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CONTROLLED STUDY ON L-CARNITINE THERAPEUTIC EFFICACY IN POST-INFARCTION

DAVINI P., BIGALLI A., LAMANNA F.,[1] BOEM, A.

Department of Cardiovascular Medicine, Santa Chiara Hospital, U.S.L., Via Roma 67, Pisa, Italy.

Summary: *A controlled study was carried out on 160 patients of both sexes (age between 39 and 86 years) discharged from the Cardiology Department of the Santa Chiara Hospital, Pisa, with a diagnosis of recent myocardial infarction. L-carnitine was randomly administered to 81 patients at an oral dose of g 4/die for 12 months, in addition to the pharmacological treatment generally used. For the whole period of 12 months, these patients showed, in comparison with the controls, an improvement in heart rate ($p < 0.005$), systolic arterial pressure ($p < 0.005$) and diastolic arterial pressure (NS); a decrease of anginal attacks ($p < 0.005$), of rhythm disorders (NS) and of clinical signs of impaired myocardial contractility (NS), and a clear improvement in the lipid pattern ($p < 0.005$). The above changes were accompanied by a lower mortality in the treated group (1.2%, $p < 0.005$), while in the control group there was a mortality of 12.5%. Furthermore, in the control group there was a definite prevalence of deaths caused by reinfarction and sudden death. On the basis of these results, it is concluded that L-carnitine represents an effective treatment in post-infarction ischaemic cardiopathy, since it can improve the clinical evolution of this pathological condition as well as the patient's quality of life and life expectancy.*

Introduction

L-carnitine is a natural compound present in high concentrations in skeletal muscles and myocardial tissues, where it plays an important role in fatty acid metabolism, inducing, as a highly specific carrier, the transport of acyl radicals from the cytoplasm to the intramitochondrial sites of β-oxidation (1, 2, 3, 7, 12, 27, 28, 30). In cases of ischaemia or hypoxic conditions, there is in the myocardium a rapid inhibition of oxidative processes and a reduction in tissue levels of free L-carnitine, with a consequent rise within the cytoplasm of free-fatty acids and of their intermediate metabolites, mainly long-chain acyl-CoA (15, 17, 18, 19, 20, 29). Because of their detergent action, both free-fatty acids and, above all, acyl-CoA exert disintegrating effects on the cellular membranes and inhibit some enzymatic activities essential to myocardium energy metabolism. Among them, the adenin-nucleotide-translocase catalyses the ADP transport from the cytoplasm to the mitochondria and the ATP transport from mitochondria to the cytoplasm, where it is used for contractile processes and pumping activity. In addition, the inhibition of this enzyme causes a compartmentalization of ATP within the mitochondria and of ADP in the cytoplasm, with final inhibition of ATP production, due to a loss in the mitochondrial matrix of the essential substrate for the oxidative phosphorylation, represented by ADP (24, 25, 26). Moreover, several studies show that L-carnitine is able to exert,

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Table I *Individual and clinical characteristics of the two groups of patients.*

	Group A (n = 81)	Group B (n = 79)	Diff
Sex (M/F)	68/13	56/23	NS
Mean age (yrs)	65.5 ± 11.6	66.5 ± 10.7	NS
Mean weight (kg)	72.1 ± 11.7	73.1 ± 11.8	NS
Mean height (cm)	169.7 ± 7.1	167.9 ± 7.8	NS
Positive anamnesis for:			
Precoronary time (hours)	22.9 ± 10.7	17.3 ± 13.4	NS
Familial CHD	28.7%	24.2%	NS
Cigarette consumption (no.)	13.4 ± 17.1	9.7 ± 13.7	NS
Hyperlipidemia	13.8%	18.7%	NS
Arterial hypertension	17.6%	27.8%	p < 0.036
Intermittent claudication	11.1%	5.3%	NS
Cerebrovascular accidents	4.0%	11.2%	NS
Angina pectoris	40.2%	43.6%	NS
Previous MAI	15.1%	8.3%	NS
Objective examination at beginning of hospitalization:			
Heart rate (b/min)	77.0 ± 15.1	80.4 ± 17.3	NS
ASP (mm g)	129.9 ± 28.5	136.4 ± 29.6	NS
ADP (mm hg)	77.0 ± 15.8	79.1 ± 12.8	NS
Dyspnoea	44.7%	46.1%	NS
Gallop rhythm	49.5%	38.2%	NS
Murmur of the heart	10.1%	9.0%	NS
Arrhythmias	28.0%	28.1%	NS
Mean Peel index	9.9 ± 5.4	9.6 ± 4.5	NS
Maximum value of enzymes:			
CPK (μ/ml)	1372.1 ± 891.9	1427.6 ± 1020.1	NS
CKMB (μ/ml)	92.8 ± 60.2	92.7 ± 68.5	NS
GOT (μ/ml)	126.6 ± 82.8	129.7 ± 88.6	NS
LDH (μ/ml)	1108.3 ± 649.0	1075.3 ± 589.6	NS
Site of infarction:			
Anterior	33.3%	29.0%	NS
Inferior	36.3%	38.0%	NS
Other	30.4%	33.3%	NS

CHD: coronary heart disease.
MAI: myocardial acute infarction.
ASP, ADP: arterial systolic pressure, arterial diastolic pressure.
Mean values and standard deviations for the continuous quantitative variables; percentages and standard error for the qualitative variables.

through various mechanisms, protective effects on the ischaemic or hypoxic myocardium (11, 14, 16, 31, 33, 34).

Clinical studies in patients with angina who had undergone atrial pacing showed that L-carnitine improved myocardium energy metabolism, thus increasing the use of free fatty acids and reducing the lactic acid flux in the coronary sinus (10, 34).

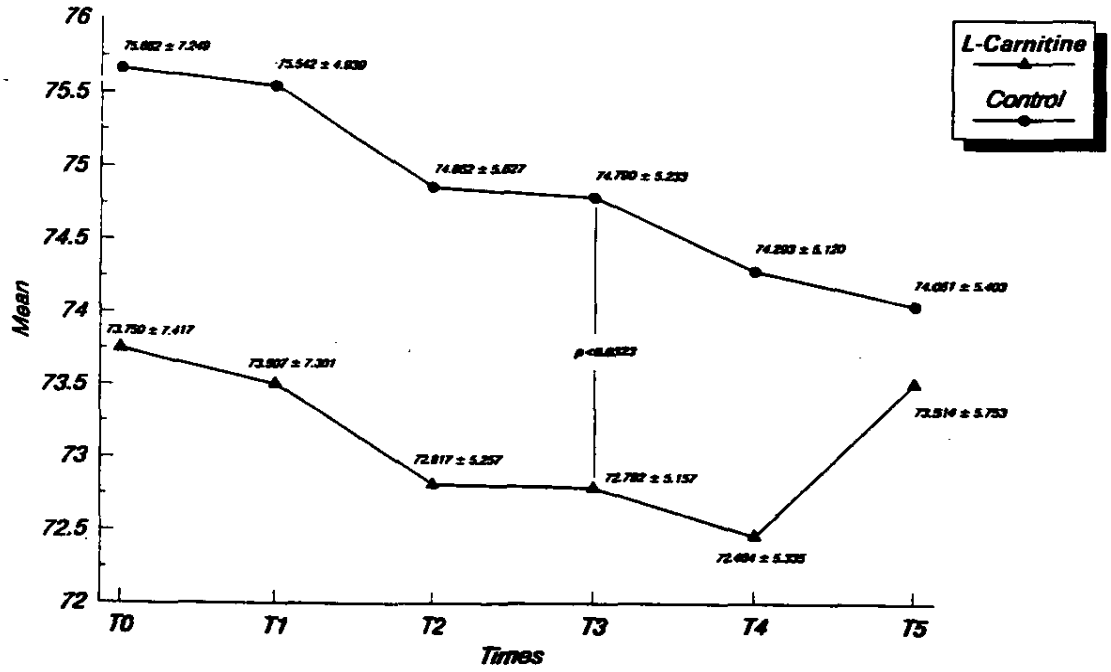

Fig. 1 Heart rate.

Furthermore, it is able to improve the angor threshold and the tolerance to the pacing, with a reduction of left ventricular telediastolic pressure and of anomalies in the ST segment and T wave (32). In patients with effort-stable angina, a multicentre, double blind, crossover, controlled study, in confirmation of previous analogous results (4), showed that L-carnitine administration determines a higher tolerance to physical effort, an increase in the maximum work load and of the angor threshold, and a decrease in the ECG signs of ischaemia (5). In patients with acute myocardial infarction, treatment with L-carnitine determined a reduction in the area of necrosis (6, 7, 21), a lower mortality within 28 days after hospitalization (8), an improvement in general condition and of the functional NYHA class, a more rapid regression of supraventricular and ventricular ectopic beats and a mortality reduction after one and six months from the ischaemic event (9). In patients with symptomatic ventricular extrasystoles and previous infarction or stable angina, a reduction of ectopic beats and of their clinical severity was observed together with a consistent extension of coupling intervals (22, 23). On the basis of these observations, the authors wished to ascertain, in patients who survived a myocardial infarction, if chronic treatment with L-carnitine was able to modify the incidence of complications and deaths in the year after discharge from hospital.

Materials and methods

The research was carried out on 160 patients of

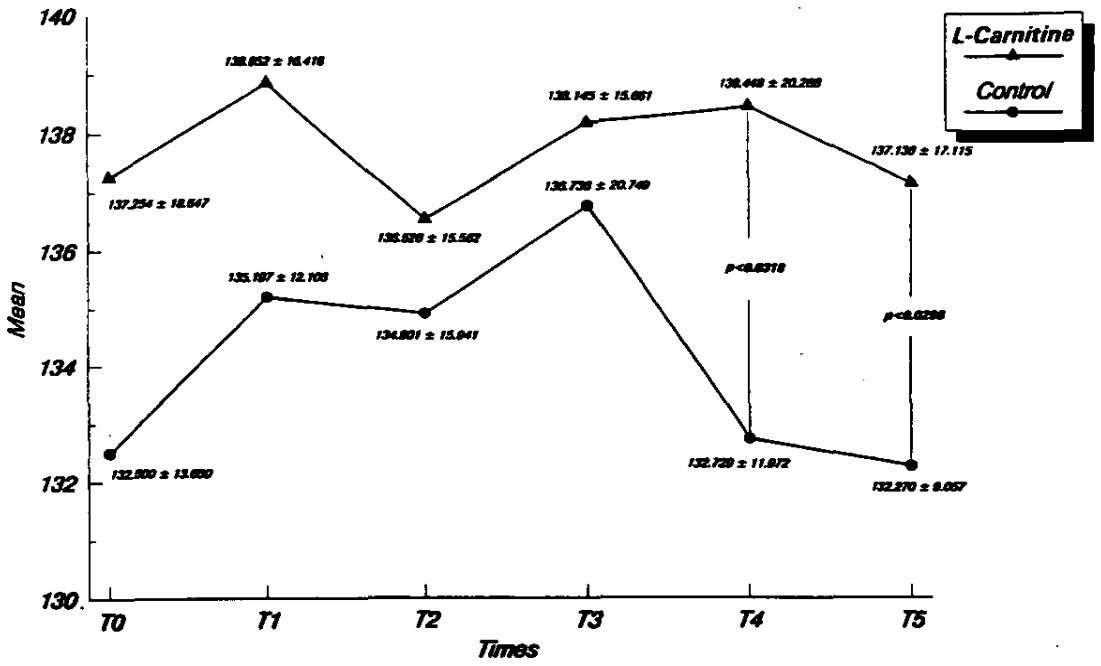

Fig. 2 Systolic arterial pressure

both sexes, between 39 and 86 years of age, who had suffered recent acute myocardial infarctions, necessitating their admission to the Department of Cardiovascular Medicine of the Santa Chiara Hospital near Pisa, Italy.

All 160 patients were enrolled on discharge from hospital after giving informed consent. The study design was open, with a control group, with treatment assigned according to a randomized list. Two groups were designated, one consisting of 81 patients (group A) treated with L-carnitine, and the other of 79 patients (group B) as the control group. The L-carnitine was kindly supplied by Sigma-Tau S.p.A., Pomezia, Rome, Italy. It was administered per os. for one year at the daily dose of 4 g/die (2 g every 12 h).

Before onset of treatment, no washout was performed because, in each patient in the trial, the drug under study was combined to the standard therapy. This was essentially represented by nitro-derivatives and calcium antagonists with or without ace-inhibitors, beta blockers, diuretics, myocardial kinetics, anti-arrhythmics, anti-aggregants, lipid lowering agents or anticoagulants. Considering aims and the type of study and the nature of the examined substance (L-carnitine), no exclusion criteria or contra-indications were considered necessary. Moreover, no concomitant pathology was listed among exclusion criteria. However, all the pathological conditions which could modify the probabilities of survival were reported.

In order to verify the homogeneity of the two

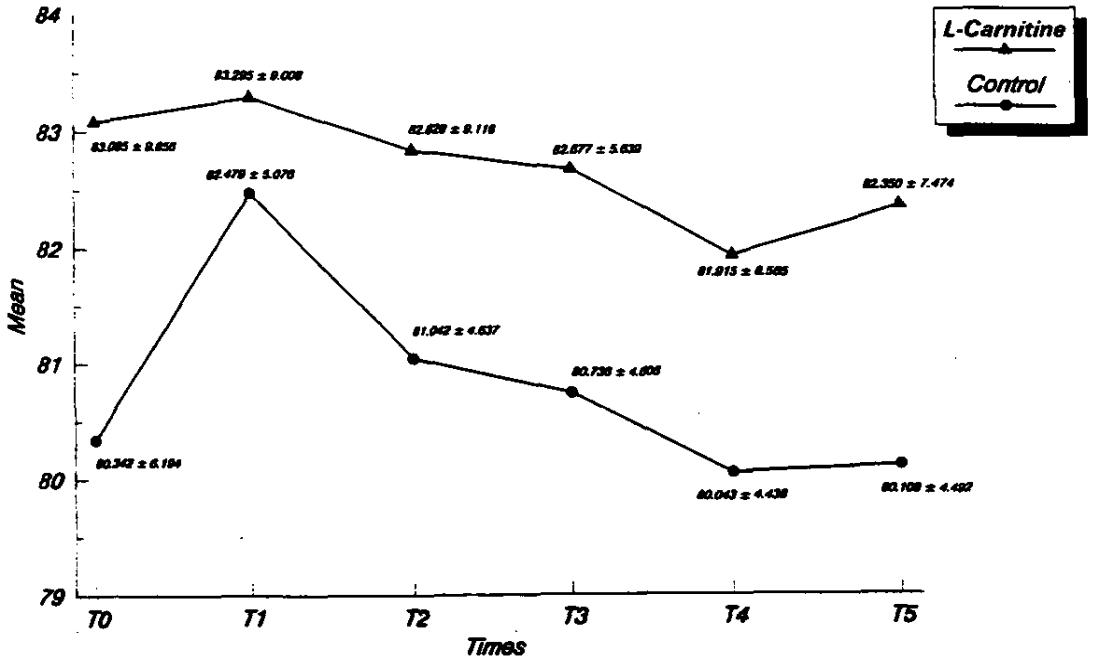

Fig. 3 Diastolic arterial pressure

groups, reference was made to some individual and clinical characteristics noticed during hospitalization, represented by sex, age, weight, height and by some anamnestic data previous to the coronary event. These included a family history of ischaemic cardiopathy, cigarette consumption, the possible presence of hyperlipidemia, arterial hyprtension, intermittent claudication, previous cerebrovascular accidents, angina pectoris or previous myocardial infarction. Other considerations were clinical data noted at the time of admission to hospital, such as heart rate, systolic arterial pressure, diastolic arterial pressure, possible presence of dyspnoea, gallop rhythm, heart murmur or arrhythmias, the Peel index, the maximum values reached by cardiospecific enzymes, and, lastly, the infarction site.

At discharge, and on the occasion of outpatient controls scheduled after 30, 90, 180, 270 and 360 days, the following parameters were studied: heart rate, systolic arterial pressure, diastolic arterial pressure, anginal attacks, rhythm disorders or clinical signs of impaired myocardial contractility, the lipid pattern and death rate. In addition the frequency was studied of different causes of death.

All the collected data were expressed in means and standard deviations and with minimal and maximal frequency values. The Mann-Whitney test was used for statistical evaluation, the Chi square test for qualitative variables, the Student's "t"-test for the continuous quantitative variables. The difference with $p < 0.005$ was considered significant.

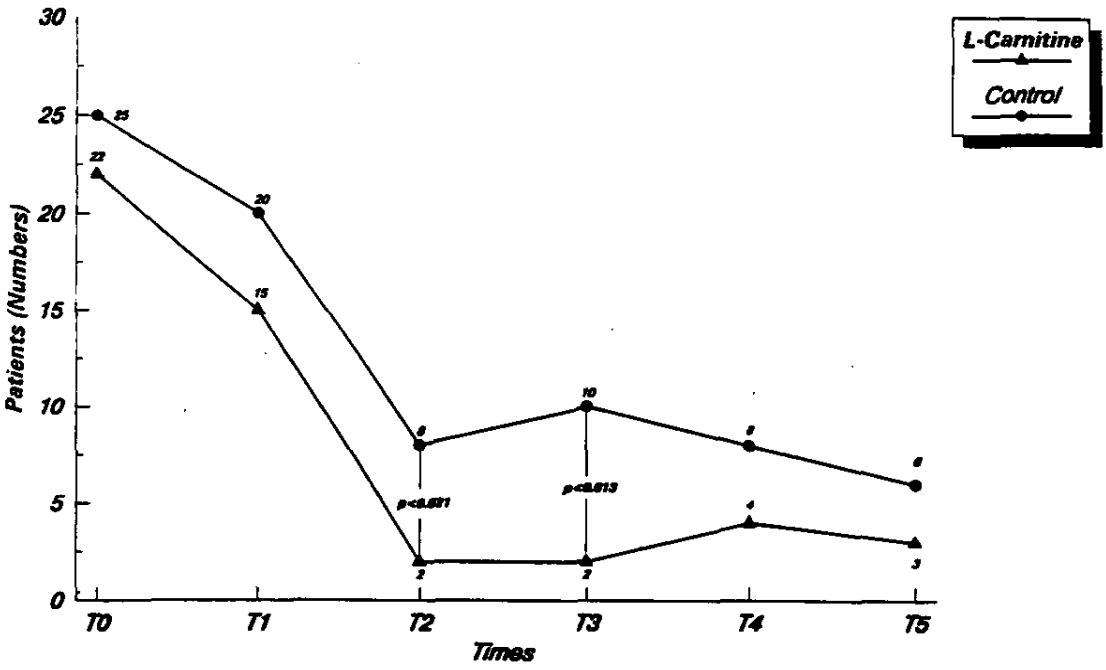

Fig. 4 Anginal attacks.

Results

In Table I, some individual and clinical characteristics noticed in the two treatment groups during hospitalization are reported as mean values or percentages. On the basis of these characteristics, both groups were suffficiently homogeneous.

Concerning heart rate (Fig. 1), systolic arterial pressure (Fig. 2) and diastolic arterial pressure (Fig. 3), the group treated with L-carnitine had on an average, always lower values in comparison with the control group. Significant differences between the two groups were registered for heart rate at the third outpatient control ($p < 0.0323$), and for the systolic arterial pressure at the last two controls, respectively at $p < 0.0318$ and $p < 0.0296$.

During the observation period, a decrease of anginal attacks (Fig. 4), of rhythm disorders (Fig. 5) and of clinical signs of impaired myocardial contractility (Fig. 6) were noticed, by means of the frequency analysis, in the group treated with L-carnitine. However, the differences observed between the two groups were statistically significant only for angina attacks at the second and third outpatient controls, respectively at $p < 0.021$ and $p < 0.013$. Alterations in the lipid pattern (Fig. 7), were less frequently observed in the group treated with L-carnitine, where the differences appeared statistically significant only at the first out-patient control ($p < 0.049$).

Finally, in terms of death rate (Fig. 8), from the first outpatient control, mortality was higher in the control group, with values of 7.6% six months after discharge, and 12.5% after 12 months; while, in

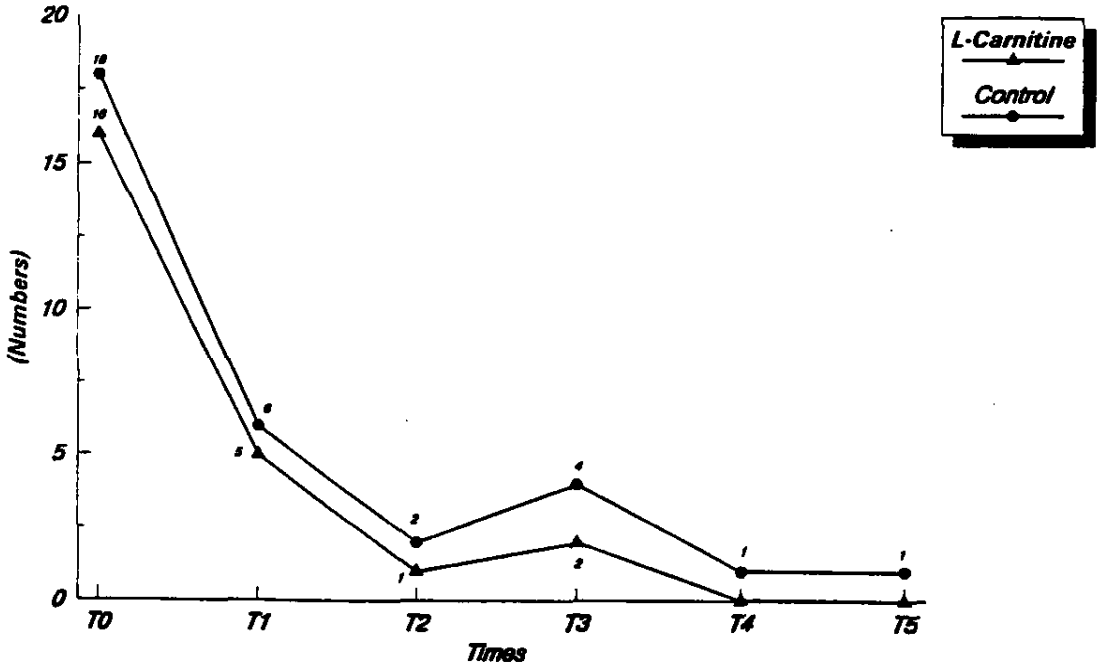

Fig. 5 Arrhytmias.

the group which had been treated with L-carnitine, there was a mortality of only 1.2% ($p < 0.005$). From Table II, it is apparent that causes of death were different in the two groups: in the control group (B) there were ten deaths: two due to extracardiac causes and eight due to cardiovascular causes (of which three were reinfarctions, two sudden deaths, two heart failures and one thromboembolism); while in group (A) treated with L-carnitine, there was only one death and this was caused by thromboembolism.

Discussion

The present study showed that L-carnitine administration at the dose of 4 g/die, in addition to the pharmacological treatment generally used, during the 12 months after hospitalization for acute myocardial infarction, can exert beneficial effects on the clinical evolution of post-infarction cardiopathy, improving the patient's quality of life and life expectancy. In fact, over the 12 month period and, in comparison with the controls, the patients treated with L-carnitine showed an improvement of heart rate, systolic arterial pressure and diastolic arterial pressure, a decrease of anginal attacks, of rhythm disorders and of clinical signs of impaired myocardial contractility and a clear improvement of the lipid pattern. These results are very important and acquire even greater significance if we consider that, in the meantime, there was a high reduction of mortality to 1.2% in the L-carnitine group as compared with a mortality

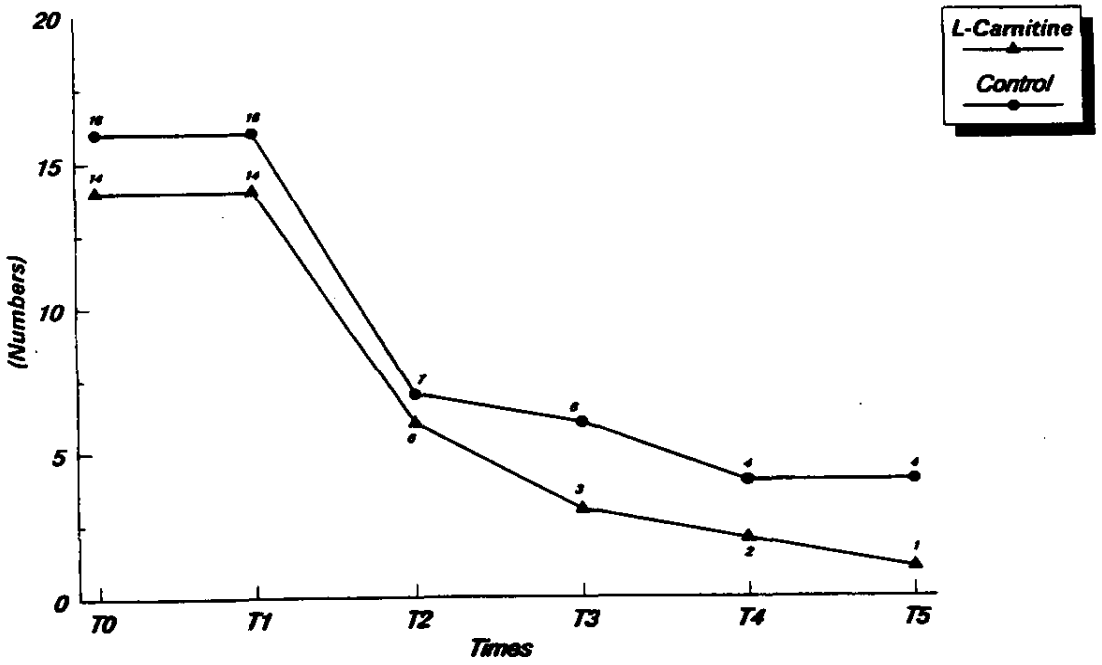

Fig. 6 Impaired contractility.

rate of 12.5% in the control group. Moreover, it must be stressed that in the group treated with L-carnitine death was caused by thromboembolism, while in the control group, death was caused mainly by cardiovascular causes, with reinfarction and sudden death in eight cases, and extracardiac causes in the remaining two cases.

Because of the high statistical significance ($p < 0.005$) of the differences observed in the two treatment groups for nearly all the parameters studied, the above positive effects must be attributed to the metabolic action exerted by L-carnitine in the myocardium. This action, already noticed and demonstrated by numerous studies, is responsible for the transport of long-chain acyl-CoA, which, through acyl-transferase, is incorporated in acyl-carnitine molecules during ischaemia or myocardial hypoxy. Acyl-carnitine has not only a minor damaging action, but it also has a major diffusibility; therefore it can be more easily removed by the myocardial tissue damaged by hypoxy or ischemia. Moreover, by removing acyl-CoA, L-carnitine eliminates the inhibition of adenyl-translocase, thus inducing the transport of ATP from mitochondria to cytoplasm, where it can be used for the contractile processes and pumping activity. Lastly, L-carnitine enhances the oxidative metabolism not only of fatty-acids, but also of piruvate. Piruvate oxidation to acetyl-CoA and further oxidation of this intermediate in the Krebs cycle is highly stimulated by L-carnitine.

On the basis of these results, it is clear that L-carnitine represents a beneficial therapy to be used in association with the usual treatment, in

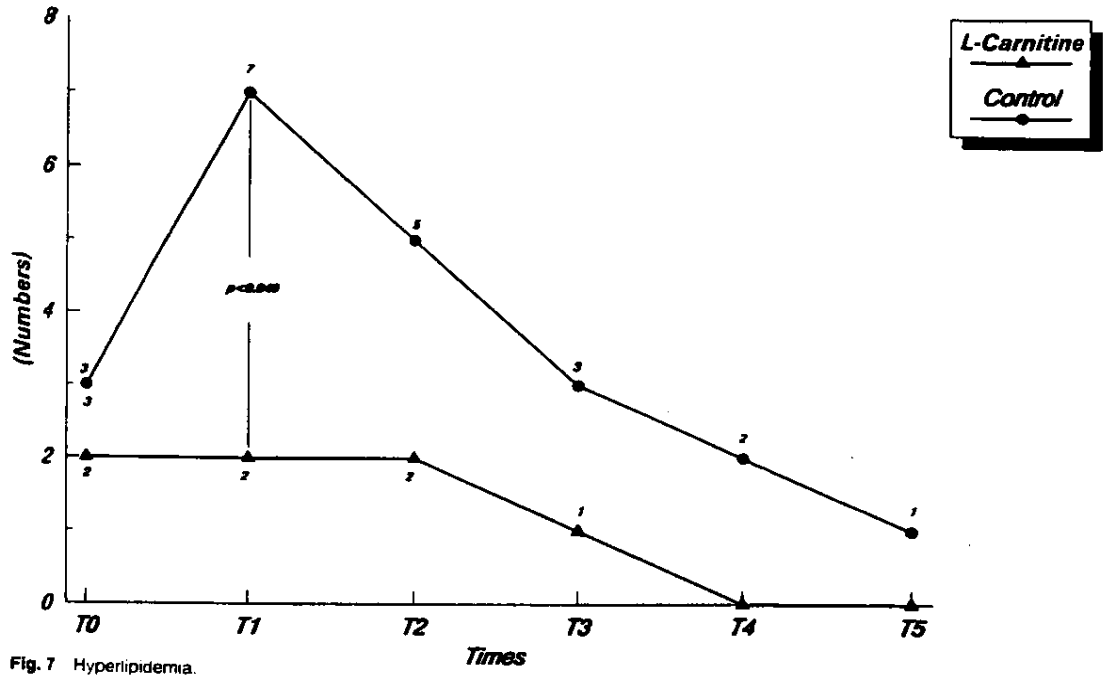

Fig. 7 Hyperlipidemia.

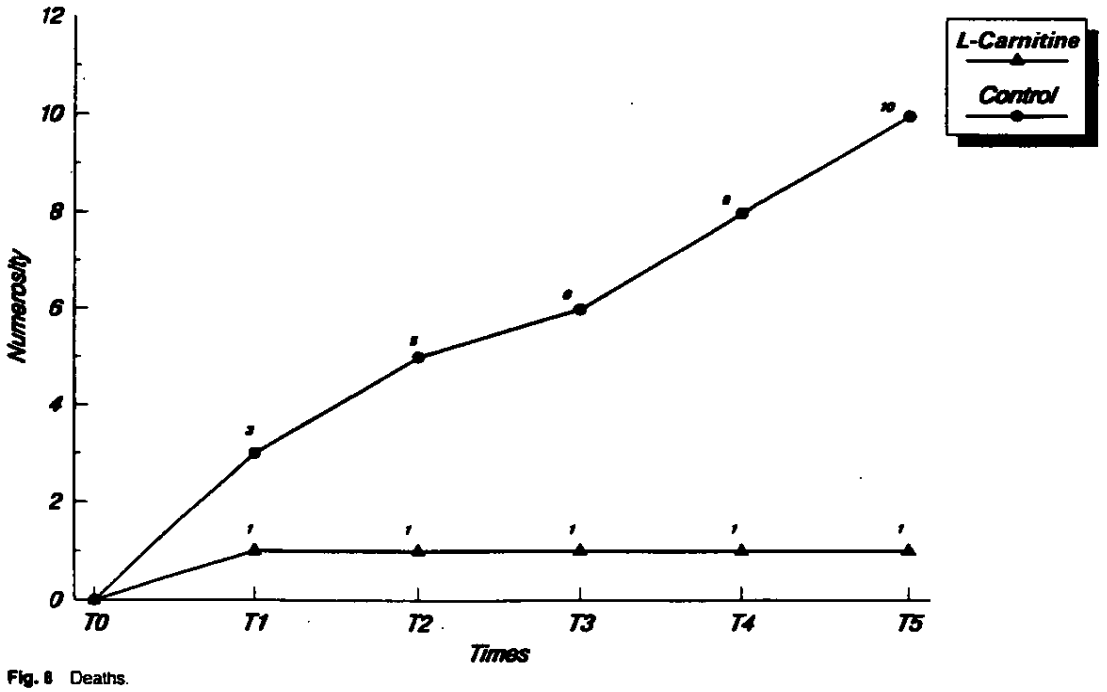

Fig. 8 Deaths.

Table II *Causes of death in the two groups of patients.*

Cause of death	Group A (n = 81)	Group B (n = 79)
New infarction	–	3
Sudden death	–	2
Heart failure	–	2
Thromboembolism	1	1
Extracardiac causes	–	2
Total	1	10

patients with post-infarction cardiopathy. In fact, because of its characteristics, L-carnitine is able to exert cardioprotective effects, not only on the metabolic, but also on the functional level, thus improving the clinical evolution of this pathological condition, by improving the heart rate, by decreasing complications and, above all, by significantly reducing mortality.

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