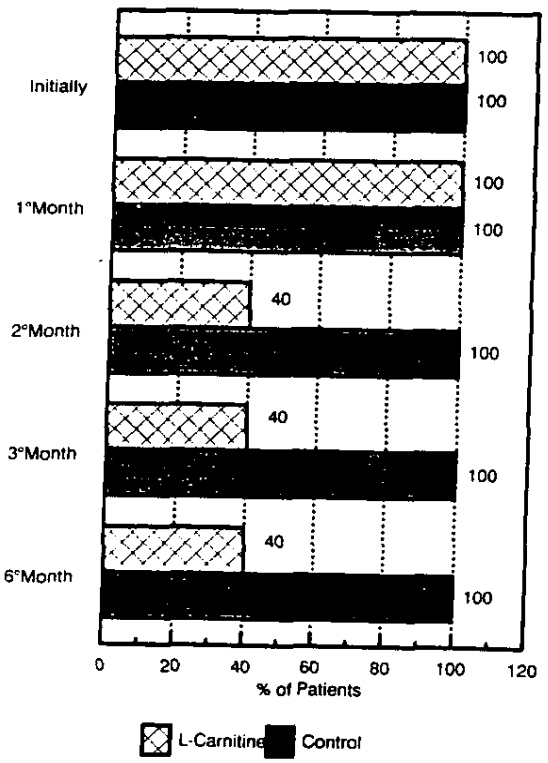

Fig. 13 Current therapy: haemokinetics and vasodilators.

of drugs was greater than 40% and was already evident from the first control for diltiazem, β-blockers, antihypertensives and cardiac glycosides and from the second control for all of the other drugs with the exception of the nitro derivatives, which showed a reduction of 20% only at the third control.

Concerning blood analysis (Table II), both groups of patients demonstrated no alterations in glycaemia or HDL cholesterolaemia throughout the entire investigation, with only the L-carnitine group showing moderate but significant changes in total cholesterol ($p < 0.001$) and triglyceride ($p < 0.001$) levels, with a progressive reduction beginning from the first control. The addition of 2 g of L-carnitine daily caused a decrease in plasma cholesterolaemia of 21.28 mg/ml and triglyceridaemia of 19.73 mg/ml, responsible for a fall in the initial 230.00 mg/ml ± 25.6 of cholesterol and 174.13 mg/ml ± 27.7 of triglyceride levels to final values of 208.72 mg/ml ± 15.6 and 154.40 mg/ml ± 17.2 respectively. The control group on the other hand demonstrated no variation in either total cholesterol or triglyceride levels; in fact a slight but insignificant increase was noticed.

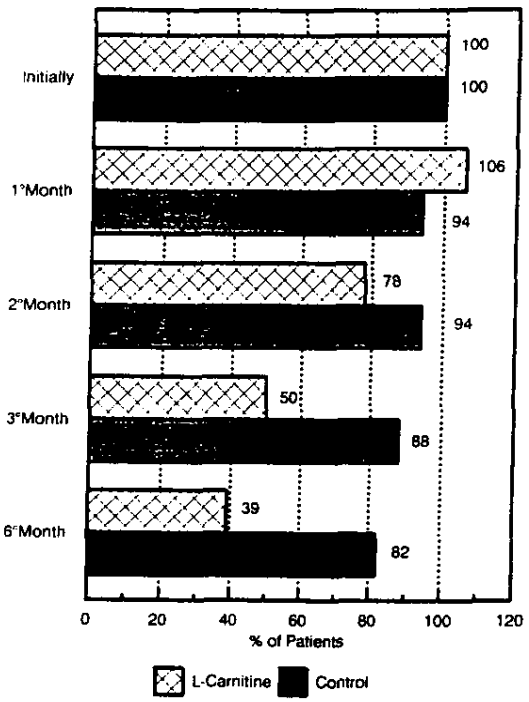

Fig. 14 Current therapy: hypolipidaemics.

Discussion

The present investigation has demonstrated that patients with exercise-induced stable angina showed significant and progressive improvement in both cardiac function and quality of life during the 6 months following the addition of 2 g of L-carnitine to their therapeutic regime. The L-carnitine group, as opposed to the control group, showed a significant reduction in the number of premature ventricular contractions, exercise-induced electrocardiographic signs of ischaemia and increased exercise tolerance. During the 6 months of therapy, a progressive improvement in cardiac performance was documented, showing an increase in the number of patients belonging to NYHA class I and therefore a reduction in the number of patients in class II.

The results are without doubt of clinical relevance and become increasingly important considering the concomitant reduction in the consumption of all other cardioactive drugs.

Only patients treated with L-carnitine showed a moderate but significant reduction in total cholesterol and triglyceride levels. These positive effects are obviously due to the metabolic activity of L-carnitine, as already demonstrated in several other investigations, and that the administration of L-carnitine in the presence of myocardial ischaemia is associated with the removal of long chain acylene-CoA, which is incorporated in acylene–carnitine molecules facilitated by acyl transferase. In addition to being less toxic, it is characterized by its marked diffusability, thus explaining why it can be easily displaced from ischaemic myocardial tissue. L-carnitine-induced removal of acetylene-CoA is responsible for antagonizing the inhibition of adenine translocase, thus permitting the transportation of ATP from the mitochondria to the cytoplasm where it is used in the myocardial contractile process. The advantage derived from CoA accumulation is the stimulation of oxidative metabolism not only of fatty acids, but also of pyruvate. The oxidation of pyruvate to acetylene-CoA and its further oxidation in the Krebs cycle is markedly increased.

Based upon the results obtained, L-carnitine due to its intrinsic metabolic and cardioprotective effects, particularly during myocardial ischaemia, is without a doubt a drug of great interest, especially in patients with exercise-induced stable angina, both as a single drug therapy or in association with other traditionally used agents.

Table II *Blood analysis.*

Variable	Periodic	L-carnitine	Control
Glycemia	intially	78.78 ± 5.69	77.78 ± 5.36
	1st month	77.57 ± 4.58	78.24 ± 5.06
	2nd month	77.32 ± 4.21	78.54 ± 5.88
	3rd month	76.70 ± 4.11	78.51 ± 6.22
	6th month	77.29 ± 4.36	78.42 ± 4.98
Cholesterolaemia	initially	230.00 ± 25.68	228.34 ± 31.64
	1st month	224.14 ± 21.59	228.68 ± 32.33
	2nd month	221.71 ± 18.72	229.99 ± 31.25
	3rd month	219.67 ± 17.03	230.73 ± 32.59
	6th month	208.72 ± 15.69	229.09 ± 33.52
HDL cholesterolaemia	initially	55.84 ± 7.98	54.42 ± 7.11
	1st month	55.52 ± 6.63	54.77 ± 6.67
	2nd month	55.36 ± 6.09	54.30 ± 7.76
	3rd month	55.12 ± 5.88	54.84 ± 7.77
	6th month	55.34 ± 5.39	54.89 ± 8.04
Tryglyceridaemia	initially	174.13 ± 27.75	173.25 ± 22.35
	1st month	164.60 ± 29.92	172.48 ± 24.94
	2nd month	159.24 ± 23.52	174.41 ± 22.28
	3rd month	157.56 ± 21.39	172.30 ± 22.96
	6th month	154.40 ± 17.24	174.53 ± 23.62

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