Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, cross-over study

GREGORIO BREVETTI, M.D., MASSIMO CHIARIELLO, M.D., GIUSEPPE FERULANO, M.D., ANTONIO POLICICCHIO, M.D., EDOARDO NEVOLA, M.D., ARTURO ROSSINI, M.D., TIZIANA ATTISANO, M.D., GIUSEPPE AMBROSIO, M.D., NORIS SILIPRANDI, M.D., AND CORRADO ANGELINI, M.D.

ABSTRACT A double-blind, cross-over study was designed to evaluate the effects of L-carnitine in patients with peripheral vascular disease. After drug washout, 20 patients were randomly assigned to receive placebo or L-carnitine (2 g bid, orally) for a period of 3 weeks and were then crossed over to the other treatment for an additional 3 weeks. The effect on walking distance at the end of each treatment period was measured by treadmill test. Absolute walking distance rose from 174 ± 63 m with placebo to 306 ± 122 m ($p < .01$) with carnitine. Biopsy of the ischemic muscle, carried out before and after 15 days of L-carnitine administration in four additional patients, showed that treatment significantly increased total carnitine levels. An additional goal of this study was to ascertain the effects of L-carnitine on the metabolic changes induced by exercise in the affected limb. In six patients under control conditions, arterial and popliteal venous lactate and pyruvate concentrations were determined at rest, when the maximal walking distance was reached, and 5 min after the walking test. Twenty-four hours later, L-carnitine was administered intravenously (3 g as a bolus followed by an infusion of 2 mg/kg/min for 30 min) and metabolic assessments were repeated. Five minutes after the walking test, popliteal venous lactate concentration increased by 107 ± 16% before treatment and by only 54 ± 32% ($p < .01$) after carnitine. Furthermore, carnitine induced a more rapid recovery to the resting value of the lactate/pyruvate ratio. These data suggest that carnitine improves pyruvate utilization and oxidative phosphorylation efficiency in the skeletal muscle of the ischemic leg. L-Carnitine, administered intravenously to 18 patients at the same dosage as above, did not modify blood flow or the ankle/arm systolic blood pressure ratio. In an additional eight patients, this intravenous dose produced an increase in walking distance similar to that observed with oral treatment. In conclusion, this study demonstrates that L-carnitine, although not affecting the general or regional hemodynamics, improves the walking capacity of patients with intermittent claudication, probably through a metabolic mechanism.
Circulation 77, No. 4, 767–773, 1988.

THE MOST IMPORTANT problem in the treatment of obstructive vascular disease is to make the energy supply adequate to the metabolic demand in the hypoxic area. In peripheral vascular disease, this goal is sought only by interventions aimed at increasing blood flow to the ischemic muscle. Many reports on ischemic heart-disease, however, suggest that a metabolic agent such as carnitine (3-hydroxy-4N-trimethylaminobutyrate) may protect the ischemic myocardium[1] and improve the stress tolerance of the heart[2–4] by increasing the availability of substrates required for energy production. A decrease in myocardial free L-carnitine content has been observed in experimental animals as a result of acute[5, 6] and chronic[7] myocardial ischemia. Similarly, a decrease in free carnitine concentration has been demonstrated in the skeletal muscle during exercise.[8]

Therefore, we designed this study to evaluate whether L-carnitine may enhance the walking ability of patients with intermittent claudication by interfering with the metabolic events taking place in the ischemic skeletal muscle.

Patients and methods

A total of 56 patients referred to our outpatient clinic for intermittent claudication were enrolled in the study. They gave

From the Departments of Medicine, Cardiology and Surgery, Second Medical School, University of Naples, Naples; and the Institute of Biological Chemistry and the Neurological Clinic, University of Padua, Padua, Italy.

Address for correspondence: Gregorio Brevetti, M.D., Via G. Jannelli n. 45/A, 80131 Napoli, Italia.

Received Dec. 9, 1985; revision accepted Dec. 17, 1987.

informed consent before participation. All of them had been affected by peripheral arterial insufficiency at the second stage of Fontaine's classification (i.e., claudication on effort without pain at rest and/or trophic lesions in the affected leg) for at least 1 year before enrollment in the study. The diagnosis was established in advance on the basis of history, physical examination, impedance plethysmography, and decrease in the ankle/arm systolic blood pressure ratio after exercise. Patients with heart failure, coronary artery disease, and severe hypertension were excluded from the study. At the time of the first visit, all of the patients were treated with one or more of the following drugs: flunarizine, papaverine, pentoxifylline, and raubasine. A pretrial drug washout period of 2 weeks was allowed in all cases. During the entire period of the study, diuretics and oral hypoglycemic agents were the only drugs allowed. All tests were carried out in the morning after an overnight fast in a quiet room at the constant temperature of 21 ± 1° C. All patients were on a low-fat, low-cholesterol diet; diabetics were also on a standard low-carbohydrate diet (150 g/24 hr). Ankle/brachial systolic blood pressure ratio was obtained by Doppler ultrasound. The blood perfusion was measured by impedence plethysmography according to the method of Nyober et al.[9] and was calculated from an average of five consecutive waves. Walking distance before the occurrence of claudication was measured by treadmill and expressed as absolute walking distance (AWD), i.e., the maximum distance in meters walked by the patient at a speed of 2.5 mph and a grade of 7 degrees.

Hemodynamic assessment. After drug washout, 18 patients (17 men, one woman) ranging in age from 51 to 66 years (mean 60.3 ± 4.1) were randomly assigned to receive placebo or L-carnitine (3 g iv as a bolus, followed by continuous infusion of 2 mg/kg/min for 30 min). Heart rate, arterial blood pressure, ankle/brachial systolic blood pressure ratio of the affected limb, and blood flow were evaluated under control conditions and 2, 4, 6, 8, 10, 15, 20, and 30 min after the bolus. A week later, patients crossed over to the other treatment and the same protocol was followed.

Clinical assessment. Two double-blind, cross-over studies were carried out to assess the ability of L-carnitine to improve walking distance when given orally for long-term or intravenously for short-term treatment. To ensure that the patient admitted to the double-blind treatment phase of the study had a stable AWD, three treadmill tests were conducted on all patients during the second week of the washout period, and only those exhibiting a change in AWD of 20% or more were included in this protocol.

The effect of the oral treatment was assessed in 20 male patients aged 40 to 69 years (mean 59.8 ± 7.0) who fulfilled all the inclusion criteria. Patients entered the first drug treatment phase, in which they were randomly assigned to receive placebo or L-carnitine (2 g bid, orally). Placebo and carnitine tablets were identical in size, shape, and color. After 3 weeks, each patient crossed over to the other drug, and treatment was continued for an additional 3 weeks. At the end of each treatment period, at 9 A.M., before the morning dose, blood flow and ankle/brachial systolic blood pressure ratio were measured in the affected limb at rest. Patients then performed a treadmill test, during which arterial blood pressure and the electrocardiogram were monitored continuously and AWD was assessed. The evaluation of subjective symptoms such as coldness, paresthesias, tiredness, and pain during walking was a secondary aim of this study. The intensity of each symptom was scored on a six-point scale: −3 = total relief, −2 = marked improvement, −1 = slight improvement, 0 = no change, 1 = slight deterioration, 2 = marked deterioration.

The effect of short-term intravenous administration of L-carnitine was assessed in an additional eight patients who were randomly assigned to placebo or L-carnitine 3 g iv as a bolus followed by continuous infusion of 2 mg/kg/min for 30 min. After 1 week patients received the other treatment. At the end of the infusion, blood flow and ankle/arm systolic blood pressure ratio were measured at rest. Patients then performed treadmill exercise and AWD was assessed.

Metabolic assessment. The metabolic changes induced by exercise were assessed, before and after carnitine administration, in six male patients (mean age 61.0 ± 7.1 years). After inducement of local anesthesia with 1% procaine, catheters were placed into one radial artery and into the popliteal vein of the affected leg, i.e., as close as possible to the ischemic area. Control measurements were carried out on the following day. Ten milliliters of arterial and venous blood was drawn after 5 min of standing. The patients then performed a treadmill exercise as described above, and blood samples were taken when the maximal walking distance was reached as well as 5 min after cessation of exercise. Twenty-four hours later, carnitine was administered intravenously at the same dose as above. Blood samples were taken at rest, then exercise was started and blood samples drawn at the same walking distance as under control conditions and 5 min after exercise. By this method it was possible to assess the metabolic effect of L-carnitine on the ischemic muscle undergoing the same workload as with placebo. Plasma lactate and pyruvate concentrations were determined in duplicate by an enzymatic method.[10, 11]

Muscle carnitine assay. Carnitine and carnitine fractions were measured in the ischemic muscle of four patients before and after 15 days of oral L-carnitine supplementation (2 g bid). Muscle specimens, obtained from the gastrocnemius of the affected leg under local anesthesia, were frozen in liquid nitrogen–cooled isopentane and stored at −70° C. Free carnitine was assayed by the radiochemical method of Cederblad and Linstedt[12] in the presence of 0.5 mM *N*-ethylmaleimide. Acid-soluble and insoluble acylcarnitines were measured upon alkaline hydrolysis, as described by Pearson and Tubbs.[13] Noncollagen proteins were determined according to the method of Lilienthal et al.[14]

Statistical analysis. Comparison between placebo and carnitine treatment was performed by analysis of variance for a cross-over design. Differences from baseline were analyzed with the t test for paired data. The Mann-Whitney U test was used to compare the effect of the two treatments on clinical variables. Group values are expressed as mean ± SD.

Results

Hemodynamic assessment. Intravenous administration of carnitine did not modify the blood perfusion in the affected limb. Blood flow and ankle/brachial systolic blood pressure ratio remained unchanged at all times of recording compared with baseline values. Similarly, no statistical difference in these variables was found between placebo and carnitine treatment (table 1).

Clinical assessment. The analysis of variance, which did not show interaction between treatments and periods, demonstrated that carnitine was able to induce a marked increase in AWD compared with placebo. In the long-term study, AWD was 174.7 ± 63.1 m on placebo and 306.5 ± 121.8 m ($p < .01$) on carnitine. After the first phase of treatment, patients assigned to carnitine showed an increase in AWD from the washout value of 147.0 ± 67 to 288.0 ± 97 m ($p < .01$); when they crossed to placebo, AWD returned to a value similar to

TABLE 1
Effect of placebo (P) and intravenous L-carnitine (C) on perfusion volume and ankle/brachial systolic blood pressure ratio

Assessment	Treatment	Baseline	Times of recording (min) 2	4	6	8	10	15	20	30
Perfusion volume (ml/min/100 mg tissue)	P	2.02± 0.95	2.10± 0.89	2.00± 0.99	2.05± 0.94	2.12± 0.92	2.12± 0.96	2.07± 0.98	2.04± 0.98	2.03± 0.98
	C	2.06± 0.87	2.11± 0.88	2.15± 1.02	2.05± 0.93	2.02± 0.87	2.17± 0.97	2.19± 0.90	2.14± 1.01	2.08± 0.83
Ankle/brachial systolic blood pressure ratio	P	0.62± 0.15	0.62± 0.15	0.63± 0.16	0.61± 0.14	0.62± 0.16	0.62± 0.16	0.62± 0.16	0.62± 0.15	0.63± 0.15
	C	0.65± 0.14	0.65± 0.15	0.66± 0.15	0.67± 0.15	0.66± 0.15	0.66± 0.16	0.67± 0.14	0.69± 0.15	0.67± 0.15

Data expressed as mean ± SD.

that observed after washout (178.0 ± 66 m). In patients assigned to placebo, AWD was 155.0 ± 64 m after washout and 171.0 ± 63 m (NS) after the first phase of treatment; when they crossed to carnitine, AWD increased to 324.0 ± 146 m ($p < .01$). These data are shown in figure 1. This improvement was independent from the severity of arterial disease, since percent changes in walking distance did not correlate with AWD nor with the ankle/arm systolic blood pressure ratio. No statistical difference between placebo and carnitine was found in the resting values of blood flow and ankle/arm systolic blood pressure ratio. Changes in heart rate and blood pressure induced by exercise during treatment with placebo were not modified by carnitine.

Table 2 illustrates the changes in subjective symptoms observed throughout the study. Patients assigned to placebo showed slight changes after the first phase of treatment; when they crossed to carnitine, all symptoms improved. Patients assigned to carnitine reported improvements in all symptoms compared with the washout period after the first phase of treatment; this improvement vanished when they crossed to placebo. As shown in table 2, many of the patients reported marked improvement or total relief of symptoms during treatment with L-carnitine. As a consequence, comparison between treatments by the Mann-Whitney U test indicated a significant improvement ($p < .01$) after L-carnitine.

With the exception of one patient who experienced pyrosis during both placebo and carnitine treatment, no side effects were observed during the trial.

In the short-term study, intravenous carnitine increased AWD from 171.0 ± 32 m during placebo to 286.0 ± 155 m ($p < .05$). Therefore the intravenous administration of L-carnitine increased AWD by 67%, a value similar to that observed with oral treatment (75%).

Individual data on the ankle/arm systolic blood pressure ratio and the treadmill tests throughout the study are reported in table 3.

Metabolic assessment. Before carnitine treatment, the

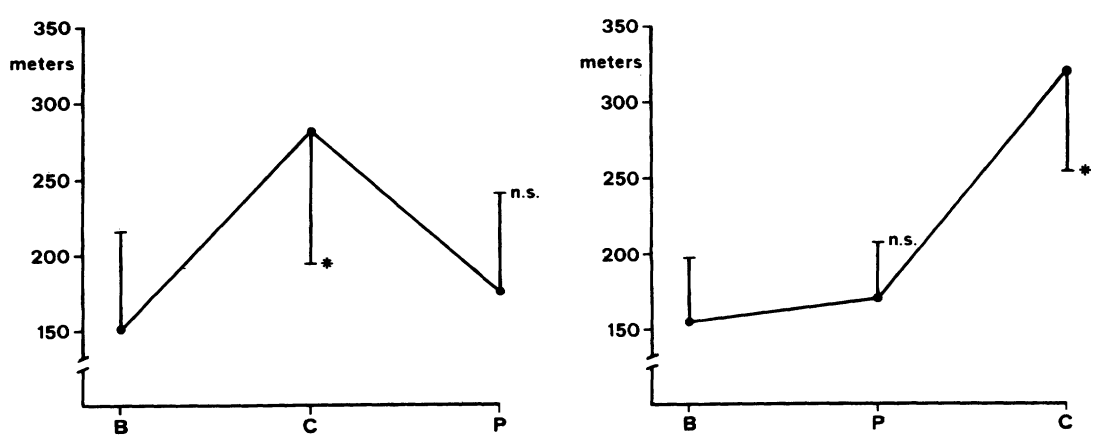

FIGURE 1. Effect of the two treatments (placebo and L-carnitine) on absolute claudication distance during the entire study period. Note the sharp increase in walking capacity whenever L-carnitine is given. Data are expressed as mean ± SD.* Different from baseline value, $p < .01$; B = baseline value (after washout period); C = end of L-carnitine period; P = end of the placebo period.

TABLE 2

Changes in subjective symptoms observed throughout the study in patients randomly assigned to receive placebo (*top*) and in patients randomly assigned to receive carnitine (*bottom*)

	Paresthesias		Tiredness		Pain during walking		Coldness	
Patient	P vs WO	C vs P	P vs WO	C vs P	P vs WO	C vs P	P vs WO	C vs P
1	0	−3	+1	−3	0	−2	0	−2
2	+1	−3	0	−3	0	−3	0	−2
3	−1	0	0	−1	0	−1	−1	0
4	0	−1	0	−2	−1	−2	0	0
5	0	−1	−1	−1	−1	0	0	0
6	0	−2	0	−3	0	−2	0	0
7	+1	−2	−1	−3	0	−3	0	0
8	0	−2	0	−2	0	−1	0	−1
9	0	−3	−1	−2	−1	0	0	0
10	−1	−3	−1	−3	−1	−3	0	−1
	C vs WO	P vs C	C vs WO	P vs C	C vs WO	P vs C	C vs WO	P vs C
1	−3	+2	−3	+1	−3	+2	−2	0
2	−3	+1	−3	+2	−2	+2	−2	−1
3	−2	+1	−3	+1	−2	0	−1	0
4	−3	+1	−3	+1	−3	+2	−1	0
5	−3	0	−2	+2	−2	+2	0	0
6	−3	+2	−1	+1	−1	−1	0	0
7	−3	+2	−1	+2	−2	+2	−1	0
8	−2	+1	−2	+2	−2	+1	0	0
9	0	0	0	0	−1	0	0	0
10	−1	+1	−2	+1	−2	+1	−1	+1

WO = washout; P = placebo; C = carnitine.

All symptoms were significantly ($p < .01$) improved by carnitine (Mann-Whitney U test).

mean AWD was 168.0 ± 34 m. After carnitine, none of the six patients experienced ischemic pain in the affected leg at the same walking distance. As shown in table 4, in the absence of carnitine, exercise induced an increase in popliteal venous lactate concentration from the rest value of 1.36 ± 0.28 to 3.63 ± 1.2 mmol/liter ($p < .05$). After carnitine treatment, at the same walking distance as before, lactate concentration increased from 1.30 ± 0.40 to 2.75 ± 0.22 mmol/liter ($p < .01$). In all patients 5 min after cessation of exercise, popliteal venous lactate level was still higher than at rest, 2.83 ± 0.6 mmol/liter ($p < .01$) in the absence of carnitine but only 1.96 ± 0.55 mmol/liter ($p < .01$) with carnitine. Actually, 5 min after termination of walking test, venous lactate concentration increased by 107 ± 16% as compared with the rest value in untreated patients; after treatment with carnitine the increase was only 54.2 ± 32% ($p < .01$).

Under basal conditions, popliteal venous pyruvate concentration rose during exercise from the rest value of 0.064 ± 0.01 to 0.096 ± 0.03 mmol/liter ($p < .05$). Five minutes after the walking test it was 0.101 ± 0.04 mmol/liter ($p < .05$). Similar changes were observed after carnitine (table 4). Therefore, as shown in figure 2, in the absence of carnitine the popliteal venous lactate/pyruvate (L/P) ratio increased from 21.9 ± 6 to 40.2 ± 14 ($p < .05$) during exercise, and 5 min after exercise L/P was still higher than at rest (31.6 ± 13); $p < .01$). After carnitine, the L/P ratio during exercise increased from 21.7 ± 13 to 30.0 ± 15 ($p < .01$) and returned to the rest value during the recovery period (20.1 ± 8). Throughout the study, L/P ratios were similar in the treated and in the control groups. Furthermore, arterial lactate and pyruvate concentration and L/P ratios were similar in treated and untreated patients at rest, during exercise, and after recovery (table 4).

Muscle carnitine assay. Table 5 shows changes in total, free, and esterified carnitine concentrations induced by L-carnitine in patients with peripheral vascular disease. Normal values were obtained from six normal subjects matched to the patients with peripheral arterial disease with respect to age and sex, chosen from a group of 46 normal individuals previously studied in our laboratory.

Before treatment, total carnitine in the biopsied muscle was 19.3 ± 3.6 nmol/mg noncollagen protein, a value not different from that found in normal muscle. After treatment, total carnitine increased in all subjects to a level as high as 24.6 ± 2.9 nmol/mg noncollagen

TABLE 3
Individual data of ankle/arm systolic blood pressure ratio and walking distance measured at the end of wash-out, placebo, and carnitine periods

	Ankle/arm SBP ratio			Walking distance (m)		
Patient	WO	P	C	WO	P	C
Long-term study						
1	0.71	0.65	0.61	118	122	302
2	0.59	0.73	0.85	302	290	578
3	0.53	0.46	0.57	196	198	254
4	0.53	0.60	0.58	143	156	327
5	0.56	0.46	0.45	181	227	232
6	0.60	0.58	0.51	90	88	241
7	0.56	0.57	0.71	107	103	303
8	0.73	0.71	0.69	130	133	209
9	0.90	0.66	0.70	143	194	205
10	0.90	0.94	0.95	200	202	604
11	0.78	0.70	0.61	176	207	388
12	0.85	0.80	0.85	94	78	251
13	0.62	0.58	0.70	104	148	146
14	0.60	0.56	0.56	83	98	279
15	0.50	0.46	0.50	142	203	163
16	0.85	0.77	0.73	139	174	362
17	0.62	0.52	0.66	191	254	338
18	0.30	0.29	0.37	152	150	203
19	0.69	0.58	0.60	295	300	428
20	0.66	0.61	0.63	180	168	318
Mean	0.65	0.61	0.64	158.2	174.7	306.5
±SD	0.15	0.11	0.14	59.8	63.1	121.8
Short-term study						
1	0.54	0.56	0.60	227	187	505
2	0.61	0.60	0.60	228	223	551
3	0.60	0.66	0.73	120	128	185
4	0.55	0.50	0.56	160	164	266
5	0.59	0.63	0.66	140	202	240
6	0.69	0.77	0.70	150	147	162
7	0.54	0.54	0.54	141	174	232
8	0.69	0.65	0.62	89	143	147
Mean	0.60	0.61	0.62	156.9	171.0	286.0
±SD	0.06	0.08	0.06	49	32	155

SBP = systolic blood pressure; other abbreviations as in table 2.

protein ($p < .05$), thus demonstrating a direct uptake of the administered L-carnitine by the biopsied muscle. The observed increase in total carnitine is accounted for by an increase in both free carnitine and short-chain acylcarnitine. On the contrary, the concentration of long-chain acylcarnitine decreased, although not significantly, after L-carnitine supplementation. It must be noted that free and total carnitine values before treatment are within the normal range.

Discussion

The pharmacologic treatment of intermittent claudication still represents a challenge. Vasodilators are the most used drugs in the therapy of chronic obstructive vascular disease, although their efficacy is far from being proved.[16, 17] Much more effective seem to be drugs capable of reducing blood viscosity. Among these, pentoxifylline has been demonstrated to increase walking distance[18, 19] as a result of increased blood flow and enhanced tissue oxygenation in the affected limb.[20, 21] Other reports, however, failed to demonstrate any objective benefit.[22] Our study describes a new approach to the treatment of peripheral vascular disease. We have shown that L-carnitine, although not affecting general or regional hemodynamics, improves the walking ability of patients with intermittent claudication, probably through a metabolic mechanism.

Carnitine has been found to protect ischemic myocardium in animals[1] and to improve the stress tolerance in patients with coronary artery disease.[2–4] The results of the present double-blind, placebo-controlled study demonstrate that in patients with chronic obstructive vascular disease of the lower limbs, carnitine induces a statistically significant and clinically relevant increase in walking distance. Given the spontaneous fluctuation in the severity of intermittent claudication

TABLE 4
Lactate and pyruvate concentrations (mmol/liter) at rest and during and after exercise (mean ± SD)

	Venous			Arterial		
	Rest	Exercise	Recovery	Rest	Exercise	Recovery
Lactate						
Control	1.36±0.28	3.63±1.20	2.82±0.60	0.97±0.29	2.21±0.70	1.50±0.47
p<		.05	.01		.01	.05
Carnitine	1.30±0.41	2.75±0.72	1.96±0.55	0.83±0.43	2.05±1.12	1.45±0.68
p<		.01	.01		.01	.01
Pyruvate						
Control	0.064±0.01	0.096±0.03	0.101±0.04	0.049±0.01	0.148±0.05	0.117±0.04
p<		.05	.02		.01	.01
Carnitine	0.072±0.03	0.106±0.04	0.108±0.04	0.053±0.02	0.093±0.02	0.080±0.02
p<		.01	.01		.01	.05

p values refer to differences from rest values.

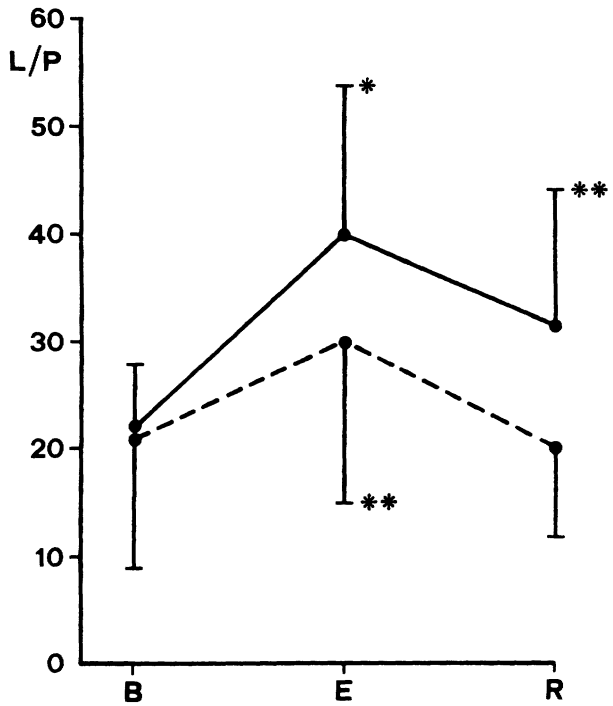

FIGURE 2. Popliteal venous L/P ratio at rest (B), during exercise (E), and during the recovery period (R), under control conditions (solid line) and after administration of L-carnitine (interrupted line). Data are expressed as mean ± SD. *Different from rest value, $p < .05$; **different from rest value, $p < .01$.

experienced by such patients, only an increase in AWD of 25% over baseline was accepted as clinically relevant. The results indicate that, compared with placebo, 12 of the 20 patients who completed the oral carnitine study showed an increase in AWD of 60% or more, four subjects had 25% to 59% improvement, and only four showed no difference in AWD between placebo and carnitine treatment. Moreover, the L/P ratio during recovery was still higher than at rest during treatment with placebo and returned to the rest value on carnitine.

A reasonable interpretation of these metabolic effects may be the following: Oxygen availability in skeletal muscle is critical for the conversion of pyruvate either to lactate or to acetylcoenzyme A (acetyl-CoA). The latter reaction is catalyzed by pyruvate dehydrogenase, the activity of which is controlled by the acetyl-CoA/CoA ratio.[23, 24] Through the action of CoA:carnitine acetyl transferase, carnitine may decrease such a ratio[25] and stimulate the activity of pyruvate-dehydrogenase, consequently preventing the formation of lactate. In patients with peripheral vascular disease, pyruvate oxidation is presumably limited by two conditions: (1) the inadequacy of oxygen supply and (2) the accumulation of acetyl-CoA caused by a decreased flux into the Krebs cycle.

Carnitine does not apparently influence tissue oxygen supply but is able to decrease the acetyl-CoA concentration by virtue of the presence of a very active CoA:carnitine acetyl transferase in the muscular tissue.[15, 26] This assumption is supported by the finding that administration of carnitine resulted in a significant increase of total carnitine in muscles of the affected leg. Both the increase of free carnitine and short-chain acyl carnitine contributed to such an increase. These changes in the concentrations of muscular carnitine fractions indicate that part of the administered carnitine was taken up by muscles of the affected leg and that a consistent portion was transformed into short-chain acyl carnitine, presumably acetyl carnitine.[15] This implies that a corresponding amount of short-chain acyl-CoA, presumably acetyl-CoA, was removed along with a concurrent release of free CoA. The consequent decrease of the acetyl-CoA/CoA ratio would explain the above-mentioned stimulation of pyruvate dehydrogenase.

TABLE 5
Changes in free and esterified carnitine concentration induced by L-carnitine treatment in patients with peripheral arterial disease (mean ± SD, nmol/mg noncollagen protein)

	PAD before treatment	PAD after treatment	Normals
Free carnitine	16.31 ± 2.30	20.07 ± 4.67	16.46 ± 4.58
Short-chain acylcarnitines	2.49 ± 1.51	4.11 ± 2.54	3.40 ± 1.69
Long-chain acylcarnitines	0.51 ± 0.09	0.41 ± 0.27	0.88 ± 0.59
Total carnitine	19.31 ± 3.56	24.59 ± 2.94[A]	21.15 ± 5.01

PAD = peripheral arterial disease.
[A]Significantly different from the pretreatment value: $p < .05$.

In our short-term exercise protocol, the preferentially utilized substrate was conceivably muscle glycogen or blood glucose.[27] As a consequence, a large increase of pyruvate production should be expected. The stimulation of pyruvate dehydrogenase activity by the increased availability of carnitine might explain both the decreased production of lactate and the higher yield of energy, resulting from pyruvate oxidation. It is well known that glucose utilization in anaerobic glycolysis yields 2 ATP, whereas its utilization in the aerobic pathway produces 36 ATP. This enhancement of pyruvate oxidation, hence in energy production, may result in an improvement of walking ability after treatment with L-carnitine.

An additional mechanism by which treatment with carnitine might be beneficial is the removal of long-chain acyl-CoA.[28] An accumulation of these metabolites in oxygen-deficient conditions may be detrimental to the cellular membrane stability. An improvement

of long-chain fatty acid utilization by supplemented L-carnitine seems to be ruled out by the observation that in muscles of the affected leg even before L-carnitine, the concentration of total carnitine is above the value considered rate-limiting for the optimal fatty acid oxidation.[29]

Therapeutic implications. The results of this study suggest that carnitine may allow ischemic skeletal muscle to reach a higher level of energy expenditure before claudication develops. Therefore L-carnitine may represent an effective agent for treating peripheral vascular disease. Furthermore, because the mechanism of action of this factor differs from that of other available therapeutic agents, a combination of more traditional drugs with carnitine may be regarded as a useful means for treating this disease.

References

1. Folts JD, Shug AL, Koke JR, Bittar N: Protection of the ischemic myocardium with L-carnitine. Am J Cardiol **41:** 1209, 1978
2. Thomsen JH, Shug AL, Yap VU, Patel AK, Karras TJ, De Felice SL: Improved pacing tolerance of the ischemic human myocardium after administration of carnitine. Am J Cardiol **43:** 300, 1979
3. Kosolcharoen P, Nappi J, Peduzzi P, Shug AL, Patel AK, Filipek T, Thomsen JH: Improved exercise tolerance after administration of carnitine. Curr Ther Res **30:** 753, 1981
4. Ferrari R, Cucchini F, Visioli O: The metabolic effects of L-carnitine in angina pectoris. Int J Cardiol **5:** 213, 1984
5. Schwartz A: Cellular and molecular mechanism involved in cardiac cell function: effects of an antibiotic ionophore. Acta Med Scand [Suppl] **1:** 71, 1976
6. Shug AL, Thomsen JH, Folts JD, Bittar N, Klein MI, Koke JR, Huth PJ: Changes of tissue levels of carnitine and other metabolites during myocardial ischemia and anoxia. Arch Biochem Biophys **187:** 25, 1978
7. Schwartz A, Wood JM, Allen JC, Barnet EP, Entman ML, Golstein MA, Sordahl LA, Suzuki M, Lexis RM: Biochemical and morphologic correlates of cardiac ischemia. Am J Cardiol **32:** 46, 1973
8. Lennon DLF, Stratman FW, Stirago E, Nagla FJ, Madden M, Hanson P, Carter AL: Effects of acute moderate intensive exercise on carnitine metabolism in men and women. J Appl Physiol **55:** 489, 1983
9. Nyober J, Murray P, Sedensky JA: Blood flow indices in amputee and control limbs by mutual electrical impedance plethysmography. Am Heart J **87:** 704, 1974
10. Hohorst HJ: L(+)-lactate determination with lactate dehydrogenase and DPN. *In* Bergmeyer H, editor: Methods of enzymatic analysis. New York, 1968, Academic Press Inc., p 266
11. Czok R, Lamprecht W: Pyruvate, phosphoenolpyruvate and D-glycerate-2 phosphate. *In* Bergmeyer H, editor: Methods of enzymatic analysis. New York, 1974, Academic Press, Inc., p 1491
12. Cederblad G, Lindstedt S: A method for the determination of carnitine in the picomole range. Clin Chim Acta **37:** 235, 1972
13. Pearson DJ, Tubs PK: Tissue levels of acid-insoluble in rat heart. Biochem Biophys Acta *84:* 772, 1964
14. Lilienthal JL Jr, Zierler KL, Folk BP, Buka R, Riley MJ: A reference base and system for analysis of muscle constituents. J Biol Chem **182:** 501, 1950
15. Bremer J: Carnitine: metabolism and functions. Physiol Rev **63:** 1420, 1983
16. Coffmann JD, Mannick JA: Failure of vasodilator drugs in arteriosclerosis obliterans. Ann Intern Med **76:** 35, 1972
17. Hansteen V, Lorentsen E: Vasodilator drugs in treatment of peripheral arterial insufficiency. Acta Med Scand [Suppl] **556:** 3, 1974
18. Brevetti G, Abate S, Lavecchia G, Ferulano GP, Paudice G, Acunzo R: La pentossifillina nel trattamento delle arteriopatie periferiche al II stadio. Il Progresso Medico **35:** 363, 1979
19. Porter JM, Cutler BS, Lee JB, Reich T, Reich FA, Scogin JT, Strandness DE: Pentoxifylline efficacy in the treatment of intermittent claudication: multicenter controlled double blind trial with objective assessment of chronic occlusive arterial disease patients. Am Heart J **104:** 66, 1982
20. Brevetti G, Abate S, Lavecchia G, Ferulano GP, Paudice G, Fasano S: Adaptation of arterial wall to physical stress before and after pentoxifylline administration. *In* Reims Z, Pokorny J, Linhart J, Hild R, Schirger A, editors: Adaptability of vascular wall. Berlin, 1980, Springer-Verlag, p 555
21. Ehrly AM: The effects of pentoxifylline on the deformability of erythrocytes and on the muscular oxygen pressure in patients with chronic arterial disease. J Med **10:** 331, 1979
22. Mashiah A, Patel P, Schraibman IG, Charlesworth D: Drug therapy in intermittent claudication: an objective assessment of the effects of three drugs on patients with intermittent claudication. Br J Surg **65:** 342, 1978
23. Randle PJ: Pyruvate-dehydrogenase complex: meticulous regulator of glucose disposal in animals. Trends Biochem Sci **3:** 217, 1978
24. Denton RM, Halestrop AF: Regulation of pyruvate metabolism in mammalian tissue. Essays Biochem **15:** 37, 1979
25. Bieber LL, Emaus R, Valkner K, Farrel S: Possible functions of short-chain and medium-chain carnitine acyl transferases. Fed Proc **41:** 2858, 1982
26. Alkonyi I, Kerner J, Sandor A: The possible role of carnitine and carnitine acetyl-transferase in the contractile frog skeletal muscle. FEBS Lett **52:** 265, 1975
27. Bjorkman O: Fuel utilization during exercise. *In* Benzi G, Packer L, Siliprandi N, editors: Biochemical aspects of physical exercise. Amsterdam, 1986, Elsevier Science Publications p 245–260
28. Di Lisa F, Bobyleva-Guarriero V, Jocelyn P, Toninello A, Siliprandi N: Stabilizing action of carnitine on energy linked processes in rat liver mitochondria. Biochem Biophys Res Commun **1341:** 968, 1985
29. Long CS, Haller RG, Foster DW, McGarry JD: Kinetics of carnitine-dependent fatty acid oxidation: implications for human carnitine deficiency. Neurology **32:** 663, 1982

Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, cross-over study.

G Brevetti, M Chiariello, G Ferulano, A Policicchio, E Nevola, A Rossini, T Attisano, G Ambrosio, N Siliprandi and C Angelini

Circulation. 1988;77:767-773
doi: 10.1161/01.CIR.77.4.767
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539