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Cardiovascular Drugs and Therapy 1999;13:537–546
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Prolonged Oral L-carnitine Substitution Increases Bicycle Ergometer Performance in Patients with Severe, Ischemically Induced Cardiac Insufficiency

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Summary. **Acute and chronic L-carnitine application exerts protective effects in a number of cardiac diseases. These favourable effects are attributed to improvements of the energy metabolism and have been found both in animal experiments and in man. In order to investigate the effect of long-time oral L-carnitine substitution on physical performance, 41 patients suffering from class NYHA II or III cardiac insufficiency were recruited for a clinical study. Following the double-blind, randomized, placebo-controlled design of the study, 20 patients were given 3 × 1g L-carnitine daily for 120 days whereas the control group (21 patients) received placebo. Bicycle ergometer tests were used to determine maximum performance, systolic and diastolic blood pressure, heart rate, and ST changes. Four series of tests were carried out: on day 0 (before the first substrate application), on the 60th and the 120th day (during L-carnitine or placebo application), and on the 180th day (60 days after the end of substitution). A significant improvement in performance (significantly higher maximum performance during bicycle ergometry) could be found within the carnitine group on the 60th and 120th day of L-carnitine application; and haemodynamical parameters showed a tendency to improve, too. These effects, which were attributed to L-carnitine, could be detected even 60 days after the end of substitution. No corresponding changes were found in the placebo group.**

The findings presented in this paper support suggestions of other authors that L-carnitine in combination with the usual medication (digitalis, β-blockers, calcium antagonists, nitrates) improves performance and effort tolerance in patients with cardiac insufficiency. Moreover, the findings suggest a favourable long-term effect, which lasts beyond the actual L-carnitine application, on the performance of patients with advanced cardiac insufficiency.

Key words. **L-carnitine, chronic ischemic cardiac disease, bicycle ergometry, long term treatment**

Introduction

The primary metabolic function of L-carnitine is the transport of long-chain fatty acids through the inner mitochondrial membrane into the matrix of the mitochondria [1–4], especially in the skeletal and heart muscle. In the heart, under aerobic metabolic conditions, fatty acid oxidation is the main source of myocardial energy production [5,6]. Under anaerobic conditions, however, fatty acid oxidation is depressed [7–9], but this is counterbalanced by an increase in anaerobic glycolysis. This results in a reduction of ATP production, and an accumulation of long-chain acyl-CoA compounds (LC-acyl-CoA) [9] which, in turn, leads to an inhibition of the adenine nucleotide translocase [10].

An increase in the intramitochondrial L-carnitine concentration by oral or parenteral substitution in patients heightens the formation of acylcarnitines from acyl-CoA and free L-carnitine [11]. This enables the carnitine shuttle system to transport acylcarnitines from the mitochondria in exchange for free carnitine [3]. The resulting decrease in intracellular levels of LC acyl-CoA esters is part of the cardioprotective effects of L-carnitine [4]. During myocardial ischemia, which is the main cause of cardiac insufficiency and one of the most frequent causes of death, the myocardium loses L-carnitine [12,13].

It has been demonstrated in various animal models [14–16] and in man [17–19] that L-carnitine deficiency adversely influences ventricular function, whereas oral or parenteral substitution of L-carnitine, and its esters acetyl- and propionyl-L-carnitine resp., improves physical capability, increases fatty acid oxidation, and effects a general improvement of the myocardial en-

The work was supported by SIGMA-TAU Industrie Farmaceutiche Riunite s.p.a., Via Pontina km 30,400, *00040 Pomezia (Roma)*, Italy

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Received 25 February 1999; receipt/review time 48 days; accepted 22 June 1999

19129701

ergy metabolism under aerobic and anaerobic conditions [14–16,20–25]. In order to investigate the effectiveness of oral L-carnitine substitution in cases of severe, ischemically induced cardiac insufficiency, 41 patients with clinical and paraclinical symptoms of cardiac insufficiency, which had to meet certain inclusion criteria, were included in the study. The criteria for selection were comparable with those used by other authors [21,22,26–28,35,36].

To this end, changes in the exercise tolerance of patients were to be evaluated by means of bicycle ergometry according to a double-blind, placebo-controlled, randomized study design. The study was also interested in the course of possible changes in performance during L-carnitine substitution and in possible long-term effects after the end of medication.

So far, there are different interpretations of the influence of L-carnitine substitution on haemodynamic parameters (heart rate, systolic and diastolic blood pressure) and on ischemic marks in the ECG (ST segments). A number of authors reported improved haemodynamics and reduction of ischaemic marks [26–32], whereas others found no changes or even worsening in various parameters [21,24,33,34].

In addition to the investigation of changes in exercise tolerance, the present study wants to contribute to the question whether and how L-carnitine influences haemodynamic parameters and ST segment changes.

Materials and methods

Patients

The patients who participated in our study were selected from the cardiological consultation at Medical Clinic I, University of Leipzig. All patients were suffering from advanced cardiac insufficiency with definitely ischemic genesis, diagnosed by coronary angiography, or had had myocardial infarction more than two years ago and they were still able to develop a certain, although low, physical performance. The inclusion criteria asked for at least one clinical symptom of cardiac insufficiency (dyspnoea, fatiguability, weakness, cardiomegaly, ventricular filling sound, pulmonary stasis, neck vein distention, stasis-induced hepatic enlargement, ascites, or peripheral oedemata). Moreover, all of the following criteria had to be met:

NYHA class II or III, cardiac insufficiency of ischemic genesis,
left ventricular diameter >55 mm, left ventricular ejection fraction <40%,
resting dyspnoe or paroxysmal dyspnoe at night,
no changes in medicamentous therapy within the last 30 days.

The 41 patients who met these criteria were included in the study. On an average, they were 61.5 years old, 170 cm tall, and weighed 75.5 kg (Table 1). The patients

Table 1. Characterization of the patients included in the study

Carnit. Group	Age (Years)	Tallness	Weight (kg)	Gender	Placebo group	Age	Tallness	Weight (kg)	Gender
1	76	168	71.5	m	2	75	160	84	f
3	56	172	79	m	4	38	172	76	m
6	62	176	84	m	5	68	168	72	m
8	64	172	82	m	7	68	170	86	m
10	62	174	82	m	9	64	165	72	m
12	54	167	61.5	f	11	62	172	71.5	m
13	72	158	66.5	f	14	64	164	63	m
15	58	172	80	m	16	63	150	50	f
17	58	181	81	m	18	68	163	67	f
20	66	179	83	m	19	49	175	74	m
23	49	173	78	m	21	62	176	74	m
24	55	176	80	m	22	58	171	64	m
27	44	168	70	f	25	64	153	73	m
28	70	166	74	m	26	60	167	76	m
31	69	178	78	m	29	70	168	75	f
32	74	172	73	m	30	59	160	68	m
35	60	176	89	m	33	54	182	100	m
36	49	161	60	m	34	59	161	71	m
38	59	183	96	m	37	66	186	83	m
40	61	172	75	m	39	63	166	65	f
					41	73	175	91	m
Mean values	60.9	172.2	77.1			62.2	167.8	74.1	
Stand. Deviat.	8.38	6.12	8.33			7.98	8.53	10.43	

were randomized in a double-blind way in a L-carnitine group (20 patients) and a placebo group (21 patients).

Ethics

The protocol of the study was controlled and accepted by the ethical commission of the Medical Faculty of the Leipzig University.

Medication

From the 1st to the 120th day the verum group was given 3 × 1g L-carnitine/d; the control group received placebo correspondingly. Both the L-carnitine and the placebo used were produced by the SIGMA-TAU company in Rome, which made both preparations available for this study. The medication each patient had received prior to the study was continued (Fig. 1).

Bicycle ergometer tests

The tests were carried out in a lying position. At the beginning the haemodynamic parameters (heart rate, systolic and diastolic blood pressure) were measured at rest (0 watt) and ST segment changes determined. Starting with an initial load of 20 watts, the load was increased minutely by 10 watts until one of the usual break-off criteria, e.g., exhaustion, angina pectoris, fall of blood pressure, was reached.

Design of the study

On day 0 (screening day, prior to first substrate administration) the patients did their first bicycle ergometer test. Then L-carnitine respectively placebo application began, which lasted for 120 days (Fig. 2). Ergometer tests took place on the 60th and 120th day. In order to investigate the long-term effect, a fourth bicycle ergometer test took place on day 180, i.e., 60 days after the last L-carnitine administration. The state of the patients was monitored closely by clinical and paraclinical examinations throughout the study.

Measuring devices

A bicycle ergometer M 700 (MEDIOTRONIC, Freiburg, Germany) was used for the ergometry tests. The accompanying electrocardiographic leads with automatic measuring of heart rate and ST segment alterations were made with the device EK 512 (HELLIGE, Freiburg, Germany). Blood pressure was measured with the automatic sphygmomanometer HELLIGE BP 511; as of a load of 50 watts the blood

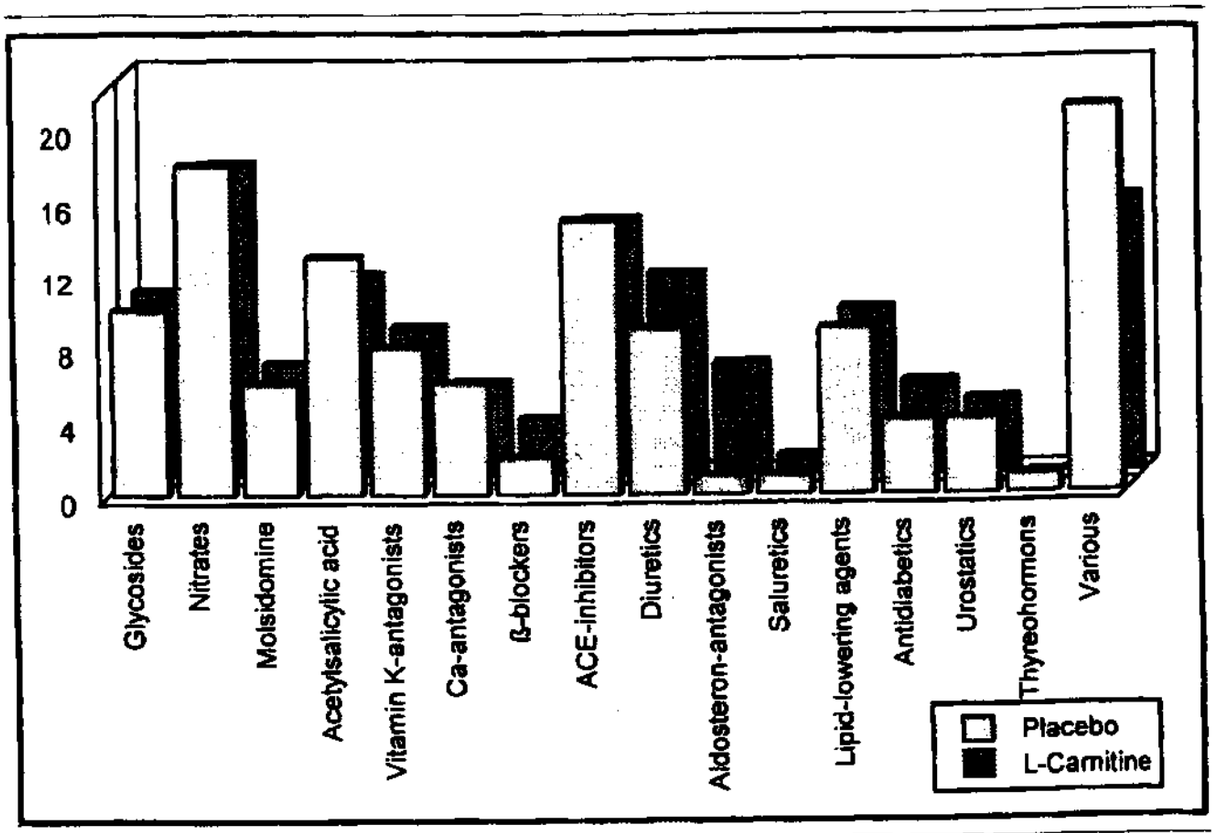

Fig. 1. Concomitant medication of the patients included in the carnitine and the placebo group

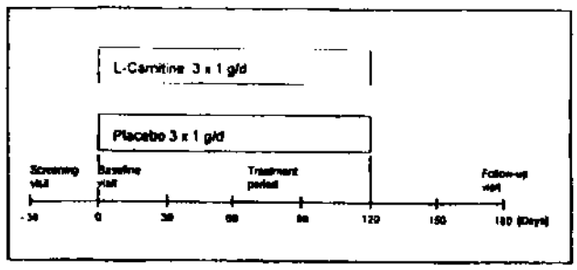

Fig. 2. Scheme of the study protocol

pressure was also manually controlled according to Riva-Rocci. Based on heart rate (HR) and systolic blood pressure (SBP), the tension-time-index (TTI) was calculated.

Statistics

The values measured at the end of each minute, immediately prior to the following higher load, were used for statistical evaluation. Differences between the two groups of patients were checked for statistical significance by means of the t-test for independent random samples. Changes within the groups were evaluated using the pair-t-test (in cases of even distribution) and the u-test (for unevenly distributed values).

Results

Resting parameters

On all four test days no significant differences in heart rate (HR) and systolic blood pressure (SBP) were found between the two groups of patients prior to exercising (i.e., at rest). However, there was a tendency towards alterations in the resting tension-time-index (TTI), which was particularly pronounced on the 120th day. During our investigation a tendency of decrease was found for the mean heart rates at rest in the carnitine group, whereas irregular alterations of the mean heart rate could be detected in the placebo group. The values of the mean systolic blood pressure (SBP) did not change in both groups during the investigation; and the values of the tension-time-index, too, were different only in tendency but not in significance in both groups (Table 2).

Heart rate during ergometry

On day 0 the mean heart rates of the two groups of patients showed no differences under load. On the 60th day the mean heart rates of the carnitine group were lower in the sector with higher load (50 watts and more) than those of the placebo group; and on the 120th day this difference was evident in the whole load spectrum (Fig. 3). The control examination on the 180th day found no differences between the mean heart rates of the two groups of patients (Table 3). Under L-carnitine substitution therapy, the verum group showed no marked differences in mean heart rate on all four test days. No differences were found in the control group, too.

Systolic blood pressure during ergometry

At the beginning (day 0) only slight differences were found when the mean systolic blood pressure (SBP) values of the carnitine group and the placebo group were compared. Whereas no differences were evident on the 60th day, too, differences between the mean systolic values were clearly visible on the 120th day. In the whole spectrum investigated, the mean values of the systolic blood pressure (SBP) of the verum group were lower than the comparable values of the placebo group (Fig. 4). No differences in the mean values of systolic blood pressure were found in both groups on the 180th day. A comparison of changes in the mean values of the systolic blood pressure within the groups of patients showed that there were no outstanding changes between the four test days both in the carnitine group and the placebo group.

Tension-time-index during ergometry

The evaluation of the tension-time-index means mirrored the results found for its initial values (heart rate and blood pressure). The most pronounced differences were evident on the 120th day. On this day the values of the mean TTI of the carnitine group were, in tendency, lower than the values of the placebo group. The differences found between the two groups on day 120 were more pronounced in the higher load sector than at a lower load (Fig. 5).

ST segment changes during ergometry

When the mean ST segment changes were compared, very high standard deviations (up to 100 %) made it

Table 2. Mean values of heart rate (HR), blood pressure (BP), and tension-time-index (TTI) of both groups of patients at rest

	Day 0		Day 60		Day 120		Day 180	
	Carnitine	Placebo	Carnitine	Placebo	Carnitine	Placebo	Carnitine	Placebo
HR	86,05	79,61	82,69	79,89	79,79	83,53	79,36	75,67
BP	132,00	137,14	139,38	136,05	131,43	139,41	140,00	135,00
TTI	112,81	108,82	114,90	107,84	104,63	114,96	110,96	101,66

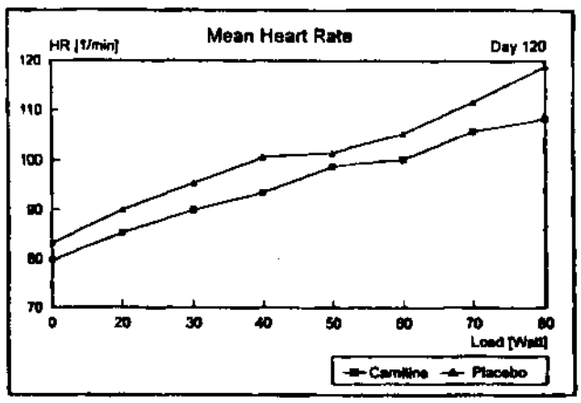

Fig. 3. Mean heart rates (HR) of the carnitine and the placebo group depending on ergometer load on day 120

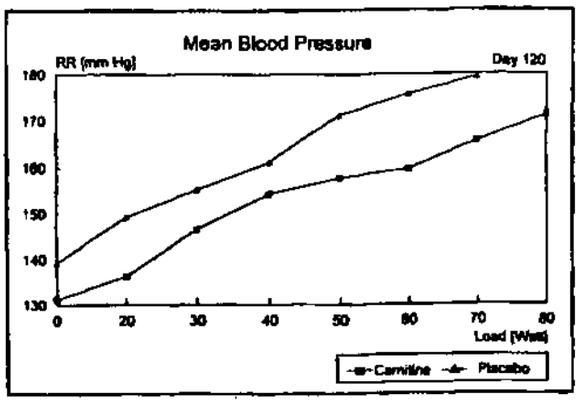

Fig. 4. Mean systolic blood pressure (SBP) of the carnitine and the placebo group depending on ergometer load on day 120

impossible to find a tendency. Thus, an interpretation is not possible.

Maximum ergometer performance

As could be expected, the mean values of the maximum exercise tolerance showed no difference between the two groups of patients at the beginning (day 0). However, on the 60th and 120th day it was evident that the verum group had a markedly higher exercise tolerance than the control group (Table 4, Fig. 6). Compared to the beginning, the mean value of bicycle ergometer performance achieved by the carnitine group increased under L-carnitine substitution by 30% during the study. On the 180th day (60 days after the last carnitine administration) the mean values of performance in the carnitine group were still about 30% higher than those in the placebo group (Fig. 6).

Detailled examination of the changes that occurred within the two groups during the investigation shows marked differences between the verum group and the control group. As Figure 7 shows, the placebo patients achieved a mean ergometer performance of only 40 to 80 watts on all four test days of the study. In the carnitine group, 65% of the patients achieved a maximum performance between 40 and 60 watts (mean value of all patients = 54.5 watts) on day 0. The patients' performance increased under L-carnitine substitution: 69% of the verum patients achieved a maximum performance of 50 to 80 watts (increase by an average of 22% to 66.9 watts) on day 60. As compared to the values achieved on day 0, this increase in performance is statistically significant ($p < 0.01$). At the end of the L-carnitine application, which lasted 120 days, the values of 64% of all patients examined were in the 50 to 90 watts range (the mean value reached 70.7 watts, thus being 30% higher than on day 0). This increase is significant, too, in comparison with day 0 ($p < 0.01$), whereas the difference between days 60 and 120 is not significant (Fig. 8). Even 60 days after the end of the L-carnitine application, 70% of the patients who were still included in the study achieved a maximum performance of 50 to 90 watts, which is significantly higher than that on day 0 ($p < 0.01$). Obviously, L-carnitine increased the patients' exercise tolerance not only during its application; its effect could still be found during the control examination.

Table 3. Mean heart rates of the two groups of patients depending on ergometer performance

Load	Day 0		Day 60		Day 120		Day 180	
[Watt]	Carnitine	Placebo	Carnitine	Placebo	Carnitine	Placebo	Carnitine	Placebo
0	85	80	83	80	80	84	79	76
20	94	90	92	88	86	90	88	87
30	98	95	98	94	90	95	93	92
40	101	100	106	98	98	101	99	99
50	101	102	98	102	99	102	97	102
60	103	106	103	107	100	106	98	100
70	108	108	107	112	106	112	106	103
80	118	116	113	115	109	119	110	98

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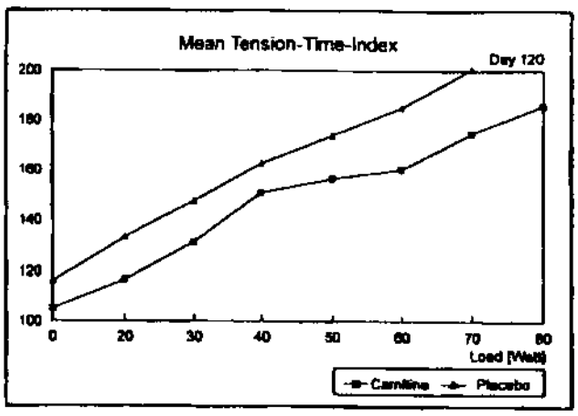

Fig. 5. Mean tension-time-index (TTI) of the carnitine and the placebo group depending on ergometer performance on day 120

Discussion

The present study was aimed at investigating the effect of prolonged oral L-carnitine administration on the performance of patients suffering from advanced cardiac insufficiency. The patients were given 3 × 1g L-carnitine or placebo p.o (in tablet form) per day. This relatively high dosage corresponded with the design chosen by Cherchi et al. [27], Canale et al. [28], and Ghidini et al. [31]. Other authors described studies involving doses of only 900 mg/d [21] or 500 mg/d [22]. Contrary to other authors which applied L-carnitine just acutely [24,37] or for a few days [29,32], the present study was designed to investigate a prolonged L-carnitine application of 120 days. The inclusion of two additional tests made it possible to investigate progress (60 days) and long-term effects (180 days). (Statistical evaluation of hemodynamic parameters was restricted to values up to 80 watts since only a few patients showed a higher performance (up to 110 watts)).

Even if the values found at rest are of limited evaluability as they were determined immediately before a planned exercise (expectational stress), it was evident that, in correspondence with the findings of most of the other authors, L-carnitine has no significant effect on haemodynamic parameters at rest [22,24,29,31,36,37]. This contradicts the assumption L-carnitine could improve the oxygen supply of the myocardium respectively reduce its oxygen consumption. However, the in tendency lower tension-time-index found in the L-carnitine group at rest on the 120th day hints at a more economic cardiac work under L-carnitine [38].

Bicycle ergometry resulted in medium heart rates (Fig. 3) and in mean systolic blood pressure values (Fig. 4) that were in tendency decreasing the longer L-carnitine therapy was continued. A decrease in the

Table 4. Development of maximum performance (in watts) in the carnitine and the placebo group

	Test day					Test day			
Carnitine-patient	0	60	120	180	Placebo-patient	0	60	120	180
1	100	100	100		2	40	40	10	
3	60				4	80	90	80	
6	90	80	80		5	50	40	40	
8	40	70	70		7	80	80	90	
10	30				9	80	80	80	
12	50	50	50	50	11	90	60	80	70
13	20	30	40	40	14	40	50	70	60
15	50	70		80	16	40	60	40	50
17	60	70	100	110	18	20	40	40	40
20	50				19	70	70	10	
23	40				21	80	90		
24	40	50	50		22	50	50	60	80
27	50	50	50	50	25	60			
28	70	70	90	80	26	20	20	30	20
31	60	60	80	90	29	30	40	40	50
32	50	70	80	60	30	60	80	80	80
35	90	100	100	110	33	70	60	80	
36	60	90			34	120	90		
38	60	80	80	80	37	60	80	80	70
40	20	30	20		39	50			
					41	80	80	70	
Mean values	54,50	66,88	70,71	75,00	Mean values	60,48	63,16	57,65	57,78
Stand. deviat	20,85	20,53	24,04	23,35	Stand. deviat.	24,20	20,53	25,33	18,72

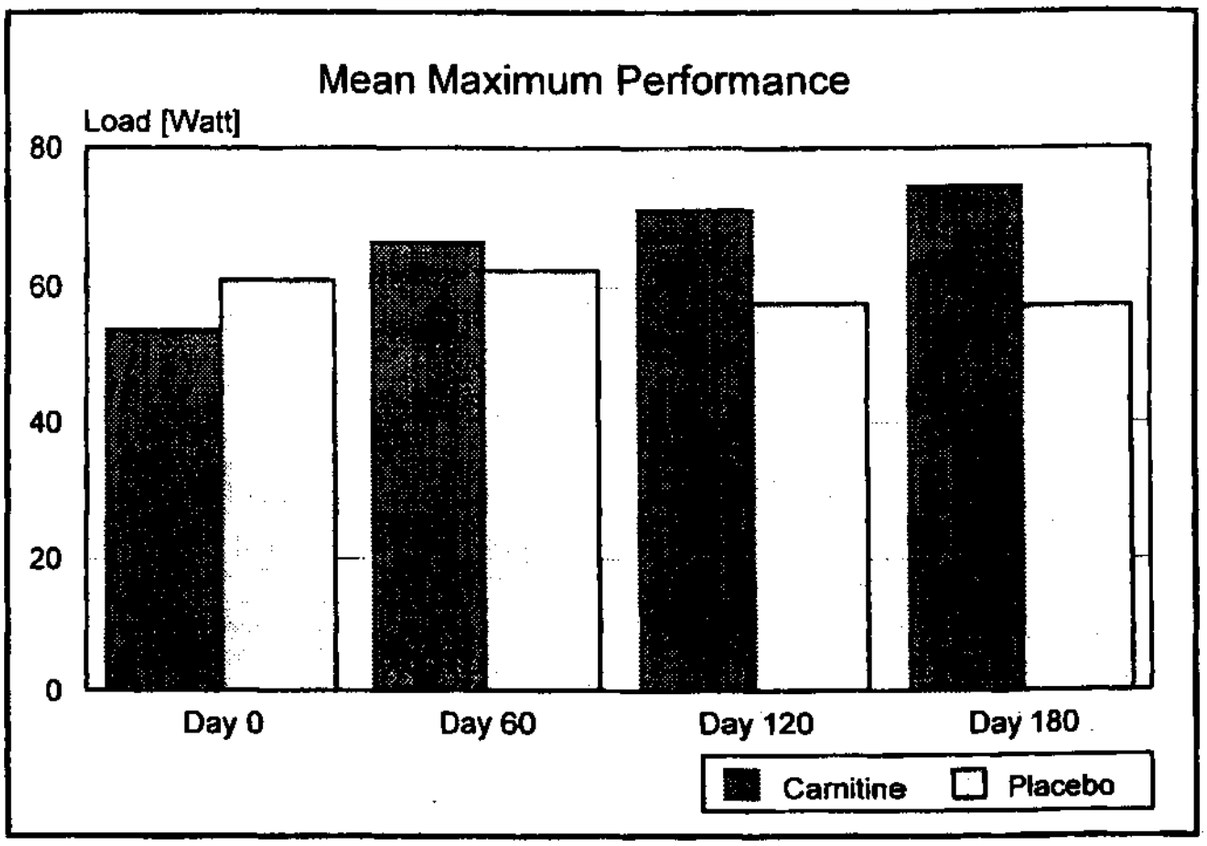

Fig. 6. Mean values of maximum performance of carnitine and placebo patients on the four test days

exercise heart rate can be taken as an indicator of more efficient cardiac work. However, the lower mean value of the systolic blood pressure under load can be interpreted in different ways. Arterial blood pressure increases with growing physical load since the share of the cardiac output needed by skeletal musculature increases. Therefore, L-carnitine makes it possible to achieve a comparable ergometer performance at a lower systolic pressure. One reason for this might be the systemic effect of L-carnitine. Carnitine stimulates muscular pyruvate dehydrogenase activity [39] and has a direct vasodilatatory effect.

Observations made by other authors [30] that L-carnitine effects, in tendency, a lowering in heart rate and systolic blood pressure were confirmed by the present study. Nevertheless, there is a certain number of reports about an increase in heart rate and blood pressure [26], whereas most authors found no changes in the exercise heart rate under L-carnitine [20,21,37,40]. Explanations for changes in heart rate and blood pressure vary in the literature; in order to explain the positive effects found in the present study, i.e., lowered exercise heart rate and systolic blood pressure, one has to consider not only a cardiac but also a peripheral effect of L-carnitine on skeletal muscles and blood vessels because of the systemic application. The tension-time-index, which is an indicator of the quality of cardiac work, did not differ very much on day 60, a more pronounced difference was found on day 120: Within the whole exercise range investigated, the TTI means of the carnitine group were lower than those of the placebo group (Fig. 5). Although the differences are not significant ($p = 0.057$ at 60 watts), a tendency is clearly visible. Obviously, this higher efficiency can be achieved both by a lower heart rate and lower systolic blood pressure because on the 120th day these two parameters showed mean values that were in tendency lower in patients treated with carnitine than in patients receiving placebo. The results found during our investigation differ from the findings of other authors [21,22,27,40] who had found no changes in the pressure-rate-product. It should be noted that although our design of the study is quite similar to that used by Cherchi et al. [27], the dosage is different. Whereas Cherchi et al. had found no changes in the pressure-rate-product up to the 60th day of treatment with 2 × 1g L-

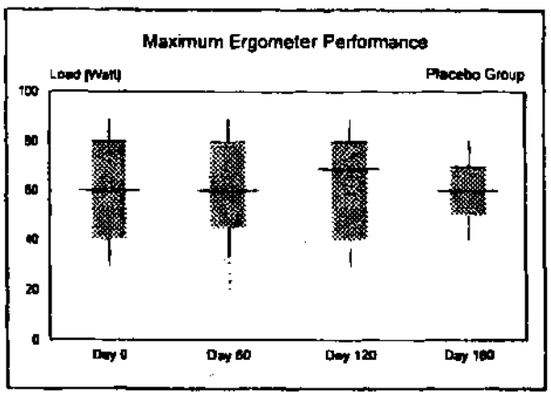

Fig. 7. Maximum ergometer performance of the placebo group (Each box comprises the area between 1st and 3rd quartile; the horizontal line marks the median. The vertical lines represent the nearest higher and lower observation values.)

carnitine per day, we chose a higher dose (3 × 1g/d) and a longer period of application (120 days). This might explain the different findings.

The ST segment changes measured during our study cannot be evaluated statistically. A review by Ferrari and Visioli (1992) [38] sums up previous publications on this subject and states that carnitine exerts no direct influence on the oxygen supply of the myocardium. However, they also pointed out that ischemic symptoms, including ST segment depression, are quite often reduced under carnitine.

Comparison of the maximum performance in the placebo group shows that there are no differences between the values found on all four test days (Fig. 6).

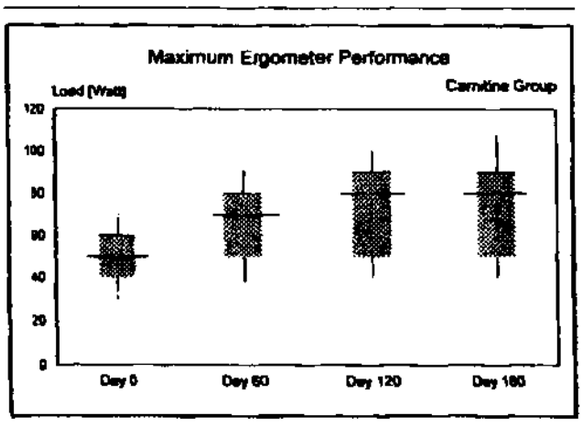

Fig. 8. Maximum ergometer performance of the carnitine group (Each box comprises the area between 1st and 3rd quartile; the horizontal line marks the median. The vertical lines represent the nearst higher and lower observation values.)

Contrary to this, the carnitine group improved its maximum performance in a significant way. An increase in exercise tolerance had already been found by Thomsen et al. [41] in their experiments dealing with the influence of L-carnitine on myocardial tissue. There is a number of publications which point out that L-carnitine improves exercise tolerance in patients with chronic ischemic cardiac disease, too [21,22,28,42]. After application of 2 × 1g L-carnitine daily for 45 days, Ghidini et al. [31] found improvements in exercise tolerance that made it possible to downgrade all patients treated with L-carnitine in NYHA classification. In an investigation involving 200 patients with exercise-induced angina pectoris, Cacciatore [26] found improved exercise tolerance after L-carnitine application, too. After 10 days of treatment with 2g/d L-carnitine iv., Giordano et al. [32] were able to prove a positive inotropic effect with shortened preejection time and increased left ventricular ejection time in patients suffering from coronary heart disease. Canale et al. [28] found that L-carnitine therapy increased ergometer performance by 20 watts as an average compared to a control group. In a multicenter study including 44 angina pectoris patients from seven centres, Cherchi et al. [27] demonstrated increased performance in 48% of all L-carnitine patients, whereas only 11% of the placebo patients showed an increase in performance. Kamikawa et al. [21] studied exercise performance after 4 and 12 weeks of L-carnitine therapy; they found a better performance after 12 weeks than after 4 weeks, too. In their overview, Ferrari and Visioli [38] noted the favourable effect of L-carnitine on exercise tolerance in patients with cardiac diseases and its reduction of clinical symptoms of ischemia in patients with coronary artery disease. Most authors [21,27] explained the positive effect on performance with improvements in myocardial metabolism due to L-carnitine. Improved performance in the carnitine group can also be explained with a direct influence of L-carnitine on skeletal musculature: L-carnitine stimulates oxidative phosphorylation in skeletal muscle and reduces ischemically induced acidosis [43].

During the tests on day 180 our study confirmed an increased exercise tolerance of those patients receiving L-carnitine: Maximum performance was 37% higher than on day 0 (Fig. 6). This difference in performance between days 0 and 180 is statistically significant too ($p < 0.01$). However, it cannot be ruled out that the small number of patients examined on day 180 is the reason for the higher mean performance of the carnitine group (positive selection). The same is true for the placebo group: the most severely ill patients left the study before day 180.

Another approach to explain the prolonged effect of L-carnitine on performance results from the observation made by Regitz and Fleck [44] that myocardial L-carnitine levels are reduced in cases of cardiac insufficiency. Oral L-carnitine administration of 3 × 1g/d might be a compensation for pathologic L-carnitine

concentrations, therefore only a slow decrease in myocardial L-carnitine levels occurs after therapy. The authors mentioned above have proven that L-carnitine increases exercise tolerance in patients suffering from ischemic cardiac disease and angina pectoris. The present investigation was able to prove that the same holds true for patients with ventricular dilatation, i.e. an advanced stage of cardiac disease.

The mechanism of how L-carnitine exerts its effect on exercise tolerance has not been fully discovered yet [20]. Higher exercise tolerance under L-carnitine in patients with chronic ischemic cardiac disease is sometimes explained with a beneficial effect of L-carnitine on the disturbed metabolism of the heart [38], whereas other authors suggest that the increase in performance is due to improvements in the myocardial lactate metabolism [41]. It was also demonstrated that L-carnitine infusions lower the lactate level in the sinus coronarius in humans, which suggests an improved oxygen supply [37]. Furthermore, the favourable effects of L-carnitine on exercise tolerance in patients with stable angina pectoris are attributed to a decrease in the acyl-CoA concentration and the reduction in adenine nucleotide translocase inhibition that goes with it: This is said to support ATP transport from the mitochondria into the cytoplasma. The accumulation of free CoA increases the oxidative metabolism of fatty acids and pyruvate. This explanation is supported by the observation that investigations of chronic ischemic dog hearts showed significantly higher ATP concentrations in the myocardium after L-carnitine administration than the control animals [45].

The beneficial effects on exercise tolerance found in our study correspond with the results of other authors [27,31,37,45] who examined patients suffering from chronic ischemic cardiac disease or stable angina pectoris. Moreover, the present study supports and confirms the findings that L-carnitine increases performance and exercise tolerance in patients treated for ischemically induced cardiac diseases and for ischemically induced cardiac insufficiency [21,26,27,35,36,42]. Our study confirmed this beneficial effect in patients with ventricular dilatation, too. Therefore, L-carnitine substitution will also be useful in cases of advanced ischemic cardiac disease. The effect of L-carnitine increases with the duration of therapy.

It seems that the increase in physical performance is not due, as previously assumed, to a direct inotropic effect of L-carnitine, but to a modulatory influence on the metabolism of the heart. Since the accumulation of LC acyl-CoA inhibits the adenine nucleotide translocase, L-carnitine effects a reduction of the LC acyl-CoA level in the ischemic myocardium, which permits a more efficient utilization of the remaining oxygen.

The mode of action of L-carnitine differs from that of other substances such as β-blockers, calcium antagonists, and nitrates; consequently L-carnitine can be used in combination with them. It can be concluded that both a prolonged treatment with L-carnitine and a sufficiently high dosage are necessary for a successful therapy.

Acknowledgment

The authors wish to thank Dr. Claudio Cavazza and Dr. Carlo Trevisani of SIGMA-TAU Pharmaceutics, Pomezia, Rome, for their interest, support, and helpful advice during the course of this study.

References

1. Bremer J. Carnitine—Metabolism and functions. *Phys Rev* 1983;63:1420–1480.
2. Bieber LL. Carnitine. *Ann Rev Biochem* 1988;57:261–283.
3. Ramsay RR, Tubbs PK. The mechanism of fatty acid uptake by heart mitochondria: An acylcarnitine-carnitine exchange. *FEBS Lett* 1975;54:21–25.
4. Bremer J, Hokland B. Role of carnitine-dependent metabolic pathways in heart disease without primary ischemia. *Z Kardiol* 1987;76(Suppl 5):9–13.
5. Liedtke AJ. Alteration of carbohydrate and lipid metabolism in the acutely ischemic heart. *Prog Cardiovasc Dis* 1981;25:321–330.
6. Opie LH. Carbohydrates and Lipids. In: L Opie, *The Heart: Physiology, Metabolism, Pharmacology and Therapy*. London: Grune & Stratton Inc., 1986: 118–135.
7. Feuvray D, Leblond Y. Metabolism of long chain fatty acids in the normal and in the pathological heart: Effects of ischemia. *Diabetes Metab* 1984;10:316–323.
8. Schoonderwoerd R, Broekhoven-Schokker S, Hülsmann WC, Stam HCG. Enhanced lipolysis of myocardial triglycerides during low-flow ischemia and anoxia in the isolated rat heart. *Bas Res Cardiol* 1989;84:165–173.
9. Van der Vusse GJ, Glatz JFC, Stam HCG, Reneman RS. Fatty acid homeostasis in the normoxic and ischemic heart. *Phys Rev* 1992;72:881–940.
10. Shug AL, Subramanian R. Modulation of adenine nucleotide translocase activity during myocardial ischemia. *Z Kardiol* 1987;76(Suppl 5):26–33
11. Bieber LL, Emaus R, Valkner K, Farrell S. Possible functions of short-chain and medium-chain carnitine acyltransferases. *Fed Proc* 1982;41:2858–2862.
12. Spagnoli LG, Corsi M, Villaschi S, Palmieri G, Maccari F. Myocardial carnitine deficiency in acute myocardial infarction. *Lancet* 1982;1:1419–1420.
13. Suzuki Y, Masumura Y, Kobayashi A, Yamazaki N, Harada Y, Osawa M. Myocardial carnitine deficiency in chronic heart failure. *Lancet* 1982;1:116
14. Paulson DJ, Shug AL. Tissue specific depletion of L-carnitine in rat heart and skeletal muscle by D-carnitine. *Life Sci* 1981;28:2931–2938.
15. Löster H, Punzel M. Effects of L-carnitine on mechanical recovery of isolated rat hearts in relation to the perfusion with glucose and palmitate. *Mol Cell Biochem* 1998;185:65–75.
16. Broderick TL, Quinney HA, Lopaschuk GD. Carnitine stimulation of glucose oxidation in fatty acid perfused isolated working rat heart. *J Biol Chem* 1992;267:3758–3763.
17. Engel AG, Angelini C. Carnitine deficiency of human muscle with associated lipid storage myopathy: A new syndrome. *Science* 1973;179:899–902.
18. Borchard U. L-Carnitin—ein neuer therapeutischer Ansatz

bei Kardiomyopathie und ischämischen Herzerkrankungen. *Z prakt Kardioangiologie* 1987;(Sonderheft II):3–5.
19. Opie LH. Role of carnitine in fatty acid metabolism of normal and ischemic myocardium. *Am Heart J* 1979;97:375–388.
20. Bartels GL, Remme WJ, Pillay M, et al. Acute improvement of cardiac function with intravenous L-propionylcarnitine in humans. *J Cardiovasc Pharmacol* 1992;20:157–164.
21. Kamikawa T, Suzuki Y, Kobayashi A, et al. Effects of L-carnitine on exercise tolerance in patients with stable angina pectoris. *Jpn Heart J* 1984;25:587–597.
22. Lagioia R, Scutinio D, Mangini SG, et al. Propionyl-L-carnitine: A new compound in the metabolic approach to the treatment of effort angina. *Int J Cardiol* 1992;34:167–172.
23. Liedtke AJ, De Maison L, Nellis SH. Effects of L-propionylcarnitine on mechanical recovery during reflow in intact hearts. *Am J Physiol* 1988;255:H169–H176.
24. Schiavoni G, Pennestri F, Mongiardo R, Mazzari M, Manzoli U. Cardiodynamic effects of L-carnitine in ischemic cardiopathy. *Drugs Exptl Clin Res* 1983;11:171–185.
25. Yang XP, Samaja M, English E, et al. Hemodynamic and metabolic activities of propionyl-L-carnitine in rats with pressure-overload cardiac hypertrophy. *J Cardiovasc Pharmacol* 1992;20:88–98.
26. Cacciatore L, Cerio R, Ciarimboli M, et al. The therapeuthic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study. *Drugs Exptl Clin Res* 1991;17: 225–235.
27. Cherchi A, Lai C, Angelino F, et al. Effects of L-carnitine on exercise tolerance in chronic stable angina: A multicenter, double-blind, randomized, placebo-controlled crossover study. *Int J Clin Pharmacol Ther Toxicol* 1985;23:569–572.
28. Canale C, Terrachini V, Biagini A, et al. Bicycle ergometer and echocardiographic study in healthy subjects and patients with angina pectoris after administration of L-carnitine: Semiautomatic computerized analysis of M-mode tracings. *Int J Clin Pharmacol Ther Toxicol* 1988;26: 221–224.
29. Cherchi A, Lai C, Onnis E, et al. Propionyl carnitine in stable effort angina. *Cardiovasc Drugs Ther* 1990;4:481–486.
30. Gasparetto A, Corbucci GG, De Blasi AA, et al. Influence of acetyl-L-carnitine infusion on haemodynamic parameters and survival of circulatory-shock patients. *Int J Clin Pharmacol Res* 1991;11:83–92.
31. Ghidini O, Azzurro M, Vita G, Sartori G. Evaluation of the therapeutic efficacy of L-carnitine in congestive heart failure. *Int J Clin Pharmacol Ther Toxicol* 1988;26:217–220.
32. Giordano MP, Corsi M, Roncarolo P et al. Effect of L-carnitine on systolic time intervals in coronary artery disease. *Curr Ther Res* 1983;33:305–311.
33. Fazekas T, Csati S, Selmeczi A, Udvary E, Szekeres L. Effects of L-carnitine in acute myocardial ischemia. *Acta Physiol Hung* 1986;67:199–205.
34. Biagini A, Opie LH, Rovai D, Mazzei MG, Carpeggiani C, Maseri A. Intravenous dl-carnitine fails to increase the double-product during atrial pacing in patients with effort angina. A double-blind randomized study. *G Ital Cardiol* 1983;13:291–294.
35. Bartels GL, Remme WJ, Pillay M, Schönfeld DHW, Kruijssen, DACM. Effects of L-propionylcarnitine on ischemia-induced myocardial dysfunction in men with angina pectoris. *Am J Cardiol* 1994;74:125–130.
36. Ferrari R, Di Lisa F, De Jong JW, et al. Prolonged propionyl-L-carnitine pre-treatment of rabbit: biochemical, hemodynamic and electrophysiological effects on myocardium. *J Mol Cell Cardiol* 1992;24:219–232.
37. Ferrari F, Cucchini F, Visioli O. The metabolic effects of L-carnitine in angina pectoris. *Int J Cardiol* 1984;5:213–216.
38. Ferrari R, Visioli O. Effects of L-carnitine in coronary artery disease patients. In: Ferrari R, DiMauro S, Sherwood G, eds. *L-Carnitine and Its Role in Medicine: From Function to Therapy*. New York: Academic Press, 1992:265–282.
39. Brevetti G, Perna S. Metabolic and clinical effects of L-carnitine in peripheral vascular disease. In: Ferrari R, DiMauro S, Sherwood G, eds. *L-Carnitine and Its Role in Medicine: From Function to Therapy*. New York: Academic Press, 1992:359–378
40. Cherchi A, Fonzo R, Lai C, Mercuro G, Corsi M. Influence of carnitine on the effort tolerance test in angina pectoris. *Boll Soc Ital Cardiol* 1978;23:71–89.
41. Thomsen JH, Shug AL, Yap VU, Patel AK, Karras TJ, DeFelice SL. Improved pacing tolerance of the ischemic human myocardium after administration of carnitine. *Am J Cardiol* 1979;43:300–305.
42. Kosolcharoen P, Nappi J, Peduzzi P, et al. Improved exercise tolerance after administration of carnitine. *Curr Ther Res* 1981;30:753–764.
43. Hülsmann WC, Dubelaar N. Carnitine in metabolism of paced cardiac and skeletal muscles: prevention of acidosis and improvement of vascular flow. In: Ferrari R, DiMauro S, Sherwood G, eds. *L-Carnitine and Its Role in Medicine: From Function to Therapy*. New York: Academic Press, 1992:345–358
44. Regitz V, Fleck E. Role of carnitine in heart failure. In: Ferrari R, DiMauro S, Sherwood G, eds. *L-Carnitine and Its Role in Medicine: From Function to Therapy*. New York: Academic Press, 1992:295–323
45. Kobayashi A, Fujisawa S. Effect of L-carnitine on mitochondrial acyl CoA esters in the ischemic dog heart. *J Mol Cell Cardiol* 1994;26:499–508.