Eur J Appl Physiol (1990) 61:486-490

European Journal of Applied Physiology and Occupational Physiology


# Influence of L-carnitine administration on maximal physical exercise

**L. Vecchiet[1], F. Di Lisa[2], G. Pieralisi[1], P. Ripari[1], R. Menabò[2], M. A. Giamberardino[1], and N. Siliprandi[2]**

[1] Istituto di Fisiopatologia Medica, Università di Chieti, 66100 Chieti, Italy
[2] Dipartimento di Chimica Biologica, Università di Padova and Centro Studio Fisiologia Mitochondriale, Via Trieste 75, CNR, I-35121 Padua, Italy

Accepted April 18, 1990

**Summary.** The effects of L-carnitine administration on maximal exercise capacity were studied in a double-blind, cross-over trial on ten moderately trained young men. A quantity of 2 g of L-carnitine or a placebo were administered orally in random order to these subjects 1 h before they began exercise on a cycle ergometer. Exercise intensity was increased by 50-W increments every 3 min until they became exhausted. After 72-h recovery, the same exercise regime was repeated but this time the subjects, who had previously received L-carnitine, were now given the placebo and vice versa. The results showed that at the maximal exercise intensity, treatment with L-carnitine significantly increased both maximal oxygen uptake, and power output. Moreover, at similar exercise intensities in the L-carnitine trial oxygen uptake, carbon dioxide production, pulmonary ventilation and plasma lactate were reduced. It is concluded that under these experimental conditions pre-treatment with L-carnitine favoured aerobic processes resulting in a more efficient performance. Possible mechanisms producing this effect are discussed. **Key words:** Maximal exercise - L-carnitine - Lactate

## Introduction

Physical exercise sometimes promotes a marked increase in mitochondrial enzymes in skeletal muscle (Holloszy and Coyle 1984; Gollnick 1986), thus enhancing the utilization of fatty acids, ketone bodies and pyruvate. This implies an increased recycling of muscle carnitine and thus its more abundant extraction from the blood. It also seems possible that in prolonged exercise endogenous free carnitine might not be sufficient to meet the increased muscle demand. Indeed, it has been shown that physical exercise increases the rate of esterification of carnitine so that it is mainly present in an acylated form, principally as acetylcarnitine (Carlin et al. 1986; Ciman et al. 1978; Foster and Harris 1987; Harris et al. 1987; Lennon et al. 1983; Marconi et al. 1985). The consequent deficiency of free carnitine in muscles may affect, to a greater or lesser extent, the efficiency of physical exercise. Hence the present experiment aims to establish the effects of administration of L-carnitine on physical performance.

Marconi et al. (1985) have studied the effects of L-carnitine loading ($4\ g \cdot d^{-1}$ per os over a 2-week period) on the aerobic and anaerobic performances of six long distance competitive walkers. As a result of this treatment maximal oxygen consumption ($\dot{V}O_{2max}$) was significantly increased, whereas other parameters (heart rate ($f_c$), pulmonary ventilation, oxygen consumption ($\dot{V}O_2$) and respiratory quotient) remained unchanged. Both Greig et al. (1987) and Soop et al. (1988) failed however to confirm these results. They reported that L-carnitine administration did not affect the submaximal performance at 50% of $\dot{V}O_{2max}$ either in untrained or moderately trained young subjects.

The discrepancy in the above-mentioned results may be due to differences in the conditions either of the imposed exercise, or the training, or both. Also the different amount of L-carnitine administered and the time elapsed from the L-carnitine administration might explain the conflicting results.

We have now approached the problem by studying the effect of a single L-carnitine administration on the $\dot{V}O_{2max}$ and maximal work capacity of young non-competitive volunteers. The results reported in the present paper show that L-carnitine administration in two strictly controlled double-blind trials significantly increased both $\dot{V}O_{2max}$ and the maximal work capacity and decreased lactate accumulation in plasma.

## Methods

*Subjects.* The study was conducted on a group of ten healthy male volunteers aged 22–30 years (body mass 72.3 kg, SEM 3.0). They were all students at an Institute of Advanced Physical Education and were similar with respect to the intensity and quality of their

*Offprint requests to:* N. Siliprandi

**Table 1.** Selected characteristics of the subjects ($n = 10$)

| Age (year) | | Height (cm) | | Mass (kg) | | $f_{c,rest}$ (beats·min$^{-1}$) | |
|---|---|---|---|---|---|---|---|
| mean | SEM | mean | SEM | mean | SEM | mean | SEM |
| 25.1 | 1.0 | 176.1 | 2.2 | 72.3 | 3.0 | 71.9 | 2.6 |

$f_{c,rest}$, Resting heart rate

non-athletic activities and also their life styles. Selected characteristics of the subjects are shown in Table 1.

The experiments were designed using the cross-over technique, i.e. control against placebo, with random allocation of the subjects to the different sequences of treatment and using double blind conditions. Students were only admitted after medical [physical examination, electrocardiogram (EKG)] and laboratory (blood and urine assays) tests had shown the absence of any impending pathologies.

*Experimental procedure.* The following procedure was used for the study. Three tests to maximal exercise intensity were carried out, each separated by an interval of 72 h. The first was done without any pretreatment (baseline), while the other two began 90 min after taking L-carnitine (2 g per os; single dose) or placebo in random order. The exercise intensities were applied using a Fleish cycle ergometer (Sanitas METABO, Switzerland) with mechanical braking starting from zero, increments of 50 W being added every 3 min. The tests were interrupted after muscular exhaustion or upon reaching the theoretical maximal heart rate ($f_{c\max} = 220$ minus age).

The three tests were always carried out at the same time of day. The students were required to abstain from eating and smoking for at least 2 h prior to testing and to wear light clothing only. The ambient temperature was within a 20°–24° C range and the local relative humidity not above 55%.

During the tests the following parameters were monitored and recorded: EKG and ($f_c$), pulmonary ventilation ($\dot{V}_E$), $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$) (using equipment comprising an Ergopneumotest Jager (Jaeger, FRG) connected to an ASEM PC100 computer (ASEM, Italy). For lactate determinations (Gutman and Wahlefeld 1974) capillary blood samples were withdrawn from the ear lobe at the end of each successive increment in exercise intensity. The lactate values of these samples were almost identical with those obtained from venous samplings.

Cross-over variance using the untreated control data was used to disclose the possible trends due to the order of administering placebo or carnitine. No such effects were found. Variance analysis of repeated measures was used to detect the occurrence of significant differences between the parameters after each treatment.

## Results

As the exercise intensity was progressively increased both $\dot{V}O_2$ and blood lactate increased correspondingly as expected (Fig. 1). All subjects tolerated increasing exercise intensities up to 200 W ("common" work). Above this level, the number of subjects capable of continuing became progressively smaller and only one subject was able to attain a maximal exercise intensity of 350 W. After L-carnitine treatment, all the subjects tolerated similar exercise intensities but with a significant reduction of $\dot{V}O_2$ and blood lactate. Conversely as indicated in Fig. 2, when required to exercise to their

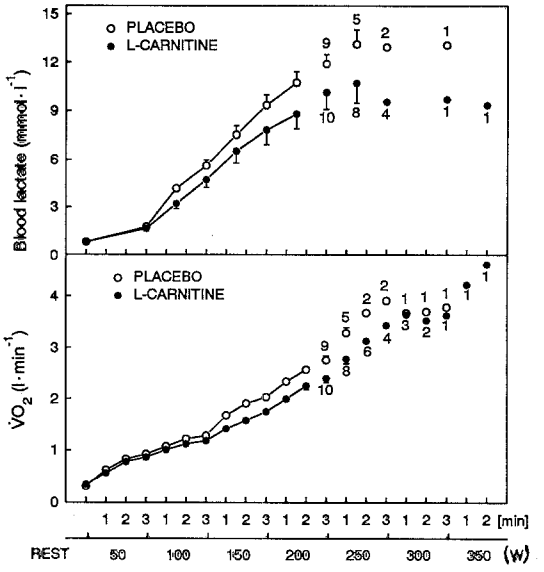


**Fig. 1.** Changes in oxygen consumption ($\dot{V}O_2$) and capillary blood lactate as a function of the progressive increments of exercise intensity (W) after administration of placebo or L-carnitine. The extent of "common" work, that is the exercise performed by all ten subjects, is indicated by *circles joined by lines. Circles without lines* refer to exercise intensities carried out by a progressively smaller number of subjects which are indicated by the *numbers*. The *SEM* indicated by *vertical bars* have been omitted for $n < 5$. Variance analysis for repeated measures gave values of $P < 0.01$ and $P < 0.02$ for lactate and $\dot{V}O_2$ respectively

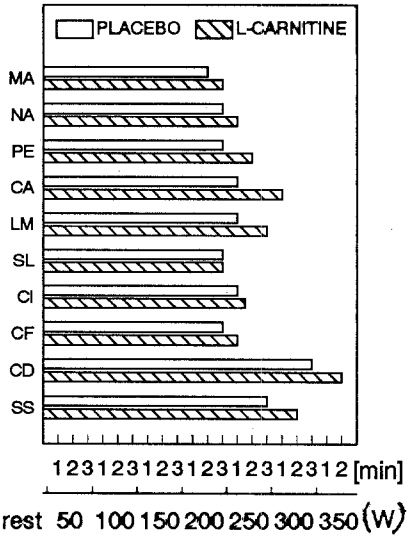


**Fig. 2.** Maximal exercise intensity of each subject indicated by *their initials* after administration of either placebo or L-carnitine

maximal capacity, all the subjects, with only one exception, were able to do substantially more work in the session in which they received L-carnitine. This could have been due either to the fact that subjects were able to continue at the same exercise intensity for a longer period or attain a higher exercise intensity. Consequently, the maximal work output of the tested subjects, again with only one exception, was higher after L-carnitine than placebo administration (Fig. 3).

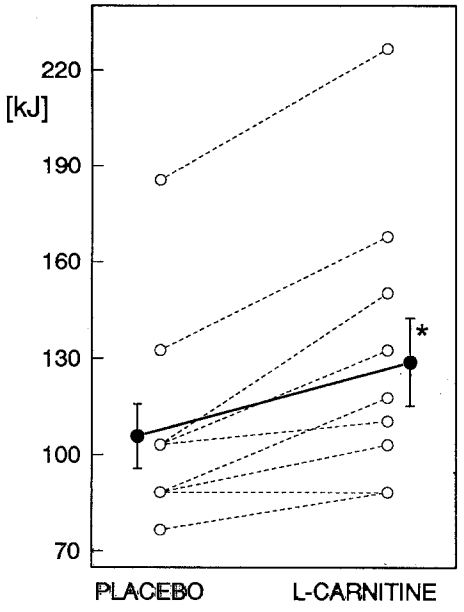


**Fig. 3.** Maximal work output of the subjects tested ($n=10$) after administration of either placebo or L-carnitine. *Open circles represent individual subjects. Filled circles* are the means and SEM. * $P<0.001$ (Student's $t$-test used for paired data)

**Table 2.** Physiological parameters of the subjects ($n=10$) at maximal exercise intensity upon administration of placebo or L-carnitine

| | Placebo | | $P$ | L-carnitine | |
|---|---|---|---|---|---|
| | mean | SEM | | mean | SEM |
| $f_c$ (beats·min$^{-1}$) | 179 | 8 | NS | 177 | 11 |
| $\dot{V}_E$ (l·min$^{-1}$) | 104.49 | 17.40 | NS | 99.89 | 23.80 |
| $\dot{V}O_2$ (l·min$^{-1}$) | 3.17 | 0.63 | <0.05 | 3.39 | 0.71 |
| $\dot{V}CO_2$ (l·min$^{-1}$) | 3.21 | 0.72 | NS | 3.42 | 0.91 |
| $\dot{V}O_{2max}$ (ml·min$^{-1}$·kg$^{-1}$) | 43.91 | 7.87 | <0.05 | 47.18 | 9.59 |
| Total work (kJ) | 105.69 | 10.09 | <0.001 | 128.80 | 13.60 |

$f_c$, heart rate; $\dot{V}_E$, pulmonary ventilation; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbondioxide production; $\dot{V}O_{2max}$, maximal oxygen consumption

Table 2 summarizes the values of the physiological parameters of the subjects examined at the maximal exercise intensity either upon placebo or L-carnitine administration. Both the work output and $\dot{V}O_{2max}$ were significantly increased by carnitine pretreatment, whereas the other parameters either did not change ($f_c$, $\dot{V}_E$) or changed only slightly ($\dot{V}CO_2$).

Taken together these results show that L-carnitine administration allows more physical work to be done without a greater output of metabolic energy.

## Discussion

These findings demonstrated that a single oral administration of L-carnitine to moderately trained subjects produced two relevant effects: an increase in power output, implicit in the decrease of $\dot{V}O_2$ for the same exercise intensity and an increase of the work yielded by the same $\dot{V}O_2$.

These results are at variance with those obtained by Greig et al. (1987) and Soop et al. (1988). However, in their experiments, both the exercise conditions and the L-carnitine administration were somewhat different. Soop et al. (1988) imposed a submaximal exercise intensity (50% of $\dot{V}O_{2max}$) and Greig et al. (1987) gave 2-g L-carnitine·day$^{-1}$ for 2 weeks without indicating the time interval between the last administration and the exercise trial. This interval is relevant considering that orally administered L-carnitine reaches its maximal level in the plasma in approximately 2 h (Harper et al. 1988); at this time the most obvious effects of administered L-carnitine should be expected. The increase in the average of $\dot{V}O_{2max}$ after L-carnitine administration has previously been observed by Marconi et al. (1985) and Angelini et al. (1986). One explanation applicable to our moderately trained subjects is that after placebo they stopped exercising due to muscle pain or exhaustion, before they could reach their $f_{cmax}$. Against this interpretation, however, is the fact that similar results from selected endurance athletes have been reported by Marconi et al. (1985). Also, in our experiments, no difference has been found among subjects of different physical power (Fig. 2). Another possibility is the enhancement, in the presence of carnitine, of mitochondrial oxidation of carnitine-requiring substrates and the consequent increased demand for oxygen (see the increase of the average $\dot{V}O_{2max}$ in Table 2). This might have occurred both in muscles in the aerobic phase of exercise, as well as in other tissues (liver and brain) less intensely involved. Furthermore, the stimulation of pyruvate dehydrogenase activity by carnitine (see below) and the consequent increased utilization of pyruvate in mitochondria may have further increased oxygen utilization, compatible with its availability. It must be noted that mitochondria are the target of carnitine action and that ultimately $\dot{V}O_{2max}$ reflects the person's capacity for the resynthesis of adenosine 5'-triphosphate in mitochondrial oxidative phosphorylation (Di Prampero 1986). The significantly higher output at maximal exercise intensity (Table 2) is not easily explained because of the different mechanisms which are most probably involved. Two possible explanations are:

1. In physical exercise, fatty acid supply to muscles generally exceeds the energy requirement or oxygen availability (Bjorkman 1986). The consequent excess of acyl-coenzyme A (acyl-CoA) has many adverse effects (Brecher 1983) which might decrease effective energy production. It is known that long-chain acyl-CoA may act both as uncouplers as well as inhibitors of adenylate translocase (Paulson and Shug 1984). Although in pathological conditions and at rest, endogenous carnitine should be sufficient to prevent the damaging accumulation of these noxious amphiphiles, during strenous exercise carnitine might not be available in sufficient quantities. The consequent accumulation of long-chain acyl-CoA may induce a transient uncoupling state

which would explain the lower power output, achievable at the maximal exercise intensity, of the placebo treated subjects. Administration of L-carnitine might prevent, or reduce, acyl-CoA accumulation, thereby improving the power output.

2. An additional carnitine function is the buffering of the intra-mitochondrial acetyl CoA:CoA ratio. In muscle mitochondria, endowed with a high CoA:carnitine acetyl transferase (Bremer 1983), the excess of acetyls accumulated during strenous exercise may be exported from mitochondria, provided that free carnitine is available. Indeed, Hiatt et al. (1989) have shown that free carnitine content of human skeletal muscle falls dramatically with high intensity exercise as short-chain acyl carnitines are generated. Furthermore, we have recently shown that L-carnitine administration under the conditions herein described induced a significant increase of acetylcarnitine in blood and urine (Siliprandi et al. 1990). A consequence of the removal of acetyls from mitochondria is an increase in the pyruvate dehydrogenase activity (Uziel et al. 1988). Thus, administration of L-carnitine might preferentially increase the rate of aerobic glycolysis, thereby the energy yield of glucose utilization. Notably, the augmented pyruvate dehydrogenase flux, in our case afforded by carnitine via a decrease of the acetyl CoA:CoA ratio, seems to expedite cellular energization (Bünger et al. 1989). Furthermore, as pointed out by Zweier and Jacobus (1987) on the basis of their results with nuclear magnetic resonance spectroscopy in perfused hearts, the oxidative utilization of pyruvate would result in an establishment of a higher steady-state cytosolic phosphorylation potential and in an augmented contractile performance. The same authors have also found that switching from glucose to pyruvate as substrate induced a significant increase in the $\dot{V}O_2$ consumption which may account, in part, for the higher $\dot{V}O_{2\,max}$ reported in this paper as well as by previous authors (Marconi et al. 1985; Angelini et al. 1986).

The extent to which such a carnitine action may account for the observed decrease in blood lactate concentration (Fig. 1) would require a quantitative estimate of the pyruvate dehydrogenase flux, that is, knowledge of the time course of the concentration changes of both carnitine and CoA esters in muscle. This is made necessary by the fact that lactate diffuses readily into the blood stream, while carnitine and its esters are taken up slowly and released from tissues in a well-regulated process. (Siliprandi et al. 1989). This is the reason why, as demonstrated by Hiatt et al. (1989), the variations of carnitine fractions in muscle poorly reflect the plasma and urine levels. However, even if, for the above mentioned reasons, the overall production of short-chain acyls could not be quantified, their removal (Siliprandi et al. 1990) seems to be the only reasonable mechanism underlying the observed decrease of blood lactate concentration induced by carnitine administration.

*Acknowledgements.* This work was supported in part by Sigma Tau S.p.A. Pomezia (Rome), Italy. We are grateful to Prof. P. Jocelyn (Edinburgh, UK) and Prof. P. E. Di Prampero (Udine, Italy) for helpful discussion and to Dr. A. Cessario for suggestions for improvements of the manuscript.

## References

Angelini C, Vergani L, Costa L, Martinuzzi A, Dunner E, Marescotti C, Nosadini R (1986) Use of carnitine in exercise physiology. Adv Clin Enzyme 4:103–110

Bjorkman O (1986) Fuel utilization during exercise. In: Benzi G, Packer L, Siliprandi N (eds) Biochemical aspects of physical exercise. Elsevier, Amsterdam, pp 245–260

Brecher P (1983) The interaction of long-chain acyl-CoA with membranes. Mol Cell Biochem 57:3–15

Bremer J (1983) Carnitine metabolism and functions. Physiol Rev 63:1430–1480

Bünger R, Mallet RT, Hartman DA (1989) Pyruvate-enhanced phosphorylation potential and inotropism in normoxic and postischemic isolated working heart. Near-complete prevention of reperfusion contractile failure. Eur J Biochem 180:221–233

Carlin JJ, Redoan WG, Sanjak M, Hodach R (1986) Carnitine metabolism during prolonged exercise and recovery in humans. J Appl Physiol 55:489–495

Ciman M, Caldesi-Valeri V, Siliprandi N (1978) Carnitine and acetylcarnitine in skeletal and cardiac muscle. Int J Vitam Nutr Res 48:177–181

Di Prampero PE (1986) Central and peripheral factors limiting $\dot{V}O_{2\,max}$ in humans. In: Benzi G, Packer L, Siliprandi N (eds) Biochemical aspects of physical exercise. Elsevier, Amsterdam, pp 63–71

Foster CVL, Harris RC (1987) Formation of acetylcarnitine in muscle of horse during high intensity exercise. Eur J Appl Physiol 56:639–642

Gollnick PD (1986) Adaptation in skeletal muscle to endurance training: implication for metabolic control and performance. In: Benzi G, Packer L, Siliprandi N (eds) Biochemical aspects of physical exercise. Elsevier, Amsterdam, pp 159–169

Greig C, Finch KM, Jones DA, Cooper M, Sargeant AJ, Forte CA (1987) The effect of oral supplementation with L-carnitine on maximum and submaximum exercise capacity. Eur J Appl Physiol 56:457–460

Gutmann I, Wahlefeld AW (1974) L-(+)-lactate. Determination with lactate dehydrogenase and NAD. In: Bergmeyer HU (ed) Methods of enzymatic analysis. Verlag Chemie, Weinheim, pp 1464–1468

Harper P, Elwin CE, Cederblad G (1988) Pharmacokinetics of intravenous and oral bolus doses of L-carnitine in healthy subjects. Eur J Clin Pharmacol 35:555–562

Harris RC, Foster CVL, Hultman E (1987) Acetylcarnitine formation during intense muscular contraction in humans. J Appl Physiol 63:440–442

Hiatt WR, Regenstein JG, Wolfel EE, Ruff L, Brass EP (1989) Carnitine and acetylcarnitine metabolism during exercise in humans. J Clin Invest 84:1167–1173

Holloszy JO, Coyle EF (1984) Adaptation of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol 56:831–838

Lennon DLF, Stratman FW, Shrago E, Nagle FJ, Madden M, Hanson P, Carter AL (1983) Effects of acute moderate intensity exercise on carnitine metabolism in man and woman. J Appl Physiol Respir Environ Exerc Physiol 55:489–495

Marconi C, Sassi G, Carpinelli A, Cerretelli P (1985) Effects of L-carnitine loading on the aerobic and anaerobic performance of endurance athletes. Eur J Appl Physiol 54:131–135

Paulson DJ, Shug AL (1984) Inhibition of the adenine nucleotide translocator by matrix-localized palmitoyl-CoA in heart mitochondria. Biochim Biophys Acta 766:70–76

Siliprandi N, Sartorelli L, Ciman M, Di Lisa F (1989) Carnitine: metabolism and clinical chemistry. Clin Chim Acta 183:3–12

Siliprandi N, Di Lisa F, Pieralisi G, Ripari P, Maccari F, Menabo' R, Giamberardino MA, Vecchiet L (1990) Metabolic changes induced by maximal exercise in human subjects following L-carnitine administration. Biochim Biophys Acta 1034:17–21

Soop M, Björkman O, Cederblad G, Hagenfeldt L, Wahren J (1988) Influence of carnitine supplementation on muscle substrate and carnitine metabolism during exercise. J Appl Physiol 64:2394–2399

Uziel G, Garavaglia B, Di Donato S (1988) Carnitine stimulation of pyruvate dehydrogenase complex (PDHC) in mitochondria isolated from human skeletal muscle. Muscle Nerve 11:722–724

Zweier JL, Jacobus WE (1987) Substrate-induced alterations of high-energy phosphate metabolism and contractile function in the perfused heart. J Biol Chem 263:8015–8021