ABOUT carnitine

Beneficial Effects of Carnitine Use on Myocardial Function

ABOUT PUBLISHING

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Benefical Effects of Carnitine Use on Myocardial Function

ISBN 978-88-97719-16-8

Health Publishing & Services S.r.l.
Piazza Duca d'Aosta 12 – 20124 Milan, Italy
Via Nairobi 40 – 00144 Rome, Italy

Printed by Litografia Bruni S.r.l. - Pomezia (RM) in August 2014.

by Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

SGT292-13_HCC

Summary

CARNITINE IN DOXORUBICIN CARDIOTOXICITY

Introduction

Fatty acids (FAs) enhance energy production through β-oxidation in the mitochondria and L-carnitine is essential in this pathway, because the inner membrane of the mitochondria does not transport FAs without the action of L-carnitine[1].

Oxidation of FAs accounts for the vast majority of adenosine triphosphate (ATP) generation in the healthy adult heart. In particular, cardiac muscle cells meet 90% of their ATP demands by oxidizing FAs. Although these proportions may fall to about 60% depending on the nutritional status and the intensity of contractions, fatty acids are considered the major fuel consumed by cardiac muscle. Skeletal muscle cells also oxidize lipids. Indeed, fatty acids are the main source of energy in skeletal muscle during rest and mild-intensity exercise[2].

L-carnitine is widely distributed in nature, especially in red meats and dairy products. In normal human omnivores (non-vegetarians), approximately, 75% of L-carnitine is obtained from the diet. The percentage not obtained from food is synthesized endogenously from two essential amino acids, lysine and methionine. This occurs in kidney, liver and brain[3,4].

Metabolically, L-carnitine performs four key activities, strictly linked to cell metabolic life. Besides its primary role in the mitochondrial oxidation of long-chain FAs, L-carnitine is also involved in buffering of the acyl coenzyme A (CoA)-CoA ratio, branched-chain amino acid metabolism, removal of excess acyl groups and peroxisomal fatty acid oxidation. L-carnitine also participates in metabolism of branched chain aminoacids and stabilizes cellular membranes (*Table 1*)[5,6].

As skeletal and cardiac muscles are the richest tissues in L-carnitine, it is just in these tissues that a L-carnitine deficiency causes the most striking evidence of structural and metabolic alterations[7,8].

Table 1. Main physiological functions of L-carnitine (adapted from[6])

Long-chain fatty acids mitochondrial transport and β-oxidation with ATP production
Removal of toxic compounds of fatty acid metabolism from the mitochondria and eventual excretion in the urine
Modulation of the mitochondrial acetyl-CoA/free CoA ratio
Stabilization of cell membranes and prevention of apoptosis

CoA=coenzyme A.

L-carnitine deficiency is a metabolic impairment in which L-carnitine concentrations in plasma and tissues are less than the levels required for normal function of the organism. Biologic effects of low L-carnitine levels may not be clinically significant until they reach less than 10-20% of normal. The endogenous plasma levels of free L-carnitine in the healthy human are 40-50 μmol/L[9].

Pathological manifestations of chronic L-carnitine deficiency include accumulation of neutral lipids within skeletal and cardiac muscle paving the way to life-threatening alterations of these tissues[4,10].

Accumulation of FAs in the cytoplasm is highly toxic to cell membranes and structure; they contribute to insulin resistance and are elevated in obesity and type 2 diabetes[11-13]. Recent studies suggested that FAs also exert negative effects on the vessel wall by triggering endothelial apoptosis and impairing endothelium-dependent vasodilation[14,15]. The involvement of FAs in atherosclerosis is supported by observations of an increased risk for cardiovascular disease (CVD) associated with high levels of FAs (*Figure 1*)[10,16,17].

Although L-carnitine is supplied exogenously as a component of the diet and can also be synthesized endogenously, evidence suggests both primary and secondary deficiencies do occur. Carnitine deficiency can be acquired or a result of inborn errors of metabolism.

Primary carnitine deficiencies (PCDs) are caused directly by insufficient carnitine content, typically characterized by impaired fatty acid oxidation, and are not associated with any other systemic disease state. Patients with PCDs develop progressive cardiomyopathy, encephalopathy and muscle weakness, resulting in death from heart failure. For these patients, L-carnitine supplementation is a life-saving treatment[18].

Secondary carnitine deficiency, more common than PCD, can result either from a genetic or an acquired condition that result in a decrease in plasma or tissue carnitine levels. Hereditary causes include genetic defects in amino-acid degradation or certain lipid disorders[19].

Malfunction of the kidney can result in increased urinary losses of carnitine that lead to depletion of carnitine. Further, patients with renal disease who undergo hemodialysis are at risk for secondary carnitine deficiency because hemodialysis removes carnitine from the blood[20].

The finding in experimental animals and human studies that the failing myocardium has a low content of L-carnitine supports the concept that CVD is often ac-

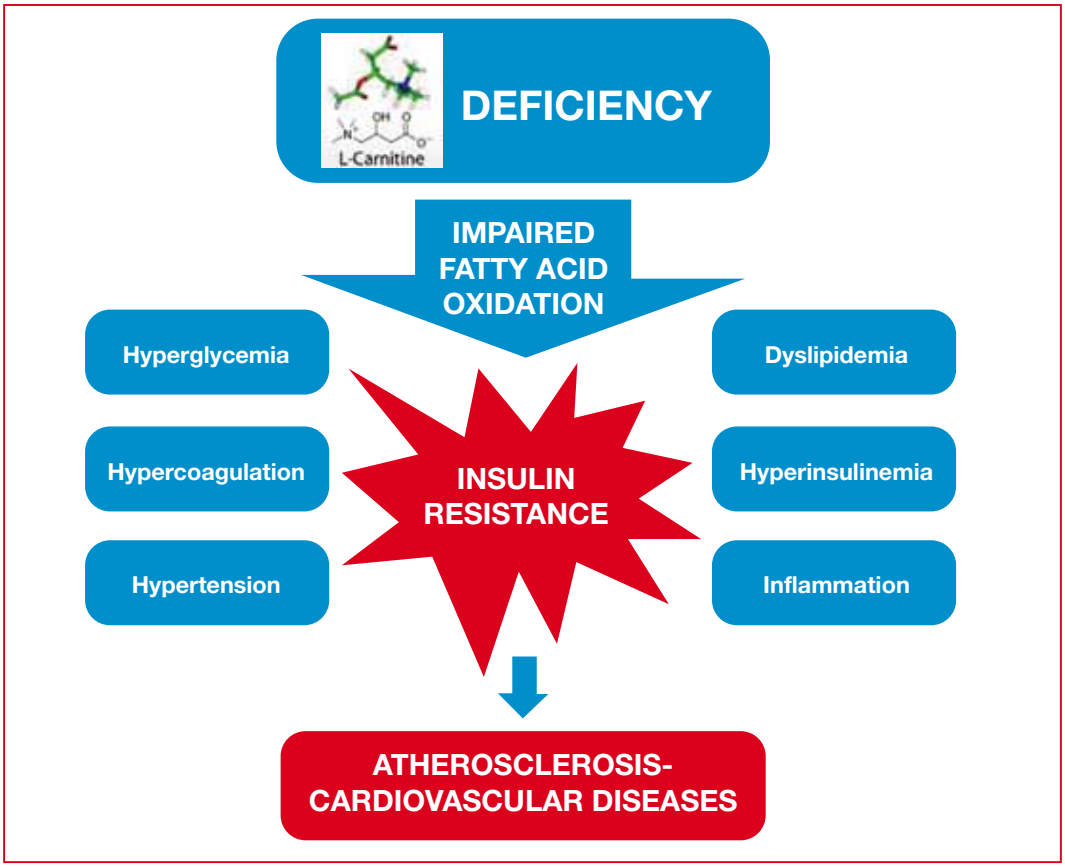

Figure 1. L-carnitine deficiency in the pathogenesis of insulin resistance (adapted from[10,17]).

companied by carnitine deficiency most likely due to a combination of increased utilization and the inability of myocardiocytes to synthesize carnitine endogenously[1]. Cardiac ischemia is well recognized in the literature to be accompanied by a rapid depletion in myocardial carnitine content and a concurrent rise in intracellular long chain free FAs[21]. In patients with heart failure (HF), serum carnitine has been correlated with impaired left ventricular systolic function as measured by echocardiography[22]. During ischemia L-carnitine is thought to offset rising concentrations of free fatty acids by facilitating mitochondrial uptake and utilization, thereby preventing the damaging effects of elevated free FAs: membrane damage with consequent cell swelling and microvascular compression, arrhythmias, and metabolic inefficiency with consequent deterioration of myocardial function[23]. In addition to its facilitating FAs transport into the mitochondria, L-carnitine performs a second key metabolic function: the removal from the mitochondria of short and medium chain fatty acids (acetyl groups) formed as products of β-oxidation and bound to CoA as acetyl-CoA. Mitochondrial accumulation of this product is toxic and has been implicated in the development of insulin resistance in skeletal muscle and heart[17].

The primary feature of HF is myocardial dysfunction (systolic or diastolic) and accordingly, improving myocardial function is the most important target for therapy.

HF is a syndrome which develops as a consequence of cardiac disease, and is recognized clinically by a constellation of symptoms and signs produced by complex circulatory and neurohormonal responses to cardiac dysfunction[24]. The manifestation of the clinical syndrome of chronic HF is a result of a complex process leading to alterations of cellular and molecular components in the myocardium. This process of gradual transition from cardiac dysfunction into manifest chronic HF is referred to as "cardiac remodeling".

An important change in energy metabolism observed in hypertrophied and failing hearts is the shift in the preference of substrates for energy generation. Although the heart is able to utilize a variety of substrates, preference in substrate utilization has been documented and it can change in response to altered substrate availability or altered regulation of metabolic pathways. As illustrated in *Figure 2A*, healthy cardiomyocyte mainly uses FAs that enter into the cell and are converted in the mitochondria through the carnitine palmitoyltransferase type 1 and type 2 (CPT-1 and CPT-2), and the carnitine acylcarnitine translocase (CT) before being used by β-oxidation to produce $FADH_2$, H_2O, NADH and acetyl-

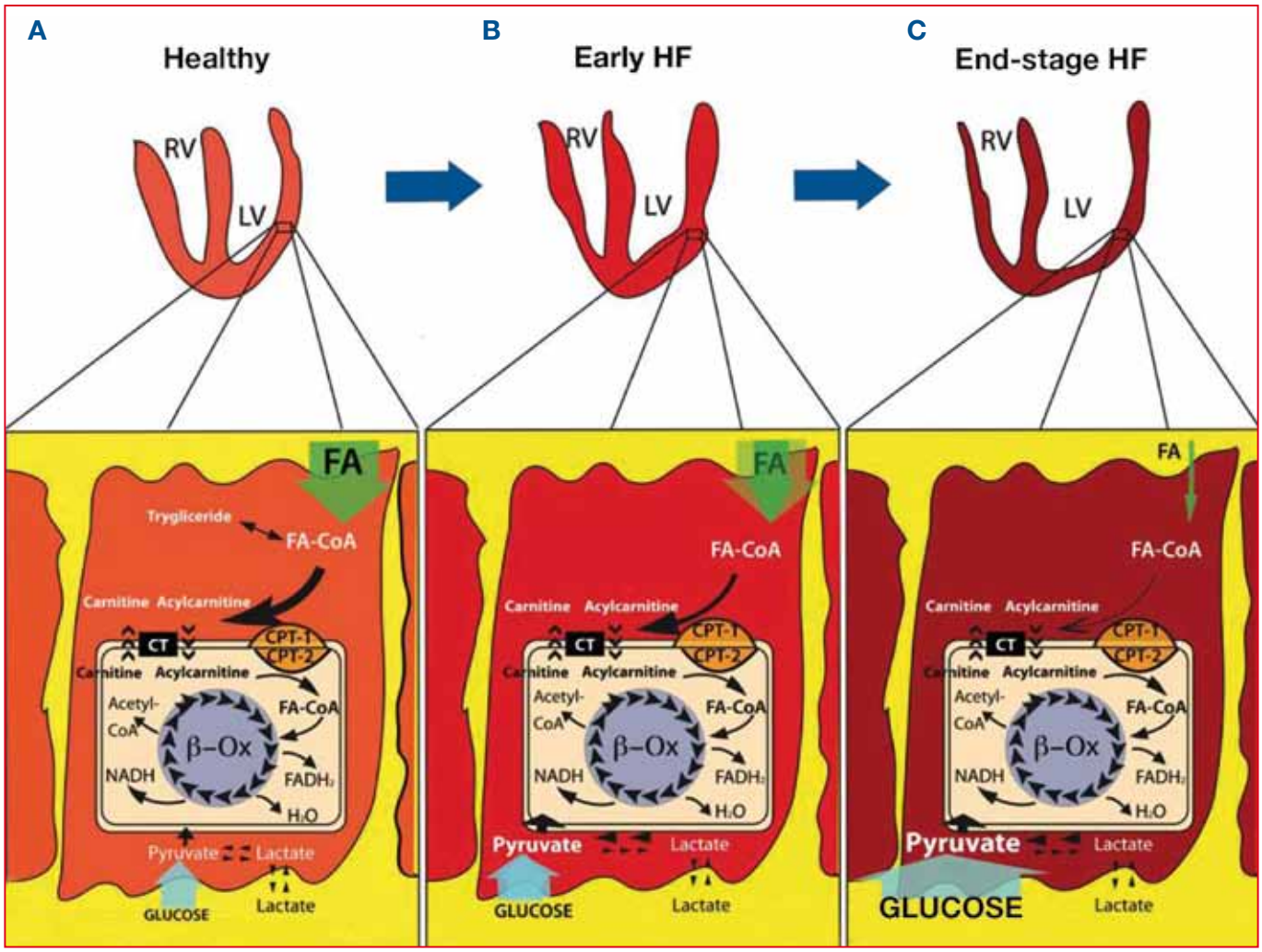

Figure 2. Cardiomyocyte substrates utilization. (A) Healthy cardiomyocyte. (B) Early HF cardiomyocyte. (C) End-stage HF cardiomyocyte. β-Ox=β-oxidation; CPT=carnitine palmitoyltransferase; CT=carnitine acylcarnitine translocase; FA=fatty acid; FA-CoA=fatty acyl-coenzyme A; $FADH_2$=reduced form of flavine adenine dinucleotide; HF=heart failure; LV=left ventricle; NADH=reduced form of nicotinamide adenine dinucleotide; RV=right ventricle (adapted from[25]).

CoA[25]. Glucose and lactate enter into the cells and are transformed into pyruvate by glycolysis and lactate dehydrogenase, respectively. During the development of cardiac hypertrophy and progression to HF, the myocardial energy source switches from fatty acid oxidation to glycolysis and myocardial ATP content can decrease and can drop to 60–70% of normal levels (*Figure 2B*)[25].

This altered fuel selection is a reversion to the fetal energy substrate preference pattern which may initially be a structural and metabolic adaptive response of the overloaded ventricle to maximize efficiency and decrease oxygen consumption. In particular it appears to involve changes in the transcriptional control of genes implicated in the transport and metabolism of fatty acids and glucose, which are mainly regulated by a class of transcription factors termed peroxisome proliferator-activated receptors (PPARs)[24].

At the organ level, the remodeling process results in increased LV mass and volumes and changes in cardiac geometry and the heart becomes more spherical and less elliptical. These changes help maintain cardiac output in the short term, but lead to a progressive loss of myocardial function and finally to development of overt chronic HF (*Figure 2C*)[25-29].

Alternatively, the inability to metabolize fatty acids in the presence of excess availability may be associated with accumulation of non-oxidized toxic fatty acid derivatives, resulting in lipotoxicity[30]. In fact, this metabolic profile is inefficient in utilizing carbon substrates for ATP production during increased energy demand as only two-thirds of the carbon found in glucose is oxidized compared with the complete oxidation of fatty acid[31,32].

Modern therapies for HF, such as angiotensin-converting-enzyme-inhibition, β-blockade, aldosterone an-

tagonism, diuretics, digoxin and inotropic agents have all been shown to attenuate clinical symptoms and slow the progression of contractile dysfunction and expansion of LV chamber volume, however they do not target the metabolic needs of the failing heart and progression can still be observed; the prognosis remains poor even for optimally treated patients[33,34].

In this context, targeting the cardiac metabolic pathways using L-carnitine may represent a suitable therapeutic intervention[35]. Clinical experience has shown that supplementation with L-carnitine can improve myocardial function in patients with PCD. A rapid, dramatic clinical response characterized by improvement in cardiac function has been noted in patients with PCD treated with supplemental L-carnitine[36-40]. Other signs of improvement in cardiac function in carnitine-treated patients include decreases in LV-chamber dimensions. Some investigators have also reported a reduction in the amplitude of abnormally high T-waves recorded in the precordial leads[41].

These data provide strong evidence to suggest that L-carnitine therapy may reverse the cardiac manifestation of L-carnitine deficiency.

L-carnitine has also been found to improve tachycardia and exercise tolerance and to reduce signs and symptoms of ischemia in patients with coronary artery disease. Maintenance of adequate carnitine reserves may also help to preserve myocardial function improving the metabolic derangements associated with ischemia in patients undergoing aortocoronary bypass surgery[42]. Several studies also suggest that carnitine may have potential in the prevention of cardiac arrhythmias and the cardiotoxicity associated with anthracycline therapy[43-45]. Oral and intravenous L-carnitine has been shown to be beneficial for a number of cardiovascular conditions[46,47]. Thirteen controlled trials, that have examined the effect of L-carnitine in the treatment of acute myocardial infarction (AMI), indicated that carnitine administration subsequent AMI may have the potential to reduce risk for ventricular arrhythmias and sudden cardiac death; decrease the extent of cardiac necrosis, postinfarct cardiac remodeling, and ventricular dilatation; lessen the damage to the microvasculature that often impedes restoration of appropriate cardiac blood flow following thrombolytic therapy; and improve survival (*Table 2*)[48]. A recent meta-analysis found analogous results with a 27% decrease in all-cause mortality, a 65% decrease in the incidence of ventricular arrhythmias and a 40% decrease in the incidence of angina in 3629 patients experiencing AMI[49]. Thus, based on the totality of the clinical evidence, as much as 4 grams L-carnitine per day administered up to 12 months not only improved cardiac function, but also increased life expectancy.

Table 2. Benefits of L-carnitine administration in patients with acute myocardial infarction (adapted from[48])

Reduced risk for ventricular arrhythmias*
Decreased necrosis and infarct size
Decreased oxidative stress
Decreased ventricular remodeling
Reduced risk for angina*
Decreased risk for vascular events
Decreased mortality*

**Confirmed by meta-analysis.*

The main aim of the current collection of papers is to focus on the discussion of the clinical data supporting the beneficial effects of L-carnitine supplementation on myocardial function.

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Clinical presentation and therapeutic outcomes of carnitine deficiency-induced cardiomyopathy

Fu LJ, Chen SB, Han LS et al.

Zhonghua Er Ke Za Zhi 2012;50(12):929-34

BACKGROUND AND AIM

- L-carnitine deficiency has been associated with progressive cardiomyopathy due to compromised energy metabolism that often leads to heart failure or sudden cardiac death. Early recognition of the disease and treatment with L-carnitine may be life-saving.
- The aim of this study was to investigate clinical features of carnitine deficiency-induced cardiomyopathy and the therapeutic efficacy of L-carnitine administration.

MATERIALS AND METHODS

- Between January 2010 and December 2011, free carnitine and acylcarnitine profiles were measured in 75 children with cardiomyopathy by tandem mass spectrometry (MS/MS). For those in whom carnitine deficiency was demonstrated, treatment was begun with L-carnitine at a dose of 150-250 mg/kg/day.
- Clinical evaluation, including physical examination, electrocardiography, chest x-ray, echocardiography and MS/MS, was performed before treatment and during follow-up beyond 6 months of treatment.

RESULTS

- Of 75 cardiomyopathy patients, the diagnosis of carnitine deficiency was confirmed in 6 patients (1 boy and 5 girls) ranged from 0.75 to 6 years of age.
- After 10-30 days of therapy with L-carnitine, free carnitine levels significantly increased to 30.59 ± 15.02 μmol/L ($p<0.01$). Left ventricular end-diastolic diameter (LVDd) significantly decreased to 4.42 ± 0.67 cm ($p<0.01$) and left ventricular ejection fraction (LVEF) significantly increased to 49.1 ± 7.6% ($p<0.01$) [*Figure panel A* and *B*].
- Follow-up evaluations showed dramatic clinical improvement with LVEF that returned to normal completely in all the 6 patients (*Figure panel B*) and LVDd that decreased in all the 6 patients and returned to normal levels in 3 patients.

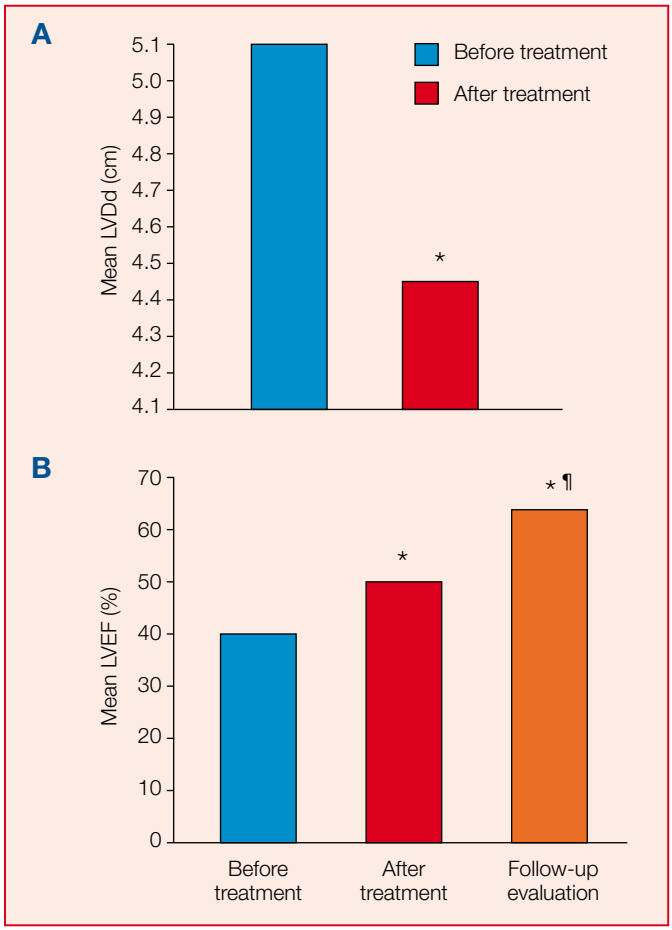

Figure. A Mean LVDd values (cm) before and after treatment and **B** Mean LVEF values (%) before and after treatment and at follow-up evaluation (*$p<0.01$ *vs* before treatment, ¶$p<0.01$ *vs* after treatment). LVDd=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction.

KEY POINTS

- L-carnitine has a good therapeutic effect in children with carnitine deficiency-induced cardiomyopathy
- In these patients, L-carnitine supplementation is associated with rapid beneficial effects characterized by improvement in cardiac function

The effects of L-carnitine treatment on left ventricular function and erythrocyte superoxide dismutase activity in patients with ischemic cardiomyopathy

Gürlek A, Tutar E, Akçil E et al.

Eur J Heart Fail 2000;2(2):189-93

BACKGROUND AND AIM

- The rationale for the use of L-carnitine in patients with ischemic heart disease initially originated from the finding that myocardial carnitine concentrations were lower in these patients. It was also shown that there is a role of oxygen free radicals in the pathogenesis of post-ischemic myocardial dysfunction after acute myocardial infarction.
- Increase in erythrocyte superoxide dismutase (SOD) activity was a sign of increased oxidative stress in patients with ischemic cardiomyopathy.
- The aim of this study was to study the effects of L-carnitine on left ventricular systolic function and SOD activity.

MATERIALS AND METHODS

- A total of 51 patients with the diagnosis of ischemic cardiomyopathy was randomized into two groups on a 3:2 basis. In group I (n=31), 2 g/day oral L-carnitine was added to therapy (angiotensin-converting enzyme inhibitor, digitalis and diuretics). L-carnitine was not given to the other 20 patients (group II). 20 age-matched healthy subjects constituted the control group.
- In each group, left ventricular ejection fraction (LVEF) by echocardiography and SOD activity by spectrophotometric method were measured initially and after 1 month of randomization.

RESULTS

- At the end of 1 month of L-carnitine therapy, LVEF showed a significant improvement in the L-carnitine group with a mean percent increase of +12.5% (*Figure*).
- Red cell SOD activity also showed an increase in group I (5918±1448 to 7218±1917 U/g Hb, p<0.05). In group II, red cell SOD activity showed no significant change after 1 month of randomization.

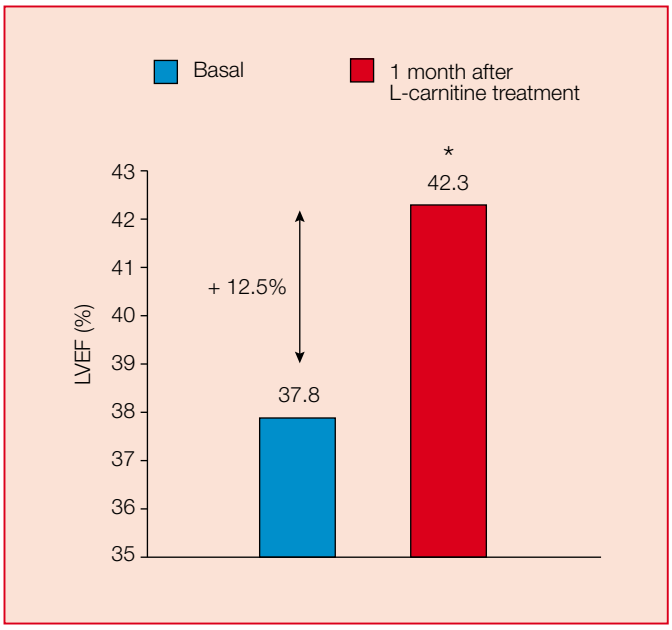

Figure. LVEF improvement in L-carnitine group at the end of 1 month of treatment (*p<0.001 *vs* basal). LVEF=left ventricular ejection fraction.

KEY POINT

- Prescription of 2 g/day carnitine for 1 month has a useful effect on the function of left ventricle in patients suffering ischemic cardiomyopathy

Metabolic aspects of myocardial disease and a role for L-carnitine in the treatment of childhood cardiomyopathy

Helton E, Darragh R, Francis P et al.

Pediatrics 2000;105(6):1260-70

BACKGROUND AND AIM

- Cardiomyopathy is an associated symptom in metabolic disorders, where the intra-mitochondrial accumulation of toxic organic acid intermediates leads to the depletion of L-carnitine.
- The aim of this study was to investigate the possible metabolic causes of pediatric cardiomyopathy and evaluate the outcome of patients treated with L-carnitine.

MATERIALS AND METHODS

- In this multicenter retrospective study, 76 patients diagnosed with cardiomyopathy were treated with L-carnitine (mean dose of 96 mg/kg/day) in addition to conventional cardiac treatment and 145 patients were treated with conventional treatment only (control group).
- The duration of L-carnitine treatment ranged from 2 weeks to >1 year. Information was collected on length of survival (time-to-event), clinical outcome, echocardiogram parameters and clinical assessments.

RESULTS

- L-carnitine treated patients showed lower mortality from cardiomyopathy (6.8% *vs* 17.9%) and less transplantation (9.6% *vs* 15.0%) than control patients (*Figure*). The distribution of clinical outcomes was significantly different (p=0.010) in an overall sense.
- Unexpectedly, the patients treated with ACE inhibitors (40%) revealed significantly poorer survival *versus* who did not receive ACE inhibitors (p=0.0001).
- A significant improvement in survival was observed for L-carnitine treated patients who did not receive ACE inhibitors *versus* control patients (p=0.046).

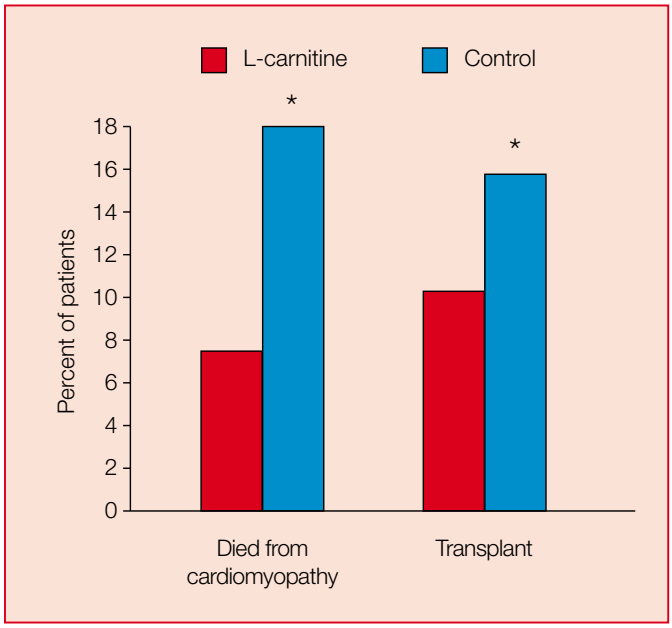

Figure. Cardiomyopathy-related death and transplantation in L-carnitine and control patients (*p=0.010).

KEY POINTS

- L-carnitine supplementation is the keystone of treatment for pediatric cardiomyopathy with significant improvement in clinical severity and functioning in myocardial disease
- In the L-carnitine treated group, the poorer survival of ACE inhibitor treated patients may be the most supportive to the benefits from L-carnitine treatment

Prolonged oral L-carnitine substitution increases bicycle ergometer performance in patients with severe, ischemically induced cardiac insufficiency

Löster H, Miehe K, Punzel M et al.

Cardiovasc Drugs Ther 1999;13(6):537-46

BACKGROUND AND AIM

- Previous studies showed that L-carnitine increases performance and exercise tolerance in patients treated for ischemically induced cardiac diseases and insufficiency. The mechanism of how L-carnitine exerts its effect on exercise tolerance is explained with a beneficial effect on the disturbed metabolism of the heart.
- This study investigated the effect of L-carnitine on exercise performance in patients with severe cardiac insufficiency. The long-term effect of L-carnitine on exercise performance after treatment discontinuation was also investigated.

MATERIALS AND METHODS

- A total of 41 patients suffering from NYHA (New York Heart Association) class II or III cardiac insufficiency was enrolled in this double-blind, placebo-controlled trial. From the first to 120th day, 20 patients were randomly assigned to receive L-carnitine (3 g/day orally), while the control group (n=21) 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 day 60 and 120 (during L-carnitine or placebo application), and on day 180 (60 days after the end of substitution).

RESULTS

- An improvement in performance could be found within the L-carnitine group on day 60 and 120 of L-carnitine administration (*Figure*). These effects could be detected even 60 days after the end of substitution. At day 180 the mean values of performance in the L-carnitine group were still about 30% higher than those in the placebo group.
- Bicycle ergometry resulted in medium heart rates and in mean systolic blood pressure values that were in tendency decreasing when the longer L-carnitine therapy was continued.

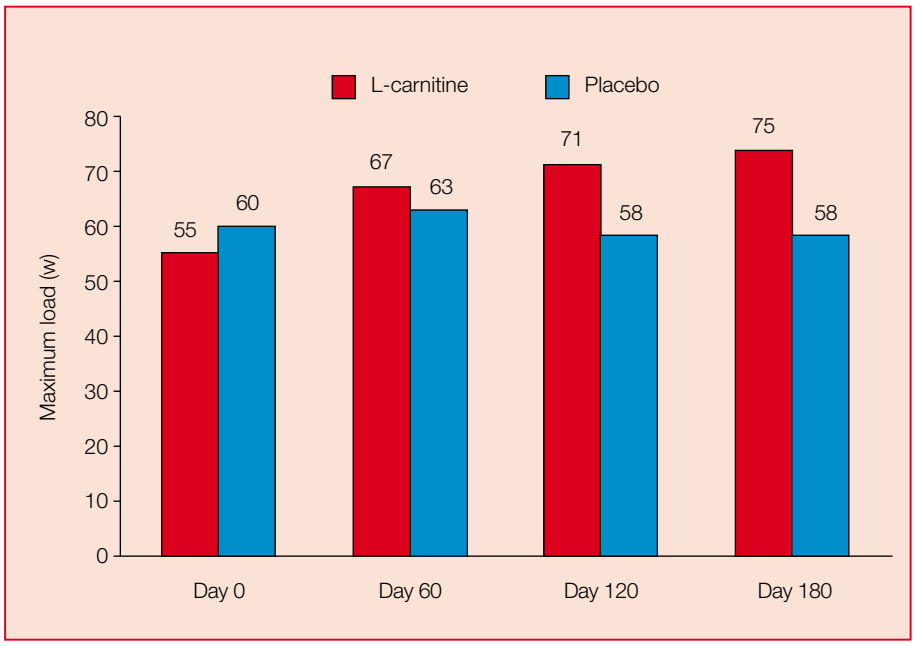

Figure. Mean values of maximum performance of L-carnitine and placebo patients.

KEY POINTS

- L-carnitine supplementation (1 g three times daily for 120 days) resulted in improvements in exercise performance and hemodynamic parameters in patients with ischemia-induced NYHA II or III cardiac insufficiency
- Beneficial effects of L-carnitine continued to persist for up to 60 days after cessation of treatment

Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration

Rizos I.

Am Heart J 2000;139(2 Pt 3):S120-3

BACKGROUND AND AIM

- In adults the course of dilated cardiomyopathy is usually characterized by progressive disability and death that commonly ensues within 6 months to a few years from the onset of symptoms.
- Increased plasma and decreased myocardial carnitine have been described in these patients, but relatively few studies have examined the efficacy and safety of carnitine treatment for cardiomyopathy.
- The aim of this study was examine the efficacy of long-term L-carnitine administration on mortality in adult patients with chronic heart failure caused by dilated cardiomyopathy.

MATERIALS AND METHODS

- A total of 80 patients, with moderate to severe heart failure (NewYork Heart Association classification III to IV) caused by dilated cardiomyopathy, after a 3-month period of stable cardiac function on standard medical therapy, was randomly assigned to receive either L-carnitine (2 g/day orally) or a matched placebo.

RESULTS

- After an average of 33.7 months of follow-up, 70 patients were in the study (33 taking placebo and 37 supplementing with L-carnitine) and at the end of the study period 63 had survived (27 in the placebo group and 36 in the L-carnitine group).
- The 3-year mortality rate was found to be statistically significant in favor of the carnitine group with a mortality rate of only 3% *versus* 18% in the placebo group ($p<0.04$) [*Figure*].

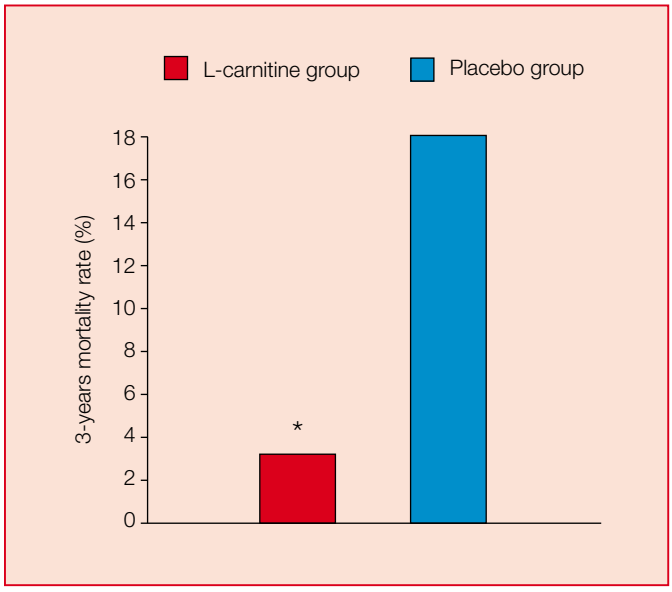

Figure. Three-year mortality rate in placebo and L-carnitine groups (*p<0.04).

- In addition, only 1 patient in L-carnitine group developed arrhythmias compared with 7 in the placebo group.

KEY POINT

- **Long-term treatment with L-carnitine significantly increases the chances of survival in patients with moderate to severe heart failure attributable to dilated cardiomyopathy**

L-carnitine in children with idiopathic dilated cardiomyopathy

Kothari SS, Sharma M.

Indian Heart Journal 1998;50:59-61

BACKGROUND AND AIM

- The utility of L-carnitine in the rare disorder of dilated cardiomyopathy secondary to carnitine deficiency in children has been reported; however, no systematic studies have been conducted.
- The aim of this study was to evaluate the effects of L-carnitine in children with idiopathic dilated cardiomyopathy.

MATERIALS AND METHODS

- 13 children (8 males, 5 females; mean age 3.29 years) who presented with idiopathic dilated cardiomyopathy over a 1-year period were included in this prospective study. All patients had NYHA (New York Heart Association) class III or IV congestive heart failure. Mean duration of symptoms was 9.7 months and mean left ventricular ejection fraction (LVEF) was 36.9%. Symptoms, LVEF and the pre-ejection period/left ventricular ejection time ratio (PEP/LVET) were assessed.
- In group 1, these parameters were recorded after patients had been receiving L-carnitine (50 mg/kg/day) for 3 weeks, and again 3 weeks after stopping L-carnitine. In group 2, parameters were recorded prior to initiation of L-carnitine and after 3 weeks' therapy with L-carnitine.

RESULTS

- The two objective myocardial function parameters that significantly improved during L-carnitine therapy were LVEF and PEP/LVET (*Figure*).
- There was a symptomatic improvement noticed by parents in patient's appetite, wellbeing and social interaction while on L-carnitine treatment. NYHA class improved overall in both groups while on carnitine treatment.

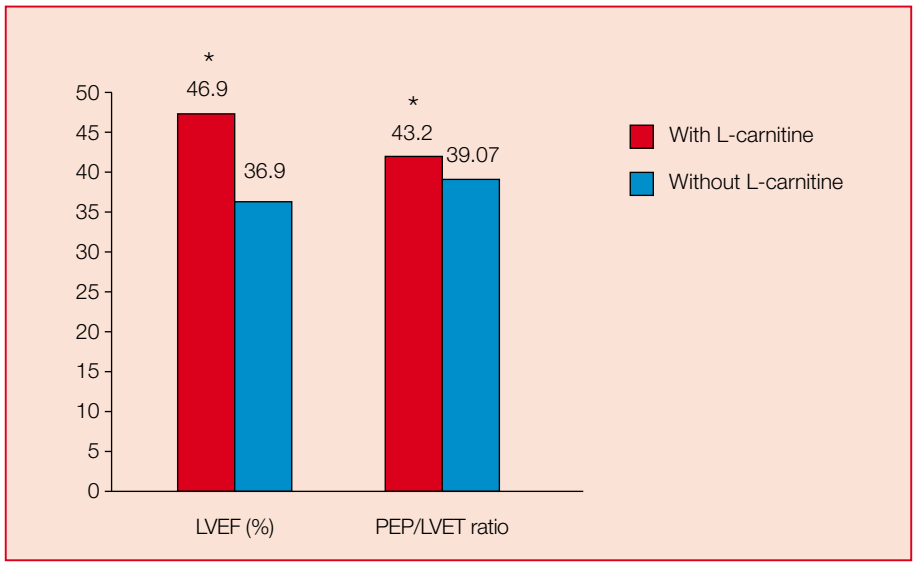

Figure. Myocardial function parameters improved during L-carnitine therapy (*p<0.01 *vs* without L-carnitine). LVEF=left ventricular ejection fraction; PEP/LVET=pre-ejection period/left ventricular ejection time.

KEY POINT

- L-carnitine therapy is beneficial for children with idiopathic dilated cardiomyopathy and leads to an improvement in myocardial function

L-carnitine for treatment of cardiomyopathies

Winter SC, Zorn E, Birek L et al.

Cardiologia 1998;43 (Suppl.2):685-6

BACKGROUND AND AIM

- Inborn errors of energy metabolism, including fatty acid oxidation defects and mitochondrial disorders, often present with skeletal muscle weakness and cardiomyopathy.
- Treatment with L-carnitine can restore metabolism to a more normal state with improvement in muscle tone and strength and myocardial contractility.
- The aim of this study was to evaluate the effect of L-carnitine treatment on disease course and survival in children with cardiomyopathy.

MATERIALS AND METHODS

- In this retrospective chart analysis conducted on 50 pediatric patients with echocardiographic finding of cardiomyopathy (48 with dilated cardiomyopathy and 2 with hypertrophic cardiomyopathy), all children were treated with L-carnitine both intravenous (300 mg/kg/day) during acute illness and oral therapy (100-200 mg/kg/day) after. Length of follow-up was on average 32.7 months.

RESULTS

- The overall survival rate (84%) is exceedingly high with 72% of patients showing complete resolution of cardiomyopathy (*Table*).
- Interestingly, the survival rate in those patients with deficiency or insufficiency of L-carnitine (n=33) was the same of all patients (12% mortality) [*Table*].

Table. Influence of L-carnitine therapy on patient outcome

	Death (%)	Cardiac transplantation (%)	Persistent disease (%)	Complete resolution (%)
All patients (n=50)	12	4	12	72
Patients with disease onset at >24 months of age (n=10)	30	10	20	40
Patients with plasma carnitine deficiency or insufficiency (n=33)	12		6	

KEY POINT

- **L-carnitine therapy improves the outcome of cardiomyopathy even in the absence of carnitine deficiency or insufficiency**

Protective effect of L-carnitine during the cardiosurgery

Fischer V, Rendeková V, Minárová H et al.

Lekarsky Obzor 2000;49:313-8

BACKGROUND AND AIM

- In previous studies the beneficial protective effects of natural antioxidants have been demonstrated in patients undergoing complex cardiosurgical procedures.
- The aim of this study was to assess the protective effect of further natural cell metabolite – L-carnitine – applied to patients undergoing multiple coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass.

MATERIALS AND METHODS

- 20 patients scheduled for CABG were randomly divided in two groups. One group of 10 patients received just before surgery an intravenous infusion of 5 g L-carnitine in isotonic solution of sodium chlorate. The administration of L-carnitine (2 intravenous infusions of 2 g) was repeated during the first postoperative day. In the same time intervals, the second group of patients (control group, n=10) received only intravenous infusions of isotonic solution of sodium chlorate.
- In both groups of patients the blood gas parameters, the activities of creatin kinase-MB, superoxide dismutase and glutathione peroxidase as well as the plasma levels of lactate and uric acid were determined from the beginning of the operation until 44 hours after surgery.

RESULTS

- The administered L-carnitine significantly reduced the rise of plasma lactate level from pulmonary artery and from the coronary sinus (*Table*).
- The plasma level of uric acid also decreased and a stabilization of reduced glutathione erythrocyte concentration – as the most significant endogenous antioxidant – was detected (*Table*).

Table. Beneficial effects of L-carnitine in patients undergoing cardiosurgery (mean values)

	L-carnitine	Placebo	p-value
Plasma lactate level (pulmonary artery; mmol/L)			
20 h post-surgery	8.12	13.50	<0.05
44 h post-surgery	4.05	7.84	<0.01
Plasma lactate level (coronary sinus; mmol/L)			
5 min post-aorta declamping	9.85	15.51	<0.05
Plasma uric acid level (μmol/L)			
36 h post-surgery	908.6	1215.3	
44 h post-surgery	955.5	1291.0	<0.05
Reduced glutathione erythrocyte concentration (μmol/g haemoglobin)			
44 h post-surgery	7.24	5.43	<0.05

KEY POINTS

- L-carnitine was beneficial in patients undergoing the complex cardiosurgery with cardiopulmonary bypass
- L-carnitine markedly decreased the plasma level of lactate and uric acid and augmented the antioxidant capacity of patients

Effect of L-carnitine on cardiomyocyte apoptosis and cardiac function in patients undergoing heart valve replacement operation

Xiang D, Sun Z, Xia J et al.

J Huazhong Univ Sci Technolog Med Sci 2005;25(5):501-4

BACKGROUND AND AIM

- During cardiac operations, myocardial preservation has remained the major concern of cardiac surgeons, because cardiac dysfunction after cardiopulmonary bypass (CPB) is a common clinical problem.
- Several studies showed that total and free carnitine levels were significantly reduced immediately after CPB; these depressed free carnitine levels might affect cardiac metabolism in the heart after open heart surgery.
- The aim of this study was to investigate the myocardial protective effect of L-carnitine, as an ingredient of cardioplegia solution, in patients undergoing heart valve replacement operation.

MATERIALS AND METHODS

- 23 patients undergoing heart valve replacement with CPB were randomly allocated into two groups: L-carnitine group (n=12, 12 g/L) and control group (n=11, identical to the L-carnitine group except that normal saline was administered instead of L-carnitine).
- Serum cardial troponin I (cTnI) levels, the left ventricular ejection fraction (LVEF) and cardiac index (CI) were measured perioperatively. A bit of myocardial tissue obtained from right atrium was taken before CPB and by the end of intracardiac procedure to undergo electron microscopy examination and estimate apoptosis by terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL).

RESULTS

- From the end of CPB to 3 days after operation, the serum levels of cTnI in the L-carnitine group were significantly lower than in the control group (5.71±1.14 ng/mL *vs* 7.87±1.89 ng/mL on 1 day after operation respectively, p<0.05; and 5.01±0.89 ng/mL *vs* 7.53±1.43 ng/mL on 3 day after operation respectively, p<0.05) [*Figure*].
- At 7 day post operation, heart color ultrasonogram demonstrated that the CI and LVEF were significantly higher in the L-carnitine group than in the control group (2.86±0.55 *vs* 2.11±0.35; 64.3±8.6 *vs* 51.7±4.9 respectively, p<0.05).
- Compared to the control group, L-carnitine significantly alleviated the morphologic changes of cardiac muscle cells (electron microscopy examination) and decreased the amounts of apoptotic cardiac muscle cells (TUNEL). Furthermore, the dosage of vasoactive drugs used after operation was significantly less in the L-carnitine group (p<0.01).

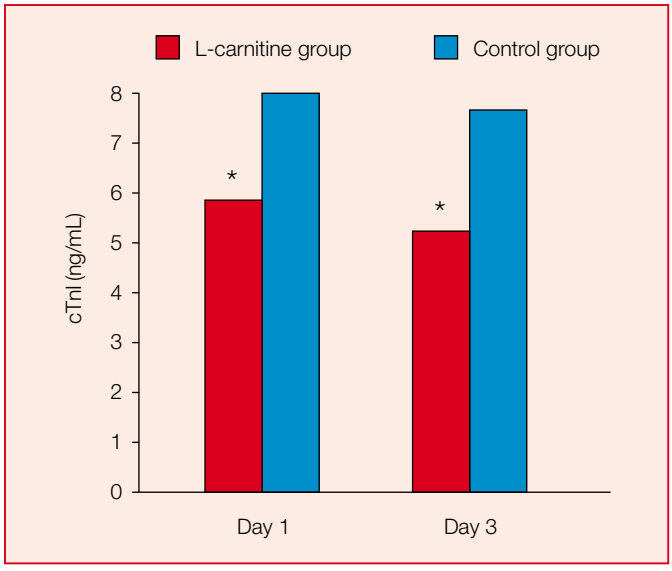

Figure. Serum levels of cTnI in the L-carnitine and control groups on day 1 and 3 after CPB (*p<0.05).

KEY POINT

- L-carnitine is a relevant target to improve cardiac function and reduces apoptosis of cardiomyocytes during cardioplegic myocardial ischemia in patients undergoing heart valve replacement operation

Plasma carnitine concentrations in patients undergoing open heart surgery

Nemoto S, Yasuhara K, Nakamura K et al.

Ann Thorac Cardiovasc Surg 2004;10(1):19-22

BACKGROUND AND AIM

- Changes in cardiac metabolism can lead to decreased cardiac carnitine concentration. In the absence of carnitine, β-oxidation ceases, lipids accumulate, and organ dysfunction results.
- The open heart procedure may be more a factor of impact on the levels of carnitine. Thus it is important to evaluate plasma levels to preserve the myocardial metabolic disorders resulting from deficiency of free carnitine.
- The aim of this study was to determine the incidence of abnormal plasma carnitine concentrations in open heart surgery.

MATERIALS AND METHODS

- 11 patients (mean age 55.5 years) undergoing elective open heart surgery entered the study. Blood samples were obtained before, immediately after, and two hours after cardiopulmonary bypass (CPB). Plasma carnitine profiles (free carnitine [FC], acyl carnitine [AC] and total carnitine [TC]) were determined.

RESULTS

- FC and TC levels were significantly reduced immediately after CPB ($p<0.01$) and remained depressed until two hours after CPB ($p<0.01$ *vs* pre CPB) [*Figure*].
- AC levels were unchanged over the course of this study.

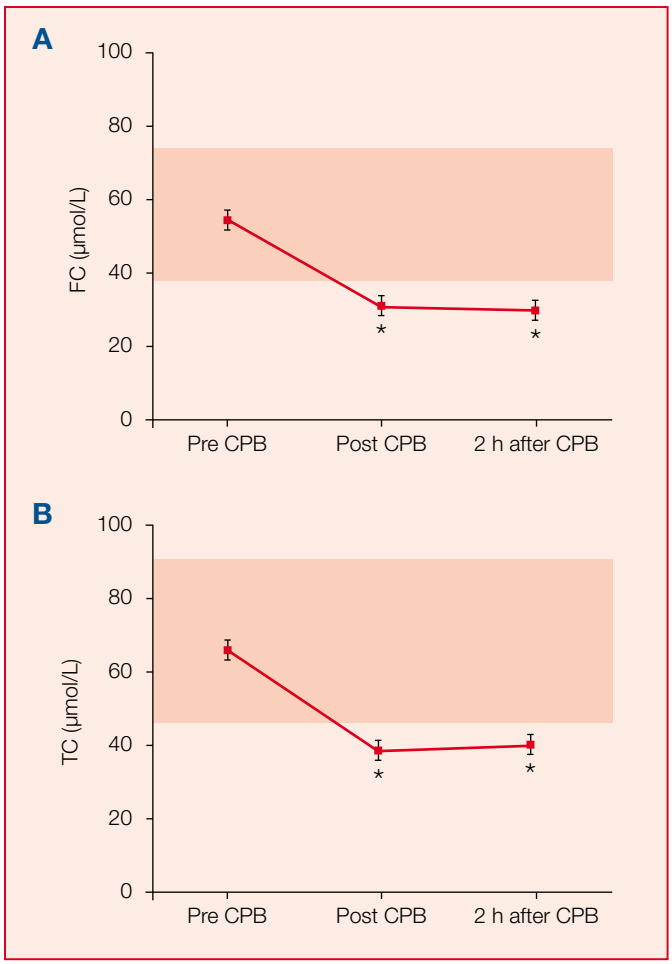

Figure. A Plasma free carnitine (FC) concentration and **B** Plasma total carnitine (TC) concentration before and after cardiopulmonary bypass (CPB) [*$p<0.01$ *vs* pre CPB].

KEY POINTS

- Total and free carnitine levels are decreased during and after cardiopulmonary bypass
- Carnitine supplement could be an effective therapeutic approach to abnormal cardiac metabolism and cardiac dysfunction after open heart surgery

Effect of L-carnitine on myocardial metabolism: results of a balanced, placebo-controlled, double-blind study in patients undergoing open heart surgery

Pastoris O, Dossena M, Foppa P et al.

Pharmacological Research 1998;37:115-22

BACKGROUND AND AIM

- Myocardial carnitine depletion has been reported during ischaemia; since myocardial ischaemia always occurs during open heart surgery, cardiac surgery with cardioplegic arrest represents an experimental model in man for the evaluation of the cardiac effects of carnitine.
- The aim of this study was to determine the effects of L-carnitine on cardiac performance after open heart surgery.

MATERIALS AND METHODS

- In this double-blind study, 38 patients (age 45-70 years; 22 male and 16 female) undergoing elective coronary artery bypass graft surgery (CABG) or mitral valve replacement surgery were randomized to receive placebo (n=19) or L-carnitine (5 g given intravenously twice daily for 5 days pre-surgery and 10 g in 1500 mL cardioplegic solution given at surgery) [n=19].
- The post-ischemic functional recovery of the heart was assessed by clinical parameters as well as by biochemical and ultrastructure evaluations on biopsy specimens.

RESULTS

- After CPB no differences were found between the control and the treatment group with respect to all clinical parameters of cardiac performance; at anaesthesia induction, serum carnitine was significantly increased in treated patients, but right atrial biopsy concentrations were similar in the two groups.
- In patients with mitral valve replacement, L-carnitine was associated with significantly higher concentrations of pyruvate, ATP and creatinine phosphate in papillary muscle (*Figure 1*).
- In the L-carnitine treated patients, myocardial ultrastructure on septal biopsies showed lower scores (indicative of a better myocyte preservation) for all considered parameters (nucleus, sarcoplasmic reticulum, mitochondria and cellular oedema) [*Figure 2*].
- L-carnitine was well tolerated, with no drug-related adverse effects being reported.

KEY POINTS

- **The positive effects of L-carnitine on cardiac recovery after CABG might become clinically relevant in the setting of surgery on haemodynamically compromised patients**
- **The biochemical and ultrastructure assessment data suggest that L-carnitine improves myocardial metabolism**

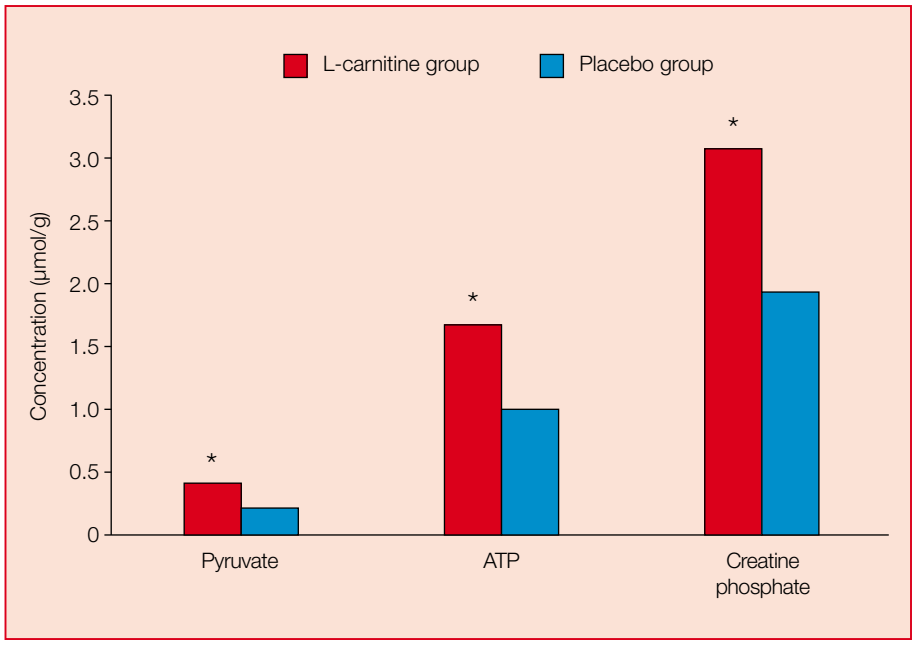

Figure 1. Papillary muscle concentration of energy mediators in patients with mitral valve disease (*p<0.05 *vs* placebo).

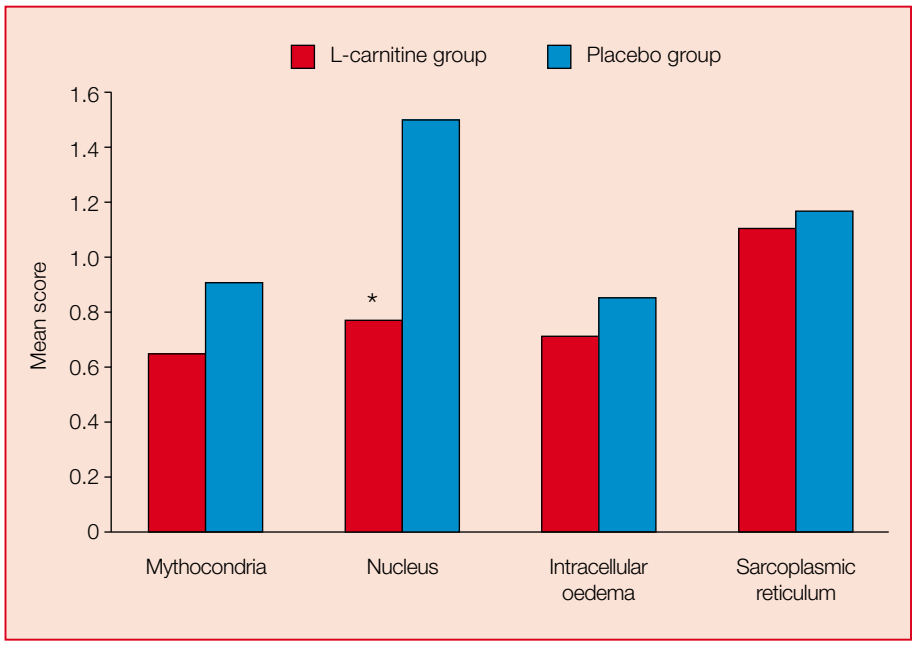

Figure 2. Mean scores (on a 5-point scale; 0=normal to 4=irreversible damage) for ultrastructure parameters on interventricular septum biopsy specimens from patients who received L-carnitine or placebo (*p=0.002 *vs* placebo).

Cardioplegia supplementation with L-carnitine enhances myocardial protection in patients with low ejection fraction

Golba KS, Wos S, Deja MA et al.

Kardiologia Polska 2000;52:181-6

BACKGROUND AND AIM

- Low cardiac output syndrome after coronary artery bypass grafting (CABG) remains a considerable clinical problem with complex aetiology. The degree of myocardial damage will affect early postoperative course as well as life expectancy.
- Cytoprotective action of carnitine during ischaemia has been confirmed in both experimental and clinical studies.
- The aim of this study was to assess the effects of intracoronary L-carnitine on electrical and systolic myocardial function, and myocyte damage in patients with a moderately impaired left ventricular ejection fraction (LVEF) who underwent CABG with the use of cardiopulmonary bypass (CPB).

MATERIALS AND METHODS

- 33 patients with either unstable or stable Canadian Cardiovascular Society (CCS) class 4 angina, undergoing CABG, were randomized to receive a crystalloid cardioplegic solution supplemented with L-carnitine 1 mmol/L (n=16) or without L-carnitine (control group, n=17).
- Total carnitine concentration in coronary sinus samples was determined before, immediately after, and 12 hours after CPB. Cardiac output was measured before anaesthesia, just after the patient was weaned off CPB and 4 hours postoperatively.
- The incidence of ventricular fibrillation was recorded during cardiac arrest induction and during reperfusion. Serum activity of cardiac enzymes was determined several time after CPB.

RESULTS

- Compared with pre-bypass values, carnitine level in blood from coronary sinus just before the end of CPB significantly increased in carnitine treated patients (from 34.2 to 50.6 mmol/L, $p<0.05$) and decreased in control group (from 35.3 to 24.7 mmol/L, $p<0.05$) [*Figure 1*]. Cardiac output immediately after CPB was significantly higher in carnitine group than control (4.8 *vs* 3.2 L/min, $p<0.05$).
- Enzyme activity was reduced in the L-carnitine group *versus* controls (*Figure 2*).
- A significantly higher incidence of ventricular fibrillation during reperfusion period was observed in control group compared to carnitine treated patients (8/17 *vs* 2/16, $p<0.05$).

KEY POINTS

- Administration of L-carnitine with cardioplegic solution in patients with reduced LVEF enhances myocardial protection from ischaemia and reperfusion injury
- L-carnitine appears to be an interesting tool that can be used to improve myocardial management during CABG

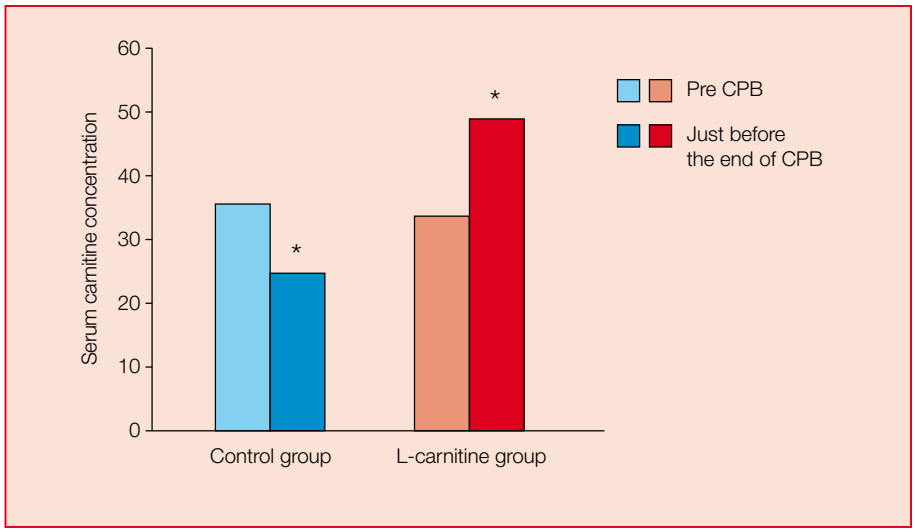

Figure 1. Serum L-carnitine concentration in patients with and without L-carnitine just before the end of cardiopulmonary bypass (CPB) and in pre CPB (*p<0.05).

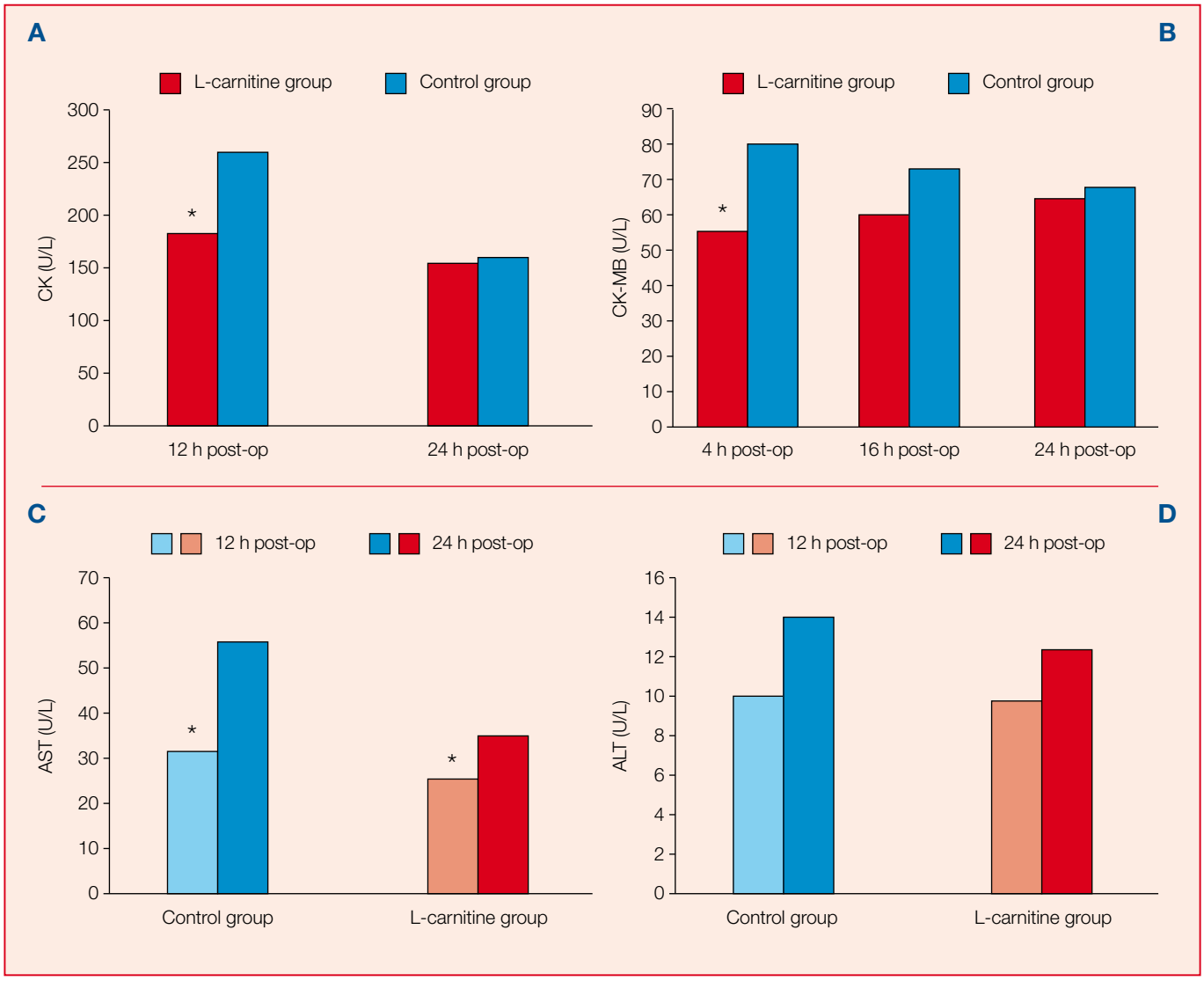

Figure 2. Serum activity of **A** creatinine phosphokinase (CK); **B** CK-MB; **C** aspartate aminotransferase (AST) and **D** alanine aminotransferase (ALT) to different times in patients with and without L-carnitine underwent CABG (*p<0.05).

The treatment of perioperative ventricular systolic dysfunction with carnitine

Iliuta L, Vasilescu A, Candea V et al.

Eur J Heart Fail 2000;2(Suppl.2):54

BACKGROUND AND AIM

- L-carnitine treatment may be beneficial in the treatment of perioperative ventricular systolic dysfunction.
- The aim of this study was to assess the effects of L-carnitine treatment on: 1) haemodynamic and heart function in perioperative ventricular systolic dysfunction; and 2) perioperative morbidity and mortality outcomes in ischaemic and valvular ventricular systolic dysfunction.

MATERIALS AND METHODS

- 276 patients with perioperative ventricular systolic dysfunction were randomized to receive L-carnitine 2 g/day (n=138) or no L-carnitine (n=138) for 10 days and were followed-up for 6 months.
- Clinical and paraclinical (echocardiography, ECG, Holter ECG) parameters were assessed at 0, 14, 30 and 180 days.

RESULTS

- L-carnitine intake improved left ventricular insufficiency signs and decreased of frequency of perioperative arrhythmic episodes. In addition, a statistically significant direct correlation between duration of L-carnitine intake and ventricular performance was reported (*Figure*).
- L-carnitine treatment was also protective, reducing the risk of an increase in ventricular chamber size and in use of diuretic drugs, a decrease of ventricular EF and an increase of degree of valvular regurgitation.
- Perioperative carnitine intake improved the early and late (at 6 months) clinical course in operated patients with systolic ventricular dysfunction. It shorten the Intensive Care Unit (ICU) stay with an average of 8.5 hours, reduced the need for inotropic support and the mortality at 6 months (by 1.6%).

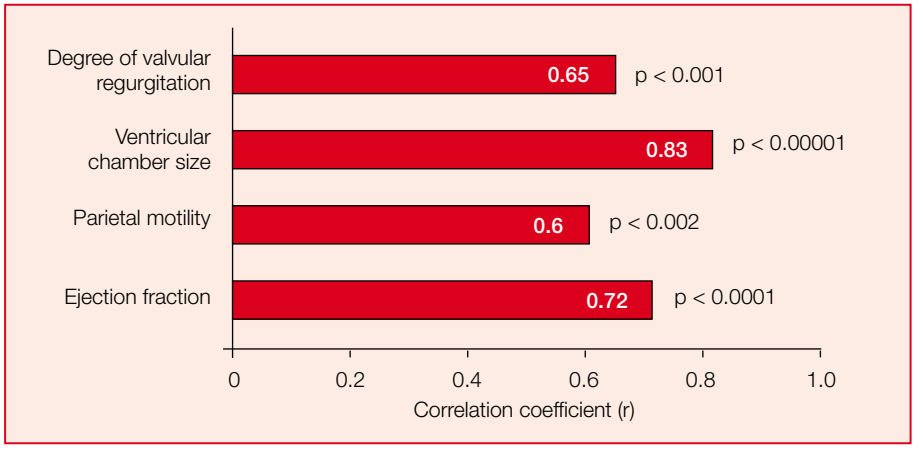

Figure. Beneficial effects of L-carnitine on ventricular performance in patients with perioperative systolic ventricular dysfunction undergoing cardiac surgery.

KEY POINTS

- Intake of L-carnitine in case of perioperative ventricular systolic dysfunction produces an improvement of the clinical and hemodynamic status and heart function indices
- L-carnitine therapy in ventricular systolic dysfunction is a protection factor against ventricular dysfunction progression
- L-carnitine given perioperatively reduces ICU stay, requirement for inotropic support and late postoperative mortality

The effect of preoperative L-carnitine supplementation on myocardial metabolism during aorto-coronary bypass surgery

Böhles H, Noppeney T, Akcetin Z et al.

Zeitschrift für Kardiologie 1987;76(Suppl.5):14-8

BACKGROUND AND AIM

- It has been ascertained that anoxia or even ischemia cause an accumulation of long-chain fatty acids and their metabolites with a concomitant decrease of free carnitine.
- In animal experiments it was reported that replacement of carnitine alleviates the accumulation of long-chain acylcarnitine and results in the improvement of energy metabolism and mechanical performance.
- The aim of this study was to investigate whether carnitine administered preoperatively improves the metabolic changes of ischemically compromised heart muscle in patients undergoing cardiac surgery.

MATERIALS AND METHODS

- 68 patients with ischaemic heart disease were assigned to a group supplemented with L-carnitine (n=41, 1 g/die orally and 0.5 g intravenous immediately before the operation) or a control group (n=27).
- When extracorporeal circulation was established, a small piece of the right atrial appendage was biopsied and prepared for analysis of ATP, lactate and carnitine fractions.

RESULTS

- The amount of total carnitine was similar in both groups. However, free carnitine was significantly higher and long-chain acylcarnitine was significantly lower when L-carnitine was supplemented (both $p<0.05$).
- Myocardial ATP concentrations were higher in the patients supplemented with carnitine. A negative correlation existed between ATP and lactate levels.
- The use of inotropic medications was significantly lower in the L-carnitine group than in controls ($p<0.02$) [*Figure*].

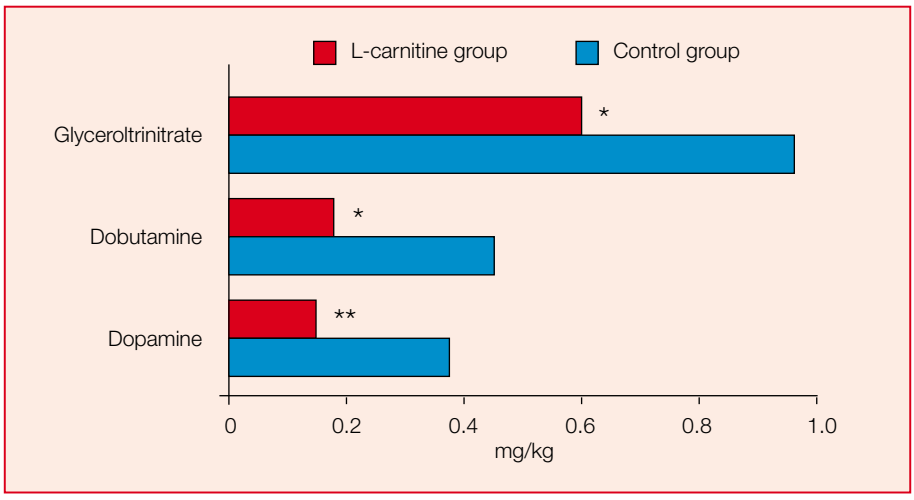

Figure. Postoperative inotropic medications in control and L-carnitine groups (*$p<0.01$, **$p<0.02$).

KEY POINTS

- Preoperative L-carnitine supplementation in patients undergoing aorto-coronary bypass surgery was proved to be effective and beneficial with respect to the normalization of parameters of myocardial energy metabolism
- L-carnitine supplementation reduced the need for inotropic medications

Myocardial protection by L-carnitine in children treated with Adriamycin®

Anselmi Chávez G, Machado Hernández I, Febres Ollarve C et al.

Revista Latino-Americana Cardiología 1997;18:208-4

BACKGROUND AND AIM

- The major risk in using doxorubicin hydrochloride (Adriamycin®) to treat neoplastic diseases is cardiotoxicity, which is dose-dependent. Early detection of myocardial damage is of the utmost importance for discontinuing chemotherapy.
- L-carnitine has demonstrated to be really effective in preventing cardiotoxicity, both experimentally and clinical trials in adults.
- The aim of this study was to evaluate the possible cardioprotective effects of L-carnitine used in children treated with Adriamycin® for the treatment of several types of tumors.

MATERIALS AND METHODS

- Adriamycin® cardiotoxicity was compared in 2 groups of patients: one group (n=20), non-protected group, was treated only with Adriamycin®, and a second group (n=108), protected group, was treated with Adriamycin® plus L-carnitine (1-2 g i.v. on the same day the children received Adriamycin®, and 175 mg/kg/day up to one year after the end of Adriamycin® treatment).
- Clinical and laboratory heart function testing were performed at baseline and periodically throughout the study and included ECG, echocardiography and cardiac enzyme level assessment.

RESULTS

- In the non-protected group, 2 patients developed marked myocardial toxicity necessitating the withdrawal of doxorubicin, one of them also developing a severe congestive heart failure (NYHA IV) which did not responded to standard treatment. This child recovered to NYHA I after 3 months of L-carnitine treatment.
- There was no evidence of doxorubicin-induced cardiotoxicity in any patient who received L-carnitine plus chemotherapy.

KEY POINT

- The protective effect of L-carnitine against doxorubicin cardiotoxicity, showed for the first time in children in a clinical setting, appears to be very encouraging

Effects of doxorubicin-containing chemotherapy and a combination with L-carnitine on oxidative metabolism in patients with non-Hodgkin lymphoma

Waldner R, Laschan C, Lohninger A et al.

J Cancer Res Clin Oncol 2006;132(2):121-8

BACKGROUND AND AIM

- Chemotherapy regimens based on anthracycline (doxorubicin) are well established in lymphoma therapy. Unfortunately the dose-dependent cardiotoxicity of doxorubicin limits its clinical use; it has been suggested that doxorubicin may exert at least part of its effect by inhibiting fatty acids (FAs).
- The aim of this study was to examine the effects of L-carnitine with a view to reducing cytotoxic side-effects.

MATERIALS AND METHODS

- In this randomized controlled trial, 20 patients were scheduled to receive 3 g L-carnitine before each chemotherapy cycle, followed by 1 g L-carnitine/day during the following 21 days, while 20 patients received a placebo.
- The plasma lipid profile and relative mRNA levels of key enzymes of oxidative metabolism (carnitine acyltransferases) were measured at three points of time. In addition to the clinical parameters, mRNA of white blood cells was used to evaluate the toxic effects on cardiomyocytes.

RESULTS

- No cardiotoxicity of anthracycline therapy was detected. Carnitine treated patients showed a rise in plasma carnitine, which led to an increase of relative mRNA levels from CPT1A (liver isoform of carnitine palmitoyltransferase) and OCTN2 (carnitine transporter).
- Following chemotherapy, an activation of carnitine acyltransferases was associated with a stimulation of OCTN2 in both groups.

KEY POINT

- Increased plasma carnitine levels following supplementation with L-carnitine induce enzymes of FA metabolism and change the serum lipid profile

Serum carnitine levels during the doxorubicin therapy. Its role in cardiotoxicity

Yaris N, Ceviz N, Coskun T et al.

J Exp Clin Cancer Res 2002;21(2):165-70

BACKGROUND AND AIM

- The optimal clinical usefulness of doxorubicin is usually limited secondary to the development dose-dependent and irreversible cardiotoxicity. It has been proposed that with higher cumulative exposure to doxorubicin, serum levels of L-carnitine drop.
- Supplemental L-carnitine has been shown to reverse cardiomyopathy in patients with serum carnitine deficiency and prevent chemotherapy-induced cardiotoxicity.
- The aim of the study was to monitor the serum carnitine levels during the treatment with doxorubicin and to determine a relationship between serum carnitine levels and cardiac dysfunction.

MATERIALS AND METHODS

- 15 previously untreated patients with non Hodgkin's lymphoma, who were given a chemotherapy protocol containing doxorubicin, were prospectively investigated.
- Measurement of serum carnitine levels and cardiological evaluation were performed prior to therapy and 3 or 4 weeks after cumulative doses of both 180 mg/m^2 and 300 mg/m^2.
- A group of 20 healthy children served as control group to obtain reference values of left ventricular dimensions, systolic and diastolic functions and serum carnitine levels.

RESULTS

- The mean left ventricular end-diastolic diameter (LVEDd) of patients after cumulative doses of 180 mg/m^2 and 300 mg/m^2 of doxorubicin increased significantly compared with the initial value (p=0.02 and p=0.007, respectively).
- The ejection and shortening fractions in the patient group after cumulative doses of 300 mg/m^2 of doxorubicin were significantly lower than those in the control group (*Figure*). A statistically significant augmentation was observed in mitral A, with a decrease in mitral E/A ratio.
- There was a trend towards lower serum carnitine levels with higher cumulative doses of doxorubicin.

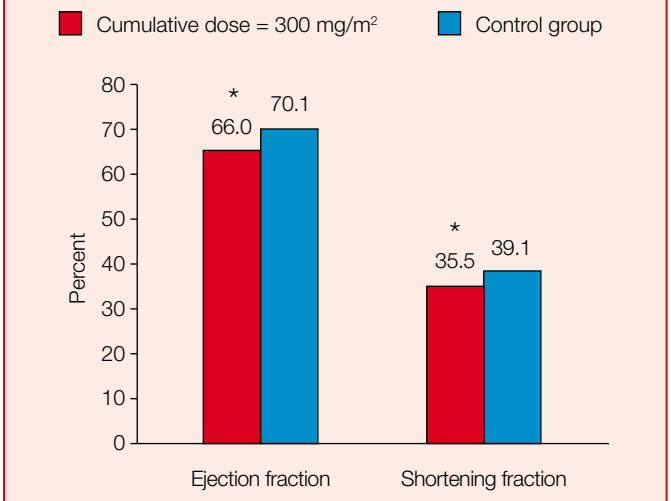

Figure. Effect of cumulative dose of doxorubicin on cardiac functions of patients (*p<0.05).

KEY POINTS

- Alterations in left ventricular dimensions, systolic and diastolic functions could be observed when the cumulative doxorubicin dose has reached the dose of 300 mg/m^2
- These results invite more investigations to evaluate possible roles of L-carnitine in the prevention of doxorubicin-induced cardiotoxicity

Carnitine and cardiac dysfunction in childhood cancer survivors treated with anthracyclines

Armenian SH, Gelehrter SK, Vase T et al.

Cancer Epidemiol Biomarkers Prev 2014;23(6):1109-14

BACKGROUND AND AIM

- Anthracyclines are widely used in the treatment of childhood cancer. Unfortunately, their use is limited by the occurrence of cardiac damage by their strong dose-dependent association with late-onset congestive heart failure (CHF).
- As the precise mechanism underlying is still not fully understood, metabolomic profiling of asymptomatic childhood cancer survivors could help to identify molecular pathways involved in the pathogenesis of anthracycline-related CHF and help identify druggable targets.
- The aim of this study was to describe how metabolomic profiling of anthracycline-exposed survivors may provide new information for the development of targeted primary or secondary prevention strategies.

MATERIALS AND METHODS

- 150 asymptomatic childhood cancer survivors (age 2.6-37.9 [mean 12.4] years; 65 female and 85 male) previously treated with anthracyclines (mean dose 350 mg/m^2 [range 25-642 mg/m^2]) were included in this cross sectional study between October 2010 and September 2012.
- Study participants underwent a detailed cardiac evaluation with echocardiographic assessment. For metabolomic profile, blood samples were collected on the same day of the echocardiographic assessment, and plasma was extracted within 1 hour of sample collection. Plasma samples were stored at –80°C and shipped to Metabolon, Inc. (Research Triangle, NC) for batched analytic studies.

RESULTS

- Thirty-five (23%) participants had cardiac dysfunction, defined as left ventricular end-systolic wall stress >2SD by echocardiogram.
- Plasma levels of 15 compounds in three metabolic pathways (carbohydrate, amino acid, and lipid metabolism) were significantly different between individuals with cardiac dysfunction and those with normal systolic function.
- Individuals with cardiac dysfunction had significantly lower plasma carnitine levels (relative ratio [RR] 0.89, $p<0.01$) when compared to those with normal function.

KEY POINTS

- Childhood cancer survivors with cardiac dysfunction occurring years following completion of cardiotoxic therapy showed significantly lower plasma carnitine levels compared to those with normal function
- Treatment of carnitine deficiency prior to/during anthracycline administration may facilitate the primary prevention in patients at highest risk for congestive heart failure

Echocardiographic assessment of anthracycline cardiotoxicity during different therapeutic regimens

De Leonardis V, De Scalzi M, Neri B et al.

Int J Clin Pharmacol Res 1987;7(4):307-11

BACKGROUND AND AIM

- The use of doxorubicin (Dx) in treating malignancies is limited by a potentially fatal cardiomyopathy. Prevention of this related cardiotoxicity has been attempted either by using doxorubicin analogues such as 4′-epidoxorubicin (4′-EpiDx) or by simultaneous administration of other pharmacological substances.
- The aim of this study was to assess the effects of three therapeutic regimens (Dx alone, Dx and L-carnitine, and 4′-EpiDx) on left ventricular performance, in the effort to predict the effectiveness of L-carnitine in preventing doxorubicin-induced cardiotoxicity.

MATERIALS AND METHODS

- 15 patients with breast and lung cancer were divided into three groups. Group 1 (breast cancer, n=4) was treated with 60 mg Dx/m^2 i.v. every 3 weeks; Group 2 (lung cancer, n=5) received 60 mg Dx/m^2 i.v. every 3 weeks and L-carnitine 1 g orally 3 times daily for 3 days before and for 3 days after the treatment, plus 1 g i.v. just prior to the anthracycline infusion; Group 3 (breast cancer, n=6) was treated with 60 mg 4′-EpiDx/m^2 i.v. every 3 weeks. 25 healthy subjects were evaluated as control group.
- All patients and subjects underwent M-mode echocardiography testing.

RESULTS

- Systolic VCF Max (maximum velocities of fibre shortening and lengthening) values were significantly lower in the doxorubicin treatment group before the 5th therapy cycle compared with baseline control group values and both epidoxorubicin and doxorubicin + L-carnitine groups before the 5th treatment cycle (*Figure 1*).
- Diastolic VCF Max values were significantly lower in the epidoxorubicin group *versus* baseline control, and doxorubicin and doxorubicin + L-carnitine groups before 5th therapy cicle (*Figure 2*).

KEY POINT

- The addition of L-carnitine to chemotherapy decreases the potential cardiotoxicity of anthracyclines on left ventricular function

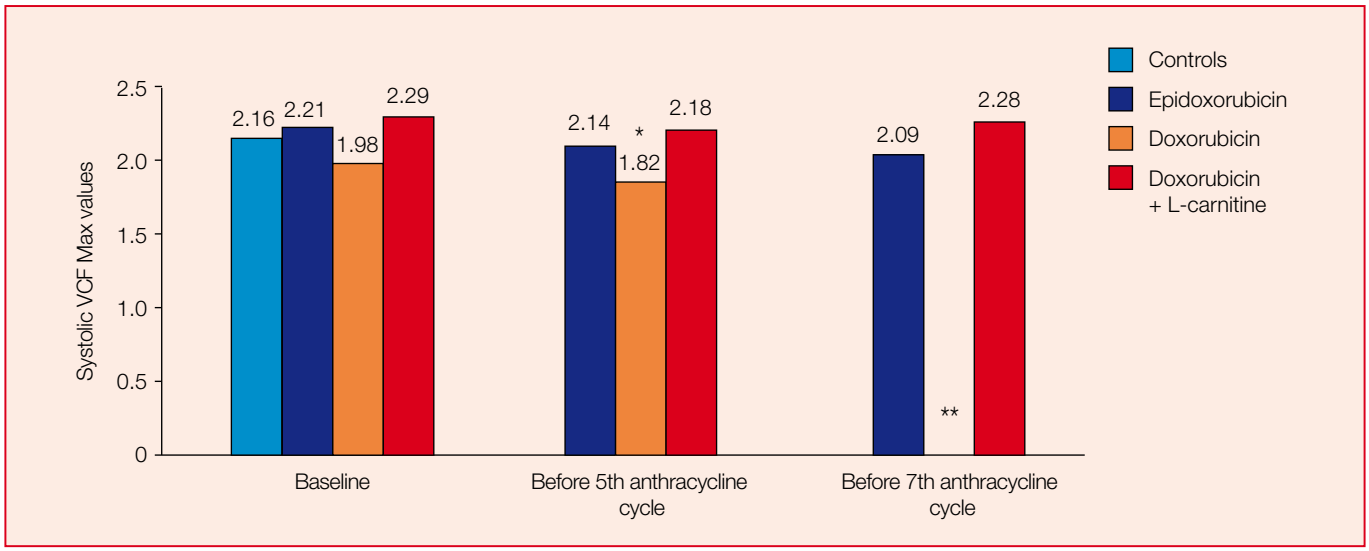

Figure 1. Systolic VCF Max values at baseline and before the 5th and 7th anthracycline cycles (where available) [*p<0.05 *vs* the other 2 treatment groups before 5th cycle and baseline control levels; **VCF values fell below normal limits in the doxorubicin group, therefore therapy was discontinued after the 4th cycle]. VCF Max=maximum velocities of fibre shortening and lengthening.

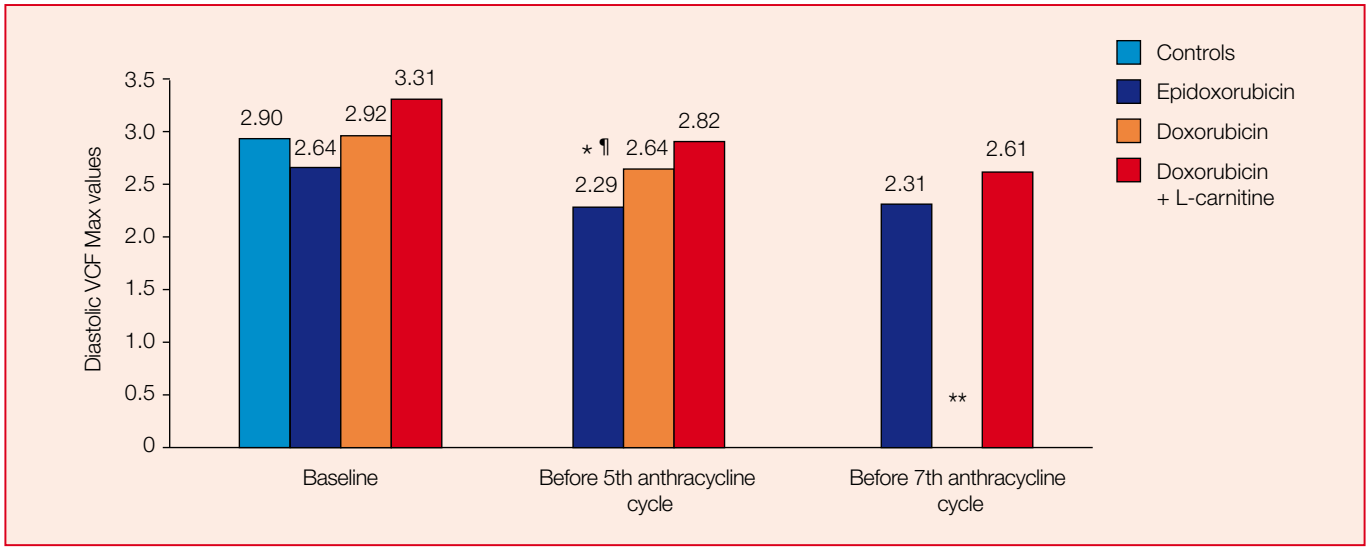

Figure 2. Diastolic VCF Max values at baseline and before the 5th and 7th anthracycline cycles (where available) [*p<0.01 *vs* controls at baseline and ¶p<0.05 *vs* the other 2 treatment groups before 5th cycle; **VCF values fell below normal limits in the doxorubicin group, therefore therapy was discontinued after the 4th cycle]. VCF Max=maximum velocities of fibre shortening and lengthening.

Reduction of cardiac toxicity of anthracyclines by L-carnitine: preliminary overview of clinical data

De Leonardis V, Neri B, Bacalli S, Cinelli P.

Int J Clin Pharmacol Res 1985;5:137-42

BACKGROUND AND AIM

- Early manifestations of the cardiotoxic and dose-dependent effects of anthracyclines (daunorubicin and doxorubicin) include transient, reversible tachycardia, constriction of the coronary arteries, and elevated serum levels of the creatine kinase-MB (CK-MB) isoenzyme. In the later phase of anthracycline-induced cardiotoxicity, cellular damage is accompanied by congestive heart failure and electrocardiographic abnormalities.
- Preliminary evidence suggests that carnitine may have potential in the prevention of anthracycline-induced cardiotoxicity.
- The aim of this study was to assess the role of L-carnitine in preventing or protecting from anthracycline-induced cardiomyopathy.

MATERIALS AND METHODS

- A total of 9 patients (aged 18-72 [mean 54] years; 7 male and 2 female) was enrolled in this study. Seven patients were receiving doxorubicin and 2 patients daunorubicin, with cumulative doses of 200-490 mg/m^2. L-carnitine was administered to each patient as follows:
  - 3 g orally/day for the 3 days preceding the anthracycline therapy
  - 1 g intravenous the same day as the therapy
  - 3 g orally/day for the 3 days after the therapy.
- Acute cardiotoxicity has been evaluated by CK-MB serum levels before and 15 hours after treatment.
- Chronic cardiotoxicity has been monitored studying the electrocardiography and the left ventricular performance by computerized M-mode echocardiography measuring the maximal velocity of circumferential fiber shortening (VCF Max).

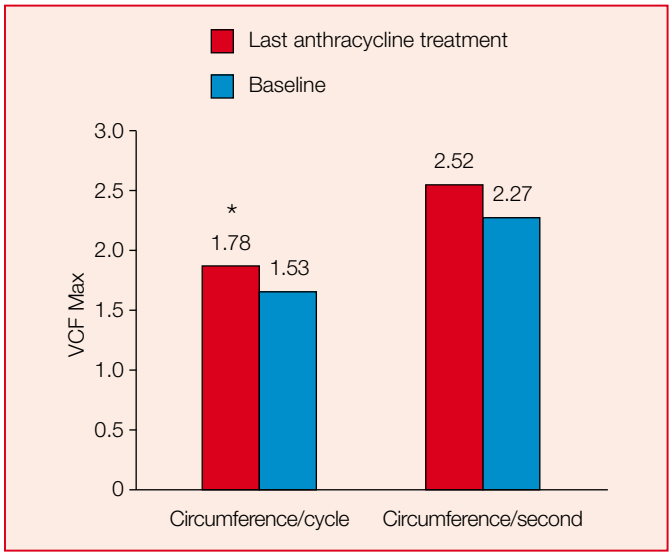

Figure. VCF Max expressed in circumference/cycle and in circumference/second before the first and after the last anthracycline treatment (*p<0.05 *vs* last anthracycline treatment).

RESULTS

- No significant increase in CK-MB serum levels occurred after administration of either doxorubicin or daunorubicin given in combination with L-carnitine. A significant decrease was observed in the VCF Max measured in circumference/cycle (p<0.05) [*Figure*].
- When individual patient data were evaluated, VCF Max fell to below the normal value in one patient who had received the highest cumulative dose of 490 mg/m^2 of doxorubicin, but anthracycline therapy had no significant effect on VCF Max (measured in circumference/second) in any of the other eight patients (*Figure*).

KEY POINTS

- L-carnitine treatment may reduce anthracyclines-dependent acute cardiotoxicity measured as CK-MB isoenzyme levels and also positively affect the cardiac contractility as shown by VCF Max values measured during the course of chemotherapy
- The systematic use of L-carnitine as adjuvant therapy during doxorubicin administration may be of value to reduce myocardial damage